DEVELOPMENT OF THE ROLE OF CANCER NURSE COORDINATOR; A WEST AUSTRALIAN APPROACH

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Western Australia is a vast state, there are over 2 million people living in an area of approximately 2 ½ million sq kilometres.

Thirty percent of the population lives in rural and remote areas.

Literature reveals a number of issues and disadvantages for Indigenous cancer patients and those from rural and remote areas.

For best outcome it is important that all cancer patients have access to the full range of services, evidence based treatments, clinical trials and a multidisciplinary team approach to care.

Since West Australian specialised cancer treatment centres are based in the metropolitan area, this poses a major challenge for the provision and equity of access to services. Patients may have to travel for many hours or days and spend weeks in the city away from familiar surroundings, family and friends.

In addition, patients with cancer face a complex journey; they often receive multiple treatments from different services and many healthcare providers.

At a time of high anxiety and stress this can add to their burden.

This presentation is about the development of the role of Cancer Nurse Coordinator - Gynaecology in Western Australia. A state wide position offering a point of contact for women with gynaecologic malignancies across and between services. This includes coordination of care, assessment of needs and support as required throughout the trajectory of their illness, liaison with health care professionals across and between treatment centres and linking them with services in metropolitan, regional and remote W.A.
THE NURSES ROLE IN IMPROVING NUTRITIONAL STATUS FOR WOMEN WITH GYNAECOLOGICAL CANCER: AN EVIDENCE IMPLEMENTATION STUDY

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Weight loss and loss of physical condition are known consequences of gynaecological cancer (GC) which can delay treatment delivery and recovery. Improved health outcomes can result when women with cancer and their health care providers proactively manage nutrition. However, despite evidence based guidelines, malnutrition screening is not routinely undertaken at the time of diagnosis or during the course of the disease at most GC centres in Australia. The overall aim of this study is to improve patient outcomes by implementing a nutritional care program. Specific aims include:

1. To establish the attitudes and educational needs of health professionals towards nutritional screening in women affected by GC

2. To determine the knowledge and needs of patients regarding attention to nutritional status

3. To implement a nutritional screening protocol in liaison with the multidisciplinary team

4. To develop referral pathways for the nutritional management of women affected by GC.

Multiple data collection methods were used to gain information. Patient chart audits, nursing staff surveys, focus group interviews (FGI) with nursing staff and patients. Documentation relating to nutritional status was absent from most charts audited. Staff surveys yielded an 85% response and demonstrated that nursing staff consider nutritional screening an important part of their role. FGI with 66% of staff confirmed that an education program and access to referral pathways would support this role. Nutritional support is recognised as a necessary component of care in women with GC. Supporting nurses to fulfil this role leads to improved patient outcomes.
DEVELOPMENT AND IMPLEMENTATION OF THE OVARIAN CANCER CENTRE AT THE EUROPEAN INSTITUTE OF ONCOLOGY

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Background: Ovarian cancer is a long and disabling disease. Until September 2008 there wasn’t a clinical pathway with data missing, no personalized care and healthcare providers’ dissatisfaction. The European Institute of Oncology founded the Ovarian Cancer Centre (EIO-OCC) dedicated to patients with ovarian cancer from the diagnosis until the end of life.

Aims: The mission of the EIO-OCC is to ensure a holistic multidisciplinary approach for research, prevention and treatment of ovarian cancer, defining a clinical pathway with the involvement of patient. Other secondary aims are:

- To Benchmark for other centers
- To implement early diagnosis
- To develop information, training and research
- To improve patient awareness

Methods: A multidisciplinary team guided by the clinical nurse coordinator defines a clinical pathway to assist ovarian cancer patients. The nurse coordinator’s key role allows to assess patients’ needs and clinical problems to give them the right answer in the right moment with the right resources.

Results: on February 2010 we founded the Italian patients' association named Associazione Contro il Tumore Ovarico (ACTO) to improve awareness, we also performed the first congress with patients and relatives to share our objectives. In one year the pathway’s introduction allows an increase of 5% early debulking surgery with the same resources. A definition of a new nursing record allows a complete data collection useful to nursing survey

Conclusion: This is a long way, but now we know: the centralized patient’s care destination is attainable, this has improved health professional satisfaction even if work has increased.
LIVING ON THE PEAK- THE LIVED EXPERIENCES OF PATIENTS UNDERGOING EXTENSIVE CHEMOTHERAPY FOR RECURRING OVARIAN CANCER

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Background: Effectiveness of chemotherapy agents to restrain recurring ovarian cancer has improved. Patients live with cancer longer than ever before. However, little is known about ways in which patients define their worlds.

Aim: This study aimed to illuminate the phenomenon of living with extensive chemotherapy of recurring ovarian cancer.

Methods: 4 patients were interviewed, 3 and 5 years after first recurrence. The method was based on Giorgi's phenomenological method, i.e., situated structure for each patient was identified, and then the four structures were condensed into a general structure for all patients; this general structure communicates the most invariant meaning of the phenomenon.

Results: The general structure revealed that patients perceived time as extendable, which led to gratitude to postpone death. Increased fragility of the body forced attention to signs from the body. Body strength was increasingly weakened, and unpredictable that led to an eagerness to catch the moment. Strength had to be captured, retained, and nurtured. The wish to share the meaning of the disease with others was expressed as unattainable. In encounters with others, the cancer-affected body constituted a barrier to communication. Inability to share their experience was manifested in encounters that were characterized by caregivers' objective attitudes.

Conclusion: For these patients, the meaning of living with extensive chemotherapy of recurring ovarian cancer involved acquisition of a life-affirming approach for capturing and maintaining strength and for holding body and mind together to survive a while longer.
SUMMARY OF CLINICAL TRIAL EFFICACY RESULTS OF GARDASIL® (QUADRIVALENT HUMAN PAPILLOMAVIRUS [HPV] 6/11/16/18 VACCINE)

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Background and aims: At licensure (2006), GARDASIL was shown to prevent HPV16/18-related high-grade lesions (CIN2/3 and AIS) with up to two years follow-up (protocols 013/015, women aged 16-26). Here we present end-of-study vaccine efficacy (VE) for up to four years for women aged 24-45 (protocol 019), men aged 16-26 (protocol 020), and long-term VE for the HPV16 monovalent prototype-vaccine (protocol 026).

Methods: Per-protocol VE was reviewed in five protocols.

Results: In the per-protocol-population of women aged 16-26, end-of-study VE for HPV16/18-related CIN2/3 or AIS was 98% (95%CI:94-100); VE for HPV6/11/16/18-related condyloma, VIN1-3, and ValN1-3 was 99%, 100% and 100%, respectively. In subjects PCR-negative for HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59 pre-vaccination, Gardasil significantly reduced CIN2-3/AIS associated with the 10 non-vaccine HPV types which cause ~20% of cervical cancers. In women aged 16-26 who had cleared a previous infection with one of the vaccine-HPV types at the time of vaccination, Gardasil recipients were protected against recurrence of disease from that type, unlike placebo recipients. Among women aged 24-45, per-protocol VE for any HPV6/11/16/18-related disease was 92% (95%CI: 50-100%). In men aged 16-26, VE against any HPV6/11/16/18-related external genital lesion in the per-protocol-population was 90% (95%CI: 69-98%). In the extended follow-up of women aged 16-23 up to 9 years after vaccination with the HPV16 monovalent prototype-vaccine, per-protocol VE against HPV16 CIN was 100%.

Conclusions: Disease prevention remains the most important measure of long-term VE. Vaccination with GARDASIL is expected to reduce significantly the burden of cervical and other cancers, dysplasia, and genital warts in women and men.
END-OF-STUDY EFFICACY OF GARDASIL® AGAINST HP6/11/16/18-RELATED PERSISTENT INFECTION AND DISEASE IN WOMEN AGED 24 TO 45

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Background and aims: Prophylactic administration of quadrivalent HPV (types 6/11/16/18) vaccine (Gardasil) is highly effective in preventing HPV6/11/16/18-related cervical and genital disease in adolescent and young adult women. Preliminary analyses (2.2 years mean follow-up per subject) demonstrated the efficacy of Gardasil against the incidence of vaccine-type related CIN or external genital lesions (EGL) was 92.4% (95% CI: 49.6, 99.8) women aged 24 to 45. We performed an end-of-study analysis of efficacy against CIN or EGL (including vulvar, vaginal intraepithelial neoplasia and condyloma).

Methods: A total of 3819 women aged 24-45 were enrolled. Women received Gardasil or placebo at Day 1, Month 2 and 6. Pap testing, genital inspection and cervicovaginal sampling were performed every 6 months. A per-protocol (3 doses of vaccine/placebo within 1 year of enrollment, naïve to the relevant HPV types, free of infection throughout vaccination) analysis was conducted. Mean follow-up was 3.8 years (+1.6 years compared with the previous analyses).

Results: Gardasil efficacy in preventing HPV6/11/16/18-related CIN or EGL was 95.7% (95% CI: 73.4, 99.9) (23 vs. 1 in the placebo and vaccine groups, respectively). The one (previously-reported) vaccinated case was an HPV16-related CIN2. No new CIN or EGL cases were seen during the additional follow-up. Efficacy against HPV6/11/16/18-related persistent infection was 89.6% (95%CI: 79.3, 95.4) (85 vs., 9 in the placebo and vaccine groups, respectively).

Conclusions: Gardasil is highly efficacious in preventing HPV6/11/16/18-related persistent infection, CIN and EGL in women aged 24 to 45, naïve to vaccine HPV types.
PARAMETRIAL INVOLVEMENT IN WOMEN WITH EARLY STAGE CERVICAL CANCER WITH TUMOR LESS THAN 20MM AND WITH NEGATIVE SENTINEL LYMPH NODES

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Objective: To estimate the incidence of parametrial involvement in women with early-stage cervical cancer with tumor less than 20 mm and with negative sentinel lymph nodes (SLN).

Methods: We reviewed all patients who underwent radical hysterectomy and pelvic lymphadenectomy with SLN biopsy for invasive cervical cancer between April 2004 and December 2009. Parametrial involvement was defined as direct microscopic extension, spread of tumor to parametrial lymph node or tumor emboli in-transit found within lymphovascular channels in the parametrial tissue.

Results: From the 204 patients who underwent a radical surgery with SLN biopsy, 63 patients (FIGO stage IA2-10, IB1-53) met the inclusion criteria: tumor less than 20 mm in the largest diameter regardless of deep of stromal invasion (less or more than half stromal invasion) and negative sentinel lymph nodes. Median age was 44.3 (24-72). Lymph-vascular space invasion was present in 25 patients. The histology identified squamous carcinoma in 50 women, adenocarcinoma in 11 women and adenosquamous carcinoma in 2 women. Tumor grade 1 was in 41, grade 2 in 16 and grade 3 in 6 of the cases. No parametrial involvement was observed. False negativity rate of SLN biopsy was 0%.

Conclusion: No parametrial involvement was observed in women with early stage cervical cancer with tumor less than 20 mm and negative sentinel lymph nodes regardless of presence of lymph-vascular space invasion, histology subtype and grade of the tumor. Radical removal of parametrium in this low risk group of patients is questionable.
BRACHYTHERAPY VERSUS RADICAL HYSTERECTOMY AFTER CHEMORADIATION WITH GEMCITABINE PLUS CISPLATIN. A RANDOMIZED PHASE III STUDY IN IB2-IIIB CERVICAL CANCER

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Purpose: To compare intracavitary brachytherapy (B) versus radical hysterectomy after external beam chemoradiation (EBRT-CT) with gemcitabine and cisplatin (GC) in FIGO stage IB2, IIA and IIIB cervical carcinoma (CC). End points were overall survival (OS), progression free survival (PFS) and toxicity.

Patients and methods: In this randomized study EBRT-CT treatment consisted of: six doses of G at 125mg/m² plus C at 40mg/m² per week concurrent with 50 Gy of EBRT. In the Standard treatment arm, EBRT-CT was followed by intracavitary Cesium (low-dose rate) applications within 2 weeks of EBRT-CT to reach a point A dose of 85 Gy. In Surgical arm a radical hysterectomy type III with bilateral pelvic lymph node dissection and para-aortic lymph node sampling (HTAR+DRP) was performed within 4-6 weeks after EBRT-CT.

Results: We included 220 patients assigned to Surgery (113 patients) or Standard treatment (107 patients). There were no differences in clinicopathological characteristics or in EBRT-CT. Toxicity secondary to EBRT-CT was similar (p> 0.05). Standard treated patients had more chronic proctitis while the surgically treated had acute complications of surgery (4%) and hydronephrosis. At 60 months follow-up, PFS is not statistically different, 10 and 16 patients per group have recurred and died, respectively. OS is 80% vs 75%, respectively (p> 0.05).

Conclusions: Our results support that HTAR+DRP is an alternative after EBRT-CT without compromising PFS or OS in FIGO stage Ib2- IIb Cervical Carcinoma in settings where Brachytherapy is not available. Toxicity and complications are comparable.
ENDOMETRIAL CANCER IN THE OLDEST OLD: TUMOR CHARACTERISTICS, PATTERNS OF CARE, AND OUTCOME

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Objective: Despite the fact the endometrial cancer commonly occurs in elderly women, little is known about the treatment and outcome of women > 80 years of age.

Methods: An analysis of women > 65 years of age with endometrioid adenocarcinoma of the uterus diagnosed between 1988-2006 and registered in the Surveillance, Epidemiology, and End Results database was performed. Patients were stratified by age into the following groups: 65-69, 70-74, 75-79, 80-84, and > 85 years of age. Multivariable logistic regression models were constructed to examine treatment while adjusting for other confounders. Cancer-specific survival was examined using Cox proportional hazards models adjusted for other prognostic variables.

Results: A total of 37,718 women including 5289 aged 80-84 and 3446 > 85 years of age were identified. Older women had higher grade tumors (p< 0.0001) and more advanced stage disease (p< 0.0001). After adjusting for tumor characteristics, patients > 85 years of age were 86% (OR=0.14; 95% CI, 0.12-0.16) less likely to undergo hysterectomy, 52% (OR=0.48; 95% CI, 0.44-0.54) less likely to undergo lymphadenectomy and 59% (OR=0.41; 95% CI, 0.36-0.46) less likely to receive pelvic radiation. After adjustment for treatment and prognostic factors, cancer-specific mortality was 53% (HR=1.53; 95% CI, 1.39-1.67) greater in women 80-84 and 89% (HR=1.89; 95% CI, 1.71-2.08) greater in those > 85 years of age than in women 65-69 years old.

Conclusion: Women > 80 years of age receive less aggressive care than younger women. Even after adjusting for treatment differences cancer-specific mortality is higher in the older women.
A RANDOMIZED PHASE II TRIAL OF RIDAFOROLIMUS COMPARED WITH PROGESTIN OR CHEMOTHERAPY IN FEMALE ADULT PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA

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Background: To evaluate activity of ridaforolimus (R) observed in early phase endometrial cancer studies, this open-label, randomized phase 2 trial compares R with progestin (P) in women with advanced endometrial cancer.

Methods: Patients with unresectable stage III or IVa or metastatic endometrial cancer treated with at least 1 (but ≤2) line(s) of chemotherapy were randomized to oral R 40 mg daily for 5 days/week or P (medroxyprogesterone 200 mg/day or megestrol 60 mg/day). A protocol amendment added chemotherapy as a control; however, these patients (n=2) were not included in this unplanned interim analysis. The primary endpoint was progression free survival (PFS).

Results: As of March 24, 2010, 87 of 150 patients had been randomized—44 and 41 treated with R and P, respectively. Clinical characteristics were well-balanced between groups. Median PFS was 19.0 weeks for R compared with 8.3 weeks for P (Hazard Ratio=0.49 p=0.01). Response rate was 13.6% (CI 5.2-27.4) and 7.0% (CI 1.5-9.1) for R and P, respectively. The most common adverse events for R were diarrhoea (39%), anorexia (34%), mucosal inflammation (29%), rash (29%), hyperglycemia (27%), stomatitis (27%), nausea (27%) and asthenia (24%). In total, 73 serious adverse events (R=48; 17 treatment-related) and 8 non-treatment-related deaths (R=5; P=3) were reported.

Conclusions: In this study, oral ridaforolimus prolongs PFS in women with advanced endometrial cancer when compared with P. The safety profile is consistent with previous R experience, and similar to other mTOR inhibitors. These preliminary data indicate R is a promising agent for treatment of advanced endometrial cancer.
SYSTEMATIC COCHRANE REVIEW EXAMINING THE ROLE OF ADJUVANT CHEMOTHERAPY FOR ENDOMETRIAL CANCER

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A Cochrane systematic review assessed the role of adjuvant chemotherapy after hysterectomy for endometrial adenocarcinoma. The search strategy identified 698 unique references. Seven randomised trials met our inclusion criteria.

Four randomised trials studied adjuvant chemotherapy added to radiotherapy and 3 compared platin based combination chemotherapy directly with radiotherapy. Data from 1919 women shows an overall survival advantage from adjuvant chemotherapy (RR [95%CI]=0.85 [0.75, 0.96]). This is the same whether radiotherapy was used randomly or routinely. The risk ratio is 0.80 [0.70, 0.92] if the analysis is restricted to modern adjuvant platin based regimes (NNT=14; relative risk reduction =20% with an absolute risk reduction =7%). The ln(RH) [95%CI] for overall and progression free survival restricted to trials of modern conventional adjuvant chemotherapy regimes is -0.30 [-0.48, -0.12] and -0.29 [-0.47, -0.11] respectively, favouring post-operative chemotherapy. Data on the pattern of initial treatment failure from 1992 women shows that chemotherapy reduces the risk of developing a recurrence outside the pelvis (RR=0.73 [0.59, 0.92]). Chemotherapy may reduce the risk of a pelvic recurrence (RR=0.36 [0.13, 1.03] but only when radiotherapy was given to both groups. However, substituting radiotherapy for chemotherapy may increase the risk of pelvic recurrence (RR= 1.28 [0.89, 1.84]).

In conclusion, postoperative high dose cyclical platin based chemotherapy for high risk endometrial carcinoma has a small survival advantage and reduces the risk of metastatic disease irrespective of radiotherapy. It is an alternative to radiotherapy and has added value when used with radical radiotherapy.
WHAT IS THE STANDARD, POSTOPERATIVE CHEMOTHERAPY FOR HIGH-RISK ENDOMETRIAL CANCER?

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Doxorubicin plus Cisplatin (AP) had been used as the standard chemotherapy regimen for endometrial cancer. Recently, however, Paclitaxel plus Carboplatin (TC) has often been used from a practical clinical standpoint due to its favorable feasibility and good response rates in several phase II studies. Yet evidence regarding the survival benefits of a combination of taxane plus platinum is not sufficient. GOG177 demonstrated that TAP (Doxorubicin plus Cisplatin plus Paclitaxel with G-CSF) is superior to AP in terms of both response rate and overall survival; but TAP is considerably toxic and thus not appropriate for practical clinical use.

We have previously completed a phase II trial and determined the response rates of Docetaxel plus Cisplatin (DP), Docetaxel plus Carboplatin, and TC to be 51.7% (15/29, 95%CI: 32.5-70.6%), 48.3% (14/29, 95%CI: 29.4-67.5%), and 60.0% (18/30, 95%CI: 40.6-77.3%), respectively. Based upon these results, we are currently conducting a randomized phase III trial selecting DP and TC as the experimental arms and AP as reference. The purpose of this trial is to compare the PFS of AP as a post-operative chemotherapy regimen with that of DP or TC regimens in patients with high and high intermediate risk group of endometrial carcinoma. This trial should allow for clarification of the position of taxane plus platinum in the management of patients with endometrial carcinoma.
TARGET VOLUMES, ORGAN MOTION AND CONTOURING PITFALLS FOR IMRT
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The increasing use of intensity-modulated radiotherapy (IMRT) for the treatment of gynaecological malignancies potentially paves the way toward an improvement in the therapeutic ratio between tumour control and normal tissue toxicity. Cervix cancer is one tumour site which serves as a prototype for the potential gains but also the inherent dangers associated with highly conformal radiotherapy. The unpredictable and individualised intra-pelvic organ dynamics that can occur during radiotherapy treatment mandates a careful and conservative approach toward target delineation if we are to improve upon the outcomes of traditional radiotherapy strategies. The development of consensus guidelines for clinical target volume delineation is intended to provide radiation oncologists in the wider community with guidance and facilitate more consistent practice in target contouring for cervix cancer.
ROLE OF COMMON LOW PENETRANCE GENES (POLYMORPHISMS) IN OVARIAN CANCER SUSCEPTIBILITY AND CHEMO RESPONSE

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About 10% of ovarian cancers are attributable to rare high penetrance mutations in BRCA1/2. Common low penetrance polymorphisms present throughout the genome could also affect risk. Identification of single nucleotide polymorphisms (SNPs) that affect ovarian cancer risk is accomplished through studies involving thousands of ovarian cancer cases and control women. An international Ovarian Cancer Association Consortium (OCAC) was formed in 2005 to facilitate collaboration between studies. Initially, OCAC focused on candidate gene and pathway studies, but associations were weak and inconsistent. More recently genome wide association studies (GWAS) have led to the identification of risk SNPs on chromosomes 9p22 (BNC2), 8q24, 2q21 (HOXD1), 3q25 (TiPARP) and 17q21 (SKAP1). Fine mapping studies will be performed to identify the causal loci and this will facilitate functional analyses. Rare variants may also contribute to ovarian cancer susceptibility and it will become increasingly feasible to study these in the future. The long-term goal of OCAC is to identify a panel of susceptibility SNPs that can be used in combination with known predisposing factors, such as parity, OC use and endometriosis, to better stratify ovarian cancer risk. This would greatly facilitate implementation of screening and prevention strategies by focusing these on high-risk women. OCAC also has performed a survival GWAS and the MERIT40 locus on 19p13 was found to be most highly predictive of outcome. The ability to predict outcome in ovarian cancer would be valuable, and if some genetic variants affect sensitivity to specific drugs this information could help guide individualized therapy.
PHASE III TRIAL OF BEVACIZUMAB IN THE PRIMARY TREATMENT OF ADVANCED OVARIAN, PERITONEAL OR FALLOPIAN TUBE CANCER: A GOG STUDY

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Background: BEV, a humanized anti-VEGF monoclonal antibody, has demonstrated single-agent activity in patients with recurrent EOC, or PPC. The therapeutic impact of concurrent +/- maintenance BEV with standard chemotherapy (CT) was evaluated in an international, double-blind, placebo-controlled phase III trial.

Methods: Eligible patients had newly diagnosed, previously untreated EOC, PPC or FTC following abdominal surgery for staging and maximal effort at tumor debulking; stage III (macroscopic residual disease) or stage IV disease. The randomly allocated regimens were: CT (IV paclitaxel 175 mg/m² + carboplatin AUC 6 cycles 1-6) + placebo cycles (C)2-22 (R1); CT + concurrent BEV (15 mg/kg) C2-6 + placebo C7-22 (R2); CT + concurrent BEV C2-6 + maintenance BEV C7-22 (R3). Infusions were administered d1 of a 21d cycle. The primary endpoint is progression-free survival (PFS) (radiographic, CA125, clinical criteria or death); secondary endpoints include overall survival, safety, and QoL.

Results: 1,873 patients, were enrolled from 9/05 - 6/09. Stage III optimally debulked (34%), stage III sub-optimally debulked (40%), and stage IV (26%) patients were similarly distributed in each treatment group. Adverse events were similar to those of previous BEV trials in non-gynecologic cancers. Relative to R1, the hazard of first progression or death for R2 was 0.908 (95% CI: 0.795 - 1.04, p=0.16) and for R3 was 0.717 (95% CI: 0.625 - 0.824, p< 0.0001).

Conclusions: Front-line treatment of EOC, PPC, and FTC patients with CT plus concurrent and maintenance BEV prolongs PFS. This is the first anti-angiogenic agent to demonstrate benefit in this population.
ICON7: A RANDOMISED CONTROLLED TRIAL OF BEVACIZUMAB IN WOMEN WITH NEWLY DIAGNOSED EPITHELIAL OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCER

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Objectives: To evaluate the safety and efficacy of adding bevacizumab to standard chemotherapy with carboplatin and paclitaxel in the first-line treatment of EOC, PPC or FTC.

Methods: Eligible women with high-risk early (FIGO stage I or IIa (grade 3 or clear cell), capped ≤10%) or advanced (stage IIb-IV) EOC, PPC or FTC were randomised (1:1) to 6 cycles of 3 weekly chemotherapy (carboplatin AUC 6 and paclitaxel 175mg/m²) alone, or the same chemotherapy given concurrently with bevacizumab (7.5mg/kg) for 6 cycles followed by maintenance bevacizumab continued 3-weekly for 12 additional cycles or until progression whichever was the earlier. The primary outcome measure was investigator-determined RECIST-defined progression free survival (PFS). Secondary outcome measures include response, overall survival, safety and quality of life. To show a 28% improvement in median PFS from 18 to 23 months (hazard ratio (HR) = 0.78) with 5% significance level and 90% power) 684 progressions/deaths were required.

Results: From 12/2006 to 02/2009, 1528 women (90% with EOC) were randomised from 263 centres in 7 GCIG groups. Baseline characteristics were balanced between arms: median age (57 years); ECOG performance status 0-1 (47%); high-risk early-stage disease (9%); histology (69% serous, 8% endometrioid, 8% clear cell). Adverse events were consistent with previous bevacizumab studies. With 759 (50%) progressions/deaths a HR of 0.81 (95%CI 0.70, 0.94) and p-value (log-rank test) of 0.0041, favouring the bevacizumab arm, were observed. There was evidence of non-proportional hazards and other summary statistics were explored.

Conclusion: Bevacizumab improved PFS in women with EOC, PPC or FTC.
ROLE OF CYTOREDUCTIVE SURGERY IN RECURRENT OVARIAN CANCER (ROC).
INTERNATIONAL DESKTOP SERIES OF AGO-KOMMISSION OVAR, AGO-STUDY GROUP,
NOGGO, MITO, AGO-AUSTRIA


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Background: Surgery in primary ovarian cancer for maximal cytoreduction is widely accepted. Role of surgery in ROC is less clear, especially regarding following questions:

(1) surgical aim,
(2) identification of potential candidates for surgery, and
(3) prognosis improvement by cytoreductive surgery?

Methods: Retrospective multicentre study for identification of surgical aim and hypothesis for a score to identify surgery candidates (DESKTOP I-trial). Validation of AGO-score for platinum-sensitive ROC in a prospective multicentre trial (DESKTOPII).

Results: DESKTOP I-trial analyzed 267 patients. Complete macroscopic tumor resection was associated with significant longer survival compared with surgery leaving postoperative tumor residuals (median 45.2 vs 19.7months; HR:3.71; 95%-CI: 2.27-6.05). Good performance status, complete resection at 1st-surgery and absence of ascites were identified as independent predictors for complete debulking. If all 3 factors were positive, the AGO-score was stated positive. The predictive value of a positive score for complete resection was subsequently confirmed prospectively. DESKTOPII-trial screened 516 patients. 51% patients were classified as score-positive, 129 patients with positive-score and first recurrence underwent surgery. Complete resection was achieved in 76% (95%-CI:69%-84%). Peritoneal carcinomatosis was a negative predictor for complete resection, but had no effect on prognosis if complete resection could be achieved. Surgery co-morbidity in DESKTOPII cohort was comparable to primary surgery.

Conclusions: In contrast to primary surgery in advanced ovarian cancer, only patients with complete resection benefit from surgery at relapse. AGO-score was validated as reliable predictive tool for patient selection. Based on these data DESKTOPIII was started to evaluate the role of complete tumor resection on overall survival.
EFFICACY OF THE AS04-ADJUVANTED HPV-16/18 VACCINE IN WOMEN AGED 18-25 YEARS: PATRICIA END-OF-STUDY RESULTS


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Background: The AS04-adjuvanted human papillomavirus (HPV)-16/18 vaccine (GlaxoSmithKline Biologicals), shows high prophylactic vaccine efficacy (VE) against cervical intraepithelial neoplasia (CIN)2+. We evaluated VE in 18-25-year-old women from PATRICIA (NCT00122681).

Methods: 18,644 women aged 15-25 years were randomised (1:1) to receive HPV-16/18 vaccine or control at Months 0, 1 and 6. Baseline HPV-DNA status and serostatus were assessed by PCR and ELISA, respectively. Cervical samples were collected every 6- and 12-months for HPV-DNA typing and gynaecological/cytopathological examinations, respectively. We report VE against HPV-16/18-CIN2+ stratified by HPV-DNA/serostatus in women 18-25 years in the total vaccinated cohort (TVC, all women regardless of baseline HPV-DNA/serostatus, received ≥1 dose; N=12,665), using the primary analysis and the Type Assignment Algorithm (TAA), which assigns probable causality in lesions containing multiple HPV-types.

Results: At end-of-study (median follow-up 47.4 months), VE (95% CI) against HPV-16/18-CIN2+ in women HPV-DNA-negative/seronegative for the corresponding HPV-type at baseline was 95.3% (85.5-99.1) [TAA: 98.3% (90.3-100)]. VE in women HPV-DNA-negative at baseline regardless of serostatus was 90.6% (79.7-96.4) [TAA: 95.8% (87.0-99.1)]. Overall VE against HPV-16/18-CIN2+ (regardless of baseline HPV-DNA/serostatus) was 46.3% (27.5-60.5) [TAA: 49.0% (30.5-62.9)].

Conclusions: In women 18-25 years, the age group targeted by some catch-up vaccination programs, the vaccine showed high efficacy against HPV-16/18-CIN2+ in women presumably naïve to HPV-16 and -18 (seronegative and DNA-negative). As expected, in the analysis including women who were infected with HPV-16 and/or -18 at study entry, the efficacy was lower although still substantial.
THE METASTASIS OF DEEP OBTURATOR AND PARA-AORTIC LYMPH NODE IN 383 PATIENTS WITH CERVICAL CARCINOMA

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Objective: The extent of retroperitoneal lymph node dissection for early cervical cancer remains debatable. Our study was to investigate the rates of metastases to deep obturator and para-aortic lymph nodes and its association with clinic-pathological factors in early cervical carcinomas.

Method: The 383 patients with stage IB to IIB cervical cancer underwent radical hysterectomy, pelvic lymphadenectomy and/or para-aortic lymphadenectomy. The incidence and distribution of metastases to retroperitoneal lymph nodes and the associated factors were observed and analyzed.

Results: The metastases to pelvic lymph nodes occurred in 113 (27%) of 383 patients. Of 113 cases with positive pelvic lymph nodes (PLN), only 9 cases had deep obturator lymph node (DOLN) metastases. Whereas none of cases presented positive DOLN in those without pelvic lymph node metastases. There was no significant correlation between the DOLN metastasis with the tumor histology, differentiation and lymphovascular space involvement. Para-aortic lymph node (PALN) metastasis occurred in 11 (19%) of 58 patients who had cervical lesion larger than 2cm in diameter. Ten of the eleven patients also had PLN involvement. Logistic regression analysis showed that pelvic lymph node metastasis and larger tumor in size were the independent risk factors for the metastasis of PALN.

Conclusion: Because of the low rate of DOLN metastasis in early stage cervical cancer, the removal of deep obturator lymph node as a routine procedure might not be necessary, especially when other group of pelvic nodes are negative. Para-aortic lymphadenectomy is recommended when any pelvic lymph node are positive or cervical lesion is lager than 2cm.
BILATERAL LYMPHADENECTOMY FOR MIDLINE SQUAMOUS CELL CARCINOMA OF THE VULVA IS NOT ALWAYS NECESSARY: AN ANCILLARY ANALYSIS FROM GOG-173

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Objective: To determine which patients with near midline lesions can safely undergo unilateral groin dissection based on clinical exam and lymphoscintigraphy (LSG) results.

Methods: Patients had an interpretable LSG and at least one sentinel lymph node (SLN) identified. Primary tumor location was categorized as lateral, true midline, and lateralized within 2 cm of the midline (LA). To assess the reliability of clinical assessment, we related tumor location with LSG and surgical pathology.

Results: 297 patients had an interpretable LSG and at least one SLN identified. Seventy-nine had lateralized lesions where 72 underwent unilateral and 7 bilateral dissection. Of 218 “midline lesions”, 134 were midline; 84 (39%) were LA. LSG results from these tumor locations are depicted in the Table. Two(3%), 12(9%) and 14(17%) patients, respectively had SLN identified by intraoperative mapping despite uninformative LSG.

<table>
<thead>
<tr>
<th>LSG</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateralized</td>
<td>69</td>
<td>8</td>
<td>77</td>
</tr>
<tr>
<td>True Midline</td>
<td>51</td>
<td>71</td>
<td>122</td>
</tr>
<tr>
<td>LA</td>
<td>9</td>
<td>61</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>140</td>
<td>269</td>
</tr>
</tbody>
</table>

Among the 69 LA with unilateral LSG, 24(35%) had ipsilateral metastatic nodes; only 6(9%) had contralateral metastatic disease.

Conclusion: It’s rare for patients predicted to have unilateral drainage based on physical exam to have bilateral drainage on LSG. Patients with LA primaries and unilateral drainage on LSG may safely undergo unilateral SLN.
ROBOT-ASSISTED SURGERY FOR GYNAECOLOGICAL CANCER

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Background and aims: Robotic surgery is the latest innovation in the field of minimally invasive surgery, which has been reported in endometrial cancer (EC) and cervical cancer (CC). This Cochrane systematic review aims to evaluate the evidence for and against robot-assisted surgery in gynaecological cancers.

Methods: We searched the electronic databases (CENTRAL, MEDLINE, EMBASE) comprehensively, and the citation lists of relevant publications. All randomised controlled trials (RCTs) comparing robot-assisted surgery to laparoscopic or open surgery were included. Since no RCTs were available, controlled clinical trials (CCTs) were included. We assessed risk of bias and extracted data from included studies.

Results: Seventeen CCTs have been identified involving patients with EC (1640 patients) and CC (652 patients). When compared to laparoscopic surgery for EC, robotic surgery was associated with comparable length of stay (LOS), perioperative complication rate, but with significantly lower estimated blood loss (EBL) and conversion rate. When laparotomy was performed for EC, intraoperative complication rate was comparable, but postoperative complication rate and EBL were significantly lower in robot group.

When compared to laparoscopic surgery for CC, robotic surgery was associated with comparable perioperative complications rate, disease-free and overall survival, but with significantly lower EBL. When laparotomy was performed for CC, intraoperative complication rate, disease-free and overall survival were comparable, but LOS and postoperative complication rate were significantly lower in robot group.

Conclusions: Evidence from CCTs supports the use of robotic assisted surgery for EC and CC. Further well-designed RCTs are warranted to confirm or refute the current evidence.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Robot vs. laparoscopy MD/ RR [95% CI]</th>
<th>Robot vs. laparotomy MD/ RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (day)</td>
<td>-0.20 [-0.44, 0.04]</td>
<td>null</td>
</tr>
<tr>
<td>Intraoperative complication rate</td>
<td>0.57 [0.19, 1.66]</td>
<td>0.97 [0.19, 4.99]</td>
</tr>
<tr>
<td>Postoperative complication rate</td>
<td>0.80 [0.57, 1.12]</td>
<td>0.30 [0.21, 0.44]</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>-75.21 [-98.97, -51.45]</td>
<td>-160.09 [-203.93, -116.24]</td>
</tr>
<tr>
<td>Transfusion rate</td>
<td>0.58 [0.24, 1.40]</td>
<td>0.28 [0.12, 0.63]</td>
</tr>
<tr>
<td>Conversion rate</td>
<td>0.42 [0.24, 0.72]</td>
<td>null</td>
</tr>
</tbody>
</table>

[Robot-assisted surgery for endometrial cancer]

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Robot vs. laparoscopy MD/ RR [95% CI]</th>
<th>Robot vs. laparotomy MD/ RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival rate</td>
<td>0.98 [0.90, 1.06]</td>
<td>1.13 [1.04, 1.24]</td>
</tr>
<tr>
<td>Overall survival rate</td>
<td>0.99 [0.91, 1.08]</td>
<td>1.02 [0.97, 1.07]</td>
</tr>
<tr>
<td>Length of stay (day)</td>
<td>null</td>
<td>-1.81 [-2.45, -1.16]</td>
</tr>
<tr>
<td>Intraoperative complication rate</td>
<td>1.17 [0.32, 4.33]</td>
<td>0.64 [0.21, 1.99]</td>
</tr>
<tr>
<td>Postoperative complication rate</td>
<td>1.43 [0.77, 2.66]</td>
<td>0.68 [0.53, 0.87]</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>-76.60 [-132.7, -20.49]</td>
<td>null</td>
</tr>
<tr>
<td>Transfusion rate</td>
<td>3.56 [0.58, 21.76]</td>
<td>0.27 [0.12, 0.62]</td>
</tr>
</tbody>
</table>

[Robot-assisted surgery for cervical cancer]
CHEMOSENSITIVITY AND OUTCOME OF BRCA1- AND BRCA2-ASSOCIATED OVARIAN CANCER PATIENTS AFTER FIRST LINE CHEMOTHERAPY COMPARED WITH SPORADIC OVARIAN CANCER PATIENTS

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Background: In vitro and small retrospective studies suggested that patients with BRCA-associated epithelial ovarian cancer (EOC) have a better survival, compared to sporadic EOC patients. This might be caused by an increased chemosensitivity. Data, however, are inconsistent. Therefore we evaluated response to chemotherapy, progression-free (PFS) and overall survival (OS) in BRCA1- and BRCA2-associated patients, compared with sporadic EOC patients.

Methods: Ninety-nine BRCA1- and 13 BRCA2-associated EOC patients, diagnosed between 1980-2008 and treated with chemotherapy for primary treatment, were included and matched for age and period of diagnosis with 222 sporadic patients. Analyses were done using a χ² or Fisher Exact Test, and Kaplan-Meier and Cox-regression method.

Results: Complete response (CR) was observed in 87% of the BRCA1 patients and progressive disease (PD) in 2%, compared to in 71% and 15% respectively of the sporadic EOC patients (p=0.002). In BRCA2 patients 92% had CR/NED, and none PD (p=0.27). Median PFS in BRCA1- was 2.1 years (p=0.006), in BRCA2- 5.6 years (p=0.008) and in sporadic patients 1.3 years.

Median OS for BRCA1 and BRCA2 patients was 5.9 (p< 0.001) and >10 years (p=0.008), respectively, versus 2.9 years for sporadic patients. A trend for a longer PFS and OS in BRCA2-compared to BRCA1-associated EOC was observed.

Conclusion: Both BRCA1-and BRCA2-associated EOC have a better response to primary treatment and a longer PFS and OS, compared to sporadic EOC. Information about genetic status of EOC patients should be incorporated as stratification factor in clinical studies, and is important regarding counselling and treatment decisions.
CONTRACEPTION METHODS, BEYOND ORAL CONTRACEPTIVES AND TUBAL LIGATION, AND RISK OF OVARIAN CANCER

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Purpose: We present one of the first studies to examine a range of contraceptives including oral contraceptives, birth control shots or implants, intrauterine devices (IUDs), barrier methods, tubal ligation, or vasectomy (in a partner) in relation to ovarian cancer risk.

Methods: 902 cases with incident ovarian/peritoneal/tubal cancer were compared to 1800 population-based controls. Methods of contraception were obtained by self-report using life calendars.

Results: Each of the contraceptive methods examined reduced the risk of ovarian cancer as compared to use of no effective method. Comparing ever versus never use, after adjustment for potentially confounding factors, the three methods of contraception that emerged as protective were OCs (adj OR 0.66, 95% CI 0.54-0.81); tubal ligation (adj OR 0.62, 95% CI 0.51-0.75); and IUDs (adj OR 0.70, 95% CI 0.54-0.89). While for oral contraceptives and tubal ligation, the longer the duration of use, the greater the effect, for IUDs the pattern was reversed. Significant protection occurred with short duration and progressively greater risk (which never achieved significance) was seen with longer duration of use (adj OR 0.53, 95% CI 0.39-0.72 for < 4 years; adj OR 1.11, 95% CI 0.63-1.97 for 5-9 years; adj OR 1.44, 95% CI 0.84-2.47 for >10 years).

Conclusions: We report here the largest case-control study to examine a range of effective methods of contraception in relation to risk for ovarian cancer. OCs and tubal ligation reduced ovarian cancer risk in a duration-response fashion whereas IUDs reduced risk overall, having the greatest impact with short duration of use.
MICROARRAY-BASED OVARIAN CLEAR CELL CARCINOMA SIGNATURE PREDICTS SORAFENIB AS A PROMISING REAGENT TARGETING SPECIFIC CELL SIGNALING

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Endometriosis-associated cancer, especially clear cell carcinoma (OCCC), is becoming an important clinical issue since a majority of them are chemo-resistant and hard to treat the refractory case. No clear explanation has been made why OCCC frequently arise in endometriosis. We have reported the possibility that the unique microenvironment in endometriotic cyst, especially accumulated high concentration iron, may play a crucial role in carcinogenesis via production of persistent oxidative stress. In the current research, by microarray-based selection of genes specifically expressed in ovarian clear cell carcinoma, we identified "OCCC signature" which consisted of 437 genes. A categorical analysis revealed that these genes are mainly composed of stress and inflammation-related genes, possibly reflecting the microenvironment within the endometriotic cyst. The OCCC signature also contained known markers of clear cell carcinoma such as HNF1β and VCAN, indicating that OCCC signature is representative of mRNA expressions of OCCC. Treatment of OSE cells with the contents of endometriotic cysts induced OCCC signature, indicating that it is largely dependent on the tumor microenvironment. OCCC signature genes were partly regulated epigenetically. Finally, by screening of malignancies of various organs, we found that renal cell carcinoma (RCC) has similar gene expressions to OCCC signature. We then examined if Sorafenib, a reagent used for RCC is also effective in OCCC, and found significant reduction of MAP-kinase and marked anti-tumor effect in mouse xenograft of OCCC cell line, RMG-2, while it was resistant to cisplatin. OCCC signature may be useful for the development of novel treatment options for OCCC.
ROLE OF NOTCH SIGNALING IN OVARIAN CANCER

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**Background:** The Notch pathway plays a critical role in the development of a number of malignancies. The Notch receptors and ligands function as oncogenes and also directly promote tumor angiogenesis. We examined Notch signaling in ovarian cancer.

**Methods:** Using a panel of ovarian cancer cell lines we determined expression of the Notch receptors and ligands by RT-PCR. The effect of Notch inhibition was evaluated using the gamma secretase inhibitor Compound E in cell cytotoxicity studies, anchorage-independent growth assays (Matrigel), and in a murine model of ovarian cancer. Compound E was tested alone and in combination with cisplatin.

**Results:** Compared to ovarian surface epithelium, Notch3 was overexpressed in a number of ovarian cancer cell lines. There was only focal upregulation of the Notch1 and Notch2 receptors. We noted widespread overexpression of the Notch ligand Delta-like 4 and focal overexpression of the Jagged-1 ligand. The downstream Notch targets Hes1 and Hey1 were overexpressed in all the ovarian cancer cell lines indicating activation of the Notch signaling cascade in ovarian cancer. Inhibition of the Notch pathway with Compound E had little direct effect on ovarian cancer cell growth in cell cytotoxicity and Matrigel assays. Notch inhibition had minimal effect on decreasing tumor growth in vivo but appeared to attenuate angiogenesis.

**Conclusion:** Notch signaling appears to play an important role in ovarian cancer tumorigenesis. Notch3 appears to be the dominant Notch receptor while Delta-like 4 is an important ligand. Notch inhibition may attenuate angiogenesis in ovarian cancer.
A PHASE II TRIAL DEMONSTRATING ACTIVITY OF SINGLE AGENT OLAPARIB IN WOMEN WITH RECURRENT SEROUS OVARIAN CARCINOMA

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Introduction: Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor with activity in BRCA mutation carriers. This phase II trial assessed olaparib activity in women with recurrent advanced ovarian or breast cancer with/without known BRCA mutations.

Methods: We report clinical results of two ovarian cohorts (D0810C00020) at entry; patients reported as high grade serous/undifferentiated disease with unknown/negative BRCA status (n=54) and a reference group with reported BRCA mutations (n=10). Exploratory post-hoc analysis by platinum sensitivity (using new GCIG criteria and determined by blinded review) and confirmed BRCA status was performed. Patients were treated with olaparib 400 mg bid continuously in 4-week cycles. Response was assessed by RECIST and CA-125.

Results: After BRCA testing, 47 women with negative BRCA status and 17 with BRCA mutations were treated. Among patients with negative BRCA status, confirmed radiological responses by RECIST were seen in 11/46 (23.9%) evaluable patients; 10/20 (50.0%) platinum-sensitive and 1/26 (3.8%) platinum-resistant/refractory disease. In the same group, CA125 responses were seen in 10/38 (26.3%) evaluable patients; 6/15(40.0%) platinum sensitive and 4/23 (17.4%) platinum resistant/refractory. BRCA mutation patients had RECIST and CA-125 response rates of 7/17 (41.2%) and 7/16 (43.8%), respectively. Median PFS in all ovarian patients was 219 days (95% CI 110-273). Olaparib was well tolerated.

Conclusion: This is the first trial demonstrating evidence of activity of olaparib in women with high grade serous ovarian cancer in non-BRCA mutation carriers. Although responses were seen in both platinum-sensitive and resistant populations using the new criteria, activity was seen predominantly in patients with platinum-sensitive disease.
THE IMPACT OF ADJUVANT CHEMOTHERAPY FOR STAGE I CLEAR CELL CARCINOMA OF THE OVARY: JAPAN CLEAR CELL CARCINOMA STUDY

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Background: Ovarian clear-cell carcinoma (CCC) is regarded as grade 3 tumor, and NCCN Clinical Practice Guidelines recommended adjuvant chemotherapy for CCC, even at stage Ia. However, CCC often showed chemo-resistant phenotype, and the effect of adjuvant chemotherapy still remained uncertain.

Methods: CCC cases treated at institutions belonging to Japan Clear Cell Carcinoma Study Group during the period 1995-2005 were retrospectively identified. After central pathologic review, survival analysis was estimated by Kaplan-Meier methods, and prognostic factors were evaluated using a Cox regression model.

Results: Among 219 patients with stage I CCC, 195 cases received adjuvant chemotherapy (C+), and 24 cases (C-) did not. C+ group had 77 pT1a and 118 pT1c cases, and C- group included 18 pT1a and 6 pT1c tumors (p< 0.001). Mean age was 52.3 years in C+ and 56.9 years in C- (p=0.02). During mean follow-up period of 48 months (range; 7-130), relapse was observed in one case (4%) of C- and 35 cases (18%) of C+ group. There were no statistical differences of relapse-free survival (RFS) and overall survival (OS) between C+ and C-. Multivariate analysis revealed that peritoneal cytology status (p=0.02) and pT status (p=0.04) were independent prognostic factors for RFS, however, adjuvant chemotherapy was not a prognostic factor (p=0.80).

Conclusions: Although the present study was a limited retrospective study, it suggested adjuvant chemotherapy had little impact upon survival of CCC patients. Further strategy, such as a molecular targeting agent, is needed to improve survival of CCC, especially with pT1c and positive peritoneal cytology.
SECOND-LINE TREATMENT OF PARTIALLY-PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER: A MANGO - PIEMONTE E VALLE D’AOSTA CANCER NETWORK ITALIAN MULTICENTRIC RETROSPECTIVE STUDY

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Background: Second-line treatment of partially platinum-sensitive (6-12 months) recurrent ovarian cancer (ROC) is not so far standardized. Although preliminary results of phase III studies showed that the disease is still responsive to both platinum and non platinum-based regimens most of the patients eventually face progression. Extending the platinum-free interval (PFI) with non platinum therapies could increase the efficacy of a later platinum re-challenge in partially platinum-sensitive ROC.

Methods: A retrospective analysis of 213 patients with 6-12 months ROC treated in 17 Italian centers between January 2003 and December 2006 was done through chart review. Response to 2nd line chemotherapy and overall survival (comparing platinum with non platinum-based regimens) were analyzed.

Results: The median PFI was 8.7 months. At 2nd line, 95/199 patients (48%) received a platinum-based regimen (group A), and 104 (52%) a non platinum chemotherapy (group B). For 14 patients data were not available. Eighty-eight percent of patients in group A underwent multiple-drug chemotherapy (taxol-carboplatin 46%) whereas 75% of group B underwent single-agent chemotherapy (topotecan or PLD 56%).

The complete plus partial response rates observed in group A and B were 74% and 33%, respectively (P< 0.01). In a multivariate Cox proportional hazard model which included age, PFI and type of recurrence (single vs. multiple) as covariates, the hazard ratio for death favored group A (HR= 0.52;95%CI= 0.35-0.80).

Conclusions: Although retrospectively garnered, our data showed that the overall performance of current non-platinum regimes is low and that immediate platinum re- challenge remains the best option in partially platinum-sensitive ROC.
A GEICO RANDOMIZED PHASE II STUDY OF PACLITAXEL-CARBOPLATIN (PC) VERSUS GEMCITABINE-CARBOPLATIN (GC) FOLLOWED BY PACLITAXEL-CARBOPLATIN IN PLATINUM-SENSITIVE RECURRENT OC (PSROC)

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Background: A more active and less toxic regimen with a sequential doublet of GC followed by PC was investigated in PSROC.

Patients and methods: Pts with PSROC >6 months after first or second line with platinum-based chemotherapy, were randomized to either (arm A) PC (P175mg/m2 + C AUC5/21 days) x8 cycles, or (arm B) GC (C AUC4 d1 + G1000 mg/m2 d1-8/21 days) x4 cycles followed by PC (as in arm A) x4 cycles. Primary endpoint was RR by RECIST and/or CA-125 Rustin criteria. Secondary endpoints: toxicity, PFS and OS.

Results: 117 pts were included. No significant differences in well known prognostic factors. No significant differences in toxicity except for: G3-4 thrombocytopenia (B 15.8% vs A 3.4%, p 0.023), and Grade 3-4 neutropenia (B 61.4% vs A 23.7%; p < 0.001). Grade 2-4 neuropathy was higher in arm A (35.6% vs 22.8%; p=ns). In the intent to treat analysis, RR (CR+PR) was higher in arm B: 87.7% (95%IC: 59.7-83.6%) vs Arm A: 72.9% (95%IC: 76.3-94.9). The difference in RR of 14.8% was statistically significant (95%CI: 0.65-29%; Chi-square p=0.045; Fisher-exact test p=0.067). Median PFS was 13.3 m in arm B vs 11.2 m in arm A (HR 0.88; 95% CI 0.59-1.30). An exploratory sub-group analysis showed a trend to higher OS in pts with PFI 6-12 m.

Conclusion: GC followed by PC was associated with a trend to higher efficacy compared to PC. These data can not exclude a significant benefit of the sequential arm, especially in the partially sensitive population.
PHASE I STUDY OF A SRC INHIBITOR, DASATINIB, IN COMBINATION WITH PACLITAXEL AND CARBOPLATIN IN PATIENTS WITH EPITHELIAL OVARIAN CANCER

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Background: We conducted a phase I study of dasatinib, an oral SRC tyrosine kinase inhibitor, in combination with paclitaxel and carboplatin in advanced and recurrent epithelial ovarian cancer (EOC).

Methods: The primary objective was to determine the MTD. Secondary objectives included toxicity, response rate (RR), pharmacokinetics and pharmacodynamics. Based on the 3+3 design, cohorts of 3-6 pts received paclitaxel 175 mg/m² and carboplatin AUC 6 every three weeks with escalating doses of dasatinib (100, 120, 150 mg PO daily), followed by an 8 patient expansion cohort. Pre- and post-treatment tumor biopsies were obtained to assess for surrogate biomarkers of SRC inhibition and SRC pathway deregulation.

Results: Twenty patients were enrolled between 06/07 and 12/09. The median age was 61 yrs (42-82) with a median of 2 prior regimens (0-6), and 71% had platinum-sensitive disease. There were 3-6 pts in each cohort, and 8 in the expansion cohort. One DLT was observed in the 100 mg dasatinib cohort (grade 3 abdominal pain). Other toxicities in all cycles included neutropenia (69% gr 3-4), thrombocytopenia (43% gr 2-4), and fatigue (11% gr 3). The RR (CR + PR) was 50% (3/18(17%) + 6/18(33%)) and 50% (9/18) had stable disease. The median PFS and OS were 9.0 and 16.2 months, respectively.

Conclusions: Due to the high incidence of myelosuppression with subsequent cycles the recommended phase II dose is 150 mg daily of dasatinib in combination with paclitaxel and carboplatin. The combination was safe with evidence of clinical activity in advanced EOC.
POTENTIAL FOR TARGETED CHEMOTHERAPY WITH PARP INHIBITORS IN HOMOLOGOUS RECOMBINATION DEFICIENT EPITHELIAL OVARIAN CANCERS AND CLINICO PATHOLOGICAL CORRELATION


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Background: PARP inhibitors (PARPi) selectively target cells deficient in homologous recombination (HR) pathway of DNA repair. Up to 50% of epithelial ovarian cancers (EOC) could be deficient in HR due to genetic/epigenetic inactivation of BRCA1/BRCA2 or other HR genes. There is a potential for extending the use of PARPi to these patients if HR status could be identified. We developed a functional assay to determine HR status in primary cultures of EOCs and correlated with in vitro PARPi sensitivity, in vivo platinum sensitivity and patient survival.

Methods: Primary cultures were derived from ascitic fluid from patients with EOCs. HR status was investigated by γH2AX/Rad51 focus formation by immunofluorescence. Cytotoxicity to PARPi AG014699 was tested by SRB and survival assay. Overall and disease free survival at 1 year and in vivo platinum sensitivity was recorded from cancer database at NGOC, Gateshead (analyses to be completed on September, 2010).

Results: 40 primary cultures were evaluated for HR status; increase in Rad51 foci (HR competent) was seen in 40 % but no increase (HR deficient) in 60 % cultures. Cytotoxicity to PARPi was observed in approximately 90 % HR-deficient samples but no cytotoxicity seen in HR-competent cultures.

Conclusion: HR status can be determined in primary cultures by Rad51 focus formation, and this correlates with in vitro response to PARPi. Potentially 50-60% of EOCs could benefit from PARPi. Data on survival studies and in vivo platinum chemosensitivity could provide more insight in planning appropriate chemotherapy in EOCs based on HR status.
TRABECTEDIN PLUS PEGYLATED LIPOSOMAL DOxorubicin (PLD) IN RELAPSED OVARIAN CANCER (ROC): AN ANALYSIS OF THE PARTIALLY PLATINUM-SENSITIVE (PPS) SUBSET OF PATIENTS


Objective: OVA-301 was a large, randomized phase III trial that showed superiority of trabectedin plus PLD over single-agent PLD in 672 patients with ROC. To aid patient selection for future use of trabectedin a subset of analysis based on prior platinum exposure was conducted.

Methods: Outcomes of the subset of PPS patients (n=214), with a platinum-free interval (PFI) of 6-12 months are presented.

Results: Trabectedin+PLD resulted in a significant 35% risk reduction of disease progression (HR=0.65; p=0.0152; median PFS: 7.4 vs. 5.5 months) and a 41% decrease in the risk of death (HR=0.59; p=0.0015; median survival: 23.0 vs. 17.1 months) compared to PLD. The safety of trabectedin+PLD in this subset was not different from the overall population. Subsequent therapy was given to 80% of patients in each treatment arm; this comprised further platinum-based regimens in 56% vs. 57% of patients, favoring PLD. Patients in the trabectedin+PLD arm had a significantly longer time from randomization to subsequent platinum (HR=0.64; p=0.0167; median 9.8 vs. 7.9 months) and lived longer after subsequent platinum (HR=0.63; p=0.0357; median 13.3 vs. 9.8 months); differences were more pronounced in patients who received platinum as first subsequent chemotherapy, in whom platinum was delayed by a median of 4 months (HR=0.61; p=0.0203) and survival from first platinum was extended by a median of 8.7 months (HR=0.54; p=0.0169).

Conclusion: This analysis demonstrates the superior benefits with second-line trabectedin+PLD in terms of PFS and survival when the time to recurrence is between 6-12 months. This may be related to prolongation of the PFI and deserves prospective study.
HUMORAL AND CELLULAR IMMUNITY INDUCES APOPTOSIS(PCD) IN CIN2-3, HPV16+ CERVICAL CA AFTER DIVALENT GENETIC VACCINATION WITH CRS TARGETING P53 AND RB

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Introduction: Prophylactic vaccines have no therapeutic capacity for the women, who are infected with HPV16, and have developed cervical intraepithelial neoplasia(CIN) or cervical cancer. Approximately, 300 million women with CIN, and cervical cancer require therapy in the next decades.

Methods: We developed a cytomegalovirus (CMV) replicon system (CRS) for delivery of the HPV16 recombinantly mutated E6, and E7 genes replacing part of the CMV genome for the HPV genes, which were genetically altered to block binding sites for p53 and Rb. The replicon-vectors infected, and co-transfected CIN, and cervical Ca cells in animal-models derived from HPV16(+) CIN, and cervical Ca cells obtained from patients. The genetic vaccine was administered subcutaneously (SC) with a needless injection system.

Results: After vaccination, the viral E6 oncogene did not degrade apoptotic p53, and it blocked activation of telomerase. This induced apoptosis and DNA repair in CIN, and cervical Ca cells. Furthermore, the E7 viral oncogene did not degrade the retinoblastoma oncogene (Rb) protein releasing transcription factor E2F. This vaccination led to scheduled cell cycle entry, genetic stability, and mortalization of tumor cells. Humoral and cellular immune responses were exhibited, which led to irreversible D2 apoptotic stage of PCD type I leading to a bystander killing effect of CIN, and cervical Ca cells. BrdU and MTT analysis exhibited inhibition of DNA synthesis, and metabolic activity of vaccinated tumor cells compared to controls.

Conclusion: This genetic divalent vaccine coding for E6 and E7 mutations designed to prevent p53 and Rb binding sites activated humoral, and cellular immune responses leading to apoptosis of CIN, and cervical Ca cells. It is up to translational medicine to bring this therapeutic vaccine into the clinic for patients with CIN2, CIN3, and cervical cancer patients.
ABSENCE OF HIGH-RISK HUMAN PAPILLOMAVIRUS (HPV) DETECTION IN ENDOCERVICAL ADENOCARCINOMA WITH GASTRIC MORPHOLOGY AND PHENOTYPE

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A subset of endocervical-type mucinous adenocarcinoma of the uterine cervix shows a gastric phenotype and morphology, as reported in cases of minimal deviation adenocarcinoma (MDA), in which the presence of human papillomavirus (HPV) has been only rarely demonstrated. To address the HPV-independent pathway of carcinogenesis in cases of gastric-type adenocarcinoma, we investigated the common high-risk HPV (hr-HPV) status in 52 non-squamous cell carcinomas, using a PCR-based typing method and p16INK4a immunohistochemistry. Using novel morphologic criteria, seven of 52 (13.5%) carcinomas were designated as gastric-type adenocarcinoma, all of which were negative for both hr-HPV DNA and p16INK4a. Non-gastric-type adenocarcinomas were frequently positive for both hr-HPV DNA (90%, 28/31) and p16INK4a (94%, 29/31) with adenosquamous and neuroendocrine carcinomas demonstrating the presence of hr-HPV DNA in 86% (6/7) and 83% (5/6) of cases, respectively. In these carcinomas, 86% (6/7) and 100% (6/6) were positive for p16INK4a, respectively. Our data suggests that gastric-type adenocarcinoma appears to represent an oncogenic hr-HPV-independent neoplasm, and therefore is a potential pitfall of HPV DNA test and vaccination.
A PROSPECTIVE STUDY CORRELATING NATURAL HISTORY OF LOW-GRADE SQUAMOUS INTREPIHELIAL NEOPLASIA TO SYSTEMIC HPV16-SPECIFIC T-CELL RESPONSE

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Natural history studies suggest that the majority of low grade squamous intraepithelial lesions (LGSIL) regress spontaneously and this is attributed to the development of HPV antigen specific cellular immune responses. The identification of target antigens for an effective cellular immune response is critical for development of therapeutic HPV vaccines, aimed at eradication of HPV induced disease. Correlating the immune responses to regression of LGSIL should provide important information towards identification of potential target antigens.

This study investigates the natural history of LG-SIL, HPV status and HPV16-specific immune responses prospectively for one year. Colposcopy, cervical biopsy, HPV typing, HPV16-specific T-cell responses as defined by ELISPOT was performed at recruitment and upon completion of study (0 and 12 months). At 6 months, Colposcopy, ELISPOT and HPV typing was also performed.

In this cohort, infection with multiple HPV types were detected in 70% of all patients with HPV16 found in 42%. LGSIL progressed to HGSIL in 24%, persisted in 60% and regressed in 16%. HPV16-specific T-cell responses were detected in 50% of patients with HPV16+LSIL which was predominantly to E2 and E6. The presence of HPV16E2-specific T-cell responses correlated with the absence of progression of HPV16+lesions while HPV16 E6 specific reactivity was associated with disease persistence.

Conclusions: Progression of LGSIL correlates with the inability to mount an effective immune response to HPV16 E2 and E6 protein. This suggests that HPV16 E2 should be considered as a target antigen in the development of therapeutic HPV vaccines.
LONG-TERM FOLLOW-UP OF A PHASE II FEASIBILITY STUDY OF REGIONAL HYPEROTHERMIA ADDED TO CHEMORADIOThERAPY IN ADVANCED CERVICAL CANCER

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Introduction: In advanced cervical cancer, cisplatin-containing chemotherapy (CT) and regional hyperthermia (HT) added to radiotherapy (RT) have each been proven superior to RT alone in randomized controlled trials. We previously reported on the feasibility of combining all three modalities (triple therapy) in 68 patients in three simultaneous phase II trials in the Netherlands, Norway and the USA. Here we present long-term follow-up of the Dutch patients in this prospective study.

Methods: Eligible patients had FIGO stage IB-IVA cervical cancer not previously treated, good performance status and were able to tolerate cisplatin treatment. The study was IRB approved and all patients gave written informed consent. Triple therapy consisted of 5 weeks of external radiotherapy (45-50 Gy) and brachytherapy (minimum of 70 Gy bio-equivalent dose, depending on technique used, to point A), with weekly cisplatin 40 mg/m² and weekly HT during external RT.

Results: Thirty-six patients were included in the Dutch study, with stages IIB (n=26), III B (n=9) and IVA (n=1). Complete remission was achieved in 32 patients (88%). After a median follow-up of 62 months (range, 6-97 m), twelve patients have died of disease and one is alive with disease. Five year disease free survival is 66% (95% CI: 52 - 84) and overall survival is 74% (95% CI: 60 - 90).

Conclusion: Triple therapy is not only feasible, but has good long-term results in the treatment of advanced cervical cancer. An international phase III study testing RT/CT +/- HT is underway.
INCIDENCE OF MICROMETASTASES IN HISTOLOGICALLY NEGATIVE PARA-AORTIC LYMPH NODES IN ADVANCED CERVICAL CANCER PATIENTS

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Objective: The aims of the present study were to identify the incidence of micrometastases in negative para-aortic lymph nodes, and to assess the utility of ultrastaging in histologic evaluation of para-aortic lymph nodes.

Material and methods: Patients with advanced cervical cancer and negative para-aortic lymph nodes after routine histology examination were included in the study. Paraffin-embedded tissue blocks were cut into 5-µm-thick slides at step serial sections at 200 µm intervals until there was no lymph node tissue left. 7 to 14 slides were obtained per lymph node and an immunohistochemistry staining with anti-cytokeratin antibody (EA1/EA3) was performed.

Results: 581 histologically negative aortic nodes of 24 patients with advanced cervical cancer were assessed for para-aortic micrometastases (PAM). The incidence of micrometastases by the total number of studied lymph nodes was 0.003 %. PAM were identified in 2 patients (8.3%), and additional submicrometastases were also found in one of them (4.1%). A single metastatic cluster of less than 0.2 mm was found in an afferent lymphatic vessel of another patient, not considered as a submicrometastases. PAM incidence was too low to allow for evaluation of associated risk factors, and for analysis of prognostic significance.

Conclusion: The low incidence of PAM does not justify ultrastaging of aortic nodes in advanced cervical cancer patients. However, the results of the present study support current literature on therapeutic effect of para-aortic lymphadenectomy. Removal of aortic nodes may benefit a subgroup of advanced cervical cancer patients with negative aortic lymph node at imaging techniques including PET-scan.
PROGNOSTIC MODEL FOR SURVIVAL IN PATIENTS WITH SURGICALLY TREATED EARLY-STAGE CERVICAL CANCER

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Background: In the management of early-stage cervical cancer, knowledge on the prognosis is critical. Although many factors have an impact on survival, their relative importance remains controversial. This study aims to develop a prognostic model for survival in early-stage cervical cancer patients and to reconsider grounds for adjuvant treatment.

Material and methods: A multivariate Cox regression model was used to identify the prognostic weight of clinical and histological factors for disease-specific survival (DSS) in 710 consecutive patients who had surgery for early-stage cervical cancer (FIGO stage IA2-IIA). Prognostic scores were derived by converting the regression coefficients for each prognostic marker and used in a score chart. The discriminative capacity was expressed as the area under the curve (AUC) of the receiver operating characteristic.

Results: The 5-year DSS was 92%. Tumor diameter, histological type, lymph node metastasis, depth of stromal invasion, lymph vascular space invasion and parametrial extension were independently associated with DSS and were included in a Cox regression model. This prognostic model, corrected for the 9% overfit shown by internal validation, showed a fair discriminative capacity (AUC 0.73). The derived score chart predicting 5-year DSS, showed a good discriminative capacity (AUC 0.85).

Conclusion: In patients with early-stage cervical cancer DSS can be predicted with a statistical model. Models, such as the one presented here, should be used in clinical trials on the effects of adjuvant treatments in high-risk early cervical cancer patients, both to stratify and to include patients.
MOVING BEYOND PRIMARY SCREENING FOR CERVICAL CANCER IN LOW-RESOURCE SETTINGS

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Introduction: The burden of cervical cancer is highest in the developing world where resources are limited. Screening programs using visual inspection with acetic acid (VIA) and see and treat programs with cryotherapy are well described in the literature and have been shown to be effective. In developed countries, follow-up of a positive screen is well established utilizing cytology, colposcopy and even HPV testing. However in the low-resource setting repeated cytology is not feasible. Cost effective, resource appropriate strategies need to be developed to address follow-up after treatment for a positive screen.

Objective: To develop a protocol for follow-up screening of women treated with cryotherapy for cervical dysplasia in resource poor settings.

Method: Evidenced-based protocol design.

Results: Eight studies were found that address follow-up screening after treatment for cervical dysplasia and six looked at re-screening with VIA after cryotherapy. Sensitivities and specificities for detecting ≥CIN2 were 60% and 87-94% respectively. Based on the evidence, screening with VIA should commence at age ≥30. Following an initial negative screen, a second screen after age 40 is recommended. A positive screen should be treated with immediate cryotherapy and repeat VIA screen in one year. LEEP is recommended after a positive follow-up screen. If the squamocolumnar junction is not visible at any stage of the screening process, cytology is recommended followed by possible colposcopy and endocervical curettage.

Conclusions: An evidence-based, comprehensive follow-up strategy was developed for resource poor settings that addresses the ongoing management of women who have been treated for cervical dysplasia.
IMPACT OF THE NUMBER OF METASTATIC LYMPH-NODES FOR LOCO-REGIONAL CONTROL IN VULVAR CANCER

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Background: Lymph-node metastases are the most important prognostic factor for recurrence and survival in vulvar cancer. Adjuvant radiotherapy is currently recommended for ≥3 metastatic nodes by German guidelines. This standard is based on small and heterogeneous patient cohorts.

Methods: One-hundred-and-fifty-seven consecutive patients with primary squamous-cell cancer of the vulva treated at our center were analyzed. All patients underwent primary surgery by triple incision resulting in complete tumor resection.

Results: Median age was 61 years; 49 patients (31%) had lymph-node metastases; 21 patients had 1, 13 had 2 and 15 had >2 metastatic lymph-nodes. Median follow-up was 23 months; 22 patients (14%) developed disease-recurrence (77% vulva, 18% groins and 5% both). There was a trend towards shorter disease-free survival in patients with >2 metastatic nodes compared to those with 1 or 2 (p=0.052 and p=0.057). However, compared to node-negative patients survival in all node-positive patients was significantly impaired (p< 0.001, disease-free patients after 2 years: 88% in node negative patients, 59%, 69% and 27% in patients with one, 2 and >2 affected nodes, respectively). 31% of the patients received adjuvant radiotherapy. There was no significant difference between the node-positive groups regarding adjuvant radiotherapy with respect to disease-free survival.

Conclusions: Lymph-node metastases remain the most important prognostic factor in patients with vulvar cancer. However, the detrimental effect of nodal involvement is already evident in patients with only 1 or 2 affected lymph-nodes. Therefore, it might be justified to consider adjuvant radiotherapy of the groins even in patients with only one metastatic node.
POSTOPERATIVE CHEMOTHERAPY IS SUPERIOR TO WHOLE ABDOMINAL IRRADIATION IN SINGLE NODE-POSITIVE AND/OR CERVICAL STROMA-POSITIVE ENDOMETRIAL CANCER: GYNECOLOGIC ONCOLOGY GROUP STUDY

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Objective: To evaluate the association of the number of positive nodes (PN) and cervical stromal involvement (CSI) with survival and homogeneity of treatment effect in advanced endometrial carcinoma treated with WAI or adriamycin plus cisplatin (AP).

Methods: Data were extracted from patients who received adjuvant WAI or AP in a GOG randomized trial. Cox proportional hazards models and forest plots were used to estimate the association of PN and CSI on PFS and OS while adjusting for treatment, stage, residual disease, age, race, cell type, grade, and cytology.

Results: WAI was randomly allocated to 202 and AP to 194. CSI was significantly associated with 44% increase in progression and 33% increase in risk of death. A trend for increasing number of PN removed was associated with 7% increase in risk of progression/death. The estimated unadjusted treatment hazard ratios for those with (n=93, PFS 0.85, OS 0.81) and without (n=290, PFS 0.79, OS 0.75) CSI were consistent with the overall treatment effects favoring AP for both endpoints. This was also observed for the presence of a single PN (n=25, PFS 0.96, OS 0.73), endometrioid histology, grade 3, stage IV, and white race. The confidence intervals for non-endometrioid histology and black ethnicity are wide but tests for homogeneity were not significant.

Conclusions: The positive effect of AP relative to WAI in the presence of a single PN and/or CSI is consistent with the overall treatment effect. Both the presence of CSI and the number of PN were associated with poor prognosis.
THE INTERACTION BETWEEN EPITHELIAL BIOMARKERS, LOCAL IMMUNE RESPONSE AND HPV GENOTYPE IN REGRESSION AND PERSISTENCE OF CIN2-3

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15-30% of cervical intraepithelial grades 2-3 (CIN2-3) lesions in punch biopsies regress spontaneously (i.e., show CIN1 or less in the follow-up cone). Epithelial retinoblastoma protein (pRb), p53, HPV genotype and immunoreactive cells can help to predict regression-or-not but their interaction in regression prediction is unknown.

We studied retrospectively 55 cases of CIN2-3 in cervical biopsies with subsequent cervical cones to assess how epithelial biomarkers, immune-reactive cells (with immuno-histochemistry) and hrHPV-genotypes (by the AMPLICOR® and Linear Array tests) prognostically interact with epithelial pRb and p53.

Eighteen percent of CIN2-3s regressed (median biopsy-cone interval of 12.0 weeks, range: 5.0-34.1). Regressive CIN2-3s had higher epithelial pRb and p53, lower stromal CD25+ and CD138+, and higher CD8+ cells than persistent lesions. They also had higher ratios of CD4+/CD25+ and CD8+/CD25+ ratios in stroma and epithelium. None of the regressing lesions contained hrHPV-16 (p=0.02) and HPV-16 correlated with low pRb and low CD8+. With multivariate analysis a combined high ratio of CD8+/CD25+ in stroma, high epithelial pRb and p53 expression had independent value to predict regression.

In conclusion, CIN2-3 lesions with a non-hrHPV16 infection, high ratios of stromal CD8+/CD25+ and high epithelial expression of pRb or p53 are associated with spontaneous regression.

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GROIN ULTRASOUND (USS) AND FINE NEEDLE ASPIRATION CYTOLOGY (FNAC) - AN ALTERNATIVE TO Lymphadenectomy IN PRIMARY VULVAL SQUAMOUS CELL Carcinoma (VScc)

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Objective: To investigate the safety of ultrasound + FNAC as an alternative to inguinofemoral lymphadenectomy (IFL) in the management of primary VSCC.

Methods: In patients with primary VSCC and normal groin USS and FNAC no IFL was performed. These patients were monitored with bilateral groin ultrasound +/- FNAC every 3 months post-operatively. Outcomes were compared to patients managed with IFL who did not receive adjuvant groin radiotherapy.

Results: In 218 patients with primary VSCC, no IFL was performed in 50 patients with normal ultrasound and FNAC. Median follow up was 43 months (1-209). There were 8 IGR (isolated groin recurrences) all detected by surveillance ultrasound (16.0%) in the USS group, and 9 (5.4%) IGR in the IFL group (p = 0.0129). USS detected metastatic groin disease before it was clinically evident. There was no difference in overall or disease specific survival (p = 0.5815, p = 0.3617).

Conclusions: The rate of IGR was, as anticipated, higher in patients with a normal pre-operative ultrasound/FNAC in whom no IFL was performed initially. These recurrences were detected earlier by ultrasound surveillance than by clinical examination. The most clinically significant findings were: (1) In patients without IFL, post-treatment detection of groin nodal metastasis by USS did not reduce overall, or disease specific survival; (2) 84% of patients without IFL were spared the morbidity of groin node dissection. These data provide further evidence that Ultrasound +/- FNAC is a safe alternative to IFL, in patients with primary VSCC.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

RISK OF NEW INFECTION WITH THE SAME HPV-TYPE IN WOMEN WITH NATURALLY-ACQUIRED HPV-16/18 ANTIBODIES

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We evaluated whether women with naturally-acquired HPV-antibodies who were HPV-DNA-negative at baseline are less likely to develop new infection with the same HPV-type than HPV-antibody-negative and DNA-negative women.

HPV infection rates were assessed over 4-years in the control group of PATRICIA (a randomised, phase III study of HPV-16/18 AS04-adjuvanted vaccine). New infections were detected by type-specific PCR according to baseline HPV-16/18 serostatus measured by ELISA. Incidence rates (IR) were calculated using the person-time method (Table) and rate ratios (RR) estimated using multivariate Poisson regressions.

<table>
<thead>
<tr>
<th></th>
<th>HPV-16 (N=8711)</th>
<th>HPV-18 (N=8988)</th>
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<tbody>
<tr>
<td></td>
<td>Seronegative</td>
<td>Seropositive</td>
</tr>
<tr>
<td></td>
<td>(N=7415)</td>
<td>(N=1296)</td>
</tr>
<tr>
<td>New incident</td>
<td>1062 (4.37)</td>
<td>126 (3.00)</td>
</tr>
<tr>
<td>infection (Incidence/100 person-years)</td>
<td>(N=8030)</td>
<td>(N=958)</td>
</tr>
<tr>
<td>New 6-month</td>
<td>560 (2.26)</td>
<td>66 (1.54)</td>
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<tr>
<td>persistent</td>
<td>(Incidence/100</td>
<td>272 (0.99)</td>
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<tr>
<td>infection</td>
<td>person-years)</td>
<td>(N=958)</td>
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[Table]

For HPV-16, multivariate analysis by antibody titre quartile demonstrated a reduced risk of new infection with increasing titre, with a statistically significant rate difference for the upper quartile compared to seronegative women. RR adjusted for confounders were 0.33 [95% CI: 0.21,0.53] and 0.32 [0.17,0.63] for incident and 6-month persistent infection, respectively. For HPV-18, no decreased risk of infection with increasing naturally-acquired antibody titre was observed.

Our findings suggest that natural immunity as measured by ELISA does not reliably protect against new infection with high risk oncogenic HPV types. Only a small proportion of women with naturally-acquired antibodies had limited protection against incident and persistent infection with one HPV type. Therefore, our results support vaccination of all women regardless of HPV naturally-acquired antibody status.
IMPLANT STRATEGIES FOR CATHETER-BASED ULTRASOUND HYPERTHERMIA ADJUNCT TO HDR BRACHYTHERAPY IN THE UTERINE CERVIX

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**Purpose:** We have developed catheter-based ultrasound applicators with arrays of sectored tubular transducers that provide targeted, localized hyperthermia with 3D control in length and angle. Intrauterine and interstitial ultrasound devices can be used to heat the cervix while minimizing thermal dose in non-targeted tissues. Heating capabilities of these devices with current brachytherapy implant catheter positions are explored.

**Methods:** Hyperthermia target volumes (HTVs) and organ volumes are taken from patients treated for cervical cancer with HDR brachytherapy. Contours are imported into COMSOL and 3-D temperature profiles are simulated in uterine tissue. Interstitial applicators (1.5mm diameter) with single 180°, 270° or 360° sectors are modeled with/without an intrauterine applicator (3.5mm) with 2x180° or 360° sectoring. Power levels are optimized to maximize T₉₀ in the HTV while maintaining Tₘₐₓ < 47°C and rectum and bladder temperatures < 41.5°C.

**Results:** 1-6 360° interstitial applicators provide 41°C coverage of 3.4-9.5 cm diameter regions (22.0-198.4 cc). A single endocavity applicator alone or in combination with 1-4 interstitial devices at 3-4 cm spacing can heat to 41°C over 4.8-11.3 cm in diameter (57.5-168.3 cc). HTVs could be treated with T₉₀ = 41.9°C, Tₘₐₓ = 46.7°C; rectum: 37.6°C and 41.4°C; bladder: 40.9°C and 41.1°C. HTV < 4-5cm diameter could be treated by the endocavity applicator alone. Larger volumes require additional interstitial catheters aimed inward to increase coverage while limiting rectum and bladder temperature.

**Conclusions:** A combination of interstitial and endocavity ultrasound applicators can be used for targeted therapeutic heating of cervix tumors using standard brachytherapy catheter positions. (R01CA122276)
CORRELATION BETWEEN PREOPERATIVE SERUM CA 125 AND SURGICOPATHOLOGIC PROGNOSTIC FACTORS IN ENDOMETRIAL CANCER

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CA 125 is widely used to follow the course of ovarian cancer. Its application and significance in primary and recurrent endometrial malignancies, however, have yet to be defined.

Objective: This prospective study aimed to determine the correlation between preoperative serum CA 125 and surgicopathologic prognostic factors in endometrial cancer. It also intended to determine the CA 125 value which best predicted the prognostic factors to which it was correlated.

Methods: Endometrial cancer patients eligible for primary surgery were included. CA 125 was determined by chemiluminescent enzyme immunoassay (CLEIA) prior to laparotomy, peritoneal fluid cytology, extrafascial or radical hysterectomy, bilateral salpingooophorectomy, pelvic lymph node dissection and para-aortic lymph node sampling. All specimens were examined for tumor differentiation, lymphovascular space invasion, myometrial invasion, cervical, adnexal, and vaginal involvement, pelvic and para-aortic lymph node metastases, and peritoneal fluid cytology.

Results: Ninety patients with endometrioid type endometrial adenocarcinoma underwent complete surgical staging. Preoperative CA 125 was significantly correlated with deep myometrial invasion (p = 0.02), adnexal metastasis (p = 0.01), pelvic lymph node involvement (p < 0.01), para-aortic lymph node involvement (p < 0.01), and extrauterine disease (p = 0.01). A cutoff value of 55 U/mL can predict extrauterine spread with 53.85% sensitivity, 84.38% specificity, and 75.56% accuracy.

Conclusion: CA 125 has significant correlation with deep myometrial invasion, adnexal metastasis, pelvic and para-aortic lymph node involvement, and extrauterine disease, with 55 U/mL as cutoff value. It is recommended that CA 125 determination be routinely included in the preoperative work-up of endometrial cancer patients.
INCREASED EPITHELIAL STEM CELL TRAITS IN ADVANCED ENDOMETRIAL ENDOMETRIOID CARCINOMA

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It has been recognized cancer cells acquire characters reminiscent of those of normal stem cells, and the degree of stem cell gene expression correlates with patient prognosis. Lgr5(+) or CD133(+) epithelial stem cells (EpiSCs) have recently been identified and these cells are susceptible to neoplastic transformation. Endometrial endometrioid carcinoma (EEC) is a dominant type of the endometrial cancers and is still among the most common female cancers. Clinically it is classified into 4 FIGO stages by the degree of tumor invasion and metastasis. Identifying genes shared between advanced tumors and stem cells will not only unmask the mechanisms of tumor malignancy but also provide novel therapeutic targets. To identify EpiSC genes in late (stages III-IV) EECs, a molecular signature distinguishing early (stages I-II) and late EECs was first identified to delineate late EECs at the genomics level. MAPK pathway was significantly up in late EECs, indicating drugs targeting this canonical pathway might be useful for treating advanced EECs. A six-gene mini-signature was further identified to differentiate early from advanced EECs. Advanced, invasive EECs possessed a clear EpiSC gene expression pattern, explaining partly why these tumors are more malignant. Our work provides new insights into the pathogenesis of EECs and reveals a previously unknown link between adult stem cells and the histopathological traits of EECs. Shared EpiSC genes in late EECs may contribute to the stem cell-like phenotypes shown by advanced tumors and hold the potential of being candidate therapeutic targets and novel prognosis biomarkers.
HIGHER SENSITIVITY TO PATUPILEONE VERSUS PACLITAXEL CHEMOTHERAPY IN PRIMARY UTERINE SEROUS TUMORS WITH HIGH VERSUS LOW HER-2/NEU EXPRESSION IN VITRO


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Objective: To compare the in vitro sensitivity/resistance to patupileone versus paclitaxel in uterine serous papillary carcinoma (USPC) with high versus low HER-2/neu expression.

Study design: Six primary USPC cell lines, half of which overexpress HER-2/neu at 3+ level, were evaluated for growth rate and tested for their in vitro sensitivity/resistance to patupileone versus paclitaxel by MTS assays. Quantitative RT-PCR was used to identify potential mechanisms underlying the differential sensitivity/resistance to patupileone versus paclitaxel in primary USPC cell lines.

Results: Cell lines overexpressing HER-2/neu showed higher proliferation when compared to low HER-2/neu-expressing cell lines. Compared to low-expressing cell lines, high HER-2/neu expressors were significantly more sensitive to patupileone than to paclitaxel (P < 0.0002). In contrast, no difference in sensitivity to patupileone versus paclitaxel was detectable in primary USPC cell lines with low HER-2/neu expression. The presence/absence of Her2/neu amplification significantly affected the magnitude of the differential response to patupileone versus paclitaxel (P = 0.014). Higher levels of Tubulin B3 (TUBB3) and P-glycoprotein (ABCB1) were detected in USPC cell lines with high versus low HER-2/neu expression (P < 0.05).

Conclusions: USPC overexpressing HER-2/neu display greater in vitro sensitivity to patupileone and higher levels of the patupileone molecular target TUBB3 when compared to low HER-2/neu expressors. Due to the adverse prognosis associated with HER-2/neu overexpression in USPC patients, patupileone may represent a promising novel drug to combine to platinum compounds in this subset of aggressive endometrial tumors.
PEGYLATED LIPOSOMAL DOXORUBICIN AND CARBOPLATIN IN MALIGNANT MIXED EPITHELIAL MESENCHYMAL GYNECOLOGIC TUMOURS. A PHASE-II TRIAL OF THE AGO STUDY GROUP

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Background: There is very limited data on treatment options in patients with malignant mixed epithelial mesenchymal gynecologic tumours. An internationally accepted treatment standard does not exist. Therefore, we conducted a prospective a Phase II trial to determine the efficacy and toxicity of combination therapy with pegylated liposomal doxorubicin and carboplatin.

Methods: Patients with recurrent or advanced gynecologic sarcomas were treated with pegylated liposomal doxorubicin 40mg/m² and carboplatin AUC 6, q28. The endpoint was tolerability.

Results: 40/41 registered patients started chemotherapy. Patients were included in this study within 11 months. 38 pts had first line chemotherapy (F) and 2 pts had second line treatment (S). Altogether, 20 pts with carcinomas (20 F/0 S), 14 pts with leiomyosarcoma (13 F/1 S) and 6 pts with endometrial stromal sarcoma (5 F/1 S) were treated. The median age was 59 years (range 29-77), 44% had ECOG performance status 0. The incidence of grade 3/4 hematologic toxicities was: anemia 15%, neutropenia 50%, and thrombocytopenia 17.5%. There were no episodes of febrile neutropenia or any grade 4 non-hematologic toxicities. Grade 3 non-hematologic toxicities were: Elevation of GGT 5.1%, elevation of GPT 2.6%, hypersensitivity 2.5%, and urinary tract infections 7.5%. Further toxicities of interest were: Grade 2 PPE in 10% and stomatitis in 5%.

Conclusions: A trial in rare diseases is feasible within national cooperation of the AGO Study Group. The safety profile of the combination therapy seems to be acceptable. Efficacy data regarding PFS and OS are pending.

This study was supported by Essex Pharma.
EUROPEAN ORGANISATION FOR THE RESEARCH AND TREATMENT OF CANCER (EORTC) QUALITY OF LIFE QUESTIONNAIRE FOR ENDOMETRIAL CANCER: A VALIDATION STUDY

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Background: Compared to other women’s cancers endometrial cancer has been studied less. More international trials are commencing and a robust quality of life (QoL) measure is needed for women recruited to these, to assess disease and treatment specific aspects of QoL, and to inform patient treatment choices.

Aim: To test the scale structure, reliability and validity of a site specific QoL questionnaire for endometrial cancer (QLQ-EN24) designed for use with the core EORTC QLQ-30.

Methods: The study, conducted by the EORTC Gynaecological Cancer QoL group, recruited 268 women with endometrial cancer from eight European countries, Australia and Taiwan: after pelvic surgery; during adjuvant chemotherapy and/or radiotherapy; and after completion of treatment. Patients completed the core EORTC QLQ-C30, the new EN24 which was translated into 7 languages, and a debriefing questionnaire.

Results: Multi-trait scaling analyses confirmed the hypothesized scale structure of the QLQ-EN24. Internal consistency reliability was good with Cronbach’s alpha coefficients ranging from 0.74 to 0.86 (Lymphoedema 0.80, Urological symptoms 0.75, Gastrointestinal symptoms 0.74, Body Image problems 0.86, and Sexual/Vaginal problems 0.86). Convergent and discriminant validity revealed no scaling errors. The QLQ-EN24 was capable of discriminating between clinical subgroups. Overall there was a high completion rate, with less than 2% missing values.

Conclusions: The study supports the reliability, and validity of the EORTC QLQ-EN24. It is a robust QoL instrument for use in endometrial cancer clinical trials and has potential to contribute to the patient reported outcome measurement agenda.
ENDOMETRIAL CANCER SIDE-POPULATION CELLS SHOW PROMINENT MIGRATION AND HAVE A POTENTIAL TO DIFFERENTIATE INTO THE MESENCHYMAL CELL LINEAGE

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Cancer stem-like cell subpopulations, referred to as “side-population” (SP) cells have been identified in several tumors based on their ability to efflux the fluorescent dye Hoechst 33342. While SP cells have been identified in the normal human endometrium and endometrial cancer, little is known about their characteristics. In this study, we isolated and characterized the SP cells in human endometrial cancer cells and in rat endometrial cells expressing oncogenic human K-Ras protein. These SP cells showed

1) reduction in the expression levels of differentiation markers

2) long-term proliferative capacity of the cell cultures

3) self-renewal capacity in vitro

4) enhancement of migration, lamellipodia and uropodia formation

5) enhanced tumorigenicity. In nude mice, SP cells formed large, invasive tumors, which were composed of both tumor cells and stromal-like cells with enriched extracellular matrix.

The expression levels of vimentin, α-smooth muscle actin and collagen III were enhanced in SP-tumors compared with the levels in non-SP -tumors. Analysis of microdissected samples and fluorescence in situ hybridization of Hec1-SP-tumors showed that the stromal -like cells with enriched ECM contained human DNA, confirming that the stromal-like cells were derived from the inoculated cells. In a matrigel assay, SP cells differentiated into α-SMA-expressing cells. These findings demonstrate that SP cells have cancer stem like cells features including the potential to differentiate into the mesenchymal cell lineage.
ADJUVANT RADIOTHERAPY FOR ENDOMETRIAL CARCINOMA: A COMPARISON OF TOXICITY WITH CONFORMAL AND INTENSITY MODULATED TECHNIQUES

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Background and aims: Planning studies have reported significantly reduced dose to pelvic organs at risk with IMRT compared to conformal radiotherapy (3D-CRT). This study assessed whether this dosimetric advantage translates into clinical benefit by comparing toxicity profiles for each technique.

Methods: Our analysis included women receiving adjuvant pelvic radiotherapy for endometrial cancer between December 2006 and July 2009. Radiotherapy was delivered as either 3D-CRT (4 field) or IMRT (7 field dynamic). Toxicity data was recorded using CTCAEv3.0 at baseline, during radiotherapy, at 4-6 weeks and then 6 monthly post-radiotherapy. Overall complication rates at completion of radiotherapy and at 6 months were compared using Fishers exact test.

Results: 68 patients were analysed with median follow up of 28 months, 49 patients receiving 3D-CRT and 19 IMRT. No patients discontinued treatment due to toxicity and there was no severe (G3/4) acute or late toxicity. Acute bowel toxicity with 3D-CRT: G1 32.7%, G2 36.7% and IMRT: G1 36.8%, G2 31.6%. Acute genitourinary toxicity with 3D-CRT: G1 46.9%, G2 14.3% and IMRT: G1 42.1%, G2 10.5%. Overall acute complication rates were 81.6% with 3D-CRT and 78.9% with IMRT (p=1.000). Late toxicity rates were 20.4% with 3D-CRT (G1 14.3%, G2 6.1%) and 0% with IMRT (p=0.052).

Conclusions: Our results suggest acute toxicity is similar with 3D-CRT and IMRT, while late toxicity is markedly reduced with IMRT. Both techniques compare favourably to historical data with conventional radiotherapy. The absence of any long-term toxicity with IMRT is very encouraging although a larger cohort and longer follow up is required.
LYMPHADENECTOMY IN APPARENT EARLY-STAGE ENDOMETRIAL CANCER - CLINICAL UTILITY AND COST EFFECTIVENESS

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The aim of the study was to determine whether lymphadenectomy has an impact on survival and cost effective management of stage I endometrial carcinoma.

Between 1992 and 2002, 965 patients with clinical stage I endometrioid carcinoma of the endometrium were recruited for the study.

All patients underwent TAH & BSO and were categorized in 3 groups. Group A patients underwent a routine surgical staging, group B were staged based on intraoperative findings and group C were not staged.

The mean age was 62.1 years (range 18-96). There were 578 staged patients with a median number of 18 resected lymph nodes (range 14-34). High risk patients requiring adjuvant radiotherapy were 99/473 (20.9%) of group A, 74/194 (38.1%) of group B and 155/298 (52%) of group C (p< 0.001).

Overall 5-year survival was not significantly different and was recorded as 95.2% for group A 93.3% for group B and 83.9% for group C.

Patients with Grade 1 and 2 disease had a non significantly different 5-year survival among staged and unstaged patients. Staged patients with Grade 3 disease had a 72.7% 5 year-survival comparing with that of 50% of unstaged patients (p< 0.005). Complications were not significantly different among the 3 groups. The higher complication rate (20%) was observed among staged patients who received adjuvant external beam radiotherapy.

Lymphadenectomy is a safe and cost-effective procedure that offers no survival benefit but a significantly reduced need for adjuvant radiotherapy. Patients with Grade 3 disease had a significantly improved survival when surgical staging was performed.
EVALUATION OF THE ENDOMETRIUM IN POSTMENOPAUSAL WOMEN USING TRANSVAGINAL ULTRASONOGRAPHY: OUTCOME OF INVESTIGATIONS WHEN ENDOMETRIUM IS NOT IDENTIFIED USING ULTRASONOGRAPHY

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Aim: Transvaginal ultrasonography is commonly used as the first tool for investigation of women with postmenopausal bleeding. The objective of this study is to estimate the incidence of cases where endometrial thickness could not be identified on ultrasound and analyse the outcome of investigation in this subgroup of women.

Methods: This prospective study, carried out at a gynaecological oncology cancer centre in the United Kingdom included 3533 women with postmenopausal bleeding that underwent initial evaluation of endometrium using transvaginal ultrasonography.

Results: In 1732 (49%) women endometrial thickness measured less than 5 mm. No further investigation was performed in this group of women. Endometrial thickness measured between 5 to 10 mm in 981 (27.7%) women; 27 (2.7%) cases of endometrial cancer were diagnosed in this subgroup. 684 (19.3%) women had endometrial thickness measurement equal to or greater than 10 mm; 136 (19.8%) cases of endometrial cancer were diagnosed. Endometrial thickness was not visualised in 136 (3.8%) of women. Histology report in this subgroup showed 101 (74.2%) benign cases, 19 cases of endometrial cancer (13.9%), 10 benign endometrial polyps (7.3%), 4 cases of endometritis (2.9%) and 1 case of ovarian ca (0.7%).

Conclusion: The risk of endometrial cancer rises with increasing endometrial thickness. The likelihood of diagnosing endometrial carcinoma in cases when endometrial thickness is not visualised on transvaginal ultrasonography is 13.9%. This is significantly higher compared with women with endometrial thickness less than 10 mm. These women would require further evaluation by performing an endometrial biopsy or hysteroscopy.
STATHMIN OVEREXPRESSION IDENTIFIES HIGH RISK PATIENTS AND LYMPH NODE METASTASIS IN ENDOMETRIAL CANCER

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Overexpression of the oncogene Stathmin has been linked to aggressive endometrial carcinoma and a potential for PI3Kinase inhibitors in this disease (Salvesen, PNAS 2009). We wanted to validate the prognostic value of Stathmin expression in a large prospective multicentre setting. As lymph node sampling (LNS) is part of surgical staging today, we also wanted to test if Stathmin expression in curettage specimen was associated with presence of lymph node metastasis.

Materials and methods: 1076 endometrial cancer patients have been recruited from 10 centres to investigate clinical and biological tumour markers in relation to lymph node status and survival. (MoMaTEC, http://www.clinicaltrials.gov/ct2/show/NCT00598845).

Results: 71\% of the patients (n=763) were subjected to LNS, of which 12\% (94/763) had metastatic nodes. Overexpression of Stathmin was detected in 37\% (302/818) of the curettage- and 18\% (84/477) of hysterectomy specimens investigated. Stathmin overexpression in curettage- and hysterectomy specimens were highly correlated, and significantly associated with presence of lymph node metastases, non-endometrioid histology, high grade, aneuploidy and pathologic expression of hormone receptors (ER, PR) and p53. High Stathmin expression in hysterectomy and curettage specimens were associated with poor recurrence-free survival (p=0.002 and p< 0.001 respectively) when compared to low expression.

Conclusion: Stathmin immunohistochemical staining identifies endometrial carcinomas with lymph node metastases and poor survival. The value as predictive marker for response to PI3Kinase inhibition and as a tool to stratify for lymph node sampling in endometrial carcinomas remains to be determined.
HORMONE RECEPTOR STATUS IN ENDOMETRIAL CARCINOMA CURETTAGE INDEPENDENTLY PREDICTS LYMPH NODE METASTASIS AND PROGNOSIS IN A MULTICENTRE SETTING

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Lymphadenectomy is part of surgical staging for endometrial carcinomas. Detection of lymph node metastasis (LN+) yields prognostic information, but the value of lymphadenectomy to improve survival is unsettled. Immune markers for estrogen- and progesterone receptors (ER, PR) and p53 status have been found to predict prognosis. We wanted to evaluate immunohistochemical staining of these markers in curettage samples as predictors of LN+ and survival in a prospective international multicentre setting.

Materials and methods: 1076 endometrial cancer patients have been recruited from 10 centres to investigate clinical and tumour biological markers in relation to lymph node status and survival. (MoMaTEC, http://www.clinicaltrials.gov/ct2/show/NCT005988845).

Results: 71% of patients were subjected to nodal sampling, of which 12% were LN+. Loss of ER and PR was found in 23% and 24% respectively, overexpression of p53 in 18%. Pathologic expression of each marker correlated highly with presence of LN+, high FIGO stage, high grade, non-endometrioid histology, aneuploidy and poor prognosis (p< 0.001). Double negative receptor status (ER-/PR-) independently predicted lymph node metastasis (OR 2.1, 95% CI 1.1-4.1) adjusted for high-risk preoperative curettage histology (high grade/non-endometrioid). ER-/PR- status independently influenced poor survival adjusted for age, FIGO stage, histological subtype and grade (HR 2.4 95% CI 1.3-4.5). Also for endometrioid, LN- patients, ER-/PR- status independently influenced survival adjusted for grade.

Conclusion: Double negative hormone receptor status in endometrial cancer curettage specimen predicts lymph node metastasis and poor survival in a prospective multicentre setting. Implementation of these data in decision-making regarding lymphadenectomy and adjuvant therapy is subject for further studies.
The diagnostic criteria and prognostic factors for uterine sarcomas are controversial. Recently, we suggested that Bcl-2 expression is of prognostic value in uterine leiomyosarcomas. Using tissue microarrays of 115 uterine sarcomas (84 leiomyosarcomas, 24 endometrial stromal sarcomas, and 7 undifferentiated sarcomas), we investigated the expression of Bcl-2, Ki67, p53, and p16 attempting to distinguish leiomyosarcomas with favorable outcome. Tumor size and mitotic index were significant prognostic factors by univariate (p= 0.018 and p=0.003, respectively) and multivariate (p=0.006 and p=0.001) analysis. By univariate analysis, only Ki67 immunostaining was significant and was associated with adverse prognosis. Moreover, Ki67 plus Bcl-2 worked even better. Using these 2 markers, unsupervised hierarchical clustering identified 3 groups with significant differences in survival (p=0.001). Leiomyosarcomas with low Ki67 were associated with good prognosis regardless of their immunoreactivity for Bcl-2 (group 1); leiomyosarcomas positive both for Ki67 and Bcl-2 had an intermediate prognosis (group 2); leiomyosarcomas lacking Bcl-2 that reacted for Ki67 had the worse prognosis (group 3). These cluster groups were of prognostic significance by univariate analysis. Most endometrial stromal sarcomas (20/24; 83%) clustered in the group with favorable prognosis. In contrast, all undifferentiated endometrial sarcomas (7/7; 100%) clustered in the group with poor prognosis. This study confirms the significance of tumor size and mitotic index as morphologic predictors of malignancy in uterine leiomyosarcomas and strongly supports the prognostic value of Ki67. Combination of Ki67 and Bcl-2 protein expression allows distinguishing 3 groups of leiomyosarcomas with significant differences in survival.
A COMPARISON OF STAGING SYSTEMS FOR VULVAR SQUAMOUS CELL CARCINOMA (VSCC)

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Background: New FIGO staging system for vulvar cancer was introduced in 2009. It should replace the previous one (1988), last modified in 1996.

Aim: To find differences in prognosis for the patients staged according to the FIGO 1996 and 2009 and to analyze stage distribution in both systems.

Methods: We studied 110 patients with primary vSCC who had been treated in our institution between 2002 and 2006. Histopathological data were obtained by blind re-review of all samples retrieved from the archives for the purpose of this study. All patients were staged according to the new and previous FIGO system for vulvar cancer. Finally, 76 patients with verified histopathological data and full clinical history were included into the survival analysis. The Kaplan-Meier method was used to estimate overall survival and survival differences were analyzed by the log-rank test and F Cox test.

Results: There were no differences in survival between the same stages of compared FIGO systems (Fig.1).

[Overall survival between the same stages]

FIGO 2009 showed irregular stage distribution caused by extremaly small number of patients with stage II in our cohort (Fig.2).

[The FIGO stage distribution]

Conclusion: Irregular 2009 FIGO stage distribution provides a worse discrimination of survival between stages than 1996 FIGO Staging System. If this rare frequency of stage II were confirmed in big cohort studies it might suggest next FIGO modifications.
RISK FACTORS FOR SHORT AND LONG TERM COMPLICATIONS AFTER GROIN SURGERY IN VULVAR CANCER

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Background: The cornerstone of treatment of squamous cell carcinoma (SCC) of the vulva is surgery predominantly consisting of wide local excision with uni- or bilateral lymphadenectomy. Aim of this study was to determine risk factors for short term (wound breakdown, infection and lymphocele) and long term (lymphedema and cellulitis/erysipelas) complications after groin surgery. The second aim was to analyze differences in complication rate between inguinofemoral lymphadenectomy and sentinel lymph node (SLN) procedure.

Methods: Between January 1988 and June 2009 208 consecutive patients underwent an inguinofemoral lymphadenectomy and/or a SLN procedure as part of their surgical treatment for vulvar SCC at the Department of Gynecologic Oncology at the Radboud University Nijmegen Medical Center. Clinical and histopathological data were retrospectively analyzed.

Results: Multivariate analysis showed that older age, ‘en bloc’ surgery, peripheral vascular disease and higher drain production on the last day the drain was in situ gave a higher risk of developing short term complications. Younger age, ligation of the vena saphena magna (VSM) and a higher number of dissected lymph nodes gave higher risk of developing long term complications. Both short- and long term complications were less common in patients who underwent SLN procedure.

Conclusions: Our retrospective analysis shows that patient characteristics, extension of surgery and postoperative management influence short and/or long term complications after inguinofemoral lymphadenectomy. The introduction of the SLN procedure in vulvar SCC has led to an impressive decrease in complication rate. However, further research is necessary to analyze possibilities to decrease the complications of inguinofemoral lymphadenectomy.
SENTINEL LYMPHNODE DETECTION IN CERVICAL CANCERS: “WHERE IS THE NODE?”

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Background and aims: The sentinel lymphnode(SLN) is the first regional node to receive lymphatic drainage from a tumour. In cervical cancers, selective sampling of SLN carries lower morbidity compared to complete lymphadenectomy. Our aim was to assess the location of the SLN in cervical cancer patients and to get a better understanding of the lymphatic drainage from the cervix.

Methods: We selected women with cervical cancer undergoing SLN detection. SLN were first identified by lymphoscintigraphy using Technetium-99m nanocolloid injection. Methylene-blue dye was then injected into the cervix. During surgery, gamma-probe (Navigator) & blue dye were used to locate the SLN. The location of the SLN was recorded and the detection rate calculated.

Results: Sixty-four women underwent SLN detection for cervical cancer ≤FIGO stage-IIa. Median age was 36.5 years (24-66 range). Histology included 46 squamous-cell carcinomas, 16 adeno-carcinomas, one adeno-squamous type and another neuro-endocrine carcinoma. Twenty-seven women had lympho-vascular space invasion. The detection rate of sentinel nodes was 96.9%. SLN detection was highest using all three techniques- lymphoscintigraphy, gamma-camera and Methylene-blue dye. Median SLN yield was 2 (0-7 range). Six women had lymphnode metastases on final histology. Thirty-three women had laparoscopic sampling of SLN while thirty-one women had sampling at laparotomy. External iliac lymphnodes(36%) was the commonest site of SLN followed by internal iliac(27%), obturator(24%), common iliac(11.5%) and para-aortic(1.5%) lymphnodes.

Conclusion: The commonest site of SLN detection in cervical cancer is the external iliac lymphnodes. The detection of SLN in cervical cancer is high using pre-operative Technetium-99m lymphoscintigraphy, intra-operative gamma-probe and Methylene-blue dye.
SENTINEL LYMPH NODE BIOPSY IN EARLY CERVICAL CANCER: HOW TO REDUCE THE FALSE NEGATIVE RATE?

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Objective: To describe the false negative cases of Sentinel Node (SN) biopsy in early cervical cancer.

Methods: Prospective study in 7 centers (01/2005-06/2007), enrolling 145 patients with stage IA1 and LVSI to IB1 cervical cancer (SCC, adenocarcinoma or adenosquamous carcinoma). Non-inclusion criteria were age < 18 years, pregnancy, other histological types or pre-operative radio/chemotherapy. SNs were detected with a combined method (Tc99m + blue dye) and then removed laparoscopically. A complete pelvic lymphadenectomy was then performed. Histological examination included HES staining and immunohistochemistry (IHC). False negative cases were defined by negative SNs with involved non-SNs.

Results: 128 patients were considered. Combined detection rate was 98.4% per patient (95%CI: 94.4-99.9%). Of 430 identified SNs, 26 were involved in 21 patients and of 1870 sampled non-SNs, 11 were involved in 7 patients. The rate of nodal metastases was 18.7% (24 patients in 128).

Sensitivity was 91.3% [CI 95%: 71.9%-99.0%] and negative predictive value was 98.1% (CI95%: 93.2%-99.8%). There were 2 false negative cases with unilateral peroperative detection and 1 case without any detection. In the first 2 cases, there was a discrepancy between the number of SNs in lymphoscintigraphy and in peroperative period. All of these false negative cases were localized in interiliac area.

Conclusions: SN biopsy in cervical cancer is associated with a low false negative rate. Bilateral detection seems to prevent false negative cases. Preoperative lymphoscintigraphy also appears of a great interest and should alert the surgeon in case of discrepancy between pre and peroperative detection.
THE LAPAROSCOPIC APPROACH TO CARCINOMA OF THE ENDOMETRIUM (LACE) RANDOMIZED TRIAL: ADVERSE EVENTS COMPARING TOTAL LAPAROSCOPIC HYSTERECTOMY VERSUS TOTAL ABDOMINAL HYSTERECTOMY


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Purpose: The LACE trial compares quality of life (QoL) and disease-free survival (DFS) in patients who had a Total Laparoscopic Hysterectomy (TLH) or Total Abdominal Hysterectomy (TAH) for stage I endometrial cancer. This paper compares the incidence of intra-operative and post-operative adverse events (AEs) between the two treatment groups.

Patients and methods: Patients were eligible for randomisation if they had apparent stage 1 endometrioid adenocarcinoma of the endometrium. AEs among 332 LACE participants (TAH n= 141, TLH n=191) who were enrolled and completed 6 months of follow-up were evaluated. AEs were coded using CTC criteria (version 3). Descriptive statistics were used and intention-to-treat analysis was performed. Serious AEs are defined as any event that result in death, are immediately life threatening, requires prolongation of existing hospitalization or inpatient hospitalization or that result in persistent or significant disability/incapacity.

Results: Patients randomised to TAH or TLH had similar demographic characteristics. Conversions from allocated treatment were noted in eight patients (2.4%) with seven of the eight patients converted from TLH to TAH. Intraoperative AEs were similar in patients who underwent a TLH (7.3%) or a TAH (5.7%) (p=0.549). Postoperative AEs (CTC 3+) were significantly more frequent in patients who had a TAH (23.4%) compared to TLH (11.5%),p=0.004. Similarly, serious AEs were more common in the TAH (19.1%) than in the TLH (7.5%) group (p=0.002).There were no deaths in either treatment group.

Conclusion: Postoperative AEs and Serious AEs are more common subsequent to TAH than TLH. Intraoperative AEs are comparable amongst both surgical groups.
LAPAROSCOPIC PARA AORTIC LYMPHADENECTOMY AS STAGING IN ADVANCED CERVICAL CANCER

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The FIGO cervical cancer classification is clinical, therefore subjective and inexact increasing the failure rates with advancing stage. Surgical staging is superior to clinical staging since histologic verification of tumor extent correlates better with the biologic behavior of disease. The laparoscopic lymphadenectomy approach offers less morbidity than laparotomy reducing adhesion, bowel injury without delay the chemoradiotherapy.

Objectives: To compare clinical staging versus laparoscopic surgical staging in patients with advanced cervical cancer.

Method: Thirty five patients with FIGO clinical stage IB2 - IIIB cervical cancer underwent a laparoscopic staging. The first 17 patients were transperitoneal route and the next 18 a left extraperitoneal.

Results: The mean age of the patients was 41 years (26-63), mean body mass index was 27(19-38). The histology was squamous. Clinical FIGO stages were 3 patients in IB2, two in IIA, 17 in IIB and 13 in IIIB. The median operative time was 130 min ( 80-180). Median estimated blood loss was 90 ml (20-300). Paraaortic lymph node removed ranged from 3 to 19 (median 10). The mean postoperative time was 60 hrs. Final pathology revealed five patients (14%) with metastatic paraaortic lymph nodes, two of this patients had normal CT scan. Four patients had suspicious nodes at CT scan but the histology was normal. There was no intraoperative complication.

Conclusions: Laparoscopic surgical staging is a feasible technique, with low morbidity. This approach provides an important number of patients with subclinical paraaortic metastasis, without suspicious nodes on CT scan who may benefit from extended field radiation therapy.
LAPAROSCOPIC EXTRA PERITONEAL PARA-AORTIC LYMPH NODE DISSECTION (LEPAND) IN WOMEN WITH LOCALLY ADVANCED CERVICAL CANCER - INDIVIDUALISED TREATMENT

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Introduction: Laparoscopic extra peritoneal para-aortic lymph node dissection is carried out in women with locally advanced cervical cancer to improve survival and reduce the morbidity from extended field radiotherapy.

This study describes the experience of LEPAND in a regional cancer centre. It highlights the feasibility and safety of this technique and correlates histopathologic results with preoperative radiological findings.

Methods: Women with locally advanced cervical cancer who underwent LEPAND both prior to and on completion of chemo-radiation from November 2006 to November 2009 were retrospectively assessed. The criteria to perform PAND were positive pelvic nodes on imaging and large tumour volume.

Results: 36 women had LEPAND (16 patients prior to and 20 patients on completion of chemo-radiation). The mean age was 42 years, mean BMI was 28. All women had MRI and CT for radiotherapy planning. The average number of nodes harvested was 13.4. Mean operating time was 147 minutes. The median length of time from the LEPAND to start the chemo-radiation was 16 days. No significant change in women’s Hb pre and post LEPAND. The only major complication was lymphocyst formation in 5.5%. The final pathology revealed that 7 patients (20%) had metstatic disease within para-aortic lymph nodes.

Discussion: LEPAND assessment of locally advanced cervical cancer offers valuable information for individualized radiation treatment with minimal morbidity.
ANALYSIS OF LOWER EXTREMITY LYMPHEDEMA AFTER GYNECOLOGIC CANCER TREATMENT

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Background: Gynecologic cancer treatment including pelvic lymphadenectomy and whole pelvic irradiation often leads to lymphedema of the lower extremity as a long-term complication, and tends to reduce quality of lives of the survivors. Therefore, detailed analyses on the risk factors for lymphedema are needed.

Method: Thus we retrospectively evaluated incidence of lymphedema in patients who received various gynecologic cancer treatment in Okayama University Hospital during the last two decades, and analyzed high risk factors for lymphedema among 660 patients who could be followed up at least 5 years without any signs of recurrence.

Results: The incidence of clinically relevant lymphedema in cervical cancer patients underwent radical hysterectomy and radiotherapy were 23.1% and 17.7%, respectively. Only 4.5% of the patient underwent only radical hysterectomy developed lymphedema, whereas as high as 54.2% of the patients underwent radical hysterectomy followed by irradiation developed lymphedema. The incidence of lymphedema in ovarian and endometrial cancer patients who received operation including para-aortic lymphadenectomy remained 10.0% and 11.9%, respectively. Monovariate analysis among cervical cancer patients after radical hysterectomy indicated age, clinical stage, lymphnode metastasis, parametrial involvement, vaginal invasion and adjuvant irradiation as high risk factors, whereas multivariate analysis revealed only age and post-operative irradiation as independent risk factors for lymphedema.

Conclusions: Although long-term complications are not limited to lymphedema, concurrent chemoradiotherapy or adjuvant chemotherapy instead of radiotherapy might be taken into consideration in order to reduce unnecessary lymphedema after cervical cancer treatment. Careful evaluation before treatment including MRI and PET-CT would contribute to the appropriate treatment.
COMORBIDITY IS A CRITICAL FACTOR IN INFORMING OUTCOMES IN GYNAECOLOGICAL CANCER

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Survival outcomes for cancer treatment depend on the stage at presentation and the type of treatments offered to the patient. UK cancer survival is lower than others in Europe. This may be explained by later presentation with less investigation and poorer treatments. An alternative may be the UK figures represent true outcomes from the more complete population-based data compared with the selected published populations from other countries. We examined the effect of comorbidity as measured using the Charlson score on survival and treatment for gynaecological cancer in England.

Methods: 134,176 records from the matched Cancer Registry/Hospital Episode Statistics database were examined in women with gynaecological cancer in England from 1998-2006. The comorbidity status (measured by the Charlson score as none vs any comorbidity), deprivation status (derived from the postcode) were calculated and assessed against tumour type, age, treatment modalities used and survival using logistic and Cox proportional hazards regression analysis.

Results: The presence of comorbidity present in 10% of patients reviewed was associated with a highly significant reduction in survival, both before and after adjustment for age, deprivation, stage and grade of tumour. Furthermore, the presence of comorbidity significantly reduced the likelihood of surgical intervention before and after adjustment for age, deprivation and type of cancer.

Conclusion: In gynaecological cancer, the co-existence of comorbidity is equivalent to treating a patient approximately ten years older than their true age.

As comorbidity plays a highly significant role in predicting survival and use of surgical treatment, prospective collection of comorbidity data is important.
WHOLE PELVIC RADIOTHERAPY AND THE RISK OF SECONDARY LYMPHOMA

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**Objectives:** While radiation is known to increase the risk of development of a number of secondary malignancies, the association between radiation and non-hodgkin lymphoma (NHL) is uncertain. The goal of our study was to determine the risk of NHL after pelvic radiotherapy. We analyzed a large cohort of patients with long-term follow-up to determine the association of pelvic radiation and NHL.

**Methods:** Patients with invasive tumors of the vulva, cervix, uterus, anus, and rectosigmoid treated from 1978-2005 and recorded in the Surveillance, Epidemiology and End Results (SEER) database were analyzed. Patients were stratified based on receipt of pelvic radiotherapy. The incidence of non-hodgkin lymphoma (NHL) was examined. Multivariable Cox proportional hazards models and Kaplan-Meier curves were constructed to examine the association between pelvic radiation and the development of subsequent lymphoma.

**Results:** A total of 216,983 patients including 72,483 (33%) that received radiation and 144,500 (67%) that did not undergo radiotherapy were identified. During 1,757,371 person-years of follow-up (mean 7.0 years for radiated patients and 8.7 years for non-irradiated, p< 0.0001), 904 cases of NHL were observed. A multivariable proportional hazards model accounting for time of follow-up as well as clinical and pathologic characteristics demonstrated that increased age was strongly associated with NHL (p< 0.0001). Pelvic radiotherapy was associated with a 24% increased risk for the development of NHL (HR=1.24; 95% CI, 1.07-1.46).

**Conclusions:** Pelvic radiotherapy is associated with an increased risk of non-hodgkin lymphoma.
**PIK3CA, RAS AND RAF MUTATIONS IN PATIENTS WITH BREAST, CERVICAL, ENDOMETRIAL, AND OVARIAN CANCER TREATED WITH PI3K/AKT/mTOR AXIS INHIBITORS**


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**Background:** Activating mutations of the p110α subunit of phosphatidylinositol 3-kinase (*PIK3CA*) have been identified in various malignancies. Preclinical data suggest that these mutations may predict for response to PI3K/AKT/mTOR inhibitors. Concomitant *RAS* and *RAF* mutations may mediate resistance.

**Methods:** Tumors from patients with breast, cervical, endometrial, and ovarian cancer referred to the Phase I Program for targeted therapy from 10/08 to 05/10 were analyzed for *PIK3CA* mutations using PCR-based DNA sequencing of exon 9 and exon 20. Patients with *PIK3CA* mutations were treated whenever possible with agents targeting the PI3K/AKT/mTOR pathway.

**Results:** Hundred-and-forty patients were analyzed and 25 (18%) had *PIK3CA* mutations; 36% (5/14 patients) with squamous cervical, 24% (7/29) with endometrial, 21% (6/29) with breast, and 12% (7/60) with ovarian cancers. Of the 25 patients with *PIK3CA* mutations, 23 (median number of prior therapies, 2) were treated on a protocol that included a PI3K/AKT/mTOR pathway inhibitor. Of the 23 patients, 7 (30%) had a PR (2/5 squamous cervical; 2/6 endometrial; 2/7 ovarian; 1/5 breast). Of these 23 patients, 7 (30%) had coexisting *RAS* and/or *RAF* mutations (ovarian, 5; endometrial, 2). Of these 7 patients, 2 patients (ovarian) achieved PR, while endometrial progressed.

**Conclusion:** *PIK3CA* mutations were detected in 18% of patients with breast, cervical, endometrial, and ovarian cancer. Seven patients (30%) had a PR (30%) on PI3K/AKT/mTOR axis inhibitors. These preliminary results are encouraging and although the number of patients is small, they suggest that coexisting *RAS* and/or *RAF* mutations may be associated with resistance to PI3K/AKT/mTOR axis inhibitors in endometrial, but not in ovarian cancers.
CONTINENT CUTANEOUS ILEOCECAL RESERVOIR USING THE SUBMUCOSALLY EMBEDDED APPENDIX AFTER ANTERIOR EXENTERATION FOR GYNAECOLOGICAL MALIGNANCIES: TECHNIQUE AND COMPLICATIONS

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Introduction: Patients with advanced gynecological malignancies or recurrences of gynecological malignancies (vaginal carcinoma, endometrial carcinoma and cervical carcinoma), who had to be treated by anterior exenteration and did not have an appendectomy, were reconstructed by continent cutaneous ileocecal reservoir using the submucosally embedded appendix. Data of 7 patients from the years 2008 and 2009 were analysed for intraoperative and early postoperative complication rate.

Material and methods: The appendix-pouch technique starts with the transsection of the terminal ileum about 12 cm away from the ileocecal valve and of the colon ascendens about 15 cm away from the hepatic flexure. In order to reduce the tension of the wall of the pouch a teniamyotomy of the colon is performed. The efferent segment of the pouch is built by the appendix and is passed out at the umbilicus.

Results: The mean operation time for the complete anterior exenteration was 280 (range 230 - 320) minutes, for the reconstruction by the appendix pouch 75 (range 60 - 90) minutes. The main complications were: problems with wound healing and retention of secretion in the small pelvis. Insufficiencies of the sutures were not observed.

Conclusion: Our experience shows, that the appendix-pouch-technique is a good alternative for continent reconstruction of the bladder after anterior exenteration. This technique is combined with a quite low complication rate.
THE CAIRO BREAST SCREENING TRIAL (CBCST)

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Background: The Cairo Breast Screening Trial (CBST) was designed to evaluate the role of clinical breast examination (CBE) as a primary screening modality in the context of primary care coupled with the provision of adequate treatment for detected cases, in reducing both the morbidity and mortality from breast cancer.

Materials and methods: An initial pilot phase of the CBST has been completed. In that phase a specialised medical centre in Cairo was selected as the headquarters of the study. An area around the hospital was geographically defined. The target group was the approximately 5,000 women age 35-65. Social workers conducted door to door visits, and invited women to participate in the study and invited them to attend a primary health centre for CBE. Those found abnormal were referred to the hospital. In the second year, cluster randomization was performed and half the women were re-contacted, and invited to attend for screening. In the third year, the other half were visited at home and their health status determined.

The study has been expanded within Cairo to two other areas and approximately 10,000 women are now under observation.

Results: High rates of breast cancer were detected; about 8 per 1000 at the first examination and 2 per 1000 among those who attended for re-screening.

Conclusion: Encouraging is the fact that 68% of the screen-detected cancers are stage II or less, whereas experience in the National Cancer Institute - Cairo suggests that only 20% are normally diagnosed in an early stage.
SINGLE INCISION LAPAROSCOPIC SURGERY HYSTERECTOMY
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The Single incision laparoscopic surgery starts to belong to our daily practice. In our service of gynecologic surgery from June 2009, 83 patients have been operated of hysterectomy. We have identified two groups; group A ; 40 patients operated with traditional laparoscopic approach, and the group B ; 43 patient submitted to the single incision laparoscopic surgery approach ; SILS of "covidien.". The patients admitted to the study had an uterus with ultrasound measured dimensions among: 7/16cm longitudinal, 3.5/6cm transversal, 2.5/5cm front rear. The aim of the study was to evaluate the advantage of the use of this new approach to the gynecological laparoscopic surgery, applied to the hysterectomy, analyzing the operating time, the cost of the technique, use of drugs, the hospitalization and the pain. In conclusion the belonging patients to the group B take advantage of a precocious discharge 33% less, of an important reduction of the pain score. The operating time seems to be of little superior to the classical laparoscopic surgery, with a learning curves of 4 interventions. The single incision laparoscopic surgery, finds frankly the place in the conventional gynecologic surgery.
FERTILITY SPARING THERAPY IN EARLY ENDOMETRIAL CARCINOMA


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Summary: Endometrial carcinoma is the most commonly seen gynecological cancer in developed countries. Typically, endometrial carcinoma is a disease of postmenopausal women. However, approximately 5% of women with this disease are diagnosed before the age of 40 years, and 20-25% are diagnosed before menopause. The standard procedure is a total abdominal hysterectomy and bilateral salpingooophorectomy with/without lymphadenectomy for surgical treatment of endometrial carcinoma. Consideration should be given to pelvic and paraaortic lymphadenectomy in high-risk cases. The issue of sparing fertility emerges as a challenge in some cases, especially in patients who have been diagnosed at a very early stage and who have not already had children. There are increasing evidences that hormonal therapy can be safe and effective as primary treatment in young, nulliparous women, who refuse standard surgical approach in order to preserve their reproductive potential.

Since 2003, 7 women less than 40 years of age with a diagnosis of well differentiated EC who desired childbearing were considered for a conservative management. We have performed laparoscopic staging in 4 of 7 cases prior the hormonal treatment. All of these patients underwent medical therapy by using progestins. Results of the endometrial biopsy, follow up and fertility status were evaluated.
RADICAL HYSTERECTOMY WITH RELIABLE NERVE SPARING PROCEDURE IN PATIENTS WITH CERVICAL CANCER OF WHICH TUMOR SIZE IS LESS THAN 2CM

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Objective: We propose a new idea of radical hysterectomy to alleviate the urinary dysfunction.

Material and methods: A new radical hysterectomy was performed for stage Ib1 cervical cancer of which tumor size is less than 2cm in diameter from November 2008. We determine the day on which both voluntary urination and sensation of bladder fullness recovers and evaluate the 2-year progression free survival. The points of this surgery are 1) to remove the vessel part of the cardinal ligament, 2) to cut the uterine branch of pelvic splanchnic nerve close to the uterus, 3) to preserve the hypogastric nerve, and 4) to preserve vesicovaginal ligament. According to these steps, the uterus with surrounding tissue is resected closer to the cervix than Okabayashi’s radical hysterectomy, and consequently the bladder branch of pelvic nerve is preserved more certainly.

Result: We performed this surgery for 33 patients. The median day of complete voluntary urination is the 10th day. The sensation of bladder fullness as same as before surgery recovers in 27 patients 2 weeks after surgery. So far all patients are alive without recurrence.

Conclusion: We confirm the utility of the new radical hysterectomy.
V-Y ADVANCEMENT SKIN FLAPS BASED ON THE PUDENDAL ARTERY PERFORATORS: PRELIMINARY RESULTS OF A SERIE OF 24 FLAPS

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Objective: Vulvar cancer accounts for 3 to 5% of all cancers of the female genital tract. The mean age of diagnosis is about 70 years. Thus it is not uncommon to have to deal with patients with multiple comorbidities. Radical surgery with large vulvar defect is often needed because of the high local recurrent rate associated with the advanced stage at the moment of diagnosis. The aim of our study is to describe the surgical technique of the V-Y advancement skin flaps based on the pudendal artery perforators and to present the preliminary results of our serie of 24 flaps.

Methods: This is a retrospective and descriptive study of 24 flaps on 12 patients who underwent either total vulvectomy or abdomino-perineal amputation from november 2006 to november 2009 in the gynecologic and oncologic surgical department of the university teaching hospital of Bordeaux.

Results: In our serie all flaps succesfully survived without partial or total necrosis. Secondary healing for dehiscence more than 5 cm was necessary for two flaps. Two patients operated had positive surgical margins. The quality of life after surgery was satisfactory in all patients with no dysfunctional urinary or anal impact.

Conclusion: The V-Y advancement skin flap based on the pudendal artery perforators represent a simple, reliable and reproductible, first choice technique for vulvar reconstruction.
ROBOTIC EXTRAPERITONEAL PARA-AORTIC STAGING (REPPS) IN CERVICAL CANCER

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Multiple studies have documented the superiority of surgical staging over radiographic imaging for determining spread of cervical cancer to the para-aortic lymph nodes. Recent GOG data has also suggested that survival may be improved in those patients who have surgical staging. Staging via an extra-peritoneal approach has the advantage of not creating bowel adhesions within the peritoneal cavity, therefore reducing the risk of radiation injury to the intestine. For a minimally invasive approach in a small space such as the para-aortic region, the robot is an ideal tool due to the three-dimensional optics and "wristed" flexibility of the instruments.

This presentation will feature a surgical film of a REPPS procedure representative of the six cases we have performed to date.
LAPAROSCOPIC VERSUS LAPAROTOMIC APPROACHES IN WOMEN WITH EARLY STAGE ENDOMETRIAL CANCER

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Objective: The purpose of this study was to evaluate the feasibility and complications of laparoscopic surgery in women with early endometrial cancer and to compare surgical outcome and postoperative and perioperative complications with results of traditional laparotomy.

Study design: 89 women with early endometrial cancer was treated with surgery. Fifty-seven of them women with early endometrial cancer was performed laparoscopic surgery and thirty-four of them was treated with traditional laparotomic surgery. We evaluated properties and differences between two type surgical approach.

Results: A total of 91 cases were identified. Two cases were excluded because of converted to laparotomy. Thirty-four patients underwent laparotomy. Fifty-seven patients underwent the surgery by laparoscopy, of which 55 were successfully carried out (laparoscopy group). Two cases were converted to laparotomy. The mean operation time (OT) in the laparoscopy group was longer when compared with the laparotomy group ($P < 0.001$). The post-operative hospital stay was shorter in the laparoscopy group ($P < 0.001$). There was no statistically significant difference in the mean number of lymph nodes between the laparoscopy and laparotomy groups. The mean estimated blood loss in the laparoscopy group was less in same operation between laparoscopy and laparotomy groups ($P < 0.001$). There was no statistically significant difference in intraoperative complications but laparotomy groups include significant postoperative complications (wound infection).

Conclusion: Laparoscopic surgery for endometrial carcinoma is associated with significantly less blood loss, shorter hospital stay, longer OT time, quicker postoperative recovery, shorter hospital stay, and no wound complications.
VAGINOSCOPIC HYSTEROSCOPY IN THE EVALUATION OF UTERINE CANCER OF UNCERTAIN CERVICAL OR ENDOMETRIAL ORIGIN

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Objective: Vaginoscopic (non touch) hysteroscopy does not involve the introduction of speculum, catching the cervix or cervical dilatation. This makes it a perfect way for studying the vagina, cervix and uterine cavity without disturbing the anatomy. This study evaluates the value of this modality in the staging of uterine cancer when cervical or endometrial origin is uncertain.

Material and methods: 28 patients presenting with postmenopausal bleeding and endocervical curettings indicating adenocarcinoma of uncertain origin were included. Vaginoscopic hysteroscopy with saline distension was performed as a part of the staging examination under anaesthesia.

Results: Vaginoscopic hysteroscopy was achieved successfully in 27 of 28 women. In one patient the endometrial cavity was not entered or evaluated. Vaginoscopic hysteroscopy could diagnose a primary endometrial cancer extending into the cervix in 13 of 13 women with final diagnosis of endometrial carcinoma and primary endocervical carcinoma in 14 of 15 women with final diagnosis as such. Vaginoscopic hysteroscopy could detect vaginal extension in 2 patients with endometrial cancer (not detected by naked eye or palpation).

Conclusion: Vaginoscopic hysteroscopy is useful tool in the staging procedure of cervical and endometrial cancer where tumour origin is uncertain. Such evaluation is useful for tailoring treatment.
RECONSTRUCTIVE PLASTIC OPERATIONS IN VULVA CANCER

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Local tumor involving to the surrounding organs and tissues are required the necessity and expedience for performing to do reconstructive plastic operations (RPO) in some anatomical areas. The aim to study the using of RPO in advanced vulva cancer (VC). 28 RPO were performed in patients with VC in the oncologic gynecologic department №1 of NCC of N.N. Alexandrov from 2004 to 2009. The mean age was 68 (min-36, max-85). 18 patients were with III stage VC, 7 - IVa, 3-IVb by means of pelvic lymphatic nodes involving. The operations were observed in the volume of extended vulvectomy, bilateral inguinal-femoral-iliac lymphadenectomy with plastic of wound area one of methods. Lymphadenectomy was performed in different incisions or in one whole block with removing primary tumor. Plastic operations of TRAM-flaps were done in 3 cases, VRAM-flap was in 1 case, VY-plastic operation was performed in 2 cases, and plastic operations of musculocutaneous lower clunis bilateral insular flaps on vascular pedicle were done in 21 cases. RPO of musculocutaneous bilateral lower clunis total flaps were performed in one case. Flaps form anterior abdominal wall and from lateral femur surfaces were used the tumor localization on the upper half vulva. Flaps form posterior femur surfaces were used the tumor localization on the lower half vulva. One team work was used. The mean duration of clinic patient bed was 24 days.

Conclusion: Using RPO in advanced VC gives the chance to enlargement surgical treatment and greatly improves life quality of patients without patients’ age depending.
LAPAROSCOPIC RETROPERITONEAL SALVAGE LYMPHADENECTOMY FOR RECURRENCE OF CERVIX CANCER WITH PREVIOUS RADIATION IN A PATIENT WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA (IPT)

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Background: Retroperitoneal recurrence is a frequently observed condition in locally advanced cervix cancer after radiation. Surgery is an option of palliative treatment in selected cases.

Aims: To describe the case of a patient with external iliac and paraortic nodal recurrence, previously treated with standard radiation, and no indication for palliative chemotherapy.

Patient/method: 41 years-old female, with previous hysterectomy for FIGO IB2 squamous cell carcinoma of the cervix, was admitted for adjuvant treatment. She received pelvic radiation (5400cGy) until April 2009. She recurred with bulky lymphadenopathy up to the left renal vein in October 2009, and was diagnosed for IPT (started Prednisone 80mg/day). She received one cycle of cisplatin plus infusional 5-FU, developing grade 4 thrombocytopenia, which precluded subsequent cycles. Laparoscopic transperitoneal lymphadenectomy was indicated. Two 11mm trocars were placed at the umbilicus and right lower quadrant; and three 5mm, in the right flank, left lower quadrant and hypogastric. After adequate exposure, the dissection was performed with Harmonic scalpel and dissector forceps. The vessels were isolated, dissected and preserved. Specimens were retrieved with endobags through the umbilicus incision. Total procedure length was 270 minutes, with estimated blood loss of 90ml. The patient was discharged 18 hours later, with uneventful post operative period (platelet count = 47,000). The pathology report revealed at least 8 positive lymph nodes in 15, some of them confluent.

Conclusion: Laparoscopic retroperitoneal lymphadenectomy is a feasible procedure after radiation therapy, achieving adequate debulking even in challenging cases, with rapid recovery and low morbidity.
TIPS AND TRICKS ON LAPAROSCOPIC MANAGEMENT OF LARGE OVARIAN CYST

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Background: A 36 years old nulliparous woman, presented with a one year history of increased abdominal distension and discomfort. Clinical examination revealed a mass reaching up to xiphisternum. Subsequent USS and MRI revealed a large ovarian mass 30x20cm with fine septations. Ca125 was 183. Preoperative multidisciplinary review considered the risk of malignancy to be low. Following consultation the patient consented to undergo laparoscopic salpingo-oophorectomy, omentectomy and peritoneal cytology. The procedure was performed successfully and the final histological diagnosis was benign mucinous cystadenoma.

Description of video presentation: One of the main problems in managing large ovarian cysts with suspicion of early malignancy is the spillage of cyst fluid and increased risk of upstaging the disease which has inverse effect on survival. The video illustrates few tips of how to safely aspirate cyst fluid and prevent spillage while performing laparoscopic procedure for large ovarian masses when there is a potential risk of malignancy.
RADICALITY OF LAPAROSCOPIC SURGERY COMPARED TO TRADITIONAL ABDOMINAL SURGERY IN THE MANAGEMENT OF CERVICAL CANCER

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Objective: Laparoscopic surgery has been applied to cervical cancer management in recent 18 years. Until now, very few centers have reported their experience in radical total abdominal hysterectomy. In cervical cancer surgery, parametrial and vaginal resection are important part of surgery. However resection of parametrium in type 3 radical hysterectomy is defined to remove of parametrium as much as laterally near the pelvic wall, this is just theoretical defining. Parametrial resection in lateral and deep part is not present well. So in this report we present laparoscopic radical total abdominal hysterectomy with deep, lateral parametrium, vaginal and paravaginal enough tissue.

Material and method: The cases having radical hysterectomy between 2007 and 2010 were collected prospectively. Margin positivity was evaluated according to type of surgery as laparoscopy or laparatomy. Also lymph node status, resection of parametria and vagina were evaluated.

Results: Totally, 51 cases had classical abdominal radical hysterectomy and 25 laparoscopic radical hysterectomy, respectively. Parametrial involvement was detected in 3(12%) cases in laparoscopic radical surgery versus 9(17.7%) in laparatomic surgery(p>0.05). All the cases having parametrial involvement were free of surgical margin of tumor. Also there were no significant statistical difference in lymph node number and metastasis between two groups.

Conclusion: There is no difference in radicality between laparoscopic and laparatomic radical surgery in the surgical management of cervical cancer. Also it is possible to remove as much as vagina and parametria with laparoscopic surgery.
PRO-CADHERIN 10 - A NOVEL METHYLATION BIOMARKER FOR CERVICAL CANCER SCREENING

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Infection with hrHPV is a necessary though insufficient cause of cervical cancer. Progression of hrHPV-infected premalignant lesion to invasive cancer is driven by additional (epi)genetic events in the host cell genome. Recent studies indicate that testing for hrHPV will significantly improve current cytology based cervical screening, particularly owing to its excellent negative predictive value.

Objective: We hypothesize that the rather low specificity may be improved by testing for (epi)genetic changes driving cervical carcinogenesis. Tumor suppressor gene silencing via promoter hypermethylation is an important event in cervical carcinogenesis, which can be detected in cervical scrapings.

Methods: We recently identified PCDH10 (pro-cadherin 10) as one of the progressively methylated genes in cervical oncogenesis. PCDH10 methylation was studied by methylation specific PCR (MSP) in cervical cancer cell lines and HPV transfected keratinocytes mimicking all stages of cervical carcinogenesis. Initial results were validated by quantitative MSP of 184 biopsy and 81 cytology samples. PCDH10 methylation was detected in 1/19 (5.3%), 4/35 (11.4%), 10/42 (23.8%), and 38/43 (88.3%) of normal, CIN1, CIN3 and squamous cell carcinoma samples, respectively. PCDH10 methylation was also evident in 21/26 (80.7%) of adenocarcinoma, but not in adenocarcinoma in situ samples (n=19). Cytology samples revealed PCDH10 methylation to be significantly more frequent in abnormal cytology samples of women who developed CIN3 lesions within 18 months compared to Pap 1 smears of women without cervical disease during 5 year follow-up.

Conclusion: In conclusion, testing for PCDH10 promoter methylation may provide a valuable triage marker for risk assessment of hrHPV-positive women.
ELEVATED EXPRESSION OF P53 GAIN-OF-FUNCTION MUTATION R175H IN ENDOMETRIAL CANCER CELLS CAN INCREASE INVASION BY ACTIVATION OF EGFR/PI3K/AKT PATHWAY

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Background: p53 is the most commonly mutated tumor suppressor gene in human cancers. In addition to the loss of tumor suppression function and exertion of dominant-negative effects over the remaining wild-type protein, several p53 mutants can gain novel oncogenic functions (gain-of-function, GOF) that actively regulate cancer development and progression. In human endometrial cancer, p53 mutation is more often associated with aggressive nonendometrioid cancer. However, it was unknown if p53 mutants contributed to endometrial cancer progression through the GOF properties.

Methods: To clarify the relationship between expression of p53 GOF mutation (p53-R175H) and invasive potential of human endometrial cancer KLE cells, we tested the consequences of up-regulation and down-regulation of p53-R175H in KLE cells by inducing p53-R175H expression vector or suppressing the p53 gene with short hairpin RNA.

Results: We found that forced over-expression of p53-R175H significantly promoted cell migration and invasion, and induced activation of the epidermal growth factor receptor (EGFR)/phosphatidylinositol 3-kinase (PI3K)/AKT pathway. Conversely, suppression of p53-R175H with short hairpin RNA significantly inhibited cell migration and invasion, and resulted in attenuation of EGFR/PI3K/AKT pathway.

Conclusion: These findings show for the first time that elevated expression of p53-R175H mutant may exert gain-of-function activity to activate the EGFR/PI3K/AKT pathway and thus may contribute to the invasive phenotype in endometrial cancer.
PHARMACOKINETICS OF CHEMOTHERAPEUTIC AGENTS IN PREGNANT WOMEN

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Background: Physiological changes during pregnancy affect major pharmacokinetic processes. However, data on pharmacokinetics of chemotherapeutic agents during pregnancy are scant.

Methods: In pregnant and nonpregnant patients receiving the same chemotherapy schemes, pharmacokinetic parameters were determined based on serial plasma concentrations over the first 48 h after drug administration. Drug levels were measured using high performance liquid chromatography (doxorubicin, epirubicin and paclitaxel) or atomic absorption spectrometry (carboplatin). Area under the curve (AUC), maximal plasma concentration (Cmax), terminal half life (t1/2), drug clearance and distribution volume (Vd) were determined using a non-compartmental pharmacokinetic analysis with WinNonLin Software. Bone marrow toxicity was used as a surrogate marker for tissue toxicity.

Results: Sixteen and 11 chemotherapy cycles were available from pregnant and nonpregnant patients, respectively. Numbers of pregnant/nonpregnant patients tested for paclitaxel, doxorubicin, epirubicin and carboplatin equaled 5/2, 7/5, 4/4 and 2/2, respectively. During pregnancy distribution volume and clearance were increased and the AUC and Cmax decreased. Changes were consistent for all tested drugs. In addition, a lower reduction in platelet count and hemoglobin was seen during pregnancy.

Conclusion: Current data support the hypothesis that physiologic changes of pregnancy alter the disposition of chemotherapeutic agents resulting in a decreased plasma drug exposure. The importance of long-term follow-up of women treated with chemotherapy during pregnancy is underscored.
ANTI- INVASIVE AND ANTI- METASTATIC ACTIONS OF METFORMIN IN HUMAN ENDOMETRIAL CARCINOMA CELLS: ROLE OF NUCLEAR FACTOR-KAPPA-B, MMP-2/9, AKT, ERK1/2

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Background and aims: Endometrial cancer is the commonest malignancy of the female genital tract in the developed world fuelled by the pandemic of obesity and the metabolic syndrome. Polycystic ovary syndrome (PCOS), a pro-inflammatory state, is associated with obesity, diabetes, cardiovascular complications and endometrial cancer. Recent reports have suggested that metformin (used in PCOS women) may benefit cancer treatments. We studied the effects of sera from PCOS women against matched controls on in vitro invasion and metastasis in Human Endometrial Carcinoma Cells (ECC-1), before and after metformin treatment. Given the link between inflammation with endometrial cancer invasion and metastasis, we explored Nuclear Factor-kappaB (NF-κB), matrix metalloproteinases (MMPs), Akt and Erk1/2 pathways (important regulators of inflammation, tumour invasion and metastasis).

Methods: Invasion in ECC-1 cells was assessed by wound-healing motility assay. NF-κB was studied by stably transfecting ECC-1 cells with a cis-reporter plasmid containing luciferase reporter gene linked to five repeats of NF-κB binding sites. The gelatinolytic activities of secreted MMP-2 and MMP-9 in conditioned media were measured by gelatin zymography. Akt and Erk1/2 phosphorylation were assessed by western blotting.

Results: In vitro invasion, NF-κB, MMP-2, MMP-9, Akt and Erk1/2 activities were significantly increased in serum from PCOS women compared to matched controls; these effects were significantly attenuated by metformin treatment.

Conclusions: We present novel data that demonstrate the anti-invasive and anti-metastatic actions of metformin in human endometrial adenocarcinoma cells via NF-κB, MMP-2, MMP-9, Akt and Erk1/2 pathways. Our findings indicate metformin as potential adjuvant treatment to deter endometrial cancer metastasis.
PARENTAL ACCEPTANCE OF HUMAN PAPILLOMAVIRUS (HPV) VACCINATION IN INDONESIA
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\textbf{Background:} Cervical cancer ranks the second most frequent cancer in Indonesian women. In Indonesia, HPV vaccine acceptance has not been studied before.

\textbf{Objective:} To determine parental HPV vaccine acceptance in Indonesia, and factors that influence their decision. Factors include sociodemographic factors, knowledge about HPV, HPV vaccination & cervical cancer, health beliefs about cervical cancer and attitudes towards vaccination in general.

Materials\&methods: 746 parents, with at least 1 daughter aged 0-14, were interviewed using questionnaires. Interviews were done in subdistrict public health centers, governmental hospitals, and via house-visits, in 5 Indonesian regions.

\textbf{Results:} Parental HPV vaccine acceptance was 96.1%. Logistic regression revealed that age, beliefs about cervical cancer, and attitudes towards vaccination in general were significantly associated with HPV vaccine acceptance. Of the participants, 16.6%, 66.0% and 15.8% had heard about HPV, cervical cancer, and HPV vaccination respectively. The mean total knowledge score was 1.91(SD 2.31) on a 0-8 scale. Health beliefs about cervical cancer and attitudes towards vaccination in general were positive. Participants named the high cost of the vaccine, fear for side-effects, the best age for HPV vaccination, and chosen vaccination locations as possible barriers towards HPV vaccine implementation.

\textbf{Conclusion:} Parental HPV vaccine acceptance is high, but knowledge about HPV and cervical cancer is low. During awareness campaigns, focus should not only be on providing information, but also on existing beliefs and attitudes towards cervical cancer and vaccination in general. If HPV vaccination programs were to be implemented in Indonesia, the indicated barriers should be taken into account.

For: Female Cancer Program (Leiden University Medical Center), Udayana University (Bali), Lambung Mangkurat University (Banjarmasin), University of Indonesia (Jakarta), Samratulangi University (Manado), University of Sumatera Utara (Medan), Erlangga University (Surabaya)
SMOKERS WITH CERVICAL CANCER HAVE MORE UTERINE CORPUS INVASIVE DISEASE AND AN INCREASED RISK OF RECURRENCE FOLLOWING TREATMENT WITH CHEMO-RADIATION

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Background: Smoking is a risk factor for cervical cancer, causing hypoxaemia which promotes tumour infiltration and potentially impacts treatment outcome. We performed a retrospective study to determine if smokers had an increased risk of uterine corpus infiltration, associated with more advanced disease and/or treatment failure following primary chemo-radiation.

Methods: Results from a prospective database of patients treated with primary chemo-radiation for locally-advanced cervical cancer (12/1995-08/2008), with a pre-treatment MRI, were analysed. Smoking status was assessed by self-report at presentation.

Results: Smoking status was recorded for 346/362 patients with 98(28%) current smokers, 56(16%) ex-smokers and 192(55%) non-smokers. Median age was 58 with baseline characteristics below. Ever-smokers were more likely to have corpus uterine invasion than non-smokers. Ever-smokers had more recurrences than non-smokers, with non-smokers having a longer median overall survival (50.1 vs 38.7 months; p=0.004) and failure-free survival (46.8 vs 28.5 months; p=0.003). However, node-positive disease (p=0.003) and adenocarcinoma histology (p =0.016) were the only significant predictors of inferior failure-free survival in multivariate analysis.

Conclusions: Smokers have a greater risk of developing corpus invasive cervical cancer. Although non-smokers have an older age at diagnosis, they live longer and have fewer recurrences after a diagnosis of locally-advanced carcinoma of the cervix. Further research is needed into the biology behind this observation.

<table>
<thead>
<tr>
<th>Non-smoker (N=192)</th>
<th>Median age</th>
<th>Squamous histology</th>
<th>FIGO stage 3-4</th>
<th>Median Tumour volume (cc)</th>
<th>Node-positive</th>
<th>Corpus invasion</th>
<th>Tumour recurrence</th>
<th>Died from recurrence</th>
</tr>
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<tbody>
<tr>
<td>60 (28-94)</td>
<td>169 (88%)</td>
<td>42 (22%)</td>
<td>38.3 (0.1-269.5)</td>
<td>59 (30%)</td>
<td>115 (60%)</td>
<td>63 (33%)</td>
<td>51 (27%)</td>
<td></td>
</tr>
<tr>
<td>Ever-smoker (N=154)</td>
<td>54 (22-87)</td>
<td>136 (88%)</td>
<td>36.5 (0.5-628.3)</td>
<td>56 (36%)</td>
<td>113 (73%)</td>
<td>67 (44%)</td>
<td>53 (34%)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.013</td>
<td>1</td>
<td>0.560</td>
<td>0.914</td>
<td>0.183</td>
<td>0.009</td>
<td>0.045</td>
<td>0.126</td>
</tr>
</tbody>
</table>

[Non-smoker vs Ever-smoker]
NOVEL INFLAMMATORY SIGNATURE PREDICTS OUTCOME IN EPITHELIAL OVARIAN CANCER

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Introduction: Members of our group previously demonstrated that CD4+ T effector lymphocytes potentiate mammary adenocarcinoma metastasis by modulating the pro-tumour properties of tumour-associated macrophages [1]. These results predict immune cell infiltrates consisting of CD4+ T cells and CD68+ macrophages, and decreased CD8+ T cells possess an increased metastatic risk. We therefore developed a prognostic signature consisting of CD68high/CD4high/CD8low, which has been validated in over 1000 breast cancer cases. The aim of this study was to investigate the prognostic significance of this signature in epithelial ovarian cancer (EOC).

Methods: CD4, CD8, CD68 expression was evaluated using immunohistochemistry in a tissue microarray containing 76 EOC cases, Lymphocytic infiltrate was quantified using an automated algorithm. High and low thresholds for each marker were established using decision tree analysis with 10-fold cross-validation.

Results: This signature was not associated with tumour stage, grade or residual disease. CD68high/CD4high/CD8low patients had a reduced recurrence free survival (RFS) compared to CD68low/CD4low/CD8high patients (p < 0.001). Multivariate Cox regression analysis revealed the CD68high/CD4high/CD8low signature was an independent predictor of RFS (HR 2.26, 95%CI 1.27-3.98, p=0.006) indicating that the immune signature predicts EOC survival independently of the typical clinical histopathological characteristics.

Conclusion: We present a novel 3 marker inflammatory signature associated with reduced RFS and represents a robust and unique diagnostic tool for improving risk stratification for ovarian cancer patients.

DYNAMIC SPECTRAL IMAGING COLPOSCOPY: HIGHER SENSITIVITY FOR DETECTION OF PREMALIGNANT CERVICAL LESIONS

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Objective: This study aims to validate the dynamic spectral imaging (DSI) colposcope’s colour-coded map in discriminating high- from low-grade cervical lesions and non-neoplastic tissue.

Methods: The study was designed as a prospective, comparative clinical trial. The study population consisted of women 18 years or over with an intact cervix, referred for colposcopy. During a three minute image acquisition phase, the DSI colposcope (DySIS, Forth Photonics Ltd, Livingston, UK) was used as a regular video colposcope: the colposcopist located and graded potential lesions based on conventional colposcopic criteria. Subsequently, a colour-coded map was calculated and displayed, representing localisation and severity of the cervical lesion. Biopsies were collected from all atypical sites, as identified by digital mapping and/or conventional colposcopy. Furthermore, one additional biopsy was taken.

Results: In total 275 women were included in the study: 183 women were analysed in the ‘according to protocol’ (ATP) cohort and 239 women in the ‘intention to treat’ (ITT) cohort. In the ATP cohort, the sensitivity of DSI colposcopy to identify patients with high-grade (CIN2+) lesions was 79% (95%CI 70 to 88) whereas the sensitivity of conventional colposcopy was 55% (95%CI 44 to 65) (p=0.0006, asymptotic McNemar test). When the DSI colour-coded map was combined with conventional colposcopy, the sensitivity was 88% (95%CI 82 to 95).

Conclusions: DSI colposcopy has a statistically significant higher sensitivity to detect cervical lesions than conventional colposcopy. If the colour-coded map is combined with conventional colposcopic examination, the sensitivity increases further.
PROGNOSTIC VALUE OF SERUM CA125 IN OVARIAN TUMORS OF LOW MALIGNANT POTENTIAL: A MULTICENTER COLLABORATIVE STUDY


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Background: Ovarian tumors of low malignant potential (LMP) account for 15% of all epithelial ovarian malignancies. Recurrence rates range from 5-20% and survival is very good with 95% at 10 years from surgery. The role of CA125 in ovarian LMP tumors is not well established.

Objectives: To evaluate the distribution and association of preoperative CA125 with tumor stage and histological cell types and to determine the potential prognostic effect of preoperative CA125 in ovarian LMP tumors.

Methods: We collected data from 856 patients with ovarian LMP tumors diagnosed between 1985 and 2008 from 5 gynaecological oncology centers around the world. Information including demographics, histology, stage, preoperative CA125 level, treatment and relapse details as well as follow up and survival data was collected and analyzed with Stata. Multivariate Cox proportional hazard models were calculated to determine independent prognostic effects. A preoperative serum CA125 level >35 U/mL was considered “elevated”.

Results: CA125 was elevated in serous tumors and advanced stages of the disease. FIGO stages 2, 3, and 4, as well as preoperative CA125 levels >35 U/mL, were associated with impaired overall and relapse-free survival. The 5-year overall survival was 90% among patients with elevated CA125 compared to 96% among patients with normal levels of CA125 (p=0.004). Relapse-free survival showed similar patterns with 89% of those with elevated CA125 surviving 5 years compared to 95% of those with normal CA125 levels (p=0.021).

Conclusions: Preoperative CA125 level is an important and independent prognostic factor for survival in ovarian tumors of low malignant potential.

[Overall Survival by CA125]
EFFECTS OF DIHYDROARTIMINISIN ON THE PROLIFERATION, ADHESION, MIGRATION, AND INVASION OF EPITHELIAL OVARIAN CANCER CELLS IN VITRO

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Objective: To determine the effect of dihydroartiminisin, a deviate of artemisinin, on the cell proliferation, adhesion, migration, and invasion ability in cultured epithelial ovarian cancer cell lines.

Methods:

(1) MTT assay was performed to determine the anti-proliferative effect of dihydroartiminisin in ovarian cancer cell lines SKOV3 and OVCAR3, and Western blot was used to evaluate its effect on phosphorylation of MAPK.

(2) Matrigel coated plate method and transwell membrane chamber model was applied to evaluate the effect of dihydroartiminisin on adhesion, migration and invasion of these cells, and Western blot was performed to analyze its effect on phosphorylation of focal adhesion kinase (FAK).

Results:

(1) Dihydroartiminisin inhibited proliferation of ovarian cancer cells in vitro, with a mean IC50 at 72 h of 9.0 µM for SKOV3 and 5.5 µM for OVCAR3 respectively.

(2) Compared to cells without dihydroartiminisin treatment (control group), adhesion ability of SKOV3 and OVCAR3 treated with 12.5 µM dihydroartiminisin decreased by 76.1% and 57.9% respectively (P < 0.05), migration decreased by 59.3% and 69.7% respectively (P < 0.05), and no or slight change in invasion ability.

(3) Compared to control group, ERK 1/2 phosphorylation level in SKOV3 and OVCAR3 cells treated with dihydroartiminisin decreased by 64.2% and 75.3% respectively (P < 0.05), and FAK phosphorylation level decreased by 42.9% and 44.8% respectively (P < 0.05).

Conclusion: Dihydroartiminisin has inhibitory effects on proliferation, adhesion and migration of ovarian cancer cells in vitro, which probably mediated by down-regulating the phosphorylation of ERK 1/2 and FAK.
HELPING WOMEN MAKE INFORMED TREATMENT CHOICES: DECISION AIDS FOR TWO STAGES OF OVARIAN CANCER

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Aims: Women with ovarian cancer (OC) face difficult treatment decisions with uncertain QoL and survival outcomes. Decision Aids (DAs) have been shown to improve informed decision-making, but no such tools are available to women with OC. Study 1 involves an RCT to evaluate the effectiveness of a DA for asymptomatic women with rising CA-125 following initial treatment; Study 2 involves a pilot study to develop and assess a DA for women with resistant or refractory recurrent OC.

Methods: In Study 1, 178 women with rising CA-125 are randomised to receive either the DA or a general Cancer Council booklet, and complete standardised measures at baseline and 4-month follow-up. This DA helps women to make a decision about further treatment. In Study 2, 30 women with resistant or refractory recurrent OC provide feedback on the newly developed DA via a questionnaire and telephone interview. This DA helps women decide whether or not to continue active treatment.

Results: Overview and current progress on both studies will be presented.

Conclusions: This research program addresses a neglected area in the management of women with OC. It is anticipated that the DAs will lead to improved understanding of treatment options, reduced decisional conflict and regret, and increased satisfaction with the decision-making process. If effective, this relatively simple intervention has the potential to improve the clinical care, and ultimately quality of life, of women with OC.

Acknowledgments: This research is supported by the Cancer Institute NSW, Australia.
OVARIAN TUMOR MULTITARGETING WITH MABS AGAINST GP38, MUC1, AND TAG72 ON PEGYLATED NANO DELIVERY PLATFORM OF CYLD AND RIP-1 LEADS TO NECROPTOSIS/APOPTOSIS

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Introduction: Inhibition of mitochondrial apoptosis leads to potent chemoresistance in advanced and metastatic ovarian Ca. We aim to circumvent this chemoresistant mechanism leading to eradication of metastatic ovarian Ca.

Methods: We prepare pegylated nanosomes and we entrap inside wild type genes cylindromatosis tumor suppressor CYLD and receptor interacting protein(RIP-1) while we link on the nanosomal surface with the diazotization process MAb against ovarian tumor antigens gp38,MUC1, and TAG72.

Results: The pegylated nanosomes circumvented opsonin adsorption in the blood and circumvented RES elimination by the sinusoidal Kupffer cells in the liver and macrophages in the spleen. After administration the nanosomes with the adsorbed MAb targeted the metastatic ovarian carcinoma cells by binding on the tumor antigens gp38, TAG72, and MUC1 exerting an immunotherapeutic effect. The genes CYLD and RIP-1 intracellularly activate autophagy dependent necroptosis which is caspase independent bypassing the block in mitochondrial apoptosis leading to a bystander killing effect. TEM exhibited disintegration of the plasma membrane which is a hallmark of necroptosis, ATP dependent chromatin condensation and oligonucleosomal DNA fragmentation which are indicative of mitochondrial apoptosis, and autophagocytosis of apoptotic bodies by adjacent tumor cells which indicates a bystander killing effect. Overexpression of wt CYLD inhibited NF-κB activation by interaction with TRIP, deubiquitination, and inactivation of TRAF2 and TRAF6. MTT exhibited inhibition of metabolic activity, and BrdU indicated inhibition of DNA synthesis of ovarian tumor cells.

Conclusion: Multitargeted MAb linked on pegylated nanodelivery of CYLD and RIP-1 eradicated chemoresistant metastatic ovarian Ca by inducing caspase independent autophagy dependent necroptosis overcoming block of mitochondrial apoptosis leading to a bystander killing effect.
UPFRONT SURGERY VS NEOADJUVANT CHEMOTHERAPY IN ADVANCED EPITHELIAL OVARIAN CARCINOMA (EOC): A RANDOMIZED STUDY

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Background: Neoadjuvant chemotherapy (NACT) is associated with high optimum debulking rate (residual disease ≤1cm) in advanced EOC. We compared upfront surgery with neoadjuvant chemotherapy in women with ovarian cancer.

Patients and methods: Between October, 2001 and April, 2009, 147 women with advanced EOC (stage IIIC, stage IV with pleural effusion only) were randomly assigned to either primary debulking surgery followed by 6 cycles of paclitaxel and carboplatin (TC) or NACT - 3 cycles of TC followed by debulking surgery then 3 more cycles of TC.

Results: 139 women met all the eligibility criteria; upfront surgery, n=68, NACT, n=71. Baseline characteristics were similar in both groups. Patients in NACT group had higher optimum debulking rate (84.5% vs 22.6%, p< 0.0001), decreased blood loss during surgery (mean vol 428.3 vs 642.8 ml, p< 0.0001), less postoperative infections (1.41% vs. 13.2%, p< 0.01), reduced operative time (75.4 vs 89.2 minutes, p< 0.024) and shorter hospital stay (7.6 vs 11.8 days, p< 0.001). Grade 3/4 toxicities were not significantly difference in 2 groups. The QOL scores at the completion of treatment was higher in NACT group (113 vs 95, p< 0.001). At a median follow up of 42 months, the progression-free survival is 15 months in both groups, p=0.32. Overall survival is also similar in both groups; 41 vs 39 months, p=0.45.

Conclusions: Neoadjuvant chemotherapy in advanced EOC is associated with higher optimum debulking rate with reduced operative morbidity and improved quality of life. Survival is similar in both groups. (Clinical trial No NCT00715286).
SECONDARY CYTOREDUCTIVE SURGERY BASED ON AN INTERNATIONAL COHORT: REDEFINING A NEW STANDARD OF CARE FOR PATIENTS WITH PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER

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Background: This study aims to idevelop a risk model predicting the survival in patients undergoing SCR for platinum-sensitive recurrent epithelial ovarian cancer.

Methods: Data of 1,100 patients with recurrent epithelial ovarian cancer who underwent secondary cytoreduction from seven worldwide centers were pooled analyzed. Based on the results in Cox regression analysis, the scoring system for survival was developed. Internal validation was performed to assess the discrimination of the model.

Results: Complete SCR was strongly associated with the improvement of survival, with a median and estimated 5-year survival of 57.7 months and 48.1%, respectively, when compared to 27.0 months and 17.1% in those with residual disease of 0.1-1cm; 15.6 months and 6.2% in those with residual disease of >1cm, respectively (P < 0.0001). Grade at diagnosis, Progression-free interval, ascites at recurrence, extent of recurrent tumors and residual disease after SCR were significant identified as survival predictors and entered into the risk model for survival. In the model, total scores ranged from 0-8 points, and the receiver operating characteristics curve area was 0.736 with a cut-off at 4 point. In the cohort, patients were divided into three groups of 0-4, 5-6, and 7-8 points, with the median survival of 43.0 months, 17.6 months, and 10.9 months, respectively. (P < 0.0001).

Conclusions: Based on the international multi-center database, this risk model could well predict that which patients would benefit most from secondary cytoreduction. And secondary surgical cytoreduction should be standard care for recurrent ovarian cancer patients with a score less than 4 point.
IMPACT OF LYMPH NODE STATUS AND LYMPHADENECTOMY IN ADVANCED OVARIAN CANCER CORRELATED TO RESIDUAL DISEASE: AN AGO-OVAR META-ANALYSIS

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Objective: Positive lymph nodes are regarded as a poor prognostic factor in ovarian cancer. However, even among experts exists still a controversial discussion about the impact of lymph node status and lymphadenectomy on survival.

Methods: An exploratory analysis of three prospectively randomized trials (AGO-OVAR 3,5 +7) investigating platinum-taxane based chemotherapy regimens in advanced ovarian cancer (AOC) FIGO IIB-IV was performed. The studies were conducted 1995-2002 comprising 3388 pts. By means of uni- and multivariate analysis we investigated the impact of lymph node status on survival in a large cohort treated with standard chemotherapy and primary debulking surgery including lymphadenectomy (LNE) with no gross or small (< 11mm) residual disease.

Results: 1048 pts. had LNE, of whom 610 (58.2%) underwent complete pelvic and para-aortic LNE and 438 pts. received a less systematic LNE. 658 (62.8%) pts. had complete tumor resection, whereas 390 (37.2%) showed residuals < 11mm after surgery. Lymph node metastasis were present in 547 (52.2%) pts. Positive lymph node status showed a significant impact on survival in all patients regardless any other prognostic factor. Survival was longest in patients with no gross residual tumor and pathologically negative nodes (median:109 mon; 5YSR: 72.8%), whereas it was shortes in patients with positive lymph nodes and small residual disease (median:37 mon; 5YSR:28.2%). Pelvic and para-aortic LNE reduced the risk about 28% and 22%, respectively.

Conclusions: Positive lymph nodes alter the prognosis of patients with AOC. Prospectively randomized trials like AGO-LION have to prove the retrospectively seen benefits of pelvic and para-aortic LNE.
PACLITAXEL/CARBOPLATINUM +/- LONAFARNIB IN FIRST-LINE TREATMENT OF OVARIAN CANCER: A RANDOMIZED PHASE II STUDY BY THE AGO-OVAR STUDY GROUP

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Aims: Lonafarnib is a farnesyltransferase inhibitor with proven efficacy in several solid tumors. This randomized phase II study was conducted to assess the activity and tolerability of lonafarnib in addition to standard chemotherapy in patients with primary epithelial ovarian cancer IIB-IV.

Methods: This was an open label multi-center randomized phase II study comparing paclitaxel/carboplatinum and lonafarnib (LTC) to paclitaxel/carboplatinum (TC) alone. Stratification was done for tumors less or equal (stratum 1) or more than 1 cm (stratum 2). TC was given for 6 cycles in each arm, lonafarnib was administered in a dose of 100 mg per os during chemotherapy and 200 mg for the following 6 months after completion of chemotherapy. Primary endpoint was PFS, secondary endpoints were response, OAS and safety.

Results: Within 6 months 105 patients were enrolled by 22 sites of the AGO-OVAR Study Group, 53 (38 patients stratum 1) to the LTC and 52 (35 patients stratum 1) to the TC arm. Age, ECOG, FIGO stage, histology and grading were well balanced. There was no significantly difference in hematologic toxicity, in non-hematologic grade III/IV toxicity diarrhea was more frequent in LTC patients (23% vs. 4%, p=0.0046).

Conclusion: This is the first randomized study in ovarian cancer evaluating the efficacy of a farnesyltransferase inhibitor added to standard chemotherapy. Both therapy arms showed similar toxicity profiles. The addition of lonafarnib to standard chemotherapy caused a significantly higher percentage of grade III/IV diarrhea, the toxicity profile was well manageable. Data for PFS, response and OAS will be presented.
PROGNOSTIC IMPACT OF THE TIME INTERVAL BETWEEN SURGERY AND CHEMOTHERAPY IN ADVANCED OVARIAN CANCER - ANALYSIS OF PROSPECTIVE-RANDOMIZED PHASE-3 TRIALS

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Background: Surgery followed by platinum-taxane chemotherapy is the standard approach to treat advanced ovarian cancer. However, the impact of the time interval between surgery and initiation of chemotherapy for the clinical outcome has not been clarified yet.

Methods: Analysis based on individual patient data of three prospective randomized phase III trials conducted between 1995 and 2002 to investigate platinum-taxane based chemotherapy regimens in advanced ovarian cancer. Time to chemotherapy was analyzed as continuous variable and correlated with outcome.

Results: A total of 3326 patients were analyzed. The median time to initiation of chemotherapy was 19 days (range 1 - 56 days). Patients with no residual tumor after surgery and longer time to chemotherapy start tended to experience earlier relapse of disease (HR 1.005, 95% CI 0.996; 1.02, p=0.257) with a significantly decreased overall survival (HR 1.01, 95% CI 1.001; 1.02 p=0.038). In contrast, in patients with residual disease after surgery, a longer time to chemotherapy was significantly associated with a later progression (HR 0.99, 95% CI 0.984; 0.996, p< 0.001) and a trend towards increased overall survival (HR 0.998, 95% CI 0.991, 1.004, p=0.452).

Conclusions: Our findings suggest that patients with no residual disease after surgery benefit from an early initiation of chemotherapy, while individuals with residual disease have no disadvantage if chemotherapy needs to be postponed.
STANDARDISED STUDY OF HUMAN PAPILLOMAVIRUS TYPE DISTRIBUTION IN WOMEN WITH HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA AND INVASIVE CERVICAL CANCER IN EUROPE

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Human papillomavirus (HPV) type distribution was assessed in women with high-grade cervical intraepithelial neoplasia (HG-CIN) and invasive cervical cancer (ICC) in Europe where data are incomplete. Formalin-fixed, paraffin-embedded biopsy specimens from women ≥18y with HG-CIN (CIN2/CIN3, adenocarcinoma in situ) and/or ICC (squamous cell carcinoma [SCC], adenocarcinoma [ADC], other types) were sent for central histopathological review and standardised HPV DNA typing for 14 high-risk types. Data are available for 3103 women with HG-CIN (13 countries) and 3162 with ICC (12 countries) (median age: 34y and 49y, respectively). HPV+ rates were 98.5% for HG-CIN and 91.8% for ICC, with mostly single infections (80.0% and 93.5% of HPV+ cases, respectively). In CIN2/CIN3/ADC/SCC cases, single HPV16 accounted for (42.5/64.5/54.2/66.2%), single HPV18 for (3.3/2.8/40.4/10.8%), single HPV31 for (13.3/8.4/1.4/4.1%), single HPV33 for (10.2/10.9/1.5/5.2%), and single HPV45 for (2.1/1.4/8.3/5.0%), respectively. Median age of women with CIN2/CIN3/ADC/SCC was 32.5/34/42/49y for HPV16, 33/36.5/43/47y for HPV18, 31/34/48/54y for HPV31, 35/35/54/57y for HPV33 and 34.5/40/44/43y for HPV45. In 8 countries providing data for HG-CIN and ICC, HPV16/18/45 were 1.1/2.6/1.8 times more common and HPV31/33 were 0.3/0.4 times less common in ICC versus HG-CIN, in women with single and multiple infections. Therefore women with HPV16/18/45 infections may be at greater risk of progression from HG-CIN to ICC, with cancer occurring at a younger age, closer to that of HG-CIN, than for other HPV types. Implementation of a HPV16/18 vaccine with a broad cross-protection profile against other oncogenic HPV types may reduce the burden of cervical neoplasia in Europe [Study: 108288/108920].
THE NEED TO LOWER THE LOWER AGE LIMIT OF THE CERVICAL CANCER SCREENING PROGRAM IN ENGLAND

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Background: Cervical cancer is the 12th most common cancer in women in the UK. The incidence of cervical cancer in the UK is 9.3 per 100,000 women per year and mortality is 3 per 100,000 women per year. The incidence of cervical cancer below the age of 30 is 16 per 100,000 women. Currently cervical screening in England cervical screening begins at the age of 25.

Aims: To review the lower age limit of the national screening program for cervical malignancies in England.

Method: Retrospective case note review of patients presenting to the gynaecological department of the Royal Marsden Hospital with a new diagnosis of cervical cancer under the age of 30 between the 1st January 2000 and 31st December 2009.

Results: The study shows that 30% of cervical cancer patients were under the age of 30 and 6% under the age of 25. This is almost 1/3 of the Royal Marsden Hospital cervical cancer population and above the national peak incidence of cervical cancer at 17 per 100,000 women. It also shows a clear trend of rise in cervical cancer under the age of 30 from 2000 to 2009. A longitudinal analysis performed between 2000-2004 and 2005-2009 shows a double in cervical cancer incidence rates.

Conclusion: This data raises the question as to when screening for preventable diseases including cervical cancer should commence. It also demonstrates the need for selecting high-risk patients for individualized advice and screening before the age of 25.
FERTILITY PRESERVATION IN CERVICAL CANCER - THE DIFFICULTY OF TEACHING TECHNICAL SKILLS IN RARE EVENTS

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Every oncologist seeing reproductive-aged patients for consideration of cancer therapy must address potential treatment-related infertility.

In patients with gynaecologic tumours, treatment is more or less mutilating, either by direct surgical resection of pelvic organs or by destruction of their function after chemotherapy or radiation therapy. The gynaecologic oncologist must know the techniques currently available to preserve fertility, and their indications and limits, according to the tumour type.

However, according to a recent survey (driven by the ESGO) sent to all accredited Gynaecological Cancer Centres in Europe only a median of 8 patients per year per centre (less than 40 years of age, desire to retain fertility, and eligible for fertility preserving management) receive fertility sparing surgery.

In the majority of patients (e.g. ovarian and endometrial cancers), fertility sparing management is more a question of the correct indication than the difficulty of the surgical technique itself, except for vaginal radical trachelectomy in patients with cervical cancer. According to recent estimates, in the developed world for each 10 million inhabitants an annual caseload of 10-15 patients with cervical cancer eligible for fertility sparing management can be extrapolated from epidemiologic data. Such a low prevalence of disease and low application rate as demonstrated by our survey results promote a strict referral system in order to centralize specific expertise. In such an ideal setting, those highly selected patients would be counselled and treated by well trained experts in specifically accredited centres for fertility sparing management.
CHANGING TRENDS IN THE PATTERN OF CARE FOR WOMEN WITH CERVICAL CANCER IN LOW RESOURCE SETTINGS

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Cervical cancer is a disease of disparity. More than 80% of new cases occur in developing countries, which hold only 5% of global resources for control of cervical cancer. Medical professionals in developing countries are aware of the problems leading to late diagnosis and, as a final consequence, high mortality. They know what should be done to improve cervical cancer control. The main challenge, however, is how to translate this knowledge into action.

Over the past decade, trends in pattern of care for women with cervical cancer at low resource settings have been changing. The efforts are now focusing first to prevention and awareness rising and secondly on early detection. The absence of cytology brought up other non-cytological approaches such as VIA/”see and treat” policy or HPV testing. HIV/AIDS care and treatment programmes provide an ideal platform to integrate cervical cancer prevention activities in countries which face a dual burden of both AIDS and cervical cancer. For places where prevention resources are suboptimal, there is hope for prophylactic immunization against cancer-causing HPV infection.

Along with prevention and early detection, much effort is put to developing both proper surveillance and cancer control systems, and effective strategies that can increase survival of those with advanced and disseminated cancer. These strategies, however, require substantial economic and human resources as well as political will and also equitable and enduring partnership with international organizations. Redesigning the service and changing attitudes in public, profession and government will be the main ways to improve cervical cancer outcomes.
PROGNOSTIC IMPACT OF CONCOMITANT P53 AND PTEN ON OUTCOME IN EARLY STAGE (FIGO I-II) EPITHELIAL OVARIAN CANCER (EOC)

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Aims: Patients with early stages of EOC have a 75% 5-year survival. Different biological behavior of the tumor could explain different survival between clinically similar cases. The prognostic impact of the apoptosis regulators p53 and PTEN together in EOC was evaluated.

Methods: In a series of 131 patients the clinical outcome in relation to p53 and PTEN were evaluated after primary surgery and chemotherapy. Tissue-microarray and IHC were used. The monoclonal antibody DO-7 for p53 and PTEN/MMAC1 for PTEN were used.

Results: Positive staining for p53 and PTEN were found in 25% and 22% of cases, respectively. In total series recurrent disease was found in 33/131 (25%) patients after a mean follow-up time of 65 months. DFS was 68.0%. The p53-status was associated with tumor grade and DFS. The PTEN-status alone was not associated to any of the factors analyzed. However, in concomitant analyses for p53 and PTEN in four subgroups, 12/22 (54%) recurrences were found in the second subgroup of patients whose tumors had concomitant p53-positivity and PTEN-negativity compared to 4/11 (36%) recurrences in the first subgroup whose tumors had positivity for both. In survival analysis DFS in the second group (N=22) was worse (p=0.006) compared to others (N=109) (figure 1). In separately Cox multivariate regression analysis both p53 (OR=2.60) and p53PTEN (OR=0.47) were significant and independent prognostic factors for DFS

Conclusion: PTEN expression status divided 53 positive tumors in two distinct groups after prognosis in this study.
WOMEN WITHOUT OVARIAN CANCER WHO REPORT DISEASE-SPECIFIC SYMPTOMS

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Background: We recently examined symptom patterns reportedly related to the presence of ovarian malignancy and found them to be absent in 80% of ovarian malignancies (Cancer 2009;115:3689-98). The present studies examine women without ovarian cancer who report disease-specific symptoms.

Methods: 13569 women were recruited from 35,000+ women enrolled in the ovarian screening program and completed the symptoms evaluation between April 2008 and May 2009 during their screening appointment. These women remained free of an ovarian cancer diagnosis for at least 12 months of follow-up to May 2010. Symptom results were correlated to ultrasound as well as to clinical/demographic characteristics.

Results: Of the 13189 women considered to be free of malignancy, 380 reported disease-specific symptoms. Disease-specific symptoms decreased with age >60yrs, but increased with weight & BMI and were not significantly different in normal vs abnormal TVS findings (p< .05). However, an abnormal finding associated with an ovarian volume >10cm³ was 27X more likely to be accompanied by reports of disease-specific symptoms than when the volume was < 10cm³. Pre-menopausal women reported pelvic pain 2X more than postmenopausal women. 88.9% reporting a disease-specific symptom also reported other symptoms so that coincident disease-specific & disease nonspecific reporting was frequent.

Conclusions: Disease-specific symptoms are reported by women who do not have ovarian cancer at a rate that is 50-60X higher than the estimated prevalence of ovarian cancer. Weight, pre-menopausal status, large ovarian volumes, and coincident nonspecific symptoms reports are most associated with disease-specific reporting in women that do not have ovarian cancer.
POSSIBLE PROTECTIVE EFFECT OF STATINS IN GYNECOLOGICAL CANCERS

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Background: Statins have been shown to be associated with risk reduction of a variety of malignancies, including a survival benefit in ovarian cancer.

Methods: The Cancer in the Uterus and Ovary Study (CITUOS) is a case-control study of consecutive gynecological cancer cases treated at Carmel Medical Center and age/clinic/ethnic-group matched population controls. Use of statins was assessed in 302 consecutive gynecological malignancies and their matched controls.

Results: Statins were used, for one year or more prior to diagnosis, by 32.5% of the ovarian cancer cases and by 36.1% of the endometrial cancer cases. One year use of statins was associated with a significantly reduced risk of endometrial cancer (Odds Ratio=0.54, 95% CI: 0.35-0.83) and a reduction of borderline significance in risk of ovarian cancer (Odds Ratio=0.62, 95% CI: 0.36-1.07). The association with endometrial cancer remained significant after adjustment for confounding factors (OR=0.53, 0.30-0.94, p=0.03). The use of statins after the cancer diagnosis and at the end of the follow-up was associated with a significantly better overall survival of endometrial cancer patients (HR=0.17, 0.04-0.74, p=0.02) and with a better survival of borderline significance of ovarian cancer patients (HR=0.46, 0.21-1.04, p=0.06) compared to non-users of statins.

Conclusions: The use of statins for more than one year was associated with a 47% relative reduction in the risk of endometrial cancer and a reduction of borderline significance in risk of ovarian cancer. Statin use after diagnosis was associated with better overall survival.
CONSERVATIVE TREATMENT OF EARLY STAGE MALIGNANT EPITHELIAL OVARIAN CANCER: ONCOLOGICAL AND FERTILITY OUTCOME IN A SERIES OF 189 PATIENTS

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Introduction: Approximately 10% of epithelial ovarian cancer (EOC) is diagnosed in premenopausal women. In these patients the identification of risk factors is crucial for choosing fertility-sparing treatment, and for planning subsequent management and follow-up.

Patients and methods: All patients treated in our centre with fertility-sparing surgery for stage I-II EOC were considered for this analysis. Demographics, anatomopathological, clinical data, recurrence and survival, as well as number of pregnancies obtained after treatment were recorded. Univariate and multivariate analysis were used to test demographic characteristics and clinical features for their association with OS, PFS and fertility.

Results: From 1981 and 2008 38 patients were treated in our centre and 151 patients were referred after first conservative surgery. At a median follow up of 10.3 years 25 patients relapsed (13%) and 12 patients (6%) died for progressive disease. At the univariate analysis age, clear cell histotype, grade 3 and chemotherapy treatment were significantly associated with a worsening of both PFS and OS. However, at the multivariate analysis only grade 3 confirmed to be a negative prognostic factor (OS: p-value=0.0067; PFS:p-value=0.0044). A total of 74 (40%) patients tried to conceive after treatment, 51 (69%) successfully. At the multivariate analysis the only factors affecting fertility were age and chemotherapeutic treatment. Patients who received chemotherapy had a lower probability of becoming pregnant (OR:0.26, p-value:0.0503).

Conclusion: Women with early stage EOC can be safely treated with conservative surgery. Patients with G3 tumors should be intensively monitored. Chemotherapy should be administered with caution, as it could impair fertility.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

TRIAGE WITH RMI RESULTS IN BETTER TREATMENT OF EARLY AND ADVANCED OVARIAN CANCER: A PROSPECTIVE POPULATION STUDY

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Introduction and aims: The Risk of Malignancy Index (RMI) was used in a prospective study to decide if a patient had to be referred to a cancer centre or if a gynaecologic oncologist had to be involved in the surgical treatment. The objective is to increase optimal staging of clinical early disease, stage I (CED) and to increase the optimal debulking rate (residual tumour < 1 cm) and overall survival in advanced ovarian cancer, stage IIIC/IV (AOC).

Patients and methods: From 2004 till 2007 533 consecutive women with an ovarian mass were triaged. Ovarian cancer was diagnosed in 218 patients (of which 39 with CED and 122 with AOC). Two cohorts of consecutive patients with CED and AOC from 1998 (n=164) and 2003 (n=156) were used as historical controls.

Results: Of 218 patients with ovarian cancer 51 (23%) were treated by a gynaecologist while 75 (34%) and 92 (43%) were treated either with or only by a consultant gynaecologic oncologist, respectively. Optimal staging in CED was performed in 9/54 (17%), 12/35 (34%) and 22/39 (56%) patients in 1998, 2003 and in the triage study respectively. Optimal debulking rate for AOC increased from 31/66 (47%) in 1998 and 55/87 (63%) in 2003 to 84/122 (69%) in the triage study. Overall median survival for AOC increased from 21 months and 28 to 29 months respectively.

Conclusion: Introduction of a triage policy in patients with ovarian cancer in the population, using the RMI, further increased the rate of optimal debulking, optimal staging and overall survival.
MORPHOLOGIC, IMMUNOHISTOCHEMICAL AND MOLECULAR CORRELATIONS OF OVARIAN AND TUBAL DYSPLASIA IN PROPHYLACTIC OOPHORECTOMIES FOR GENETIC RISK

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Background: Histopathological examination of material from prophylactic salpingo-oophorectomies (pBSO) performed in patients at genetic risk has revealed frequent abnormalities interpreted as possible pre-cancerous “ovarian dysplasia” lesions. We sought to study their morphologic, immunohistochemical and molecular features.

Materials and methods: Morphologic features and immunohistochemical expression patterns of Ki-67, p53, Bcl2 and ALDH1 (an enzyme significantly associated with early-stage ovarian cancer) were blindly evaluated in 90 pBSO and 100 normal salpingo-oophorectomies (nBSO). Tubal and ovarian epitheliums from normal and dysplastic tissues were laser microdissected and studied by comparative genomic hybridization.

Results: Mean ovarian and tubal dysplasia score were significantly higher in the genetic risk group than in controls (respectively 9.2 vs .3, p< 0.002, for ovaries and 7.8 vs 3.5, p< 0.007 for tubes). Increased ALDH1 expression was observed in pBSO compared with nBSO whereas expression patterns of Ki67, p53 and bcl2 were low at moderate in pBSO group. Interestingly, ALDH1 expression was low in non dysplastic epithelium, high in dysplasia and constantly low in the carcinoma found incidentally on pBSO. Genomic alterations were found in all of the dysplastic ovarian and tubal epitheliums.

Conclusion: The increased dysplasia score, the strong ALDH1 expression and the genetic alterations might be consistent with progression towards neoplastic transformation and could justify the use of the term “dysplasia”. Ovarian and tubal dysplasia may be a pre-malignant, non-invasive histopathological abnormality that could be an important step in early ovarian neoplasia. The ALDH1 activation in pBSO could be considered as a target for early diagnosis and prevention.
U.S. GOG 218 VS. EURO ICON7 - A COST ANALYSIS OF BEVACIZUMAB IN THE PRIMARY TREATMENT OF OVARIAN CANCER

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Objective: Recent results from GOG218 showed that the addition of bevacizumab (B) and maintenance bevacizumab (mB) (15mg/kg) to chemotherapy improved the outcome of ovarian cancer patients. The results of ICON7 with a lower dose Bevacizumab (ld-B) (7.5mg/kg) are pending. We evaluated the cost effectiveness of GOG vs. ICON trials.

Methods: Cost of drugs, rates of complication, and progression-free survival were assessed. Incremental cost-effectiveness ratio (ICER) per life-year saved (LYS) was established.

Results: Estimated cost of B (15mg/kg) is $6,450 and ld-B (7.5mg/kg) is $3,225 per cycle. Compared to GOG cost / cycle = [PC ($440) + B ($6450)] + $6,450/maintenance, ICON = [PC ($440) + ld-B ($3,225)] + $3,225/ low dose maintenance was less. We estimated PFS to be 16 months with chemotherapy alone and 22 months with the addition of B. Of 600 patients, the GOG arm was $84.2 million vs. $43.5 million for ICON arm after adjusting for baseline estimates of PFS and bowel perforation risk. Assuming a 6 month improvement in PFS, the ICER was $270,900 per LYS for GOG arm, and $135,450 for ICON. If we assumed a 9 month additional PFS benefit associated with B, the ICER would be $180,600 for the GOG ARM and $90,300 for ICON arm. With a cost-effective ICER threshold of $100,000 per LYS, the ICON arm appears closest to being cost-effective.

Conclusions: In this economic model, our data suggest that a lower dose Bevacizumab, if proven to be effective, is more cost effective in the treatment of primary ovarian cancer.
HIGH THROUGHPUT DRUG SCREENING USING OVARIAN CANCER STEM CELLS IDENTIFIES NOVEL COMPOUNDS FOR OVARIAN CANCER THERAPY


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Background and aims: Ovarian cancer is one of the most common gynecological cancers. The high fatality-to-case ratio of ovarian cancer remains staggered in the past decades. Adding to our previous work in isolating ovarian cancer stem cells from human ovarian cancer tissues, the present study enriched ovarian cancer stem cells from cancer cell lines and discovered novel compounds preferentially targeting cancer stem cells.

Methods and results: Our previous work isolated ovarian cancer stem cells (OVCSC) from human ovarian cancer tissue using spheroid formation and characterized CD44+/CD117+ as surface markers. To explore the translational relevance of this cancer stem cell concept in ovarian cancer, we combined the dye-exclusion and spheroid formation methods to enrich OVCSC from ovarian cancer cell lines. The stem cells characteristics derived from this marker-free method were analyzed by various stem markers and validated by serial transplantation in immunocompromised mice. The OVCSC demonstrated chemoresistance. Loss of chemoresistance was noted as CSCs differentiate. High throughput drug screening using a chemical library of >1200 compounds discovered potential generic drugs preferentially targeting OVCSC derived from cell lines and human ovarian cancer tissues in vitro. The therapeutic effects were confirmed in animal models.

Conclusion: These results shed a new light on a better chance of survival for patients with ovarian cancer in the near future. A collaborated effort on the trial of these compounds is warranted. The paradigm shift from a stochastic model to cancer stem cell model has profound implications in cancer diagnostics and therapies.
MICROARRAY ANALYSIS OF ONCOGENIC PATHWAYS IN ADVANCED SEROUS PAPILLARY OVARIAN CARCINOMA

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**Background:** The aim of this study is to identify important processes which could lead to possible candidates for targeted therapies in ovarian cancer.

**Methods:** Two publicly available microarray datasets of advanced stage (III and IV) ovarian cancer samples (N=244, N=122) were analysed for oncogenic pathways (AKT, BetaCatenin, E2F1, EGFR, ER, HER2, MYC, INFa, IFNγ, p53, p63, PI3K, PR, RAS, SRC, STAT3, TNFa, TGFb) of which gene signatures were generated and validated by Gatza et al. (PNAS 2010). A VEGFA response gene signature was generated and validated based on in vitro experiments of VEGFA-stimulated HUVEC cells. These pathway gene signatures were correlated with clinicopathological findings and 3 prognostic gene signatures (Wound Response Signature, Genomic Grade Index and the Invasiveness Gene Signature).

**Results:** In both independent datasets, activation of BetaCatenin(R≥0.54), E2F1(R≥0.39), MYC(R≥0.35), p63(R≥0.35), PI3K(R≥0.20), RAS(R≥0.25) pathways were positively correlated with the 3 prognostic gene signatures (p< 0.001) while the EGFR(R≤-0.27) and HER2(R≤-0.26) pathway was negatively correlated (p< 0.003). Survival analysis confirmed reduced survival or time to progression for patients with an activated BetaCatenin(HR=0.78; p< 0.003), p63(HR=0.76; p< 0.034) and RAS(HR=0.48; p< 0.039) pathway. This was concordantly found in both datasets. Borderline significance was found for E2F1(HR=0.82; p< 0.07) and MYC(HR=0.70; p< 0.068) pathway.

**Conclusions:** Microarray analysis of two independent datasets showed that BetaCatenin, RAS and p63 pathway were consistently of prognostic value in advanced stage serous papillary ovarian cancer. Additional studies are needed.
A PHASE 2 STUDY OF PEMETREXED IN COMBINATION WITH CARBOPLATIN IN PATIENTS WITH PLATIN-SENSITIVE RECURRENT OVARIAN OR PERITONEAL CANCER

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Background: Carboplatin (Cb)-based combinations are commonly used in PSOC. Pemetrexed at 500 mg/m² with carboplatin at an AUC of 6 was found feasible.

Aims: The primary objective was to determine overall response rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary objectives included progression free survival (PFS), overall survival (OS) and toxicity.

Methods: Patients with PSOC defined by recurrence >6 months after 1st-line therapy, measurable disease, ECOG PS 0-2, adequate organ function, age > 18 were eligible. In August 2008, protocol was amended to allow pts who had received 2 prior platin-based therapies. Cb AUC 6 was infused over 30 minutes, 30 minutes after a 10-minute infusion of pemetrexed 500 mg/m².

Results: Sixty-six patients were accrued (June 2007-Feb 2009). Sixty-one patients were eligible for response. ORR was 32.8% (95% CI = 21.3% to 46.0%). There were 20 responders (1 CR, 19 PR, 32.8%). Median PFS was 9.4 months (95% CI 8.3 to 11.1); 18.0% censoring. Median OS was not reached (censoring rate of 67.2%). 12-month survival rate was 86% (95% CI 74% to 93%). There was 1 drug-related death (sepsis). The most common G3/4 toxicities were nausea (6.1%), vomiting (6.0%), platin hypersensitivity (9.1%), neutropenia (39.3%), leukopenia (9.1%), and thrombocytopenia (24.2%).

Conclusions: Cb AUC 6 and pemetrexed 500 mg/m² is well tolerated. The activity seems to be in the range of the other proven carboplatin-based doublets in PSOC pts. Defining the platinum-based combination with the best therapeutic index would require a prospective phase III study.
A NOVEL TREATMENT STRATEGY FOR OVARIAN GRANULOSA CELL TUMORS BASED ON IMMUNIZATION AGAINST ZP3

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Background: Ovarian granulosa cell tumors pose a therapeutic challenge with high mortality. We tested a novel strategy of immunotherapy against the zona pellucida glycoprotein 3 (ZP3), expressed in granulosa cell tumors.

Methods and aims: Transgenic mice expressing the Simian Virus 40T-antigen under the inhibin-promoter, presenting with ZP3 positive granulosa cell tumors, were treated with human ZP3 protein to induce T-cell mediated autoimmune oophoritis (IAO). Early immunization (at 2 mo of age) was expected to prevent tumorigenesis, and delayed immunization (at 4.5 mo) to eradicate existing tumors. Mice were immunized with 4-5 boosts at 3 weeks’ intervals, and the treatment effects were inspected 2 weeks after the last boost.

Results: Immunization reduced the ovarian tumor weight significantly in both treatment groups (by 86 and 75%, respectively; p< 0.001) in comparison to persistent tumor growth in controls (n=9-16/group). Significantly lowered tumor-produced progesterone and inhibin, and increased LH, supported the positive response. Liver metastases (n=4) were found in non-treated/vehicle-treated controls, but none following active immunization. Histological analyses confirmed that the ZP3 immunization prevented formation and abolished existing tumor cells by a mixed cellular/humoral immunological response.

Conclusion: These results prove the principle of active ZP3 immunization as a potential lead into the immunotherapy of ovarian granulosa cell cancer expressing ZP3.
FACTORS INFLUENCING UPTAKE OF RISK REDUCING SALPINGO-OOPHORECTOMY (RRSO) IN WOMEN AT HIGH RISK OF FAMILIAL OVARIAN CANCER

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Objective: To evaluate factors influencing uptake of risk-reducing salpingo-oophorectomy (RRSO) in women at ‘high-risk’ for ovarian cancer.

Methods: Prospectively collected data from women attending a tertiary high-risk familial gynaecological cancer clinic between March-2004 and November-2009 were analysed. Risk management options discussed include RRSO, participation in a national screening trial, as well as lifestyle and reproductive issues. Statistical analysis was undertaken using SPSS 12.0.1.

Results: Of 2193 women seen in clinic, 1639 from breast and/or ovarian cancer families had a high (≥10%) estimated life-time risk for ovarian cancer. 318(19.4%) high-risk women opted for RRSO and 1151(70.3%) for screening. 170(10%) were < 35years and deferred decision making. Women undergoing RRSO were older (median age 49.9, IQR 12.5years) than those opting for screening (median age 42.3, IQR 13.1 years) (p< 0.0005). Having a BRCA1/2 mutation, postmenopausal status, personal history of breast cancer, and family history of breast cancer only, was significantly associated with increased RRSO uptake (p< 0.0005) on univariate analysis. While, family history of breast and ovarian cancer(p=0.035), and ovarian cancer < 50years (p=0.004) was significantly associated with screening. Parity and Jewish ethnicity were not found to influence decision making. The only factors found to significantly influence RRSO uptake on multivariable regression analysis were age, BRCA mutation status and a personal history of breast cancer (p< 0.0005).

Conclusions: Various factors affect RRSO decision making in high-risk women. Women who are older, carry a BRCA mutation and have had breast cancer themselves are more likely to opt for surgery over screening.
REVISING THE ROLE OF PARAMETRIAL BOOST IN LOCALLY ADVANCED CERVIX CANCER PATIENTS STAGED WITH POSITRON EMISSION TOMOGRAPHY

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Purpose: The primary objective was to validate the practice of not treating clinically involved parametria by parametrial boost in the absence of metastatic pelvic lymph nodes. Secondary objective was to validate the adequacy of nodal boost in node positive patients regardless of the parametrial status.

Methods: A total of 193 loco-regionally advanced cervical cancer patients were treated with curative intent using external beam radiotherapy and intracavitary brachytherapy. All patients were clinically staged (FIGO), their tumour volume and nodal status determined using pre-treatment magnetic resonance imaging and positron emission tomography (PET). The PET positive nodes were boosted to an additional dose of 6-10Gy following 40Gy to whole pelvis. None of the patients received parametrial boost. Staging, treatment and follow-up data were collected prospectively. Patterns of failure and potential prognostic factors such as parametrial invasion, tumour volume, corpus invasion and pelvic nodal involvement were examined.

Results: There was no significant difference in the rates of pelvic relapse in both node positive and negative patients with or without parametrical involvement. In multifactor analysis, tumour volume was significantly associated with pelvic failure (p=0.009) and node positivity with extra pelvic failure (p=0.002). In particular, clinical parametrial involvement in the absence of parametrial boost was not related to either pelvic or extra-pelvic failure. None of the node positive patients had isolated pelvic failure.

Conclusion: Cervix cancer patients with clinically involved, parametrial disease, in the absence of nodal disease can be adequately treated without parametrial boost.

Keywords: Cervical cancer, FIGO stage, parametrial infiltration, lymph node metastasis
P16INK4A IMMUNOSTAINING AS AN ALTERNATIVE TO HISTOLOGY REVIEW FOR RELIABLE GRADING OF CERVICAL INTRAEPITHELIAL LESIONS

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Histomorphological grading of CIN is crucial for clinical management, however is subjective and affected by substantial rates of discordance among pathologists, which may lead to overtreatment. To minimise this problem, histology review of CIN lesions by a consensus panel of pathologists is often used. Diffuse p16INK4A immunostaining has been proposed to aid identification of true high-grade lesions. The aim of the study was to assess the value of additional interpretation of p16INK4A immunostains for making a more reproducible diagnosis of CIN2/3 lesions. We used 409 biopsies of cervical lesions, stained for both H&E and p16INK4A. First, in 49 biopsies, we examined the effect of interpretation of p16INK4A staining, on the agreement of CIN diagnosis among three pathologists. Second, all samples were used to assess the accuracy of p16-supported lesion grading by a single pathologist, by evaluating diagnostic agreement with the consensus diagnosis of expert pathologists based on H&E-stained sections only.

Agreement between three pathologists, for routine H&E-based diagnosis, ranged from fair (kappa 0.44 (95% CI: 0.19-0.64)) to moderate (kappa 0.66 (95% CI: 0.47-0.79)). The concordance increased substantially for p16-supported grading (mean kappa 0.80 (95% CI: 0.67-0.88)). Furthermore, an almost perfect agreement was found between the p16-supported diagnosis of a single pathologist and the consensus diagnosis of an expert panel (kappa 0.86 (95% CI: 0.83-0.88)).

Our data demonstrate that use of p16INK4A-IHC significantly improves the accuracy of grading CIN by a single pathologist, equalling expert consensus diagnosis. Hence, we advocate the combined use of p16INK4A-stained and H&E-sections in routine histopathology to improve accuracy of diagnosis.
TO TREAT OR NOT TO TREAT, THE CLINICAL DILEMMA OF ASC-US


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Objectives: Management of patients diagnosed with two consecutive atypical squamous cells of undetermined significance (ASC-US) cervical smears remains a clinical dilemma. We described a study on a period of more than 10 years to determine whether aggressive or conservative treatment is preferable.

Patients and methods: A total of 230 patients referred for primary colposcopy because of two ASC-US smears were evaluated for 125 months. In 112 patients conservative management was followed in case low grade cervical intraepithelial neoplasia (CIN) lesions were found at colposcopy (conservative strategy). One-hundred-eighteen patients underwent direct loop excision of all colposcopically detected abnormalities, even if not suspected for CIN (aggressive strategy). The number of loop excisions, detection of CIN lesions and cytological follow-up of both groups were analyzed to develop an optimal treatment strategy for patients with two consecutive ASC-US smears.

Results: Conservative management resulted in less loop excisions (p< 0.001). At initial colposcopy, the aggressive group revealed a tenfold of histologically detected CIN lesions compared to the conservative group (1.8% vs 19.5%). During ten years of follow-up, both groups revealed the same percentages of CIN lesions (8.1% vs 8.4%). Aggressive management resulted in faster normalization of cervical smears (p< 0.001). However, at 125 months follow-up, there was no statistical difference in the percentage of normalization of cervical smears between both treatment strategy groups.

Conclusions: Conservative colposcopic treatment is a safe strategy for patients with two consecutive ASC-US smears, without the risk of leaving CIN 3 lesions untreated. Treatment decisions, however, must be adjusted to individual needs.
EFFICACY OF GARDASIL® AGAINST PERSISTENT INFECTION OR DISEASE IN WOMEN WITH PRIOR VACCINE HPV TYPE INFECTION

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Background and aims: In the quadrivalent HPV (types 6/11/16/18) vaccine (Gardasil) clinical program, at vaccination 15% of women showed past cleared infection with one or more vaccine HPV types (seropositive and DNA negative). Analyses in women aged 16-26 demonstrated that no women seropositive and DNA negative for a vaccine type at enrollment were diagnosed with disease related to the previously cleared HPV type. Fifteen placebo subjects developed disease related to previously cleared vaccine types. Vaccination may prevent recurrence or reactivation of infection or disease. Here we present data for women aged 24-45.

Methods: 3819 women aged 24 to 45 with no history of cervical disease in the past 5 years, LEEP, hysterectomy, or genital warts were enrolled in an international randomized trial. Women received either Gardasil or placebo at Day 1, Month 2 and 6. Pap testing, genital inspection and cervicovaginal sampling were conducted every 6 months. Analyses were performed in women who were seropositive and negative to ≥1 vaccine HPV type at enrollment. Mean follow-up time per subject was 3.8 years.

Results: Persistent infection with vaccine HPV types occurred in 5 vaccine and 15 placebo subjects. No cases of CIN or EGL occurred. Vaccine efficacy against persistent infection was 66.8% (95% CI: 3.8, 90.5), and was 81.3% (95% CI: 14.4, 98.0) in women aged 35-45 (11 placebo, 2 vaccine cases).

Conclusions: Vaccination with Gardasil is associated with a lower incidence of reactivation/recurrence of persistent infection related to vaccine HPV types in women aged 24-45.
PROGNOSTIC FACTORS FOR IMPROVED SURVIVAL IN FIGO STAGE IVB CERVICAL CANCER

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**Background:** Prognostic factors for FIGO stage IVB cervical cancer have not been well-known because it was rare. Thus, we sought to evaluate prognostic factors for improving clinical outcomes in the disease.

**Methods:** Among 2,322 patients with cervical cancer between January 2000 and March 2010, 43 (1.9\%) had FIGO stage IVB disease. After we excluded 13 patients due to insufficient data, 30 (1.3\%) were enrolled, who received chemotherapy alone or concurrent chemoradiation (CCR) using platinum agents. Distant metastasis defining FIGO stage IVB disease included extra-peritoneal lymph node, lung, liver parenchyme and bone metastases.

**Results:** The median follow up was 17.5 months (1.8 to 100.1 months). Among all patients, 17 (56.7\%) and 13 (43.3\%) underwent chemotherapy alone and CCR, and 15 (50\%) received taxane- and platinum- based chemotherapy. Complete response (CR) and partial response (PR) were 23.3\% and 40\% (CR, n=7 vs. 0; PR, n=4 vs. 8 in CCR and chemotherapy alone; p< 0.05). Squamous cell carcinoma was only a favorable factor for progression-free survival (adjusted HR, 0.15; 95% CI, 0.02 to 0.88), whereas CCR (adjusted HR, 0.02; 95% CI, 0.01 to 0.39), taxane- and platinum-based chemotherapy (adjusted HR, 0.12; 95% CI, 0.02 to 0.93) and ≥6 cycles of chemotherapy (adjusted HR, 0.10; 95% CI, 0.02 to 0.52) were prognostic factors for improved overall survival on multivariate analyses.

**Conclusions:** These findings suggest that squamous cell carcinoma, CCR, taxane- and platinum-based chemotherapy and ≥6 cycles of chemotherapy may be associated with improved progression-free and overall survivals in FIGO stage IVB cervical cancer.
HIGH DOSE - DENSITY NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SIMPLE TRACHELECTOMY. ONCOLOGICAL AND PREGNANCY RESULTS

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Objective: In our prospective study were included fifteen patients with early stage cervical cancer that do not fulfill standard criteria for fertility-sparing surgery (tumor more than 2 cm in the biggest diameter or infiltrating more than half of stroma). All women had strong desire to save fertility.

Patients and methods: All patients received three cycles of dose-density neoadjuvant chemotherapy (NAC) at a 10-day interval: cisplatin plus ifosfamide in squamous cell cancer or plus doxorubicin in adenocarcinoma with good tolerance. After NAC, they underwent laparoscopic pelvic lymphadenectomy and vaginal simple trachelectomy. Sentinel lymph node (SLN) mapping was performed in all cases.

Results: Five patients had no residual tumor, six had only microscopic residual disease and four had macroscopic residual disease. Four women lost fertility (radical hysterectomy - 1 decision of patient, 1 positive endocervical margins, 1 positive SLN, 1 endocervical recurrence). Seven women delivered babies (one premature six term delivery); one woman is pregnant 3rd trimester. Three women had recurrence, (two endocervical and they are after radical hysterectomy without evidence of disease, one with recurrence in ovary died of disease).

Conclusion: NAC followed by fertility-sparing surgery seems to be feasible treatment for women with tumor bigger than 2 cm or infiltrated more than half of the stroma.

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CERVICAL CANCER CURE FRACTIONS IN RELATION TO SCREENING. FURTHER EVIDENCE FROM THE SWEDISH NATIONWIDE AUDIT

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Cervical screening reduces the incidence of cervical cancer but also detects invasive disease at early stages. It is not known to what extent this also implies better chances of cure.

Methods: A cohort of all cervical cancer cases in Sweden diagnosed 1999-2001 (n=1230) was followed prospectively until 2008, and the cure fraction, a measure of survival not affected by lead time bias, was estimated for different screening histories, mode of detection, and stratified by age at cancer diagnosis, histopathological type and FIGO stage.

Results: Overall cure fraction was 68%(CI 64-71), under age 65 it was 75%(72-78), and above age 65 43%(36-50). 52% of lethal cancers were diagnosed after the age of 65. 82% of women who died had overdue or no smear. Cure fraction for screen-detected cervical cancer cases in ages 23-65 was 90%(73-97), for symptomatic cancers 67%(62-71). Symptomatic interval cancer had a cure rate of 74%(68-79), symptomatic cases with a overdue or missing smear 60%(54-66). Cure fraction was well related to FIGO Stage and was equal for all histopathological types except small cell carcinomas.

Conclusion: Early stage detection of invasive cervical cancer in screening implies improved cure for squamous cancer as well as for adenocarcinoma. These findings are unaffected by lead time or length bias. Few deaths remain be prevented among regularly screened women. Any further reduction of death in cervical cancer will require excellent organization to detect the last few cases among participants and to cover more under-screened women in the population.
PHOTODYNAMIC THERAPY FOR PRECANCER AND EARLY STAGE CANCER OF THE UTERINE CERVIX WITH FERTILITY PRESERVATION

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The number of the patient with dysplasia and CIS of the uterine cervix has been increasing recently, especially in the younger ages who need fertility preservation. Although cervical conization is standard therapy for dysplasia and CIS, the significant increase in the obstetrical risks such as premature delivery after conization has been reported. On the other hand, PDT is an excellent procedure to treat CIN3 by photochemical reaction generated by laser irradiation to the lesion after injection of tumor-specific photosensitizer. We have developed protocol and applied PDT to CIN3 and early stage cervical cancer since 1989. PDT was performed for 520 cases (146 dysplasia, 342 CIS, 4 AIS, 24 MIC, 1 MIAC, 2 invasive SCC, and 1 invasive adenocarcinoma.) 97\%(503/520) of PDT cases were CR by the single PDT procedure. CR rates for dysplasia, CIS, MIC were 99\%, 97\%, and 92\%, respectively.

As a retrospective cohort study, two kinds of uterine preservation therapy (PDT and conization) for dysplasia, CIS and early stage cervical cancer were compared with respect to cure rate and fertility after therapy. Although cure rate by PDT is nearly equal to that by conization, pregnancy rate and delivery rate after PDT were significantly higher, and premature delivery rate after PDT was lower than those after conization. Especially, cumulative delivery rate curve of PDT cohort was significantly higher than that of conization cohort (p=0.009, Log-Rank test). These data suggested that PDT for CIN3 and early stage cervical cancer might be superior therapy for fertility preservation as compared to conization.
HUMAN PAPILLOMAVIRUS PREVALENCE AND TYPE DISTRIBUTION IN CERVICAL ADENOCARCINOMA: RESULTS FROM A MULTINATIONAL EPIDEMIOLOGICAL STUDY IN EUROPE

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A study of human papillomavirus (HPV) infection in invasive cervical cancer (ICC) assessed the prevalence of HPV types in invasive cervical adenocarcinoma (ADC) and squamous cell carcinoma (SCC) in 12 European countries.

Formalin-fixed, paraffin-embedded specimens from women ≥18yrs with ICC were HPV-DNA-typed by PCR for 14 high-risk HPV types and histopathological review including blinded expert review of HPV+/- ADC.

Agreement between original and expert diagnoses was 80.1% for ADC (85% for HPV+ ADC and 57% for HPV- ADC). New expert diagnoses for HPV- cases included non-cervical ADC and histological subtypes of cervical ADC considered unrelated to HPV. Following expert review, ADC cases, described in analysis, included most commonly mucinous ADC (86.0%), clear cell ADC (6.9%), minimal deviation ADC (1.7%) and serous ADC of cervix (5.4%). ADC accounted for 13.4% of all ICC (n=3162). Median age for ADC was 45yrs. Overall HPV+ rate was 94.2% for SCC, 81.3% for ADC, and 90.4% for mucinous ADC. A single HPV type was found in 93.3% of HPV+ ADC, predominantly HPV16 (54.2%), HPV18 (40.4%) and HPV45 (8.3%). Of 17 multiply infected women with ADC, 15 had been infected with HPV16, HPV18 or HPV45. Women diagnosed with ADC and single HPV16/18/45 infections were younger than those infected with other single HPV types (42/43/44yrs versus 56yrs, respectively). HPV16/18/45-related ADC occurs at an earlier age than HPV-16/18/45-related SCC, and accounts for 98.1% of all single HPV infected ADC.

Implementation of a HPV16/18 vaccine including HPV45 cross-protection would reduce the burden of ADC [Study ID: 108288/108920].
Efficacy of the HPV-16/18 AS04-adjuvanted vaccine in women according to their initial DNA and serostatus: PATRICIA end-of-study results


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Objectives: The AS04-adjuvanted human papillomavirus (HPV)-16/18 vaccine shows high prophylactic vaccine efficacy (VE) against cervical intraepithelial neoplasia (CIN)2+ associated with HPV-16/18. We report VE stratified by initial cervical DNA/serostatus from the PATRICIA (NCT00122681) end-of-study analysis.

Methods: Women aged 15-25 years, irrespective of baseline HPV DNA status, serostatus, or cytology, were randomised to receive HPV-16/18 vaccine (n=9,319) or hepatitis A vaccine (n=9,325) at Months 0, 1 and 6. Cervical samples were collected every 6 months for HPV DNA typing; gynaecological and cytopathological examinations were performed annually. VE is reported for the total vaccinated cohort (women receiving ≥1 vaccine dose).

Results: At baseline, 5.4% women were DNA-positive for HPV-16, 2.3% for HPV-18, and 0.5% for HPV-16/18; 13.9% women were DNA-negative but seropositive for HPV-16, and 10.6% for HPV-18. VE against CIN2+ at end-of-study by baseline DNA/serostatus is shown below.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Baseline HPV serostatus and/or DNA status</th>
<th>VE against CIN2+ associated with HPV-16 and/or HPV-18 detected in the lesion % (95% CI)</th>
<th>VE against CIN2+ associated with HPV-16 and/or HPV-18 detected in the lesion % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16/18 CIN2+</td>
<td>DNA-negative and seronegative</td>
<td>95.6 (90.2-98.4;p&lt;0.0001)</td>
<td>98.5 (94.3-99.8;p&lt;0.0001)</td>
</tr>
<tr>
<td>HPV-16/18 CIN2+</td>
<td>DNA-negative, regardless of serological status at baseline</td>
<td>93.4 (87.5-96.9;p&lt;0.0001)</td>
<td>97.2 (92.7-99.3;p&lt;0.0001)</td>
</tr>
<tr>
<td>HPV-16/18 CIN2+</td>
<td>DNA-negative and seropositive for HPV-16 and/or HPV-18</td>
<td>65.3 (&lt;0.918;p=0.0770)</td>
<td>81.1 (13.3-98.0;p=0.0225)</td>
</tr>
<tr>
<td>HPV-16/18 CIN2+</td>
<td>DNA-negative for the type considered but DNA positive for the other vaccine type; regardless of serostatus</td>
<td>91.8 (43.8-99.8;p=0.0023)</td>
<td>100 (54.4-100;p=0.0012)</td>
</tr>
<tr>
<td>HPV-16 CIN2+</td>
<td>DNA-positive for HPV-16/DNA-negative for HPV-18, regardless of serostatus</td>
<td>84.4 (&lt;0.997;p=0.0644)</td>
<td>100 (&lt;0.100;p=0.0284)</td>
</tr>
<tr>
<td>HPV-18 CIN2+</td>
<td>DNA-positive for HPV-16/DNA-negative for HPV-18, regardless of serostatus</td>
<td>100 (3.4-100;p=0.0226)</td>
<td>100 (&lt;0.100;p=0.0484)</td>
</tr>
</tbody>
</table>

[Table 1]

Conclusions: The vaccine demonstrated high efficacy against CIN2+ associated with HPV-16/18 in HPV-16/18 DNA-negative women, even those seropositive for HPV-16 and/or -18. Women currently infected (DNA-positive) with one vaccine HPV type were protected against the other vaccine type, if DNA-negative for that type.
HIGHLY EFFECTIVE RISK STRATIFICATION BY HUMAN PAPILLOMAVIRUS TESTING IN WOMEN WITH ABNORMAL CERVICAL CYTOLOGY; 17.5 YEARS PROSPECTIVE COHORT STORY

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Aims: To evaluate the long-term cumulative incidence of cervical intraepithelial neoplasia grade 3 or carcinoma (CIN3+) following an abnormal cytological result (mild to moderate and severe dyskaryosis) and determine the additional value of human papillomavirus (HPV) testing.

Methods: 353 women with abnormal cytology referred to a Dutch gynaecological outpatient clinic between 1990 and 1992 were followed until December 2009 for CIN3+.

Results: The median follow-up was 17.6 years. During follow-up 31.4% (111/353) developed CIN3+. Women with mild to moderate dyskaryosis had a risk for CIN3+ of 26.6% (79/297) and women with severe dyskaryosis of 57.1% (32/56). The vast majority (107/111, 96.4%) of CIN3+ lesions were detected within 5 years of the first abnormal smear, hereafter their risk is similar to the general population (1.8%). Among women with mild to moderate dyskaryosis, HPV-testing at baseline discriminated significantly for CIN3+. A negative HPV-test decreased the risk to 2.6% (3/114) whereas the risk increased to 41.5% (97/183) if a positive test result was detected (RR 15.78, 5.10 to 48.84). In women with severe dyskaryosis HPV testing at baseline did not have clinical benefits (RR 3.04, 0.52 to 17.79).

Conclusions: Women with abnormal cytology have an increased risk to develop CIN3+ for the first 5 years after detection. Hereafter their risk is similar to women in the general population. For women with mild to moderate dyskaryosis an additional HPV-test at baseline is very distinctive to identify women at risk for CIN3+, whereas women with severe dyskaryosis should always be referred for colposcopy.
EFFICACY OF GARDASIL® IN WOMEN AGED 16 TO 26 WHO HAVE UNDERGONE DEFINITIVE CERVICAL THERAPY

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Background and aims: Prophylactic HPV vaccination is highly efficacious in preventing pre-cancerous lesions and genital warts (GWs). It is not known if women with a history of cervical, vulvar, or vaginal pre-cancers (CIN, VIN, VaIN) or GWs will benefit from vaccination. We report results in women who underwent definitive cervical therapy during two randomized phase 3 clinical trials of GARDASIL.

Methods: A total of 17,622 women aged 16 to 26 were enrolled. Gardasil or placebo was given at Day 1, Month 2 and 6. Pap testing was performed at Day 1 and every 6 to 12 months. Definitive therapy referral was per standard of care. An intention-to-treat analysis was performed in women who underwent excisional therapy for CIN, VIN, VaIN or GWs. Case counting began after the definitive cervical therapy.

Results: Within an average of 3.6 years, 587 vaccine recipients and 763 placebo recipients underwent definitive cervical therapy. Vaccine efficacy for any CIN1 or worse post-definitive therapy was 47% (95%CI: 17, 66). Efficacy for CIN1 or worse associated with HPV6/11/16/18 was 74% (95%CI: 25, 97). In the same period, 229 vaccine recipients and 475 placebo recipients had a pathology panel diagnosis of VIN1-3, VaIN1-3 or GWs. Vaccine efficacy for these endpoints post-diagnosis was 23% (95%CI: -12, 48) and for HPV6/11/16/18-related endpoints was 59% (95% CI: 24, 79).

Conclusions: Our data suggest that women who have undergone cervical conization or treatment for VIN, VaIN or GW will benefit from HPV vaccination through prevention of recurring disease.
CONFORMAL TECHNIQUES LEAD TO A HIGH COMPLETION RATE OF EXTERNAL BEAM RADIATION FOR CERVIX CARCINOMA IN A DEVELOPING WORLD SETTING

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Introduction: Access to good quality oncology care in Africa is beset by many challenges. To improve outcomes for cervix carcinoma patients referred for radical treatment at a public hospital in South Africa, CT-planned conformal external beam radiotherapy (EBRT) was instituted on an 18 megavoltage (MV) linear accelerator. This technique allows shielding of organs at risk with a multi-leaf collimator and skin sparing with the use of high energy, with a presumed reduction in toxicity.

Objectives: Primary end point

• determine the percentage of patients completing a minimum of 45Gy EBRT

Secondary end point

• overall treatment time.

Methods: A retrospective analysis was made of all Stage Ib-IIib patients referred to radiation oncology from June 2007 to December 2009. Patient demographics, stage, and investigations were recorded. Treatment parameters were noted. Descriptive statistics were used.

Results: Of the initial 339 patients referred, 26 patients (7.7%) did not attend. 32 patients (10.2%) were treated with palliative intent. 282 patients were treated with radical intent. 241 patients (85.4%) completed a minimum of 45 Gy EBRT and 18Gy HDR brachytherapy. 20 patients (7.1%) completed a minimum of 45Gy and an EBRT boost. 6 patients completed EBRT only. In total 267 patients (94.6%) completed the intended minimum dose of EBRT. Average overall treatment time was 41 days (range 35-77).

Conclusion: With the use of conformal planning and high energy MV, a very high percentage of cervix carcinoma patients completed EBRT. The overall treatment time was equivalent to international standards. Impact on survival will be follow up in this cohort.
DUTCH ALGORITHM FOR FOLLOW-UP AFTER TREATMENT FOR CERVICAL INTRAEPITHELIAL NEOPLASIA; EFFECTIVE TO PREDICT RECURRENCES UP TO 7.5 YEARS AFTER TREATMENT


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Background and aims: In the Netherlands women treated for high-grade cervical intraepithelial neoplasia (CIN) are monitored for recurrence (rCIN) using cytology. After three subsequent negative smears women return to the population-based screening program. We evaluate this policy and describe the long-term cumulative incidence of rCIN3+.

Methods: In three hospitals 440 women with CIN2/3 were treated between 1988 and 2004. They were monitored by cytological screening until the study cut-off point in December 2009.

Results: The median follow-up was 7.5 years. During follow-up 39/440 (8.9%) developed rCIN3+ of whom 26 within 2 years of treatment (Figure 1). To predict rCIN3+ after the first two years, women with three consecutive negative smears had a significantly lower risk to develop CIN3+ after the first two years of follow-up than those who did not have three negative smears (1/257, 0.4% versus 12/157, 7.6%; p< 0.001, Figure 2).

Conclusions: Women treated for CIN2/3 in the Netherlands have a risk of only 9.9% to develop rCIN3+. Women with three consecutive negative smears within 2 years should be referred to the 5-yearly population-based screening program as their risk for rCIN3+ is lower than the risk in the general population.
LIPOSOMAL DOXORUBICIN (LD) AND CARBOPLATIN (CP) IN PRIMARY ADVANCED OR RECURRENT ENDOMETRIAL CANCER - A PHASE-II-TRIAL OF AGO AUSTRIA

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Introduction: Endometrial carcinoma with recurrence or advanced stage at diagnosis carries a poor prognosis. Chemotherapy is used more frequently, consisting of cisplatin/doxorubicin/paclitaxel, if tolerated, or the doublet of carboplatin/paclitaxel. These are the results of the first 23 patients from an ongoing trial of LD and CP in patients with primary advanced or relapsed endometrial cancer. Primary endpoint is RR (response rate).

Methods: 39 patients will be recruited in this trial. All patients should receive 60mg/m2 LD and CP AUC 5 for 6-9 cycles or until progression. A first analysis was planned after 23 patients to ascertain activity of the regimen. Activity was defined to be present if ≥7 responses occur.

Results: At baseline, 11 (48%) patients had stage I tumor, 1 (4%) stage II, 6 (26%) with stage III and 5 (22%) patients with stage IV. 5 (22%) tumors with grade I, 11 (48%) grade II and 6 (26%) grade III tumors were diagnosed. Of the first 23 patients 7 (30%) had primary advanced, 16 patients (70%) recurrent disease. Tumors were found to be adenocarcinomas in 18 (79%), serous papillary carcinomas in 3 (13%) cases, clearcell- and mixed mullerian carcinomas in 1 (4%) case each.

RR was defined as best response during therapy. Of the first 23 patients, we observed no complete response, but partial response in 11 (48%) patients.

Discussion: After stage I of this trial, due to a RR of 48% the protocol is considered to be active and the trial will be continued.
MULTIMODALITY TREATMENT WITH CARBOPLATIN AND TAXOL IMPROVES SURVIVAL IN ADVANCED STAGE UTERINE SEROUS CARCINOMA

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Objective: To evaluate the clinical and treatment characteristics affecting survival in patients with advanced stage uterine serous carcinoma (UPSC).

Methods: All patients with Stage III-IV UPSC diagnosed 1/95-12/08 at a tertiary referral center were retrospectively identified. Patients underwent either neoadjuvant chemotherapy or primary surgical cytoreduction. Adjuvant treatment included platinum-based chemotherapy and/or pelvic, vaginal, or whole abdominal radiation. Kaplan-Meier and Cox regression analyses were performed.

Results: Seventy-three UPSC patients met criteria with a mean age of 68.7 years. Median follow-up was 23.3 months with 67.1% optimally debulked. Four patients received neoadjuvant chemotherapy, 27 postoperative chemotherapy, 20 sequential chemoradiation, 6 radiation only (2 whole abdominal), and 16 no further treatment. Sequential chemoradiation was associated with a superior progression free (33.9 months vs 11.7 and 17.3 months, p< 0.01) and overall survival (37.3 months vs 17.7 and 33.1 months, p< 0.01) compared to chemotherapy or radiation alone. In those optimally debulked, adjuvant carboplatin and taxol led to an improved overall survival (37.3 vs 23.3 months, p=0.04), and the combination of carboplatin and taxol was associated with a better overall (27.3 vs 13.6 months, p=0.03) but not progression free survival (16.9 vs 8.8 months, p=0.07) when compared to other platinum-based regimens. On multivariate analysis, only the utilization of carboplatin and taxol and postoperative radiation independently predicted survival outcome.

Conclusion: Adjuvant chemoradiation, particularly with carboplatin and taxol, allows for the most favorable outcome in advanced stage UPSC. However, given the poor prognosis in these patients, newer synergistic treatment modalities still need to be investigated.
MICROARRAY ANALYSIS OF THE GENES INVOLVED IN ENDOMETRIAL CARCINOGENESIS: UP-REGULATION OF LIPOCALIN2 IN NEOPLASTIC ENDOMETRIA, AND ITS FUNCTIONAL RELEVANCE

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Background: Endometrial carcinoma often arises from normal endometrial glandular cells via a precursor, atypical endometrial hyperplasia. However, the genetic changes involved in this carcinogenetic process are not fully understood.

Methods: Differentially expressed genes were selected from glandular cells of normal proliferative phase endometria, endometrial hyperplasia and endometrial carcinoma using laser-captured microdissection (LCM) and microarray.

Results: The microarray analysis revealed a total of 51 genes to be up-regulated, and 23 genes to be down-regulated in neoplastic endometrial epithelia. We focused on lipocalin2 (LCN2), which showed the largest magnitude of up-regulation. Immunostaining for lipocalin2 confirmed a stepwise increase in its expression in endometrial hyperplasia and carcinoma. The subcellular distribution of lipocalin2 was both cytoplasmic and nuclear, despite reports that lipocalin2 is a secretory protein. Treatment of endometrial carcinoma cells with 5-azacytidine increased the expression of lipocalin2, suggesting the expression to be controlled by methylation of the promoter. The forced expression of lipocalin2 resulted in the enhanced cell proliferation and invasion in vitro.

Conclusions: The expression of lipocalin2 increased with the endometrial carcinogenesis, and accumulation of the protein conferred biological aggressiveness to endometrial carcinoma cells. These results suggest lipocalin2 to be a novel target in the treatment of endometrial carcinoma.
MULTICELLULAR SPHEROIDS OF EPITHELIAL ENDOMETRIAL CANCER: CHARACTERISATION AND APPLICATION FOR ANTI-CANCER DRUG SCREENING

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Multicellular spheroids of cancer cells generated in vitro are considered to resemble the physiological origin of tumours. Hence spheroids may provide substantial advantages for study over traditional monolayer cell culture on plastic, cell architecture and heterogeneity of cell population may be more useful.

**Aim:** We are characterising and utilising multicellular spheroids of epithelial endometrial cancer cells and investigating the effects of chemotherapeutic agents.

**Methods:** First, endometrial cancer cell lines (Ishikawa, RL95-2, KLE and EN-1078D) were cultured within 3D matrigel. Second, cancer cell lines were cultured on a non-adhesive surface to form “microtumours”. Third, monolayer cultures were performed. Cell growth, proliferation and metabolism and protein expression, and production of vascular endothelial growth factor (VEGF) were determined. The inhibitory effects of conventional and targeted chemotherapeutic agents, including doxorubicin, cisplatin, paclitaxel, tyrphostin AG1478, LY294002 and natural compound EGCG, were investigated.

**Results:** Following 8 days of culture in 3D matrigel, the well differentiated cell line (Ishikawa) formed central lumen with well defined apical and basal regions. β4-integrin was located at the basal region of Ishikawa cells whereas β4-integrin was diffusely stained in RL95-2, KLE and EN-1078D cells. Proliferation of cells in 3D matrigel was less than for cells grown in a monolayer. The level of VEGF production was dramatically reduced in 3D matrigel. Chemotherapeutic agents had substantially less effect on microtumours.

**Conclusion:** Our findings suggest that multicellular spheroids (“microtumours”) of endometrial cancer cells may offer great potential for investigating novel pathways which regulate drug resistance resembling in vivo tumours.
PROGNOSTIC INDICATORS IN ENDOMETRIAL STROMAL SARCOMAS AND UNDIFFERENTIATED ENDOMETRIAL SARCOMAS

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Background: Endometrial stromal sarcomas (ESS) have been traditionally divided into low/high grade but the World Health Organization (WHO2003) has changed the definition. Since 2003, many studies still used the old criteria and few focused on WHO2003-defined ESS low grade (ESS-LG) and undifferentiated endometrial sarcomas (UES).

Patients and methods: We reviewed in 91 tumors (previously classified as ESS low and high grade) the diagnostic WHO2003 criteria, CD10 positivity and JAZF1/JAZZ fluorescence in situ hybridisation. In the ESS-LGs, the prognostic value of clinicopathological features were studied.

Results: There were 68 ESS-LGs and 23 UES with median follow-up of 79 (range: 20-474) and 36 (5-329) months. The recurrence and death rates were 5/68 (7%) and 1/68 (1.5%) in the ESS-LG and in the UES patients 13/23 (57%) and 12/23 (52%) (P< 0.0001, Hazard Ratio=HR=10.5 for recurrence; P < 0.0001, HR=45.3 for death). In the ESS-LG, ovary saving surgery-or-not (P< 0.0001, HR=10.4) and MAI (0-3 versus >3, P=0.005, HR=8.6) had independent prognostic value. Other frequently used MAI thresholds, age, stage, tumor diameter and vessel invasion were not prognostic. In patients without ovary-saving operation (n=61), 0/53 with MAI 0-3 recurred, contrasting 2/8 (25%) with MAI>3 (P=0.003) and 1 of these 2 recurrence patients died (P=0.02). In patients with ovary saving (n=7), 3 (43%) recurred but none died and MAI had no additional prognostic value.

Conclusion: The WHO-2003 criteria for ESS-LG and UES are prognostically strong. In ESS-low grade, ovary-saving operation and mitotic activity >3 are associated with increased recurrence risk.
EARLY-ONSET ENDOMETRIAL CANCER IN METROPOLITAN DETROIT, MICHIGAN: A 20 YEAR REVIEW

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Background: Endometrial cancer, the most commonly diagnosed female cancer in the US, is primarily diagnosed in postmenopausal women; however, age at diagnosis is an important biological variable as it often impacts treatment.

Methods: Endometrial cancer cases were identified from the Metropolitan Detroit Cancer Surveillance System, between 1988 and 2007. Differences in tumor characteristics, treatment and survival were examined by age at diagnosis. Chi-square tests were used to assess differences in distribution of clinical and demographic variables. Cox proportional hazards models were used to assess the risk of death.

Results: 6,034 women diagnosed with endometrial cancer during this period, including 202 ages 20-39, 628 ages 40-49, and 5204 age 50+. 30% of women under the age of 40 were African American (AA), higher than expected given that 25% of the population in metro-Detroit is AA. Among young (< 40 yrs) AA women, 50% of the tumors were of non-endometrioid histology. Young women are more likely to present with stage I tumors, compared to patients ages 40-49 (p-value=0.01). 18% of young women did not receive surgery, compared to 7% of women ages 40-49 (p-value< 0.0001) and 12% of women over 50 (p-value=0.01). AA race is a negative predictor of survival for all patients, but particularly for those under 40 (HR=4.22, 95% CI: 1.87-9.52) compared to their white counterparts, after adjusting for other prognostic factors.

Conclusions: Race is an independent predictor of poor prognosis, particularly among young women. These results highlight the importance of examining early-onset endometrial cancer in multi-ethnic populations.
INTRAOPERATIVE ASSESSMENT OF MYOMETRIAL INVASION AND HISTOLOGICAL GRADE IN ENDOMETRIAL CANCER USING REVISED FIGO STAGING SYSTEM

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Objectives: The objective of this study is to assess the value of intraoperative frozen-section diagnosis for myometrial invasion and histological grade in endometrial cancer using the revised FIGO staging system.

Methods: The records of 303 patients of endometrial cancer who underwent surgery with intraoperative diagnosis at the Osaka University Hospital between January 1999 and December 2008 were reviewed. Intraoperative frozen-section diagnosis was retrospectively analyzed for the accuracy rates of myometrial invasion and histological grade compared with preoperative prediction by MRI and endometrial curettage.

Results: When using the previous FIGO staging system, the accuracy rate of intraoperative frozen section for the diagnosis of myometrial invasion was 77%, while the accuracy rate of preoperative prediction by MRI was 54%. However, for myometrial invasion, using the revised FIGO staging system, the accuracy rate of frozen section was 87% and preoperative prediction by MRI was 82% respectively. The accuracy rate of intraoperative frozen section for the diagnosis of histological grade was 71%, whereas the accuracy rate of preoperative prediction by endometrial biopsy was 68% respectively.

Conclusion: Although intraoperative frozen-section diagnosis is more accurate than preoperative prediction by MRI in the previous FIGO staging system. There is no significant difference between value of intraoperative diagnosis and preoperative diagnosis in the revised FIGO staging system. The accuracy of intraoperative frozen-section, however, trend to better than preoperative procedure by MRI and endometrial biopsy. Thus intraoperative frozen-section diagnosis is useful for directing primary operative management.
MORBIDITY AND MORTALITY OF THE SURGICAL TREATMENT OF THE OLDEST OLD WOMEN WITH ENDOMETRIAL CANCER

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Objective: Despite the fact the endometrial cancer commonly occurs in elderly women, little is known about the perioperative outcomes of women > 80 years of age treated surgically.

Methods: An analysis of women > 65 years of age with endometrial cancer who underwent hysterectomy with or without lymphadenectomy between 1998-2007 and registered in the Nationwide Inpatient Sample was performed. Patients were stratified by age: 65-69, 70-74, 75-79, 80-84, and ≥ 85 years of age. Multivariable logistic regression models were constructed to examine morbidity and mortality based on age while adjusting for confounding variables.

Results: A total of 25,698 women including 3789 aged 80-84 and 2024 ≥ 85 years of age were identified. Compared to women 65-69 years of age, those ≥ 85 were more likely to have perioperative surgical complications (12% vs. 17%) (adjusted OR=1.53; 95% CI, 1.34-1.76), postoperative medical complications (24% vs. 34%) (adjusted OR=1.69; 95% CI, 1.52-1.89), require a transfusion (6% vs. 10%) (adjusted OR=1.86; 95% CI, 1.55-2.24) and have a longer length of stay (3.8 days vs. 5.0 days) (adjusted OR=1.66; 95% CI, 1.44-1.88). Perioperative mortality was 0.4% in women 65-69 years of age compared to 1.6% in those ≥ 85 (p< 0.0001). Adjusting for other prognostic variables, women ≥ 85 were more than three and a half times more likely to die during hospitalization (OR=3.64; 95% CI, 2.23-5.99).

Conclusion: The complication rate associated with the surgical treatment of endometrial cancer is significantly higher in women > 80 years of age even after accounting for medical comorbidities.
EVALUATION OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED CERVICAL CANCER AND ANALYSIS OF RISK FACTORS

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Sichuan University, Chengdu, China

Objective: Neoadjuvant chemotherapy (NACT) is becoming the therapeutic trend for young cervical cancer patients. In order to evaluate the short-term effect of NACT in locally advanced cervical cancer (LACC), to study the effect of NACT on risk factors of postoperative recurrence, this paper sums up clinical, pathological and follow-up data of patients with LACC in West China second hospital during past two years.

Method: From 2008 to 2009, 414 patients with FIGO stage IB2-IIA (tumor > 4 cm) were assigned to receive either NACT followed by surgery or radical surgery directly.

Results: Patients had poorer situation in NACT+Surgery group than in Surgery group like Anemia (36.1% vs 15.6%, P=0.00) and local lesion (5.5±0.91cm vs 4.9±0.58cm, P=0.00) before therapy. The overall clinical response rate was 89.6%. The effective rates of squamous cell carcinoma and adenocarcinoma were 89.4% and 83.3% respectively. The clinical response was only associated with FIGO stage (P=0.04). The rate of positive pelvic lymph nodes metastasis (25.4% vs 47.6%, P=0.03) and deep stromal invasion > 1/2 (68.0% vs 90.5%, P=0.03) in complete and partial response patients was lower than that in stable response ones. Besides, 78.5% of effective patients underwent additional therapy, while 95.2% of ineffective patients did (P < 0.05). Two-year disease-free rate and two-year survival rate in NACT+Surgery group were 95.4% and 96.0%, in Surgery group were 96.9% and 96.2% (P>0.05).

Conclusion: NACT has a satisfactory effect on LACC. The clinical response is only related to FIGO stage. NACT can decrease risk factors of the effective patients, so these patients have less opportunity for postoperative supplementary therapies.
THE ROLE OF D2-40 (PODOPLANIN) AS A MARKER FOR LYMPH VESSEL INVASION IN PRIMARY ENDOMETRIAL CANCER

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Background: Lymph node metastasis (LN+) plays a key role in the spread of endometrial cancer and predicts prognosis. Tumors confined to the uterus show LN+ in up to 30%. The evaluation of lymph vessel invasion (LVI) as marker for LN+ is of great importance. D2-40, a monoclonal antibody might be able to increase the detection rate of LVI compared to conventional Haematoxylin-Eosin (H.E.) staining. The aim of this study was to evaluate the eligibility of D2-40 for prediction of LN+.

Methods: Immunohistochemical staining with D2-40 was performed on paraffin-embedded tumors of 182 patients with endometrioid adenocarcinoma. Slides were screened for the presence of LVI. Correlation with clinico-pathological features was assessed. Treatment modalities and patients follow-up were available.

Results: Immunostaining with D2-40 significantly (p=0.001) increases LVI detection compared to conventional H.E. staining. LVI was identified by D2-40 (D2-40-LVI+) in 53/182 (29.1%) of tumor specimen as compared to 34/182 (18.3%) by H.E. (H.E.+LVI). D2-40-LVI+ was detectable in 90% of the nodal positive tumors and (p=0.001) predicted significantly LN+. Furthermore, D2-40 was the only independent prognostic factor for patients overall survival (p< 0.01) considering tumor stage, LN+, H.E.-LVI and tumor differentiation.

Conclusion: Our study demonstrated the superiority of D2-40 staining for LVI in endometrial cancer. D2-40-LVI+ was a strong predictor for LN+ and prognostic relevant parameter. Further studies on large patient groups are required to evaluate the clinical role of D2-40-LVI+ in endometrial cancer. These studies have to be focused on patients in which lymph node dissection could be omitted without worsening outcome.
THE EVOLUTION OF TREATMENT FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN): THE FIRST FIVE DECADES AT THE JOHN I BREWER TROPHOBLASTIC DISEASE CENTER

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Background and rationale: The Brewer Trophoblastic Disease Center of Northwestern University was established in 1962 and has treated over 850 women with GTN during the last five decades. The goal of this retrospective study is to chronicle the evolution of chemotherapy for low-risk and high-risk GTN, as well as placental site trophoblastic tumor. During this time, the chemotherapy and bone marrow support options have evolved significantly. The outcomes for high-risk disease and PSTT are correlated with this evolution of chemotherapy options.

Methods: This is a retrospective review of previously published results from the Brewer Trophoblastic Disease Center between 1962 and 2008. These results are qualitatively aligned with the introduction of new chemotherapy regimens to document the evolution of primary and salvage therapy for GTN.

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The overall complete response rate to the initial chemotherapy regimen given at the Brewer Center was 77%; 92% for sequential single-agent chemotherapy for nonmetastatic and low-risk metastatic disease (78% for primary methotrexate and 73% for secondary actinomycin D) and 82% for sequential multiagent chemotherapy for high-risk metastatic disease (67% for primary MAC or EMA-CO and 44% for secondary platinum-based regimens). The overall survival rate was 94%: 87% from 1962-1978 and 98% from 1979-2008. All patients treated for low-risk disease since 1962 were cured, however, the cure rate for patients with high-risk disease increased from 78% during 1962-1978 to 92% during 1979-2008.
THERAPEUTIC IMPACT OF PARA-AORTIC LYMPHADENECTOMY IN PATIENTS WITH HIGH-RISK, EARLY STAGE AND ADVANCED STAGE ENDOMETRIAL CARCINOMA

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Background: Recently, two prospective randomized trials on pelvic lymphadenectomy failed to show any therapeutic benefit for pelvic lymphadenectomy in endometrial cancer. However, they did not clarify whether complete, systematic lymphadenectomy, including the para-aortic lymph nodes, should be part of surgical therapy for high-risk patients.

Methods: A comparative cohort study with 815 patients was conducted at two tertiary centers to clarify the survival effect of para-aortic lymphadenectomy in endometrial carcinoma between January 1984 and June 2004. Surgery at one institute included both pelvic lymphadenectomy (PLX) and para-aortic lymphadenectomy (PALX), while at the other PLX alone was routinely performed. We selected 215 patients with high-risk, early stage and advanced stage endometrial carcinoma. A total of 125 patients underwent PLX+PALX and 90 patients underwent PLX alone. Patients included in the study were recommended to receive adjuvant therapy either with radiotherapy or chemotherapy.

Results: The survival rate in the PLX+PALX group was significantly better than that in the PLX alone group for patients who had adjuvant therapy (p=0.0006). Multivariate analysis confirmed that Age, histology, lymph node metastasis, type of lymphadenectomy, and type of adjuvant therapy were independent prognostic factors.

Conclusion: PALX and chemotherapy improved the survival of patients with high-risk, early stage and advanced stage endometrial carcinoma. A randomized trial aiming to validate the therapeutic effect of lymphadenectomy in endometrial cancer should include PALX and focus on patients with high-risk, early stage and advanced stage endometrial carcinoma.
NEOADJUVANT CHEMOTHERAPY PRIOR TO PELVIC EXENTERATION IN PATIENTS WITH RECURRENT OR ADVANCED CERVICAL CANCER


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Background and aims: The aim of this study is to determine the impact of neoadjuvant chemotherapy on the outcomes of patients with recurrent or advanced cervical cancer candidates to a pelvic exenteration procedure who had either bulky tumours (>5cm in diameter) or a pelvic wall fixation.

Methods: Retrospective: review of all patients charts with gynecological cancer candidates to a pelvic exenteration who received neoadjuvant chemotherapy (Platinum-based) from 1997 to 2009 at cancer referral center.

Results: A total of 44 patients received neoadjuvant chemotherapy and underwent pelvic exenteration. Among them we analyzed the clinical, the surgical outcomes, and pathological response of 32 patients (73%) with cervical cancer. Reduction in tumor size after neoadjuvant chemotherapy was achieved in 21 patients (65%), whereas in 11 patients (35%) displayed either stable disease or an increase in tumor size. Total pelvic exenteration was performed in 18 patients (56%), anterior and posterior in 13 (41%) and 1 patient (3%) respectively. Four patients (13%) underwent IORT. Pathological findings confirmed the clinical results with one complete pathological response among the responders. Margins of resection were positive in 12 patients (36%). After a median of follow up of 25,5 months (range 3-145) thirteen patients are NED, one is AWD and eighteen are DOD.

Conclusions: Neoadjuvant chemotherapy can be very useful in the treatment of advanced or in the recidive of cervical cancer that require a pelvic exenteration even in that cases with pelvic wall involvement. A tumor size reduction can be achieved making the procedure feasible in more selected cases.
TEACHING CERVICAL CANCER SURGERY IN LOW OR MIDDLE RESOURCE COUNTRIES

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Background: There is a 30% rise in stage 1 cervical cancers, when a country adopts a once in a life time cervical screening strategy. That country's cancer system needs to have the ability to provide either radical surgery or radiation for this potentially curable group of women.

Methods: The GOC undertook to develop a teaching module to intensively train a small number of locally identified gynaecologists to perform radical hysterectomy and pelvic lymphadenectomy. The process was based on adult learning principles, mutual respect with a Canadian gynaecologic oncologist working in the low or middle resource country with the gynaecologists and problem solving local issues in health care delivery.

Results: The teaching process included a pre and post test based on the objectives in the module. There were 7 modules including preoperative evaluation of the patient, cone biopsy, radical hysterectomy, pelvic lymphadenectomy, ureteric injury, vascular injury and followup after surgery. Each module was divided into background information, techniques and complications. There were video clips imbedded in the modules. After the educational modules had been reviewed, the learners were walked through the surgical procedures repeatedly with a detailed assessment of performance after each case. Participants had the opportunity to provide feedback on the training program.

Conclusion: In low and middle resource countries where there is an urgent need to provide a curative surgical option for the management of early cervical cancers, a focused high intensity curriculum delivered by a trained surgeon can translate in to immediate change in clinical and surgical practice.
DOES PRE-OPERATIVE PET-CT REDUCE THE RATE OF POST-OPERATIVE RADIOTHERAPY IN PATIENTS WITH EARLY CERVICAL CANCER TREATED BY PRIMARY SURGERY?

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Objective: To study whether patients with early cervical cancer who undergo PET-CT prior to surgery are less likely to receive post operative radiotherapy.

Methods: A multicenter study of 471 patients with stage IA2- IIA cervical cancer, who underwent primary radical hysterectomy and pelvic lymphadenectomy. One hundred and twenty one who underwent a pre-operative PET-CT were compared with the control group of 350 patients with regard to histological characteristics and postoperative radiotherapy (or chemoradiation).

Results: The Control and PET group had comparable tumor diameter (27.5±13.6 vs. 25.4± 14.3, p=0.86; respectively), depth of invasion (10.9±7.5 vs. 9.5±5.2, p=0.15; respectively), rate of lymphvascular space involvement, (32% vs. 34%, p=0.67; respectively), rate of involved surgical margins (10% vs. 5%, p=0.17; respectively), and rate of parametrial involvement (12% vs. 8%, p=0.30; respectively). There was no significant difference between the control and PET groups with regard to the number of nodes extracted (24.4±19.9 vs. 22.4 ±12.6, p=0.25; respectively), the rate of involved nodes (21% vs. 19%, p=0.75; respectively), and the rate of post operative radiotherapy (or chemoradiation) (50% vs. 49%, p=0.90; respectively).

Conclusions: Preoperative PET CT studies are not associated with a smaller proportion of patients with involved lymph nodes or the rate of postoperative radiotherapy (or chemoradiation).
THE NERVE SPARING RADICAL HYSTERECTOMY (NSRH) FOR CERVICAL CANCER (CC): UPDATE OVER 246 PATIENTS EVALUATED

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Objectives: To present the NSRH, feasibility, results, and survival.

Methods: 246 pts. stages Ib-Ilb CC underwent NSRH between 5/02 and 11/09. Stages Ib2-Ilb received neoadjuvant chemotherapy. The first 73 pts (2/02-10/05) underwent standardized questionnaire and urodynamic evaluation before and after surgery. The other 173 pts.(11/05-11/09) answered only the questionnaire. Surgical technique: 1- dissection of the hypogastric nerve in the sacrouterine ligament. 2- Dissection of the inferior hypogastric plexus in the lateral parametrium. 3- Mobilization in the vesicouterine ligament followed by anterior ligament transection. 4- Transection of the ligaments. Results of the first 73 pts.were compared to a consecutive previous historical control group (n=72) with non NSRH.

Results: NSRH was performed in all 246 cases. In the first 73 NSRH pts., 5/73 (6.8%) had urological-urodynamic disorders (grades 1&2) vs. 26.3% (19/72) in the control group (n=72) (p<0.003). Hydronephrosis evaluation: 1/73 (1.3%) in the NSRH group vs. 15/72 (20.8%) in the control, p<0.001. In the NSRH group no differences were found between pre and postsurgical urodynamic evaluation. One case of constipation. No differences were found in the surgical specimens between NSRH vs. non NSRH group (pNS). One late urethral fistula was observed in the last 173 NSRH pts. (1/173-0.57%). Three patients died (3/246 -1.21 %) by intercurrent disease, and 6/246 (2.43%) by CC. Recurrences: Local: 7/246 (2.85%); Distant & local: 3/246 (1.21%), in the NSRH group. DFS: 95.8%. O.S: 96.4%. Follow up: 6-90 months.

Conclusions: The NSRH had low complications and morbidity, without modifying radicality and survival rates.
TREATMENT-TRENDS IN LOCALLY ADVANCED CERVICAL CANCER CARE BETWEEN 2000 AND 2007 IN THE SOUTH OF THE NETHERLANDS

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Background: Based on randomized trials, either chemoradiation (CRT) or radiotherapy with hyperthermia (RHT) has become the standard of care for locally advanced cervical cancer (LACC) in the new millennium. This study analyzed the implementation of CRT and RHT in cervical cancer care in the South of the Netherlands.


Results: The use of surgery (with or without adjuvant therapy), radiotherapy (RT), CRT and RHT changed significantly over time (cohort 2000-2003: 9(13.3%), 7(11.2%), 5(7.9%) and 42(66.7%) versus 2004-2007: 5(9.6%), 4(7.7%), 23(44.2%) and 20(38.5%) (Figure 1). No survival difference was found between the two cohorts (5-year overall survival: 58.1% versus 46.9% (p=.098)). 5-year overall survival of the total group (2000-2007) was 68.8% for surgery (with or without adjuvant therapy), 27.3% for RT, 42.6% for CRT and 58.8% for RHT. However, treatment groups differed significantly by age, co-morbidity and performance status. RT alone was mainly reserved for patients with old age, poor performance and/or co-morbidity. In a multivariate survival analysis, lymph node-involvement, age ≥70 years and WHO-performance ≥1 were independent prognostic factors (hazard ratio(95%Cl): 2.6(1.1-4.0), 2.9(1.2-7.0) and 3.4(1.7-6.7)) in addition to FIGO-stage and treatment.

Conclusions: The implementation of CRT did not result in an improvement of survival. This is most likely because RHT was widely used already since 2000 and both modalities are considered equally effective.

[Figure 1: Treatment-trends in LACC care]
CYTOREDUCTIVE SURGERY FOR RECURRENT OVARIAN CANCER. SINGLE CENTER EXPERIENCES WITH THE APPLICATION OF THE AGO SCORE TO PREDICT COMPLETE RESECTION


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Background: The role of surgery for recurrent ovarian cancer is still unclear. Complete resection is reported as major prognostic factor. We report our experiences before and after introduction of the AGO score to select suitable patients for SCS.

Methods: Descriptive analysis of surgery for recurrent ovarian cancer at our institution between 1999 and 2009. Evaluation of the clinical impact of the AGO score (complete resection at 1st surgery, good performance status and absence of ascites) which was introduced in 2005 (comparison of the interval 1999-2004 vs 2005-2009).

Results: Between 1999 and 2009 (163) patients had secondary cytoreductive surgery (SCS). The rate of complete resection was 76%. The median survival for the entire cohort after recurrence was 48,4 months. Median OS for pts with complete resection was 54,6 months compared to 30,6 months in patients with residual disease. The number of patients with SCS increased from 75 to 88 in the second study period. The rate of complete resection increased from 66,6% to 84% after introduction of the AGO score. Overall survival for all patients with SCS improved from 38,5 months to 55 months.

The mortality within 60 days after surgery was 0.8%, The rate of re-laparotomies was 6,1%.

Conclusions: Complete cytoreduction is feasible for the majority of selected patients with recurrent epithelial ovarian cancer with low rates of mortality and morbidity and show promising survival rates in case of complete resection. The application of the DESKTOP-criteria (AGO score) enhances the results of SCS in daily clinical routine.
QUALITY OF SURGERY IN ADVANCED OVARIAN CANCER: VALIDATION OF THE EORTC-GCG QUALITY INDICATORS

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Background: Quality of surgery is an important determinant of outcome for advanced-stage ovarian cancer. Maximum diameter of residual disease is adversely associated with survival and surgery has no curative effect if end result of surgery is suboptimal. Hence, evaluation of disease at the start of surgery is important to determine surgical strategy in order to optimize the chance for survival but avoid unnecessary morbidity. The quality of surgery performed in the EORTC55971/NCIC-CTGOV13 study was assessed following these principles.

Methods: Completeness of disease assessment at start of surgery (DAS) was scored per assessed item. Adequate surgery was defined as removal of all macroscopic tumour or diagnostic and symptomatic intervention only. Inadequate surgery was defined as extensive surgery not resulting in complete debulking. Correlation between DAS-score and adequacy of surgery was tested using logistic regression and Cox PH modelling for progression-free survival (PFS).

Results: 434 surgery reports from primary or interval debulking were assessed. In 147 patients all macroscopic tumour was removed; 81 patients underwent diagnostic or symptomatic intervention only. 206 patients underwent inadequate surgery. Completeness of DAS is positively related with adequacy of surgery (p=0.0019). Extensive surgery does not significantly influence PFS for incompletely debulked tumours (p=0.618). Centres with a higher average DAS-score have higher complete debulking rates and better PFS (p=0.0042).

Conclusion: Complete DAS is important to determine surgical strategy. If no complete debulking is expected, surgical morbidity can be minimized without compromising PFS. Centres that perform more complete DAS have higher complete debulking rates and better PFS.
PSYCHO-ONCOLOGY: STRUCTURE AND PROFILES OF EUROPEAN CENTERS TREATING PATIENTS WITH GYNECOLOGICAL CANCER

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Aim: Psycho-oncological counseling, should be an integrated part of modern cancer therapy. The aim of this study was to assess the structures and interests in psycho-oncology services within ESGO (European Society of Gynecological Oncology) accredited centers.

Methods: In 2010 a survey which consisted of 15 questions regarding organisation of psycho-oncological services and interests in training and research, was sent to all ESGO accredited centers (n=41).

Results: The response rate was 51%. 95% of the surveys came from universities and 5% from non-academic institutions. Most of the institutions (95,5%) offer psycho-oncological care, mainly by psychologists (78%) or psycho-oncologists (38%). Approximately 60% of patients are evaluated for sexual dysfunction as sequelae of the disease or treatment related side-effects. 50% of institutions offer psychological support for cancer care providers. 82% of all centers are interested in psycho-oncological training and the preferred teaching tools are educational workshops. Main issues of interest are sexual problems in cancer patients, communication and interpersonal skills, responses of patients and their families, anxiety and adjustment disorders and palliative care. Eighty eight percent of all institutions look for research in the field of psycho-oncology and 59% are already involved in some kind of research.

Conclusion: Although psychoncological care is provided in the vast majority of consulted ESGO accredited centers, 40% of women lack information about sexual problems. The results of the survey show the need and interest for psycho-oncology training and research, including sexual dysfunction. Furthermore, psychological support should be offered to all cancer care providers.
POPULATION BASED CASE CONTROL STUDY OF A VEGF GENE DIMORPHISM AND OVARIAN CANCER RISK AMONG PAKISTANI WOMEN

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Background: Angiogenesis has been shown to be increased in various human tumours including ovarian cancers. Vascular endothelial growth factor (VEGF) is thought to be one of the most important angiogenic factors in tumourigenesis, and polymorphisms within this gene are thought to play a role in the modulation of an individual's genetic susceptibility to cancers in several tumour types.

Aim: To investigate whether VEGF 1154A>G dimorphism is associated with altered risk of epithelial ovarian cancer (EOC).

Methods: We designed a retrospective case-control study based in 3 tertiary care centres in Karachi and Lahore, Pakistan, which included 296 EOC cases and 298 age- and ethnicity-matched control subjects. VEGF 1154A>G genotypes were detected by a tetra primers ARMS-polymerase chain reaction procedure. Analyses were done using STATA version10.

Results: The per-allelic model showed that VEGF 1154GG genotypes occurred more frequently in the group of EOC patients (age-adjusted odds ratio=1.90 [CI=1.05-3.42], P=0.03). Interestingly, we observed a higher frequency of homozygous subjects, reflecting the high levels of consanguinity known to exist within Pakistan (with reported rates up to 60%). Kaplan-Meier analysis indicated that GG genotypes are associated with survival estimates of 50 weeks, compared to 80 weeks for AA or AG (log rank test P<0.0001).

Conclusion: Our data provides evidence that VEGF 1154A>G dimorphism is associated with higher EOC risk, and that presence of VEGF 1154G alleles may thus constitute an EOC susceptibility factor amongst Pakistani women. We also hypothesize that consanguinity is a risk factor for EOC predisposition in this population.
CA125 RESPONSE COMPARED TO RADIOLOGIC RESPONSE IN PATIENTS WITH RECURRENT OVARIAN CANCER UNDERGOING CLINICAL TRIALS OF MOLECULARLY TARGETED AGENTS

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Background and aims: Our aim was to compare CA125 and Response Evaluation Criteria in Solid Tumors (RECIST) response criteria in clinical trials for recurrent epithelial ovarian cancer (rEOC) involving molecularly targeted agents (MTAs).

Methods: A review of phase 2 trials of MTAs in rEOC was conducted using published literature (2005-2010) and American Society of Clinical Oncology annual meeting abstracts (2006-2009). Individual patient data were pooled from 4 Princess Margaret Hospital Consortium (PMHC) phase 2 trials involving MTAs in rEOC. RECIST and CA125 response rates were compared as predictors of survival benefit using the landmark method and Bayesian analysis.

Results: 43 trials were reviewed (19 abstracts, 24 publications). Primary endpoint was radiologic response alone in 65% of trials reviewed and CA-125 data was not reported in 42%.

In the PMHC cohort, 80 patients were evaluable for both RECIST and CA125 criteria. There was no concordance between RECIST (3.8%) and CA125 response (26.3%). Landmark analysis suggests improved survival for CA125 responders (median survival = 13.6 months (95% CI: 12.1-19.7) versus CA125 non-responders (median survival = 8.6 months (95% CI: 6.1-11), p=0.02), outperforming RECIST response as a surrogate for survival. Bayesian analysis suggests CA125 responders have a survival advantage for six months following therapy versus CA125 non-responders.

Conclusions: In phase 2 trials of MTAs in rEOC, CA125 and RECIST response rates are not concordant and CA125 response appears to have stronger prognostic value. These results need to be confirmed using larger datasets from individual patient data, rather than published literature.
D.OV.E.- DETECTING OVARIAN CANCER EARLIER - A PILOT PROJECT

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Complete tumor resection at primary surgery is the most important variable affecting survival in ovarian cancer. However, because of late presentation, this is achieved in less than 50% of patients. We hypothesized that reducing diagnostic delays in symptomatic patients may result in that earlier diagnosis. The D.Ov.E. project, designed to test this hypothesis offers eligible symptomatic women in Montreal, fast-track testing in a dedicated diagnostic centre. Our objectives are two-fold:

(1) To increase the proportion of ovarian cancers diagnosed in low volume completely resectable stages and

(2) identify the discriminatory symptoms of ovarian cancer to develop a decision-aid tool to guide patients and doctors about which symptoms warrant urgent testing.

Study methods: Women ≥ 50 years who had symptoms lasting more than two weeks and less than 12 months are assessed by a pelvic examination, blood test for CA125 and Endovaginal Ultrasound. Details of symptoms are collected before diagnostic testing.

Results: From May 1st 2008 to May 1st 2010, of the 5 ovarian cancers diagnosed in the 970 symptomatic patients enrolled in the study, three were in Stage I and two in completely resectable Stage III. The observed distribution for stage I disease or completely resectable minimum volume Stage III disease was 100% versus 46% expected from local tumor registry data. These results offers proof of principle that this approach has the potential to increase the proportion of patients diagnosed sufficiently early in the course of disease to achieve complete resection of tumors with improved prospects for survival.
OVARIAN CRYOPRESERVATION WITH SLOW-FREEZING FOLLOWED BY RE-IMPLANTATION RESTORES OESTROGEN PRODUCTION AFTER GONADOTOXIC RADIOTHERAPY TO THE PELVIS

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Stellenbosch University, Stellenbosch, South Africa

Background: Ovarian function plays a key role in the regulation of sexual development, the regulation of normal menstrual function and peripheral hormone effects on bone and other tissues. Chemotherapy is often very toxic to ovaries. Radiotherapy, even in low doses of 10 to 15 Gray will deplete the number of primordial follicles and will cause premature ovarian failure. Ovarian tissue cryopreservation and re-implantation after toxic cancer treatment may safeguard hormonal function.

Methods: 13 Pre-menopausal patients with locally advanced cervical squamous carcinoma had pre-radiotherapy bilateral laparoscopic oophorectomy. Ovarian dissection was performed to remove the cortex and the ovarian cortex then divided into small strips. Ovarian tissue cryopreservation was done with a slow freezing protocol. After completion of chemo-radiotherapy, thawed tissue was introduced back into subcutaneous tissue of the upper arm of patients with the aim of restoring ovarian function.

Results: 12 Of 13 patients had evidence of oestrogen production. Length of follow up was between 14 and 25 months after re-implantation. Oestrogen production started more than 6 months after re-implantation in 10 out of 12 cases. Levels of circulating gonadotrophins remained high despite oestrogen production and follicle formation. Oestrogen levels were generally low.

Conclusion: This is the largest reported series of hormonal follow up of cases of re-implantation of ovarian tissue after slow-freezing. Ovarian cryopreservation is a useful technique to safeguard hormonal function (and in certain cases fertility) in children and young women with cancer who are at risk of ovarian failure.
EARLY PREDICTION OF POSTMOLAR GESTATIONAL TROPHOBLASTIC NEOPLASM BY USING REGRESSION RATE OF HCG FROM WEEKLY MEASUREMENT

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Objective: For early prediction of progression to postmolar GTN (gestational trophoblastic neoplasm) after evacuation of hydatidiform mole through a comparison of hCG (human chorionic gonadotrophin) regression rate.

Patients and methods: 127 patients diagnosed H-mole (hydatidiform mole) were analyzed weekly hCG follow-up retrospectively from January 1 of 1996 to June 30 of 2009. hCG regression rate was compared between spontaneous regression group and postmolar GTN group. The sensitivity and specificity for prediction of postmolar GTN were assessed by using receiver operating characteristic curves.

Results: Mean regression rate of hCG between two groups were compared and showed significant difference from 2nd weeks. hCG regression rate were 0.50% in spontaneous regression group and 1.43% in postmolar GTN group (P=0.012) at 2nd week. At 2nd week, the prediction of postmolar GTN with hCG regression rate revealed the sensitivity of 70 % and specificity of 63% with cut-off value of 0.389% and AUC of 0.729 (p=0.038). At 3rd and 4th weeks, the sensitivities of prediction for postmolar GTN were 77 and 88% and specificities were 84 and 91 % with cut-off value of 0.178 and 0.119% while AUC displayed 0.872 and 0.946 respectively (p< 0.001 and p< 0.001).

Conclusion: The hCG regression rate after molar evacuation was obtained in uneventful mole patients. The occurrence of postmolar GTN was predicted on 2nd week.

<table>
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[the comparison of the mean regression rate of hCG]
ESTROGEN REPLACEMENT INDUCES A UNIQUE GENE EXPRESSION PROFILE IN OVARIAN CANCER THAT DIFFERS FROM BREAST CANCER

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Objectives: Estrogen replacement therapy (ERT) increases risk of ovarian cancer but not breast cancer. We sought to contrast ERT regulated genes in human ovarian cancer vs. human breast cancer.

Methods: Athymic nude mice received xenografts of human ovarian cancer cells (ER$^+$ PEO4, or ER$^-$ 2008). 17β-Estradiol (E2)-releasing pellets were implanted subcutaneously for 7 weeks; then continued or withdrawn for 4 weeks. Intraperitoneal ovarian tumors were harvested and cDNA hybridized to Affymetrix gene chip microarrays. Significant differences were ANOVA p < 0.05 and expression difference >1.2 fold. Data were compared to published ERT-regulated genes in breast cancer.

Results: A significant increase in volume of ER+ PEO4 intraperitoneal disease with E2 was confirmed by quantitative imaging. E2 withdrawal decreased expression of progesterone receptors (PR) without decreasing tumor proliferation. Three ERT responsive gene classes were defined: Class A (↓2008, ↓ Control (C) PEO4, ↑ERT PEO4); Class B (↑ 2008, ↓C PEO4, ↑ ERT PEO4); Class C (↑ C PEO4, ↓ ERT PEO4). Class A genes (146) included PR. Class B genes (152) included caveolin, CD44 and fascin 1, which have known roles in ovarian cancer; palladin was novel. Surprisingly, ERT-regulated genes in ovarian and breast cancers minimally overlap: only 6.8% (10/146) of class A genes and 9.9% (15/152) of Class B ovarian ERT-regulated genes overlapped with ERT-regulated breast cancer genes.

Conclusions: ERT induces a unique gene expression profile in ovarian cancer cells that lacks significant overlap with breast cancer genes. Novel selective estrogen response modifiers for ovarian cancer need to be developed.
CURCUMIN ENHANCED THE ANTITUMOR EFFECT OF HERPES SIMPLEX VIRUS THYMIDINE KINASE IN HUMAN BREAST CANCER THROUGH MODULATION OF ANTI-APOPTOTIC PATHWAY

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Background and aims: Suicide gene therapy using herpes simplex virus thymidine kinase (HSV-TK)/ganciclovir (GCV) has shown to be a potential strategy for cancer treatment. However, GCV-mediated cytoxicity relies on the replicating ability of the targets. In this study, we investigated whether curcumin, a chemopreventive drug, potentiates the antitumor effect of HSV-TK/GCV using an orthotopic human breast cancer model.

Methods: We used MDA-MB-435s cell line stably transfected with HSV1-tk and luciferase (luc) genes to study the anti-proliferation effect of combination therapy. The in vitro surviving fraction was measured by SRB assay. The expression of antiapoptosis-related proteins was examined by Western blotting. The in vivo therapeutic efficacy of GCV, curcumin, and GCV+curcumin was evaluated in NOD/SCID mice bearing MDA-MB-435s/tk-luc orthotopic tumors using bioluminescent imaging.

Results and conclusions: The results showed the synergistic killing effect of combination therapy on MDA-MB435s/tk-luc cells through inhibition of Bcl-2 and Cyclin D1 expression at early time points. The tumor growth rate of the combination group was significantly lower than that of GCV alone (+p<0.05) after day 22. Curcumin alone resulted in a slight, but no significant tumor regression as compared with the control.

We concluded that HSV-TK gene therapy combined with curcumin could be a potential strategy for breast cancer treatment.
COST EFFECTIVENESS OF LAPAROSCOPIC VERSUS ABDOMINAL HYSTERECTOMY IN EARLY STAGE ENDOMETRIAL CANCER

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Objective: To investigate the cost-effectiveness of total laparoscopic hysterectomy (TLH) versus total abdominal hysterectomy (TAH) in early stage endometrial cancer.

Methods: A multicentre RCT, including 26 proven skilled laparoscopic surgeons in 21 hospitals in the Netherlands. Patients with clinical stage I endometrioid adenocarcinoma or complex atypical hyperplasia were randomized (2:1) for TLH or TAH. In total 275 patients were required to detect a significant difference of 15% in major complication rate between TLH and TAH (80% power; α=0.05). The primary effect measure was major complication rate, as assessed by an independent panel. Costs were evaluated from a societal perspective including operative procedure costs, hospital stay and costs incurred during the postoperative period over a three months time horizon. Analysis was by intention-to-treat.

Findings: In total, 283 patients were randomized (TLH n=187; TAH n=96). The major complication rate was 14.6% in the TLH group versus 14.9% in the TAH group (p=0.95). The intra operative major complication rate during TLH (2.7%) was lower than during TAH (4.3%) (NS). Conversion to laparotomy occurred in 10.8% of the laparoscopic procedures. Total costs were €3,453 for a TLH and €3,577 for a TAH. An amount of €3,700 will be saved per additional major complication-free patients in case of performing TLH instead of TAH.

Interpretation: TLH is cost effective when compared to TAH. Therefore and due to comparable safety, TLH should be recommend as the standard surgical procedure in early stage endometrial cancer, on the condition of “skilled surgeons”.

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PROGNOSTIC SIGNIFICANCE OF LYMPHO-VASCULAR SPACE INVASION AND NODAL INVOLVEMENT IN INTERMEDIATE AND HIGH RISK ENDOMETRIAL CANCER PATIENTS

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Purpose: The aim of this analysis was to assess whether Lympho-vascular space invasion and nodal status provide incremental prognostic value compared with traditional prognostic factors in intermediate and high risk endometrial cancer patients treated with primary surgical staging and adjuvant radiotherapy.

Materials and methods: Prognostic factors considered were FIGO stage, grade, histology, fractional myometrial invasion, nodes, LVSI, age and type of adjuvant radiotherapy. In addition 4 new pair-wise groups using various combinations of LVSI and nodal status were also created for analyses. A pair with negative nodes and negative LVSI was used as the reference category. All other combinations were compared against this in using multivariable analyses.

Results: Three hundred and twenty four patients were available for analyses. The mean follow-up was 4.8 years. At 5 years, failure free survival rate was 79.8%. Eighty three percent of patients with endometrioid histology were alive and free from disease at 5 years compared with 69.8% patients with serous/clear cell histology. In multivariate model only three factors, patients with LVSI and positive nodes (P=0.004, HR-8.8), LVSI and negative nodes (P=0.000, HR-4.9) and age (p=0.025, HR-1.02) were significant predictors for relapses.

Conclusion: The traditionally used prognostic factors did not add to the predictive abilities for relapses in this series. A simplified model that uses nodal and LVSI status along with age has equal prognostic predictive abilities as a full model and can be used in simplifying the staging and patients selection for clinical studies of high risk endometrial cancer patients.
DIAGNOSTIC PERFORMANCE OF CONTRAST ENHANCED CT AND FDG-PET/CT IN THE ASSESSMENT OF LYMPH NODE METASTASIS IN OPERABLE CERVICAL CANCER

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Background: Pre-operative knowledge of lymph node status in early stage cervical cancer may lead to a better selection of patients for radical surgery. Conventional imaging modalities i.e. CT or MRI have low sensitivity in predicting nodal metastasis. PET-CT combines the anatomic detail from CT with metabolic information from PET and shown to be superior to CT alone.

Aim: To determine the accuracy of pre-operative PET/CT and CE-CT scan for detecting lymph node metastases in operable cervical cancers compared with histopathologic results from systemic lymphadenectomy.

Methods: Fifty operable cervical cancer patients (up-to FIGO stages-IIA) were studied prospectively. CE/CT abdomen & pelvis and whole body PET/CT were done preoperatively. All patients underwent pelvic and low para aortic lymphadenectomy. Each nodal group was labeled as per anatomical location (obturator-internal iliac, external iliac, common iliac and low para-aortic) and evaluated separately on histopathology. Histopathology was considered the gold standard.

Results: Primary tumor was FDG avid in all cases with gross disease. The median number of nodes removed was 22 (8-43). Twenty three percent patients had positive nodes. Nodal station-based analysis showed that the sensitivity, specificity, positive predictive value and accuracy of PET/CT for detecting nodal metastases were 52.4%, 99.0%, 78.6% and 95.8% while corresponding values for CE/CT were 47.6%, 97.6%, 58.8% and 94.1%, respectively.

Conclusions: Both CE/CT and PET/CT have low sensitivity in predicting lymph node metastasis in patients with operable cervical cancer. The PPV of PET/CT is higher than CE-CT. Therefore a positive PET/CT may be useful for treatment planning.
FACTORS ASSOCIATED WITH ENROLMENT IN OVARIAN CANCER CLINICAL TRIALS AND THE IMPACT ON OUTCOME

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Background: Previous studies have reported better outcomes when patients participate in clinical trials, possibly due to exposure to active new agents, entry criteria restricted to better prognosis patients or adherence to strict best practice protocols. Enrolling patients in clinical trials also improves cancer treatment, so understanding clinical trials enrolment, and ways to improve this are important goals.


Results: 1095 patients were identified, 18% (n=193) were elderly (>70 yrs). Stage breakdown was III (54%), I (26%), II (10%) and IV (10%). 862 (78.7%) patients had chemotherapy (79.5% < 70, 75.1% > 70 yrs, p=ns), 179 (20.8%) of these were treated on a clinical trial. Participation increased over time, from 1986-1997 (15.8%) to 1998-2008 (24.2%, p=0.003). Elderly patients participated less in clinical trials (11.7% vs 22.6%, p=0.002). Patients with higher stage (III & IV) disease were more likely to be enrolled versus stage I & II (26.5% vs 10.0%, p<0.001). Socioeconomic status did not impact participation. For stage III patients (n=489) there was a trend towards improved survival on clinical trials (n=141) 3.8 versus routine treatment (n=348) 3.0 years, p=0.07). Overall the elderly patients benefited most from clinical trial enrolment (median survival 3.5 versus 2.1 yrs, p=0.02). There was no difference in survival outcome when patients on the control arm (n=52) were compared to those not on trial (n=324). Multivariate analysis will follow.

Conclusions: A significant proportion of patients with ovarian cancer participate in clinical trials. There was less participation among elderly patients, the group that benefited most. Inadequate treatment of elderly patients off clinical trials is one possibility that needs to be further explored.
SYSTEMATIC PELVIC AND PARAAORTIC LYMPHADENECTOMY IN ENDOMETRIAL CANCER: LYMPH NODE METASTASIS PATTERN AND IDENTIFICATION OF PREDICTIVE FACTORS FOR LYMPH-NODE STATUS

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Background: Endometrial cancer is surgically staged since 1988; however, there is a controversy and debate about the indication and extent of lymphadenectomy, and in particular, the role of a complete bilateral infrarenal paraaortic nodal dissection.

Methods: We analysed retrospectively the data from two major gynaecological-oncology centres in Germany. Included were patients with endometrial cancer treated between 1998 and 2008 with any of the following risk factors: myometrial space invasion > 50%, G3, histological type II. All patients received a surgical staging including systematic pelvic and para-aortic lymphadenectomy.

Results: 128 patients were included, 77 patients (60.2%) had T1-Status. The median number of removed pelvic and paraaortic lymph nodes was 29 (1-66) and 21.5 (2-63), respectively. 27 patients (21.1%) had positive lymph nodes. 14 patients (10.9%) had positive pelvic and para-aortic lymph nodes; 6 patients (4.7%) presented with only para-aortic positive lymph nodes and 7 patients (5.5%) had only positive pelvic nodes.

48.1% of the affected para-aortic lymph nodes were above the level of the inferior mesenteric artery. Multivariate analysis revealed that only the T-Status (P-Value: 0.041) was a significant risk factor for N1-status. Not significant were age, histology and grading.

Conclusion: Para-aortic lymphadenectomy cannot be abandoned in the staging of high-risk endometrial cancer. The extension of dissection should always be above the level of the inferior mesenteric artery up to the renal veins. The future prospective trial (ECLAT) will investigate the prognostic effect of full lymphadenectomy in high risk patients.
HEPATIC RESECTION IS A POTENTIAL TREATMENT FOR RECURRENT METASTATIC OVARIAN CARCINOMA OR PERITONEAL CARCINOMA

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Objective: The objective of this study was to investigate the validity of hepatic resection as a treatment option for hepatic metastasis in patients with recurrent epithelial ovarian cancer or peritoneal carcinoma.

Methods: We conducted a retrospective review of 40 recurrent ovarian carcinoma or peritoneal carcinoma patients with hepatic parenchymal metastasis who were treated at the Beijing Cancer Hospital from 1996 to 2009.

Results: In one hundred and fifty one recurrent ovarian carcinoma or peritoneal carcinoma patients, there were 40 patients with hepatic metastasis (median age 59 years; range, 41-78 years) during this period of time. Twelve patients with unilobar metastasis and less than 3 numbers of tumors were underwent hepatic resection for metastatic cancer. There was no significant difference between patients underwent hepatic resection and the patients accepted salvage chemotherapy in age, primary pathology type, tumor grade, the rate of optimal primary cytoreductive surgery and the serum CA-125 level at the liver metastasis (p>0.05). There were 7 patients recurrent in the 10 patients with microscopic negative margins. The median recurrent time was 11 months (range, 3-24) following the hepatic resection. The median overall survival time and cumulative 3-years survival rates after liver metastasis for patients who accepted optimal secondary cytoreduction including hepatic resection and those who obtained only salvage chemotherapy were 62 months (range, 9-76) vs. 14 months (range, 1-68) and 66.7% vs. 18.5%, respectively (p< 0.05).

Conclusion: Our findings suggest that hepatic resection should be attempted for selective patients with hepatic metastasis from ovarian carcinoma or peritoneal carcinoma.
FORTY YEARS REVIEW FOR THE TREATMENT OF VAGINA CARCINOMA: AN INSTITUTIONAL EXPERIENCE

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Objective: To evaluate clinical outcome, prognostic factors and treatment modalities for vaginal carcinoma.

Material and methods: 105 patients with vaginal carcinoma treated in Sun Yat-Sen University Cancer Center between July 1969 and March 2009 were selected, which included 13 patients with cancer of vagina stump. 46 were at stage I disease (FIGO staging), 24 at stage II, 14 at stage III and 8 at stage IV disease. 83 patients had squamous cell carcinoma, 17 had adenocarcinoma, 2 had clear cell carcinoma and 3 had undifferentiated carcinoma. All cases were divided into five groups according to the treatment modalities that included radiation therapy only (group 1), surgery only (group 2), the combination of radiation and adjuvant chemotherapy (group 3), the combination of surgery and adjuvant radiation or chemotherapy (group 4), chemotherapy only (group 5).

Results: The 5-year survival rate was 46.7% (49/105) in all cases, 55% (22/40) in group 1, 33.3% (3/9) in group 2, 18.2% (4/22) in group 3, 69.0% (20/29) in group 4 and 0% (0/5) in group 5. The patients who were given a combined treatment with surgery and adjuvant therapy (group 4) had a better prognosis (P<0.001). Multivariate analysis revealed that FIGO stage, tumor size and superficial lymphnode enlargement were the independent prognostic factors (P< 0.05).

Conclusion: Treatment modality was not correlated to the survival of patients with primary vaginal carcinoma. However, the better prognosis may be achieved by combined therapy with surgery and adjuvant therapy.
CHEMORADIOSENSITIZATION OF BRACHYTHERAPY IN CARCINOMA OF UTERINE CERVIX: THE FRINGE EFFECTS IN ADVANCE DISEASE

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Background: 80 percent of Indian cancer cervix patients report in bulky stage II /stage III / stage IV with dismal cure rates. Carcinoma of uterine cervix afflicts middle aged in her prime of life. Conventional treatments have not been able to give long-term survivals for early stages even after the ‘megarads’ delivery in the core by brachytherapy. The culprits must be the under dosed peripheral fringed areas or radio- resistant hypoxic cells.

Aims:

- To improve disease free and cure rates in late stage cancer of uterine cervix patient assigned for radical/ palliative radiation.
- To evolve betterment of quality of life and long term survival for stage III cervical cancer.
- To provide prolonged palliation/cure in stage IV A disease.
- To find out an answer to the biological behaviour and patterns of recurrence in these cases.

Methods: Post teleradiation Chemosensitized brachytherapy was tried for the first time in the world through a multiarm trail. Study group(n=40) received 5-FU, Cis-platinum, and Bleomycin infusions over 17-20 hours when patient was receiving MDR brachytherapy. The controls (n=40) received only brachytherapy.

Results: Complete primary and complete parametrium response was observed in 36/40 and 30/40 patients respectively in study group on five year survival data. The control group showed primary and parametrium complete response in only 8/40 and 4/40 subjects respectively.

Conclusion: This hallmark observation in the treatment of cervical cancer through chemoradiosensitization of post-teleradiation brachytherapy with long term survival further advocates for future ideal modality of treatment with better response rates in these patients.
DISPARITIES IN TREATMENT FOR EPITHELIAL OVARIAN CANCER IN A LARGE UNITED STATES POPULATION

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Background: Ovarian cancer (OC) is the deadliest gynecologic malignancy among women in the United States (U.S.). Previous studies have suggested that disparities in treatment exist among certain racial populations for OC, often leading to decreased survival.

Aim: The objective of this study is to identify demographic and clinical factors associated with not receiving standard treatment for ovarian cancer in a large U.S. population.

Methods: Demographic, treatment, health insurance, and provider information was collected for over 3000 women diagnosed with epithelial ovarian cancer in Northern California and New York State between 1998 and 2000. Factors associated with not receiving standard treatment for OC (surgery and chemotherapy according to stage-specific guidelines) were assessed using multivariate logistic regression modeling.

Results: A total of 2,382 women with epithelial OC were included in this analysis. Of these, 24% did not receive standard care. Demographic characteristics associated with not receiving standard care included black race (odds ratio [OR] 1.7, 95% CI 1.1-2.6), and increasing age (ages 65-79 yrs, OR=3.2, 2.1-4.7; ages 80+ yrs, OR=11.6, 7.2-18.5). Advanced stage was also associated with not receiving standard care. Additionally, women who did not have insurance (OR=3.6, 1.8-7.4) and those who had never seen a gynecologic oncologist (OR 2.4, 1.9-3.0) did not receive standard care.

Conclusions: Our results suggest that several disparities exist in OC care in the United States. These treatment disparities may be associated with decreased survival often seen in these populations. Further assessment is needed to determine causes for the lack of standard treatment in these populations.
ANTI-GLYCAN ANTIBODIES AS NEW OVARIAN CANCER TUMORMARKERS IDENTIFIED USING PRINTED GLYCAN ARRAY

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Introduction: Epithelial ovarian cancer has the highest mortality rate among gynaecological cancers. Altered glycosylation of proteins and lipids is associated with oncogenic transformation producing tumor-associated carbohydrate antigens. We investigated the potential of anti-glycan antibodies in the diagnosis of non-mucinous ovarian cancers using a printed glycan array containing 203 glycans.

Material and methods: Serum samples were collected from healthy controls (n=24) and non-mucinous borderline tumor and ovarian cancer patients of various FIGO stages (n=33) following written informed consent. After incubation, anti-glycan antibodies bound to printed glycans were detected via biotin-streptavidin fluorescence. Following normalization and transformation, data were analyzed by univariate feature selection and multivariate hypothesis testing using Matlab and R.

Results: High reproducibility in measuring anti-glycan antibodies was found overall with cluster analysis demonstrating repetitive patterns of specific core carbohydrate structures within 21 clusters: N-linked glycans (11 clusters), O-linked glycans (3 clusters), glycosphingolipids (2 clusters), not clearly sub-specifiable structures (5 clusters). Binary classifiers revealed 24 glycans including P\textsubscript{1} (Gal\alpha\textsubscript{1}-4Gal\beta\textsubscript{1}-4GlcNAc\beta; p< 0.001) significantly discriminating between ovarian cancers, borderline tumors and healthy controls. Higher sensitivity and specificity than CA125 was achieved by a panel of multivariate selected and linear combined anti-glycan antibody signals (83.3% and 84.8%, respectively).

Conclusion: Using anti-glycan antibody profiles we detected ovarian borderline and malignant tumors with a higher sensitivity and specificity than CA125, indicating a potential for the development of a new generation of biomarkers for ovarian cancer.
OVARIAN CANCER IN HEREDITARY NONPOLYPOSIS COLORECTAL CANCER; CLINICAL CHARACTERISTICS, MORPHOLOGY AND MISMATCH-REPAIR MUTATIONS

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Ovarian cancer represents the third most common cancer type in females with hereditary nonpolyposis colorectal cancer. We characterized ovarian cancer in the Swedish and Danish HNPCC cohorts with respect to morphology, mismatch repair (MMR) protein expression, and contribution from the different MMR genes. In total, 65 epithelial ovarian cancers were identified in 65 mutation carriers. These tumors developed at mean 48 (range 32-75) years of age. Endometrioid and clear cell tumors were overrepresented and constituted 35% and 25%, respectively, whereas serous tumors represented 29% and mucinous 10% mucinous. The MMR gene mutations affected MSH2 in 53%, MSH6 in 30% and MLH1 in 17%. Our pooled analysis of HNPCC-associated ovarian cancer thus confirms differences between hereditary ovarian cancer caused by HNPCC and BRCA mutations with a lower age at onset and predominance of endometrioid-clear cell tumors in the former groups.
TOPOTECAN/CARBOPLATIN VS. PACLITAXEL/CARBOPLATIN OR GEMCITABIN/CARBOPLATIN OR CARBOPLATIN/PEGYLATED DOXORUBICIN: A PLANNED 200 PTS INTERIM SAFETY ANALYSIS OF THE HECTOR-STUDY (NOGGO/AGO-OVAR/GEICO/AGO-AUSTRIA)


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Background: We present the preliminary safety results from the phase III study of topotecan/carboplatin (TC) vs standard therapy with paclitaxel/carboplatin (PC) or gemcitabin/carboplatin (GC) or carboplatin/pegylated doxorubicin (PLDC). While the primary endpoint of the study is PFS, the specific toxicity observed from these regimens is critically relevant. Therefore this planned safety analysis on the experimental arm (TC) and the standard therapy (control arm = CA) was conducted.

Methods: From 02/07 to 12/09, 590 pts were screened and 550 pts were randomized to either T (0.75mg/m²/d1-3/q21d) + C (AUC 5/d1/q21d) or to PC or GC or PLDC based on patient preference.

Results: The data from the first 200 pts were analyzed. Median number of cycles was 6 in the two arms. Most patients preferred the standard therapy with GC (78%) due low alopecia rate since the PLDC arm was opened after the publication of CALYPSO data. Haematological toxicity contributed to 41% of cycle delays in the CA and 36% in the TC arm. Neutropenia & infection rates were similar in both arms. G-CSF was administered more frequently to pts in CA arm (26%) than in TC arm (21%). Grade (G) > 2 non-haematological toxicity was not more frequent in the C-P arm. There were more severe adverse events (SAE) in the CA (66 %) than in the TC arm (55%).

Conclusions: This planned interim safety analysis on the first 200 patients confirmed the safety of the experimental arm and allowed to continue the study enrolment. Study recruitment was completed in 12/2009.
NUTRITIONAL STATUS AND SURVIVAL AMONG PATIENTS WITH SUSPECTED OR PROVEN GYNECOLOGICAL MALIGNANCIES

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Background: Malnutrition is a complex, multifactorial problem, commonly seen in patients with aggressive cancers. Our aim was to evaluate the importance of nutritional status for survival outcomes among patients with suspected or proven gynecological malignancies.

Methods: We prospectively collected information on nutritional status of 200 patients treated between 2004 and 2006 at a tertiary referral centre for gynecological cancers in Australia. Patient Generated Subjective Global Assessment (PG-SGA) was used to assess nutritional status. Kaplan-Meier method was used to estimate survival and log rank test was used to compare survival between well-nourished (PG-SGA A) and malnourished (PG-SGA B & C) patients. Cox proportional hazards models were used to evaluate the importance of nutritional status for relapse-free (RFS), disease-specific (DSS), and overall survival (OS).

Results: The mean (SD) age at diagnosis was 57.6 (13.5) years with 57 (28.5%) patients classified as moderately (PG-SGA B) or severely malnourished (PG-SGA C). Malnourished patients had significantly worse RFS, DSS and OS (p < 0.002 for all) when compared to well-nourished patients. After adjusting for age, presence of malignancy, presence of ovarian cancer, hypoalbuminemia, obesity and multiple comorbidities, malnourished patients had a hazards ratio (95% CI) of 3.3 (1.4-8.1), 4.2 (1.5-11.5) and 2.5 (1.0-6.3) for RFS, DSS and OS respectively, when compared to well-nourished patients.

Conclusion: Nutritional status prior to treatment has a major impact on relapse-free, disease-specific and overall survival in patients with suspected or proven gynecological malignancies. To improve outcomes, evidence-based nutritional interventions are required at the time of diagnosis.
DIFFERENT AMPLIFICATION PATTERNS OF THE HUMAN TELOMERASE RNA GENE IN INVASIVE CERVICAL CARCINOMAS AND CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE III

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The aim of this study is to compare the amplification patterns of the human telomerase RNA gene (hTERC) in invasive cervical carcinomas (ICC) and cervical intraepithelial neoplasia (CIN) grade III. Cervical liquid-based cytological specimens were collected from 53 squamous cell carcinomas (SCC), 14 CIN III and 20 normal controls. Copy numbers of the hTERC gene were measured by fluorescence in situ hybridization (FISH) using a dual-color probe containing the hTERC probe and the control, centromere chromosome 3-specific probe (CEP3). Nucleus with abnormal FISH pattern for hTERC was observed in 0.94% to 90.65% of SCC cells and in 0 to 85.59% of CIN III cells. Using the threshold of 5.89%, the occurrence of hTERC amplification in SCC and CIN cases is similar (90.6% vs 85.7%, P=0.630). However, in a total of 2162 SCC cells and 502 CIN III cells with abnormal FISH pattern, even gains of hTERC (hTERC:CEP3=1) were more common in CIN cells (62.5% vs 34.9%), while, extra gains of hTERC (hTERC:CEP3>1) were more common in SCC cells (65.1% vs 37.5%). Among those cells with extra gains, the 3:2 signal pattern was the leading pattern in CIN (51.5%), while more complex signal patterns other than 3:2 pattern were predominant in SCC (60.9%). The median percentage of cells with extra gains of hTERC in SCC was higher than in CIN III (64.3% vs 31.7%, P=0.001). Thus, hTERC amplification was common in cervical exfoliated cells from SCC and CIN III. More complex amplification patterns of hTERC were present in invasive cervical cancers.
DUAL METRONOMIC CHEMOTHERAPY RESULTS IN POTENT ANTI-ANGIOGENIC EFFECTS IN OVARIAN CARCINOMA

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Objectives: Metronomically-dosed topotecan elicits antiangiogenic effects by downregulating the potent pro-angiogenic factor HIF-1α. Since metronomic paclitaxel appears to act via a different mechanism, we hypothesized that combined metronomic delivery of these agents would enhance anti-tumor and anti-angiogenic effects.

Methods: We examined the in vitro and in vivo effects of n-(ab)-paclitaxel (microalbuminized paclitaxel) and topotecan given at either maximum-tolerated dose (MTD) or metronomic dosing. For in vivo studies, we examined markers of cell proliferation (Ki67), apoptosis (TUNEL), and angiogenesis (CD31) in harvested tumors.

Results: After in vivo dose-finding studies established the therapeutic metronomic dose of n-(ab)-paclitaxel, extensive therapy experiments with chemosensitive (HeyA8 and SKOV3ip1) orthotopic ovarian cancer models demonstrated that metronomic n-(ab)-paclitaxel reduced tumor growth by ≥ 85% compared to controls (p< 0.01). In the SKOV3ip1 model, metronomic n-(ab)-paclitaxel alone resulted in a 64% reduction in tumor growth compared to metronomic topotecan alone (p< 0.01). In the taxane-resistant HeyA8-MDR model, n-(ab)-paclitaxel and topotecan (both metronomically-dosed) significantly reduced tumor weights by 40% compared to controls (p=0.01). N-(ab)-paclitaxel alone and with topotecan also significantly reduced cellular proliferation (p< 0.001). Metronomic N-(ab)-paclitaxel in the taxane-resistant model elicited notable inhibition of angiogenesis (p≤0.01). Protracted low-dose N-(ab)-paclitaxel exposure in HeyA8 cells markedly increased tumor cell expression of thrombospondin-1. Increases in apoptosis were seen in tumors treated by topotecan alone and with n-(ab)-paclitaxel (p< 0.01).

Conclusions: Metronomically-delivered topotecan and n-(ab)-paclitaxel have complementary anti-angiogenic effects in ovarian carcinoma due to their unique mechanisms of action. Given the safety/tolerance of metronomic regimens, this combination is clinically attractive.
PHASE II STUDY OF PELVIC INTENSITY MODULATED RADIOTHERAPY +/- CHEMOTHERAPY FOR POST-OPERATIVE PATIENTS WITH ENDOMETRIAL OR CERVICAL CARCINOMA (RTOG 0418)

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Purpose/objectives: The primary endpoint of RTOG 0418 was to determine the transportability of pelvic IMRT to a multi institutional setting for endometrial and cervical carcinoma patients. The secondary endpoint was to test for a reduction in grade 2 or more short-term (within 90 days) bowel injury compared to standard treatments and to evaluate chemotherapy compliance for the cervical cancer patients.

Materials/methods: Pelvic IMRT to a dose of 50.4 Gy in 28 fractions, was delivered to endometrial and cervical cancer patients requiring adjuvant pelvic radiation. Cervical cancer patients also received weekly cisplatin 40 mg/m². Adverse events (AEs) were assessed using the CTCAE v. 3.0.

Results: From March 2006 to October 2008, 106 patients were enrolled (58 endometrial and 48 cervical cancer), and 83 were eligible for analysis. There were 0 and 1 cases with deviation unacceptable scores for protocol compliance with the delineation of planning target volume for the vagina and pelvic lymph nodes, respectively. Only 21 patients (25%), developed grade 2 or higher short term bowel AEs. No patients developed grade 4 bowel AEs. In the cohort of cervical cancer patients, bone marrow toxicity was minimal thus allowing for chemotherapy completion as planned in 80% of patients.

Conclusion: This prospective multi institutional study confirms that pelvic IMRT is transportable and associated with a lower risk of bowel toxicity when compared to historical data from standard pelvic radiation. This may translate to an improved quality of life for women who need to receive pelvic radiation.
TARGETING THE IGF-I RECEPTOR IN ENDOMETRIAL CANCER WITH MONOCLONAL ANTIBODY MK-0646

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Background: The involvement of the insulin-like growth factors (IGFs) in endometrial cancer has been well established. The IGF-I receptor (IGF-IR), which mediates the activities of the IGFs, is a promising molecular target in cancer therapy. The aim of this study was to evaluate the hypothesis that interfering with the IGF-IR signaling pathway in endometrial cancer could decrease proliferation and induce apoptosis. To this end we used a recently developed humanized monoclonal antibody (MK-0646, Merck Oncology), directed against IGF-IR which blocks IGF-I binding to the receptor.

Methods: To evaluate the effect of IGF-IR inhibition on IGF-I-mediated signaling, human endometroid (ECC-1) and serous papillary (USPC-1) endometrial cancer cell lines were treated for various periods of time (40 min, 1 h, 3 h, 5 h) with antibody MK-0646, in the presence of IGF-I during the last 10 min of the incubation period.

Results: Results of Western blots using antibodies against total and phospho-IGF-IR, AKT, and ERK showed that MK-0646 decreased the IGF-I-stimulated phosphorylation of IGF-IR, AKT and ERK in both ECC-1 and USPC-1 cells. In addition, MK-0646 induced a significant decrease in total IGF-IR levels. To evaluate the potential effect of IGF-IR inhibition on apoptosis, cells were treated with IGF-I for 24-48 h, in the absence or presence of MK-0646, after which apoptosis was assessed by Caspase-3 and cleaved PARP measurements. Results obtained showed that MK-0646 abrogated the antiapoptotic activity of IGF-I.

Conclusions: Taken together, our results suggest that specific IGF-IR blockade could be a useful therapeutic approach in endometrial cancer.
HE-4 A NOVEL TUMOR MARKER FOR OVARIAN CANCER: COMPARISON WITH CA 125 IN PATIENTS WITH GYNECOLOGICAL DISEASES

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We studied the specificity and sensitivity of HE-4 a novel tumor marker for ovarian cancer and CA 125 in 111 healthy subjects, 299 patients with benign gynecological diseases (65 endometriosis, 56 myomas, 81 cysts and 97 patients with abdominal masses), and 197 patients with gynecological cancer (121 ovarian, 27 squamous cervical cancer and 49 with endometrial Adenocarcinomas). Abnormal serum tumor marker levels were found in:

Benign Ovarian Cancer Endometrial cancer Squamous cancer

HE-4 (> 150 pg/ml) 1.3% 74% 30% 0%

CA 125 (35 U/ml) 32.4% 84% 31.8% 17.6%

ROC curve showed a higher area under the curve for HE-4 (0.939) than for CA 125 (0.849). Both tumor markers were related to tumor stage and histological type, with significantly higher concentrations in serous malignancies (p< 0.001). It is interesting to indicate that HE-4 showed a higher sensitivity in early stages (I-II) and CA 125 in advanced stages (III-IV). One or another tumor marker was abnormal in 93.6% of patients with ovarian cancer. The inclusion of ROMA algorithm to suggest malignancy, increase the specificity obtained with CA 125 and the sensitivity of HE-4. In summary HE-4 is an useful tumor marker for ovarian cancer, with highest sensitivity and efficiency than CA 125. The combined use of both tumor markers increase the sensitivity obtained individually, with abnormal levels in 93.6% of patients with ovarian cancer (80% in stage I-II).
FERTILITY-SPARING SURGERY IN YOUNG WOMEN WITH BILATERAL GERM CELL TUMOR

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Introduction: Malignant germ cell tumors are frequently diagnosed in young, premenopausal women, and therefore preservation of the ovarian function and fertility is an important issue. In this study we analyzed the effect of fertility sparing surgery (FSS) on the oncological outcome and fertility of women with bilateral ovarian involvement, which is a relatively uncommon condition.

Material and methods: Between 1982 and 2009, 320 women with germ cell ovarian tumors were referred to San Gerardo Hospital. Twentyfour (7%) had bilateral involvement: 16 dysgerminoma, 4 immature teratoma, 2 mixed-germ cell, 2 endodermal sinus tumour. Six cases had a microscopic involvement of one ovary. Median age was 22 years (range 9-69).

Eleven women underwent radical surgery, while 13 were treated with FSS. Two patient treated with FSS was premenarchal and nine of them received postoperative chemotherapy.

Results: With a median follow-up of 17.8 years all 13 women treated conservatively and 9/11 treated radically are alive without disease.

Among patients treated with FSS, two underwent resection of the preserved ovary at the second look surgery: one was a premenarchal woman who had primary amenorrhea and required hormonal replacement therapy and the second was performed for a suspected, unconfirmed recurrence.

The remaining 11 patients conservatively treated maintained their menses (8 after chemotherapy) and 4 of them gave birth to 6 healthy babies.

Conclusion: Treatment with fertility-sparing surgery is safe in treating women with ovarian germ cell tumor with bilateral involvement of and should be offered to patients who wish to preserve their childbearing potential.
PATIENTS’ PREFERENCES FOR INTRAPERITONEAL CHEMOTHERAPY FOR ADVANCED OVARIAN AND RELATED CANCERS: WHAT MAKES IT WORTHWHILE?

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Background: Intraperitoneal (IP) chemotherapy for advanced ovarian cancer improves overall survival, but is toxic and inconvenient. We sought patients’ judgements about the survival benefits needed to make IP chemotherapy worthwhile.

Methods: Patients with optimally debulked stage III ovarian cancer participating in a single-arm, phase II trial of IP cisplatin and paclitaxel completed validated questionnaires before chemotherapy. Preferences were elicited for baseline survival times of 5 years and 3 years, and baseline survival rates of 50% at 5 years and at 3 years. Aspects of health-related quality of life (HRQOL) were assessed by the Patient DATA Form (0 ‘no trouble at all’ to 10 ‘worst I could imagine’).

Results: Preferences questionnaires were completed by 20 women: median (range) age 53 years (24-75), ECOG performance status of 0 (0-1). 50% of patients judged an extra 6 months beyond 3 years and 5 years, and 5% beyond survival rate of 50% at 3 years and 5 years, sufficient to make IP chemotherapy worthwhile. The benefits judged sufficient ranged from an extra: 1 day to 15 years, and from 0.1% to 50%. The most troublesome aspects of HRQOL at baseline (mean) were: thought of actually having treatment (3.6), anxiety (3.1), lack of energy (2.9), pain (2.9), and fatigue (2.7), but these were not correlated with preferences. Age was correlated with preferences (rho 0.455, p=0.044).

Conclusions: The survival benefits judged sufficient to make IP chemotherapy worthwhile were moderate and varied widely. Individual patients’ preferences for IP chemotherapy should be incorporated into clinical decision-making.
PREDICTING GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN): IS URINE HCG (UHCG) THE ANSWER?

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Background: Previous studies on significance of hCG to predict GTN have been too small for robust conclusions to be reached. We conducted the first and largest study to date using the database at Sheffield trophoblastic disease centre to analyse the significance of UhCG in predicting GTN.

Methods: Details of 5648 patients were available. Information regarding age, dates of diagnosis and registration, UhCG levels, antecedent pregnancy and chemotherapy were prospectively collected and used for analyses. Patients were stratified into different groups according to UhCG level; < 50IU/L, 50-99IU/L, 100-249IU/L, 250-499IU/L and ≥500IU/L. Multivariate analyses were used to identify the prognostic indicators of GTN.

Results: UhCG and antecedent pregnancy were the most powerful indicators for developing GTN (P < 0.01). None of the patients with partial mole and UhCG < 50IU/L (Normal level= 40IU/L) developed GTN. The risk of GTN was >35% in all patients with UhCG ≥500IU/L. GTN developed in 70% of patients with complete mole and UhCG ≥1000IU/L. Reduced time interval between diagnosis and registration increased risk of receiving chemotherapy in patients with UhCG < 500IU/L (P=0.015), however this impact wasn’t observed in patients whose UhCG was ≥ 500IU/L (P= 0.56).

Conclusions: UhCG is sensitive test for GTN. UhCG level is a powerful prognostic indicator for the GTN. Patients with partial mole could be safely discharged from the surveillance programme once their hCG have normalised. Patients with complete mole and UhCG≥ 10000IU/L may benefit from empiric chemotherapy.
GENE EXPRESSION SIGNATURE CHARACTERIZED BY PI3KINASE ACTIVATION VALIDATES TO IDENTIFY AGGRESSIVE DISEASE AND A POTENTIAL FOR PI3KINASE-INHIBITORS IN ENDOMETRIAL CARCINOMAS

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Background: Endometrial cancer is the most frequent gynecologic malignancy in industrialized countries. There is a need for more effective systemic therapies and reliable prognostic markers. We have recently reported a gene expression signature defining an aggressive subgroup of patients characterized by PI3Kinase activation, suggesting the importance of PI3Kinase inhibition for this disease (Salvesen et al, PNAS 2009). In the present study we wanted to validate the value of this gene signature in an independent patient series.

Method: Fresh frozen endometrial carcinoma samples (n=158) were prospectively collected. RNA was extracted and cDNA was synthesized for quantitative PCR. The signature score for each sample was calculated by subtracting the sum of the expression values of the down-regulated genes from the sum of the expression values of the up-regulated genes, using expression values for each gene normalized to a common mean and scaled to the same standard deviation.

Results: A high signature score was significantly associated with high age (p=0.04), high FIGO stage (p=0.04), non-endometrioid histology (p< 0.001), high grade (p< 0.001) and lymph node metastases (p=0.02). A high score also predicted shorter recurrence free survival (p=0.001).

Conclusion: A gene expression signature characterized by PI3Kinase activation, has been validated to identify aggressive endometrial carcinomas. The finding supports the potential for PI3Kinase-inhibitors in the treatment of metastatic endometrial carcinoma. Clinical trials relating the potential response to drugs targeting the PI3Kinase pathway to this gene expression signature is suggested.
PROTECTIVE EFFECT OF AMIFOSTINE DURING PELVIC IRRADIATION: LONG TERM EFFECTS AND RESULTS

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Objectives: Aim of the study is to analyze long term effect and results of protective effect of amifostine used during pelvic irradiation.

Materials and methods: Between September 2003 to August 2005, 70 patients of cervical cancer stage IIIB were chosen. They were randomized in to Arm A 35 patients treated with only radiotherapy and Arm B 35 patients treated with radiotherapy with amifostine. Age, performance status, tumor characteristics were well balanced between two arms. All patients received external beam radiotherapy 50 Gv/ 25#, 5 days per week, upto 5 weeks. Afterwards patients were given brachytherapy in on microselectron HDR 7.5 gy/2 #, 1 week apart. Arm A patients received radiotherapy only. While Arm B patients received radiotherapy with amifostine, 500 mg subcutaneously in sitting position daily half an hour before radiotherapy. Standard antiemetics were given. All patients were analyzed for acute and long term effect in form of radioprotection by amifostine to normal tissues.

Results: After mean follow up of 4 years, none of the patients receiving amifostine with radiotherapy experienced moderate or severe late toxicities to the bladder or gastrointestinal mucosa compared with 14% of patients treated with radiation therapy alone. Also patients receiving amifostine had a significantly lower incidence of bowel toxicity than patients who did not receive amifostine which proves cytoprotective efficacy of amifostine in patients receiving pelvic irradiation.

Conclusion: Cytoprotection with amifostine administration before external beam of irradiation in patients with cervical cancer reduces long term side effects of radiotherapy alone.
SYMPTOM BURDEN AMONG PATIENTS WITH PLATINUM RESISTANT/REFRACTORY RECURRENT OVARIAN CANCER (PRR ROC): STAGE 1 OF THE GCIG SYMPTOM BENEFIT STUDY

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Background: The major objective of chemotherapy in patients with PRR ROC is palliation. The symptoms in patients with PRR ROC are not well documented and the impact of chemotherapy on symptom benefit unclear. The GCIG Symptom Benefit Study (SBS) is a 2 stage study investigating how to best measure the palliative benefit of chemotherapy. We report the Stage 1 findings on symptoms prior to initiating palliative chemotherapy and duration of chemotherapy.

Methods: 77 patients with PRR ROC reported their predominant symptoms as well as pre-existing toxicities from prior therapy at study entry and completed 5 HRQOL questionnaires in Stage 1.

Results: The majority of patients were platinum resistant. 77% were symptomatic, 94% had a PS 0-1 and 64% had radiological evidence of disease. Compliance with HRQOL questionnaires was very high and over 90% were completed. The most frequent symptoms reported at baseline were pain (48%), fatigue (39%), sleep disturbance (27%), bloating (25%), nausea/vomiting (21%), bowel disturbance (18%), dyspnoea (12%), anorexia (10%) and emotional distress (10%).

82% of patients had received 3 lines or less of prior chemotherapy. Only 40% of patients completed 4 cycles of treatment with 41% stopping treatment early due to tumour progression and 9% dying of disease before cycle 4.

Conclusion: The GCIG SBS is the first study to prospectively evaluate symptom burden, toxicity and outcomes in PRR ROC. Stage 2 of this study will evaluate symptom benefit and also develop a prognostic index to allow better selection of patients for palliative treatment.
IDENTIFICATION OF POINT MUTATIONS AND LARGE REARRANGEMENTS IN THE BRCA1 GENE IN 667 TURKISH UNSELECTED OVARIAN CANCER PATIENTS

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The aim of this study was to evaluate the prevalence and spectrum of a known founder mutation, 5382insC, and large genomic rearrangements (LGRs) in BRCA1 in ovarian cancer patients in Turkey. The additional aim was to determine the genetic testing strategy in breast/ovarian cancer family. Six hundred and sixty-seven ovarian cancer patients were tested for the mutation 5382insC by mutagenically separated-PCR and direct sequencing of the entire coding sequence and the splicing sites. Additionally, MLPA was performed for large mutational scanning of BRCA1 gene in unselected ovarian cancer. BRCA1 point mutations were observed in 1% of all patients and 9.8% of familial cases: 5382insC, unique novel missense variant-G1748S and unclassified splice site variant IVS20+5A>T. 5382insC was observed in two patients. However, G1748S, previously unreported, was found in four patients and thus led to the conclusion that this mutation may be unique to Turkey. A splice site variant, IVS20+5A>T, was detected. Using MLPA, six different distinct LGRs in BRCA1 were observed: the deletion of E1A-1B-2, E11, E17-19, E18, E18-19 and duplication of E5-9. The prevalence of LGRs in this study was 40.9% among patients with family history and the deletion of E1A-1B-2 was the common mutation. LGRs in BRCA1 were strongly associated with positive family history amongst the Turkish population. On the basis of these findings it can be recommended that a low-cost screening for LGRs in BRCA1 may be the first-line mutation detection method in families with strong breast/ovarian cancer history in Turkey.
AGO-OVAR-2.11: A RANDOMIZED PHASE II TRIAL TO EVALUATE TWO DIFFERENT DOSAGES OF THE KINASE-INHIBITOR SU11248 IN PLATINUM-REFRACTORY OVARIAN CANCER


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**Background:** Sunitinib (SU11248) is a multi-targeted tyrosine kinase inhibitor blocking the activity of platelet-derived growth factor receptors and vascular endothelial growth factor receptors eventually resulting in the inhibition of angiogenesis and tumor cell proliferation.

**Methods:** A randomized phase II trial was designed to evaluate the effectiveness of sunitinib in recurrent platinum resistant ovarian cancer. A selection design was applied to compare two schedules of sunitinib: Arm 1: 50 mg sunitinib daily orally for 28 days followed by 14 days off drug. Arm 2: 37.5 mg sunitinib daily continuously. Primary endpoint was objective response rate evaluated by RECIST criteria and/or CA 125 criteria according to GCIG recommendations. Decision rule: select the treatment arm with a better response rates of p ≥ 0.11.

**Results:** 73 patients were enrolled (arm 1: 36; arm 2: 37), mean age was 58.8 and 58.5 years, respectively. Performance status was good (ECOG 0 or 1 in arm 1: 97.2%, arm 2: 100%). So far 925 adverse events have been reported (arm 1: 529; arm 2: 396). NCI-CTC grade 3 and 4 events were not different (arm 1: 11.3%; arm 2: 11.6%). According to RECIST and GCIG there were 6 responder (CR+PR) in the non-continuous (16.7%) and 2 responder in the continuous arm (5.4%).

**Conclusion:** Sunitinib treatment is feasible and active in relapsed platinum-resistant ovarian cancer. Both treatment schedules revealed a similar toxicity profile. The non-continuous treatment schedule was selected for further studies according to superior response data.
MICRORNA AS PROGNOSTIC FACTOR FOR RECURRENCE AND SURVIVAL OF OVARIAN CANCER - ANALYSIS OF THE CANCER GENOME ATLAS PROJECT

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Objective: To determine the association of microRNA expression with recurrence and survival in advanced serous ovarian cancer.

Methods: Demographic, clinico-pathologic, recurrence, survival, and genomic data were extracted from The Cancer Genomic Atlas (TCGA) data portal. TCGA collected 443 specimens with matched normal tissue controls and analyzed all specimens using Agilent microRNA array platform. Student’s t-test, Kaplan-Meier survival estimates and Cox proportional hazards models were employed for statistical analyses. Targetscan and Pictar genomic sequence analyses were utilized to identify gene targets of specific microRNAs.

Results: Of 443 patients, median age 58 (range: 30-90 years), all underwent primary surgery of which 76% underwent optimal (< 1cm residual disease) cytoreduction. The majority (92.8%) had advanced stage disease and all tumors were of serous histology. 88.3% underwent platinum and taxane-based adjuvant chemotherapy. The overall five-year survival was 32.2 ±3.3% (median survival: 29 months). Patients with elevated miR-206 expression had significantly longer mean progression-free survival (29.2 vs. 21.6 months; p=0.038) and overall survival (55.8% vs. 30.2%; p=0.009). MiR-517a was also associated with an improved survival (47.3% vs. 30.6%; p=0.055). On multivariate analysis, elevated miR-206 (HR: 0.77; 95%CI: 0.60-0.98; p=0.035) remained as an independent prognostic factor for improved survival after adjusting for age, stage and residual disease. Both mouse and human notch3 were identified as target genes associated with miR-206 under miRanda algorithm for complementarity.

Conclusions: Our data suggests that miR-206 is associated with recurrence and survival in serous epithelial ovarian cancer. Targeting microRNA expression may have significant promise in the treatment of ovarian cancer.
A PHASE 2 STUDY OF CEDIRANIB IN RECURRENT OVARIAN CANCER: FINAL RESULTS OF A PMH, CHICAGO AND CALIFORNIA CONSORTIA TRIAL


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Background: Cediranib is a potent inhibitor of all 3 vascular endothelial growth factor receptors. The study was initiated to evaluate the activity of cediranib in pts with recurrent ovarian, peritoneal or fallopian cancer.

Methods: Patients (pts) with ECOG < 2 and adequate organ function were eligible. Prior chemotherapy up to one line was permitted. The initial starting dose of cediranib was reduced from 45 mg orally daily (od) to 30 mg od continuously because of toxicity. The primary endpoint was objective response rate and progression-free survival at 16 weeks. This study was stratified into two arms: platinum-sensitive (pl-s) and platinum-resistant (pl-r).

Results: 74 pts were enrolled. 62 pts had ovarian, 8 peritoneal, 4 Fallopian tube cancer. 39 pts were pl-s and 35 pts were pl-r. Median age: 58 years (range 31-87), ECOG 0/1/2:38/30/6 pts. Most frequent adverse events were fatigue (91%), diarrhea (86%), hypertension (81%), headache (64%). Response and prolonged stable disease rate was 54%/31% for pl-s and pl-r pts respectively. In pl-s group, there have been 9 confirmed PR while no confirmed PR was observed in the pl-r arm. The median time to progression for all pts was 4.9 mo (95% CI 3.7-7.0) (7.2 mo (3.9-9.4) for pl-s, and 3.7 mo (3.3-4.5) for pl-r). The medial survival was 18.3 mo (95% CI: 13.5-35.0) (24 mo( 17.1-not reached) for pl-s, and 10.6 mo (8.1-18.9) for pl-r).

Conclusions: Cediranib is well tolerated at 30 mg od and shows significant activity in recurrent ovarian cancer.
ANTI-GLYCAN ANTIBODIES AS NEW OVARIAN CANCER TUMORMARKERS IDENTIFIED USING PRINTED GLYCAN ARRAY

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Introduction: Epithelial ovarian cancer has the highest mortality rate among gynaecological cancers. Altered glycosylation of proteins and lipids is associated with oncogenic transformation producing tumor-associated carbohydrate antigens. We investigated the potential of anti-glycan antibodies in the diagnosis of non-mucinous ovarian cancers using a printed glycan array containing 203 glycans.

Material and methods: Serum samples were collected from healthy controls (n=24) and non-mucinous borderline tumor and ovarian cancer patients of various FIGO stages (n=33) following written informed consent. After incubation, anti-glycan antibodies bound to printed glycans were detected via biotin-streptavidin fluorescence. Following normalization and transformation, data were analyzed by univariate feature selection and multivariate hypothesis testing using Matlab and R.

Results: High reproducibility in measuring anti-glycan antibodies was found overall with cluster analysis demonstrating repetitive patterns of specific core carbohydrate structures within 21 clusters: N-linked glycans (11 clusters), O-linked glycans (3 clusters), glycosphingolipids (2 clusters), not clearly sub-specifiable structures (5 clusters). Binary classifiers revealed 24 glycans including P₁ (Galα1-4Galβ1-4GlcNAcβ; p< 0.001) significantly discriminating between ovarian cancers, borderline tumors and healthy controls. Higher sensitivity and specificity than CA125 was achieved by a panel of multivariate selected and linear combined anti-glycan antibody signals (83.3% and 84.8%, respectively).

Conclusion: Using anti-glycan antibody profiles we detected ovarian borderline and malignant tumors with a higher sensitivity and specificity than CA125, indicating a potential for the development of a new generation of biomarkers for ovarian cancer.
FREQUENT INACTIVATION OF HSRBC IN OVARIAN CANCERS BY PROMOTER CPG ISLAND HYPERMETHYLATION

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Objective: Mutation and altered expression of hSRBC, a novel tumor suppressor located at 11p15, have been observed in several human cancers. To explore the implication of hSRBC abnormality in ovarian tumorigenesis, we investigated expression and mutation of hSRBC in cancer cell lines and primary carcinoma tissues.

Methods: hSRBC expression was characterized by polymerase chain reaction (PCR) analysis. Promoter CG dinucleotide (CpG) site methylation was determined using methylation specific PCR and bisulfite sequencing.

Results: Expression of hSRBC transcript was easily detectable in all normal tissues we examined, but 50% (2 of 4) of cancer cell lines and 41% (9 of 22) of primary carcinomas exhibited undetectable or substantially decreased expression. While genomic deletion or somatic mutations of the gene were not identified, its expression was reactivated in tumor cells by 5-aza-2′-deoxycytidine treatment, suggesting epigenetic inactivation of the gene in tumors. Promoter methylation was detected in all 9 tumors with low expression but in only 1 of 13 (7.7%) tumors with normal expression. Bisulfite DNA sequencing analysis of 23 CpG sites within the promoter region revealed that the CpG sites are highly methylated in low-expressing tumors. In addition, promoter CpG sites methylation status showed a tight association with gene expression level.

Conclusion: Our data demonstrate that epigenetic inactivation of hSRBC due to aberrant promoter hypermethylation is a common event and might be implicated in human ovarian tumorigenesis.
CYTOTOXIC EFFECT AND INDUCTION OF APOPTOSIS IN HUMAN OVARIAN CANCER CELLS BY ANTRODIA CAMPHORATA

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Antrodia camphorata is a Chinese herb indigenous to Taiwan. Recently, several reports have demonstrated that it can induce apoptosis in some cancer cells. The purpose of this study was to investigate whether the crude extract of A. camphorata could induce apoptosis in ovarian cancer cells and the possible mechanisms involved. We also examined the cytotoxic effects of paclitaxel, A. camphorata, and their combination.

Two human ovarian cancer cell lines, SKOV-3 and TOV-21G, were treated with A. camphorata. The cytotoxic effect was tested by MTT assay. Activities of caspase-3, -8, and -9 of the apoptotic pathways were examined using caspase activity assay. The expressions of cytochrome c and Bcl-2 family proteins were examined by Western blot analysis. Cell lines were treated with A. camphorata (30 µg/ml), paclitaxel (0.003 µg/ml), or both to compare the cytotoxic efficiency.

A. camphorata induced cytotoxic effect on both the cell lines in a dose- and time-dependent manner. Altered expression of Bcl-2 family proteins was noted with increased Bad in SKOV-3 cell and increased Bim and Bak in TOV-21G cell. The activity of caspases and release of cytochrome c in both ovarian cancer cells were also increased. These findings indicate that the cytotoxicity induced by A. camphorata is through apoptosis. Finally, an enhanced cytotoxic effect was observed by combination of A. camphorata with paclitaxel (P < 0.001 for SKOV-3 and P < 0.05 for TOV-21G).

From the results of this study, we suggest that A. camphorata could be a potentially adjunct anticancer agent in treating ovarian cancer.
TARGETED ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR PATIENTS WITH PRIMARY AND RECURRENT EPITHELIAL OVARIAN CANCER

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World wide, there are more than 190,000 new cases of ovarian cancer each year, accounting for 4% of all cancers diagnosed in women. Ovarian cancer is the second most common gynecological malignancy and the leading cause of death from gynecological malignancies in the western hemisphere. It is a unique clinical and molecular complex disease. The majority of patients with ovarian cancer present late with advanced disease (FIGO stage III/IV), and despite the evolution of surgical techniques and designed chemotherapy regimens, median survival is on average 3 years. Anti-vascular endothelial growth factor, and proapoptotic strategies are effective in both primary and recurrent ovarian cancer. Targeting of one form of DNA repair affects cell survival in those with a hereditary failure to repair DNA damage using another mechanism. The most advanced molecular therapies target angiogenesis and (VEGF, VEGFR), PARP and mTOR inhibitors represent a significant therapeutic progress. Anti-VEGF drugs, such as Bevacizumab have shown to be an effective single agents in chemotherapy-resistant ovarian cancer, supporting the rationale for the utility of this strategy. Biomarkers of response such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), Fluorothymidine (FLT) PET imaging, circulating endothelial cell (CEC), and endothelial progenitor cell (CEP) enable a better selection of patients who will benefit from treatment and ascertain optimal dosing. To conclude, the ultimate goal for a successful therapy is to individualize and tailor the drugs to ovarian cancer biology.
HUMAN TRA2-BETA1 AND ACIDOSIS REGULATE CYR61 (CCN1) ALTERNATIVE SPICING

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Background and aims: Recently, we first described alternative splicing and the existence of two mRNA variants for the tumor-relevant pro-angiogenic Cysteine rich 61 (Cyr61/CCN1) gene, whereas only one mRNA variant, that is triggered by hypoxia, contributes to the generation of biologically active Cyr61 protein, thereby promoting aggressive cancer phenotypes. Here we investigated the molecular account of the reversible alterations in Cyr61 alternative splicing caused by hypoxia or its impacts.

Methods: Acidosis treatment (0.2% lactic acid, pH of 6.2, 24hrs) in gynaecological cancer cell lines controlled by RT-PCR. Immunocytochemistry with avidin / biotin method. Transfections with Tra2-beta1-shRNA-Plasmids.

Results: Analogous to hypoxia, acidosis lead to an increased expression of the protein-generating transcript. shRNA-mediated knock-down of splicing factor Tra2-beta1 initiated the same effect on Cyr61 alternative splicing like acidosis. Tra2-beta1 protein localization switched from nuclear expression under normal culture conditions to complete deficiency of nuclear Tra2-beta1 protein, in contrast to a markedly cytoplasmatic expression under acidosis. Acidosis-driven alterations in alternative splicing pattern could be detected on mRNA and protein level. The Tra2-beta1-knockdown effect on Cyr61 alternative splicing was detectable on the mRNA level only.

Conclusion: According to our recent findings Cyr61 alternative splicing is influenced by acidosis, a concomitant phenomenon of proliferating, hypoxic cancer cells. We hypothesize that Cyr61 alternative splicing is controlled by the splicing factor Tra2-beta1. Proof is provided due to the facts that Tra2-beta1 protein localization is acidosis-dependent, and that elimination of the transcription factor Tra2-beta1 triggers the same effect on Cyr61 alternative splicing like acidosis or hypoxia, respectively.
POSSIBLE INVOLVEMENT OF BMP SIGNALING IN REGULATING T CELL DIFFERENTIATION AND IL-2 PRODUCTION

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Objectives: Morphogen have roles not only in the developmental patterning but also in the immune system. We investigated possible roles of Bone Morphogenetic Protein (BMP) in T cell function and found that BMP, which had been almost unrecognized in immunology, controlled the differentiation of T cells and their cytokine production.

Methods: We employed small molecule which inhibit the downstream signaling of BMP, then analyzed

(1) T cell proliferation,

(2) IL-2 production in T cell and T cell activation, and

(3) helper T cell differentiation.

Results: We found that BMP modulated IL-2 production in T cells. Importantly, the blockade of BMP signaling pathway by a small molecule decreased IL-2 transcription. Also, the small molecule suppressed cell proliferation in T cells via a G1/S phase cell cycle arrest in association with increased levels of the p27Kip1, a cyclin-dependent kinase inhibitor, suggesting that anergy was induced by this small molecule. Interestingly, the signaling blockade suppressed Th cell polarization in mouse T cells.

Conclusion: Collectively, our data suggest that BMP controls IL-2 production in T cell and T cell differentiation.
A POSSIBLE CLINICAL ADAPTATION OF CRM197, A SPECIFIC INHIBITOR FOR HB-EGF, WITH CONVENTIONAL CHEMOTHERAPEUTIC AGENTS ON OVARIAN CANCER

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Aim: Heparin-binding EGF-like growth factor (HB-EGF) is thought as a promising target for cancer cells with dominant HB-EGF expression. We have reported antitumor effects of CRM197, a specific inhibitor for HB-EGF, on ovarian cancer cells and already started a phase I clinical trial of CRM197 for advanced ovarian cancer. Now we discuss here a possible clinical adaptation of CRM197 in combination with conventional chemotherapeutic agents.

Methods: 5x10⁶ ES2 human ovarian cancer cells were injected subcutaneously into nude mice at 5 weeks of age. CRM197 (C; given every day for 10 doses at 1mg/kg), bevacizumab (B; given every 4 days for 5 doses at 5mg/kg), and paclitaxel (P; given every week for 4 doses at 20mg/kg) were administered intraperitoneally, alone or in combination, into tumor-bearing mice. The tumor volume and microvessel density (MVD), individual counts of microvessels highlighted with anti-CD31 mAb on a x200 field, were determined. Statistical analysis was performed to compare tumor volume and MVD between xenografted mice divided by dosing strategy on chemotherapeutic agents.

Results: Tumor volume (mean±SE, n=8) of 5 weeks after cell injection is followings, control (without administration): 5,635±517mm³, P: 3,742±310mm³, P+C: 2,154±132mm³, P+B: 3,885±350mm³, P+C+B: 2,339±316mm³. MVD (mean±SE, n=8) of 5 weeks after cell injection is followings, control: 141.3±9.9, P: 140.3±4.3, P+C: 72.0±4.3, P+B: 105.0±5.6, P+C+B: 65.3±5.5.

Conclusion: CRM197 blocked tumor formation and angiogenesis significantly in a combination with paclitaxel. These results suggested that HB-EGF control the upstream signal of vascular endothelial growth factor.
INDOLEAMINE 2,3-DIOXYGENASE (IDO) AND FOXP3 EXPRESSION IN VULVAR SQUAMOUS CELL CARCINOMA - NEW TARGETS TO PROMOTE EFFECTIVE IMMUNE RESPONSE

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Background: Regulatory T cells (Tregs), and IDO, an immunosuppressive enzyme, are associated with more advanced disease in some cancers and may promote immunologic tolerance to tumors. The aim of the study was to evaluate the expression of Foxp3, a marker of Tregs, and IDO in vulvar squamous cell carcinoma (vSCC) and to verify their prognostic significance. Inhibitors of IDO are available and could potentially be used in vulvar cancer if IDO drives progression of disease.

Methods: Seventy-six primary tumours, 32 lymph node metastases, 28 non-metastatic lymph nodes and 12 recurrences at the primary site and 3 inguinal recurrences were analysed using immunohistochemistry.

Results: Upregulation of IDO in vSCC cells was associated with an increased number of Tregs. Cytoplasmic IDO expression was present in all tumors from patients with lymph node metastases. Intensity of staining was stronger in the corresponding lymph node metastatic foci when compared with the primary tumor. Foxp3 regulatory T cells were increased in lymph nodes containing metastatic tumor cells expressing IDO. The Foxp3+/IDO+ group almost exclusively consisted of cancer patients with node positive disease. IDO expression in vSCC patients with lymph node-positive metastases correlates with decreased survival.

Conclusions: These data support the notion that metastatic vSCC cells select for overexpression of IDO to evade immunologic detection. Inhibition of IDO in vSCC patients can be useful to enhance.
PROGNOSTIC SIGNIFICANCE OF CD4+ AND CD8+ T CELLS INFILTRATION WITHIN CANCER CELL NESTS IN VULVAR SQUAMOUS CELL CARCINOMA (VSCC)

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The clinicopathological significance of the spontaneous immune reaction in situ of vSCC, remains unclear. The purpose of this study was to clarify the role of different cell types, both individually and synergistically.

Methods: 76 patients with verified histopathological data and full clinical history were included into the study. We collected 76 paraffin-embedded samples of the primary tumour and 13 cases of local recurrences. The presence of CD4+ and CD8+ T cells was evaluated by immunohistochemistry and compared with commonly recognized prognostic factors. The primary end point analyzed was the overall survival.

Results: CD4+ and CD8+ T cell infiltration was detected in the cancer cell nest as well as stroma but only the infiltration within cancer cell nests was analyzed. There was significant correlation (Spearman's rho test R= 0.282, p= 0.014) between the number of intratumoral CD4+ and CD8+ T cells. The number of CD4+ T cells was inversely correlated with depth of cancer invasion (Spearman's rho test R=0.283, p=0.022). No correlation was observed between the number of CD4+ and CD8+ T cells and patients prognosis (Fig.1). Patients were classified into the following four groups based on median value CD4+/CD8+, CD4+/CD8-, CD4-/CD8+, CD4-/CD8-. There was no difference in overall survival between these groups in our series (Fig.2).

Conclusions: These data support that CD4+ and CD8+ T cells cooperate within cancer cell nests but this spontaneous immune reaction does not correlate with vSCC patient prognosis.
A BTB/POZ GENE, NAC-1, A TUMOR RECURRENCE-ASSOCIATED GENE, AS A POTENTIAL TARGET FOR TAXOL RESISTANCE IN OVARIAN CANCER

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Purpose: We previously determined that NAC-1, a transcription factor and member of the BTB/POZ gene family, is associated with recurrent ovarian carcinomas. In the current study, we investigated further the relationship between NAC-1 expression and ovarian cancer.

Experimental design: NAC-1 expression was assessed by immunohistochemistry, and clinical variables were collected by retrospective chart review. SiRNA system and NAC-1 gene transfection were used to assess NAC-1 function in Taxol resistance in vivo.

Results: Overexpression of NAC-1 correlated with shorter relapse-free survival in patients with advanced stage (stage III/IV) ovarian carcinoma treated with platinum and taxane chemotherapy. Furthermore, overexpression of NAC-1 in primary tumors predicted recurrence within 6 months after primary cytoreductive surgery followed by standard platinum and taxane chemotherapy. NAC-1 expression levels were measured and compared among the human ovarian cancer cell line (KF28), cisplatin-resistant cell line (KFr13) induced from KF28, and paclitaxel-resistant cell lines (KF28TX and KFr13TX) induced by exposing KF28 and KFr13 to dose-escalating paclitaxel. Overexpression of NAC-1 was observed in only the Taxol-resistant KF28TX and KFr13 TX cells but not in KF28 or cisplatin-resistant KFr13 cells. To confirm that NAC-1 expression was related to Taxol resistance, we used two independent but complementary approaches. NAC-1 gene knockdown in both KF28TX and KFr13TX rescued paclitaxel sensitivity. Additionally, engineered expression of NAC-1 in RK3E cells induced paclitaxel resistance.

Conclusions: These results suggest that NAC-1 regulates Taxol resistance in ovarian cancer and may provide an effective target for chemotherapeutic intervention in Taxol-resistant tumors.
NUTRITIONAL STATUS AND SURVIVAL AMONG PATIENTS WITH SUSPECTED OR PROVEN GYNECOLOGICAL MALIGNANCIES

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Background: Malnutrition is a complex, multifactorial problem, commonly seen in patients with aggressive cancers. Our aim was to evaluate the importance of nutritional status for survival outcomes among patients with suspected or proven gynecological malignancies.

Methods: We prospectively collected information on nutritional status of 200 patients treated between 2004 and 2006 at a tertiary referral centre for gynecological cancers in Australia. Patient Generated Subjective Global Assessment (PG-SGA) was used to assess nutritional status. Kaplan-Meier method was used to estimate survival and log rank test was used to compare survival between well-nourished (PG-SGA A) and malnourished (PG-SGA B & C) patients. Cox proportional hazards models were used to evaluate the importance of nutritional status for relapse-free (RFS), disease-specific (DSS), and overall survival (OS).

Results: The mean (SD) age at diagnosis was 57.6 (13.5) years with 57 (28.5%) patients classified as moderately (PG-SGA B) or severely malnourished (PG-SGA C). Malnourished patients had significantly worse RFS, DSS and OS (p < 0.002 for all) when compared to well-nourished patients. After adjusting for age, presence of malignancy, presence of ovarian cancer, hypoalbuminemia, obesity and multiple comorbidities, malnourished patients had a hazards ratio (95% CI) of 3.3 (1.4-8.1), 4.2 (1.5-11.5) and 2.5 (1.0-6.3) for RFS, DSS and OS respectively, when compared to well-nourished patients.

Conclusion: Nutritional status prior to treatment has a major impact on relapse-free, disease-specific and overall survival in patients with suspected or proven gynecological malignancies. To improve outcomes, evidence-based nutritional interventions are required at the time of diagnosis.
THE CONTRIBUTING ROLE OF ICC (INTERSTITIAL CAJAL CELLS) IN ADENOMYOSIS SYMPTOMS

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Background: Adenomyosis is a frequent disorder in adult women characterized by haphazard location of endometrial glands and stroma within the myometrium of uterus. The conservative treatments fail and the hysterectomy is the sole choice.

Aim: The study proposes the investigation of the presence and pattern of the distribution of ICC at the boundaries of the adenomyosis nodules. The existence of ICC in myometrium enhances our understanding of uterine contractile activity.

Methods: 40 female inpatients (n=40) underwent genital surgery in the “Sfantul Ioan” Emergency Hospital in 200. for adenomyosis condition. After the histopathology diagnosis put on hematoxilin eosin stain, the specimens were analysed immunohistochemical, using the ABC method, applied on: CD10 (useful marker for normal endometrial stroma), CD117/ c-kit (selective marker for ICC) and vimentin (for ICC noncontractile types), the two lasts single and in double-staining.

Results: The most affected women were 31-40 aged (50%) and the most frequent symptoms for hospitalization were the bleeding (30/75%) and the pain (27/67.5%). The HE staining revealed the disordered arrangement of the smooth muscle of myometrium. The immunostaining of the c-kit (31/77.5%) and vimentin (11/27.5%) was around and between the stroma and glands of adenomyosis, and between the smooth muscle fibers of myometrium. The double staining of the ICC showed the location of these between the stromal elements and in the proximity of the adenomyosis glands.

Conclusions: The results suggest that the dysperistalsis of the uterus during menstrual cycle, with adenomyosis condition, might be connected on a KIT signaling pathway of ICC.
PACLITAXOL INDUCE OXIDIZED LIPID CHANGE IN HUMAN CERVICAL CANCER CELL DETECTED BY MALDI-SPECTROMETRY

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Cervical cancer is the third most common cancer in women worldwide. The Median survival of patients with advanced or recurrent cervical carcinoma is generally poor. Fewer than 20% of these patients survive beyond 1 year. In a recent GOG study, paclitaxol combined with cisplatin showed a better response and survival rate in these patients than cisplatin alone. Although the MAPK-mediated changes were well associated with the effectiveness of paclitaxol, however, the effects of MAPK alteration on the phospholipid metabolism has yet to be revealed in cancer treatment, in despite of the close association between MAPK and phospholipase A2. We first establish such connections by measuring the phospholipid changes of cervical cancer cells cultured with paclitaxol.

Hela cells, a human cervical cancer cell line, was grown into confluence, and cultured with with paclitaxol (500 mmol/ml) for 24 hours. Cells were collected for flow cytometry analysis and phospholipid lipid profiling by MALDI-MS. The flow cytometry results indicated that an increased population of cells in the sub-G1 phase associated with apoptosis was observed after paclitaxol treatment. The MALDI-MS profiling indicate that several phosphatidylcholines (PCs) was significantly reduced after treatment, whereas a few lysophosphatidylcholine (Lyso-PC) species in the paclitaxol-treated cells were increased. The result suggested that paclitaxol may express its therapeutic efficacy to cervical cancer cell through the PLA2-catalyzed hydrolysis of PCs, as well as MAPK-mediated effects to signify its therapeutical effects. Such may be an opportunity for the development of new treatment regimens that will benefit in the treatment of cervical cancer.
THE COST OF COMPLICATIONS: HOSPITAL COSTS ASSOCIATED WITH SURGICAL ADVERSE EVENTS IN GYNECOLOGICAL ONCOLOGY

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Background: The incidence of Adverse Events (AE) was prospectively studied over 18 months from January 2007 and published previously (Kondalsamy-Chennakesavan et al. Gynecologic Oncology, 2009;115(3):329-33). The aim of this current study was to evaluate hospital costs associated with AEs among patients who had an abdominal or laparoscopic procedure performed at a tertiary gynecological cancer centre in Australia.

Methods: Data on AEs were matched with cost data (AUD$) from the hospital’s clinical costing unit. Total costs were adjusted for various clinical factors and estimated using log-transformed ordinary least squared regression. From available data, we also estimated the costs of AEs Australia-wide.

Results: A total of 369 patients had a major surgical procedure of which 95 patients (26%) had at least one AE. Patients with AEs incurred an extra $12,532 on average, adjusted for age, comorbidities, cancer site, major or minor complications, surgical complexity, presence of malignancy and abdominal surgery. Mean adjusted costs of AEs were significantly higher if the complication was major ($66,054); if the AE occurred in a patient who had had complex ($16,682) or very complex surgery ($29,813), if the original operation was performed for a malignant tumor ($16,844) or if a laparotomy was performed ($17,639). Australia-wide, the cost for AEs in gynecological oncology is estimated to be $29.3 million/year. Twenty-six per cent of all patients who had at least one AE utilized 40% of the hospitalization costs in this patient group.

Conclusion: AEs are associated with significantly increased hospitalization costs. Appropriate evidence-based interventions are urgently required to minimize adverse events.
ERYTHROPOIETIN AND ANGIOPOIETIN EXPRESSION IN UTERINE TUMORS: HOW DO UTERINE TUMORS MAINTAIN CELL VIABILITY TO BECOME VERY LARGE?

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Background: Uterine smooth muscle tumors often grow very large without degeneration or necrosis. Characterizing this common tumor will contribute to understanding the mechanisms of growth and maintenance of neoplasms, including malignant tumors. The expression of erythropoietin (EPO) and its receptor in cancerous tissues produces angiogenic or mitogenic effects. We therefore determined the effects of EPO on the growth of the uterine leiomyomas and malignancies.

Materials and methods: We examined 31 leiomyomas, 5 normal myometria, 3 leiomyosarcomas, and 5 endometrial carcinomas. Expression of EPO and the EPO-induced angiogenic factors angiopoietin 1 (ANG1) and vascular endothelial growth factor (VEGF) were determined by real-time RT-PCR. Cell proliferation and blood vessel density and maturity were assessed by immunostaining for MIB-1 and CD34, respectively.

Results: In 70% of leiomyomas, EPO expression was higher than in normal myometria; however, EPO mRNA was not detected in leiomyosarcomas. Blood vessel maturity was a prominent feature of EPO-positive leiomyomas, although blood vessel density and cell proliferation were not increased compared with EPO-negative leiomyomas. ANG1 mRNA levels were correlated with EPO mRNA levels in leiomyomas. Leiomyosarcomas strongly expressed ANG1 but not EPO or VEGF, whereas endometrial carcinomas strongly expressed VEGF but not EPO or ANG1.

Summary: EPO increases leiomyoma blood supply by enhancing blood vessel maturity through ANG1, allowing the tumor to grow without degeneration. Our results also suggested that ANG1 may be involved in leiomyosarcoma growth.
HNRNP G AND HTTRA2-BETA1: OPPOSITE REGULATION OF ESTROGEN RECEPTORΑ Δ7 WITH DIVERGENT IMPACT ON TYPE I ENDOMETRIAL CANCEROUTCOME

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Background: Estrogen receptorα (ESRα) expression pattern is subjected to alternative splicing. Its exon7 skipping (Δ7) is the most frequently detected isoform in normal and cancer endometrial tissue. Δ7 higher expression was found in well/moderate differentiated than poorly differentiated endometrial cancer (EC), but its prognostic significance in EC has not been established. Two functional opponents in alternative splicing: hnRNP G and hTra2-beta1 have been shown posing opposite effects on EC prognosis. In this study we intended to find out if Δ7 concentration influence Type I EC outcome and if hnRNP G, hTra2-beta1 influence ESRα exon7 splicing pattern.

Methods: 116 Type I EC patients’ tissue RNA was extracted from paraffin samples. Δ7, hnRNP G and hTra2-beta1 mRNA levels were detected by real-time PCR, respectively. Ishikawa cells were used for analyzing hnRNP G and hTra2-beta1’s influence on endogenous expression pattern of Δ7.

Results: ESRα Δ7 was detected in 70 patients. Its mRNA level was found inversely related to tumor grade (R= -0.330, p= 0.000), FIGO stage (R= -0.243, p=0.027) and hTra2-beta1mRNA level (R= -0.337, p= 0.000), respectively. Furthermore, higher Δ7 expression correlated to an improved progression-free (p= 0.038) and disease-specific survival (p= 0.026). In vitro experiments suggested that hnRNPG/hTra2-beta1 mRNA ratio correlated with Δ7 expression ratio. HTra2-beta1 promoted exon7 inclusion, while hnRNP G antagonized this effects and promoted exon7 skipping (p= 0.020).

Conclusion: Our study demonstrates the opposite regulatory effects of hnRNP G and hTra-beta1 influence ESRα exon7 splicing pattern which is directly correlated to Type I EC patients’ outcome.
P14ARF EXPRESSION PATTERN IN PRIMARY AND METASTATIC ENDOMETRIAL CARCINOMAS

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p53-Pathway (p14ARF/MDM2/p53) alterations play a crucial role in the development and progression of various human neoplasms, including endometrial carcinoma (EC). The aim of the current research was to examine the p14ARF expression pattern in primary ECs and corresponding metastatic lesions. We studied 47 primary ECs and corresponding metastatic lesions applying immunohistochemistry. Protein expression was predominantly nuclear, present in 32 out of 47 (68%) primary cases and in 28 out of 47 (60%) metastatic lesions. There were seven p14ARF-positive primary tumors showing negative reactivity in the metastatic lesions. Three cases lacked protein immunoreactivity in the primary ECs but revealed weak nuclear staining in the corresponding metastases. A trend was found between p14ARF expression in primary tumors and the presence of the neoplasms in the fallopian tube (p=0.063), but none of other clinico-pathological variables of carcinoma was related to protein immunoreactivity in advanced-stage uterine neoplasms. p14ARF Expression in EC metastases was related to the presence of the primary tumor in the fallopian tube (p=0.036). p14ARF Expression was not associated with unfavorable outcome both in primary tumors (p=0.302) and in corresponding metastases (p=0.217). There was also no relationship between p14ARF expression pattern and TP53-pathway alterations. Altogether, p14ARF protein is expressed in more than half of primary ECs and metastatic lesions analyzed, and is associated with the transtubal dissemination of the primary tumor. The pattern of p14ARF expression is not associated with the alterations of other TP53-pathway members in advanced-stage human ECs.
SYNCHRONOUS PRIMARY NEOPLASMS OF THE FEMALE REPRODUCTIVE TRACT

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Aims: To evaluate the frequency of synchronous gynecologic cancers in Turkish women.

Methods: A population-based longitudinal cohort study was conducted using Izmir Cancer Registry (ICR) data on gynecologic cancer patients diagnosed in the period 1993 to 2005. The registry covers the 3 million population of Izmir and has been collecting data on cancer incidence and survival of cancer patients since 1992. The ICR collects data on all new cases of cancer from all the hospitals (n = 22) in the city.

Results: A total of 4185 women were identified with gynecologic cancer between 1993 and 2005. Of the 4185 patients, 1526 had endometrial tumor, 1206 had cervical cancer, 1198 had ovarian cancer, 115 had vulvar cancer, 67 had other uterine cancers (sarcoma etc.), 33 had vaginal cancers, 40 had other gynecologic cancers (tuba uterina etc.). Fifty-five (1.3%) patients with invasive synchronous primary cancers were identified among 4185 patients. 43 of 55 tumor pairs were the pair of endometrium-ovaries (81%). 66/110 (60%) cancer type were the endometrioid adenocarcinoma.

Conclusions: Independent primary tumors of the endometrium and ovary are the most commonly encountered synchronous tumors of the female genital tract and endometrioid adenocarcinoma is the most frequent cancer in synchronous gynecologic tumors.
DEVELOPMENT OF A UTERINE TRANSPLANTATION MODEL IN ANIMALS USING THE SUPERMICROSURGERY TECHNIQUE

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In recent years, the number of young patients with uterine cancer has been increasing. In addition, the loss of fertility due to the removal of the uterus leads to a decrease in QOL. Allogeneic uterus transplantation can be a promising solution for these young patients. Conventionally, in the field of plastic surgery, autologous tissue transplantation and severed tissue replantation have been performed on the microvascular anastomosis technique. Based on these experiences and techniques, we have developed an autologous uterine transplantation model in animals using the supermicrosurgery technique and hereby report the results.

With the approval of the institutional Ethical Review Board, the autologous uterine transplantation experiment was performed using two Cynomolgus monkeys (body weights 3.5 and 4.2 kg). Under general anesthesia, abdominal incisions were made and bilateral uterine arteries, comittant veins and deep uterine veins were dissected with careful attention to the ureters. The uterus was then removed with the vaginal stumps of approximately 5 mm attached. After perfusion of the uterus with heparin saline, the replantation was performed. The diameters of the uterine arteries and deep uterine veins were 0.8 and 0.6 mm, respectively. Using 11-0 and 12-0 nylon, end-to-side anastomoses were performed to the external iliac arteries and veins. The blood flow after the vascular anastomoses was satisfactory. Forty-two days after the operation, the survival of the replanted uterus was confirmed through the laparotomy. The estrogen and progesterone levels were also measured periodically.

We believe that this autologous uterine transplantation experiment model is beneficial to human uterine transplantation.
RAPID AND SENSITIVE HUMAN PAPILLOMAVIRUS GENOTYPING BY HIGH RESOLUTION MELTING ANALYSIS

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Purpose: Evidence is accumulating that HPV genotyping may be useful for patient management in the future. To establish a fast and cost-effective high resolution melting (HRM) assay system for the detection of the nine clinically most relevant high-risk HPV types.

Methods: Using high resolution melting analysis combine with multiple oligoantisense to distinguish HPV genotypes. HPV type was confirmed by sequence analysis. HPV DNA testing is done routinely for all patients who attend our dysplasia unit. We performed HRM analysis of the PCR products with the LightCycler 480 and used the melting profiles as molecular fingerprints for virus genotyping.

Results: Experiments with plasmid constructs of all 13 HR-HPV DNA showed that the HRM assay was highly sensitive and specific. Hence, an HRM database and a working protocol were established for the identification of these HPV subtypes. We are able to distinguish 9 HPV genotypes in single reaction, including HPV16, 18, 33, 39, 45, 52, 56, 58 and 68. And we can separate these 9 HPV genotypes into two groups, the single peak group (HPV18, 39, 45, 56) and the double peak group (HPV16, 33, 52, 58, 58) from derivative plot.

Conclusions: Our high resolution melting assay will be useful tool for genotyping and comparative quantitative analysis of high-risk HPV types. It is promising to use HRM to address questions related to viral persistence at the genotype level, the kinetics of viral load and disease recurrence.
A GENE EXPRESSION SIGNATURE THAT PREDICTS THE PROGNOSIS OF CERVICAL CARCINOMA PATIENTS

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Background and aims: To investigate whether gene expression profiling of cervical cancer can predict patient prognosis and establish a predictive method.

Methods: Gene expression profiles of 100 primary cervical cancer specimens obtained from patients who underwent radical hysterectomy between 2001 and 2007 were analyzed using a homemade oligonucleotide microarray containing 1440 human tumor-related gene transcripts.

Results: Supervised analysis of the gene expression data identified 19 genes that exhibited greater than a 2-fold change in expression between cervical cancer and normal cervix tissues. Real-time PCR analysis of KPNA2, SOD2 and LDHA was performed to confirm the microarray results. Based on the training data, a risk-score formula was obtained for each patient and we defined a 7-gene signature for predicting poor prognosis of patient. A comparison between expression of the seven-gene signature with clinicopathological factors showed that patients expressing the seven-gene signature (i.e. high-risk) experienced a worse prognosis than patients with a low-risk seven-gene signature for both the training set (n = 50, P = 0.026) and the testing set (n = 50, P = 0.042) of cervical cancer patients. The high-risk seven-gene signature was also found to be significantly associated with FIGO stage and tumor diameter, with multivariate analysis indicating that FIGO stage and the seven-gene signature are independent prognostic factors associated with the relapse-free survival of cervical cancer patients.

Conclusions: A seven-gene molecular signature for predicting the poor prognosis of cervical cancer patients was identified and may represent novel therapeutic targets for the treatment of cervical cancer.
HYPERTHERMIA ABROGATES THE Y-BOX BINDING PROTEIN-1 (YB-1) EXPRESSION

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**Introduction:** The application of hyperthermia as a therapy against various types of cancer started more than 100 years ago. Nowadays, in the clinic, hyperthermia can be used concomitant to chemotherapy or radiotherapy and may improve the effect of those classical treatments. In previous projects, we investigated the expression of different splicing factors, such as YB-1, in malignancies. Overexpression of YB-1 in malignant cells has been described in various studies and YB-1 seemed to play an important role in the development of tumors as well as in the occurrence of resistances to chemotherapies. In the present study we focussed on the effect of hyperthermia at a molecular level, specifically its impact on the expression YB-1 in cancers.

**Material and methods:** Various gynaecological cancer cell lines were cultured under hyperthermia (2h, 42°C) followed by maintenance under normal conditions (4h, 37°C). RNA and protein were isolated using TRIzol® method and expression levels were subsequently analysed by RT-PCR and Western Blot.

**Results:** The analyses revealed a markedly decreased level of YB-1 RNA and protein in the breast, cervical, endometrial as well as ovarian cancer cell lines treated with hyperthermia compared to the cell lines treated under normal condition.

**Conclusion:** Our results suggest that hyperthermia could have an impact on the expression of splicing factors such as YB-1. Thus, hyperthermia might be a way to influence the progression of malignancies and could improve the response to chemotherapeutical treatments.
MICROSATELLITE INSTABILITY AND PROGNOSIS IN ENDOMETRIAL CANCER IN PATIENTS AT THE BRAZILIAN NATIONAL CANCER INSTITUTE

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Defective DNA mismatch repair causes genomic instability in different regions, including those called microsatellite. The impact of microsatellite instability (MSI) on survival in endometrial adenocarcinoma was assessed. MSI frequency was evaluated in patients who underwent surgical treatment at our institution from January, 2000 to December, 2004. Tumor and normal tissue DNA was extracted from paraffin blocks. Five different microsatellite regions (from Bethesda Guidelines) were amplified by PCR technique and compared for identifying MSI by microfluidic electrophoresis.

317 patients were studied and median age was 64 (25-90). According to FIGO staging criteria 185 (58.4%) patients were stage I; 71 (22.4%) stage II; 48 (15.1%) stage III; 13 (4.1%) stage IV. Two groups of microsatellite status were compared: MSI-High and MSI-Low+Stable tumors (MSS). In 265 patients with complete panel, MSI High was present in 58 (21.9%) and MSI-Low+MSS in 207 (78%). Type I tumors were diagnosed in 81.1% (215) and MSI was present in 21.4% (46); Type II were detected in 17.7% (47) and MSI in 25.5% (12). Three (1.2%) were inconclusive. For survival tests 26 patients with a second primary tumor were excluded. In 239 remaining patients, Kaplan-Meier Test demonstrated overall survival wasn’t statistically significant (p=0.148) when MSI-High was compared to MSI-Low+MSS, but according to Cox Regression MSI-High (p=0.035), histologic grade (p=0.007) and FIGO staging criteria (p< 0.001) were significant. We conclude microsatellite instability is significant for overall survival outcome, suggesting its influence on prognosis is assertive.
DIFFERENT AMPLIFICATION PATTERNS OF THE HUMAN TELOMERASE RNA GENE IN INVASIVE CERVICAL CARCINOMAS AND CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE III

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The aim of this study is to compare the amplification patterns of the human telomerase RNA gene (hTERC) in invasive cervical carcinomas (ICC) and cervical intraepithelial neoplasia (CIN) grade III. Cervical liquid-based cytological specimens were collected from 53 squamous cell carcinomas (SCC), 14 CIN III and 20 normal controls. Copy numbers of the hTERC gene were measured by fluorescence in situ hybridization (FISH) using a dual-color probe containing the hTERC probe and the control, centromere chromosome 3-specific probe (CEP3). Nucleus with abnormal FISH pattern for hTERC was observed in 0.94% to 90.65% of SCC cells and in 0 to 85.59% of CIN III cells. Using the threshold of 5.89%, the occurrence of hTERC amplification in SCC and CIN cases is similar (90.6% vs 85.7%, P=0.630). However, in a total of 2162 SCC cells and 502 CIN III cells with abnormal FISH pattern, even gains of hTERC (hTERC:CEP3=1) were more common in CIN cells (62.5% vs 34.9%), while, extra gains of hTERC (hTERC:CEP3>1) were more common in SCC cells (65.1% vs 37.5%). Among those cells with extra gains, the 3:2 signal pattern was the leading pattern in CIN (51.5%), while more complex signal patterns other than 3:2 pattern were predominant in SCC (60.9%). The median percentage of cells with extra gains of hTERC in SCC was higher than in CIN III (64.3% vs 31.7%, P=0.001). Thus, hTERC amplification was common in cervical exfoliated cells from SCC and CIN III. More complex amplification patterns of hTERC were present in invasive cervical cancers.
HYPOXIA INDUCIBLE FACTOR-1A (HIF-1A) POLYMORPHISMS AND EARLY CERVICAL CANCER


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Human papillomavirus (HPV) could stabilize and induce hypoxia inducible factor-1α (HIF-1α) protein, which has been shown to be associated with diminished response to radiotherapy and poor prognosis for cervical cancer. HIF-1α polymorphisms (1772C>T and 1790G>A) in the N-terminal transactivation domain generate significantly increased transcriptional activity and have been associated with poor outcomes in different malignancies. The aim of this study was to analyze the possible influence of HIF-1α genetic polymorphisms on cancer susceptibility, tumor aggressiveness and survival of patients with early cervical cancer. One hundred ninety-nine patients with early cervical cancer who were treated with surgical resection were retrospectively investigated. HIF-1α 1772C>T and 1790G>A genetic polymorphisms were compared with two hundred five healthy subjects, and correlated with clinical outcomes of patients suffering from early cervical cancer. Risk of cervical cancer was not affected by HIF-1α 1772C>T and 1790G>A polymorphisms. However, lymph node metastasis was significantly increased in patients who had 1790 variant (OR=4.42; 95% CI 1.31-14.98; p=0.024). In survival analysis, HIF-1α 1772C>T and 1790G>A polymorphisms were not related to disease-free survival and overall survival. Although HIF-1α genetic polymorphisms had little association with cervical cancer risk and prognosis, individual variance of HIF-1α expression may be associated with cervical cancer invasiveness.
INCIDENCE OF BRCA FOUNDER MUTATIONS IN JEWISH PATIENTS WITH UTERINE SEROUS CARCINOMA

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Background: Uterine serous carcinomas (USC) are histologically similar to ovarian serous carcinoma. No consensus exists regarding the risk of USC in BRCA heterozygotes. We hypothesized that the prevalence of founder mutations in Ashkenazi Jewish (AJ) patients with USC is greater than population estimates.

Methods: All AJ patients diagnosed with USC between January 1998 and November 2009 at a single institution were identified. Demographic and clinical information were collected from medical records. Germline DNA was isolated from archival tissue, anonymized, and genotyped for the 3 common AJ BRCA founder mutations (BRCA1 185delAG and 5382insC; BRCA2 6174delT) using a Taqman allelic discrimination assay. Mutations were confirmed with direct sequencing.

Results: Of 71 patients identified, 68 had adequate tissue for analysis. The mean age was 68 ± 9 years. 44% recurred with a progression free survival of 65.9 months [CI 9.3-122.6] and an overall survival of 66.3 months [CI 37.7-94.9]. One patient (1.5%) was found to have a BRCA2 6174delT mutation (P = 0.98). This patient had stage IIIA USC and was diagnosed at age 47. No mutations in BRCA1 were identified.

Conclusion: In this series, the incidence of BRCA mutation is no greater than expected for the AJ population. The data suggest that AJ BRCA founder mutations do not significantly increase the risk of USC. Based on these findings and others, risk-reducing hysterectomy solely for the prevention of USC in AJ BRCA heterozygotes does not appear indicated.
ENDOCERVICOSIS: CAUSE OF AN EXTRAOVARIAN MUCINOUS CYSTADENOCARCINOMA

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Background: Although extraovarian mucinous cystadenocarcinomas (EMC) resemble primary ovarian carcinomas both histologically and clinically, their specific etiology is not clear. More insight into the specific etiology may be of value in determining adequate therapy.

Aim: To obtain more insight into the etiology of EMC.

Methods: A 40-year-old woman, with no prior history of malignancy developed an EMC. Point mutation of KRAS is the most common molecular genetic alteration in ovarian mucinous borderline tumors and ovarian mucinous carcinomas. Therefore, next to histologic analysis, KRAS mutational analysis was performed by direct sequence examination of a 169-bp semi nested PCR product.

Results: Foci of benign mucin-secreting endocervical-type glands, so-called endocervicosis, were identified either within or adjacent to the neoplastic components. In addition to this endocervicotic lesions, endocervical-type glands with variable degrees of architectural and cytologic atypia were present, showing a transition from the foci of endocervicosis to the invasive component. Further analysis of the adenocarcinoma cells by KRAS mutational analysis revealed them to be positive for a G>A mutation at position 2 of codon 12, leading to an amino acid substitution of Gly (GGC) into Asp (GAT), whereas the cells of the benign glands did not contain a mutation.

Conclusion: This is the first report that shows neoplastic transformation of endocervicosis into an EMC. The histological spectrum and specific KRAS mutational analysis for this tumor were the same as for their ovarian counterparts. This supports the current approach to treat patients with EMC the same as patients with their ovarian counterparts.
A12 MONOCLONAL ANTIBODY AGAINST IGF-IR IS A POTENTIAL THERAPEUTIC STRATEGY IN ENDOMETRIAL CANCER

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Endometrial cancer is the most frequent gynecologic cancer in Western countries. The majority of the cases can be divided into two categories: Type I and Type II cancers. The insulin-like growth factors (IGFs) have been implicated in the etiology of a number of malignancies, including endometrial cancer. However, no study has addressed the potential impact of IGF-IR targeting in endometrial cancer.

The aim of our research was to evaluate the biological and molecular effects of treatment with a monoclonal antibody against IGF-IR in endometrial cancer cell lines.

A12 monoclonal antibody effectively inhibited IGF-IR activity in Type I (ECC-1 and Ishikawa) and Type II (USPC-1 and USPC-2) endometrial cancer cell lines, whereas it abolished AKT and ERK activity only in ECC-1 and USPC-1 cells. In addition, treatment with A12 on top of IGF-1 exhibited a pro-apoptotic activity. Furthermore, proliferation assays showed that the inhibitor caused a significant decrease in proliferation rate in ECC-1 and USPC-1 cells. Cell cycle analyses revealed that the antibody caused a progressive accumulation of ECC-1 cells in G0/G1 phases compared to IGF-I-treated cells. Results of internalization assays revealed that A12 treatment shifted the distribution of IGF-IR from the cell membrane periphery to the cytoplasm. Furthermore, treatment with the antibody caused a reduction in IGF-IR expression after 24 h and 48 h in all cell lines.

Taken together, our results demonstrate that A12 may be an effective therapeutic tool for the treatment of endometrial cancer in which deregulated expression of the IGF-IR plays a critical role.
ASSOCIATION OF THE HSRBC GENE POLYMORPHISM WITH ENDOMETRIAL CANCER

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Background: hSRBC is a putative tumor suppressor located at 11p15.4, at which frequent genomic loss has been observed in several human malignancies. We explored the possible association of an intragenic SNP (T509C), which results in a Leu to Pro substitution, with risk for endometrial cancer development.

Methods: hSRBC expression was examined using semi-quantitative RT-PCR and immunoblot assays. Endometrial tissues from 147 cancer patients and 191 healthy individuals were included for test for SNP T509C by restriction endonuclease PvuII-based genotyping. Allele frequencies in cancer specimens were compared with those in healthy controls.

Results: Allelic frequencies of T and C at the T509C position was 30.27% and 69.73% in healthy control and 37.17% and 62.83% in cancer specimens, respectively. Allelic frequency at T509C in cancer specimens showed no significant difference compared to controls. However, genotype frequencies of TT, CT, and CC in healthy controls were 16.75%, 40.84%, and 42.41%, respectively, while cancer specimens displayed 14.97%, 30.61%, and 54.42%. The CC genotype frequency in cancer specimens was significantly higher (p < 0.05) compared with that in healthy controls.

Conclusion: Although the number of specimens used in this study is not enough, this study raises the possibility that the T509C SNP of hSRBC, a putative novel transcription target of TNFα and proapoptotic tumor suppressor, might be associated with endometrial cancer development. Further genotype screening of several other SNPs within hSRBC in cancer patients would provide valuable diagnostic and prognostic information for human cancers.
LEPTIN INCREASES INVASIVENESS AND ANGIOGENESIS IN HUMAN EPITHELIAL OVARIAN CANCER CELLS BY ACTIVATING MULTIPLE SIGNAL-TRANSDUCTION PATHWAYS

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Background: Epidemiological studies have established obesity as potential risk factor in the development of ovarian cancer. Ovarian cancer is the most lethal gynecologic cancer. Despite using surgery plus chemotherapy the overall survival is < 40% at 5-year. So far, it is not known how the obesity affects ovarian carcinogenesis and treatment outcome. Leptin, a peptidic hormone mainly produced by adyposites and regulating energy intake and expenditure, could be involved in ovarian carcinogenesis.

Objectives: Studying the effects of leptin in proliferation, invasiveness and angiogenesis in ovarian cancer.

Methods: Basal mRNA and protein levels of leptin Ob-receptors were measured in three human ovarian cancer cell lines (A2780/SKOV3/UCI101) through RT-PCR and W-B. Leptin dose/response and time curves were built and cell proliferation (MTS assays) migration (Wound-healing assays) and invasion (matrigel invasion assays) were measured upon leptin incubation. Effect in angiogenesis was studied by incubating endothelial EAHy cells with conditioned medium extracted from leptin treated cancer cells. Activation of different signal-transduction pathways (AKT, MAPK, RhoA) was measured by W-B.

Results: All cancer cell lines expressed the leptin Ob-receptors. Leptin activated the MAPK and RhoA pathways, inducing invasion of ovarian cells and concomitantly increased the formation of lamellipodial structures. Leptin-induced invasiveness was inhibited by AG490. Formation of capillary tube-like structures was observed in EAHy cells when treated with conditioned medium.

Conclusions: Leptin promotes invasiveness and release of angiogenic factors in ovarian cancer cells. High levels of leptin in obese women could mediate the negative impact of obesity in ovarian cancer having more aggressive behavior.

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DUAL METRONOMIC CHEMOTHERAPY RESULTS IN POTENT ANTI-ANGIOGENIC EFFECTS IN OVARIAN CARCINOMA

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Objectives: Metronomically-dosed topotecan elicits antiangiogenic effects by downregulating the potent pro-angiogenic factor HIF-1α. Since metronomic paclitaxel appears to act via a different mechanism, we hypothesized that combined metronomic delivery of these agents would enhance anti-tumor and anti-angiogenic effects.

Methods: We examined the in vitro and in vivo effects of n-(ab)-paclitaxel (microalbuminized paclitaxel) and topotecan given at either maximum-tolerated dose (MTD) or metronomic dosing. For in vivo studies, we examined markers of cell proliferation (Ki67), apoptosis (TUNEL), and angiogenesis (CD31) in harvested tumors.

Results: After in vivo dose-finding studies established the therapeutic metronomic dose of n-(ab)-paclitaxel, extensive therapy experiments with chemosensitive (HeyA8 and SKOV3ip1) orthotopic ovarian cancer models demonstrated that metronomic n-(ab)-paclitaxel reduced tumor growth by ≥ 85% compared to controls (p< 0.01). In the SKOV3ip1 model, metronomic n-(ab)-paclitaxel alone resulted in a 64% reduction in tumor growth compared to metronomic topotecan alone (p< 0.01). In the taxane-resistant HeyA8-MDR model, n-(ab)-paclitaxel and topotecan (both metronomically-dosed) significantly reduced tumor weights by 40% compared to controls (p=0.01). N-(ab)-paclitaxel alone and with topotecan also significantly reduced cellular proliferation (p< 0.001). Metronomic N-(ab)-paclitaxel in the taxane-resistant model elicited notable inhibition of angiogenesis (p≤0.01). Protracted low-dose N-(ab)-paclitaxel exposure in HeyA8 cells markedly increased tumor cell expression of thrombospondin-1. Increases in apoptosis were seen in tumors treated by topotecan alone and with n-(ab)-paclitaxel (p< 0.01).

Conclusions: Metronomically-delivered topotecan and n-(ab)-paclitaxel have complementary anti-angiogenic effects in ovarian carcinoma due to their unique mechanisms of action. Given the safety/tolerance of metronomic regimens, this combination is clinically attractive.
EFFECT OF GONADOTROPIN AND GNRH ANTAGONIST ON MORPHOLOGY, APOPTOSIS AND EXPRESSION OF P53 IN OVARIAN TISSUE OF RATS

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Background: To evaluate the effect of the gonadotropin and GnRH antagonist (GnRH-ant) on ovarian morphology, apoptosis and expression of p53 in rat ovarian tissue.

Methods: Twenty-one rats were divided into three groups and six cycles of either saline (group 1), gonadotropin (group 2) or gonadotropin and GnRH-ant (group 3) were applied. Ovarian specimens were examined by light microscope. Apoptosis was examined and the percentage of apoptotic cells (%ApC) was assessed by TUNEL assay and p53 expression was evaluated by immunohistochemistry.

Results: Ovarian cyst formation was significantly increased in group 3 compared to group 1. Epithelial tufting was significantly increased in gonadotropin group when compared to the control group. Epithelial dysplasia was significantly increased in both group 2 and 3. Epithelial stratification showed no difference in between groups. The highest %ApC in ovarian epithelium was in the control group followed by ovulation and lowest in group 3 (12.3 ± 2.1, 6.5±1.9, 4.2±0.7, respectively). In follicles and stromal cells the %ApC was significantly higher in group 2 compared to groups 1 and 3. Group 3 showed higher p53 expression in ovarian epithelium, follicles and stromal cells compared to the gonadotropin and control group.

Conclusion: Gonadotropin and GnRH-ant lead to epithelial dysplasia and cyst formation. Gonadotropins decrease DNA fragmentation in ovarian tissue and GnRH-ant addition increases p53 thus decreases apoptotic cells.
ENHANCEMENT OF PRE-EXISTING HUMORAL IMMUNE RESPONSE TO GYNECOLOGIC MALIGNANCY BY PERSONALIZED PEPTIDE VACCINE

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Background: A development of new treatment modality is needed for recurrent gynecological cancer. In this context, we previously reported the induction of CTL by personalized peptide vaccine (PPV) in the recurrent cervical cancer.

Objectives: To investigate if peptide specific IgG antibody is produced in the sera of the patients after administration of PPV in the patient with gynecologic cancer.

Methods: The candidate peptides for PPV were screened from HLA (HLA-2, A11, A24, A26, A31 or A33) matched peptide by measurement of anti-peptide antibody in pre-vaccination sera of the patients. Up to 4 peptides showing higher titer of IgG antibody were given subcutaneously 6 times with 1 week interval followed by 6 times with 2 week interval. Peptide specific humoral immune response was evaluated by Luminex method.

Results: Twenty eight patients with gynecological cancer (6 cervical cancers, 3 endometrial cancers, 18 ovarian cancers and 1 tubal cancer) were enrolled in this study. Increased IgG titer was observed in 10 of 24 patients at the 6th vaccination and in 10 of 10 at 12th vaccination. No serious adverse effects were observed at all.

Conclusion: It is clear that PPV would induce enhancement of humoral immune response to gynecologic malignancies. These results suggest that anti-tumor effect of PPV would be induced not only by cellular but humoral immune response.
HYPOXIA REGULATES YT521 EXPRESSION THROUGH COUPLING OF ALTERNATIVE SPLICING WITH NONSENSE-MEDIATED DECAY (NMD)

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Background and aims: Prognostic significance of splicing factor YT521 was shown in endometrial cancer. Decreased YT521 protein expression correlates with poor prognosis. Six YT521 mRNA isoforms occur due to alternative splicing. Only the mRNA variants characterized by exon 6 inclusion and skipping are translated into active protein isoforms. The exon8+9 skipping mRNA isoform is a potential NMD target, due to introduction of stop codons via frameshift. The functional implications of these isoforms were still not clear. Since hypoxia can influence alternative splicing as a key regulatory factor in tumor growth, we investigated its impacts on YT521 isoform expression.

Methods: Endometrial cancer cell line Ishikawa was used for \textit{in vitro} hypoxia (< 1% O\textsubscript{2}). RT-PCR analysis with YT521 isoform-specific primers was performed. Products were validated by sequence analysis. NMD target identification by puromycin assay.

Results: In exon6 specific PCR no significant changes of YT521 exon6-inclusion or exon6 skipping under hypoxia were found. Under normoxic conditions exon8+9 skipping isoform was not detectable. In contrast, hypoxia provoked the expression of exon8+9 skipping isoform and also led to induction of a novel isoform characterized by exclusive skipping of exon8 only. Both, exon8+9 and exon8 skipping isoform were identified as NMD targets by puromycin treatment assay.

Conclusion: Hypoxia regulates YT521 expression through coupling of alternative splicing with NMD. In detail, hypoxia induces a fractional mRNA degradation of YT521 isoforms resulting in the down-regulation of YT521 protein levels. As a consequence, an alteration in YT521-dependent downstream molecular events might contribute to more aggressive cancer phenotypes.
INCREASED EXPRESSION OF PLACENTAL GROWTH FACTOR, A HOMOLOG OF VASCULAR ENDOTHELIAL GROWTH FACTOR, IN HIGH GRADE ENDOMETRIAL CARCINOMAS

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Background: Placental Growth Factor (PlGF), a homolog of Vascular Endothelial Growth Factor (VEGF), exerts pleiotropic functions in cancer by affecting tumor cells as well as endothelial and inflammatory cells. Moreover, PlGF expression correlates with tumor stage, recurrence, metastasis and outcome in patients with gastric, colorectal and breast cancer. Recently, administration of anti-PlGF therapy reduced tumor growth and metastasis in preclinical tumor models.

Objective: We here aimed to evaluate the prognostic value of local and systemic expression of PlGF in primary endometrial carcinomas.

Methods: PlGF levels in tumor lysates and serum of patients with primary endometrial cancer were determined by ELISA. PlGF levels in tumor lysates were additionally corrected for total protein amount. Serum and endometrium biopsies of age-matched healthy women were taken as control.

Results: Local expression of PlGF was increased in endometrial carcinomas (n=54) as compared to healthy biopsies (n=13). In particular, PlGF expression in high grade endometrioid (n=8; P< 0.01) and serous (n=7; P< 0.01) carcinomas was significantly increased. In contrast, no differences in PlGF serum levels were observed between patients with endometrial cancer (n=40) and healthy controls (n=13). In addition, no correlation between FIGO stage or CA-125 levels and PlGF serum levels was observed, although patients with FIGO stage IV disease (n=5) showed slightly increased PlGF serum levels, an observation that needs to be confirmed in a larger dataset.

Conclusion: The increased local expression of PlGF in tumoral tissues of high-grade endometrial carcinoma underscores the need for preclinical assessment of anti-PlGF therapy in endometrial cancer.
TARGETING THE IGF-I RECEPTOR IN ENDOMETRIAL CANCER WITH MONOCLONAL ANTIBODY MK-0646

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Background: The involvement of the insulin-like growth factors (IGFs) in endometrial cancer has been well established. The IGF-I receptor (IGF-IR), which mediates the activities of the IGFs, is a promising molecular target in cancer therapy. The aim of this study was to evaluate the hypothesis that interfering with the IGF-IR signaling pathway in endometrial cancer could decrease proliferation and induce apoptosis. To this end we used a recently developed humanized monoclonal antibody (MK-0646, Merck Oncology), directed against IGF-IR which blocks IGF-I binding to the receptor.

Methods: To evaluate the effect of IGF-IR inhibition on IGF-I-mediated signaling, human endometroid (ECC-1) and serous papillary (USPC-1) endometrial cancer cell lines were treated for various periods of time (40 min, 1 h, 3 h, 5 h) with antibody MK-0646, in the presence of IGF-I during the last 10 min of the incubation period.

Results: Results of Western blots using antibodies against total and phospho-IGF-IR, AKT, and ERK showed that MK-0646 decreased the IGF-I-stimulated phosphorylation of IGF-IR, AKT and ERK in both ECC-1 and USPC-1 cells. In addition, MK-0646 induced a significant decrease in total IGF-IR levels. To evaluate the potential effect of IGF-IR inhibition on apoptosis, cells were treated with IGF-I for 24-48 h, in the absence or presence of MK-0646, after which apoptosis was assessed by Caspase-3 and cleaved PARP measurements. Results obtained showed that MK-0646 abrogated the antiapoptotic activity of IGF-I.

Conclusions: Taken together, our results suggest that specific IGF-IR blockade could be a useful therapeutic approach in endometrial cancer.
ANGIOGENESIS AND ITS ASSOCIATION WITH EXTRACELLULAR MATRIX PROTEINS IN ADVANCED CERVICAL CANCER

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Background and aim: Cervical cancer (CaCx) is the second most common cancer among women worldwide. Angiogenesis is required by tumor cells to survive, proliferate and metastasize but its role in advanced cervical cancer (ACaCx) is limited. Angiogenic factors are known to regulate matrix proteins in solid tumors and might possibly function via up-regulation of ECM proteins. The urokinase-type plasminogen activator (uPA) system and laminin are involved in cell migration, tissue remodeling, angiogenesis and cell adhesion. This study was conducted to investigate the expression of angiogenic factors along with ECM proteins at circulatory as well as cellular level and their correlation with pathogenesis of ACaCx.

Methods: Fifty patients with CaCx (stage IIIA-IVA) and fifty healthy controls were enrolled. The circulatory levels of angiogenic factors and Laminin were measured by ELISA and uPA activity by activity assay kit. The mRNA expression was further detected by RT-PCR.

Results: Statistical significant increase was observed in Ang-2, VEGF, uPA and laminin levels compared to controls and significantly correlated with each other in patients. Increased mRNA expression for VEGF, Ang-2, uPA and laminin was also observed. No significant change was found for Ang-1 levels at circulatory and cellular level.

Conclusion: Elevated expression of Ang-2 and VEGF suggest their involvement in process of angiogenesis in CaCx as they both are involved in vessel sprouting and neovessel formation. Increased expression of laminin and uPA might facilitate metastasis. Hence this study suggests that Angiopoietins, VEGF signaling and ECM proteins might contribute to this complicated and unregulated process of angiogenesis.
TARGETING A2,3-LINKED SIALYLATION BY SOYASAPONIN I MIGHT BE USEFUL IN THE OVARIAN CANCER TREATMENT

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Aims: Soyasaponin I (SsaI), a soybean extract, can be used in modifying the sialylation of the cell surface without altered cell growth and viability. A kinetic analysis of α2,3-sialyltransferase type I (ST3Gal I) inhibition demonstrated that SsaI can act as a competitive inhibitor affecting CMP-Neu5Ac binding to the enzyme. Enhanced α2,3-linked sialylation was found in ovarian cancers compared with normal ovaries. Therefore, it is rationale to suppose that SsaI might be useful in the management of ovarian cancer.

Methods: In vitro and in vivo studies were used to test this hypothesis. Ovarian cancer cell lines-SKOV-3, ES-2 and MOSEC were used in this study.

Results: SsaI inhibited tumor migration and invasion with dose-dependent manner (0, 25, 50, and 100 µM). In addition, the use of intraperitoneal inoculation of continuous delivery of SsaI with mouse ovarian surface epithelial cell (MOSEC)-carried nude mice model tested the in vivo effect of SsaI. MOSEC-carried nude mice treated with SsaI showed significantly less symptomatic and some of them were free of tumors, compared with those without SsaI treatment. All MOSEC-carried mice without SsaI treatment were complicated with apparent peritoneal carcinomatosis and massive bloody ascites.

Conclusions: α2,3-linked sialylation on ovarian cancers might be important in tumor dissemination, and blocking α2,3-linked sialylation by SsaI might be valuable in the management of these highly lethal diseases.
THE METHYLATION LEVEL OF HERV-K PROVIRUS IN OVARIAN CLEAR CELL CARCINOMA

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Objective: To study the methylation level of HERV-K provirus in ovarian clear cell carcinoma compare with normal ovarian tissue

Methods: The tumor registry of patients with ovarian clear cell carcinoma treated at King Chulalongkorn Memorial Hospital between January 1, 2005 and December 31, 2007 were reviewed. The histological diagnosis was reviewed by a gynecologic pathologist. Microdissection of cancer tissue and normal ovarian tissue from the same patient was done. DNA extraction and quantitative combined bisulfite restriction analysis (COBRA) PCR protocol were performed. The PCR products were digested with Taq I (MBI Fermentas) and electrophoresed in polyacrylamide gel. The intensities of DNA fragments were measured by PhosphorImager. The HERV-K provirus methylation level was calculated as a percentage.

Results: Twenty nine patients with ovarian clear cell carcinoma were enrolled. Mean HERV-K provirus methylation level in cancer tissues and normal ovarian tissues were 51.1 ± 4.8% and 57.9 ± 4.1%, respectively. The clear cell carcinoma group had a significantly lower methylation level than normal ovarian tissue group (p< 0.0001). The HERV-K provirus methylation level was significantly decreased in advanced stage patients (p=0.035). The patients with lower methylation level of HERV-K provirus (less than 51.1%) had shorter mean progression-free survival (p=0.06) and mean overall survival (p=0.006).

Conclusion: Ovarian clear cell carcinomas have significant lower methylation levels of HERV-K provirus than normal ovarian tissues. Progressive decrease in HERV-K methylation level might be an epigenetic process in ovarian clear cell carcinogenesis.

Keywords: Methylation; HERV-K provirus; ovarian clear cell carcinoma; epigenetic
METHYLATION PROFILING OF SEROUS CARCINOMA OF THE FEMALE GENITAL TRACT

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**Background:** Serous carcinoma is an aggressive type of cancer that may arise from various organs in the female genital tract. In general, choice of treatment is determined by the organ of origin and less by histologic subtype. However, the distinction between serous ovarian carcinoma (OVCA) and uterine papillary serous carcinoma (UPSC) can be difficult, especially in cases with advanced disease. Promoter methylation is a gene- and cancer-type specific epigenetic event that plays a major role in tumour development. Therefore, we evaluated promoter methylation of a panel of tumour suppressor genes (TSG) in USPC and serous OVCA that could be useful to distinguish the tumours on base of organ of origin.

**Methods:** Methylation specific-multiplex ligation-dependent probe amplification (MS-MLPA) was used to assess the extent of promoter hypermethylation of different TSG in UPSC and serous OVCA.

**Results:** The median cumulative methylation index (CMI) of all genes was significantly higher in UPSC (93) than in OVCA (41) (P = 0.047). Promoter methylation of CDKN2B, RASSF1(A) and TP73 was more frequently present in UPSC, while GSTP1 was more frequently methylated in OVCA. Seventy seven percent of UPSC and 73% of OVCA could be predicted by RASSF1(A) methylation status.

**Conclusion:** Despite similarities between UPSC and serous OVCA in clinical behaviour and histological appearance, significant differences in their methylation profile were found. A panel of methylation biomarkers could be useful to distinguish between the two tumour types.
IDENTIFICATION OF DIFFERENTIALLY EXPRESSED GENES USING ANNEALING CONTROL PRIMER SYSTEM IN STAGE III SEROUS OVARIAN CARCINOMA

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The ACP-based reverse transcriptase polymerase chain reaction technique was employed to identify DEGs in stage III serous ovarian carcinoma patients. Cluster analysis was performed on the basis of the expression profile produced by quantitative real-time PCR and survival analysis was carried out by Kaplan-Meier and Cox proportional hazards multivariate model between chemo-resistant and sensitive group with the information of gene expression.

A total of 114 DEGs was identified by the ACP-based RT PCR technique in stage III serous ovarian carcinoma. The DEGs related to apoptosis inhibitory process tend to be found in up-regulated clones while DEGs associated with immune response incline to be found in down-regulated clones. Cluster analysis of gene expression profile obtained by qPCR revealed two contrasting groups of DEGs. That is, a group of genes including SSBP1, IFI6 DDT, IFI27, C11orf92, NFKBIA, TNXB, NEAT1 and TFG were up-regulated while another group of genes consisting of LAMB2, XRCC6, MEF2C, RBM5, FOXP1, NUDCP2, LGALS3, TMEM185A, and C1S are down-regulated in most patients. Survival analysis revealed that the up-regulation of genes such as DDAH2, RNase K and TCEAL2 might have bad prognostic. Furthermore, the prognostic of patients with chemo-resistance was predicted severely bad when genes like RNase K, FOXP1, LAMB2 and MRVI1 are up-regulated.

The DEGs in stage III serous ovarian cancer were successfully and reliably identified by the ACP-based RT PCR technique. DEGs identified in this study would be used for estimation of the prognosis of stage III serous ovarian cancer as well as development of new treatment regimes.
FEASIBILITY OF DEVELOPING A FUNCTIONAL ASSAY FOR HOMOLOGOUS RECOMBINATION IN PRIMARY CULTURES OF EPITHELIAL OVARIAN CANCER FROM ASCITIC FLUID

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**Background:** PARP inhibitors (PARPi) selectively kill cancer cells deficient in homologous recombination pathway (HR) of DNA repair. Up to 50% of epithelial ovarian cancers (EOCs) could benefit from PARPi if HR status could be identified. We aimed to develop a functional assay for HR which is simple, reliable and suitable for widespread application in clinical settings.

**Methods:** Two different methods to assess HR function,

1. S phase dependent Rad 51 immunofluorescence (IF) and

2. Cell cycle independent DR- GFP reporter assay were optimised in cell lines with known HR status.

Primary cultures were developed from ascitic fluid from patients with EOCs and feasibility of both assays was studied under different storage and transport conditions.

**Results:** Over 90% success rate was obtained in growing primary cultures from fresh ascites and > 80% success from ascitic fluid stored at 4ºC for 24hrs or thawed from cryo frozen (10% DMSO) samples. The IF assay could predict HR status in cultures obtained under different storage conditions and this correlated with cytotoxicity to PARPi in >90% cases. A single optimised condition applicable to all primary cultures could not be developed in DR- GFP reporter assay due to a very poor transfection efficiency especially in cultures grown from cryofrozen samples.

**Conclusion:** An immunofluorescence based Rad 51 assay for HR function can be developed in primary cultures of EOCs derived from ascitic fluid under different storage and transport conditions. A DR-GFP reporter assay, although effective in cell lines may not be feasible in primary cultures.
ANALYSIS OF B7H4 AND HLA-G IMMUNOREACTIVITY WITHIN OVARIAN CANCER RELAPSE AND ITS MICROENVIRONMENT ACCORDING TO APPLIED PRECEDING CHEMOTHERAPY

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Introduction: The appearance of ovarian cancer relapse is directly linked with suppression of the host immune system. Cancer microenvironment is dominated by suppressive profile. It is composed from suppressive cells and factors (eg. cytokines), that are responsible for selective suppression of host cytotoxic immune cells. Thus, we decided to examine the immunoreactivity of two antigens (B7H4 and HLA-G) within ovarian cancer cells and within macrophages infiltrating the ovarian cancer microenvironment in relationship to applied chemiotherapy.

Methods: Immunohistochemical staining for B7H4 and HLA-G expression was performed in tissue samples collected from 17 consecutive patients who underwent surgery due to ovarian cancer recurrence. We analyzed the immunoreactivity of B7H4, and HLA-G on ovarian cancer cells and its microenvironment accordingly to number of chemotherapy regiments patients has been given between first and second line surgery.

Result: The expression of B7H4 and HLA-G ether in cancer cells and in macrophages was higher in patients who received more than one chemotherapy between first and second line surgery. We observed statistically significant (p=0.03) higher infiltration of B7H4 positive macrophages within microenvironment of ovarian cancer patients who relapsed, and had more than one chemotherapy regimen between surgical procedures.

Conclusion: The immune-suppressive ovarian cancer relapse microenvironment represented by suppressive macrophages may require additional supplementation of primary chemotherapy.
INFECTIVITY-ENHANCED ADENOVIRAL-BASED GENE THERAPEUTICS FOR GYNECOLOGIC CANCER: FROM BENCH TO BEDSIDE

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Background: We have endeavored to advance adenoviral-based gene therapeutics for gynecologic cancer by improving transduction capacity. This report focuses on translational studies evaluating the MTD, toxicities, antitumor activity, and biological effects of two infectivity-enhanced, tropism-modified adenoviral-based therapeutics.

Methods: Cohorts of patients with recurrent gynecologic cancer were treated in two phase I studies with either the infectivity-enhanced oncolytic, Ad5-Δ24RGD, or infectivity-enhanced suicide gene therapeutic, RGD.Ad5TKSSTr, daily x3 via IP catheter. Vector doses ranged from 1x10⁹ vp/D to 1x10¹² vp/D. Toxicity was evaluated utilizing CTC v3.0; efficacy was determined via CA-125 and RECIST criteria. Corollary studies included assessment of gene transfer, viral replication, wild-type virus generation, viral shedding, and neutralizing antibody response.

Results: No vector related G3/4 toxicities were noted in 30 patients treated in either trial up to 1x10¹² vp/D. Of the 28 patients with measurable disease, 17 had stable disease; 11 had progressive disease. CA-125 decreased in 8 of 29 evaluable patients; 5 had CA-125 drop by >20%. Ad5-Δ24RGD ancillary studies demonstrated a significant increase in study virus after day 3 in 7 patients, suggesting Ad5-Δ24RGD viral replication. Viral shedding was noted in serum, saliva, and urine, particularly in patients treated with ≥5x10¹⁰ vp/D. An anti-adenoviral neutralizing antibody effect was noted in all patients. Ancillary studies in the RGD.Ad5TKSSTr are in progress.

Conclusions: Collectively, these are the first studies to evaluate infectivity-enhanced adenoviral-based gene therapeutics in the context of human cancer. These trials demonstrate the feasibility, safety, and potential antitumor clinical activity associated with these advanced-generation vector systems.
THE WOMEN’S CANCER CELL GENOTYPE ATLAS (WCCGA): DNA AUTHENTICATION OF ENDOMETRIAL CANCER, OVARIAN CANCER, AND BREAST CANCER CELL LINES

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Objective: Cancer cell lines and immortalized non-malignant lines are critical research tools. One third of human cell lines may be misidentified, cross-contaminated or redundant. We sought to identify and catalog unique DNA profiles for endometrial, ovarian and breast cancer cell lines.

Methods: Genomic DNA multiplex PCR was done with ABI Identifiler kit. PCR products were analyzed on ABI 3730 50 cm capillary array with POP7 polymer. Electropherograms were analyzed with Data Collection (ABI) and GeneMapper (ABI). Genotypes were compared to ATCC, DSMZ, and UCD DNA Sequencing & Analysis Core databases.

Results: Of 96 breast cancer cell lines, 66 were authenticated, 15 had novel profiles, 9 were HeLa and 6 were misidentified/cross-contaminated. Fifty-four ovarian cancer lines profiled with 31 independent genotypes. Ten ovarian lines were identical to other lines; BG-1 genotyped as MCF-7, CH1/CH1cisR/222 as PA1, NOSE06/NOSE07 as DOV-13, and SKOV-4/SKOV-6 as cervical cancer line C33A. Ovarian lines A2008/OV2008 matched HPV positive ME-180 cervical cancer cells. Multiple Ishikawa endometrial cancer line variants were genotyped and differences confirmed by TP53 sequence analysis. Endometrial cancer RL-92, HEC-1A, 1B and HEC-50 exhibited unique uncontaminated profiles. ECC-1, reportedly derived from EnCa101 endometrial tumor, did not match EnCa101, but was identical to Ishikawa, and/or MCF-7. Normal endometrial stromal line HES was HeLa contaminated. hTERT EEC immortalized normal endometrial epithelial cell line was genotypically MCF-7.

Conclusions: These results indicate significant misidentification and loss of integrity of breast, endometrial and ovarian cell lines. Genotype data in the Womens’ Cancer Cell Genotype Atlas may be used for authentication comparison.
AVALIATION OF CYTOKINE LEVELS, NAG AND MPO ACTIVITY IN WOMEN WITH PRE-INVASIVE CERVIX LESIONS AND INVASIVE CERVICAL CANCER

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The inflammatory response is an active process in cervical cancer and may act in the progression and/or regression of the lesion. At the site of inflammation cells are present, among the most important macrophages and neutrophils and some cytokines such as TNF-α and IFN-γ. This study aims to evaluate the systemic inflammatory response level in women with pre-invasive lesions and invasive cervical cancer. There were analyzed serum samples obtained from women without evidence of disease (n = 30 - control group), with pre-invasive lesions of the cervix (n = 30) and with carcinoma of the cervix (n = 30). The activity of inflammatory enzymes N-acetylglucosaminidase (NAG) and myeloperoxidase (MPO) were obtained by enzymatic assay and serum levels of TNF-α and IFN-γ by ELISA assay. The activities of enzymes NAG, and MPO and the levels of TNF-α were higher in women with CIN compared with the group with SCC. The levels of IFN-γ were lower in the group of women with CIN compared with the group with SCC. There was not a significant association between the degree of the CIN and the staging of the SCC of the cervix with inflammation assessed by the levels of inflammatory markers used. The inflammatory response had a decrease in accordance with the progression of the carcinogenic process: control group, women with CIN and women with invasive SCC, there was no association between the degree of pre-invasive lesions and staging of the SCC of the cervix.

Keywords: Cervical cancer, inflammation, NAG, MPO, TNF-α and IFN-γ.
THE ESTROGEN RECEPTOR α-DEPENDENT SERINE PROTEASE PRSS23 MEDIATES PROLIFERATION OF ENDOMETRIAL CANCER CELLS

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Among many cases, endometrial endometrioid cancers thought to be associated with long-term unopposed estrogen stimulation. Consequently, estrogen receptor α (ERα) expression is recognized as one of the considerable factors for endometrial tumorigenesis. From our preliminary study, we have demonstrated that PRSS23 mediated cell proliferation in ERα positive breast cancer cell lines. Meanwhile, PRSS23 could affect breast cancer cell cycle via estrogen dependent mechanism. Thus, we hypothesized that PRSS23 might play an essential role to promote endometrial cancer cell proliferation under the influence of ERα.

To test this hypothesis, we first surveyed the mRNA and protein expression level of PRSS23 in two endometrial adenocarcinoma cell lines. The first is ECC-1, which is ERα positive. But the second, HEC-1B, is ERα negative. We then proceed to investigate the effect of PRSS23 on cell proliferation. Our result demonstrated that PRSS23 protein could be detected in ECC-1 by immunoblotting, but not in HEC-1B. Interestingly, the cell proliferation of ECC-1 could reduce by PRSS23 RNAi knockdown, suggesting a baseline effect of PRSS23 in regulating ECC-1 cell cycle. Furthermore, we observed PRSS23 expression level was elevated by tamoxifen, an antagonist of the estrogen receptor, treatment in a dose dependent manner in ECC-1.

Our result implied that PRSS23 served as a pivotal cell proliferation regulator of estrogen signaling in human endometrial cancer. We believe PRSS23 has the potential to be used as a prognostic marker for endometrial endometrioid cancers, and may also serve a novel target for treating early-stage endometrial cancer.
WHOLE SLIDE AUTOMATED COMPUTER-ASSISTED QUANTIFICATION OF LYMPHANGIOGENESIS Throughout THE CERVICAL CANCER Process: AN ORIGINAL METHOD

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Objective: Lymphatic vessel density (LVD) has been shown to be associated with lymphatic metastasis, overall and recurrence free survival. For methodological reasons, most studies on LVD focused on hot spot areas that lack reproducibility due to tumor heterogeneity. Since global computer-assisted evaluation of LVD could be a more reliable parameter, we developed a reproducible automated quantification method suitable for whole scanned section analysis.

Material and methods: Ten normal cervices, 10 CIN3, 10 microinvasive and 94 early cervical cancer specimens were analyzed. Co-immunostaining, with antibody directed to laminin-5 and D2-40 were used to identify migrating cells at the tumor front of invasion and lymphatic vessels respectively. Pan-cytokeratin antibody identified epithelial cells on the next serial slide. Computed superimposition of these two sections allowed the optimization of LVD calculation. We set up an original C++ program based on Pandore image analysis framework that automatically quantified these parameters. Laminin-5 stained structures and lymphatic vessels were segmented using a colorimetric method followed by mathematical morphology post processing to avoid LVD overestimation linked to artefactual vessel splitting.

Results: At least 8.5 lymphatic vessels per mm\textsuperscript{2} were identified in tissue sections. The ratio between LV staining surface and stromal surface was 2.14\%. LV size, distribution in relation to tumor bundles and the front of invasion were then successfully calculated.

Conclusion: The tools developed accurately determine the respective spatial distribution of lymphatic vessels and invasive cells. This is not only limited to hot spot areas but also applies to whole scanned sections of early cervical cancer.
P16 GENE PROMOTER REGION METHYLATION STATUS IN OVARIAN CANCER - CORRELATION BETWEEN BLOOD AND TUMOUR TISSUE

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Background: A better understanding of the molecular pathogenesis of cancer is essential to identify biomarkers to enable early detection of cancer. The promoter hypermethylation of tumour suppressor genes has been recently studied extensively as it is one of the predominant causes of inactivation of the genes. P16 is one of such tumour suppressor genes which is found to be hypermethylated in a wide range of cancers. This study was designed to compare the methylation status of p16 gene between the ovarian tissue and blood of patients with ovarian cancer. A strong correlation could raise the possibility of using blood assay in the detection or as a prognostic marker of ovarian cancer patients.

Methods: The ovarian cancer tissue and blood samples were collected from the same patient (n=50). The methylation status in blood and ovarian tissue DNA was then assessed using Methylation Specific PCR. The correlation between the methylation status in the matched blood and ovarian tissue collected from the same patient was analysed.

Results: There was only a weak statistical agreement between tissue and blood samples for the methylation status of p16 gene promoter region (Kendall’s tau b = 0.31); perfect correspondence of methylation status was observed in only 4 (8%) patients.

Conclusion: This study demonstrates poor agreement for the methylation status of p16 gene promoter region between tumour tissue and blood of ovarian cancer patients. Methylation status in blood cannot be considered to be the same as the methylation status in the malignant ovarian tissue in the same patient.
STUDY OF ADAPTATIVE IMMUNE RESPONSE IN WOMEN WITH OVARIAN CANCER

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Aims: This study aims to evaluate the adaptive immune response in peripheral blood of women with ovarian cancer.

Methods: We analyzed peripheral blood samples obtained from healthy women (n= 10 - control group) with benign ovarian tumor (n= 9) and ovarian cancer (n= 17). The samples were evaluated by the technique of flow cytometry. The panel of monoclonal antibodies included markers: CD4, CD8, HLA-DR, CD54, CD62L, CD18, CCR2, CXCR4, CCR5, CCR3, CXCR3, CD25, CD5, CD69, CD19, CD23, and isotype control. Differences with p < 0.05 were considered significant.

Results: There was a significant decrease (p < 0.05) of the percentage of T cells in the group of women with ovarian cancer when compared to the control group. The results showed that the percentage of CD4 + T cells showed significant differences between the groups (p= 0.0399). However the population of CD8+ T cells did not show significant differences (p= 0.2939). The analysis of the percentage of B lymphocytes (CD19+) identified a significant difference between the three study groups (p= 0.0463). We observed a decrease in the percentage of B cells of groups of women with benign tumor and ovarian cancer in the control group. It was possible to observe a statistically significant difference between groups CCR2+CD8+ (p =0.0294), CD8+CCR5+ (p= 0.0216) and CD4+CCR3+ (p = 0.0233).

Conclusions: It is possible to observe the participation of leukocytes in peripheral blood of patients with ovarian cancer, showing that the phenotypic events have as main feature the presence of systemic manifestations.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

HUMAN PAPILLOMAVIRUS TYPE 16 AND 18 ARE IMPORTANT ETIOLOGIC AGENTS IN PREDISPOSING WOMEN FOR OVARIAN CANCER DEVELOPMENT

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Background and objectives: Our study was designed to determine the Human Papilloma Virus (HPV) as a plausible etiologic factor for ovarian cancer predisposition and establish the route of HPV transmission.

Materials and methods: Samples from two cohorts of women (20 high risk (HR) and 67 OC) were analyzed by polymerase chain reaction (PCR) to identify HPV type 16,18 and 33; Real-Time Quantitative PCR (Q-PCR) and immunohistochemistry to detect E6 HPV16/18 protein, p53, Ki-67, pRb expression levels.

Results: We demonstrate the presence of HPV-16 in 25%, HPV-18 in 35% and HPV-33 in 10% of the 20 HR samples. Approximately 20% of the studied HR samples had a mixed infection (HPV16/18). In the OC cohort, 11.9% were HPV-16 positive and 3% were HPV-18 positive. The p53 expression was significantly lower (LI 12.8±4.5) in HPV-positive OC versus HPV-negative OC (LI 33.1±5.4) whereas pRb expression was similar (11.6±4.1 in HPV-positive and 14.3±2.2 in HPV-negative OC, respectively). The overall HPV load in the HR and OC samples was low, but the HR samples demonstrated a higher copy number. Fallopian tubes and their corresponding ovarian tissues demonstrated HPV E6 focal positivity in the surface epithelium and endothelial cells of the tubal vessels. Additionally HPV-positive OC patients were younger (mean age 42.1±2.0) than HPV-negative patients (mean age 52.6±1.8), and had G2 and G3 tumors and predominately III and IV FIGO stages.

Conclusion: HPV positively correlated with high risk of OC development and a possible route of HPV dissemination is via the endothelial cells of the blood vessels.
EXPRESSINO PROFILING OF THE OVARIAN SURFACE KINOME REVEALS CANDIDATE GENES FOR EARLY NEOPLASTIC CHANGES

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Objectives: We tested the hypothesis that co-coordinated up-regulation or down-regulation of several ovarian cell surface kinases may provide clues for better understanding of the disease and help in rational design of therapeutic targets.

Study design: We compared the expression signature of 69 surface kinases in normal ovarian surface epithelial cells (OSE), with OSE from patients at high risk and with ovarian cancer.

Results: Seven surface kinases, ALK, EPHA5, EPHB1, ERBB4, INSRR, PTK, and TGFβR1 displayed a distinctive linear trend in expression from normal, high-risk, and malignant epithelium. We confirmed these results using semiquantitative reverse transcription-polymerase chain reaction and tissue microarray of 202 ovarian cancer samples. A strong correlate was shown between disease-free survival and the expression of ERBB4. DNA sequencing revealed two novel mutations in ERBB4 in two cancer samples.

Conclusions: A distinct subset of the ovarian surface kinome is altered in the transition from high risk to invasive cancer and genetic mutation is not a dominant mechanism for these modifications. These results have significant implications for early detection and targeted therapeutic approaches for women at high risk of developing ovarian cancer.
ARRAY CGH CHARACTERIZATION OF UTERINE CERVICAL CANCER

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Background: For the development of preneoplastic and malignant lesions of uterine cervix, involvement of human papillomavirus (HPV) is of great importance. How these viruses induce cellular transformation at a molecular level has been extensively studied, yet genetic changes recognized as complex cytogenetic alterations related to the onset of carcinogenesis still needs to be characterized.

Objective: In order to identify the genomic imbalances existing in uterine cervical cancer, we used microarray-based comparative genomic hybridization (aCGH).

Methods: Using BAC microarrays (GSPArray7700TM) on which 7718 Keio BAC-DNAs are spotted in triplicate, we examined copy number changes of DNA segments in uterine cervical cancer tissues. We applied the aCGH system to various stages of both squamous cell carcinomas and adenocarcinomas.

Results: So far, we analyzed 36 tissue samples from cervical cancer patients and found that the most common segmental DNA changes were seen as gain on 1q, 3q, 5p and 20p, and loss on 11q and 6q. Gain of 1q was statistically significant (p< 0.05) for squamous cell carcinoma samples compared to adenocarcinoma samples. Whilst focusing on changes of individual BAC clones, we found several genes with high signal ratio, which also presented changes in cDNA expression.

Conclusions: Recurrent gains and losses were observed. Further analysis may lead to the discovery of novel genes important in cervical carcinogenesis.
IDENTIFICATION ISOLATION AND GENE EXPRESSION OF CD8 ALPHA/ALPHA T LYMPHOCYTES IN SEROUS OVARIAN ADENOCARCINOMA

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Aims: The aim of this study was to identify and extract CD8⁺ αα T cells from the tumour and ascites of patients with serous ovarian cancers. Isolated CD8⁺ cells were used for gene expression analysis using quantitative PCR, looking for expression of NKG2D and FasL.

Background: CD8⁺ T cells either express the αβ heterodimer or a homodimer of alpha chains. CD8αα cells are termed unconventional as their receptors do not bind the normal MHC: peptide ligands but can bind to a number of different ligands.

NKG2D is a homodimeric receptor that is expressed by human NK cells, CD8⁺ αβ and γδ T cells; and MICA is one of a number of ligands for NKG2D in humans. Binding of NKG2D enhances the cytolytic response of CD8⁺ T cells against MICA expressing tumour cells including ovarian cancers.

FasL plays a central role in the induction of apoptosis and contributes to the cytotoxic effector function of T and NK cells.

Methods: Single cell suspensions were prepared from freshly obtained ovarian tumour in one patient as well as ascites from 3 patients with serous ovarian cancer and stained with fluorescent antibodies CD3-FITC, CD8α-APC and CD8β-PE. The sample was analysed by flow cytometry and cells isolated by FACS. Production of NKG2D and FasL in CD8αα and CD8αβ cells was investigated using RT PCR.

Results: Our data confirmed that CD8αα T cells were abundant in the primary ovarian tumour and ascites. Both the CD8αα and CD8αβ populations extracted from the ascitic fluid expressed NKG2D and FasL.
RAPID AND SIMULTANEOUS DETECTION OF PROLIFERATION, APOPTOSIS, INVASIVE ABILITY, AND CYTOSKELETAL REORGANIZATION IN GYNECOLOGICAL CANCER CELLS BY NANODEVICE

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Background and aims: Extracellular matrix contains structures from micro-scale down to nano-scale. We hypothesized that cells respond to both micro- and nano-structure. The aim is to apply nano-surface device to distinguish gyn. cancer cell lines by their invasive potentials.

Methods: We have fabricated a nanodevice composed of a matrix of nine nodot arrays with various dot sizes (from a flat surface to 10-nm, 50-nm, 100-nm, and 200-nm) arrays. Cellular response was evaluated by culturing cell lines on various sizes of nanodot arrays.

Results: HELA, C33A, ES2, PA-1, TOV-112D and TOV-21G cells were seeded onto the device and cultured. Indices corresponding to cell proliferation, apoptosis, cell adhesion, and cytoskeletal organization were defined. \(VD_{50}\) is defined as the diameter of nanodots on which 50% of the cell population remains viable. \(AD_{50}\) is defined as 50% of the cell population appears to have an apoptosis-like morphology. \(FD_{50}\) is that promotes the formation of 50% of the focal adhesions compared to cells grown on a flat surface. \(CD_{50}\) is defined as cells have half the amount of microfilament bundles compared to cells grown on a flat surface. We were able to distinguish between the invasive ability of HELA versus later-staged C33A cells. Ovarian cancer cell lines (ES2, PA-1, TOV-112D, and TOV-21G) also exhibited differential growth parameters.

Conclusion: The established device (platform) can be used to assess basic parameters of cell growth, distinguish among cancer cell lines at various stages and will serve as a convenient and fast tool for tissue engineering and cancer treatment.
SIZE-DEPENDENT IMMUNE PROPERTIES OF GOLD NANOPARTICLES AS DRUG (VACCINE) TARGETING CARRIER IN NANOMEDICINE- ELICITED BY SYNTHETIC FOOT-AND-MOUTH DISEASE VIRUS PEPTIDE

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Background and aims: To elicit the size-dependent immune properties of gold nanoparticles (GNPs) for the application of drug (vaccine) carrier targeting cancer tissues, a synthetic peptide corresponding to Foot-and-mouth disease virus (FMDV) viral proteins was conjugated to GNPs (from 2nm, 5nm, 8nm, 12nm, 17nm, 37nm, to 50nm in diameter). An extra cysteine was added to the C-terminus of the FMDV peptide (pFMDV), to ensure maximum conjugation.

Methods: The pFMDV-GNP conjugates were injected into BALB/C mice. Immunization with pFMDV-keyhole limpet hemocyanin (KLH) conjugate was performed as control. Blood was withdrawn from mice on weeks 4, 6, 8, and 10, antibody titers against pFMDV and carriers were obtained. For pFMDV-GNP immunization, specific binding against peptide was detected in the sera of mice injected with 2nm, 5nm, 8nm, 12nm, and 17nm GNP conjugates.

Results: Maximum binding occurred with GNPs of sizes between 8nm to 17nm. The pFMDV-GNPs induced a 3-fold increase in antibody response compared to pFMDV-KLH. All sera exhibited undetectable binding against GNP, while antisera of pFMDV-KLH presented high levels of binding activity against KLH. The uptake of pFMDV-GNP in spleen was examined by ICP-MS and TEM.

Conclusions: The amount of GNP accumulated in spleen correlated to the immune response induced by pFMDV-GNP. We demonstrated the size-dependent immunogenic properties of pFMDV-GNP conjugates. GNPs ranging from 8nm to 17nm promotes the most intense immune response, thus should be avoided if used as drug (vaccine) carrier. GNPs of sizes outside of this zone will be potential drug (vaccine) carriers in the application of nanomedicine.
GAIN-OF-FUNCTION WNT-INDEPENDENT ACTIVITY OF THE PYGOPUS2 TRANSCRIPTION FACTOR IN GYNECOLOGIC CANCER

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Background and aims: The Pygopus2 (Pygo2) protein was originally described in embryonic development as a core component of the Wnt/b-catenin transcriptional activation complex but we previously found that it has Wnt-independent requirements for the growth of epithelial ovarian cancer. The aim of this study was to uncover novel functions of Pygo2 in gynecologic cancer by determining the proteins with which its N-terminal (Wnt-independent) homology domain interacts.

Methods: Glutathione-S-transferase (GST) fusion proteins containing either the N-homology domain or Plant Homology Domain (PHD) of Pygopus were transfected into SKOV-3 (EOC) and HeLa (Cervical) cancer cells. Complexes associating with the fusion protein were purified on glutathione beads and separated on SDS PAGE. Protein bands specific to the NHD but absent from the PHD containing complexes were analyzed by tandem Mass Spectrometry. Proteins were analyzed by in vitro and in vivo protein interaction pulldown assays, immunoblot (western) and immunofluorescence (IF).

Results: In both EOC and cervical cells, The Wnt-independent NHD of Pygo interacts strongly with the product of the TCOF1 gene in its C-terminal region. Using cell fractionation and IF, both Pygo2 and TCOF1 colocalized to the same subcellular region in both SKOV-3 and HeLa cells.

Conclusions: Our results indicate that in both epithelial ovarian and cervical cancer, the Wnt-independent function of Pygo2 requires an interaction with the TCOF1 protein.
A CASE OF BREAST CANCER WITH NEUROENDOCRINE DIFFERENTIATION AND NEW ONSET DIABETES MELLITUS

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Background: Neuroendocrine differentiation was reported in a group of human breast neuplasms. Prognostic value of neuroendocrine differentiation in breast cancer is unknown. We want to present a case of invasive ductal carcinoma with neuroendocrine differentiation.

Case report: A 40 y/o female was presented with large mass in her breast. She has new onset diabetes mellitus since one year ago. She underwent breast mass excision and pathologist reported: A 3.5 x2.5x2 Cm mass and microscopic findings included: Breast tissue with neoplastic proliferation composed of tumoral cells with eosinophilic cytoplasm, moderately pleomorphic nuclei, small nucleoli and mitotic figures arranged in solid sheets, trabecular and tubular pattern. Ductal component with comedo type necrosis and perineural invasion are seen. Immunohistochemistry staining results was included: Negative for chromogranin and positive for NSE and weakly positive for synaptophysin.

Result: In this case with new onset diabetes mellitus we found invasive ductal carcinoma with neuroendocrine differentiation which was confirmed by immunohistochemistry study.

Conclusion: In this case we concluded that a subset of breast cancers demonstrate neuroendocrine differentiation. Ectopic hormone production such as ACTH, epinephrine, gastrine, estrogen and prolactine, etc was reported in rare cases of carcinoma with neuroendocrine differentiation. Ectopic hormone production was our possible explanation for new onset diabetes mellitus in this case with breast cancer and neuroendocrine differentiation.

Keywords: Breast Cancer, Neuroendocrine Differentiation
DOCETAXEL-CAPECITABINE IN PATIENTS WITH ANTHRACYCLINES METASTATIC BREAST CANCER

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Background: Docetaxel (D) was administered with Capecitabine (C) to women with metastatic breast cancer (MBC). The aim of this trial was to evaluate the efficacy and tolerance of the combination D - C.

Methods: Patients > 18 years old with MBC, HER-2 neu negative, received an anthracycline regimen in first time and relapse after four cycles of chemotherapy were included in this study.

Four cycles of regimen with D (75 mg/m² d 1) and C (1250 mg/m² PO bid d 1-14), were both administered every 3 weeks.

Results: To date, 37 patients are evaluable for toxicity. Median age is 43 years (36-76); PS 0/1: 59%/41%. All patients had previously received neo/adjuvant anthracyclines treatment. A total of 120 cycles have been administered. D-C grade II/III toxicities: febrile neutropenia 18.9%, asthenia 32.4%, rash 5.4%, infection 2.7%, diarrhea 2.7%, nausea 62%, hand foot syndrome 54%. Four patients have dropped up the study: 1 due to D toxicity and 3 for progressive disease after 2nd D-C cycle. Of the 33 included patients, 19 patients were evaluable after achieving there cycles. 3 patients achieved complete response, 10 achieved partial response (PR) and 6 attained stable disease (SD). The median duration of response was 16 weeks and the median duration of SD was 23 weeks. The median time to progression (TTP) was 32 weeks. The median overall survival was 96 weeks.

Conclusions: The clinical utility of Capecitabine in the management of breast cancer is supported by its favorable safety profile. The combination with Docetaxel was efficacy.
GEMCITABINE - PACLITAXEL VS GEMCITABINE - VINORELBINE IN METASTATIC BREAST CANCER; AN INTERIM ANALYSIS

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Background: This study was conducted to evaluate the overall response rate (ORR) of Gemcitabine-Paclitaxel (GP) Vs Gemcitabine-Vinorelbine (GV). Secondary objectives included individual responses, time to progression (TTP), time to treatment failure (TTF), OS, and toxicities.

Patients and methods: Patients(pts) with histological diagnosis of stage IV or recurrent breast cancer who had measurable disease were randomized to receive GP (G: 1250mg/m² D1 & D8- P: 175 mg/m² D1, D1=D28) or GV (G: 1250mg/m² D1 & D8 - V: 25mg/m² D1 & D8, D1=D21). Pts received previously anthracycline and/or capecitabine chemotherapy.

Results: Of 47 patients enrolled, 24 patients were randomized to GP arm and 23 to GV arm. 72% of patients were stage IV and 28% recurrent disease. Hematologic toxicities were: Neutropenia in 23% in GP Vs 17% in GV, Anaemia in 12% in GP Vs 9% in GV. Non hematologic toxicities were nausea and vomiting grad 2-3 in 27% in GP Vs 31% in GV. The Complete Response (CR) was 27% in GP Vs 30% in GV, the Partial Response (PR) was 23% in GP Vs 17% in GV; with an ORR of 50% in GP Vs 47% in GV. Median TTF in weeks was 12 in GP Vs 14 in GV. Median TTP (weeks) was 14 in GP Vs 19 in GV. Median OS was 32 in GP Vs 50 in GV.

Conclusion: Schedules incriminating Gemcitabine are efficient and benefit. The analysis of the useful of Paclitaxel or Vinorelbine associated to Gemcitabine demonstrates that they are active and manageable.
THE USE OF TRASTUZUMAB IN ADJUVANT OR METASTATIC BREAST CANCER. AN ALGERIAN EXPERIENCE

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Background: Trastuzumab was introduced as a standard of care, three weekly for 18 cycles post chemotherapy for patients with breast cancer over-expressed Her2/neu+.

Methods: Patients were eligible if they had breast cancer over-expressed Her2/neu+. All patients had a baseline LVEF > 55% measured before therapy and had an echo/cardiology assessment before the treatment with Trastuzumab. In Algeria, Her2/neu is over-expressed in breast cancer in 25% of cases, tested by IHC.

Results: From June 2006 to March 2008, 182 Her2/neu+ patients were enrolled in the study and received Trastuzumab with 24 (13.2%) of patients receiving it in the metastatic, 158 (86.8%) in the adjuvant settings. In Centre Pierre & Marie Curie, we enrolled 152 patients, from Medical Oncology of Constantine, we had 16 patients and from the Oncology-Hematology Center of Annaba, we enrolled 14 patients.

The median age was 43 years old and 47% were hormone receptor positive. Most of patients received an anthracycline or taxane containing regimen. 7 (3.8%) patients had to stop treatment because of cardio toxicity. 5 patients were unable to tolerate Trastuzumab. All other patients, in the adjuvant setting, had a normal cardiac function. There was a significant increase in metastatic breast cancer-death if Trastuzumab started > 12 weeks after chemotherapy.

Conclusion: The review shows a good conformity to practice guidelines, a safety use of Trastuzumab. The efficiency of the use of Trastuzumab is incontestable, with a prohibitive cost, but for the safety of patients.
CLINICAL FEATURES AND PROGNOSIS OF ASSOCIATION OF TRIPLE-NEGATIVE BREAST CANCER WITH EXTRACAPSULAR EXTENSION OF AXILLARY LYMPH NODE METASTASIS

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Objective: Triple-negative breast cancers (TNBC) are defined by a lack of expression of estrogen, progesterone, and ERBB2 receptors. We compare the clinical features and prognosis of association of triple-negative breast cancer with extracapsular extension of axillary lymph node metastasis.

Methods: From January 2000 to December 2009, 591 breast cancer patients operated in General hospital “Sveti Vracevi” in Bijeljina. We selected 301 (50.9%) patients with breast cancer who had metastases to axillary lymph nodes.

Results: Extracapsular extension (ECM) was found in 122 (40.5%). Eighty-three patients (14%) were classified as TNBC. The patients were identified and divided into two groups: 22 patients with triple-negative breast cancer with extracapsular extension of axillary lymph node metastasis (TNBCECM) and 14 patients with triple-negative breast cancer without extracapsular extension of axillary lymph node metastasis (TNBCICM). With a median follow-up of 108 months factors with independent prognostic value for disease-free survival by multivariate analysis included TNBC with extracapsular extension \((P < 0.005)\), \(pN\) category \((P < 0.01)\), and presence of lymphovascular invasion (LVI; \(P < 0.005)\). An independent negative prognostic effect on overall survival was observed for TNBCECM \((P < 0.05)\), \(pN\) category \((P < 0.05)\), and presence of LVI \((P < 0.005)\).

Conclusion: In patients TNBCECM prognosis was significantly worse compared with those who were TNBCICM. These findings have led to the conclusion that TNBC is associated with a more aggressive subtype of cancer.
ELEVATED MRE11 EXPRESSION IN BREAST CANCER TISSUES IS ASSOCIATED WITH POOR PATIENT SURVIVAL

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Meiotic recombination 11 (Mre11) is regarded as the core protein of MRN (Mre11-Rad50-NBS1) complex, that play a vital role in coordinating DNA damage response, DNA replication and telomere maintenance. In this study, we explored the possible involvement of Mre11 in the carcinogenesis of breast cancer. The high Mre11 expression in breast cancer tissues, determined by immunohistochemistry analysis, was significantly correlated with lymph node metastasis as well as tumor grade, stage and size. Interestingly, the high Mre11 expression in breast cancer tissues was correlated with a negative ER status. While the high Mre11 expression alone was associated with a poor overall survival, a worse survival was observed when combined with the negative ER status. The biological activity of Mre11 was analyzed by overexpression as well as knockdown of Mre11 expression in breast cancer cells. While a decreased Mre11 expression in breast cancer cells caused a significant cell death as well as cell cycle arrest at G0/G1 phase, an increased Mre11 expression leaded to cell proliferation as well as the enriched S and G2 phases. In conclusion, our results demonstrated that, other than its role as DNA double-strand break repair protein, an elevated Mre11 expression in breast cancer cells was associated with a more malignant cancer cell behavior as well as a poor overall survival in breast cancer patients. Further studies are required to confirm the roles of Mre11 as a breast cancer prognostic factor and a therapeutic target.
PREDICTORS OF ADHERENCE TO CLINICAL BREAST EXAMINATION AND MAMMOGRAPHY SCREENING AMONG MALAYSIAN WOMEN

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Breast cancer is the most common cancer among Malaysian women. Early detection of breast cancer can play an important role in reducing cancer morbidity and mortality. The aim of this study was to determine the rates and factors related to clinical breast examination (CBE) and mammography among female teachers in Malaysia. A cross-sectional study was conducted among 425 female teachers in Selangor, Malaysia. A self-administered questionnaire that included questions on socio-demography, cancer-related knowledge, practice and an adapted version of Champion's revised Health Belief Model Scale was used. The mean age of participants was 37.17±7.16 years. Only 25% of the women ever had a CBE. Women over the age 40, (n=138) 13.6% reported having a mammography. Results showed higher susceptibility to breast cancer, higher benefits of doing CBE and regular visit with a physician were significant predictors for undergoing CBE (p< 0.05). Higher perceived susceptibility to breast cancer and regular undergoing CBE were significant predictors for having a mammography. Findings suggest a need for improving women awareness on breast cancer screening, its importance and recommended guidelines.
BREAST CANCER SURVIVORSHIP - OPTIMIZING FOLLOW-UP CARE

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A qualitative approach was used to explore breast cancer survivors' experiences since completion of treatment and preferences for survivorship care. Focus groups were conducted with 28 women with non-metastatic breast cancer, 3-12 months post-completion of last surgery, chemotherapy or radiation. Groups were stratified by age. Data was subjected to thematic analysis by age group (life stage).

Results: The impacts of breast cancer after completion of treatment are broad and vary by age group. Physical, emotional and social effects are more intense in younger patients. Older patients experience consistent, positive social support and develop closer relationships after breast cancer. Fatigue and fear of recurrence are the most universal effects.

Preferred content of survivorship care plans echoes the wide variation in impacts of breast cancer. Patients want individualized, yet comprehensive, information. While preferred content varies by life stage, preferred format is similar. Organized transition from specialist to primary care is emphasized. The ideal time for information is upon completion of treatment, or shortly after. Patients identify a health-care professional such as an oncology nurse as the best person to deliver survivorship information. Preferred medium is in-person consultation, with adjunct written materials in lay language, telephone follow-up and electronic bulletins. Qualitative information on the effects of breast cancer at different life stages can be used to help individualize the content of survivorship care plans.
GYNECOLOGIC AND BREAST CANCER PEER MENTORS: INTERPRETING PROGRAM IMPACT

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Introduction: The purpose of this study was to evaluate the existing Peer Mentor (PM) Cancer Survivors Programs at an urban Southern California Cancer Institute. An evaluation of the existing program provided evidence as to the effectiveness of this program.

Objectives:

1. Examine differences between gynecologic (GC) and breast cancer (BC) experiences of PMs,
2. Examine and identify themes to be used for the development of surveys,
3. Analyze surveys to evaluate the effectiveness of the peer mentor program.

Methods: Qualitative methodology used in the first phase utilized two semi-structured focus group interviews; GC (n=4) and BC (n=10). Thematic Analysis was used to clarify key phrases and recurrent themes. Constant comparison of the incoming data provided themes which were used to develop an eight question, on-line survey (second phase) that will be instrumental in eliciting data that will be reflective of mentors' experiences. 100 surveys have been sent out to the rest of the PM groups (n=100).

Results: Thematic analysis revealed 15 themes and four major categories. The major categories were consistent between groups, however themes differed in relation to; reoccurrence, experience of being a mentor, perceived availability of resources. Differences in perceptions between the groups may be explained by the nature of gynecologic cancer disease process. There is a high rate of recurrence especially with ovarian and less availability of dedicated resources for GC in comparison to BC. As a result of the differences two survey instruments were developed and sent to the remaining PMs from the group.
NUTRITIONAL AND HEMATOLOGICAL EFFECTS OF A DIETARY SUPPLEMENTATION WITH AGARICUS SYLVATICUS IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY

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Aims: Evaluate the nutritional and hematological effects of a dietary supplementation with Agaricus sylvaticus in breast cancer patients undergoing chemotherapy.

Methods: A randomized, placebo-controlled, double-blind clinical trial. Sample of 46 women with breast cancer at stages II (61.5%) and III (38.5%) during chemotherapy, average age 52.41±5.94 years, divided in two groups: placebo (n = 23) and experimental (n = 23). The placebo group received starch only, orally, for six months. The experimental group was received Agaricus sylvaticus fungus (2.1g/day), orally, 3 times daily for six months. The trial consisted of: evolution of the disease, gastrointestinal symptoms, response to chemotherapy, prognosis, tumor size (observed by mammography) and body weight.

Results: After six months of supplementation with Agaricus sylvaticus, it was observed a substantial improvement in clinical and nutritional status as well as reduction of vomiting (30%), nausea (20%), diarrhea (10%) and constipation (10%) in the group supplemented with mushroom when compared with the placebo group. In addition to that, in the group supplemented with mushroom there were alterations in hematocrit (from 35.32 ± 4.73 to 39.02 ± 5.80, P = 0.06), hemoglobin (from 11.68 ± 1.66 to 12.77 ± 1.89, P = 0.09), platelets (from 4.1 ± 0.56 to 4.81 ± 0.83, P = 0.03), MCH (from 29.70±3.63 to 36.90±2.90, P = 0.05), MCV (from 84.80 ± 7.81 to 86.50±4.19, P = 0.2) when compared with the placebo group.

Conclusions: The patients with breast cancer can experience significant improvement in their nutritional and hematological status if supplemented with Agaricus sylvaticus fungus.
SURVIVORSHIP CARE PLANNING FOR BREAST CANCER SURVIVORS

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Background: Range of survivorship issues that patients can encounter is broad. Although, Institute of Medicine’s report on cancer survivorship recommends that cancer patients completing treatment should be provided with a comprehensive care summary and follow up plan that is clearly and effectively explained, it is not always practiced.

Methods: A qualitative approach was used to explore impacts of breast cancer on survivors at different life stages and to determine preferred content and format of survivorship care plan (SCP). Focus group and face-face interviews were audio-recorded and transcribed with women who had non-metastatic breast cancer, 3-48 months post-treatment and were 18-75 years of age. Groups were stratified by age into < 44, 45-54, 55-64, and >65.

Results: The impacts of breast cancer were broad and varied by age group for the 16 women in the study. Physical, emotional and social effects were more intense in younger patients with women in the middle age group experiencing more concerns centered on financial and social support issues. Fatigue and fear of recurrence were the most universal effects. Important elements include: treatment summary, information on nutrition/exercise, expected side effects, signs/symptoms of recurrence, follow-up schedule, and updates on changes to recommended care. Preferred format for SCP is similar for all groups.

Conclusions: BCS are diversely impacted by the breast cancer experience. Effects vary by life stage, which impacts preferred content of SCP, but not format. Qualitative information on the impact of breast cancer at different life stages can be used to help customize content of SCPs.
LIPOSOMAL TAXOTERE WITH LINKED-PYMT-MABS INHIBITED VEGF-MEDIATED-HUMAN-TELOMERASE-REVERSE-TRANSCRIPTASE (HTTERT), C-SRC, PI3K, VEGF-A, MMP-2, AND INTEGRINS- A1- 2-6 INDUCING APOPTOSIS IN HRBC

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Introduction: HRBC is an incurable cancer of potent chemoresistance which leads to fatalities due to inhibition of apoptosis/PCD.

Methods: Hormone refractory breast cancer (HRBC) Her2/neu+ cells from a metastatic patient were obtained and they were treated with liposomal taxotere(TXT)and linked PyMT Mabs. β-galactosidase was used as a marker of cell senescence. Flow cytometry was used for examining shortening of telomeres and cell cycle. Gelatin zymography was used for analysis of MMP-2. cDNA arrays and RNase assays were used to detect expression of integrins.

Results: TXT downregulated VEGF-mediated hTERT leading to inhibition of telomerase activity in HRBC. Furthermore, TXT caused shortening of telomeres, blockage of cell cycle progression and entry of tumour cells into a senescent state. TXT besides causing inhibition of VEGF autocrine loop in tumour cells, it downregulated VEGF-A which led to inhibition of tumor lymphangiogenesis. Gelatin zymography demonstrated reduction of MMP-2 establishing TXT as an anti-invasion agent. Inhibition of VEGF-driven angiogenesis led to inhibition of integrins a1,2,6 which are receptors for extracellular matrix (ECM). PyMT Mabs inhibited PyMT, c-Src and its protein kinase activity. Furthermore, PyMT Mabs blocked PI3K dept. signaling pathways. Tdt-mediated dUTP nick-end labelling (TUNEL) analysis of HRBC cells treated with liposomal TXT with linked PyMT MAbs revealed nuclear DNA fragmentation leading to formation of apoptotic bodies which were phagocytosed by adjacent cells. BrdU and MTT exhibited inhibition of DNA synthesis and metabolic activity of post-treated HRBC.

Conclusion: Liposomal TXT with linked PyMT MAbs has inhibited VEGF-mediated telomerase activity, VEGF-induced adhesion, migration, lymphangiogenesis, c-Src, and PI3K dept signaling pathways inducing apoptosis in HRBC cells.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

ANTISENSE TREATMENT WITH PEGYLATED-LIPOSOMAL-MULTITARGETED-SIRNA AGAINST UBCH5,C-SRC,AND HSP90 COMBINED WITH BEVACIZUMAB ERADICATED HORMONE REFRAC'TORY BREAST CA(HRBC) BY INDUCTION OF APOPTOSIS/PCD TYPEI

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Introduction: Metastatic hormone refractory breast Ca can develop resistance to bevacizumab. We aim to circumvent this resistance, and eradicate chemoresistant HRBC.

Methods: HRBC were obtained from patients with metastatic HRBC resistant to bevacizumab due to insertion mutations at exon 8, ubiquitination, and overexpressed c-Src. Orthotopic mouse HRBC models generated from the patients’ tumor cells were injected with pegylated liposomal multitargeted siRNA against HSP90, Ubch5, and c-Src.

Results: Pegylated liposomal multi-targeted siRNA inhibited expression of the E2 enzyme Ubch5, blocking the covalent attachment of ubiquitin to VEGFR, and neutralizing the multienzyme cascade. E1 deactivated ubiquitin, blocking transfer to the cysteine residue of E2 ubiquitin conjugating enzyme (Ubch5). This inhibited the E2 ligation of ubiquitin via its carboxy terminus to lysine residues of the protein substrate VEGFR. Also, multitargeted siRNA inhibited expression of HSP90 resulting in degradation of VEGFR with kinase resistant insertion mutations at exon 8. Inhibition of c-Src circumvented transactivation, and inhibited VEGFR-mediated signaling. Inhibition of VEGFR blocked the activation of downstream mediators including STAT3, AKT, Erk, MAPK, and PI3K, while IRF-1 was upregulated. There was enhanced cell-to-cell adhesion, and membrane localization of b-catenin, while MMP-9 invasive activity was blocked. Furthermore, the HIF-1a/Met pathway was blocked, downregulating CAIX. VEGFR1,2,3 were blocked, inhibiting vascularization, and lymphangiogenesis. TEM exhibited type I PCD/apoptosis, type II PCD/autophagy, and type III PCD/necrosis in tumor, and angiogenic endothelial cells leading to a bystander killing effect.

Conclusions: Treatment of pegylated liposomal multitargeted siRNA against Ubch5, c-Src, and HSP90 eradicated metastatic HRBC.
COMPERETIVE KNOWLEDGE AND PRACTICE BREAST SELF EXAMINATION IN MIDWIFERY AND NURSING STUDENT ISLAMIC AZAD UNIVERSITY KARAJ BRANCH PARIDOKHT ASHKEVARI

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Aim: The aim of this study was to evaluate the level of knowledge of midwifery and nursing student regarding breast self-examination.

Materials and methods: This study is descriptive on 23 midwifery and 69 nursing student. data collection tool was a questionnaire the included 6 questions about demographic characteristics, and 14 question about knowledge breast self examination. Data analyzed by descriptive statistics.

Result: Our results show that the average age being (21-35), majority of them are single (%67/4) and (%29/3) twin. Our result showed no significant differences in midwifery and nursing knowledge. (p>5%). Our result showed the students of midwifery and nursing have mild knowledge.

Conclusion: It seems that despite of the importance of the BSE in early diagnosis of breast cancer the majority of women have poor knowledge and practice about BSE. Based on the positive attitude of most women about BSE, it is that increasing the knowledge of women by education ways of breast cancer, especially BSE, this will be available by more attention of public health centers, TV and newspaper for increasing women awareness.

Keywords: Breast, student, cancer, self examination
FURANODIENONE INHIBITS ESTROGEN RECEPTOR-ALPHA EXPRESSION AND ACTIVITY IN HUMAN BREAST CANCER MCF-7 CELLS

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Estrogen and estrogen receptor alpha (ERα)-mediated signaling play an important role in the development and progression of breast cancer. Therefore, attenuating ERα activities is a promising strategy for the treatment of breast cancer. Furanodienone is a compound isolated from Rhizoma Curcumae, which is commonly used in cancer treatment in China. In this study, we used the breast cancer cell MCF-7, an estrogen-responsive human breast cancer cell line as the model to investigate the effect of furanodienone on ERα signaling. We found that furanodienone effectively blocked 17β-estradiol (E2)-stimulated cell proliferation and cell cycle progression. Moreover, furanodienone decreased ERα protein and transcription levels so that it prevented E2 stimulation of estrogen response element (ERE)-driven reporter plasmid activity and ablated the E2-induced transcripts of c-Myc, Bcl-2 and cyclin D1, which resulted in inhibiting cell cycle progression and cell proliferation. Depletion of ERα by ERα small-interfering RNA knockdown decreased furanodienone sensitivity in MCF-7 cells. These findings suggested that the growth inhibition by furanodienone in ERα positive human breast cancer cells may be mediated, at least in part, by inhibition of ERα signaling.
EPIDEMIOLOGICAL ANALYSIS OF BREAST CANCER IN VOJVODINA IN THREE PERIODS FROM 1978 TO 2007

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Breast cancer is the most common cancer in women in Vojvodina (Serbia). Over a 30-year period 22,405 (24%) new cancer cases of breast cancer in women were registered in Vojvodina and 283 (0.3%) in men.

We used a descriptive epidemiological method to analyse incidence in three periods in Vojvodina. First period was from 1978 to 1987, second from 1988 to 1997 and third from 1998 to 2007.

In Vojvodina the annual average number of diseased in the first period was 521, average incidence rate was 50/100 000. In the second period the annual average number of diseased period was 771, average incidence rate was 74/100 000. In the third period the annual average number of diseased period was 977, average incidence rate was 94/100 000. From 1978-2007 the trend of incidence had an increasing tendency ($Y=1,11X + 29.6, R^2=0.87$). Nearly 8 percents of diseased of all breast cancer cases was from 1978 to 1987 under 40 years old, 5.75 percents were from 1988 to 1997 and 5.02 percents were from 1998 to 2007. Male participated with 0.76 percents in the first period, with 1.08 percents in the second period and with 1.60 percents in the third period.

We conclude that breast cancer have an increasing tendency in the observer period. Participation of young diseased has declined in three periods probably due to the aging of the population in Vojvodina. Participation diseased men of all breast cancer has increased in observed periods.

Keywords: Breast cancer, epidemiology, incidence
CORRELATION BETWEEN HORMONE RECEPTOR STATUS (ER, PR), HER-2, P53 IN SOUTH INDIAN BREAST CANCER PATIENTS

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Background - Breast cancer is the second most common malignancy among women in India. Presence of Estrogen receptor (ER) and Progesterone receptor (PR) and Human Epidermal Growth Factor -2 (HER-2/neu) status in invasive carcinoma is now-a-days routinely estimated as these markers are important prognostic factors. ER and PR status has been used for many years to determine a patient's suitability for endocrine therapy (tamoxifen) whereas HER-2/neu is helpful in predicting response to trastuzumab (Herceptin). p53 is a tumor suppressor gene which in the mutant for Material and methods - In this retrospective study (January 2000 - December 2008). There were 213 cases of breast carcinomas. Majority (90%) were infiltrating duct cell carcinoma (NOS). Medullary, comedone, cribriform, micropapillary, neuroendocrine, lobular, mucinous, metaplastic were other variants All the four markers (ER, PR, HER-2, p53) could be done on 149 cases and in the remaining cases only ER, PR was done. The intensity and proportion of tumor cells stained for ER, PR was assessed by Quick score system which exhibits nuclear positivity by immunohistochemistry. Results - Our data showed overall 46% ER, 71% PR, 77.9% HER-2 and p53 positivity. The Quick score for ER was mild (1-3) in 9%, moderate (4, 5) in 26% and strong (6-8) in 11% cases. Likewise the Quick score for PR was mild (1-3) in 6%, moderate (4, 5) in 45% and strong (6-8) in 20% cases. Pan receptor positivity was noted in 37 cases. All the four markers were negative in 5 cases. In Asian countries hormone receptor positive cases has been found to be lower compared to western countries.
COPING STRATEGIES IN IRANIAN BREAST CANCER PATIENT

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Background and aims: Breast cancer is a tragic experience that accompanies stressful situations for patients. Adjustment with breast cancer is affected on decline stress and increases their quality of life. In a phenomenological study we carried out the strategies adjustment to overcome the breast cancer in Iranian patients.

Method: In this study we conducted in-depth guided interviews for 15 breast cancer participants who attended in breast cancer follow-up clinic in ICBC (Iranian Center for Breast Cancer), Tehran, Iran. An informed consent obtained from each patient. The interviews were audiotape-recorded and transcribed verbatim and a thematic analysis was performed to elaborate outcomes. Each interview lasted approximately an hour.

Results: All of participants had breast surgery and also 93% had chemo and radiotherapy. The mean age of them was 50.6 (SD=± 8.2). Eleven patients (73%) were married and time period between the diagnosis and their interviews was 1-17 years. The major theme emerged from analysis were:

1) Belief in God as a reassuring recourse
2) Positive cognitive appraisals as a potent factor to adjust with cancer and
3) social and family supports as an important factor for coping with disease.

Discussion: The study data show that, trust in God, positive thinking and social and family support are the most important coping strategies for breast cancer patients. It seems that, health care providers must be much sensitive to the patient's coping strategies. Also, they must promote patients to use their positive mental powers to win the battle.
EVALUATION THE OF OVARIAN SUPPRESSION AS ADJUVANT THERAPY IN BREAST CANCER PATIENTS

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The aim of this study was to assess the additional benefit of ovarian suppression or ablation in association with tamoxifen use in premenopausal women that have not reached amenorrhea when adjuvant chemotherapy is completed.

Material and methods: 22.1 months. Then we compared three year disease free survival (DFS) and overall survival in these three groups. Statistical analyze was used through Kaplan - Mayer and NOVA test and P. Ninety - four premenopausal women in early breast cancer stage with positive estrogen and progesterone hormone receptors who underwent adjuvant chemotherapy without amenorrhea were identified in a retrospective descriptive and analytic study conducted. Tamoxifen antiestrogen therapy was used after the end of chemotherapy in all patients. 31(33%) patients underwent ovarian ablation with GNRH or double oophorectomy according to whom wanted of patients. 20(21.3%) consecutive patients underwent ovarian ablation through oophorectomy and 11(11.7%) through monthly GnRH injections and 63(67%) used tamoxifen therapy. The mean follow up and standard deviation time was 60.3< 0.05 considerd significant.

Results: 21.16 in tamoxifen only group (P-value = 0.12) Overall survival in first group in first group was 30+8.5 and in second group (ablation) 53.7+22.76 and in tomoxifen group was 41.4+ 21.51 month (P=0.006). 23.09 in ovarian ablation group and 39.7+21/16 in GnRH group and, 53.4+ Three years disease free survivals were 29.7

Conclusion: Our experience confirmed that addition of oophorectomy or GnRH to routine treatment of breast cancer (tamoxifen and chemotherapy ) improves DFS, and significant benefits in ovarian ablated patients were seen.
EXPERIENCE WITH SENTINEL LYMPH NODE BIOPSY (SLNB) USING METHYLENE BLUE DYE IN EARLY STAGE CARCINOMA BREAST

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Introduction: SLNB is the minimally invasive procedure that predicts axillary lymph node status quite accurately and avoids the morbidity of lymph node dissection. Isosulphan blue dye is the dye used most often. The dye is expensive, not readily available and few adverse effects have been reported.

Aims: To localize the sentinel lymph node in early breast cancer with clinically negative axilla by using methylene blue dye which is readily available and cheap. To assess the role of SLNB in predicting the axillary lymph node status on histopathological examination.

Material and methods: A prospective study was conducted from July 2007 to June 2009, on 50 female patients with cytologically proven early breast cancer (T1, T2) and clinically node negative axilla (N0). Methylene blue dye was injected peritumorally. Sentinel node was identified as blue stained node. The blue node was removed and sent separately for histopathology followed by axillary clearance in all patients. 24 patients had mastectomy with conservative breast surgery in 26 patients.

Results: Sentinel lymph node was identified in 94% patients. In 22 (44%) patients had single SLN 50% patient multiple SLN were identified. The sensitivity was 93.3% and the specificity was 100%. The false negativity rate of the procedure was 6.7% on histopathology. No hypersensitivity reaction was observed. 2 patients complained of blue colored urine. No soft tissue necrosis was noted.

Conclusion: SLNB can be used as a staging procedure as it carries low false negative rates. Methylene blue is good alternative to isosulphan blue specially in low resource countries.
ESTROGEN RECEPTOR-A GENE POLYMORPHISM IN IRANIAN WOMEN WITH BREAST CANCER

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Breast cancer is one of the most frequent malignancies among Iranian women. Estrogen receptor-a gene (ESR1) polymorphism has been found to be associated with breast cancer and clinical features of the disease in Caucasians and Asians. A case-control study was conducted to establish a database of ESR1 polymorphisms in Iranian population in order to compare Western and Iranian (Middle East) distributions and to evaluate ESR1 polymorphism as an indicator of clinical outcome. The ESR1 gene polymorphisms were identified in newly diagnosed invasive breast tumor Iranian patients, (150 patients) and in healthy individuals (147 control). PCR single-strand conformation polymorphism technology and direct sequencing was performed.

The single nucleotide polymorphism (SNPs) was found, as reported previously in other studies, but at different frequencies. The frequency of allele1 in, codon 10 (TCT → TCC) (T/C, S392S), exon1 was higher in breast cancer patients (45.7%) than in control individuals (39.8%; *P* = 0.148). We found that allele 1 (TCT→ TCC) in codon10 was more common in breast cancer patients with a family history of breast cancer (78.9%) than in those without such a history (40.8%; *P* = 0.001). The allele 1 in codon 10 exhibited an association with the occurrence of lymph node metastasis (58.7% and 43.3% with and without LN metastases, respectively). Therefore, this SNP marker further increased predictive accuracy in Iranian population.

Data suggest that ESR1polymorphisms are correlated with various aspects of breast cancer in Iranian, as determined during pre-surgical evaluation, might represent a surrogate marker for predicting breast cancer.
PATIENT-REPORTED OUTCOMES IN BREAST CANCER PATIENTS UNDERGOING ENDOCRINE THERAPY (PRO-BETH): ADHERENCE RATES TO TAMOXIFEN REGARDING CYP2D6 GENOTYPE AND SIDE-EFFECTS

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Background: Only few studies investigated adherence of breast cancer patients to tamoxifen therapy and factors influencing adherence behavior, especially in the context of different CYP2D6 genotypes. Variations in the CYP2D6 genotype and patients taking inhibitors of CYP2D6 (e.g. antidepressants) contribute to different side-effects and adherence rates.

Materials and methods: 106 breast cancer patients were consecutively included in the study at the outpatient unit of the Department of Gynecology, MUI. The multi-method approach comprised the Simplified Medication Adherence Questionnaire, FACT-B, HADS, a semi-structured interview, physicians’ ratings, blood levels for tamoxifen metabolites and determination of the CYP2D6 genotype.

Results: 12% patients were poor metabolizer (PM), 41% intermediate (IM), 21% extensive (EM) and 6% ultra-rapid metabolizer (UM). Significant differences regarding tamoxifen serum concentrations were found between metabolization groups (p=0.044). All non-compliant patients were EM. However, during follow-up 25% (2/6) of patients with UM genotype, 13% (4/30) of EM, 1% (1/50) of IM and 0% (0/19) of PM discontinued tamoxifen therapy due to therapy-related side-effects. Antidepressants were more frequently prescribed in the EM group leading to lower levels of the active metabolite endoxifen.

Conclusion: We didn’t find significant differences in QOL between CYP2D6 metabolizing groups, but trend level significance for global QOL, physical and emotional well-being. Non-adherence to tamoxifen therapy is more frequent in EM and UM patients. These preliminary data may explain part of the current controversy over CYP2D6 genotype predicting response to tamoxifen and suggest that patients most likely to benefit from tamoxifen are paradoxically most likely to stop tamoxifen therapy prematurely.
KIDNEY PYRROLIDONE CARBOXYPEPTIDASE ACTIVITY IS MODIFIED IN RATS WITH MAMMARY TUMOURS

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Pyrrolidone carboxypeptidase (Pcp) (E.C. 3.4.19.3) is an omega peptidase widely distributed in animal fluids and tissues and hydrolyses N-terminal pyroglutamic residues from biologically active peptides such as gonadotropin releasing hormone (GnRH). In kidney, it has been described Pcp and it has been located binding points for the GnRH and down affinity specific points for the GnRH in renal cortex, among others. Therefore, the presence in kidney of GnRH, as well as of its regulatory enzyme, Pcp, makes us suppose an important role for this hormone in this localization. In this sense, we previously described a decrease in both rat and human Pcp activity with breast cancer, suggesting that GnRH may be an important local intracrine, autocrine and/or paracrine hormonal factor in the pathogenesis of breast cancer playing a role in the tumoral process. On the other hand, the Pcp enzyme also it has been described as a renal damage marker.

In this context, the aim of the present work is to analyze soluble and membrane-bound renal Pcp activity in an animal model of breast cancer induced by NMU, using pyroglutamyl-beta-naphthylamide as substrate.

In this work we observed a significant decreased in renal cortex and a significant increased in this activity in medulla, in soluble fraction.

Modifications in renal Pcp activity in animals with breast cancer induced by NMU, would be considered good pointers of alterations in renal function, due to progression of the disease, and a mechanism for evaluate the promotion/progression grade of breast cancer.
EFFECTS OF TAMOXIFEN ON THE CERVIX AND UTERUS IN WOMEN WITH BREAST CANCER

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Objective: Invasive breast cancer is the most common malignancy in women. Due to the declining mortality rate that is partly attributable to the use of screening mammography and effective adjuvant therapy, more women survive their breast cancers. The aim of this study was to evaluate the effects of tamoxifen on the genital tract with particular attention to the uterus and cervix.

Methods: We investigated the relationship between tamoxifen and cervical or uterine cancer in Iran, reviewing all the studies performed by the Vali-Asr Gynecology Oncology Clinic in Tehran. In addition, the available data on Medline from 1980 until 2009 were reviewed.

Results and conclusions: In spite of the significant relationship between tamoxifen and endometrial cancers, cervix is rarely involved in breast cancer patients. However, vaginal bleeding or abnormal vaginal discharge has been reported in all cases before the diagnosis was made. To rule out genital tract malignancy, it is necessary, therefore, to have an annual pelvic exam, pap smear and early endometrial with endocervical curettage for tamoxifen users following a breast cancer in those with abnormal uterine bleeding or persistent vaginal discharge.
HIGH VISFATIN EXPRESSION IN BREAST CANCER TISSUE IS ASSOCIATED WITH A POOR OVERALL SURVIVAL

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Adipocytokines are the adipocyte-secreted hormones that are frequently associated with human malignancies. The role of visfatin, one of the adipocytokines, in breast cancer remains to be determined. In this study, we investigated the possible involvement of visfatin in the carcinogenesis of breast cancer. The expression of visfatin in the matched cancer and non-cancerous breast tissue specimens was analyzed by using immunohistochemistry analysis. The results were further correlated with the clinicopathological variables and overall survival. The expression of visfatin were increased significantly in the breast cancer tissues in comparison to non-cancerous breast tissue (p =0.002). An elevated visfatin expression in breast cancer tissues was significantly correlated with tumor stage, age as well as tumor size (p=0.020, 0.032 and 0.025, individually). Interestingly, the high visfatin expression in breast cancer tissues was correlated with a negative ER and PR status (p=0.007 and 0.003). While the high visfatin expression alone was associated with a poor overall survival (p= 0.005), a worse survival was observed when combined with the negative ER and PR status (p=0.004 and 0.002). Cox regression analysis showed visfatin to be an important determinant of breast cancer prognosis. In conclusion, our results suggest that the high visfatin expression in cancer tissues is associated with a more malignant cancer cell behavior as well as a poor overall survival in breast cancer patients.
TREATMENT OF PERITONEAL CARCINOMATOSIS FROM BREAST CANCER BY MAXIMAL CYTOREDUCTION AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY: A PRELIMINARY REPORT OF 4 CASES

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Introduction: Peritoneal metastases from breast cancer are rare but significant cause of mortality. Only few data are reported on treatment strategies in these patients.

Methods: Among 109 patients treated for peritoneal carcinomatosis from 2000, 4 had confirmed diagnosis of peritoneal carcinomatosis from breast cancer and were treated by maximal cytoreduction plus HIPEC with cisplatin (75 mg/m²), systemic chemotherapy (epirubicin 100mg/m², endoxan 600mg/m², 6 cycles) and hormonotherapy.

Results:

Pt#1. 58 years old, left (1993, T2N1 IDC) and right (1999, T2N0 IDC) mastectomy. Both tumors ER+, PR+ c-ERB2+. September 2004 underwent pelvic peritonectomy (total hysterectomy, bilateral ovariectomy), total colectomy, omentectomy plus HIPEC. PCI 15, CC2. Alive disease-free after 61 months.

Pt #2. 54 years old, 1977 left mastectomy for T2N3 ER+ and PR+ ILC. Refused chemotherapy. March 2006 pelvic peritonectomy, subtotal colectomy, splenectomy, ileal resection. PCI 22, CC1. Alive disease-free at 43 months.


Pt #4. 77 years old, left quadrantectomy, axillary dissection and radiotherapy for T2N1 ER+, PR+ IDC, refused chemotherapy. June 2008 pelvic peritonectomy, splenectomy, cholecystectomy, appendectomy, left hemicolecotomy and HIPEC. PCI 24, CC1. Alive disease-free at 10 months.

Conclusions: To our knowledge this is the first report on treatment of peritoneal carcinomatosis from breast cancer with maximal cytoreduction and HIPEC. Despite suboptimal cytoreduction, the relatively long survival reported suggests new treatment strategies in these patients.
HAPTOGLOBIN GENE EXPRESSION AND ITS CORELATION WITH OTHER CLINICAL PARAMETERS AND PROGNOSIS IN BREAST CANCER AMONG INDIAN WOMEN

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Background: Elevated serum levels of haptoglobin have been associated with inflammatory diseases, and worse survival in a variety of malignancies including breast cancer.

Aims: The retrospective review was undertaken to determine immunohistochemically (IHC) the prognostic implications of haptoglobin oncoprotein in breast cancers and its association with different pathobiological and prognostic parameters such as over expression of CerbB2, estrogen receptors and progesterone receptors, menopausal status, lymph nodes, stage, grade, metastasis, histological grades of tumor and disease free survival.

Materials and methods: A retrospectively collected data of breast cancer patients treated at KMIO was used for analysis. IHC was performed on tumor tissue from 119 patients for whom full clinical information and follow up was available.

Statistical analysis used: Kaplan-Meier plots were generated for the survival analyses. In all cases P values less than 0.05 were considered significant.

Results: Haptoglobin expression was noted in 80(45.0%). Haptoglobin immunoreactivity significantly correlated with lymph node status, metastasis, CerbB2, and stage of disease. At mean follow up of 55 months, disease free survival was significantly worse in subset of patients whose tumor demonstrated haptoglobin expression compared to non expressers.

Conclusions: Haptoglobin positive patients exhibited worst survival compared to non expressers at 55 months of duration. Immunoreactivity for haptoglobin was a significant predictor of breast cancer relapse in this subset of patients.

Keywords: IHC: Immunohistochemistry

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PREVALENCE OF BRCA1 GERMLINE MUTATIONS AMONG PAKISTANI WOMEN WITH TRIPLE-NEGATIVE BREAST CANCER

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Background: Current criteria for BRCA1/2 genetic testing rely primarily on family history of cancer and early age of onset. In this study we assessed if the triple-negative phenotype of breast cancer, i.e. negative for estrogen-receptor (ER), progesterone-receptor (PR) and human epidermal growth factor receptor-2 (HER2), can be used to identify candidates for BRCA1 mutation testing in Pakistan.

Methods: 137 women diagnosed with breast cancer < 30 years-of-age (n=74) or a family history of breast/ovarian cancer (n=63) were ascertained at the SKMCH & RC from June 2001 to November 2004. Clinico-pathological information and blood samples for DNA isolation were obtained from all patients. Comprehensive BRCA1/2 mutation screening was performed using protein-truncation test, single-strand conformational polymorphism analysis, and denaturing high-performance liquid chromatography analysis followed by DNA sequencing of variant signals detected by these assays.

Results: On the basis of ER, PR, and HER2 clinical testing, 65 (47.4%) of the 137 women were classified as triple-negative. Seventeen deleterious mutations were identified in the 65 breast cancer patients (26.1%); 16 in BRCA1 and one in BRCA2. Five BRCA1 mutations (13.9%) were identified in 36 early-onset patients. Triple-negative breast cancers in BRCA-carriers and non-carriers were diagnosed at a similar median age of 28 years (range 22-40 in both groups). There were no differences in the histological type, tumor size, grade and lymph node status between the groups.

Conclusion: Our data show that young Pakistani women with triple-negative breast cancer and without a family history of breast or ovarian cancer are candidates for genetic BRCA1 testing.
SATB1-EXPRESSION AND ITS PROGNOSTIC IMPACT IN BREAST CANCER IS CORRELATED WITH ESTROGEN RECEPTOR STATUS

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Background: Several recent reports have linked the expression of SATB1, a genome organizer recruiting chromatin remodeling/modifying enzymes and transcription factors, to the potential for metastasis of breast cancer cells and therefore its negative prognosis on survival. Still uncertain remains the relation of estrogen receptor (ER) status of the cancer cells to the prognostic value of the higher expression of the SATB1 in primary breast cancer cells.

Methods: A database of 3030 Affymetrix microarrays and clinical characteristics from primary breast cancer patients was established. To allow comparison of SATB1 expression between different datasets we used a quartile split of each dataset. Chi-square test was used to test for associations between SATB1 expression of tumors and categorical parameters. Kaplan-Meier curves were constructed and the log-rank test used to determine the univariate significance of the variables.

Results: Univariate analysis revealed no significant difference of SATB1 expression according to lymph node status, tumor size, histological subtype, pathohistological grading, Ki67 expression and erbB2-status. However, a strong correlation was found for patients’ age (p < 0.001) and the ER status of the tumor with higher SATB1 expression among ER-negative samples (p < 0.001). The survival analysis of our cohort revealed that while there was no significant difference among ER-negative cancers there was instead a benefit for high SATB1 expression among ER-positive tumors.

Conclusions: The prognostic impact of SATB1 expression is mainly confined to ER-positive breast cancers, suggesting that SATB1 is an estrogen dependent marker when analyzing gene expression data.
ATYPICAL DUCTAL HYPERPLASIA - CRITERIA OF UNDER-ESTIMATION AFTER DIAGNOSTIC BY STEREOTAXIC VACUUM-ASSISTED BIOPSY

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Objective: The purpose of this study was to assess the rate of underestimation of cancer after diagnosis of Atypical ductal hyperplasia (ADH) by stereotactic vacuum-assisted biopsy. The secondary objective was to analyze the clinical factors, radiological and histological predictors of carcinoma in this situation and identify a population at low risk of underestimation.

Materials and methods: Retrospective multicenter study. All patients presenting as a primary lesion HCA, diagnosed after stereotactic vacuum-assisted biopsy between January 2002 and February 2009 were included in our study. After biopsy, patients were either operated or monitored. The initial lesion (ADH) was considered as underestimated when the final analysis, concluded after surgery in ductal carcinoma in situ or invasive cancer.

Results: Sixty patients were included. Fifty-six were operated and four monitored. After final analysis, 20 patients had carcinoma in situ at least. The rate of underestimation was 35.7% (20/57). None of the clinical, radiological and histological study has proved to be a significant predictor of underestimation and could not be any individual subgroup to which a radiological and clinical surveillance might be considered.

Conclusion: In the absence of a reliable criterion to identify a population at low risk of underestimating the surgery appears indicated in cases of atypical ductal hyperplasia diagnosed after stereotactic vacuum-assisted biopsy.
DRUGS SCREENING IDENTIFIES A NOVEL COMPOUND AS AN INHIBITOR OF BREAST CANCER STEM-LIKE CELLS

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Background and aims: The primary cause of death from breast cancer is the progressive growth of tumor and resistant to conventional therapies. Current therapies in breast cancer can shrink tumors, but a frustrating observation is tumor recur rapidly and shown their limits efficiency. It is currently believed that recurrent cancer is repopulated by a recently proposed cancer stem cells theory. Thus new therapeutic strategies to specifically target cancer stem-like cells may lead a new way for cancer therapy.

Methods: High-throughput screening (HTS) using cell-based phenotypic assays offers a powerful tool to study complex cellular processes and helps discover potential compounds. To discovery new drugs for breast cancer therapy, we developed a cell-based assay for screening of a generic drugs compound library using breast cancer stem-like cells.

Results: We use side population (SP) cancer cells coupled with spheroid assays to purify and isolated breast side population sphere cells that enriched cancer stem-like cells. The side population sphere (SPS) are enriched with high CD44 and low CD24 as well as highly tumorigenic in NOD-SCID mice. From more than 1,200 compounds, we identified a potential compound targeting cancer stem-like cells from two different types of breast cancer cell lines, which was also confirmed in xenograft study. In addition, the compound down regulates self-renewal pathways.

Conclusion: This proof of principle study may help drug development using cancer stem-like cells, which may provide a new approach of breast cancer therapy.
WEEKLY EPIRUBICIN IN GESTATIONAL BREAST CANCER (GBC) PATIENTS (PTS): A COOPERATIVE STUDY GROUP

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GBC is a rare disease, with less than 3% of breast cancers diagnosed during pregnancy. Single agent weekly Epirubicin, at an average dose of 35 mg/sqm was administered because of shorter terminal half-life and lower cardiotoxicity compared to Doxorubicin. PTS eligible were locally advanced or metastatic disease, high risk of recurrence after surgery and pregnant between 16 and 30 weeks of gestational age. 20/88 PTS with GBC were treated. Median maternal age 37 yrs (23-42). Median gestational age at chemotherapy was 19 weeks (16-30). 13/20 PTS were treated after surgery because of high risk of relapse. 5/13 had positive axillary nodes, with 3 having >5 positive nodes. 6/20 PTS had locally advanced tumours. 10/20 PTS had endocrine responsive diseases; 4/20 overexpressing HER-2. Ki-67 was >20% in 13/15. Mean total Epirubicin dose was 420 mg/sqm with a median number of 12 (4-16) administrations. No G3-4 toxicities were observed. Chemotherapy was administered with obstetric monitoring. Births were induced by cesarean section in 12/20 PTS at a median gestational age of 35 weeks (28-40). 2/20 newborns required neonatal intensive care, but none had pulmonary, cerebral or infectious complications. With a median age of 2 years (0-4), neurological and immunological development was normal in all 20 children, as reported by parents. In the 7/20 PTS with evaluable disease, 5/7 had an objective response. With a median follow-up of 38 months, 17/20 PTS are alive, 14/17 disease free. Weekly Epirubicin is a safe, effective and manageable in GBC patients who need chemotherapy, with mild toxicity for the fetus.
QUALITY PERFORMANCE INDICATORS FOR BREAST CANCER STAGE AND DIAGNOSIS IN A BRAZILIAN INSTITUTIONAL MAMMOGRAPHIC SCREENING PROGRAM

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Background: In order to achieve reduction in breast cancer mortality, mammographic screening (MMGS) programs demand quality assurance. Barretos Cancer Hospital (BCH) has been offering MMGS, with a local coverage of 53%, through the Brazilian public health system since 2003.

Aims: To analyze quality performance indicators on initial stage and diagnosis at BCH MMGS program at Barretos County, between 2003 and 2008.

Methods: Women aged 50 to 69 years old with breast cancer detected by the BCH MMGS had their clinical data reviewed and compared to the European Breast Cancer Network Guidelines for quality assurance.

Results: 109 patients were included. The following clinical stage proportions were obtained: invasive lesions: 78.9% (86/109; DL: < 80-90%); stage II or more: 38.3% (33/86; DL: < 30%); node-negative invasive cancers: 71.8% (61/85; DL: >70%); less than 10mm in size invasive cancers: 29% (25/86; DL: ≥25%). Clinical stage at first evaluation was 0 or I in 53 (61.7%). Concerning diagnostic procedures, the proportions were: core-biopsies with insufficient result: 8.6% (3/35; DL: < 10%); wires placed within 1cm of an impalpable lesion prior to excision: 96.7% (29/30; 100%; DL: >90%); localized impalpable lesions successfully excised at first operation: 100% (73/73, DL: >95%).

Conclusion: According to the European criteria for breast cancer screening, clinical stages at first evaluation are more advanced then the European initial rounds, and most diagnostic procedures have been achieving adequate and desirable levels at BCH.
PRESERVATION OF FERTILITY IN YOUNG PATIENTS WITH CERVICAL AND BREAST CANCER

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There are 2.6 millions cancer patients in the Russian Federation. Among them there are about 50% reproductive-aged men and women. The specific treatment of breast and cervical cancer may reduce fertility by damage of ovaries. For preserving women fertility of reproductive age with cancer there are several options of preserving fertility before cancer treatment like ovarian tissue and eggs cryopreservation; ovarian transposition out of the irradiation field before radiotherapy. Because of the variations in type and dose of chemotherapy, the type of cancer, the time available prior to onset of treatment, the patient's age, each case is unique and requires a different strategy of fertility preservation. We collected the 20 samples of ovarian tissue from patients with breast and cervical cancer from 23 to 35 years old before starting cancer therapy. There was 15 patients with breast cancer and 5 patients with cervical cancer. A total of 20 samples were frozen at our own cryobank. Samples were cryopreserved as follows: each aliquot was diluted in the same volume of cryoprotectant medium consisting of 15% glycerin, 2% sucrose, 0.4% human serum albumin in aqueous solution. Cryoprotectant medium was added sequentially drop by drop, with constant mixing. Each aliquot was then placed in cryotubes, frozen and transferred to a liquid nitrogen tank, until use. There samples can be stored for years. Fertility preservation should be an integral part of improving the quality of live in cancer survivors, but the first goal is to cure the cancer, even if the treatment causes sterility.
THREE-DIMENSIONAL QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP ANALYSIS AND ADME PREDICTIONS OF GUANYLHYDRAZONE COACTIVATOR BINDING INHIBITORS OF ESTROGEN RECEPTORS

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The estrogen receptors (ER) refer to a group of the nuclear hormone receptor superfamily of ligand-mediated transcriptional factors. They bind to a DNA and regulate gene expression. Overexpression of this type of receptors leads to a breast cancer progression. Hormone-responsive breast cancer develops resistance to conventional anti-cancer therapy, and this becomes a major problem in a breast cancer therapy. ER inhibitors can effectively block ER to treat the tumour but no more effective due to ER resistance to them. The three-dimensional database was created on a basis of the MOE package. The molecules contained different IC50 values for cell-based assay of reporter gene activity and mammalian two-hybrid assay. The IC50 was converted to pIC50 scale (-log IC50), in which higher values represent higher exponential potency. The QSAR models were built for both sets of pIC50 values separately to distinguish the best model. The predicted pIC50 parameters of entire training set (best-fit model) were cross evaluated and validated with the descriptors of the test set of molecules. The molecules were aromatic, polar and properties such as molar refractivity and the logarithm of the (octanol/water) partition coefficients were implemented for describing such systems. IC50 values were converted to Gibbs free energy of binding parameters to evaluate deviations in experimentally obtained and predicted in silico data. Additional work related to the activity and receptor specificity of these coactivator binding inhibitors will be the subject of the further analyses.
POPULATION BASED MAMMOGRAPHIC SCREENING PROGRAMME IN LATVIA- THE FIRST RESULTS

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Oncology Center of Latvia, Riga, Latvia

Background: The incidence of breast cancer is increasing in Latvia. Breast cancer mortality is increasing as well during last decades, mainly due to the fact that breast cancer is diagnosed in more advanced stages. There was a need for mammographic screening programme to diagnose breast cancer in earlier stages when treatment results are better.

Material and methods: Population based mammographic screening programme in Latvia was started in January 2009. The programme offers a biennial mammography screening to women aged between 50 and 69 years.

Results: Target population for mammography screening was estimated around 300 000 women. 90 207 women were invited to have the screening mammography from Jan 2009 to Feb 2010. 20 703 (23%) women had screening mammography done. Participation varied from 18.4% to 27.7% in different regions of Latvia, average participation rate is low.

Screening mammography results: BIRADS 1 category was assigned in 6755 cases (32.63%), BIRADS 2- 9685 (46.78%), BIRADS 3- 3995 (19.3%), BIRADS 4- 243 (1.17%), BIRADS 5- 25 (0.12%).

Conclusions: It is necessary to improve participation by raising public awareness on mammography screening benefits to diagnose breast cancer in earlier stage. Mammography quality control programme should be implemented, including double reading of mammograms by radiologists, to reduce the rate of BIRADS 3 category as a final result.
BREAST CANCER AND MULTIPLE PRIMARY TUMORS IN THE BELORUSSIAN CANCER REGISTRY

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Background: Breast cancer is the leading cause of cancer-related death for women in Belarus. The risk of breast cancer after an earlier primary cancer, as well as the risk of developing multiple primaries after an earlier breast cancer was studied.

Methods: The retrospective cohort study used a cohort consisting of 643693 cancer cases diagnosed between 1990 and 2007. Cases were identified from records of the Belorussian National Cancer Registry and followed for breast cancer development through 2007. Proportion and Standardized Incidence Ratios (SIR) of synchronous (latency between diagnosis's less than a year) and metachronous primary multiple breast cancers (PMBC) were investigated. It was considered 3070 PMBC (898 synchronous and 2172 metachronous with first tumor in breast).

Results: More often synchronous breast cancer combines with tumors of breast, skin and corpus uteri. Significant difference between observed and expected (on the base of population incidence level) numbers was noted for all synchronous PMBC and for secondary cancers of breast, kidney, thyroid, ovary, skin melanoma. The highest risk of synchronous PMBC was for combination with salivary glands (SIR=5,19; 95%CI 1.07-15.16) and breast tumors (SIR=5,14; 95%CI 4.52-5.74). Metachronous PMBC with first breast cancer was more frequently noted with tumors of skin, breast and corpus uteri. The highest risk of metachronous PMBC was for combination with esophagus (SIR=3,17; 95%CI 1,45-6,01).

Conclusions: High risk of PMBC could be caused by common etiological factors. Low rates (as for cervix uteri and liver cancer) could give evidence that breast cancer treatment decreases the risk of secondary tumors.
SENTINEL LYMPH NODE BIOSPY IN BREAST CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Background: Sentinel lymph node biopsy (SLNB) as a reliable surrogate for the standard axillary dissection has become a widely used staging method for patients with primary operable breast cancer. Neoadjuvant chemotherapy modifies the anatomical conditions in the breast and axilla and thus SLNB in patients treated with preoperative cytotoxic therapy still remains controversial technique. The aim of our study is to demonstrate reliability and accuracy of this procedure in patients treated preoperatively.

Methods: During the years 2005-2009 were in our institutions surgically treated 546 patients with histologically verified primary breast cancer. From this group 73 patients received neoadjuvant chemotherapy and after its completion they were able to undergo breast and axillary surgery. In all the subjects were attempt to perform SLNB as well as standard axillary dissection without regard to the extent of surgery of the breast.

Results: One or more sentinel lymph nodes (SLN) were successfully detected in 68 patients (93.15%). In 2 of these there were identified metastatic malignant cells in non-sentinel lymph nodes event in the negativity of SLN - thus defining the false negative rate of 2.94%. Positive predictive value of SLN is 62.5%, negative predictive value 95.45%. In 376.5% SLN were the only positive lymph nodes in the axilla.

Conclusions: We have demonstrated that SLNB is accurate and reliable method for investigation of lymph node status in the axilla event in patients who underwent preoperative cytotoxic therapy. Its detection rate and false negative rates are comparable with the figures of patients without neoadjuvant chemotherapy.
COMPARISON OF TRAM-FLAP AND DIEP-FLAP IN RECONSTRUCTIVE SURGERY OF BREAST CANCER

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TRAM-Flap as a reconstructive technique is competing with uprising techniques like DIEP-Flap with microsurgery of vessels - both procedures being used after ablative therapy for resection of gross volumes of breast tissue.

The TRAM-Flap is held responsible for higher rates of abdominal herniation as the main part of its morbidity.

In a center of maximal care the herniation rate is being explored by conducting a long-term follow-up of TRAM-patients - exploring possible side effects and patients satisfaction or discomfort with the result.

In a retrospective Case Series Study of a series of more than 250 TRAM-patients the rate of herniation and other potential side effects are being focussed on, and compared with the results of the DIEP technique.
IMPACT INDICATORS OF BREAST CANCER

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Background: Breast cancer is a major cause of loss of the female population. It’s important evaluate the women with breast cancer and have valid and reliable data about the impact of disease on society.

Methods: We found crude rates and age-specific standardized rates using as numerator breast cancer cases from Arequipa Poblational Cancer Registry, Perú from 2004-2007 and as denominators the female population. Calculation of life expectancy was used the method Reed-Merrell modified and the calculation of potential years of life lost we use Measurement Index Potential Years of Life Lost.

Results: Mortality crude rate from breast cancer is 9.7/100,000, being the second leading mortality cancer cause in women. Mortality median age was 60 years. Difference between the life expectancy of breast cancer patients and general female population was significant coming to be 324.8 years between 15 and 65 years old. The Potential Years of Life Lost added important social and economic losses for the population, making a total of 2096.0 years of life lost of which were 2225.0 economically productive ages consolidating a total economic loss for the Arequipa region of USD 5´438,888.9.

Conclusions: Are calculated impact indicators of breast cancer in the population, in terms of mortality rates, life expectancy and potential years of life lost to the object of giving a broad view of the relative importance of the most relevant causes of mortality premature. It is also expected that this information constitutes an essential tool for decision making at all levels of management.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of deaths</th>
<th>Potential years of life lost (PYLL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>12</td>
<td>385.20</td>
</tr>
<tr>
<td>45-49</td>
<td>15</td>
<td>406.50</td>
</tr>
<tr>
<td>50-54</td>
<td>16</td>
<td>353.60</td>
</tr>
<tr>
<td>55-59</td>
<td>26</td>
<td>444.60</td>
</tr>
<tr>
<td>60-64</td>
<td>22</td>
<td>266.20</td>
</tr>
<tr>
<td>65-69</td>
<td>14</td>
<td>99.40</td>
</tr>
<tr>
<td>PYLL overall</td>
<td></td>
<td>2096.00</td>
</tr>
<tr>
<td>PYLL productive</td>
<td></td>
<td>2225.00</td>
</tr>
<tr>
<td>Economic loss</td>
<td></td>
<td>5´438,888.90 USD.</td>
</tr>
</tbody>
</table>
IN VITRO AND IN VIVO CHARACTERIZATION OF NOVEL ENO1-TARGETING MONOCLONAL ANTIBODY FOR DETECTION OF BREAST CANCER

H.-Y. Chuang¹, Y.-F. Chang¹, N.-Y. Shih², J.-J. Hwang¹

¹Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, ²National Health Research Institutes, Miaoli, Taiwan R.O.C.

Purpose: In preliminary results, we demonstrated that alpha-enolase (ENO1) was overexpressed over 95% patients with breast or lung, suggesting that ENO1 could be a good target protein for molecular image and targeting therapy. Our study aimed to use ENO1 as a target antigen, and establish radiolabelled anti-ENO1 antibody for preclinical diagnosis and therapy in human breast cancer bearing animal models.

Method: To generated ENO1-specific monoclonal antibody, we selected anti-ENO1 variant-chain fragments via phage displaying system, and validate the specificity of monoclonal antibody by flow cytometry and confocal microscopy. In vivo targeting was evaluated in MDA-MB-435s human breast cancer xenografts. Mice were injected with 3.7-5.1 MBq (100-140 uCi) of ¹³¹I-anti-ENO1 antibody via intratumoral injection and imaged at 1, 2, 4, and 24 h by gamma scintigraphy.

Results: In vitro experiments demonstrated that scFv ENO1 antibody had higher affinity to bind cell-surface ENO1of MDA-MB-435s. There was relatively high radioactivity in the tumor site showed in gamma scintigraphy, which could echo our assumption that ENO1 could be a good target antigen in human breast cancer. But non-specific targeting showed in the liver, it would be a task we have to solve in the future. We concluded that the combination of ¹³¹I and tumor-specific antibody can provide a novel molecular probe for imaging human breast cancers based on overexpression of cell-surface antigen. In the future, anti-ENO1 antibody-conjugated liposome encapsulated with Auger electron-emitting ¹¹¹In or anti-cancer drugs would be useful as a tumor-targeting therapeutic strategy in human breast cancer animal models.
SIGNIFICANCE OF HER-2/NEU POSITIVITY IN BREAST CANCER CASES IN PROGNOSTICATION IN FIVE YEAR FOLLOW-UP

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NSC Bose Cancer Research Institute, Kolkata, India

Objective: These molecular subtypes and their combinations taken together with reproductive history of woman may help prognostication of breast cancer cases. We report a series of 102 cases of breast cancer treated in our institution over last five years (2004-08).

Methods: Paraffin-embedded primary breast cancers from 102 patients with invasive and ductal carcinoma were studied immunohistochemically. Markers along with reproductive history were analysed.

Result: 88 invasive and 14 ductal type cases were found 43 cases were postmenopausal. Luminal type hormone receptor positive cases were 63 (61.7%) ER+, 34 (33.3%) & PR+ 29 (28.4%). HER-2/neu + cases were 34 (33.3%). There were 11 cases of triple negative (basal-like) breast cancer. Significant inverse correlation was found between HER-2/neu and hormone receptor. Early age at menarche was only found to be associated with risk of HER-2/neu+, whereas breastfeeding had protective. Both late age at menopause, hormone therapy were associated with poor prognosis. age at first child birth was significantly associated with poorer outcome & no difference in risks with parity. HER-2/neu was not associated with response rate but their prognosis was worse. Triple negative had 3 survivors at three years. Significant associations were observed between HER-2/neu and increasing number of involved and metastases (p = 0.01). Analysis demonstrated that HER-2/neu overexpression (p = 0.02) and age (p = 0.01) were independent predictors for disease-free survival (DFS).

Conclusion: Reproductive history had significant bearing in prognosis and receptor expressing subsets of breast cancer which may be clear by further study.
TRIPLE-NEGATIVE BREAST CANCER AND THE EXPRESSION OF SELECTED TUMOR MARKERS IN AFRICAN AMERICAN AND CAUCASIAN BREAST CANCER PATIENTS

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\textsuperscript{1}Karmanos Cancer Institute, \textsuperscript{2}Wayne State University, Detroit, MI, USA

**Background:** African-American (AA) breast cancer patients experience higher mortality rates than Caucasian (C) patients. To better understand this disparity we compared various clinico-pathologic factors including the incidence of triple-negative breast cancer between AA and C breast cancer patients. The expressions of selected markers (Glut-1, EGFR, and COX-2), associated with poor outcome were also evaluated, between the two groups.

**Materials and methods:** We identified patients with invasive breast cancer between 2004 and 2006. The clinicopathologic findings and the ER, PR and Her-2 status were reviewed. Immunohistochemical stains for Glut-1, EGFR, and COX-2 were performed on tissue micro-arrays. Clinical follow up was obtained. Statistical analysis included Chi square, Fisher´s exact test and Kaplan Meier.

**Results:** 523 cases were identified. 317 (60.6\%) were AA versus 196 (37.5\%) C. Compared to C, AA patients had larger tumors (\(p=0.006\)), tumors negative for ER and PR (\(p=0.007\) and 0.03) and significantly poorer survival (\(p=0.002\)). AA patients also had higher frequency of grade III tumors and lymph node-positive disease, compared to C patients. Triple-negative tumors were significantly more prevalent among AA patients (34.4\%) compared to C patients (25\%) (\(p=0.03\)). Expression of Glut-1, EGFR, and Cox-2 was significantly higher in AA patients (\(p< 0.04\))

**Conclusions:** To conclude, In addition to triple-negative tumors, AA patients were more likely than C patients to express Glut-1, EGFR and Cox-2. This indicates that differences in tumor biology may exist between these two groups warranting further investigation.
THE STUDY OF THERMODYNAMIC PARAMETERS OF THE BLOOD PLASMA IN THE WOMEN WITH BREAST TUMOURS

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Background and aims: It’s known that during tumour development the quantitative and qualitative changes of blood plasma proteins take place. That’s reflected in increased number of “Acute phase” proteins and in occurrence of modified forms of native proteins.

The aim of the study was to investigate the thermodynamic parameters of the blood plasma proteins (albumin and “acute phase” proteins) in the women with breast tumours.

Methods: The blood plasma of patients with benign (fibroadenoma) and malignant breast tumours (cancer) has been studied. Thermodynamic parameters of blood plasma was investigated by the method of differential scanning microcalorimetry.

Results and conclusions: The study of blood plasma calorimetric curve of patients with breast benign tumour has revealed the main peak maximum in 65-66°C temperature range. This fact indicates on increased number of “Acute phase” proteins. Besides the peak on the curve there is a slope (70-71°C) that indicates on a high content of immunoglobulins.

The occurrence of modified albumin can be observed on the calorimetric curve of patients with breast cancer, that is reflected in 57-58°C peak maximum. The other peak (87-88°C temperature range) indicates the higher amount of “acute phase” thermostable (orosomucoid, α1-antitrypsin and others) proteins. As for the shift of main peak to more high temperatures 74-75°C, it can be caused by the dramatically increased level of immunoglobulins in the blood.

On the basis of obtained results we can evaluate the specificity of above mentioned changes and the diagnostic importance of the differential scanning microcalorimetry in diagnosis of breast tumours.

<table>
<thead>
<tr>
<th>Object (blood plasma)</th>
<th>peak °C</th>
<th>slope °C</th>
<th>Main peak °C (Hd)</th>
<th>slope °C</th>
<th>peak °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>–</td>
<td>–</td>
<td>62-63</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Benign tumour</td>
<td>–</td>
<td>–</td>
<td>65-66</td>
<td>70-71</td>
<td>–</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>57-58</td>
<td>68-69</td>
<td>74-75</td>
<td>–</td>
<td>87-88</td>
</tr>
</tbody>
</table>

n = 12 (the number of patients in each group)  
The mean age of patients = 56-65; p ≤ 0.03
TRIPLE NEGATIVE BREAST CANCER: AN INSTITUTIONAL REVIEW

L. Heras¹, A. García-Arias¹, M. Pujol², C. Buqueras³, R. Villanueva¹, O. Serra¹, F. Losa¹

¹Medical Oncology Department, ²Pathology Department, ³Surgery Department, Hospital General de L’Hospitalet, L’Hospitalet de Llobregat Barcelona, Spain

Background: Triple negative breast cancer (TNBC) comprises 8 to 20% of all breast cancers and is a distinct group of tumors that show especial aggressiveness associated with poor clinical outcomes.

Methods: Between January 2005 and December 2009, we retrospectively analyzed pathological and clinical parameters of 163 breast cancer patients (pts).

Results: 20 of 163 pts (12%) had a TNBC. The median age at diagnosis was 57 years. 6 pts had a family history of breast cancer (33%) and 2 of them had a determination of BRCA mutation. The most common histology was ductal carcinoma (80%) followed by lobular and medullary carcinoma (10% both). The distribution by stages was: 1 pt (5%) in stage I, 10 pts (50%) in stage II, 5 pts (25%) in stage III and 3 pts (15%) in stage IV. The most striking is probably that 16 out of 20 pts (80%) had a grade 3 tumor and the other 4 had a grade 2, also 17 out of 20 pts (85%) had a Ki67 superior to 20%, even in 12 pts (60%) it was equal or superior to 60%. After a median follow up time of 23 months (Range: 1-51), 16 out of 20 pts (80%) are still alive.

Conclusions: These retrospective data demonstrate that TNBC is a subgroup of breast cancer strongly associated with high tumor grade and proliferative index. In the future it will be important to select those patients for different therapies and a strict follow-up.
THE ROLE OF TRANSVAGINAL ULTRASONOGRAPHY AND SYMPTOM-BASED TRIAGE FOR DETECTION OF PATHOLOGICAL ENDOMETRIAL CHANGES IN BREAST CANCER PATIENTS USING TAMOXIFEN

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Obstetrics and Gynecology, Ankara University School of Medicine, Ankara, Turkey

Background: Tamoxifen has a partial agonist effect on the endometrium, which may cause various pathological changes including endometrial hyperplasia, polyp, and carcinoma.

Aim: To estimate the value of transvaginal ultrasound screening and symptom-based triage for detection of endometrial pathologies in breast cancer patients using tamoxifen.

Methods: 292 women using tamoxifen were included retrospectively.

Results: The mean age of 201 post- and 91 premenopausal patients were 55.2 and 39.0 years old, respectively. Endometrial biopsy was performed in 39 postmenopausal asymptomatic women in whom endometrial thickness was ≥8 mm and revealed 17 (43.5%) endometrial polyps, five (12.8%) simple hyperplasia, one endometrial cancer. Endometrial biopsy was performed in 10 postmenopausal women in whom the endometrial thickness was less than 8 mm, revealing two (20%) endometrial polyp and one submucous myoma. In 26 women with postmenopausal bleeding, histopathological examination revealed five (19.2%) polyps, five (19.2%) simple hyperplasia, one complex hyperplasia with atypia, and one endometrial cancer. In 30 premenopausal women with abnormal uterine bleeding, pathological changes were found in 11 (36.6%) patients, five with polyps (16.6%) and six with simple hyperplasia (20%). When endometrial thickness of 8 mm was taken as the cut-off for asymptomatic postmenopausal patients, the positive predictive value of transvaginal ultrasound for endometrial pathologies was 59%. The positive predictive value of only symptom-based triage for pre- and postmenopausal patients was 46% and 36%, respectively.

Conclusion: Transvaginal ultrasonography may be a useful screening method for detection of pathological endometrial changes in asymptomatic postmenopausal patients.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Premenopausal patients</th>
<th>Postmenopausal patients</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathological findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial polyp</td>
<td>5 (16.6%)</td>
<td>24 (32.0%)</td>
<td>29 (27.6%)</td>
</tr>
<tr>
<td>Simple hyperplasia without atypia</td>
<td>6 (20.0%)</td>
<td>11 (14.6%)</td>
<td>16 (15.2%)</td>
</tr>
<tr>
<td>Complex hyperplasia with atypia</td>
<td>-</td>
<td>1 (1.3%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma</td>
<td>-</td>
<td>2 (2.6%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Submucous myoma</td>
<td>-</td>
<td>1 (1.3%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td><strong>Non-pathological findings</strong></td>
<td>19 (63.3%)</td>
<td>37 (49.3%)</td>
<td>56 (53.3%)</td>
</tr>
<tr>
<td>Functional endometrium</td>
<td>15 (50%)</td>
<td>22 (29.3%)</td>
<td>37 (35.2%)</td>
</tr>
<tr>
<td>Atrophic/inactive endometrium</td>
<td>4 (13.3%)</td>
<td>15 (20.0%)</td>
<td>19 (18.0%)</td>
</tr>
</tbody>
</table>

[Histological findings of pre and post-menopausal p]
BRCA-ASSOCIATED BREAST AND OVARIAN CANCER SYNDROMES - A RETROSPECTIVE ANALYSIS


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Background and aims: Early detection of BRCA1 and BRCA2 mutation carriers is important, since they have a significantly cumulative lifetime risk of ovarian (OC) and breast cancer (BC). We aimed to analyse the main clinico-pathologic findings and outcomes of our patients with BRCA1/BRCA2 positive BC.

Material and methods: Retrospective analysis of consecutive patients with BRCA1/BRCA2 positive BC. Survival curves were calculated by the Kaplan-Meier method.

Results: 49 patients were evaluated, 18 BRCA1 (all female, with median time follow-up of 7.5 years (range: 0.5-24.5)) and 31 BRCA2 (2 male and 29 female, with median time follow-up of 7.1 years (0.8-20.2)). At diagnosis of 1st event, the majority were premenopausal, with median ages of 46 (range 31-61) for BRCA1 and 44 years (range 26-61) for BRCA2 patients.

BRCA1 tumours were mainly ductal carcinomas, grade III, negative for hormone receptors and HER2 and BRCA2 tumours were ductal carcinomas, grade II/III, hormone receptors positive and HER2 negative. Prophylactic surgeries were bilateral salpingo-oophorectomy in 22% and 32% and contralateral mastectomy in 22% and 23% in BRCA1 and BRCA2 patients, respectively.

BRCA1 and BRCA2 patients developed contralateral BC in 22% and 26% and OC in 27.8% and 9.7%, respectively. The median time until second BC was 1.9 years (0.5-4) for BRCA1 and 8.5 yrs (range: 0.3-13)) for BRCA2 patients. Five-year overall survival was 86.5% and 100% for BRCA1/2, respectively.

Conclusions: BRCA1 and BRCA2 positive BC patients have different clinico-pathologic features, often develop second primary tumours and have a relatively good prognosis.
BREAST CANCER AND ITS RELATIONSHIP WITH MITOCHONDRIAL UNCOUPLING PROTEIN 4 (UCP4), APOPTOTIC MARKERS, AND OTHER PROGNOSTIC FACTORS: AN IMMUNOCYTOCHEMICAL STUDY

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Background: Oxidative stress and its productions (ROS), has a complex effect on cancer development. Uncoupling proteins (UCPs) are key regulators of mitochondrial energy efficiency and have recently emerged as negative regulators of mitochondrial oxidant production. The bcl-2 family of proteins comprises both cell death inhibiting such as bcl-2 anti-apoptotic protein, and death promoting members such as Bax pro-apoptotic protein. Bcl-2 is positively regulated by hormonal receptor pathways in breast cancer.

Objective: To investigate the expression of UCP4 protein in breast cancer imprint smears in correlation with ER status and proapoptotic and antiapoptotic markers Bax and bcl-2 expression, DNA ploidy and other prognostic factors.

Methods: One hundred twenty-four (124) imprint smears from surgically resected breast cancers were studied immunocytochemically with the use of UCP4, bcl-2, ER and P53 proteins. Immunostaining was performed by using Avidin Biotin Complex method. DNA ploidy classification was made by image analysis cytometry in smears stained using Thionin-Feulgen procedure.

Results: UCP4 positive expression was detected in 90 (72,6%), bcl2 in 48 (38,7%), Bax in 76 (61,3%), ER in 84 (67,7%) and P53 in 88 (71%) of breast cancer smears. Eighty cases (64,5%) were aneuploid tumors. Increased UCP4 expression was significantly correlated with ER (p=0,014), P53 (p=0,0001), aneuploid tumors (p=0,039) and poorly differentiated carcinomas (p=0,034).

Conclusion: The results of our study indicate a strong correlation between the immunocytochemical expression of UCP4 of breast cancer tumors and several clinicopathologic parameters and encourage future investigations regarding the potential role of uncoupling proteins into mechanisms underlying breast cancer.
PHYLODES TUMOR. REVIEW OF CASES IN OUR ENVIRONMENT

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Objective: Phyllodes tumor is an uncommon, so there are few data in the literature regarding its clinical course and prognosis. Review of phyllodes tumor present in our environment to analyze clinical course and prognosis.


Results: The mean age of the study was 42 years (34-51 years). 88% of cases, patients complain of symptoms such as breast lump fast growing. 100% negative axillary nodes. 60% good form benign clinical course without evidence of recurrence after excision (100% lumpectomy for palpable lesions). 33% of the cases were malignant phyllodes tumors confirmed by pathology. Malignant forms treated with simple mastectomy. Confirmed history of benign phyllodes tumor in same breast in one of malignant tumors in our series.

Comment and evolution: Rare neoplasm composed of a proliferation of stromal and epithelial elements, similar to fibroadenoma, with a predominance of stromal component. The malignant forms ranging between 1.9% -48% according to reports. Age of presentation 35-55 years. Feature the absence of axillary lymph nodes affected. The risk of local recurrence is low in benign forms (6-10%) increasing to 40-60% in malignant forms. It was described a half systematic recurrence 13.6% (range 3.2% -25%). This tumor does not respond well to radiotherapy, chemotherapy or hormonal-therapy. Prognosis is favorable localized forms after optimal local therapy. In our series, recurrence was confirmed after surgical treatment in subsequent revisions or new findings of axillary involvement.
FIRST CASE OF DOSE-DENSE SEQUENTIAL CHEMOTHERAPY WITH EPIRUBICIN, PACLITAXEL AND CYCLOPHOSPHAMIDE IN A PREGNANCY-ASSOCIATED BREAST CANCER PATIENT

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Background and aims: Pregnancy-associated breast cancer (PABC) is a rare disease state facing the challenge to control the cancer of the expectant mother and to safe the health of the developing fetus. Here, we describe the first case of a high-risk PABC patient being treated by a dose-dense sequential chemotherapy with epirubicin, paclitaxel and cyclophosphamide (ddETC) plus granulocyte colony-stimulating factor (G-CSF).

Methods: We describe the management of this PABC patient and give an overview of the literature focusing on the cytotoxic drugs.

Results: A 32-year-old patient presented at 18 weeks of gestation in her third pregnancy with a bilateral, triple negative, lymph node positive breast cancer. After breast-conserving operation six courses of the ddETC has been administered before and three courses after the induced vaginal delivery at 36 weeks of gestation avoiding cyclophosphamide application during pregnancy. The fetus has been monitored by consecutive biometrics and Doppler ultrasound examinations and presented as a healthy newborn without malformations and signs of myelosuppression or cardiac dysfunction. The most common regimes for PABC are doxorubicin, cyclophosphamide and fluorouracil or anthracycline combined with cyclophosphamide. There is little experience with taxanes and G-CSF. Beyond the first trimester, chemotherapy appears not to increase the risk of fetal malformations. The potential fetal impairments are low birth weight, preterm delivery, cardiotoxicity, myelosuppression and their sequelae. Long-term effects might be gonadal dysfunction, carcinogenesis, impaired physical and neurologic development.

Conclusions: ddETC is a feasible regime for high-risk PABC. Further cases have to be collected to improve estimation of the fetal risk.
CORRELATION OF CEA, CA 15-3 LEVELS WITH MAMMOGRAPHY IN POSTMENAPOUSALE WOMEN

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Introduction: The dose of radiation received with mammagrapy cannot be underestimated. CA 15-3 and CEA are tumor markers that tend to increase in benign or malign lesions of breast. The aim of this study is to try to explain the coordination of CEA and Ca15-3 levels with the lesions identified by mammography.

Method: The data of 134 postmenapousale women who admitted to GATA General Surgery Clinic Breast Disease Department for breast screening between January 2009 and January 2010 were analyzed retrospectively. The patients who were diagnosed before, in the postoperative period and whose comparison parameters (CEA, CA15-3 and mammography) were not complete were excluded from the study. The parameters of 70 patients were analysed statistically.

Results: 26 patients who had BIRADS 3 and higher lesions were explored. Among these patients, 10 patients were interpreted as a benign pathology, 4 patients had tumors located outside the breast. Remaining 12 patients had breast cancer. The level of tumor markers were correlated with mammography especially in women who were diagnosed as breast cancer.

Conclusion: The incidence of breast cancer begins to increase after 40 ages; the screening mammography expose the breast cells to radiation. It is important to find another alternative for screening benign or malign breast lesions which can be easily performed, low-cost, with less side effects. It was observed in this small-sample study that while deciding about the operation, tumor marker levels were in parallel with mammography in postmenopausal women.
PATTERNS OF GRP78 EXPRESSION IN BREAST CANCER PATIENTS TREATED WITH ADJUVANT DOXORUBICIN-BASED CHEMOTHERAPY

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Background: GRP78 is an endoplasmic reticulum (ER) chaperone highly expressed in breast cancer. This study is aimed to test whether GRP78 expression in breast cancer patients treated with adjuvant doxorubicin chemotherapy is associated with overall survival (OS) and progression-free survival (PFS).

Methods: Retrospective chart review was undertaken at a single cancer center and tumor samples were obtained from 106 patients with stages II/III breast cancer. Tissue Microarray was constructed and GRP78 expression was assessed by immunohistochemistry. Four hypothetical scenarios were developed: two for ER and two for cell membrane (CM).

Results: In the high-threshold scenarios, 16% of our cases were GRP78-positive for ER, and 40% were GRP78-positive for CM. In the low-threshold scenarios, 74% of our cases were GRP78-positive for ER, and 87% were GRP78-positive for CM. 10% of all cases showed strong (3+) CM staining of GRP78. By the end of the follow-up, no relation was found between GRP78 expression and disease progression and the relative risk of death. The same was true for the PFS probabilities, except for women above 50 years of age and postmenopausal, who had a reduced risk (RR=0.03; 95%CI 0.01 to 0.40) of disease progression if positive for GRP78. There was no statistically significant difference between the survival probabilities in any scenarios examined.

Conclusions: In our cohort, GRP78 overexpression was not a predictor of OS or PFS of patients receiving doxorubicin adjuvant chemotherapy. This study provides evidence supporting strong GRP78 activity in the CM of breast cancer cells.
UPTAKE OF CANCER SURVEILLANCE AND RISK REDUCTION SURGERY BY FEMALE BRCA CARRIERS IN MALAYSIA

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Malaysia is multi-ethnic, -cultural and -religious country, with the Malays, Chinese and Indians being the three main ethnic groups. Breast cancer is the most common female cancer. The University Malaya and Cancer Research Initiatives Foundation (CARIF) have collaborated in the establishment of the Malaysian Breast Cancer Genetic Study (MyBrCa Study) which has largest prospective cohort of breast cancer patients in Malaysia recruiting 1245 breast cancer patients to date. Of the 363 women tested for mutations in BRCA1 and BRCA2, 50 index cases and 21 family members were found to have BRCA mutations. The study provided counselling services after result disclosure by a multi-disciplinary team comprising of a clinical geneticist, an associate genetic counsellor, breast surgeons and gynaecologists. Information on risks, surveillance and risk reduction measure were initially given during the counselling sessions with the genetics counsellor. Subsequently, the BRCA carriers are reviewed at a specialist risk management clinic jointly by specialist breast surgeon and gynaecologist to discuss risk management options. Of the 50 BRCA carriers who have had breast cancer, only 3 (6%) opted for prophylactic contralateral mastectomy with 47 (94%) opting for surveillance. In this group, 8 carriers (16%) underwent prophylactic oophorectomy to reduce their risk of ovarian cancer and breast cancer and the rest (84%) have started on an ovarian screening programme. Of the 21 family members who are BRCA carriers, only 1 (5%) chose to have prophylactic contralateral mastectomy with none opting for prophylactic oophrectomy.

Factors influencing decision making of the carriers in this population will be discussed.
LAPAROSCOPIC OOPHORECTOMY FOR BREAST CANCER PATIENTS: EXPERIENCES FROM A CANCER CENTRE AND COMPARISON WITH GNRH ANALOGUES

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Background: Oophorectomy is an alternative to gonadotropin releasing hormone analogues for the treatment of premenopausal women with hormone sensitive breast cancer. The aim of our study was to evaluate our institutional experiences of laparoscopic salpingo-oophorectomy for breast cancer patients and compare the two modalities of ovarian ablation.

Patients and methods: One hundred and three breast cancer patients had laparoscopic salpingo-oophorectomy under the gynaecology oncology team at Addenbrooke's hospital between January 2004 and December 2009 as part of their treatment. Histology and cytology results were reviewed and all hospital records checked for subsequent recurrences.

Results: One (1%) of the 103 women in our study had occult primary ovarian cancer on histopathological examination and 2 (2%) had ovarian metastasis from breast cancer. Three women (3%) developed recurrence of breast cancer subsequently but none had primary peritoneal/ovarian cancer within a median follow-up interval of 34 months (range 0 - 70 months). No operative complication was noted in these women.

Conclusion: Laparoscopic salpingo-oophorectomy is a safe, permanent and cost-effective option of ovarian ablation. Also, this significantly reduces the risk of subsequent ovarian/ fallopian tubal malignancy. This is especially relevant for women who have genetic predisposition for breast/ovarian cancers.
TREATMENT AND FOLLOW-UP OF IN SITU BREAST CARCINOMA. NATIONWIDE CROSS SECTION STUDY OF SPANISH SOCIETY OF OBSTETRICS AND GYNAECOLOGY (SEGO)

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Introduction: Insitu breast cancer has a low incidence among all different histotypes, so data concerning follow-up and treatment is limited. The aim of this study was to know the current management of this cancer in spain as well as the oncological results after 5 year follow-up.

Methods: Medical records of all insitu carcinomas diagnosed in Spain from January 1st to December 31st of 2004 were reviewed. An online collecting form was used to get the data across the country. 5 year follow-up (until december 31st 2009) was included in data collection.

Results: Since data collection concludes next September 15th, we have incomplete data from 150 insitu breast cancers. Most of the investigators did not perform lymph node dissection with survival rates after 5 years over 95%.

Conclusions: Before closing the study, data suggest lymphadenectomy is not neccessary and survival rates are higher than invasine breast carcinomas. We stimate to collect around 250 patients só data will be more accurate.
ADVANCED STAGES OF BREAST CANCER ARE ASSOCIATED TO LOW SCHOLARITY LEVEL IN PATIENTS TREATED IN A BRAZILIAN CANCER CENTER

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Background: Barretos Cancer Hospital (BCH) is a comprehensive cancer center, reference for breast cancer (BC) treatment in Brazil. Advanced stages of BC still have a high prevalence in developing countries, determined by several sociodemographics conditions. Furthermore, the scholarity level measured by years of study (yos) could surrogate potential risk for delayed BC diagnosis.

Aim: To evaluate any possible association between scholarity level and stages distribution in patients with breast cancer.

Methods: The database from BCH cancer registry between 2000 and 2006 was reviewed. All cases of breast cancer were analyzed, and classified based on the level of scholarity as: 1) Low: Illiteracy or Elementary level (< 4 yos); 2) Medium: Incomplete high-school (4 to 15 yos); 3) High: Completed high-school or higher (>15 yos). \( \chi^2 \) test was used to compare proportions among the scholarity groups and stages.

Results: 3,491 pts were evaluated (see table).

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<tr>
<th>Stages / Low (%) / Medium (%) / High (%) / Total</th>
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<tr>
<td>I or II /1284 (61.6) /523 (25.1) /276 (13.3) /2083</td>
</tr>
<tr>
<td>III or IV /970 (68.9) /333 (23.7) /105 (7.5) /1408</td>
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Stage Scholarity Groups - OR [P value]

I / II
- Low versus Medium -1.39 [0.031]
- Low versus High -1.83 [< 0.001]
- Medium versus High -1.32 [0.169]

III / IV
- Low versus Medium -1.65 [0.001]
- Low versus High -3.63 [< 0.001]
- Medium versus High -2.2 [< 0.001]

Conclusion: In this population, the group of low scholarity level had a statistically significant association with more advanced stages of breast cancer.
IMPROVING INFORMED CONSENT: EVALUATING THE FIRST DECISION AIDS IN A CLINICAL TRIAL SETTING (IBIS-II)

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Aims: Recruitment to clinical trials is generally suboptimal, with both patients/consumers and clinicians reporting difficulties with the consent process. Decision Aids (DAs), which present evidence-based information in a clear graphical form and facilitate participation in decision-making, may improve this process. This RCT aims to evaluate the efficacy of DAs for women at increased risk of breast cancer who are considering participation in the IBIS-II trial (Prevention and DCIS arms).

Methods: Women from Australia, New Zealand and the UK are invited to take part in the DA study. Participants are randomised to receive either the standard IBIS-II information alone (Control group), or in combination with a DA booklet (DA group). Participants complete standardised and purpose-designed measures 1 week and 3 months after deciding whether or not to participate in IBIS-II.

Results: In the Prevention arm, the majority of women (84%) reported the DA made it easier to understand IBIS-II, and 89% recommended providing the DA to potential participants. No group differences were detected due to floor and ceiling effects. Recruitment for the DCIS arm is ongoing, and progress will be reported.

Conclusions: This is the first study to assess the effectiveness of DAs in a clinical trial setting. The DAs have been strongly endorsed by participating women and clinicians so far. Challenges of evaluating DAs in a Prevention trial setting and progress on the DCIS arm will be discussed. The DAs have the potential to enhance the process of informed consent and reduce dropout rates in clinical trials.
GERMLINE MUTATIONS OF BRCA2 GENE: A MOLECULAR GENETIC PROGNOSTICATOR OF BREAST AND OVARIAN CANCER

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Worldwide, Breast Cancer is the most common cancer in women and comprises 18% of all female malignancies. In Regional Cancer Centre, Thiruvananthapuram, Kerala, India, breast cancer accounts for 29% of all female cancers of which 4.6% are hereditary. BRCA2 is the second major breast cancer susceptibility gene conferring an increased risk of breast cancer in both women and men. Since the contribution of BRCA2 gene to breast/ovarian cancer susceptibility remains completely unexplored among Kerala population, the present study was undertaken to identify the frequency and pattern of germline BRCA2 gene mutations thereby assessing its utility as a molecular genetic prognosticator. Study subjects included 102 hereditary breast/ovarian cancer patients (HBOC), 72 sporadic breast cancer patients (SBC) and 90 controls. BRCA2 gene mutation was studied by Conformation Sensitive Gel Electrophoresis and sequencing. Mutation analysis of BRCA2 gene in HBOC showed sequence variations in 31.3% of patients. Nineteen distinct BRCA2 sequence variants were detected of which twelve were pathogenic and 10 were novel. 6.94% SBC showed BRCA2 sequence variants. BRCA2 mutated HBOC harboured significantly worse survival than non mutated groups. Clinicopathologic parameters like tumour size, metastasis, stage, and laterality were significantly associated with poor prognosis in HBOC. Overall survival was comparable between the HBOC and SBC. Thus the adverse clinicopathologic features and survival observed in BRCA2 mutated cases underlines the need for surveillance in families that carry a BRCA2 mutation. BRCA2 mutation status could be considered as a prognostic index in HBOC patients which could have important implications in genetic counseling, screening and disease management.
IMPACT OF LOW INCOME AND OLDER AGE IN ADJUVANT CHEMOTHERAPY INDICATION FOR BREAST CANCER (BC) IN BRAZIL

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**Background:** Multiple comorbidities might limit the use of more active chemotherapy regimens in elderly patients, who are usually underrepresented in clinical trials for breast cancer (BC). Low-income elderly patients represent an even greater challenge, and a common issue in developing countries. Barretos Cancer Hospital (BCH) is a comprehensive cancer center that provides treatment through the public health system in Brazil, 80% of our patients have limited incomes.

**Aims:** To evaluate the rate of chemotherapy indication and to describe clinical and pathological profile of patients over 70y.o. treated for BC in 2001 and 2006 at BCH.

**Methods:** Social-demographic, clinical and pathological data were retrieved from charts.

**Results:** During the period 1,304 patients with BC were treated by the medical oncology department, including 129 women older than 70y.o. Median age: 78y.o. (70 - 94). The histology was ductal carcinoma in 85%; 60% of tumors were grade 2, and hormone receptors were positive in 52%. Stage distribution was: I- 17%, II- 44%, III- 24%, IV- 6%. Chemotherapy was administered in 50 patients (neoadjuvant in 9 and adjuvant in 41). CMF regimen was prescribed for 40 patients while antracyclin plus taxane combination was used in 3. Five-year disease free survival was 85%. Five-year overall survival was 59%.

**Conclusions:** Financial status and age cannot be overlooked while considering cytotoxic chemotherapy in “era of personalized medicine”, and may also contribute to a lower rate of chemotherapy indication in the analyzed population.
ORAL CONTRACEPTIVES AND BREAST CANCER RISK IN YOUNG WOMEN
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Background: Oral contraceptives (OCs) have been suggested to elevate breast cancer risk in young women. Being widely used in contraception and therapy of common menstruation disorders, it is important to pinpoint whether such a correlation exists.

Methods: Review of recent studies and publications.

Results: Long-term use of combination OCs before age 25 is associated with increased breast cancer risk: Relative risk is approximately 4 after 5 years of using high estrogen/progestogen component pills, while low component preparations affect risk significantly less. Risk appears to be greater for long-time, current and recent users, and those before their first full-time pregnancy. Nevertheless, OCs do not further increase risk of women with BRCA1/2 mutations.

The estrogen component stimulates cancer growth by increasing proliferation of epithelial cells in the normal breast and decreasing their content of estrogen receptors (ER). At the same time the significant changes that occur in proliferating cells' proportions and ER during natural menstrual cycles are perturbed, so there is greater ER suppression and longer periods of high proliferation. Of progestogens, levonorgestrel imparts the highest risk. Also, the 19-norprogestins norgestrel and gestodene used in pills have been shown to stimulate MCF-7 breast cancer cell growth by activating the ER.

Conclusions: The relationship between OCs and breast cancer in young women has a biologic basis but new low-estrogen pills impart a smaller risk than earlier counterparts and do not add to the risk of women with familial predisposition.
WOMEN'S BREAST CANCER RISK PERCEPTION AND ATTITUDES TOWARD SCREENING TESTS

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Objective: To identify women's breast cancer risk perceptions and their attitudes and knowledge on screening tests.

Design: The cross-sectional research.

Patients/participants: The population of 188 females who applied for gynecological examination.

Main outcome measure: A semi-structured questionnaire form was used. Questions such as female’s demographic data, attitudes based on screening tests of breast cancer, family history, perceived risk breast cancer and questions with regard to patients’ fear of breast cancer were included in the survey.

Results: Only 21.3% of the women perform breast self examination (BSE) regularly; 33.0% of them have clinical breast examination (CBE) and 21.3% have mammography done at least once. The reason for not performing the BSE was declared with a rate of 50.8% as “Do not know how to perform”. 20.2% of the women were fully acknowledged about BSE. The 40.4% of the women perceived 50% or more risk of becoming breast cancer and this rate increases as they get older. The risk perception and educational status increased CBE and mammography application rates and the BSE knowledge positively, but because of insufficient abilities, it cannot have BSE application rate increase as much.

Conclusions: It is recommended that nurses put forward the initiatives in training programs to increase women's BSE application abilities. In planning such an education program risk perception and information of women about breast cancer should be considered.

Keywords: Screening tests of breast cancer, Breast self examination, Perceived risk of breast cancer
RISK FACTORS FOR BREAST CANCER IN ELDERLY WOMEN-OWN EXPERIENCES OF 300 PATIENTS

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Breast cancer (BC) is the most frequent cancer in women. Several risk factors (RF) have been reported including familiar, personal and reproductive history and hormonal and medical factors. The aim of the study is to evaluate retrospectively the importance of RF of BC in women over 65 years.

Material and method: It was analyzed 150 women in age over 65 years (range 65-84) with confirmed primary BC cases and 150 population-based age-matched patients—a control group, who underwent physical breast examination and routine mammography. Patients with previous malignances were excluded. Following parameters were considered: age, family, history of BC, menstrual and reproductive data, use of contraceptives and hormonal replacement therapy and BMI.

Results: It was found differences between cases and controls with regards to:

1. median age and menarche (11.5 vs 13.7), 2. median age and menopause (53.4 vs 49.6),
3. years between menarche and menopause (14.4 vs 11.7), 4. number of birth (2.3 vs 1.7),
5. median BMI 74.2 vs 67.5. It was observed 5 parameters correlated with BC: age at menarche, menopause, number of birth and BMI

Conclusions: Most of the classic RF are associated with BC in our population.
IS HIGH BONE MASS DENSITY A MARKER FOR BREAST CANCER IN POSTMENOPAUSAL WOMEN?

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Background and aims: Bone mineral density (BMD) may be considered a marker of lifetime estrogen exposure, therefore, higher levels of BMD are expected to be associated with an increased risk of breast cancer. The present study was carried out to test this hypothesis.

Methods: A retrospective case-control study was conducted in a tertiary care hospital, with 18 cases of breast cancer and 37 controls. All were postmenopausal women who had lumbar spine and femoral neck BMD measured by dual-energy X-ray absorptiometry (DXA). Data as age at menarche and menopause, parity, history of oral hormonal contraception and hormone replacement therapy use were obtained both through hospital records and telephone questionnaire. Osteoporosis status was defined using BMD T-score according to WHO criteria. Statistic analysis was performed with SPSS.

Results: The number of women that used hormone replacement therapy was higher among controls (p=0.001), but there were no statistical significant differences between the cases and controls for age, number of reproductive years, parity, oral hormonal contraception use, lumbar spine and femoral neck BMD. There were no differences in breast cancer risk by tertile of BMD or osteoporosis status.

Conclusions: The initial hypothesis was not confirmed by this study, however the results are limited by a small sample size.
LONG-TERM SURVIVAL OUTCOMES OF LAPAROSCOPIC ASSISTED RADICAL HYSTERECTOMY IN TREATING EARLY STAGE CERVICAL CANCER

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Objective: To determine the long-term disease-free and overall survival outcomes of laparoscopic surgery in the treatment of early stage cervical cancer.

Study design: A longitudinal study of prospectively registered patients of cervical cancer undergoing laparoscopic surgery from June 1994 to December 2005.

Results: Total 139 patients, with mean±SEM age 48.1±0.9 years and mean body mass index 24.3±0.3 Kg/m2, were included, in which 60 patients were in FIGO stage IA, 76 in IB, and 3 in IIA. Mean operation time was 231.1±6.1 minutes. Median number of pelvic lymph node retrieval was 16. Major intraoperative complications included 1 great vessel injury, 1 ureteral injury, 1 colon injury and 6 cystotomies. In a median follow-up of 92.1 months, the mean±SEM cumulative disease-free and overall survival rates were 91.01±2.77% and 92.78±3.06%, respectively.

Conclusion: Laparoscopic approach has favorable long term survival outcomes and perioperative morbidity. With the advantage of minimal invasiveness, laparoscopic radical hysterectomy with pelvic lymphadenectomy by experienced surgeons is an ideal alternative for treating early stage cervical cancer.
MAGNESIUM AND POTASSIUM DEPLETION IN CERVICAL CANCER PATIENTS RECEIVING WEEKLY CISPLATIN CHEMOTHERAPY CONCURRENT WITH RADIOTHERAPY: A RETROSPECTIVE COHORT STUDY

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Objectives: This study was conducted to determine the association of low dose weekly Cisplatin chemotherapy with serum magnesium and potassium levels of cervical cancer patients undergoing concurrent chemoradiation.

Methods: One hundred fourteen cervical cancer patients who underwent radiotherapy concurrent with weekly Cisplatin for at least 3 cycles in 2007 were included. Sociodemographic and clinicopathologic data, details of each chemotherapy cycle and laboratory results were obtained. Repeated measures analysis of variance, Sidak multiple comparison test and rank correlation test were the statistical tools used to determine the correlation of magnesium and potassium levels with each chemotherapy. A logistic regression model was derived to show the association of factors with either hypomagnesemia and hypokalemia. All statistical tests were computed at 95% confidence interval.

Results: Calculation of the relative mean change in magnesium, creatinine and potassium showed a significant decrease only in the serum magnesium levels (p value = 0.001). The incidence of hypomagnesemia is 46.49%, the degree of which is mild in 55%, moderate in 30% and severe to life-threatening in 15% of patients. There is progressive decline in serum magnesium levels with each successive cycle. Only the cumulative dose of the chemotherapy was statistically associated with hypomagnesemia and hypokalemia.

Conclusion: Noteworthy in this study was that even at a low dose of Cisplatin, hypomagnesemia still developed. The cumulative dose of the chemotherapeutic agent is the only factor noted to significantly affect the level of decline in serum magnesium level, which in this study, is 120 mg/m².
ANALYSIS OF 89 PATIENTS WITH POSITIVE MARGINS AFTER CONIZATION

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Objective: To assess the factors associated with conization margin status of the patients with cervical intraepithelial neoplasia (CIN), and analyze follow-up results with positive margin.

Methods: A retrospective analysis of 350 patients diagnosed CIN II-III by colposcopy and undergoing conization during Jan, 1st 2006 and Jun, 30th 2008 was performed, to assess the relationship of the positive margin of conization with the patient's age and severity of disease. The management and follow-up of the patients with positive margins were evaluated.

Results: For 350 patients who had their first conization, the mean age of 89 patients with positive margins was (36.9±8.2) years, and that of other 261 patients was (37.0±7.6) years, which gave no much difference (P=0.931, t=0.087). The positive margin was related with the severity of disease (P<0.001, z=4.731). There were 16 patients accepted second surgery and 8 residual disease were confirmed. For the follow-up patients, 2 patients had recurrent CIN3, 2 patients progressed to invasive cervical carcinoma, and all of this 4 patients were HPV16 (+) after conization.

Conclusions: The resection margin status of the conization may be related with the severity of disease, the CIN patients with positive cone margin should have a regular postoperative follow-up. HR-HPV examination should be emphasized, and CIN recurrence and invasive cervical carcinoma should be excluded in patients with HPV16 (+) after conization.
COMPARISON OF OUTCOMES FOR BONE METASTATIC CERVICAL CANCER PATIENTS PRIMARY TREATED WITH CONCURRENT CHEMORADIATION VS. RADIATION THERAPY ALONE

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Introduction: Bone is the third most common site of cervical cancer distant metastasis after the lungs and liver. Since 1999, concurrent chemoradiation become standard treatment of locally advanced disease. Then the aims of the study were to retrospectively compare outcomes for bone metastatic cervical cancer patients primary treated with concurrent chemoradiation to radiation therapy alone.

Patients and methods: We retrospectively analyzed thirty-five cervical cancer patients with bone metastasis primary treated with concurrent chemoradiation or radiation therapy alone during the period from January 1998 to December 2007. Of these, 11 patients received concurrent chemoradiation as their primary treatment.

Results: Among 4,620 cervical cancer patients, only thirty-five patients who had bone metastasis received primary treatment with concurrent chemoradiation (CCRT) or radiation therapy alone (RT). The two groups of patients (CCRT vs RT) were similar in age, histology and the International Federation of Gynecology and Obstetrics (FIGO) stages. The characteristics of bone metastasis in both groups were also not significant difference. Patients who received CCRT had not better overall survival than the patients who received RT (median, 19 vs 22 months; 95% CI 14.68-23.32 vs 8.56-35.44). There were comparable the duration from cervical cancer diagnosed to bone metastasis diagnosed and the survival after diagnosis of bone metastasis between both groups.

Conclusions: Our retrospective analysis suggests that concurrent chemoradiation therapy may not provide a survival benefit for bone metastatic cervical cancer patients when compared to radiation therapy alone. Larger group of the focused patients with prospective trial would be study in further trial.
A SURVEY OF THE KNOWLEDGE AND ATTITUDE OF JORDANIAN OBSTETRICIANS AND GYNAECOLOGISTS TO CERVICAL CANCER SCREENING

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Background: Cervical cancer is the second most prevalent cancer in women worldwide. In the developing world, it is the most common cancer and it remains the fifth most common reason for cancer mortality in women (Wilson et al. 2004).

In Jordan, cervical cancer is the third most common gynaecological cancer.

Objective: The aim of the survey was to investigate the knowledge and attitudes of Jordanian gynaecologists toward cervical cancer screening.

Methods: A pre-tested postal questionnaire was mailed to 462 licensed gynaecologists in Jordan. Three questions were designed to assess knowledge and two questions to assess attitudes to screening for cervical cancer.

Results: A total of 392 gynaecologists completed the survey with a response rate of 84.4%. Most respondents (77.4\%) agreed that the role of HPV in the causation of pre-invasive and invasive carcinoma of the cervix is well established. However, only 48.5\%, were confident that the Pap smear is the most cost-effective public health tool for cervical cancer screening. 68.6\% of respondents routinely screened their patients. Only 44.3\% of them agreed that there is a significant improvement in sensitivity of detection cervical cancer when Pap smear and HPV tests were combined. 76.4\% of them would refer their patients to colposcopy when they have a positive smear test.

Conclusion: Although the majority of Jordanian gynaecologists were able to identify the aetiological factors of cervical cancer, many of them were not confident that Pap smear was the most cost-effective screening test, or that HPV testing improved the sensitivity of detection of cervical disease.
REDUCING CERVICAL CANCER INCIDENCE IN NIGERIA

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Cervical cancer is an important woman’s reproductive health problem especially developing countries like Nigeria; it is the third most common cancer worldwide. Four out of five new cases are reported from developing countries including high incidence of mortality this is because there are little or no facilities for screening programmes to detect precancerous lesions early and treat especially the preventable ones like breast and cervical cancers, and another reason for the high incidence is that there is generally low awareness about the disease in the populace most women attending public hospitals are not aware that cervical cancer can be prevented by regular screening to detect premalignant lesions. The Visual screening approaches are employed for screening for cervical cancer because it is simple, not a cytological based screening procedure, it is least expensive can be easily taught and learnt by health workers; it involves application of 3-5% acetic acid to the cervix and observe for colour changes. After application a positive acetowhite area in the transformation zone, treatment is given in form of cryotherapy and lEEP. Since 2006 about 3000 women has been screened and 3% were positive these had treatment thus preventing the lesion from becoming cancer. The International network for Cancer Training And Research [INCTR] sponsored us for the training.
EFFECTS OF QUERCETIN-INDUCED APOPTOSIS ON HELA CELLS THROUGH THE MITOCHONDRIAL PATHWAY

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Objective: To investigate the effects of Quercetin-induced apoptosis on Hela cells and study the mechanism.

Methods: Antiproliferative effects were measured by MTT assay after the cells were treated with quercetin at different concentrations (6.25, 12.5, 25, 50µmol/L) for 24h. Cell apoptosis rate was detected by flow cytometry with annexin V-FITC/PI technology. The changes of intracellular calcium ion concentration ([Ca²⁺]) and mitochondrial membrane potential (Δψm) in HeLa cells induced by quercetin were observed with laser scanning confocal microscope combining with specificity fluorescent probes Fluo-3/AM and JC-1 respectively. Colorimetric method was used to measure caspase-3 activity.

Results: Then treated with different concentrations of quercetin (6.25, 12.5, 25, 50µmol/L), the proliferation was inhibited and the apoptosis was induced in HeLa cells with the inhibition rate of (13.4±2.2)%, (26.2±6.8)%, (39.8±11.4)%, and (48.5±9.1)% respectively, apoptosis rate of (9.0±1.4)%, (13.3±1.1)%, (22.5±2.3)%, and (44.7±4.2)% respectively, and which was dose-dependent (p< 0.01). The apoptosis of HeLa cells was induced by quercetin, which significantly reduced mitochondrial membrane potential, effectively enhanced [Ca²⁺], and the caspase-3 was activated in a dose-dependent manner (p< 0.01).

Conclusion: Quercetin can markedly inhibit cell proliferation, and induce apoptosis of cervical cancer cells, possibly via a Ca²⁺-dependent mitochondrial apoptosis pathway.
CERVICAL CANCER SCREENING METHODS - PILOT STUDY IN URBAN AREA FROM ROMANIA

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Background: Knowing the fact that Romania is one of the European Union countries with the highest rate of mortality due to cervical cancer, 961 women were randomly selected and questioned about the last Pap test and, if necessary, about the reasons for not having a Pap test in the last three years (2005-2007)

Methods: The target was to identify the characteristics of women with a low degree of addressability for Pap testing and, thus, with a higher risk of oncological cervical pathology. We worked on a group of women from different areas of Romania and used logistical regression, cluster analysis in latent classes, arborescent classification analysis and the SPSS software. We also evaluated in two focus groups attitudes and opinions regarding the significance of a gynecological examination.

Results: Only 17.9 % from the sexually active women reported that they had recently a Pap test. The most “at risk” group included women with a low income and degree of education, under 24 or over 50 years of age.

Conclusions: There are urgent measures to be taken regarding the education of those groups of women with low addressability at Pap test and that of an utmost importance is the advise received by women from the general practitioner, who has to send them periodically to perform the test. In fact, it is a question of equity; every woman has to have equal chances of cancer detection and treatment indifferently of her social and economical position in the society.
EXPRESSION AND CLINICAL SIGNIFICANCE OF TGF-β AND SMAD7 IN CERVICAL CARCINOMA

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Background and aims: Transforming growth factor β (TGF-β) signaling pathway is involved in variety of important cellular function. SMAD7 is an important member of the Smad family that functions as a feedback regulator of TGF-beta responses. However, their roles in the cervical cancer are unclear. This study was to detect the expression of TGF-β and SMAD7 protein in different cervical lesions and to investigate the correlation of TGF-β signal transduction pathway to biological behavior of cervical carcinoma.

Methods: The expression of TGF-β and SMAD7 protein in 76 specimens of cervical carcinoma, 21 specimens of cervical intraepithelial neoplasia and 10 specimens of normal cervical epithelium were detected by immunohistochemistry.

Results: The positive rates of TGF-β (8.6% and 42.9% vs. 69.7%, P< 0.01) and SMAD7 (21.7% and 52.4% vs. 75.0%, P< 0.05) were significantly lower in normal cervical epithelium and cervical intraepithelial neoplasia than in cervical carcinoma. The expression of TGF-β and SMAD 7 protein were correlated with clinical stages and pathological grades (P< 0.05), but there was no difference with regard to patient’s age, cancerous focus size, histological types and lymph node metastasis (P>0.05).

Conclusions: TGF-β signaling pathway is involved in the tumorigenesis of cervical carcinoma.
EARLY DIAGNOSTIC OF CERVICAL CANCER CELLS IN REFLECTED LIGHT

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Background: In oncocytology the main testing tool is optical microscopy of transmitted light, which usually can not reveal a fine morphology of the cell membrane surface. Besides the surface membrane structures are destroying after smears preparation (fixing, cleaning, staining and others) what leads to artifacts too.

Objectives: The objective of the present work is revealing strongly specific morphologic features of the epithelial cervical cells surface without its treatment.

Methods: Biospecimens - fresh, native cervical smears of the healthy patients (10 samples) and women with diagnosis Cr. colli uteri (150 samples) has been investigated under reflected optical microscope Neophot-2 (Carl Zeiss, Jena).

Results and conclusion: For smears of cervix epithelium throughout the field of view of a microscope numerous ballooning-outs, which have a mean size from 0.1-0.5 to 1.2 -1.3 mkm, are seen located on the cell surface. It is accepted that in result of a cancer cell metabolism a granules or vesicles originate inside of cell and move towards cell surface to release its contents. Visualization of such morphological formations has however been limited, partly due to the difficulties with imaging native living or structurally intact cells because convenient transmitted light microscopy technique do not reveal surface cell features which are usually removed after fixing, drying and other treatments of smears. We suppose that offered method to visualize cell topography in air without fixation and dehydration may be alternative and complementary to Pap-test.
SEXUALLY RESPONSIBLE BEHAVIOR AMONG ADOLESCENTS-PROJECT-KNOWLEDGE IS PLEASURE

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A necessary condition prior to the onset of sexual intercourse is a physical and mental maturity of both partners. It is recommended that the partner who has a urinary or sexually transmitted infection should first recover and then together with the partner maintain normal sexual hygiene. For systematic prevention of sexually transmitted infections diseases in this moment it is necessary: introduce an effective sexual education in schools starting from primary school, develop interdisciplinary cooperation between social and medical sciences, including all experts. In appropriate assembly rooms of some Grammar and Secondary School of Zagreb during weekend evenings (Fridays, Saturdays) educational lectures held by medical specialist were given about sexually transmitted diseases, particularly HPV and after the lectures adolescents multimedia presentations (posters, scene performances, poems, web presentations-all about std thema). Lectures were short (each 20-30 min) accompanied with discussion. By organizing multimedia presentations the interest of that population to attend would be greater. By offering free refreshing beverages and media support by radio listened mostly by the young as well as the musical web portal, it has been tried to make popular the whole project. Questions made after the lecture were those usual for that age. They asked about the way of contracting HPV, medical treatment of partners and use of contraceptives and aslo about vaccina. Booklets explaining in a popular way the sexually transmitted diseases, way of catching infection and protecting methods were distributed. Mass media have excellently marked the whole project with almost everyday information. We continued with this project also in the this school year. So - KNOWLEDGE, SCREENING and VACCINATION can help prevent HPV
REVISING THE ROLE OF PARAMETRIAL BOOST IN LOCALLY ADVANCED CERVIX CANCER PATIENTS STAGED WITH POSITRON EMISSION TOMOGRAPHY

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Purpose: The primary objective was to validate the practice of not treating clinically involved parametria by parametrial boost in the absence of metastatic pelvic lymph nodes. Secondary objective was to validate the adequacy of nodal boost in node positive patients regardless of the parametrial status.

Methods: A total of 193 loco-regionally advanced cervical cancer patients were treated with curative intent using external beam radiotherapy and intracavitary brachytherapy. All patients were clinically staged (FIGO), their tumour volume and nodal status determined using pre-treatment magnetic resonance imaging and positron emission tomography (PET). The PET positive nodes were boosted to an additional dose of 6-10Gy following 40Gy to whole pelvis. None of the patients received parametrial boost. Staging, treatment and follow-up data were collected prospectively. Patterns of failure and potential prognostic factors such as parametrial invasion, tumour volume, corpus invasion and pelvic nodal involvement were examined.

Results: There was no significant difference in the rates of pelvic relapse in both node positive and negative patients with or without parametrial involvement. In multifactor analysis, tumour volume was significantly associated with pelvic failure (p=0.009) and node positivity with extra pelvic failure (p=0.002). In particular, clinical parametrial involvement in the absence of parametrial boost was not related to either pelvic or extra-pelvic failure. None of the node positive patients had isolated pelvic failure.

Conclusion: Cervix cancer patients with clinically involved, parametrial disease, in the absence of nodal disease can be adequately treated without parametrial boost.

Keywords: Cervical cancer, FIGO stage, parametrial infiltration, lymph node metastasis
ASSESSMENT OF DIFFERENT TYPES OF CYTOLOGICAL FINDINGS IN PAPANICOLAOU TEST (A 3 YEAR STUDY) IN AN IRANIAN HOSPITAL KERMANSHAH /IRAN

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Objectives: This study was performed to report frequency of different cytological findings of conventional Papanicolaou test as screening test based on Bethesda system in women attending in clinic of Gynecology in Motazed teaching hospital in Kermanshah - Iran.

Methods: This was a case series study including all cases of pap smears in different age groups (15 - 60 years old) from 2000 -2002.

Data collected from pathology report of patients and analyzed through SPSS version 12.

Results: 1188 cases of Pap smear were identified mean age of 37/7 years. Most of patients (33%) were 26-35 years old of which 1164 (98%) had normal Pap smear, 6 cases (0/5%) had abnormal Pap smear, and 18 cases (1.5%) were unremarkable. Among abnormal Pap smears 5 cases (83/3%) were ASCUS and one case (16/7%) was HSIL.No cases of invasive cervical carcinoma and LSIL were determined. In general ASCUS and HSIL were found in 42% and 8% of cases respectively.

Conclusion: Abnormal results were seen in 0/5% of specimens including ASCUS (83/3%), HSIL (16/7%) and inflammation (84%).

Recommendation: Prevalence of dysplasia in study group was low. It might be due to high false negative rate of conventional Pap smear results. A new technique of Pap smear with high accuracy rate, such as liquid-based Pap smear is recommended.

Keywords: Pap smear, dysplasia. ASCUS.HSIL
CLINICAL ANALYSIS OF 37 CASES WITH URINARY RETENTION AFTER RADICAL TOTAL HYSTERECTOMY

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Objective: To investigate the causes, the risk factors and the effective therapeutic methods of urinary retention after radical total hysterectomy.

Methods: Department of Gynecology of Beijing University Shenzhen Hospital received 127 patients and they underwent radical total hysterectomy including sub-radical total hysterectomy during May 2003 and August 2007, of which 37 had postoperative urinary retention. A retrospective analysis was done on the causes, the risk factors and the therapeutic methods of urinary retention.

Results: The 50 years or older patients were prone to have postoperative urinary retention than the cases younger than them. The cases in urinary catheter was removed 14 days after operation more difficult to happen than 7 days and 10 days cases. The postoperative urinary infection cases were one of the causes of urinary retention and the difference was statistically significant (P< 0.05) than the patients without urinary system infection.

Conclusion: Postoperative urinary retention of radical total hysterectomy is the common complication of cervical cancer operation and the main causes of it are pelvic nerve injury and urinary system infection. So the important managements to prevent postoperative urinary retention are reasonable and meticulous operations.
RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY IN THE MANAGEMENT OF CERVIX CANCER: A RETROSPECTIVE REVIEW

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Aim: To evaluate implementation of chemotherapy in patients treated with radiotherapy for cervical carcinoma.

Method: Retrospective audit of records conducted for cervical cancer patients treated between 1/1 2000 and 31/12/2006 to a minimum dose of 45Gy. Data were collected on patient and tumour characteristics, toxicities and outcome. Chi-squared tests and Kaplan Meier survival analysis were used for statistical analysis.

Results: There were 67 patients with FIGO stage IBI (n=14, 20.9%), IB2 (n=14, 20.9%), IIA (n=6, 9%), IIB (n=19, 28.4%), IIIA (n=2, 3%), IIIB (n=11, 13.4%), IVA (n=3, 4.5%). The median follow up time was 41.5 months. 76% (n=51) had squamous cell carcinoma. Thirty-four patients received definitive chemoradiotherapy, 11 received definitive radiotherapy alone, 11 adjuvant chemoradiotherapy and 11 had adjuvant radiotherapy alone. Median age of women receiving definitive chemoradiotherapy was 56 years compared to 74 in women who did not receive chemotherapy. Eighteen (40%) patients treated with definitive radiotherapy had a radiotherapy duration exceeding 56 days. 46.7% of women in the definitive radiotherapy group and 54.5% of women in the post-operative radiotherapy group experienced Grade 2 or more bowel toxicity. 11 of 45 women (24.5%) treated with definitive radiotherapy and 2 of 22 (9.1%) women treated with adjuvant radiation developed a recurrence. The 5 year overall survivals were 71% for women treated with definitive radiotherapy and 83% for those treated with post-operative radiotherapy.

Conclusion: 76% of patients receiving definitive radiotherapy and 50% of patients receiving adjuvant radiotherapy had concurrent chemotherapy. Acute toxicity and survival were comparable to published data.
PHYSICAL AND PSYCHOLOGICAL ANALYSIS OF FEMALES TREATED FOR CERVICAL CANCER WITH RADIATION THERAPY. WHAT IS STILL NEEDED?

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Objectives: Diagnosed with cancer and going through treatment and its side effects, impacts on patients quality of life. The aim of this analysis was to assess the physical and psychological impact of radiation treatment on patients treated for cervical cancer.

Materials and methods: We randomly analyzed 100 patients who had completed pelvic radiation for cervical cancer in our center between 2003 and 2009. After routine physical examination by the oncologist they underwent assessment by the psychologist. Structured questionnaire was filled by the psychologist and oncologist.

Results: Twenty seven patients experienced sexual discomfort due to vaginal stenosis while 73% (73) did not. 29% (29) were emotionally distressed due to sexual discomfort while 71% had no such problem. 61% (61) had used vaginal dilator while 39% (39) did not. The incidence of vaginal stenosis dropped in our center since we introduced customized vaginal dilator. 52% experienced hot flushes while 48% (48) had no complaint. 67% (67) had mood irritability while 33% (33) adapted well. 16% patients experienced grade 2-3 rectal toxicity post treatment, 14% had grade 2 bladder toxicity which were managed conservatively. Overall depressive behavior was found in 71%. 62% patients worried about their health and self image causing emotional distress.

Conclusion: Rectal, bladder and vaginal toxicity contributes to depressive behavior. High incidence of post treatment depressive behavior is related to the toxicities discussed above and can be reduced by appropriate precautions as well as psychological help during and after treatment which is currently lacking in most of the cancer centers in the developing countries.
PROGNOSTIC VALUE OF HISTOLOGY IN CERVICAL CANCER PATIENTS

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According to the epidemiological data, the rising tendency of cervical adenocarcinoma morbidity and the decrease of cervical squamous cell carcinoma, especially in the age group between 20 and 39 years, are observed. Many authors emphasize the worse outcome of cervical adenocarcinoma patients, when compare to squamous cell cancer.

Aim: The assessment of prognostic value of histology in cervical cancer patients.

Material and methods. The retrospective analysis of 142 cervical adenocarcinoma and 242 squamous cell cancer patients, treated between January 1989 and December 1999 at Maria Sklodowska - Curie Memorial Cancer Center in Warsaw, was performed. All patients were treated with surgery and complementary radiotherapy, or radiotherapy alone. The analysis of the overall and disease-free survival in dependence on the most important clinic - pathological factors, was performed.

Results: The percentage of overall 5-year survival for cervical adenocarcinoma patients achieved 45%, whereas for squamous cell cancer, 62%. The difference was statistically significant (p=0.05).

Conclusions: Regardless of the other factors, the influence of histopathology on the treatment results in cervical cancer patients was demonstrated. The prognosis of cervical adenocarcinoma patients was statistically significantly worse, than squamous cell cancer patients.
THE CORRELATION BETWEEN THE CYTOLOGICAL AND COLPOSCOPIC FINDINGS AND PATHOHISTOLOGICAL FINDINGS OF CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

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Objectives: Colposcopy and Pap smears (PA) are standard screening methods used within the majority of programs to diagnose the early, pre-malignant stadium of Cervical Cancer.

The objective of this paper was to analyze the correlation between the cytological and colposcopic findings and the pathohistological (PH) findings of cervical intraepithelial neoplasia (CIN).

Methods: The paper examined 64 subjects aged between 23 and 60, whose CIN findings were obtained through biopsy in 2009. An analysis was carried out of the link between the PH findings and findings obtained through classical procedures of cytological smears and colposcopy classified as: Nothing Abnormal Detected (NAD), leukoplakia, iodine-negative epithelium, acetowhite epithelium (AW), atypical blood vessels, mosaic and punctation. Descriptive statistics and the chi-square test were used.

Results: The Pap smears of our patients showed a significant correlation with the pathohistological findings (p=0.0264), unlike the colposcopic findings which did not display any significance in relation to the pathohistological findings (p=0.8874).

With our test subjects, a suspicious PA III finding was pathohistologically confirmed as CIN in 78.13% of the cases, while a suspicious lesion observed colposcopically was confirmed in 70.31% of the cases. The most frequent colposcopic image was mosaic 31 (32.63%).

Conclusions: Pap smears are statistically the most significant in detecting pre-malignant cervical lesions in our patients compared to colposcopy. Given the diagnostic limitations, it is necessary to employ both methods.

Keywords: Cytology, colposcopy, cervical intraepithelial neoplasia
CORRELATION BETWEEN HOMEODOMAIN-INTERACTING PROTEIN KINASE 2, HUMAN PAPILLOMAVIRUS AND APOPTOSIS IN CERVICAL CANCER

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Background: Cervical cancer is one of the most common female cancers. Human papillomavirus (HPV) infection is the main cause of cervical cancer. However, some other genetic and epigenetic factors may contribute to cervical carcinogenesis. Homeodomain-interacting protein kinase 2 (HIPK2) is a serine/threonine nuclear kinase that involved in the enhancement of apoptosis, inhibition of cell growth and is also thought to participate in the process of tumorigenesis.

Methods: In the present study, HIPK2 mRNA and protein expression levels were analyzed in normal and cervical cancer tissues by quantitative real-time PCR and Western blot analysis. Reverse transcription PCR was used to investigate HPV-16 and -18 in cervical cancer. To explore the mechanism of action of HIPK2 in cervical cancer development, RNA interference technology was used to analyze the effect of HIPK2 on apoptosis, cell proliferation, cell migration and invasion in cervical cancer cell lines.

Results: We found that HIPK2 mRNA and protein expression were significantly higher in cervical cancer than in normal cervical tissues. There was significant correlation between HIPK2 and HPV-16 and -18. Inhibition of HIPK2 by RNA interference caused dramatic reduction in apoptosis compared with controls in cervical cancer cells by down-regulating caspase-3. We also observed that HIPK2 RNAi induced cell proliferation as well as cell migration in cervical cancer cell lines.

Conclusions: There is a close correlation between HIPK2 and HPV-16 and -18. HIPK2 RNAi can inhibit cell apoptosis, induce cell proliferation and cell migration-stimulated in cervical cancer cells. HIPK2 may play an important role in cervical cancer development.
COLD COAGULATION: EVALUATION OF A TREATMENT MODALITY FOR HIGH GRADE CIN

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Introduction: Adverse obstetric outcomes are associated with excisional treatments as compared to destructive treatments for cervical intraepithelial neoplasia (CIN). Some have suggested a return to destructive treatments for CIN, particularly in young women, especially for low grade CIN. We compared the success rates following cold coagulation for CIN.

Methods: We performed a retrospective cross-sectional study of 172 women who had cold coagulation performed between 1st January 2000 and 31st December 2005. The outcomes were measured in terms of cytology results at 6 and 12 months following the treatment. Success rates, odds ratio and relative risk of having an abnormal smear in the two cohorts were calculated.

Results: Eighty-nine women with low-grade CIN and 83 women with high-grade CIN confirmed by colposcopically directed biopsy were included in the study. The overall success rate at 6 months was 94.7% (98.8% for low-grade CIN and 90.3% for high-grade CIN). The overall success rate at 12 months was 97.09% (100% for low-grade CIN and 93.9% for high-grade CIN). None of the women developed microinvasive/invasive cancer or CIN 3 at 12 months post-treatment. In our cohort, women with high-grade CIN were more likely to have an abnormal smear post-treatment as compared to women with low-grade CIN at 6 months (RR 8.57 Odds ratio 0.1 95%CI 0.01-0.8 P=0.03) as well as at 12 months (RR 11.78 Odds ratio 0.07 95%CI 0.004-1.46 P=0.08).

Conclusion: Cold coagulation in the presence of a satisfactory colposcopy is as effective a treatment for high-grade CIN as for low-grade CIN.
PREVALENCE OF HIGH-GRADE CIN IN THE PRESENCE OF A TYPE 3 TRANSFORMATION ZONE AND A SMEAR SUGGESTIVE OF LOW-GRADE DYSKARYOSIS

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Introduction: There appears to be conflicting evidence in the management of low-grade dyskaryotic smears in the presence of an unsatisfactory colposcopy. Some suggest conservative management with long-term cytology follow-up whilst others support surgical intervention in the form of a diagnostic as well as therapeutic LLETZ biopsy.

Study objective: We have determined the prevalence of high-grade CIN in the presence of unsatisfactory colposcopy and a referral smear suggestive of low-grade dyskaryosis.

Methods: We performed a retrospective cross-sectional study of 380 women who attended our colposcopy unit on account of a low-grade dyskaryosis smear (BSCC terminology 2008) and had an unsatisfactory colposcopy between 1st January 2000 and 31st December 2005. The study population was identified using an Infoflex database. The outcomes were measured in terms of histology results obtained as a result of a diagnostic LLETZ.

Results: Three hundred and eighty women with a referral smear suggestive of a low-grade dyskaryosis had a diagnostic LLETZ biopsy. The histology results were not available in 7 cases (1.8%). No CIN was found in 45 women (11.8%) and 25 women (6.5%) had HPV changes only. CIN 1 was found in 100 women (26.3%), CIN 2 in 123 women (32.3%), CIN 3 in 78 women (20.5%) and 2 cases (0.5%) of microinvasive carcinoma were diagnosed.

Conclusion: There is significant prevalence of high-grade CIN in the presence of a type 3 transformation zone and a smear suggestive of low-grade dyskaryosis in our study population. A diagnostic LLETZ is recommended.
THE USE OF INTEGRATED HUMAN PAPILLOMAVIRUS TYPE16 AS A SURROGATE MARKER IN PREDICTING DISEASE FOR PATIENTS WITH CERVICAL INTRAEPITHELIAL NEOPLASIA

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The purpose of this study was to assess the effectiveness of the use of human papillomavirus type 16 (HPV16) physical status to predict clinical outcome during cervical intraepithelial neoplasia development.

A follow-up study was monitored in association with HPV integration in 43 patients with abnormal smears (as ASC-US, ASC-H, LSIL, HSIL, AGC) which refered to the gynecology and obstetrics outpatient clinic of Gulhane Military Medical Academy, with the use of multiplex quantitative polymerase chain reaction.

Concerning HPV-16 integration, the integrated HPV-16 forms, already present in women with abnormal histology, decreased to the benefit of pure episomal forms with the severity of lesions (normal&CIN1 cervix: 100%; CIN2&CIN3: 0%).

It is now accepted that the integration of human papillomavirus DNA into host genome is one of the major contributing factors to genital malignant transformation. The integration often leads to the disruption of E2 viral gene with consequent removal of E6/E7 viral oncogene inhibition and transformation progression. Our results showed that the HPV 16 integration status has potential to be a marker for risk assessment of CIN progression.
Clinical Impact of Re-Staging Recurrent Cervical Cancer with FDG-PET

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Background and aims: Selecting the optimal treatment for individual patients with recurrent cervical cancer is difficult since conventional imaging techniques have a low sensitivity and specificity for detecting tumor spread. To assess the impact of FDG-PET on the clinical management of patients with recurrent cervical cancer we performed this prospective trial.

Methods: Twenty-seven consecutive patients with histologically verified recurrent cervical cancer were included. Mean age was 53 years (range, 31-76). FDG-PET was performed before starting relapse treatment. Software fusion with simultaneously obtained CT images was performed. The impact of FDG-PET results on the already defined treatment plans and intentions was recorded. FDG-PET results were compared with the results of the conventional work-up. Median follow-up time after FDG-PET was 25 months (range, 8-59).

Results: For 56% (15/27) of the patients more sites of metastases were detected with FDG-PET compared with the conventional work-up. The findings on FDG-PET were consistent with the planned management, led to a change in treatment modality, or led to a change in dose of therapy for 44% (12/27), 30% (8/27), and 22% (6/27), respectively. The planned treatment was decreased or withheld for 48% (13/27) of the patients and intensified for one patient. Treatment intentions were altered for 30% (8/27) and all but one went from curative to palliative intentions.

Conclusion: Clinically valuable information was gained by adding FDG-PET to the re-staging procedure of recurrent cervical cancer. The findings led to a decrease in treatment delivery. This may in turn potentially have spared patients from unnecessary toxicity.
RESULTS OF A RANDOMIZED TRIAL FROM THE FNCLCC COMPARING HYSTERECTOMY VERSUS NO HYSTERECTOMY AFTER CHEMORADIOThERAPY FOR STAGE IB2/II CERVICAL CANCER

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Background: Concomitant chemoradiation (including brachytherapy) (CRT) is considered as the standard management of stage IB2/II cervical cancer by many countries. Nevertheless, some of them, discuss a completion surgery (hysterectomy (HT)) after CRT. The aim of this study is to investigate the therapeutic impact of such surgery.

Methods: A randomized trial was opened in France in 2003 to evaluate the interest of HT after CRT. Inclusion criteria were: 1. stage IB2/II cervical cancer without extrapelvic disease on conventional imaging; 2. pelvic external radiation therapy (45 Gy +/- parametrial or nodal boost) with concomitant cisplatin chemotherapy (40mg/m²/week) and followed by utero-vaginal brachytherapy (15 Gy to the intermediate risk CTV); 3. “complete” clinical and radiological response 6 to 8 weeks after brachytherapy. Patients were randomized between HT (arm A) versus no HT (arm B). Unfortunately this trial was closed because of poor accrual: 61 patients were enrolled (between 2003 to 2006) and were reported in this study.

Results: Thirty one and 30 patients were enrolled respectively in arm A and B. Twelve patients recurred (5 of them died): respectively 8 and 4 in the arm A & B. Three-year EFS was 72% (SE=9%) and 89% (SE=6%)(NS) in arm A & B, respectively. Three-year overall survival was 86% (SE=6%) and 97% (SE=3%)(NS) in the arm A & B, respectively.

Conclusions: The results of the current trial seem to suggest that completion hysterectomy had no therapeutic impact in patients with clinical and radiographical complete response after CRT.
PROGNOSTIC FACTORS AND MORBIDITIES AFTER COMPLETION SURGERY IN PATIENTS UNDERGOING INITIAL CHEMORADIATION THERAPY FOR LOCALLY ADVANCED CERVICAL CANCER


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Purpose: The aim of this study was to evaluate the prognostic factors and morbidities of patients undergoing completion surgery for locally advanced-stage cervical cancer after initial chemoradiation therapy (CRT).

Patients and methods: Patients fulfilling the following inclusion criteria were studied: stage IB2-IVA cervical carcinoma; tumor initially confined to the pelvic cavity on conventional imaging; pelvic external radiation therapy with delivery of 45 Gy to the pelvic cavity and concomitant chemotherapy (cisplatin 40 mg/m²/week) followed by utero-vaginal brachytherapy; completion surgery after the end of radiation therapy including at least a hysterectomy.

Results: One-hundred and fifty patients treated between 1998 and 2007 fulfilled inclusion criteria. Prognostic factors for overall survival in the multivariate analysis were the presence and level of nodal spread (positive pelvic nodes alone: HR=2.03, positive para-aortic nodes: HR=5.46; p< .001) and the presence and size of residual disease (RD) in the cervix (p=.02). Thirty-seven (25%) patients had 55 post-operative complications. The risk of complications was increased with a radical hysterectomy (p=.04) and the presence of residual cervical disease (p=.01).

Conclusion: In this series, the presence and size of RD and histologic nodal involvement were the strongest prognostic factors. Such results suggest that the survival of patients treated using CRT for locally advanced cervical cancer could potentially be enhanced by improving the rate of complete response in the irradiated area (cervix or pelvic nodes) and by initially detecting patients with para-aortic spread so that treatment can be adapted in such patients. Morbidity of completion surgery is high in this context.
A RANDOMIZED TRIAL OF LOCAL ANESTHESIA VERSUS FORCED COUGHING FOR PAIN RELIEF DURING CERVICAL BIOPSY

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Objective: Cervical biopsy often causes discomfort and pain. To compare local anesthesia (1% lidocaine) with forced coughing as pain relief, we quantified the actual pain experienced during cervical punch biopsies.

Design: For a prospective trial conducted at the Medical University of Vienna, 68 women undergoing cervical punch biopsies for assessment of abnormal cervical smears were randomized in 2 pain relief treatment groups. Patients’ discomfort was assessed immediately after taking the biopsy using a 10-cm visual analog scale.

Results: No statistically significant difference was found between pain scores recorded for the 2 groups (P = .47, 95% confidence interval [CI], -0.4 to 1.3 cm). However, when local anesthesia was applied, the examination was significantly prolonged by a median of 2.11 min (P < .001; 95% CI, 1.6-2.8).

Conclusion: Forced coughing during cervical biopsies reduces patients’ discomfort to the same extent as local anesthesia, but is associated with a significantly reduced examination time.
RISK FACTORS FOR TUMOR RECURRENCE IN PATIENTS WITH STAGE III-IVA SQUAMOUS CELL CARCINOMA OF THE CERVIX TREATED WITH CONCURRENT CHEMORADIOThERAPY

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Objective: To identify prognostic factors for tumor recurrence in patients with FIGO stage III-IVA cervical cancer treated with concurrent chemoradiotherapy (CCRT).

Methods: We retrospectively analyzed 99 patients with FIGO stage III-IVA squamous cell carcinoma of the uterine cervix treated with CCRT between 1997 and 2008 at our institute. All patients gave their written informed consent for the study. Radiotherapy consisted of pelvic external beam radiotherapy (total dose 50 Gy) and high-dose-rate intracavitary brachytherapy (Point A; 18 Gy). Patients received cisplatin 20mg/ m² for 5 days every 3 weeks concomitant with radiotherapy. Overall survival (OS) and Disease-free survival (DFS) were estimated by Kaplan-Meier methods. The Cox proportional hazard model was used for multivariate analysis.

Results: Ninety three patients were in stage III and 6 patients in stage IVa. The median age and median follow-up period were 53 years (range; 31-71) and 48 months (range; 7-139), respectively. The 5-years OS, DFS, locoregional DFS and distant DFS were 79%, 70.8%, 85% and 76.7%, respectively. Tumor recurrence occurred in 29 of 99 patients (29.9%). Twenty two patients had distant failure, of which 15 had distant metastasis alone. The independent risk factor for locoregional recurrence was tumor size ≥7.6 cm (p=0.0021, HR 5.29). Serum hemoglobin (Hb) level < 10.8 g/dl was independent risk factor for distant failure (p=0.0336, HR 2.57).

Conclusion: CCRT is efficacious for patients with FIGO stage III-IVA squamous cell carcinoma of the uterine cervix. New strategies should be considered to control recurrence for patients with tumor size ≥7.6 cm or Hb < 10.8 g/dl.
ABDOMINAL RADICAL TRACHELECTOMY IN PATIENTS WITH EARLY INVASIVE CERVICAL CARCINOMA

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Background: Radical trachelectomy is a surgical method which represents a method of treating invasive forms of cervical carcinoma in its early stage in women who are in their fertile ages and who want to keep their reproductive function.

Material and methods: Twelve young patients with cervical cancer stage IB were operated by abdominal radical trachelectomy at Institute of oncology Vojvodina, Serbia, from 2002. Medium age was 31.16 (range 27-34). Median follow-up was 39.6 months (range 14-72). Two patients were operated in 18th and 19th gestation week of pregnancy.

Results: In 39.6 months of median follow-up there was no evidence of recurrent disease. In patient with 18th gestation week of pregnancy the first postoperative day premature rupture of membranes was occurred followed miscarriage. In patient with 19th gestation week of pregnancy, Caesarean section was performed in 36th gestation week due to a premature rupture of membranes. One patient had miscarriage, 27 months after operation, and 45 months after operation one failure of IVF procedure. Two patients were got pregnant spontaneously and pregnancies were ended in 31th and 32th gestation week by Caesarean section due to a premature rupture of membranes. The babies were well and healthy at the time of discharge.

Conclusion: The strict indications are very important because the inadequate choice of patients for this operation discredits the operation itself. Abdominal trachelectomy could be recommended as a first technical approach in medical centers that performed standard radical operations without to much experience in laparoscopic approach.
EVALUATION OF VISUAL INSPECTION WITH ACETIC ACID AND LUGOL’S IODINE AS CERVICAL CANCER SCREENING METHODS IN RURAL AREAS OF CHINA

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Objective: To evaluate the VIA/VILI followed by colposcopy as cervical cancer screening methods in rural areas of China.

Methods: In 2008, VIA/VILI were used in women aged from 30–59 years old in the six areas of north China. All these women were examined by trained grassroot gyn doctor. For the women with abnormal result, colposcopy and biopsy will be continued.

Results: 12204 cases women were examined in six areas. Among them, the positive of VIA/VILI is 11.14%, and 712 were taken biopsy. The biopsy rate in six area is from 8.26% to 100%. Pathology results of 712 is as followed, 64.47% cases are no intraepithelial lesion or malignancy, CIN 1 is 21.91%, CIN 2/3 is 12.50%, microinvasive cervical cancer is 0.42%, invasive cervical cancer is 0.70%. The diagnosis rate for cervical lesion is 16.54% with VIA/VILI, They are 12.60%, 45.27%, 2.61%, 4.80%, 2.67%, 21.60%, respectively in six area. Colposcopy diagnosis rate for CIN (≥CIN1) is 31.60%, they are 18.01%, 54.33%, 31.57%, 10.00%, 26.67%, 29.03%, respectively.

Discussion: VIA/VILI is a simple and cheap cervical cancer screen method, but it has some disadvantage. It can not found the lesion in cervical canal and cannot be recorded and reviewed. If some backward area hasn’t cytologist, it can be used as a cervical cancer screen method. If they have cytologist, cytology test is better than VIA/VILI.

Conclusion: It should be discussed again seriously that VIA/VILI followed by colposcopy is used as first cervical cancer screen method.
PREVALENCE AND TYPES OF HPV IN CERVICAL CANCER: COMPARISON BETWEEN LOCAL AND INTERNATIONAL DATA: LESSONS TO LEARN

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Background: The purpose of the study is to compare the prevalence of HPV type-specific distribution in invasive cervical cancer (ICC) from Lebanon from the data obtained locally and from the Institut Català d’Oncologia (ICO).

Materials and methods: Paraffin embedded ICC specimens were identified from the histopathological archives of the AUBMC in Lebanon. DNA extraction and HPV detection was done locally at AUBMC and then separately at the ICO through standardized protocols of pathology evaluation, amplification of HPV DNA by SPF-10 broad-spectrum primers PCR, and subsequently followed by DEIA and genotyping by LiPA\(_{25}\).

Results: 586 ICC cases were reviewed from 1983 and 2003, with a mean age of 53.2 ± 17 years. DNA was extracted on 235. Data from local analysis showed that only 44.6% of the specimens were HPV positive. At ICO, HPV prevalence on 190 evaluable specimen was 83.2%. HPV16 (48.7%), HPV18 (12.7%), HPV45 (9.5%), HPV33 (3.8%) and HPV31 and HPV58 (3.2% each type). Multiple types were identified in 8.9% of the specimen. In adenocarcinoma, HPV 18 was found in 55.6% of cases, HPV 16 for 27.8%, and HPV 45 for 16.7%.

Conclusions: There was a significant discrepancy between the data obtained locally in Lebanon and through the ICO reanalysis. HPV16/HPV18/HPV45 single cases accounted for a 70.9% of the HPV positive ICC cases. HPV 18 and 45 were disproportionately more common in cervical adenocarcinoma. This information is essential to evaluate locally produced data for accuracy and for the study of the potential impact of the HPV vaccines in each country.
DETECTION OF HUMAN TELOMERASE GENE AMPLIFICATION COMBINED WITH HUMAN PAPILLOMAVIRUS TEST: A CLINICAL DIAGNOSTIC VALUATION FOR UTERINE CERVICAL PRECANCEROSIS

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Objective: Considering the development of cervical cancer is a gradual process, an effective screening of high-risk precancerous lesion is of great importance. The objective of this study is to explore whether detection of human papillomavirus (HPV), using Hybrid Capture 2 (HC2), associated with human telomerase gene (hTERC) amplification can be helpful to distinguish high-risk precancerous lesions from lesions with abnormal cytological result.

Methods: Slides prepared from 114 cervical specimens with negative for intraepithelial lesion or malignancy (NILM, n=27), cervical intraepithelial neoplasia (CIN) 1 (n=26), CIN2 (n=16), CIN3 (n=24), or cervical carcinoma (CA, n=21) were analyzed for amplification of hTERC using a two-color fluorescence in situ hybridization (FISH) probe, and for HPV-DNA using HC2. 53 of them were taken biopsy to analyze telomerase activity using telomeric repeat amplification protocol (TRAP) and expression of hTERT using immunohistochemistry (IHC). The results were statistically compared with the histologic diagnoses.

Results: Amplification of hTERC was significantly associated with the histologic diagnoses (p< 0.05). The positive cases with hTERC amplification differentiated those histologically diagnosed as high-grade dysplasia (CIN2/3) from those diagnosed as low-grade dysplasia (CIN1) or normal (P=0.03). A marked increase in the accumulation of HPV& hTERC positive cases was observed in the CIN3 subgroup compared with the CIN2 group, 25% versus 62.96%, respectively (p=0.007).

Conclusions: FISH can be performed on exfoliated cervical cells to detect amplification of hTERC. Detection of hTERC amplification combined with HPV test can function as an effective method to distinguish high-risk cervical lesions from low-grade lesion.
ANTIBIOTIC USE AND RISK OF GYNECOLOGICAL CANCER

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Background: Several studies addressed the association between antibiotic use and breast cancer risk. The objective of this study was to assess the association between antibiotic use and risk of cervical, ovarian, and uterine cancer.

Methods: We carried out a population-based case-control study using data from Saskatchewan Health administrative databases (Canada) between the years 1981 and 2000. Cases were matched to 4 controls, using incidence density sampling. The effect of dosage and timing of antibiotic use, over a minimum of 15 years before diagnosis, on cervical, ovarian, or uterine cancer risk was assessed. Number of prescriptions and number of pills were used as exposure definitions. The effect of different classes of antibiotics on cancer risk was also studied.

Results: A total of 1,225 cancer cases [192 cervical, 445 ovarian, and 588 uterine] and 4,900 matched controls were included in this study. Antibiotic exposure (number of prescriptions) during the period of 1-15 years in the past was significantly associated with a reduced risk of cervical cancer; Relative Risk (RR) = 0.40, 0.31, 0.26, and 0.29 for the four exposure quartiles, respectively. No association was found for ovarian or uterine cancer. When number of pills was considered, similar results were found. There was no effect of the timing or class of antibiotic exposure on cervical cancer risk.

Conclusion: Antibiotic exposure up to 15 years in the past was associated with a decreased risk of cervical cancer. The lack of temporal trends and the absence of class specific effects suggest a non-causal relationship.
IRINOTECAN AND CISPLATIN FOR NEUROENDOCRINE CARCINOMA OF THE UTERINE CERVIX

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Aims: Neuroendocrine carcinoma of the uterine cervix is a rare tumor with very aggressive clinical behavior. To date, there is no consensus on the best chemotherapy regimen. Our purpose is to evaluate the efficacy and feasibility of a combination therapy with irinotecan and cisplatin for neuroendocrine carcinoma of the uterine cervix.

Patients and methods: From 2002 to 2009, 10 patients with neuroendocrine cervical carcinoma (7 small cell carcinoma and 3 large cell neuroendocrine carcinoma, Stages IB1-IIIB) were treated at Osaka Medical Center for Cancer and Cardiovascular Diseases. Four patients underwent radical hysterectomy followed by adjuvant chemotherapy with irinotecan and cisplatin. Five patients underwent radical hysterectomy followed by CCRT. In remaining one patient, radical hysterectomy was done after CCRT. Chemotherapy for all patients included irinotecan hydrochloride, 60mg/m² on day1,8,15 by intravenous infusion over 60min, plus cisplatin, 60mg/m² on day1. This regimen was repeated 6 cycles every 28 days.

Results: All of 5 patients who completed their adjuvant chemotherapy with irinotecan and cisplatin did not recur. On the other hand, three patients who could not complete died of their disease. Grade 3 or 4 the neutropenia was observed in 70% of the patients. Both grade 3 of anemia and grade 2 of diarrhea were observed in 10%. Neutropenia was the dose-limiting toxicity with 3 of 5 CCRT patients requiring a discontinuation of chemotherapy, 5 of 5 chemotherapy patients requiring dose reduction.

Conclusion: Although our study included small number of the patients, this regimen seems to be clinically active for neuroendocrine cervical cancer.
RADICAL Hysterectomy FOR FIGO STAGE IB-IIB ADENOCARCINOMA OF THE UTERINE CERVIX

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A retrospective analysis was performed to identify risk factors for survival and relapse in patients with FIGO stage IB-IIB cervical adenocarcinoma (AC), who underwent radical hysterectomy, and to compare outcome and spread pattern with those of squamous cell carcinoma (SCC). One hundred and twenty three FIGO stage IB-IIB patients with AC and 455 patients with SCC, who all underwent primary radical hysterectomy, were reviewed. Among the patients with AC, Cox model identified tumor size (95% CI 1.35-30.71) and node metastasis (95% CI 5.09-53.44) as independent prognostic factors in survival, and infiltration to vagina (95% CI 1.15-5.76) and node metastasis (95% CI 6.39-58.87) as independent prognostic factors for relapse. No significant difference was found in survival or relapse between the AC and SCC groups, after adjusting for other clinicopathological characteristics using Cox model. No significant difference was found in the positive rates of lymph nodes or location of initial failure sites between the two groups, but ovarian metastatic rate was significantly higher in the patients with pathologic stage 2b AC (p = 0.02). Positive node is a common independent prognostic factor for survival and relapse of patients with AC. FIGO stage IB-IIB patients with AC or SCC, who underwent radical hysterectomy, have similar prognosis and spread pattern, but different ovarian metastasis rates.
ROLE OF HIGH-RISK HUMAN PAPILLOMAVIRUS TESTING IN THE SCREENING AND MANAGEMENT OF CERVICAL CANCER PRECURSORS

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Objectives: To evaluate the efficacy of HPV test using Hybrid Capture II method in women whose Pap test indicated abnormal result.

Methods: Randomly selected 9885 women from the St. Vincent Hospital at The Catholic University of Korea were performed HPV test and underwent LEEP who showed abnormal PAP test. The HPV, in vitro hybridization assay (HC II HPV DNA test, Digene), testing for high risk type (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) of HPV was performed, and the results were compared with follow-up biopsies.

Results: Among the 9885 women 7128 women showed HPV test negative and 2757 women showed HPV test positive. Three-hundred fifty women who showed abnormal PAP test were performed LEEP. Among them the positive rate of HPV test is 96% (339/350). This included 20 women with negative, 160 women with inflammation, 16 women with CINI, 48 women with CIN2/3, 74 women with CIS, and 16 women with cervical cancer, and other 16 women with cervical benign lesions such as cervical poly. The sensitivity of the HPV testing for predicting worse than high-grade cervical intraepithelial neoplasia (CIN 2/3) also increased with higher grades of cytology diagnoses. A positive predictive value of 40.7%, and negative predictive value of 100% for predicting worse than CIN 2/3 lesion were observed in the abnormal PAP test group.

Conclusion: Using the HPV test with Pap specimens, the HPV has the sufficient sensitivity and HPV is useful tool for predicting CIN or cancer.
HPV INFECTION AMONG PATIENTS WITH HIGH GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA AND SQUAMOUS CELL CARCINOMA OF CERVIX IN IRAN

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Background: Cervical cancer is the second most common cancer of the women worldwide. Nearly half million of new cases are identified yearly. The incidence rate in developing countries is greater than the developed countries. The aim of this study was to determine the frequency of HPV in patients with CINIII, CIN II and SCC of cervix.

Methods: Hundred specimens from patients with SCC and CINIII, CIN II, confirmed by histological review, referring to Women's Hospital from 1999-2004 were enrolled in a cross sectional study. Polymerase chain reaction was utilized for identification and typing of HPV DNA. To increase the sensitivity of HPV detection, nested PCRs were performed using MY09/MY11 as outer and GP5/GP6 as inner primers.

Results: It was possible to extract 77 of 100 specimens that HPV DNA was detected in 47 of 77 specimens. Infection with HPV was present in 32 specimens (86.5%) among SCC patients and in 15 specimens (37.5%) among CINIII, CIN II patients. The most frequent HPV types in SCC patients were HPV 16 and 18 (59.38%) and then 33 (34.38%) and in CINIII, CIN II patients was 16 (53.33%) and 18 (40%). The most frequent co-infection in both groups was HPV 16 and 18 which was present in 40.62% and 26.7% of cases respectively.

Conclusions: The most frequent HPV types in patients with SCC and CINIII, CIN II was 16 and 18 that is identical to many other countries infection pattern.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

HPV TYPE DISTRIBUTION IN INVASIVE CERVICAL CANCER AND HIGH-GR ADE CERVICAL LESIONS IN KOREA

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Background: Implementation of vaccination against oncogenic HPV types together with cervical screening is expected to significantly reduce the burden of cervical cancer. To estimate the potential impact of HPV vaccines in Korea, data on HPV type distribution in cervical cancer and high-grade pre-invasive cervical lesions are needed.

Objectives: To evaluate the prevalence of HPV-16, -18, and other oncogenic HPV types in Korean women with invasive cervical cancer (ICC), cervical intraepithelial neoplasia (CIN) II/III or cervical adenocarcinoma-in-situ (AIS).

Methods: Korean women >21 years old diagnosed with ICC or CIN II/III/AIS were prospectively enrolled. Cervical specimens collected during routine clinical procedures were reviewed to confirm the presence of lesion and tested for HPV DNA.

Results: HPV DNA was detected in 95.9% (93/97) of ICC specimens and all 100 CIN II/III/AIS specimens. Among ICC patients, 84.5% harboured single HPV type infection, HPV-16 (64.6%), -18 (13.4%), and -33 (7.3%) were the most frequently identified types. Multiple HPV types were identified in 7.2% of ICC patients. Among CIN II/III/AIS patients, 77.0% had single HPV type infection, HPV-16 (37.7%), -58 (13.0%), and -31 (10.4%) were the commonest types. Multiple HPV types were detected in 20.0% of CIN II/III/AIS patients. Unidentifiable HPV types were found in 4.1% and 3.0% of ICC and CIN II/III/AIS patients, respectively.

Conclusions: HPV-16 and -18 were detected in the majority of Korean women with ICC in this study. Vaccination against oncogenic HPV types including and beyond HPV-16/18 is expected to significantly reduce the incidence of cervical cancer in Korea [Study ID: 110676].

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MANAGEMENT OF ‘NORMAL’ COLPOSCOPY IN THE PRESENCE OF HIGH-GRADE CYTOLOGICAL ABNORMALITY

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Aims: To compare the histology results in patients with a negative colposcopy in patients with a high grade smear and assess the management options.

Background: Colposcopy as a screening tool alone is questionable; the results are operator dependent, subjective, or sometimes inconclusive especially in low grade disease. In patients with high grade cytological abnormality, there is a good correlation between high grade smears and colposcopic findings. In this study we aim to determine the prevalence of ‘normal’ colposcopy in the presence of a high grade cytological abnormality.

Methods and results: Inflofex® database was searched for patients referred with a moderate or severe dyskaryosis smear to our colposcopy clinic between 01/01/2001 and 31/12/2009. During the study period, there were 9237 patients referred to the clinic. Of these there were 1388 (15%) patients with high grade smears. 64 (4.6%) had a satisfactory normal colposcopy. 8 (12.5%) patients had no biopsy and had negative follow-up smears. 76 (87.5%) patients had a loop biopsy. 15 (23.4%) patients had no CIN, 11 (17.1%) had CIN 1 and 29 (45%) had CIN 2 or 3.

Conclusion: In our study population, 4.6% women have a ‘normal’ colposcopy in the presence of a high grade cytological abnormality. 45% of these patients have a high grade CIN on histology.
HIGH RISK HUMAN PAPILLOMA VIRUS PREVALENCE AND ITS RELATION WITH ABNORMAL PAP TEST: A TURKISH UNIVERSITY HOSPITAL EXPERIENCE

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Aims: In our country, studies of cervical high risk human papilloma virus (hrHPV) prevalence and relation of HPV with cervical cytological abnormalities are very limited. We aimed to investigate hrHPV prevalence among Turkish women.

Materials and methods: Cervical samples for cytological screening were collected from 501 women who admitted to our outpatient clinic and hrHPV testing was performed by Digene hybrid capture 2. hrHPV prevalence and its relation with cytological results and epidemiologic data were analyzed by SPSS.

Results: The prevalence of hrHPV was 4.2 percent (21 of the 501 women). Women with abnormal cytological screening results have significantly higher risk of hrHPV positivity compared to women with normal cytological results (19% vs. 3.5%) (p≤.01). The incidence of HPV infection was only associated with number of sexual partners, but there was no association with age, contraception methods or age at the first sexual intercourse. The prevalence of hrHPV among histological-confirmed CIN 1, CIN 2 and normal cases were found 37.5%, 25% and 25% respectively.

Conclusion: Our results showed that only 19% of patients with abnormal cytological result and 4.2% of all patients have hrHPV. These low frequencies suggested that reflex cytology which described as HPV testing using alone to screen, and reserve cervical cytology as a way to determine which HPV-positive women require additional follow-up or colposcopy may be useful in our population. Thus, requirement of Pap test may be decreased dramatically. However, further studies with a larger sample size are needed to suggest our comments.
ABDOMINAL RADICAL TRACHELECTOMY IS AN OPTION FOR FERTILITY-SPARING SURGERY IN WOMEN OF REPRODUCTIVE AGE WITH EARLY STAGE CERVICAL CARCINOMA

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Objectives: The purpose of this study was to describe the surgical outcome and prognosis of women who underwent a fertility-sparing abdominal radical trachelectomy for early stage cervical carcinoma.

Methods: A prospectively maintained database of abdominal radical trachelectomy procedures was analyzed.

Results: Between 2006 and 2009, we performed a total of 21 fertility-sparing abdominal radical trachelectomies for patients with FIGO stage Ia1 to Ib1. Median time of operation was 274 min (range, 175-338). Median estimated blood loss was 350 ml (range, 150-988 ml). No recurrences were observed so far. One patient was able to conceive spontaneously and she was delivered by Cesarean section at 30 weeks’ gestation.

Conclusion: For patients with early cervical carcinoma who desire to preserve reproductive function, abdominal radical trachelectomy is a feasible operation.
BOTRYOID Rhabdomyosarcoma of the Uterine Cervix: A Case Report

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Rhabdomyosarcoma (RMS) is an extremely rare malignancy, derived from primitive mesenchyme that retained its capacity for skeletal muscle differentiation.

Nearly half of all cases occur in children younger than 5 years, with a slight male predominance. The head and neck are the most frequent sites of origin (35-40%), followed by the genitourinary tract (20%).

According to the Intergroup RMS Study (IRS) Group, this tumor is classified into three histological subtypes: embryonal, alveolar and undifferentiated. The embryonal subtype is the most common one (58%), with classic, botryoid and spindle cell variants.

Botryoid RMS, the most common variant of embryonal subtype, accounts for the majority of primary lesions of the female genitourinary tract and is associated with a very favorable prognosis (95% survival at 5 years). It typically appears in the vagina during early childhood (mean age 3 years) but, in rare cases, it can occur in the cervix or uterine fundus, with a peak incidence in the second decade and postmenopausal years, respectively.

We report a case of cervix botryoid RMS presenting as a cervical polyp in a 20-year-old female, treated with radical surgery and adjuvant chemotherapy, with a favorable outcome.
OUTCOME OF PATIENTS WITH ATYPICAL GLANDULAR CELLS DIAGNOSED DURING PREGNANCY

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Objectives: The incidence of cervical adenocarcinoma is increasing. Due to trend of increasing age of pregnancy, higher number of cytological smears are interpreted as AGC in early pregnancy. While conservative management of squamous precancer lesions in pregnancy is considered safe, the optimal management of AGC is not well established. The aim of our study was to evaluate outcome of patients with AGC found during pregnancy.

Methods: Study included 17 patients who were referred to in early pregnancy with cytological diagnosis of AGC (AGC - NOS (n=11), AGC - FN (n=5) or AIS (n=1)). All women with high risk smears were initially examined by expert colposcopy and transrectal ultrasound to exclude invasive endocervical cancer. Follow up controls proceed every 8 weeks and if there were no signs of progression, reevaluation was scheduled 6-8 weeks after delivery.

Results: Cone biopsy in one patient was performed in 16th week of pregnancy due to colposcopy signs of microinvasive squamous cancer. Progression to invasive cancer was not found in any of other 16 cases from which 12 (all with AIS and AGC-FN and all HPV positive AGC - NOS patients) underwent cone biopsy after puerperium. Histopathology results were as follows: AIS (n=1), CIN 1 (n=1), CIN3/CIS (n=6, one case with concomitant high grade CGIN) and benign changes (n=4).

Conclusions: Conservative management of women with AGC in pregnancy is safe if invasive cancer is excluded. As histopathology verification of glandular precancerous lesions by minibiopsy is not reliable, postpartum regression rate can not be exactly determined.
HIGH-RISK HUMAN PAPILLOMAVIRUS DNA IN PARAAORTIC LYMPH NODES IN ADVANCED STAGES OF CERVICAL CARCINOMA

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Background: Paraaortic lymph nodes represent the second level in the lymphatic spread of cervical cancer. Recent studies have confirmed the association of HPV DNA in pelvic lymph nodes in early-stage disease with metastatic involvement and a less favourable prognosis.

Objective: The aim of our study was to detect 13 high-risk genotypes of HPV in paraaortic nodes harvested from patients with FIGO IB2 - IIIB tumours and correlate findings with histopathology.

Study design: The study involved patients with advanced cervical cancer who had undergone low paraaortic lymphadenectomy. The cytobrush technique was used for perioperative sample collection from the tumour and fresh lymphatic tissue to avoid any loss of material for histopathology.

Results: The study involved 24 patients. High-risk HPV DNA was found in the primary tumour of all cases. The most frequent genotype was HPV 16, both in the tumour and in the paraaortic lymph nodes (83.3% and 54.2%, respectively). Metastatic involvement of paraaortic lymph nodes was identified in 8 cases (33.3%), which all were also HPV DNA positive, with correspondence of at least one genotype between the tumour and the nodes.

Conclusions: Using the cytobrush technique, the presence of at least one HR HPV genotype in the primary tumour was identified in all the patients. The metastatically involved paraaortic lymph nodes always contained the DNA of at least one HPV genotype present in the primary tumour. Determination of clinical significance of HR HPV DNA presence in histologically negative lymph nodes requires further follow-up of the cohort.
NERVE-SPARING OKABAYASHI RADICAL TRANSABDOMINAL HYSTERECTOMY (NORTH) AND ITS LAPAROSCOPIC APPLICATION


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We report the surgical and urinary outcomes of nerve-sparing Okabayashi radical transabdominal hysterectomy (NORTH) and laparoscopic nerve-sparing radical hysterectomy (LNRH) according to Shingo Fujii’s style. We performed 5 cases of NORTH and 6 cases of LNRH between January 2008 and February 2010. The way to spare nerves is to preserve both pelvic splanchnic nerves just below deep uterine veins and bladder branches of inferior hypogastric nerves by doing fine dissection. Median age was 49 years old (range 27-72). The stage was between Ia2 and IIb. Median length of operation was 6 hours 20 minutes in NORTH (range 5 hours - 8 hours 20 minutes) and 7 hours 50 minutes in LMRH (range 6 hours 20 minutes - 9 hours 15 minutes). Foley catheter was clamped on the 5th day after surgery and all patients felt sense of bladder fullness (median 6th days, range 5th - 13th day). Foley catheter was removed on the 7th days (range 6th - 21th days) after surgery. Eight out of 11 patients (72.7%) made a successful voiding between 8th and 10th days after surgery. Postoperative complication was ureter stricture in one case. A stage IIb patient had concurrent chemoradiation and the others had no adjuvant treatment. Median follow-up was 15 months (range 4 - 29 months) and all the patients have no evidence of disease as yet. In conclusion, the successful urinary outcome of NORTH and LNRH according to Shingo Fujii was able to be reproduced. Especially laparoscopic application of NORTH was feasible.
A 'SEE AND TREAT' POLICY FOR REFERRAL SMEARS SUGGESTIVE OF MODERATE DYSKARYOSIS: IS IT JUSTIFIED?

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Objective: To assess a "see and treat" policy for referrals with a moderate dyskaryosis smear.

Background: The NHSCSP guidelines states that, "Treatment at first visit for a referral of borderline or mild dyskaryosis should only be used in exceptional cases, and only when audit has identified that CIN is present in ≥ 90% of the excised specimens". There is no guidance for women presenting with moderate and severe dyskaryosis on referral smears. Whilst literature suggests 95% correlation between cytology and histology for a severe dyskaryosis referral, there is controversy regarding management of smears suggestive of moderate dyskaryosis. In this study we determine the yield of CIN when a 'see and treat' policy is employed for such referrals.

Method: A thorough search of our INFOFLEX® database between 01/01/2001 and 31/12/2009 was performed. All the cases of moderate dyskaryosis on referral smear treated with a loop biopsy at their first visit were included and histology reports were analysed.

Results: There were 9237 patients referred during the study period. There were 1388 (15.0%) patients with moderate dyskaryosis. Histology revealed 935 (68.5%) cases of high-grade CIN, 199 (14.3%) cases of low-grade CIN and in 131 (9.4%) cases, there was no evidence of CIN. There were 13 cases of micro invasion or glandular changes.

Conclusion: In our study population, a "see and treat" policy for patients with moderate dyskaryosis on referral smear is appropriate.
EXPRESSION OF CYCLIN G1 IN CERVICAL CANCER AND ITS RELATIONSHIP WITH THE SUB-GENOTYPES OF HPV

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Objective: To study the expression of cyclin G1 and its correlation with the sub-genotypes of HPV in different patients with normal cervical tissue, CIN or cervical cancer.

Methods: Flow-through hybridization and gene chip (HybrMax) was used to detect the sub-genotypes of HPV in the desquamated cervical epithelial cells and immunohisto-chemistry was used to detect the expression of cyclin G1 protein in the cervical tissure from the same patients, which include 20 cases of normal cervix uteri, 44 cases of CIN and 28 cases of cervical cancer. The potential correlation between cyclin G1 and HPV was also studied.

Results: In normal cervical tissue, CIN and cervical carcinoma, the positive-expression rate of cyclin G1 were gradually increased (the differences in each pairs of group were statistically significant, p<0.05). The infection rates of HPV, HR-HPV and HPV16 were all gradually increased (p<0.05). As well, in cervical carcinoma, the expression rate of cyclin G1 had positive correlation both with the infection rate of HR-HPV (r=0.382, p=0.045) and with the infection rate of HPV16 (r=0.519, p=0.005).

Conclusions: The overexpression of cyclin G1 might play an important role in human cervical tumorigenesis. A synergistic interaction between cyclin G1 and HR-HPV might benefit to the tumorigenesis of human cervical carcinoma.
THE CLINICAL SIGNIFICANCE OF DETECTION HPV GENOTYPES BY USING FLOW THROUGH HYBRIDIZATION AND GENE CHIP

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Objective: To discuss the distribution of human papillomavirus subtypes in south-eastern of China and the clinic significance.

Methods: In 2008.7-2008.12, 523 cases were involved in the analysis. The flow through hybridization and gene chip (HybrMax) was used to detect the subtypes of HPV.

Results: 1) In total 523 cases, 182 cases were detected with either HPV single type or multi types infection. About 31.4% were detected with single HPV subtype infection and 4.8% were detected with HPV multi subtypes infection. 2) In different age group, the infection of different HPV subtypes was different. The peak incidence of high-risk HPV infection was detected in patients with 20-29 yrs old and 50-59 yrs old. Infection of signal subtype of HPV was about 34.9%, while the diploid infection of HR-HPV or multi infection of HPV was about 2.4%-2.9%. 3) In the HPV infected population, prevalence of high cervical lesion(85/189, 45.0%) was significant higher than it in HPV negative population (32/334, 9.6%, P=0.02)

Conclusion: Using HybrMax to detect the subtypes is a suitable technology to screen the potential cervical lesion. And detection of HPV is a screen method to diagnose the high-grade cervical lesion.
THE ANALYSIS OF THE IMMUNE RESPONSE WITH REFERENCE TO THE PEPTIDE FROM HUMAN PAPILLOMAVIRUS TYPE 16-L1 IN THE CERVICAL CANCER

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Cervical cancer is the second most common malignant tumor among women worldwide.

It is estimated that the approximately 8,500 new cases and 2,500 deaths occur each year in Japan. It is widely known that prolonged infection of human papilloma virus (HPV) infection is the cause of cervical cancer. Because HPV virus like particle (VLP) vaccine was approved as a prophylactic vaccine for cervical cancer, many interests are focused on immune response against HPV. Although HPV-E6 and E7 are the main factors for carcinogenesis in cervical cancer, it was suggested that riant factor in the cacinogenesis.ancerL1, the capsid structure of HPV, possibly become the carcinogenesis factor in animal model. Therefore, we analyzed the immune response in relation to peptides from HPV 16 L1 which would bind to HLA-A24 because HLA-A24 is the most common HLA type in Japanese. The 10 peptides derived from HPV type 16 L1 were prepared based on the binding motifs to HLA-A24. Anti peptide antibody (peptide-specific immunoglobulin G) in plasma was measured by the micro suspension array in women who got HPV VLP vaccine, women who are negative for HPV and cervical cancer women. Titer of anti peptide antibody against two peptides was elevated in vaccinated women. The specificity of IgG against these two peptides was confirmed by competition assay in vaccinated women. These findings indicated that these two peptides derived from HPV 16 L1 have the possibility to become the influential peptides as therapeutic vaccine and biomarker of immune response against HPV.
MODERN TENDENCIES IN EARLY FINDING AND SCREENING OF CERVICAL PRECANCER AND CANCER

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Objective: We tried to summarize our and foreign experience in prophylaxis, early finding and screening of cervical precancer and cancer.

Methods: We assessed the methods, which are used for early finding of precancer lesions: colposcopy, cytology and biopsy.

Results: The main method of screening of cervical precancer and cancer - the cytological method was researched. We characterized the PAP smear groups. The grading of Cervical Intraepithelial Neoplasia (CIN I, CIN II, CIN III) and the way it is treated was defined. We showed the depth of invasion of cervical microinvasive cancer and the radicality of the surgical treatment. The LBC cytological screening method and its effectiveness was discussed.

Conclusions: We showed some new screening methods and programs (opportunistic screening) which are used for early finding of cervical precancer and cancer.

Keywords: Cytological screening, cervical precancer and cancer; treatment possibilities.
COMPARISON OF CERVICAL SMEAR RESULTS RECEIVED BY DOCTORS AND RECEIVED BY SERVIKS® SELF-SMEAR TEST KIT

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The purpose of Pap smear test is to screen for intraepithelial lesions before they progress to invasive disease. Patients have come to expect the Pap test to have 100% sensitivity. Many women and also many clinicians do not realize that Pap smear is just a screening test and is subjected to limitations.

Methods: 194 patients who apply for gynecological examination to University because of various reasons, were included in the study. Their age were between 19 and 67 (med. 38.1). Patients participated were informed how to take the smear with the Serviks® Self Smear Test kit when they left alone in the examination room. After that, all the same patients had conventional pap smear test using the cytobrush for control by the same gynecologist.

Results: By either way, all the smears taken, contained cervical cells. Total of 33 smears which were received by doctors did not contain endocervical cells and smear samples which was taken by SERVIKS® SST, 68 did not contain endocervical cells. According to these results, the endocervical smear detection rate is 156/189 (82.53%) in the doctor received group. Received by SERVIKS® SST the detection rate is 121/189 (64.02%).

Conclusion: Cytobrush has to be the gold standart method achieving the endocervical cells but the SERVIKS® SST kit can be used as a screening test by the patient’s who can not apply to doctors at rural areas or who are afraid to go to the gynecologist.
LOW DYNAMIN 2 EXPRESSION IS ASSOCIATED WITH TUMOR INVASION AND METASTASIS IN INVASIVE SQUAMOUS CELL CARCINOMA OF CERVIX


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Dynamin 2 is known as a protein involved in cell migration and endocytosis. We aimed to investigate the association between dynamin 2 expressions and tumor progression in early cervical carcinoma (IB1-IIA). Dynamin 2 expression was evaluated at protein level in thirty seven paraffin-embedded, formalin-fixed tissues including four normal cervix tissues and compared with pathologic risk factors for recurrence after surgery in thirty three patients with squamous cell carcinoma of the cervix. The expression of dynamin 2 was not different according to clinical stage and lympho-vascular space invasion. However, there were inverse correlations between dynamin 2 expression and depth of invasion in cervix (P = .003) and lymph node (LN) metastasis (P = .001). To evaluate mechanism of dynamin 2 in tumor invasion and metastasis, we performed in vitro experiment with dynamin 2 siRNA using several cervical carcinoma cell lines such as HeLa, MS751 and SiHa cells. We found the inhibition of dynamin 2 using specific siRNA enhanced the expression of matrix metalloproteinase-2. These results suggested that dynamin 2 might be involved in preventing tumor invasion and LN metastasis, possibly in relation with extracellular matrix degradation, and may be a prognostic marker for these risk factors in early squamous cell carcinoma of the cervix.
THE EVALUATION OF PROGNOSTIC FACTORS AND EFFECTS OF ADJUVANT THERAPY ON OUTCOMES OF EARLY STAGE CERVICAL CANCER

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Aim: To investigate the clinical and histopathological characteristics and the pretreatment that might predict prognosis and to evaluate the impact of postoperative adjuvant therapy on the outcomes of patients with early stage cervical carcinoma.

Methods: A total of 203 patients with stage IB and stage II cervical cancers treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy were reviewed at the Vali-Asr University Hospital from 1995 to 2002. The median follow-up period was 42 months.

Results: The depth of cervical stromal invasion, clinical stage, histology of pure adenocarcinoma and lymph node (LN) status were important histopathological prognostic factors of cervical carcinoma. Among the patients with pelvic lymph node metastases who were free of parametrial extension, those who received postoperative chemo-radiotherapy had significantly better RFS (p=0.021) and OS (p=0.030) than those who received no adjuvant therapy. Also of the patients without pelvic LN metastases but at a high risk of recurrence, the individuals who received adjuvant radiotherapy had a significantly more favorable RFS (p=0.038) and a marginally improved OS (p=0.064).

Conclusion: RFS is significantly improved with radiotherapy in patients who are without pelvic lymph node metastases but who are in a high risk group for recurrence.
COLPOSCOPY: CYTOLOGY: HISTOLOGY CORRELATION AT THE CERVICAL PATHOLOGY UNIT IN FUNDACIÓN LÓPEZ PEREZ (SANTIAGO CHILE). DIFFERENCES BETWEEN RESIDENTS

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Introduction: After performing cervical screening tests, colposcopy is still the study method of choice. Thus, it is important to have a continuous assessment of its diagnostic precision at any institution. The aim of this study is to evaluate our unit's and our residents' level of diagnostic precision and the colposcopy: cytology: histology correlation.

Methods: Prospective analysis of the patients assessed at our colposcopy unit and their diagnosis, making a correlation between the colposcopic diagnosis and the histologic diagnosis after the LEEP cone biopsy. We also studied the diagnostic correlation between diagnosis made by first and second-year gynecologic oncology residents.

Results: Of the 330 LEEP cone biopsies performed, there was an 88.7% correlation for a patient with an initial PAP smear showing CIN II-III, and 78.9% for patients with an initial PAP smear showing CIN with HPV. The correlation was 63% for patients with an ASCUS PAP smear. The correlation for HGSIL/invasive carcinoma for the first-year resident was 62.7% and of 70.3% for the second-year resident. The sensitivity and specificity of colposcopy as a diagnostic method for HGSIL and invasive carcinoma was 78.9% and 87.2% respectively.

Conclusions: Our unit has a colposcopy: cytology: histology correlation similar to that described in international literature. There were differences between the colposcopy: cytology: histology correlation between the first and second-year residents.
A STUDY OF CHRONIC PELVIC PAIN AFTER RADIOTHERAPY IN SURVIVORS OF LOCALLY ADVANCED CERVICAL CANCER

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**Purpose:** In quality of life (QOL) research of cervical cancer survivors (CCSs), there is a lack of studies investigating associations between self-reported pelvic pain and mental problems like anxiety and depression, and physical problems in pelvic organs (bladder and intestines). The aim of this study was to describe chronic pelvic pain and associated variables in CCSs surveyed > 5 years after radiotherapy. Prevalences of pain in hips and lower back were compared to corresponding figures in the general female population.

**Methods:** Ninety-one CCSs treated with radiotherapy between 1994 and 1999 were in 2005 included in a cross-sectional questionnaire-study. They were asked about demographic variables, clinical symptoms, mental distress, and QOL. Normative data (NORM) was acquired from a population study of Norwegian females.

**Results:** Pain in lower back and hips was significantly higher (p < .001) in CCSs compared to NORMs. One third (35/92) of the CCSs suffered from chronic pelvic pain. CCSs with chronic pelvic pain had a significantly lower QOL, higher levels of anxiety and depression, and more bladder and intestinal morbidity than those without such pain. In a multivariable regression model, use of analgesics and intestinal and bladder morbidity were significantly associated with chronic pelvic pain in the CCSs.

**Conclusions:** Pain in lower back and hips is more prevalent in CCSs than in women in the general population, which might be due to late effects of radiation. 35/92 (38\%) of the CCSs suffer from chronic pelvic pain, shown to be associated with high overall mental and somatic morbidity.
CERVICAL CANCER IN CROATIA: THE IMPORTANCE OF PUBLIC EDUCATION CAMPAIGN FOR CERVICAL CANCER PREVENTION

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In Croatia, invasive cervical cancer (ICC) continues to be the eighth most common malignancy in women. In 2007, there were 387 newly detected ICC cases and 114 related deaths (age-standardised rates for incidence -11.5/100 000 and mortality - 3.0/100 000). Although the opportunistic screening by Pap smear has been conducted since 1950s, Croatia continues with unfavourable trends in ICC mortality compared to other European countries. A downward ICC incidence trend recorded between 1970 and 1991 has been stopped and reversed upwards. The highest incidence rates of ICC and CIN III are reported in age groups 40-59/80-84 and 30-34, respectively.

The Croatian National Program for Early Detection of Cervical Cancer planned to start in 2011, envisages Pap smear for women aged 25-64 once at 3 years, and also includes public education, targeted primarily at youth, about protection against sexually transmitted infections (STIs), especially HPV infections as the major cause of ICC.

In the meantime, during the European Cervical Cancer Prevention Week, the Croatian League Against Cancer regularly organizes Mimosa Day, using this fragile symbol of female solidarity to remind women all around Croatia of the importance of cervical cancer education, vaccination and regular screening, thus raising public awareness in this matter to achieve better protection against STI, higher vaccination coverage, and larger (at least 80%) response to gynaecological screening. The result is a 15% increase in gynaecologic visits in Zagreb during the first 3 months following the campaign, which certainly contributes to a reduction of cervical cancer in Croatia.
CARCINOSARCOMA OF THE UTERINE CERVIX WITH CLEAR CELL ADENOCARCINOMA COMPONENT


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Carcinosarcoma of the uterine cervix is an extremely rare neoplasm and little information is available concerning its clinical character, treatments and prognosis. We report a case of cervical carcinosarcoma with clear cell adenocarcinoma components and its clinical, pathological, and immunohistochemical features. The patient was a 47 year-old woman who presented watery vaginal discharge. A tumor was found in her cervix and the biopsies of the tumor showed the mixture of the adenocarcinoma cells and mesenchymal malignant cells. The diagnosis of cervical carcinosarcoma was made and a modified radical hysterectomy was performed. Pathological examination of surgical specimens demonstrated the existence of clear cell carcinoma components mixed with the mesenchymal malignant tumor. Three courses of postoperative chemotherapies concurrent with the whole pelvic irradiation plus brachytherapy were performed. She remains free of disease at 31 months after the last treatment. Although it is difficult to determine the optical therapy for this rare tumor, aggressive primary therapies according to high risk cervical carcinoma might be appropriate for the cure of cervical carcinosarcoma.
INDIVIDUALIZED FOLLOW-UP FOR EARLY DETECTION OF CERVICAL CANCER BY HUMAN PAPILLOMAVIRUS (HPV) TESTING IN CASES OF ASCUS, LSIL AND HSIL

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Objective: To investigate the clinical usefulness of the combination of conventional cytology with high-risk (hr) human papillomavirus (HPV) test to individualize follow-up management for the patients with cervical intraepithelial neoplasia (CIN).

Methods: We examined seven types of hr-HPV (type 16, 18, 31, 33, 35, 52, 58) by type specific PCR and restriction fragment length polymorphism (RFLP) among 1786 patients during the follow-up period from April 2000 to March 2008 at Hokkaido cancer society cytoscreening center. Patients were diagnosed as ASCUS, LSIL or HSIL by cytology (ASCUS:73, LSIL:1048, HSIL:665). We analyzed the relation between the type of hr-HPV and the progression rate and period from ASCUS, LSIL, HSIL(CIN2) to CIN3 or invasive cancer.

Results: 267 patients progressed to CIN3 or invasive cancer in 1590 patients except for 196 who were diagnosed as CIN3 at first visit. The progression rate of hr-HPV-positive cases was 35.7%, significantly higher than that of unclassified HPV-positive cases (19.3%), and HPV-negative cases (4.7%). 30 patients progressed to CIN3 in 1048 LSIL patients. Time to progression of patients carrying type 16, 18, 33 was significantly shorter than that of patients with other hr-HPV (p=0.012). 237 patients progressed to CIN3 or invasive cancer in 469 HSIL(CIN2) patients. Time to progression of HSIL patients with type 16, 18, 33 was significantly shorter than that of patients with other hr-HPV (p=0.003).

Conclusion: We conclude that the progression from CIN depends on the presence and type of hr-HPV, and that HPV typing is a useful information to individualize management of patients with CIN.
SYSTEMIC CHEMOTHERAPY FOLLOWING CONCURRENT CHEMORADIOThERAPY IMPROVED THE SURVIVAL IN PATIENTS WITH LOCALLY ADVANCED UTERINE CERVICAL CANCER

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Methods: From April 2001 to March 2009, 73 patients with cervical cancer were treated with CCRT (weekly CDDP 30 - 40mg/m2). Medical records were reviewed retrospectively.

Results: The median follow-up was 21.5 months (14.8 - 36 months). Paraortic lymphadnopathy was demonstrated by CT scan in 16 patients. Among theses patients ten received 3 - 6 cycles of TAX / CBDCA following CCRT and six received no adjuvant systemic chemotherapy. Among ten patients with systemic chemotherapy four patients (40%) recurred, whereas five patients (83.3%) of six patients without systemic chemotherapy recurred (p 0.006). The sites of recurrences were distant lymphnodes in all cases. The toxicity was tolerable.

Conclusions: An addition of TAX / CBDCA following concurrent chemoradiation improved the prognosis in patients with locally advanced uterine cervical cancer.
OUTCOME AND EVENTS AFTER CERVICAL CANCER TREATMENT: A MONOCENTRIC STUDY FOLLOW UP

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Background: Cervical cancer ranks the second in the list of most frequent cancers in developing countries, which is often diagnosed at higher stages.

Methods: Upon diagnosis and proper treatment, a two-year follow up was performed for 63 patients with different stages of cervical cancer between 2005-2007 in our center. Patients were evaluated regarding to their carcinoma recurrence and morality rate.

Results: The follow-up episode was completed all patients. Stage IIb was the most common clinical stage detected at referral time. Stages Ia1-IIa were diagnosed in 57.1% of patients. Radiotherapy was the most utilized treatment method (47.6%) and the most common event after therapy were vaginal stricture and fibrosis (63.63%). Highest rate of events occurred after radical hysterectomy and chemotherapy treatment method (70%). The recurrence rate in patients for whom radical hysterectomy was planned was more than other treatments (15.4%). Survival rate after 2-year follow up reached to 90.5%, and the least chance for survival after therapy was attributed to utilization of chemoradiation (80%) .

Conclusion: The results of this study suggests that the risk for events after therapy increases with higher age, higher stages of carcinoma, in squamous cell type and combined therapy procedures. Relatively, young age, adenocarcinoma cell type, high stage and surgical therapy alone, increase the recurrence rate. The overall survival rate decreases with age< 60 years, adenocarcinoma cell type, higher stages and chemoradiation treatment.

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ADENOID BASAL CARCINOMA OF THE CERVIX
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Introduction: The adenoid basal carcinoma (ABC) represents less than 1\% of all cancers of the cervix, with no more than 100 cases reported since its first recognition in 1966. It is usually indolent and affects postmenopausal women almost exclusively.

Case report: A 64-year-old patient was referred because of ASC-H in a screening test. She was asymptomatic and colposcopic examination was found unsatisfactory. The patient underwent loop electrosurgical excision. Histologically, the specimen showed squamous cell carcinoma in situ and adenoid basal carcinoma was present in the deep surgical margin. It was decided to carry out total hysterectomy and bilateral salpingo-oophorectomy. Residual lesions were not identified in microscopic examination.

Discussion: The ABC is probably originated within the layer of reserve cells of cervical epithelium. Its four distinctive elements include the presence of classic HSIL, limited invasive component with squamous maturation, small basal cells and focal endocervical differentiation. Histologically, it defines a proliferation of uniform basaloid cells combined with a peripheral palisading arrangement. Mild chromatin abnormalities and rare mitoses are present. The cytological aspect consists of discohesive groups of intact cells with overlapping nuclei and hyperchromasia. The cells are positive for CK14, CK17, CK19, CK KL 1 and EMA, and typically negative for collagen IV and laminin. Genetic studies have demonstrated overexpression of p53 and integration of high risk HPV. The prognosis is favorable, regardless the therapeutic modality. ABC exhibits low potential for recurrence and metastasis. Some authors have suggested the alternative name of adenoid basal epitelioma to highlight its benign natural history.
LEIOMYOSARCOMA OF THE CERVIX
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Introduction: Leiomyosarcoma of the cervix is a rare entity, with fewer than 100 published reports.

Case report: A 42-year-old patient presented with the diagnosis of leiomyosarcoma of the cervix in the surgical specimen. It was a well differentiated tumor, classified as T1a Nx Mx, tangential to the circumferential surgical margin. She had undergone total hysterectomy for menorrhagia and clinical detection of cervical myoma surfacing to the external os. A thoraco-abdominal-pelvic computed tomography showed no signs of adenopathies or secondary lesions. Re-operation was decided due to the patient's young age and the presence of positive margins. Partial colpectomy, parametrectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy were performed.

Discussion: Leiomyosarcoma particularly affects women between 40 and 60 years of age and usually manifests with abnormal uterine bleeding or pelvic pain. These tumors tend to be large, causing expansion of the cervix or protrusion through the cervical canal. Hemorrhage and necrosis are frequent in these poorly circumscribed and relatively soft masses. They show a spectrum of histological subtypes similar to leiomyosarcomas of the uterine body, including epithelioid, myxoid, xanthomatous and osteoclast-like giant cells variants. Given the paucity of data regarding this tumor location, the diagnostic criteria have been extrapolated from the uterine body counterpart. The uncertainty about its natural history has led to different therapeutic strategies. Surgery with adjuvant radiotherapy has been the standard approach, although a role for neoadjuvant chemotherapy has been proposed. The prognosis is generally poor and death is related to the development of distant metastases.
SMALL CELL CARCINOMA OF THE UTERINE CERVIX: A CLINICAL CHARACTERISTICS AND PROGNOSTIC FACTORS OF THE 5 CASES

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Background: To investigate clinicopathologic finding of patients with small cell carcinoma of uterine cervix, and to evaluate the recurrence pattern and survival time of small cell carcinoma of uterine cervix

Methods: The medical records of four patients who were diagnosed with small cell carcinoma of the uterine cervix and whose initial treatment was between January 1990 and December 2009 were studied retrospectively

Results: Patient ages ranged between 43 and 50 years. The clinical stages at diagnosis were Ib, IIA, IIb, IIIa, and IV. All patients presented with abnormal vaginal bleeding. Tumor size at diagnosis was under 2cm in 1 patient and over 2cm in 4 patients. Disease recurred in 3 patients at 5~26 months, persisted in a stage IV patient and all of them died. Through analyzing overall survival time, FIGO stage and tumor size were significant prognostic factors in small cell carcinoma of the uterus

Conclusion: Small cell carcinoma of uterine cervix revealed poor prognosis. Our study found FIGO stage and tumor size were significant prognostic factors in small cell carcinoma of the uterine cervix. Because of limitation of number of patients, further large scaled multicenter studies are needed.

Keywords: Small cell carcinoma of uterine cervix
INTRATUMORAL LYMPHATIC MICRO VESSEL DENSITY (MLVD) AND CLINICOPATHOLOGIC FEATURES OF PATIENTS WITH EARLY STAGE CERVICAL CANCER FOLLOWING RADICAL HYSTERECTOMY

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Introduction: Lymphangiogenesis plays a key role in tumor growth, progression, and metastasis, yet few studies have investigated micro lymphatic vessel density (MLVD) in cases of cervical cancer. The aim of this retrospective study was to evaluate intratumoral MLVD, in addition to other histologic variables, in relation to lymph node metastases and survival of patients with stage IB-IIA cervical cancer following radical hysterectomy.

Methods: Between 2000 and 2008, 144 patients were diagnosed with cervical uterine cancer and underwent radical hysterectomy. Tumor stages for these patients were diagnosed based on criteria of the International Federation of Gynecology and Obstetrics (FIGO) and included 84 stage IB1 cases, 44 stage IB2 cases, and 16 IIA cases. Using an antibody directed against human podoplanin (D2-40), immunohistochemical (IHC) staining was used to measure MLVD. The correlation between MLVD and clinicopathological features of the resected tumors were analyzed.

Results: MLVD was significantly higher in tumors less than 2 cm in diameter (p = 0.001), with ≤1.0 cm of depth of invasion (p=0.007), low stage (p=0.001), with negative lymph nodes (p = 0.05). After multivariate analysis, the predictive factors associated with lymph node metastases were depth of infiltration (p=0.027), LVSI (p< 0.001) and parametrial involvement (p=0.01). For patient death, the predictive factors were FIGO stage (p=0.017), histological type (p=0.010), lymph node status (p=0.031) and histological grade (p=0.041). MLVD was not a predictive variable for lymph node metastasis or death.
TREND IN DISTRIBUTION OF HUMAN PAPILLOMAVIRUS TYPE 58 VARIANTS IN PROGRESSION OF CERVICAL DYSPLASIA IN KOREAN WOMEN

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Objectives: We aimed to analyze the sequence variations of HPV 58, the third most common genotype in Korean women.

Methods: This analysis was part of a prospective study for a hospital-based cervical cancer screening program conducted between January 2002 and July 2006. Data was collected on 1,750 Korean women aged 15-75 years with informed consent. Samples from cervical cytology were collected during clinical examination. HPV genotyping was performed using the HPV DNA oligonucleotide chip. The open reading frames (ORFs) including E2, E6, E7 and L1 of HPV 58 were amplified based on specific primers designed using the HPV prototype (GenBank Accession No. D90400). The sequences of the three regions of interest were obtained by PCR-based cycle sequencing using BigDye Terminator v. 3.1. Sequence reactions were performed on the 3130 Genetic Analyzer and the sequences of the above gene regions were aligned by the computer software SeqScape v.2.5. Distribution of HPV 58 variations with respect to disease severity were examined by the exact Haenszel's linear trend test ($P_{\text{trend}}$) and Fisher's exact test ($P$).

Results and conclusions: 53 of 1,750 women were positive for HPV 58 single infection, of whom 26 were without disease, 20 were with cervical intraepithelial neoplasia (CIN) 1, and 7 with CIN 2 or 3. Altogether, 36 different nucleotide sequence variation were identified with the L1, 20 within E2, 5 within E6, and 10 within E7. Further studies on variants of oncogenic HPVs are necessary, particularly for the purpose of developing more predictive detection methods.
COMPARISON OF PNA BASED ARRAY WITH DNA-BASED ARRAY FOR DETECTING AND GENOTYPING HUMAN PAPILLOMAVIRUS

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Objectives: Pap smear and HPV test are essential for screening of cervical cancer and its pre-invasive lesions. The aim of the study is to determine the superiority of PNA-based array compared with traditional DNA-based array.

Material and methods: A prospective analysis was made of 100 patients who underwent HPV test in Seoul St. Mary's hospital between Jan 2009 and Dec 2009. After informed consent, HPV test was run. We used peptide nucleic acid (PNA) probes (PANArray™ HPV kit; PANAGENE Inc., Daejeon, Korea) which enables the detection and genotyping of HPVs using 32 type-specific PNA capture probes for medically important HPVs. In order to exploit the superior hybridization properties of PNA with target HPV DNAs, we compared the genotyping results of the PNA array to DNA based array and sequencing with MY09/11 PCR products derived from 100 clinical samples.

Results: All tested HPV types showed highly unique hybridization patterns with type-specific PNA probes. We demonstrated the superior specificity, sensitivity, and stability of PNA arrays for HPV genotyping. The results showed that PNA array had more excellent agreement with sequencing than DNA array, except for samples reflecting multiple infections. The results from the PNA array were compared with those of type-specific PCR when discrepant results occurred owing to multiple infections. The results for the PNA array matched those of type-specific PCR in all cases.

Conclusion: Our results suggest that the PNA array represents a reliable alternative to conventional DNA arrays for HPV genotyping, as well as for detection.
DETECTION OF HUMAN PAPILLOMAVIRUS TYPE 16 E7-SPECIFIC T CELLS BY ELISPOT ASSAY

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Objectives: The study aims to evaluate the effect of a human papillomavirus type 16 (HPV16) E7 synthetic peptides on the antigen-specific T-cell response in Carcinoma in situ (CIS) and cervical cancer patients.

Methods: We characterized the HPV-16 E7 specific T-cell epitopes using E7 overlapping peptide pools with peripheral blood lymphocytes obtained from normal healthy donors and HPV-16+ 5 CI patients and 3 invasive cervical carcinoma patients with informed consent. We then analyzed the difference in the HPV-16 E7-specific T-cell immune responses in patients during or after treatment of the lesion by ELISPOT assay.

Results and conclusions: All of CIS patients were underwent loop electrosurgical excision procedure (LEEP) and all of cervical carcinoma patient were type III radical hysterectomy. Analysis of peripheral blood lymphocytes obtained from patients with HPV-16+ CIS and cervical carcinoma showed that the HPV-16+ E7 peptide pool 2-3 (aa 16-55) specific CD4+ T-cell immune response was significantly higher than other peptide pool. The HPV-16 E7 peptide specific T-cell immune response correlates with regression of established HPV16+ lesions and freedom from disease recurrence. Thus, this E7 epitope may be useful for the characterization of HPV-specific immune responses in patients infected with HPV-16 or immunized with HPV vaccines.
THE PROGNOSTIC VALUE OF HAEMOGLOBIN SERUM CONCENTRATION AND WHO STATUS IN CERVICAL CANCER PATIENTS

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The cervical cancer is the fifth cause of morbidity among the women. The WHO (World Health Organization) status and haemoglobin serum concentration before treatment planning in these patients is very often underestimated.

Objectives: The assessment of prognostic value of haemoglobin serum concentration and WHO status in cervical cancer patients.

Material and methods: The retrospective analysis of 142 cervical adenocarcinoma and 242 squamous cell cancer patients, treated between January 1989 and December 1999 at Maria Sklodowska - Curie Memorial Cancer Center in Warsaw, was performed. All patients were treated with surgery and postoperative radiotherapy, or radiotherapy alone. The analysis of the overall (OS) and disease-free survival (DFS) in dependence on the most important clinico-pathological factors, was performed.

Results: The percentage of overall 5-year survival for cervical adenocarcinoma patients achieved 45%, whereas for squamous cell cancer, 62.5%. The difference was statistically significant (p=0.05). Regardless of the other factors, the influence of haemoglobin serum concentration in cervical squamous cell cancer patients in aspect of OS and DFS was statistically significant (respectively p=0.031, p=0.019). The WHO status was statistically significant in aspect of OS and DFS in cervical adenocarcinoma patients (respectively: p=0.002, p=0.005).

Conclusions: The above results should be taken into consideration before treatment planning. It is important to balance the haemoglobin serum level before treatment for cervical squamous cell cancer patients. The proper assessment of the WHO status may be helpful in qualification to proper treatment modality in cervical adenocarcinoma patients.
ANALYSIS OF RESULTS OF INTERSTITIAL BRACHYTHERAPY USING MUPIT IN LOCALLY ADVANCED GYNECOLOGICAL MALIGNANCIES

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Purpose and objective: This prospective study was to assess treatment outcome for patients with locally advanced gynecological malignancies treated with interstitial brachytherapy using Martinez Universal Perineal Interstitial Template (MUPIT) and to study the acute and late side effects after treatment by this technique.

Materials and methods: Two hundred and fifty (350) previously untreated patients with histologically confirmed carcinoma of the cervix (128 patients), vault (97 patients), cervical stump/recurrence (49 patients), vagina (55 patients) and others (21 patients) were treated by combination of external beam radiotherapy using megavoltage radiation to the pelvis to a dose of 4000 to 5000 cGy followed by interstitial brachytherapy using MUPIT between April 2006 to April 2010 at Gujarat Cancer & Research Institute, Ahmedabad. Dose of brachytherapy were 500 cGy X 3 #, 400 cGy X 4 #, 400 cGy X 6 #, or 300 cGy X 6 #. Two fractions per day were given with minimum of 6 hours of gap between 2 fractions.

Results: Patients were evaluated 1 month after the brachytherapy. The Complete Response (CR) was seen in 178 patients whereas 137 patients showed partial response (PR). The local control was 51% at 1 year post treatment.

Conclusions: Interstitial template brachytherapy by MUPIT is a good alternative to deliver high dose radiation in locally advanced gynecological malignancies where conventional brachytherapy application is either not feasible or likely to give optimal dose distribution.
EVALUATION OF CHEMORADIOThERAPY EFFICACY AND SIDE EFFECTS IN LOCALLY ADVANCED CERVICAL CANCER- A STUDY FROM NORTH EAST OF IRAN

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Introduction: Radiation with concurrent chemotherapy (weekly cisplatin) is currently standard of care for locally advanced cervical cancer. Five randomized trials were the foundation for adopting cisplatin-based chemotherapy during radiation as the standard of care. These results were obtained in clinical trials performed in carefully prepared academic centers we sought to determine whether these results could be produced when patients were treated on an out of protocol basis.

Methods: We reviewed the files of 30 patients with locally advanced cervical cancer who received external radiation plus weekly cisplatin as routine management between 1386 to 1388 and analyzed treatment compliance response rate, toxicity and survival.

Results: A total of 30 patients who received radiation and cisplation were analyzed. Mean age was 56.13 years and distribution according to FIGO stage was as follows: IIb 76.7%, IIIa 13.3% and IIIb 10%. Complete responses were achieved in 63.3%, whereas 13.3% had partial response and 23.3% had progressive disease three month after completing treatment. At median follow up 18 months (range 10-33 months) overall survival was 60% and disease free survival was 33.30%. The most common toxicity was hematologic. Anemia was seen in 56.6% and leukopenia in 76.6%. In the majority cases toxicities were mild to moderate.

Conclusion: Cisplatine bases chemoradiation only with XRT was well tolerated in our patients and our results were comparable to other studies.

Keywords: Cervical Cancer - Chemoradiation - Cisplatin
A SURVEY OF IRANIAN WOMEN KNOWLEDGE AND ATTITUDE TO HPV AND VACCINE UPTAKE

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Aims: To determine the level of knowledge of Iranian women about Human Papillomavirus (HPV) infection and to assess their attitudes to HPV vaccine uptake.

Materials: In a population based survey, 500 women from 20 to 65 years old living in north-east Tehran were selected using stratified randomization. A consent form and a questionnaire were filled by the participants. The questionnaires were drafted following 50 volunteers discussions, and refined. Questions were designed to explore the knowledge of Iranian women regarding the HPV and its relation to cervical cancer, as well as their attitude towards vaccine policy decisions: agreement to vaccination (Likert scale), agreement with universal vaccination (Likert scale), involving the youngers, the appropriate age for vaccination and provision of the vaccine at sexual health clinics. The study were approved by Ethics Committee of the Shaheed Beheshti Medical University.

Results: One half of the women were well informed about HPV, but our results suggest that an HPV vaccine uptake rate of 90% may be achievable if the vaccine is perceived to be safe and effective. Almost all mothers (92.8%) were happy with performing HPV vaccine programme for young adolescents but some were concerned about sexual health issues, 22.5%.

Conclusion: It will be important to raise general awareness of the role of HPV in cervical cancer without emphasizing on the vaccination.
MRI-BASED PREPLANNING WITH CT/MRI DATA FUSION IN PATIENTS WITH CERVICAL CANCER TREATED WITH 3D BRACHYTHERAPY

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The aim of this study is to analyze the feasibility and determine the benefits of MRI-based preplanning with CT/MRI data fusion in patients with cervical cancer treated with radical radiotherapy. Patients underwent MRI examination prior to external beam radiotherapy and prior to the first and fourth fraction of brachytherapy with applicators in place. Insertion of applicators at the radiology department was performed under paracervical anesthesia. The benefit of MRI preplanning was determined by comparison between conventional treatment planning with dose specification to “point A”, and dose specification to 90% of high risk clinical target volume (HR-CTV D90). Tolerance of MRI evaluation with applicators, coverage of HR-CTV, and dose volume parameters for organs at risk (OAR) has been assessed in 42 brachytherapy procedures. Insertion of applicators at the radiology department was successful in all patients without any complications. Target dose was higher for MRI-planning than for conventional planning (5.3 Gy vs 4.5 Gy). Maximum doses in the bladder and rectum were significantly lower (p< 0.05) for MRI-planning than for the conventional approach (6.49 Gy vs 7.45 Gy for bladder; 4.57 Gy vs 5.06 Gy for rectum). We found no correlation between ICRU point dose for OAR and maximum dose in OAR. Nevertheless, a strong correlation between maximum dose in OAR and minimal dose in volume of 2ccm has been observed. In conclusion, MRI-based preplanning with consecutive CT/MRI data fusion is feasible and safe, with the advantage of increasing the dose to the tumour and decreasing the dose to OAR.
ANALYSIS OF RISK FACTORS FOR RECURRENCE IN PATIENTS TREATED FOR CERVICAL CANCER

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To discuss risk factors for recurrence after ovarian transposition in patients treated for cervical cancer and to discuss the indication of the ovarian transposition. METHOD Between Feb 2004 and Nov 2009, 67 cases with cervical cancer had been received unilateral or bilateral ovarian transposition in peritoneal cavity. Used univariate analysis to screen risk factors for recurrence and made a survival analysis through Kaplan-Meier analysis. RESULTS There were 5 cases (7.5%) underwent recurrence including 2 cases (3.0%) underwent ovarian metastasis. Univariate analysis showed that risk factors may be pathological type (P=0.017), clinical stage (P=0.000), differentiation grade (P=0.001). In addition, 4 patients with embolus in vessels or Lymph nodes metastasis underwent recurrence. 5 year survival rate is 98.4%.

Conclusion: The major risk factors of recurrence in cervical carcinoma may be pathological type, clinical stage, differentiation grade and cancer embolus in vessels or Lymph nodes metastasis.
ISOLATION AND IDENTIFICATION OF HUMAN CERVICAL CARCINOMA STEM CELLS

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Background and aims: The theory of cancer stem cell proposes that the tumor tissue had its own cancer stem cells in it and regards cancer stem cell as the key of regeneration, metastasis and recurrence. The properties of side population (SP) are considered as the cancer stem cell. The study was to isolate and characterize the side population of cancer stem-like cells in human cervical carcinoma Hela cell line.

Methods: Hela cell suspension was stained with Hoechst33342 and PI in the absence and presence of verapamil. Then the SP was analyzed in the fluorescence-activated cell sorter. The cloning efficiency of SP and non-SP cells was test by plate clone formation test with 500 cells respectively. And the oncogenicity was observed by implanting NOD/SCID mice model with $1 \times 10^5$ cells respectively.

Results: Side population accounted for about 1.2% in the total cells. Sorted SP was more tumorigenic than the corresponding non-side population. The clones formed by SP were more and larger than the non-SP ($P<0.05$). And $10^5$ SP cells injection could initiate tumors in three of five mice (60%), however, tumors in the mice injected of non-SP cells were not observed ($P<0.05$).

Conclusions: The side population sorted from Hela cell line may have the characteristic of cancer stem cell.
EARLY REMOVAL OF URINARY CATHETER AFTER RADICAL HYSTERECTOMY

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Background: Bladder dysfunction after radical hysterectomy seems to be transient. Prolonged catheterisation is a standard postoperative care after radical hysterectomy. A small proportion of women will need prolonged catheterisation but the majority will not need extra bladder care. Patients who have a catheter for more than two days were at higher risk of developing UTI, increased 30-day mortality as well as a decreased likelihood of early discharge home. The most important strategy to prevent UTI related to catheters is to remove the catheter as soon as possible.

Methods: Patients who had a radical hysterectomy between January 2009 and January 2010 under one surgeon at the Norfolk and Norwich University Hospital cancer centre were managed with early removal of the urethral catheter 48 hours after surgery. A bladder scan was used to assess post void residuals (PVRs). If PVRs on three occasions were less than 150 ml, the patient was sent home, otherwise the catheter remained for one week.

Results: Fifteen patients treated with radical hysterectomy were identified, Patients age ranged from 26 to 83 years, average 49 years. Median hospital stay was 3.0 days range between 2 and 6 days. 79% (11 cases) had successful removal of the catheter 48 hours after surgery with PVRs less than 150 ml and voiding volumes more than 200 ml.

Conclusions: Bladder scan post-operatively to assess PVRs will allow earlier catheter removal and earlier discharge from hospital for the majority of patients.
WEEKLY VERSUS TRI-WEEKLY CISPLATIN: WHICH ONE SHOULD BE THE STANDARD REGIMEN IN CISPLATIN-BASED CHEMORADIATION IN CERVICAL CANCER TREATMENT?

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Purpose: The aim of this study was to compare the compliance, toxicity and outcome of weekly and tri-weekly cisplatin administration during radiotherapy in loco-regionally advanced cervical cancer.

Material and methods: From January 2002 to December 2004, 104 patients with histologically proven stage IIB-IVA cervical cancer were randomized to weekly (weekly cisplatin 40mg/m², 6 cycles) and tri-weekly (cisplatin 75mg/m² every 3 weeks, 3 cycles) chemotherapy arms during concurrent radiation therapy. The differences between the two arms in compliance of treatment, toxicities and survival rates were analyzed.

Results: All the patients tolerated treatment very well with a high completion rate of scheduled chemotherapy cycles (84.6% in the weekly arm versus 92.5% in the tri-weekly arm). The grade 3-4 neutropenia was more frequent in the weekly arm (40.4%) than the tri-weekly arm (22.6%) (p< 0.05). There was no difference in the recurrence rate (30.8% in the weekly arm versus 24.5% in the tri-weekly arm) or the distant recurrence rate (25.5% in the weekly arm versus 17.0% in the tri-weekly arm). The 5 year survival rate was 66.5% in the weekly arm versus 88.7% in the tri-weekly arm and the difference was statistically significant on Cox regression analysis (Hazard Ratio 0.375, 95% Confidence Interval 0.154- 0.914, p=0.031)

Conclusion: The tri-weekly cisplatin regimen may be a strong candidate for the optimal dose and dosing schedule in cisplatin-based concurrent chemoradiation in patients with loco-regionally advanced cervical cancer.
CLINICOPATHOLOGICAL SIGNIFICANCE OF CERVICAL ADENOCARCINOMA ASSOCIATED WITH LOBULAR ENDOCERVICAL GLANDULAR HYPERPLASIA

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Lobular endocervical glandular hyperplasia (LEGH) is usually assumed to be a benign tumor-like lesion of the glands of the uterine cervix. However, LEGH has been associated with obvious cervical adenocarcinoma. The clinicopathological significance of the coexistence of LEGH and adenocarcinoma remains unclear. We microscopically examined the presence or absence of LEGH components in 95 stage Ib cervical adenocarcinoma. Gastric mucin was detected with the use of clone HIK1083. Associations of the coexistence of LEGH components with clinicopathological variables were analyzed. LEGH components were present in 16 cases (16.8%). Gastric mucin was positive in all 16 LEGH components, as compared with only 6 of the 95 adenocarcinoma components. Of the 16 adenocarcinomas with LEGH components, 15 were well-differentiated mucinous adenocarcinomas and one was poorly differentiated adenocarcinoma. The mortality rate from tumor recurrence was 25% (4 of 16) in patients whose tumors had LEGH components and 21.5% (17 of 79) in those whose tumors had no LEGH components. There was no significant difference in the survival. Early cervical adenocarcinoma was relatively frequently associated with LEGH components. LEGH may be one of the factors related to the development of cervical adenocarcinoma, but adenocarcinoma with LEGH components does not necessarily develop into a highly aggressive “adenoma malignum.”
FIBROBLAST GROWTH FACTOR RECEPTOR2 IIIC IN HUMAN UTERINE CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) AND CERVICAL CANCER

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Fibroblast growth factor receptors (FGFR)1 to 3 possess IIIb and IIIc isoforms as the result of alternative splicing. Single nucleotide polymorphisms (SNPs) of the FGFR2 gene are associated with endometrial cancer, and missense mutations or copy number gains of the FGFR2 gene occur in breast cancer. In uterine cervical cancer, FGFR2 IIIb was reported to be highly expressed in squamous cell carcinoma (SCC). In the present study, we determined the expression and roles of FGFR2 IIIc in CIN and cervical SCC. In CIN 1, FGFR2 IIIc immunoreactivity was localized at the basal of squamous epithelium, whereas FGFR2 IIIc was strongly expressed in most of the squamous epithelium in CIN 3. FGFR2 IIIc mRNA was detected in all cervical SCC examined. In situ hybridization analysis showed that the expression patterns of FGFR2 IIIc mRNA are similar to those of FGFR2 IIIc protein in CIN, and FGFR2 IIIc mRNA was strongly expressed in the invasive fronts of cancer cell nests in cancer tissues. Moreover, full-length FGFR2 IIIc cDNA was stably transfected into CaSki cells. The growth rates of the FGFR2 IIIc-transfected CaSki cells were higher than those of mock cells in vitro. As the CaSki cells were injected into nude mice, the FGFR2 IIIc-transfected CaSki cells tended to form larger subcutaneous tumors than mock cells. These findings suggest that FGFR2 IIIc plays important roles in the carcinogenesis and proliferation of cervical cancer cells. FGFR2 IIIc is considered to be a novel therapeutic target for inhibiting the growth of CIN and cervical cancer.
MEDIUM DOSE RATE BRACHYTHERAPY FOR PATIENTS WITH CERVICAL CARCINOMA; EARLY RESULT OF A PROSPECTIVE STUDY

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Purpose: This prospective analysis aims to report results from patients with cervical cancer treated by external beam radiation (EBR) with telecobalt and medium-dose-rate brachytherapy (MDR) and to establish the magnitude of brachytherapy dose reduction.

Methods: Between March 2006 and July 2008, 140 patients with histologic diagnosis of cervical carcinoma referred to TEHRAN Cancer Institute; were treated with external beam radiotherapy (44-64 Gy to whole pelvis) and MDR brachytherapy (8-30 Gy to Point A) with a dose rate of 2.2 ± 0.3 Gy/h.

Results: 121 patients were followed up for a median time of 18 months (range: 9-39 m). There were 11% (6/54) local recurrence for surgery and adjuvant radiotherapy group; 25% (16/65) for radical radiotherapy group; and 19% (23/121) for all patients. Rectal and bladder complications incidence for all patients were 10% (12/121) and 13% (16/121) respectively. High grade complication was shown only in one patient in radical radiotherapy group. In this study, 3-years disease free survival and overall survival were 73% and 92% respectively; and disease stage (p=0.007) and overall treatment time (p=0.05) were the significant factors affecting disease free survival.

Conclusion: Results of this series suggest that the use of external beam radiotherapy and MDR brachytherapy with dose reduction of about 20% in comparison LDR can be an acceptable technique with regard to local control and complications.
MALIGNANT PERICARDIAL EFFUSION IN CARCINOMA OF THE UTERINE CERVIX

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The occurrence of malignant pericardial effusion in the squamous cell carcinoma of the uterine cervix is rare. Only six previously reported cases of the antemortem diagnosis of malignant pericardial effusion from carcinoma of the cervix have been presented. We report here a patient with squamous cell carcinoma of the cervix who required emergent pericardiocentesis. In some reported cases, many women with pericardial involvement are candidates for aggressive radiation or chemotherapy. Early detection and prompt management of pericardial effusion correlates with a decrease in patient morbidity and a prolongation of useful life.

Keywords: Pericardial effusion, squamous cell carcinoma, pericardiocentesis
A COMPARISON BETWEEN SIMPLE FRACTIONATION AND HYPERFRACTIONATION IN ADVANCED CERVICAL CANCER: TUMOR CONTROL AND RADIATION COMPLICATIONS

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Objective: The aim of this study was discern in advanced cervical cancer whether Hyperfractionation is more effective in tumor control and in reducing radiation complication rates compared with simple fractionation.

Methods: We retrospectively reviewed the medical records of 184 patients with advanced cervical cancer at our hospitals from January 2000 to December 2004. All patients were treated with radiation, 114 patients with simple fractionation, and 70 patients with hyperfractionation.

Results: 48 patients (26.1%) suffered from gastrointestinal complications, 24 patients (13.0%) suffered from genitourinary complications and 18 patients (9.8%) had both complications. Complications were occurred in 72 cases in simple fractionation group and 40 cases in hyperfractionation group. 77 patients (41.8%) had acute complications and 13 patients (7.1%) had chronic complications. There was no statistically significant difference in two groups (P=0.772). Mild complication were occurred in 75 patients (40.8%) and severe complication were occurred in 15 patients (8.2%), there was no statistically significant difference in two groups (P=0.495). 66 patients (35.9%) had gastrointestinal complications and 42 patients (22.8%) had genitourinary complications, there was no statistical significance in two groups (P=0.910). The overall 5-year survival rate of all patients was 64.8% (SD 0.038). The overall 5-year survival rate of simple fraction group was 62.9% (SD 0.047) and hyperfractionation group was 68.1% (SD 0.063), there was no statistical significance in two groups (P=0.196).

Conclusion: Many complications were occurred in patients who treated with radiation therapy, but there was no statistically significant survival and complication difference in two groups. Further research is needed.
HYDRONEPHROSIS AS A PROGNOSTIC INDICATOR OF SURVIVAL IN ADVANCED CERVICAL CARCINOMA

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Objective: To determine whether hydronephrosis is an independent prognostic indicator of survival among patients with advanced cervical carcinoma.

Methods: Retrospective analysis of 199 patients with cervical carcinoma FIGO Stage IIIB or higher, treated between 1990 and 2007 was conducted. Inclusion criteria were: clinical staging according to FIGO criteria, standardized radiation treatment and cisplatin based chemosensitization regimens. Patients with incomplete data were excluded. Associations between hydronephrosis and covariates: race, nodal involvement, histopathology and GOG performance status (PS) were determined. Statistical analysis included Kaplan-Meier, log-rank test, proportional hazards (PH) regression, Fisher exact test and Mann-Whitney test were utilized where appropriate, with p < 0.05 considered significant.

Results: Of 145 included patients, 45 (63%) of 71 hydronephrosis patients died, compared with 29 of 74 (39%) non-hydronephrosis patients. Median time to death was significantly shorter for patients with hydronephrosis (20 months, 95% CI [12 - 27]) versus patients without hydronephrosis (67 months, 95% CI [39 - ∞]), p< 0.001. Unadjusted HR for hydronephrosis was 2.4 (95% CI [ 1.5 - 3.8]), p< 0.001. Of potential covariates evaluated, only GOG PS was significantly associated with hydronephrosis (p=0.038): 46 (65%) of patients with hydronephrosis had PS of 0, compared with 62 (84%) of those without. PH regression revealed that controlling for radiation, chemotherapy and PS, hydronephrosis was still significantly associated with poor prognosis (HR 2.3, 95% CI [1.4-3.7], p=0.001).

Conclusion: Hydronephrosis is an independent poor prognostic indicator of survival in patients with cervical cancer with Stage IIIB and above.
IMMUNOHISTOCHEMISTRY BASED PROFILE OF CIN MIGHT HELP FOR TRYAGING OF WOMEN GENUINELY REQUIRING TREATMENT

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Background and aims: With recent advances in knowledge about obstetrical morbidity of CIN treatments, the ambition to select out only women who truly need treatment has become paramount. The aim of this study was to establish immunohistochemistry (IHC) based profile of CIN in order to improve basic histopathological diagnosis and selection of cases being susceptible of malignant degree, greater or lower than that predictable by CIN 1, 2, 3 current grades.

Materials and methods: IHC assay was performed on 47 cervical biopsies for P16, FoxP3, PI3K, pMAPK-AKinase, pmTOR, ERK-2, CK2a et pAKT, c-met, CD44v6, HIF1a and VEGF. Blinded lecture of slides was performed with intraepithelial semi-quantitative evaluation of epithelial staining expression as well as of sub-mucosal FoxP3 positive lymphocytes. Results were correlated to the histological degree of CIN.

Results: Only p16, FoxP3, PI3K and c-met IHC staining were significantly related to the severity of CIN. Among CIN1, 4 showed P16, FoxP3, PI3K and c-met immunohistochemical profile of CIN2. Conversely 3 CIN2 had an immunohistochemical profile similar to CIN1.

Conclusion: Increased PI3K, P16 and c-met immunohistochemical expression of epithelial squamous cells associated with submucosal FoxP3 immunoreactive lymphocytes might contribute to a better prediction of the aggressivity of CIN at initial diagnostic time. Such IHC signature resulting from the 4 marker expression within CIN might help for the tryaging of CIN1 requiring treatment as well as CIN2 that could benefit of conservative management.
EVALUATION OF HPV DNA TYPING IN SENTINEL LYMPH NODE AND PRIMARY LESION OF CERVIX IN PATIENTS WITH CERVICAL CANCER

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Objectives: The aim of this study was to analyze the HPV DNA types in both sentinel lymph node (SLN) and primary lesion of cervix in patients with cervical cancer.

Methods: 45 patients who underwent radical hysterectomy and pelvic lymphadenectomy with cervical cancer were enrolled in this prospective study. SLN and primary lesion of cervix were evaluated with microscopic pathologic examination as well as HPV DNA typing using HPV oligonucleotide microarray.

Results: HPV DNA types were successfully identified in all the 45 patients studied. Sentinel node detection and frozen biopsy were performed on all 45 subjects. There were 33 benign and 12 malignant cases on frozen biopsy. On permanent histopathological specimen, there were 31 benign and 14 malignant cases. In 31 out of 33 cases determined to be benign on the sentinel node frozen biopsy, there were no pelvic lymph node metastasis on the permanent pathology. In only 2 cases found to be benign on the sentinel node frozen biopsy, there were pelvic lymph node metastasis on the permanent histopathology.

Conclusions: There was no case that newly detected HPV DNA types in SLN in case of the absent types in primary lesion of cervix. This results imply that SLNs have an essential role for biological metastasis to secondary pelvic lymph node from the primary lesion of cervix. SLN detection and frozen biopsy make it possible to minimize the unnecessary extensive pelvic lymph node dissection during radical hysterectomy.
SOLITARY RECURRENT METASTASIS OF SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX IN INGUINAL LYMPH NODE

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In cervical squamous cell carcinoma, solitary metastasis and recurrence in the inguinal area are uncommon in the absence of apparent disease in other sites. A case of a 63-year-old patient with a Stage Ib2 carcinoma of the cervix treated with radical hysterectomy and pelvic lymphadenectomy followed by radiotherapy is reported. Serial squamous cell carcinoma (SCC) antigen measurements have been performed for monitoring the course of disease, response to treatment, and detection of tumor recurrence. Recurrent disease was initially suspected on palpable mass in inguinal area of left, subsequently confirmed by magnetic resonance imaging, and positron emission tomography of the abdomen and pelvis. Wide excision of suspected site followed by chemotherapy with carboplatin was performed. The SCC antigen level was within normal limits, both preoperatively and postoperatively. This patient was treated with chemotherapy after operation and is now suffering from lymph edema.
PHASE II TRIAL OF NEOADJUVANT CHEMOTHERAPY IN CERVICAL CANCER IN INDIAN WOMEN

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Objectives: The study aimed to find out whether NACT in bulky and locally advanced cervical disease leads to improved overall survival (OAS) and disease free survival (DFS).

Methods: Thirty cases of cervical cancer of stages IB2/IIA, IIB and IVA were subjected to NACT. The cases were administered weekly, 3# or 6# multidrug (Paclitaxel, Cisplatin and Ifosphamide), chemotherapy. This was followed by surgery (Class III Wertheim's Hysterectomy with bilateral pelvic lymph node dissection) or concurrent chemoradiation (CCRT) depending upon the response to chemotherapy. Further, cases following surgery were treated with adjuvant therapy or observation depending upon the histopathological factors. Thereafter, residual, recurrence, disease free and overall survival were recorded and results tabulated after twenty four months of follow up.

Results: There were 12 cases of complete response, 13 with partial and 5 with no response. 53.3% cases underwent surgery, 43.3% CCRT and 3.3% cases received chemotherapy. 17% of cases received triple treatment modality following detection of high risk histopathological factors. There was 100% OAS and 83.3% DFS in stage IB2/IIA, 95% OAS and 85% DFS in Stage IIB and 50% OAS and 50% DFS in Stage IVA.

Conclusions: The study shows improved stage wise outcome (OAS and DFS) and decreased local recurrence following NACT when compared to the accepted five year survival pattern. NACT in the treatment of cervical cancer is an option in well selected cases to decrease the number of cases receiving radiotherapy, which has long term morbidity and simultaneously improving survival.
THE CORRELATION OF KI-67 EXPRESSION WITH TUMOR RECURRENCE AND SURVIVAL RATES IN EARLY STAGE CARCINOMA OF THE CERVIX

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Introduction: The development and progression of cervical cancer are likely to be associated with uncontrolled proliferation and recent interest has focused on immunohistochemical detection of cell proliferation. This study aims to determine if there is a correlation between Ki-67 expressions with tumor recurrence in patients with early stage cervical cancer.

Methods: Paraffin-embedded cervical tumor tissues of patients with Stage IB1 and IIA cervical cancer treated with radical hysterectomy with or without bilateral salpingo-oophorectomy and lymph node dissection with corresponding adjuvant treatment, both with histologically proven tumor recurrence (CASES) and with no evidence of disease (CONTROLS) were immunohistochemically stained for expression of Ki-67. The mean percentages of cells with immunoreactivity to Ki-67 were then compared to determine if those cases that had tumor recurrence had a higher Ki-67 proliferative index.

Results: There were a total of 6 cases of tumor recurrence with matching 6 cases of no evidence of disease included in the study. Ki-67 proliferative index mean levels for the squamous cell carcinoma were 20% and 80% for the cases and controls, respectively. On the other hand, the mean levels of Ki-67 proliferative index for the adenocarcinoma were 73.33% and 90% for the cases and controls, respectively.

Conclusion: This preliminary study did not show any association between the Ki-67 proliferative index and disease recurrence in early stage cervical carcinoma and also did not demonstrate that tumors with higher proliferative indices have more aggressive behavior than tumors with lower proliferative indices.

Keywords: Early stage cervical carcinoma, Ki67 proliferative index
PERSISTENCE AND RECURRENCE OF CERVICAL INTRAEPITHELIAL NEOPLASIA FOLLOWING LOOP ELECTROSURGICAL EXCISION (LEEP) OF HIGH GRADE LESIONS - 10 YEAR FOLLOW UP

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LEEP is widely used and acceptable therapeutic option in the treatment of cervical intraepithelial neoplasia (CIN). LEEP is associated with increased risk of preterm births and more after repeat procedure. There is an increasing trend of young women developing CIN lesions, hence the need to treat judiciously to remove the disease and not to over treat.

Aims: This is a retrospective study of the long term outcome, in a single unit, of persistent and recurrent CIN in women treated for high grade lesions by LEEP.

Method: From 1999 - 2002, a total of 150 patients with high grade CIN treated by LEEP were identified. 50 patients had positive margins in the ectocervix, 33 had positive margins in endocervix and 17 had positive margins in both ectocervix and endocervix and 50 had complete excision. A 10 year follow up of cytology and histology was done for these women.

Results: In the entire study group, 45% were less than 30 yrs old and 44% were nulliparous. Accuracy of colposcopy was 75%. There was an 8% failure of treatment with patients with positive margins and no treatment failures with complete excision. Overall failure rate after treatment of high grade CIN is 5%. A 2% recurrence rate after complete excision and 5% recurrence after incomplete excision was noted on follow up. 65% of recurrences developed after 5yrs of initial treatment. No patient developed invasive cancer during the follow up period.

Conclusions: A positive margin in LEEP justifies close long term follow up with cytology and not re-treatment.
INFLUENCE OF POST OPERATIVE ADJUVANT CONCURRENT CHEMORADIATION ON SURVIVAL FOR HIGH- RISK EARLY STAGE CERVICAL CANCER - KK HOSPITAL EXPERIENCE

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Purpose of the study: The study was conducted to evaluate the efficacy of post operative concurrent chemoradiation [CCRT] and its influence in survival in stage 1B to II A cervical cancer patients who underwent radical hysterectomy and pelvic lymphadenectomy.

Methods: From January 1997 to October 2007 we reviewed retrospectively medical records of 340 patients who had undergone radical hysterectomy and pelvic lymphadenectomy at KK Women's and Children's hospital for early cancers IB to II A. Fifty six patients with high risk factors such as positive pelvic lymph nodes, parametrial involvement, or positive resection margins recruited in the study. CCRT was recommended for them. Adjuvant chemotherapy consisted of cisplatin(70mg/m² on day 1) and 5fluorouracil(5FU;1000mg/m² on days 2-5) for 4 cycles every 4 weeks beginning 2-3 weeks after surgery. Pelvic radiotherapy was started concurrently at the 2nd and 3rd cycle of chemotherapy. We analyzed disease free survival, overall survival and pattern of recurrence and side effects of CCRT.

Results: Three forty patients underwent radical hysterectomy and pelvic lymphadenectomy in the study period. 56 patients with high risk features identified. 48 patients received CCRT. Follow up period ranges from 11 to 113 months with a mean follow up period of 48 months.11 patients died of recurrence of disease. The 5 years disease free survival rate was 84.4 % and the 10 years disease free survival rate was 63.4%.

Conclusions: This study supports good 5 years survival rate with side effects of chemotherapy and radiation treatment in acceptable range.
SEQUENCE-DEPENDENT HEMATOLOGIC SIDE EFFECTS OF TOPOTECAN AND CISPLATIN IN PERSISTENT OR RECURRENT CERVICAL CANCER


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Objective: This retrospective study evaluates the efficacy and toxicity of topotecan preceding cisplatin administration in persistent or recurrent cervical cancer patients.

Methods: Twenty-four patients were included in the study. Ninety-two cycles of chemotherapy were administered during the study period. Topotecan (0.75 mg/m²) was administered as a 30-minute infusion for 3 consecutive days and cisplatin was given at a dose of 50 mg/m² intravenously over 1 h on day 3 every 3 weeks.

Results: The median number of courses administered was 3, with a range of 1-8 cycles per patient. There were 4 (16.7%) complete responses; 3 (12.5%) partial responses; 5 (20.8%) stable disease. All of the patients with complete responses received radiation for palliation during chemotherapy for pain or surgery before chemotherapy due to an isolated solitary metastatic lesion. There were no treatment delays > 7 days per cycle. There were 59 days of delays (average, 0.6 days per cycle) in 21 of 92 (22.8%) cycles and two episodes of dose reduction (cisplatin, 50% reduction) in 2 patients due to a low creatinine clearance (30-60 mL/min). Overall, grade 3/4 anemia, thrombocytopenia, and neutropenia were experienced in 13.1%, 1.1%, and 18.5% of the courses, or 33.4%, 4.2%, and 45.8% of the patients, respectively.

Conclusion: We observed that combination chemotherapy of topotecan preceding cisplatin had a relatively low rate of hematologic toxicities compared with the results of previous study with cisplatin (day 1) and topotecan (day 1-3) in recurrent or persistent cervical carcinoma.
LOCALLY ADVANCED ADENOCARCINOMA OF THE CERVIX TREATED WITH CONCURRENT CHEMORADIOThERAPY USING PACLITAXEL AND CISPLATIN

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Objectives: The aim of this study was to clarify the efficacy of concurrent chemoradiation (CCRT) using paclitaxel (T) and cisplatin (P) (CCRT-TP) for locally advanced adenocarcinoma of the cervix.

Methods: Eligibility for CCRT-TP included FIGO stage III / IVa cervical adenocarcinoma or adenosquamous carcinoma without para-aortic lymph node enlargement. CCRT-TP consisted of pelvic external beam radiotherapy (total dose 50Gy/25 fractions) with center shielding after 40Gy, high-dose rate intracavitary brachytherapy (point A dose 18-24Gy/3-4 fractions), cisplatin 50 mg/m² every 3 weeks, and paclitaxel 50 mg/m² weekly. Overall survival (OS), central disease-free survival (CDFS), and distant disease-free survival (DDFS) were estimated in comparison with historical controls (HC), consisting of 5 patients treated with CCRT using P alone (CCRT-P) and 13 treated with radiation alone (RT).

Results: Nine patients were treated with CCRT-TP between 2003 and 2009. Seven patients were in stage III and 2 in stage IVa. The median age, median follow-up, and median tumor size were 62 years (range; 34-73 years), 41 months (range; 9-70 months), and 5.8 cm (range; 5.0-8.8 cm), respectively. Five-year OS and CDFS in the CCRT-TP/CCRT-P/RT were 74.1%/40.0%/7.7%, and 88.9%/20.0%/23.1% (p = 0.027, and p = 0.014), respectively. However, 5-year DDFS in CCRT-TP was 66.7%, which is not significantly better than those in the HC groups. No patients treated with CCRT-TP experienced severe acute and late adverse events.

Conclusion: CCRT-TP for locally advanced adenocarcinoma of the cervix showed a promising activity with favorable 5-year survival rates. This regimen should be evaluated in a large number of patients.
A PROSPECTIVE STUDY ON COLPOSCOPIC EVALUATION OF POST COITAL BLEEDING

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Introduction: Post coital bleeding is the potential symptom of cancer cervix.

Aims: To evaluate the patients with PCB and detect the incidence of pre-invasive / invasive cervical cancer.

Methods: A prospective study conducted from Jan, 2007 to Dec. 2009 where 160 patients presenting with PCB were evaluated by Pap's smear test and Colposcopy.

Results: Majority of patients were 35 - 44 yrs. (42.5%) and premenopausal (83.75%). The clinical findings were Erosion (30%), unhealthy Cx. (21.5%) and Cx polyp (10%). Inflammatory Pap's smear was reported in 66 (41%). 15 patients showed abnormal Pap's smear with ASCUS in 2, LSIL in 6, HSIL in 6 and one reported as adenocarcinoma. On colposcopy 36.2% patients had normal findings. All patients with abnormal colposcopy (74) underwent directed biopsies. 20 patients had abnormal findings on HPR - CIN 1 in 8 pts, CIN II / III in 6 pts. and 6 patients had invasive carcinomas. One patient each with CIN I & II on retrospectively showed inflammatory Pap smear .Both pts .with ASCUS showed CIN II / III on biopsy. In 6 pts.with LSIL, 4 had CIN I/II and 2 had invasive cancer. In HSIL (6) HPR showed squamous cell carcinoma5 &CIN III in one patient.. In patient with adenocarcinoma ,one patient had normal Pap Smear.

Conclusion: Women with PCB should be reassured as majority of the patients ( 87.5%) have no serious abnormality. However cervical cancer was found in 4.3% (7/160)of the patients . Colposcopy examination should always be done with Pap Smear.
PROGNOSTIC IMPLICATIONS OF LEVELS OF INSULIN LIKE GROWTH FACTOR-I & INSULIN LIKE GROWTH FACTOR-II IN PATIENTS WITH CERVICAL CANCER

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Objectives: To study the effect of chemo-irradiation on levels of insulin like growth factor (IGF I) and insulin like growth factor (IGF II) in patients with stage IIIB cancer of uterine cervix.

Materials and methods: In our study we included 100 patients of squamous cell carcinoma of stage IIIB cancer of uterine cervix from April 2009 to October 2009. Along with the routine investigations pre treatment serum levels of IGF I & IGF II were done by ELISA kits. The serum level of IGF I was 248.7±70.9 ng/ml & IGF II was 1550 ±385 ng/ml. All patients were given concurrent cisplatin (30 mg/m²) weekly along with radiation (50Gy/25#) with conventional portals followed by two sittings of intracavitary radiotherapy (7.5Gy each) on mHDR. All these patients were kept on follow up with serum levels of IGF I & IGF II done at one, three & six months post treatment.

Results: The mean serum levels of IGF I & IGF II in patients who achieved complete response (40%) returned to normal whereas the mean serum levels of IGF I & IGF II in patients who achieved partial response (50%) was 130 ng/ml and 820 ng/ml respectively. The mean serum levels of IGF I & IGF II in patients who achieved no response (10%) was 330 ng/ml and 1750 ng/ml respectively.

Conclusions: The serum levels of IGF I & IGF II may be reliable marker for early diagnosis & monitoring treatment efficacy however further large randomized studies are required to validate results.
RADICAL HYSTERECTOMY IN PREGNANT AND NON-PREGNANT WOMEN: A COMPARISON OF OPERATIVE RISKS

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Objective: To compare operative data and complications of radical hysterectomy performed on pregnant women versus those performed on non-pregnant women.

Methods: With IRB approval, we reviewed our obstetric and gynecologic surgery databases to identify women that underwent a radical hysterectomy for cervical carcinoma from 1992-2005 (n=7). A non-pregnant control group (n=35) of women who underwent radical hysterectomy during the study interval, matched for year of surgery and surgeon, were identified. Operative and outcome data were abstracted.

Results: Of the 7 women who underwent a radical hysterectomy during pregnancy, 4 had a cesarean radical hysterectomy at a mean gestational age of 35.2 weeks (range, 32.3 - 38.0 weeks) and 3 underwent a standard radical hysterectomy with a pre-viable fetus in situ at a mean gestational age of 14.3 weeks. Demographics were similar for both groups. Mean estimated blood loss was higher in pregnant women (1543 cc) vs. non-pregnant women (718 cc) (p< 0.001). Transfusion rates were significantly higher among pregnant women (57%) compared to non-pregnant controls (9%) (p = 0.009). Other operative complications were similar between the pregnant women (43%) and non-pregnant controls (40%) (p=NS) with ileus most common in pregnant women (29%) and febrile morbidity most frequent in non-pregnant women (14%). Two fistulas were noted post-op and both were in non-pregnant women.

Conclusions: Radical hysterectomy performed in pregnant women was associated with a significantly higher operative blood loss and increased need for transfusion compared to non-pregnant controls. No significant differences were observed in regards to other operative complications.
RISK STRATIFICATION IN PATIENTS WITH STAGE IB-IIA CERVICAL CANCER WITHOUT PARAMETRIAL INVASION OR PELVIC LYMPH NODE METASTASES AFTER RADICAL HYSTERECTOMY

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Aims: To identify risk factors for 5-year overall survival in stage IB-IIA cervical cancer without any of parametrial invasion (PI) or pelvic lymph node metastases (PLNM) after radical hysterectomy.

Methods: In total, 315 patients with stage IB-IIA cervical cancer without any of PI or PLNM after radical hysterectomy were included for analysis. Cox’s proportional hazards model was used for risk stratification for 5-year overall survival.

Results: Tumor size (≥3cm or ≥4cm), corpus invasion and vessel infiltration were significant predictors in multivariate analyses. Patients were divided low- and high-risk groups. The low-risk group was composed of patients with 0 or 1 factor out of these three factors. The high-risk group was comprised of patients with 2 or 3 factors out of these three factors. The 5-year overall survival for the low- and high-risk groups was 96.4% and 68.6%, respectively (p>0.0001).

Conclusion: The risk of failure in patients with stage IB-IIA cervical cancer without any of PI or PLNM after radical hysterectomy can be predicted. This study might provide patient selection criteria when considering adjuvant irradiation for patients with stage IB-IIA cervical cancer without any of PI or PLNM.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

P16\textsuperscript{INK4a} IMMUNOSTAINING AS AN ALTERNATIVE TO HISTOLOGY REVIEW FOR RELIABLE GRADING OF CERVICAL INTRAEPITHELIAL LESIONS

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Histomorphological grading of CIN is crucial for clinical management, however is subjective and affected by substantial rates of discordance among pathologists, which may lead to overtreatment. To minimise this problem, histology review of CIN lesions by a consensus panel of pathologists is often used. Diffuse p16\textsuperscript{INK4a} immunostaining has been proposed to aid identification of true high-grade lesions. The aim of the study was to assess the value of additional interpretation of p16\textsuperscript{INK4a} immunostains for making a more reproducible diagnosis of CIN2/3 lesions. We used 409 biopsies of cervical lesions, stained for both H&E- and p16\textsuperscript{INK4a}. First, in 49 biopsies, we examined the effect of interpretation of p16\textsuperscript{INK4a} staining, on the agreement of CIN diagnosis among three pathologists. Second, all samples were used to assess the accuracy of p16-supported lesion grading by a single pathologist, by evaluating diagnostic agreement with the consensus diagnosis of expert pathologists based on H&E-stained sections only.

Agreement between three pathologists, for routine H&E-based diagnosis, ranged from fair (kappa 0.44 (95% CI: 0.19-0.64)) to moderate (kappa 0.66 (95% CI: 0.47-0.79). The concordance increased substantially for p16-supported grading (mean kappa 0.80 (95% CI: 0.67-0.88)). Furthermore, an almost perfect agreement was found between the p16-supported diagnosis of a single pathologist and the consensus diagnosis of an expert panel (kappa 0.86 (95% CI: 0.83-0.88)).

Our data demonstrate that use of p16\textsuperscript{INK4a}IHC significantly improves the accuracy of grading CIN by a single pathologist, equalling expert consensus diagnosis. Hence, we advocate the combined use of p16\textsuperscript{INK4a}-stained and H&E-sections in routine histopathology to improve accuracy of diagnosis.
ADJUVANT RADIOTHERAPY AND CHEMORADIATION AFTER SURGERY FOR CERVICAL CANCER
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**Background:** The indications for, and value of, adjuvant radiotherapy after surgery in women with early cervical cancer are controversial. Certain pathologic risk factors are thought to represent sufficient risk for recurrence that they justify the use of post-operative radiotherapy, though this increases treatment side-effects and complications.

**Objectives:** To evaluate the effectiveness and safety of radiotherapy or chemoradiation after radical hysterectomy for FIGO stage IB1, IB2 or IIA cervical cancer.

**Methods:** The Cochrane Central Register of Controlled Trials (CENTRAL) and Gynaecological Cancer Group Trials Register, MEDLINE, EMBASE, and abstracts of scientific meetings were searched for randomised controlled trials (RCTs) that compared adjuvant radiotherapy with no adjuvant radiotherapy in women with early cervical cancer, who had undergone radical hysterectomy.

Two authors independently sifted titles, abstracts and full papers; abstracted data; and assessed risk of bias. Results were pooled using random effects meta-analyses.

**Results:** Two RCTs (397 women) met the inclusion criteria. Meta-analysis indicated no significant difference in survival at five years between women who received radiation and those who received no further treatment (Risk ratio (RR) = 0.8, 95% Confidence interval (CI): 0.3 to 2.4). However, women who received radiation had a significantly lower risk of disease progression at five years (RR = 0.6, 95% CI 0.4 to 0.9).

Risk of serious adverse events was consistently higher for women who received radiotherapy, but this was not statistically significant.

**Conclusions:** Post-operative radiotherapy decreases the risk of disease progression, but does not improve overall survival. The evidence on serious adverse events is equivocal.
TO TREAT OR NOT TO TREAT, THE CLINICAL DILEMMA OF ASC-US


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Objectives: Management of patients diagnosed with two consecutive atypical squamous cells of undetermined significance (ASC-US) cervical smears remains a clinical dilemma. We described a study on a period of more than 10 years to determine whether aggressive or conservative treatment is preferable.

Patients and methods: A total of 230 patients referred for primary colposcopy because of two ASC-US smears were evaluated for 125 months. In 112 patients conservative management was followed in case low grade cervical intraepithelial neoplasia (CIN) lesions were found at colposcopy (conservative strategy). One-hundred-eighteen patients underwent direct loop excision of all colposcopically detected abnormalities, even if not suspected for CIN (aggressive strategy). The number of loop excisions, detection of CIN lesions and cytological follow-up of both groups were analyzed to develop an optimal treatment strategy for patients with two consecutive ASC-US smears.

Results: Conservative management resulted in less loop excisions (p< 0.001). At initial colposcopy, the aggressive group revealed a tenfold of histologically detected CIN lesions compared to the conservative group (1.8% vs 19.5%). During ten years of follow-up, both groups revealed the same percentages of CIN lesions (8.1% vs 8.4%).Aggressive management resulted in faster normalization of cervical smears (p< 0.001). However, at 125 months follow-up, there was no statistical difference in the percentage of normalization of cervical smears between both treatment strategy groups.

Conclusions: Conservative colposcopic treatment is a safe strategy for patients with two consecutive ASC-US smears, without the risk of leaving CIN 3 lesions untreated. Treatment decisions, however, must be adjusted to individual needs.
THE FTA CARTRIDGE SELF SAMPLE: A PROMISING TOOL TO IMPROVE CERVICAL CANCER SCREENING

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Objectives: High risk HPV (hrHPV) testing on self-sampled materials shows potential to increase the efficacy of population-based cervical screening programs. The Indicator FTA elute cartridge (FTA cartridge) allows safe transport of cervical samples by ambient temperature and ordinary post. DNA can be obtained by simple elution and is therefore easy, cheap, and fast to obtain. Previous studies showed 100% agreement with amplification based systems (Lenselink et al, JCM 2009). We are now reporting on the use of the hybridization based Hybrid Capture (HC2) and GP5+/6+-PCR systems for the FTA cartridge.

Patients and methods: We recruited 105 women at our outpatient department. One cervico-vaginal sample was collected in a liquid based medium and one was applied to the FTA cartridge. DNA was eluted directly from the FTA cartridge. The HC2 assay and the GP5+/6+ PCR were performed on the liquid sample and on the eluted DNA.

Results: Twelve specimens contained insufficient DNA after elution. In total, 93 women were opt for evaluation. Of the liquid based samples, 41% was hrHPV positive on HC2 and 38% on GP5+/6+. Overall agreement between FTA cartridge samples and liquid based media for hrHPV presence was 80% with HC2 and 90% with GP5+/6+ for all ASCUS samples or worse.

Conclusions: The FTA cartridge is a promising self-sample screening tool as it is easy to use, well accepted, and allows safe transport and storage. The FTA cartridge shows high overall agreement with hrHPV detection in liquid based media using the hybridization based systems HC2 and GP5+/6+-PCR.
NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADICAL HYSTERECTOMY FOR STAGE 1B2-2B CERVICAL CANCER-PRELIMINARY RESULTS

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Background and aims: Neoadjuvant chemotherapy prior to radical surgery for locally advanced cervical carcinoma continues to be a controversial issue. We aimed to determine the efficacy and feasibility of neoadjuvant chemotherapy/NACT/ using cisplatin and etoposide in patients with stage 1b2-2b cervical cancer. Primary end point is to determine response rate to NACT, secondary end points are overall survival/OS/, progression free survival/PFS/, toxicity, and quality of life.

Methods: Previously untreated patients with histologically confirmed stage 1b2-2b cervical cancer were submitted to MRI imaging procedure and treated with three courses of NACT /40 mg/m² CDDP on days 1 and 2, plus 100 mg/m² etoposide on day 1/ every 10 days. 2 weeks after NACT, evaluation MRI was done, and response rate was established according to RECIST criteria. 2-4 weeks after radical hysterectomy Piver class III with pelvic lymph node dissection was done for responders to chemotherapy as well as for patients with stable disease. Patients determined to have progressive disease were submitted to chemoradiation.

Results: From November 2008 to March 2010, 19 patients were enrolled, and 16 were eligible. Complete, partial response, stable and progressive disease was achieved in 12.5%, 56.25%, 25% and 6.25% respectively. Chemotherapy was well tolerated, hematologic toxicity G1 was recorded in 18.75%.

Conclusion: Preliminary results suggest that NACT with cisplatin and etoposide is feasible, with acceptable toxicity. Results regarding impact on survival and quality of life are awaited.
ROLE OF PET/CT IN PREOPERATIVE LYMPH NODE STAGING IN PATIENTS WITH EARLY STAGE CERVICAL CANCER UNDERGOING RADICAL SURGERY

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Objective: The aim of the prospective study was to analyse the feasibility and accuracy of preoperative PET/CT evaluation in detection of regional lymph node metastasis in patients undergoing radical surgery as the treatment of early stage cervical cancer.

Patients and methods: From November 2008 to April 2010 36 patients with early stage cervical cancer were enrolled into the study. All patients underwent preoperative PET/CT scans and laparoscopic sentinel lymph node identification followed by radical surgery. Calculation of sensitivity, specificity, positive predictive value, negative predictive value and accuracy for lymph node metastasis detection with PET/CT was performed in relation to definitive results of histological ultramicrostaging evaluation.

Results: Ten of the 36 patients (27.7%) had lymph node metastasis. The overall side-specific sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT were 37.7%, 96.6%, 71.4%, 87.7% and 86.1% respectively.

Conclusions: PET/CT scans have limited sensitivity but high specificity and accuracy for predicting regional lymph node metastasis in preoperative staging of early stage cervical cancer. The size threshold for depiction of lymph node metastasis is diameter greater than 8mm. Preoperative PET/CT evaluation may be a useful tool for identifying patients for abandoning surgical treatment and indication of primary chemo - radiotherapy.
RELATIONSHIPS BETWEEN SENSE OF COHERENCE AND SYMPTOM OCCURRENCE, INTENSITY, DISTRESS, AND SELF CARE EFFECTIVENESS IN THAI WOMEN WITH CERVICAL CANCER

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Background and aims: Women with cervical cancer are prone to experience with symptom occurrence, intensity, and distress from pre to post treatment. Sense of coherence (SOC) is internal strength of people to manage these symptom components. To know relationships between SOC and symptom components at each time of treatment is necessary for heath care teams to promote appropriate self care for them. Aim of this prospective study was to examine the relationships between SOC and symptom occurrences, intensity, distress, and self care effectiveness in Thai women with cervical cancer at pre, during, and post treatment.

Methods: This is a part of prospective study examined in 190 women recruited from four hospitals: 1 hospital affiliated university, 2 military hospitals, and 1 hospital under the National Cancer Institute. The Memorial Symptom Assessment Scale, the Self Care Diary, the Sense of Coherence-13, and the Demographic, Disease, and Treatment Questionnaires were used at pre, during, and one month post treatment.

Results: Results revealed that there were negatively relationships between SOC and symptom occurrence and intensity (p< .01) at pre and during treatment but there was no relationship at post treatment. There was negatively relationship between SOC and symptom distress while there was positively relationship between SOC and self care effectiveness all three times of treatment (p< .01).

Conclusions: These findings indicate relationships of SOC and symptom components in Thai women with cervical cancer. Results can provide an evidence to strengthen these women and promote proper self care for each time of treatment.
The role of the colposcopist is to identify the source of abnormal cells and to make decision whether or not any treatment is required after cytological findings of atypical squamous cells of undetermined significance (ASCUS) and atypical squamous cells - high (ASC-H).

The aim of the study was to determine the frequency of high-grade lesions after ASCUS and ASC-H cytological findings.

We conducted a two-year study (1st Jan. 2008 - 31st Dec. 2009). We analysed histopathological findings of patients with ASCUS or ASC-H pap smears and pathological colposcopic findings treated by cold knife conisation, radio ray or loop excisions. Statistical analysis: methods of descriptive statistics and Student's t-test.

We performed 14,085 pap smears in the study period. ASCUS was found in 175 (1.24%) and ASC-H in 41 (0.29%). We treated surgically 29 patients (13.4%). Histopathological findings were benign in 11 patients (37.9%), LSIL in 2 (6.9%), HSIL in 15 (51.7%) and invasive cervical cancer in 1 patient (3.5%). FIGO I B. Subsequent high-grade lesions were found in 14 (8%) after ASCUS and in 3 patients (7.3%) after ASC-H. We did not find statistically significant difference in high-grade lesions after ASCUS or ASC-H (t = 0.82, p > 0.05).

We found a high percentage of high-grade lesions after ASCUS and ASC-H cytological findings. We should plan follow up or surgical treatment options based on colposcopy findings.
PROGNOSTIC VALUE OF HEDGEHOG SIGNALLING IN CERVICAL CARCINOMA

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Background: The hedgehog (Hh) pathway is an attractive therapeutic target since dysregulation of the Hh pathway is implicated in carcinogenesis and tumor progression. The aim of this study was to measure gene expression levels of Hh genes in cervical tumors and correlate these with prospectively collected clinicopathological variables, tumor microenvironmental parameters, (pO2 level and interstitial fluid pressure - IFP) and disease free survival (DFS) following chemoradiotherapy.

Methods: Frozen biopsies from 91 cervical carcinoma patients and 12 normal cervix tissue were examined for SHH, IHH, PTCH1/2, SMO, and Gli1 expression using quantitative RT-PCR.

Results: Hh gene expression was heterogeneous in the tumor samples and significantly higher than in normal cervix tissue (p< 0.001). There was no association between individual Hh gene expression levels nor between these and tumor size. Nodal status was associated with PTCH2 (p=0.032) and IHH (p=0.018) and FIGO stage with SMO (p=0.023). There was no association between Hh genes and tumor hypoxia (pO2 and CAIX) or IFP but SHH (p=0.03) and Gli1 (p=0.01) were associated with tumor stromal subclassification. No association was found between Hh gene expression and DFS.

Conclusion: Members of the Hh pathway are expressed more highly in cervical cancer than normal cervix. There is limited correlation with tumor microenvironment and disease stage but no correlation was observed with DFS. Evaluation of Hh signalling is complex and may be cancer type and stage dependent. Further investigation is required to establish how best to target the Hh signalling pathway in treatment of cervix carcinomas.
EVALUATION OF OUTCOMES IN PATIENTS WITH CARCINOMA OF THE CERVIX TREATED WITH RADIATION WITH OR WITHOUT CONCURRENT CHEMOTHERAPY

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Purpose: The objective of this study was to compare survival and recurrence rates for patients with cervical cancer treated with radiation concurrently with cisplatin, cisplatin/5-FU or without chemotherapy.

Patients and Methods: We reviewed the records of 167 eligible patients with locoregionally confined, stage IB1 through IVA, intact cervical cancer who were treated at Northwestern Memorial Hospital. All patients underwent definitive radiotherapy with combined external beam radiation, the majority with extended field (62%) and all received low-dose rate brachytherapy. Of the 167 patients, 62 had no concurrent therapy, 93 were treated with concurrent cisplatin, and 12 were treated with cisplatin/5-FU.

Results: For all patients treated with definitive radiotherapy, overall survival at 5 and 10 years was 58% and 49%, respectively. A total of 55 patients (33%) recurred, with a recurrence-free survival of 61% at 5 years. Individuals treated with chemotherapy had an overall survival rate of 75% versus 53% in patients without chemotherapy at 5 years and 71% versus 47% at 10 years (p = 0.053). Patient treated with chemotherapy had significantly improved recurrence-free survival at 5 years, 74% versus 46% (p = 0.032). Adenocarcinoma histology conferred a higher rate of recurrences compared to squamous cell (47% versus 30%), although results were not statistically significant (p = 0.184).

Conclusions: Concurrent chemo-radiotherapy regimens including cisplatin with and without 5-FU significantly improve recurrence rates and overall survival for cervical cancer patients. Toxicity was not increased significantly with the addition of chemotherapy to radiation, despite the majority of patients receiving extended field radiotherapy.
PARTICIPATION OF HEALTH WORKERS IN VIA, VILLI SCREENING IN ILE-IFE, SOUTHWESTERN NIGERIA, HOW FAR?

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Background: Low cost screening of visual inspection with acetic acid (VIA) and Lugol's iodine (VILLI) for early detection and prevention of cervical cancer was introduced to South western Nigeria in 2005. (INCTR/OAUTHC cervical cancer screening programme) This is to encourage good participation of women in the screening exercise for prevention and early treatment since it is low cost, effective and painless. Since then, regular information and mobilisation was routinely carried among the health workers and non health workers within and outside the hospital.

Aim: To find out the level of participation of women health workers working in the screening centre

Method: A retrospective study of the attendance records between March 2008 and March 2010 was carried out in the screening centre. The total number of the female health workers within and outside the screening centre that came for the screening were noted and was compared with the total number of women who had undergone the screening.

Result: Total number of health workers who has had the screening was 33 representing 7.37% of the total number of women enrollee who has had the screening, while the health workers within the screening centre who has had the screening is 14, (3.13%). There are about Seven hundred women health workers in the hospital.

Conclusion: Training and the knowledge from various ways of campaign going on all around about prevention of cervical cancer has not affected the workers participation in the screening to prevent Cervical cancer.
PHASE II TRIAL OF PACLITAXEL AND NEDAPLATIN IN PATIENTS WITH ADVANCED/RECURRENT UTERINE CERVICAL CANCER: A KANSAI CLINICAL ONCOLOGY GROUP STUDY

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Aims: A multicenter phase II trial was conducted to evaluate the activity and toxicity of paclitaxel and nedaplatin (cis-diammineglycolatoplatonum) in patients with advanced / recurrent uterine cervical cancer.

Methods: Patients were required to have measurable disease with adequate performance status, bone marrow, hepatic, and renal function. Histologic confirmation of the primary diagnosis as uterine cervical cancer was mandatory. The treatment consisted of paclitaxel 175mg/m2 and nedaplatin 80mg/m2 intravenously on day 1 every 28 days until progressive disease or adverse effects prohibited further therapy.

Results: Fifty patients were entered into the trial. 45 patients were evaluable for response (RECIST); 31 patients (68.9%) received prior radiotherapy and 23 patients (51.1%) received prior chemotherapy. A median of four cycles were administered to each patient (range: 1-16 cycles). The overall response rate was 42.2% (11 complete responses and 8 partial responses) with 26.7% of patients having stable disease. Grade 3 or 4 adverse events (NCI-CTCAE ver 3) at least possibly related to paclitaxel or nedaplatin included neutropenia (n=16, 35.6%), anemia (n=9, 20.0%), elevated serum creatinine level (n=3, 6.7%), allergy (n=1, 2.2%), anorexia (n=1, 2.2%), alopecia (n=4, 8.9%), myalgia/arthralgia (n=2, 4.4%) and sensory neuropathy (n=1, 2.2%). The median progression-free survival was 4.0 months (range: 1.0-29.8) and overall survival was 7.8 months (range: 1.6-29.8).

Conclusions: Paclitaxel 175mg/m2 and nedaplatin 80mg/m2 intravenously on day 1 every 28 days demonstrated antitumor activity and acceptable toxicity in patients with advanced / recurrent uterine cervical cancer. Evaluation of this regimen in phase III trials is warranted.
PROGNOSTIC VALUE OF TUMOR MARKER SCCA IN THE MONITORING OF CERVICAL CANCER PATIENTS

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Objectives: To investigate tumor marker dynamic during the treatment of cervical cancer patients.

Material and methods: There were analyzed results of primary level of tumor marker SCCA in 120 patients with cervical cancer at different stages of the disease, and different phase of treatment.

Results: There were revealed, that with tumor progression the level of SCCA was increased. The mean values varied from 1.14 till 8.08 ng/ml at stage I-IV of disease. We've defined the direct correlation between the level of SCCA and presence of tumor involvement of regional lymphatic nodes, which were confirmed after surgery. After adjuvant irradiation the SCCA level was decreased to 0.66 ng/ml (mean value).

Conclusion: The detection of expression level of SCCA is reasonable to make a prognosis for patients, and detection of early relapse of disease. The primary high level of SCCA correlates to high relapse-rate at follow-up, especially at advanced stages.

Keywords: Cervical cancer, tumor marker SCCA, prognostic factor.
PERSISTENCE OF HPV AFTER CONIZATION FOR CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

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Aim: To evaluate the frequency of HPV infection in patients during the follow-up period, after treatment for cervical intraepithelial neoplasia (CIN). Successful treatment of CIN results in complete eradication of HPV in most cases. Conization is the surgical technique most used for treating high-grade CIN, since it makes it possible to exclude invasive neoplasia, evaluate resection margins and preserve fertility.

Material and methods: 23 women with histologically verified CIN were tested for HPV DNA with the HYBRID CAPTURE 2 HPV DNA TEST (hc2) and were enrolled in the study. All of them had HPV testing pre- and postoperatively. Therapeutic conization was performed in all patients.

The mean follow-up period was 17 months during the period from January 2007 to December 2009.

Results: All 23 enrolled women were HPV positive. 17 conizations showed negative resection margins with 14 women becoming HPV negative. In the following months, 2 of these HPV negative women became HPV positive again. Out of 6 conizations with positive resection margins, 1 women became HPV negative. Recurrent CIN 2 lesions were observed in 1 woman, who had persistent positive HPV testing throughout the entire study period. Reconization was performed in that patient.

Conclusions: On the basis of the study results it seems recommendable that the HPV test should be used as the a method of detection of residual HPV infection after conization. Data suggest that HPV testing such as hc2 should be integrated in a follow-up algorithm after conization for CIN.
P16/Ki-67 DUAL-STAINED CYTOLOGY TESTING MAY PREDICT POST PARTUM OUTCOME IN PATIENTS WITH ABNORMAL PAP CYTOLOGY DURING PREGNANCY

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Background: Pregnancy-related changes may contribute to morphologic alterations that hinder the interpretation of cervical cytology specimens in pregnant women. In addition, neither cytology nor histology were shown to be good predictors of post partum persistence or progression of cervical intraepithelial lesions.

Aims: The objective of this retrospective cohort study was to determine whether a newly established immunocytochemical dual-staining protocol, which allows for the detection of co-expression of the p16 and Ki-67 biomarkers in the same cell as a surrogate marker for cell-cycle deregulation, may predict post partum outcome in patients with abnormal cervical Pap smears during pregnancy.

Methods: Pap smears from 27 pregnant women obtained during the first part of the first trimester and categorized as ASC-H, LSIL or HSIL were de-stained and subsequently stained for simultaneous p16/Ki-67 detection. Results were correlated to histologic outcome collected during post partum follow-up.

Results: Fourteen of 20 abnormal Pap smears during pregnancy showed a positive p16/Ki-67 dual-stained cytology result whereas 6 specimens were tested negative. Seven cases had were excluded due to technical reasons. All 14 patients positive for p16/Ki-67 dual-stain CIN in post partum histology (4 CIN1; 1 CIN2; 9 CIN3). In contrast, 5 out of 6 patients negative for p16/Ki-67 dual-stain had a negative histology post partum and during follow-up, and the remaining patient showed a CIN1.

Conclusions: P16/Ki-67 dual-stained cytology may provide a valuable novel approach to identify pregnant women with persistent or progressing CIN disease and may help improving the management of abnormal Pap cytology results during pregnancy.
THE COLUMNAR EPITHELIUM HYPOTHESIS OF CERVICAL CARCINOGENESIS

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HPV is the essential etiologic agent for intraepithelial and malignant squamous as well as glandular disease of the cervix. The science community agrees that HPV infection is initiated when a trauma exposes the reserve cells of the cervical metaplastic squamous epithelium of the transformation zone to infectious virus particles. It is now hypothesized that the major pathway of cervical carcinogenesis does not start with HPV infection of the reserve cells of the metaplastic squamous epithelium after microtraumata but with the HPV infection of a distinct number of subcolumnar reserve cells of the columnar epithelium with and without microtraumata.

This hypothesis provides explanations for the following findings:

1. Why do glandular, squamous and mixed lesions occur? The target cells for HPV, the subcolumnar reserve cells, can differentiate in both directions.

2. Why is malignant transformation of the original squamous epithelium of the cervix uncommon? The subcolumnar reserve cells are never located in the area of original squamous epithelium.

3. Why are recurrence rates low after excisional or destructive treatments of SIL and AIS? The predominant concentration of subcolumnar reserve cells is near the external os of the cervix. This area is removed or destroyed during treatment.

4. Why are early age at first intercourse and multiparity risk factors for cervical cancer? Early age shows a physiological eversion of columnar epithelium onto the ectocervix and a most active transformation. Also pregnancy shows repeated eversion of columnar epithelium onto the ectocervix. Anatomically, the subcolumnar reserve cells can now be easily reached by HPV.
COST-EFFECTIVENESS ANALYSIS OF WEEKLY VS THREE-WEEKLY CISPLATIN CHEMORADIATION IN CERVICAL CANCER

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Background and aims: Nowadays, concurrent chemoradiation has become the gold standard treatment for locally advanced cervical cancer. Weekly cisplatin has been increasingly used in many institutions, while three-weekly has been used in some. Therefore, we were interested in performing a cost effectiveness analysis comparing between the two methods of concurrent chemoradiation.

Methods: Using an economic model, we applied costs to total hospital charge to the patients and the salary/time used of the involved health personnel. We compared the costs of the two treatment types of cisplatin chemoradiation per median survival time. Our hospital data were used in the calculation of incremental cost per year of life gained (IC/YLG).

Results: Cost per year of life gained for weekly cisplatin chemoradiation regimens in stage II, III and IV were US$ 804.1, 1,399, 3,592.5 respectively. While the cost per year of life gained for three-weekly cisplatin chemoradiation regimens in stage II, III and IV were US$ 725.2, 1,262.1, 3,241 respectively. The Incremental cost per year of life gained (IC/YLG) of weekly over three-weekly cisplatin in stage II, III and IV were increasing from US$ 78.9, 136.9 and 351.5 respectively.

Conclusion: The decreased cost per year of life gained with three-weekly cisplatin chemoradiation adds a substantial benefit at an acceptable cost compared with weekly cisplatin chemoradiation particularly in more advanced stages. Three-weekly chemotherapy could save a considerable amount of resources including the total dose of the chemotherapeutic agent and the number of chemotherapy administration, thus providing an alternative approach especially in limited resource settings.
THE ASSOCIATION BETWEEN MCP-1 AND CCR2 SINGLE NUCLEOTIDE POLYMORPHISMS AND CERVICAL CANCER IN KOREAN WOMEN

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Cervical cancer is one of the most common malignant diseases among women, especially among Korean women. The pathophysiology of cervical cancer is not simple. There are multiple cofactors like viral factor, and host immunologic or genetic factors associated with cervical cancer. Monocyte chemoattractant protein-1 (MCP-1, chemokine (C-C motif) ligand 2) and chemokine (C-C motif) receptor 2 (CCR2) are suggested to involve in development and growth of tumor like breast cancer. This study was designed to investigate whether single nucleotide polymorphism (SNP) of MCP-1 and CCR2 genes are associated with the carcinogenesis of cervical cancer or not.

This study investigated 142 patients of invasive cervical cancer (ICC) and 218 patients of cervical intraepithelial neoplasia (CIN); they underwent operation, and were diagnosed with ICC or CIN histopathologically. And control group of 108 women underwent surgery with benign ovarian cyst. The SNP of MCP-1 was -2518 A>G and CCR2 was V64I. They were analyzed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP).

The result of this study showed no association among MCP-1 promoter -2518 and CCR2 exon2 V64I SNP and ICC or CIN. And clinical finding of cervical cancer like clinical stage, Human papilloma virus infection, and cervicitis were not associated with the genotype distribution of MCP-1 promoter -2518 A>G and CCR2 exon -V64I G>A polymorphism.

So, the results of this study suggest polymorphism of MCP-1 and CCR2 gene may not be associated with carcinogenesis of cervical cancer in Korean women.
THE ROLE OF HUMAN PAPILLOMAVIRUS TESTING IN PREDICTING THE RECURRENCE AFTER TREATMENT FOR HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA

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\textbf{Aims:} To examine the role of high-risk HPV DNA (HR-HPV DNA test) postconisation as prediction of recurrent or residual CIN after treatment of CIN2,3 and to compare this with follow-up cytology and the marginal status of the excised tissue.

\textbf{Methods:} 36 women treated with conisation for CIN2,3 were followed by HR-HPV DNA test every 4 months and further followed by colposcopy and cytology for 24 months at 6-month intervals to establish the presence of CIN2,3, proven with colposcopy-directed biopsy occurring within 24 months after treatment.

\textbf{Results:} In 3 of the 36 treated women (8%), residual or recurrent CIN and HR-HPV positive test occurred, 2 had a positive follow-up smear and 1 had positive section margins. From 33 cured women, 7 were HR-HPV positive, 3 had an abnormal smear and 6 had positive section margins. Women with HR-HPV DNA at 4 months showed recurrent or residual CIN in 14% (1/7) if they had normal follow-up Pap smears and in 50% (2/4) if they had abnormal Pap smears. Margin status was not statistically significantly associated with human papillomavirus status.

\textbf{Conclusions:} Persistence or clearance of HR-HPV DNA is an early valid prognostic marker of failure or cure after treatment for CIN2,3 and is more accurate than cytology or section margin status at the time of conisation. The absence of HR-HPV DNA has a 100% negative predictive value.
STUDY OF CHANGES IN LIPID PEROXIDATION AND ANTI-OXIDANTS LEVELS IN DIFFERENT STAGES OF CARCINOMA CERVIX

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Aim: To correlate the blood levels of Lipid Per oxidation (LPO) Catalase activity (CAT) Super Oxide Dismutase (SOD), vitamin-A and E with the different stages of carcinoma cervix.

Method: Total 150 women were included in this study. 90 women of H/P proved carcinoma cervix in different stages were in study group (GR.1) and 60 women without evidence of malignancy and without any other illness which altered the LPO and anti oxidants were in control group (GR.II). Each woman was subjected to detail history, examination, routine investigations and specific investigations (LPO,CAT,SOD,VIT-A & E Levels) estimation.

Results: The main LPO levels showed an increasing pattern over the four stages of carcinoma cervix. It was maximum in stage IV (5.524 +/- 0.02) and minimum in stage I (3.021 +/- 0) (p< 0.05). CAT & SOD Level decreased significantly in the higher stages of cancer (CAT 9.473 +/- 0.06, SOD 7.09 +/- 0.053) as compared to control group (CAT 16.02 +/- 0.35, SOD 10.66 +/- 0.14). Vitamin A & E levels were significantly lower in cancer cases than the control. There was significant diminution of Vitamin A & E from stage I to stage IV cancer cervix.

Conclusion: Increased LPO and decreased antioxidants levels may be taken as associated predictive markers and has prognostic significance. Thus suggesting that carcinoma cervix cases should get nutritive supplement to contain the blood LPO level and maintain a positive balance of antioxidants for better outcome in terms of delayed recurrence and better quality of life.
STUDY OF FREE RADICAL INJURY STATUS IN PRE MALIGNANT AND MALIGNANT CERVICAL LESIONS

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Aim: To assess the free radical injury status (super oxide dismutase and lipid per-oxidation) in healthy women, women with premalignant &malignant lesions of the cervix and to monitor the same two months after the treatment.

Method: Total 100 women without any illness which are known to alter free radical system were included in this study. Control group(29 cases with normal pap smear), Group I (25 women of chronic cervicitis),Group II (CIN 25 women )Group III (24 women of cancer cervix).All women had papsmear, colposcopy and cervical biopsy as and when required . 5 ml of heparinised blood was taken for estimation of Lipid peroxides ( in terms of malondialdehyde MDA) and superoxide dismutate(SOD)and it was repeated 2months after treatment.

Results: Mean age in control group and study group was comparable. Mean plasma MDA level in control group was 2.163 +/- 0.162 nmol/ml.where as in Group I 2.628 +/- 0.097 ,Group II 3.204 +/- 0.306 and Group III 4.295 +/- 0.481. Mean SOD in control group was 2.352 +/- 0.298mu/ml, group I 2.047 +/-0.157, in CIN(Group II) 1.614 +/- 0.192 , in group III 0.924 +/- 0.154. Changes in both MDA and SOD were statistically significant( p< 0.001) .After 2 months of the treatment the values of MDA were found falling and SOD were found rising.

Conclusion: Oxidative stress is one of the important factor in development of CIN and Carcinoma cervix. The use of anti-oxidants may be advocated to delay and arrest the progress of disease process.

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Introduction: Adenocarcinoma of the uterine cervix (AC) accounts for approximately 10-25% of all cases of cervical carcinoma (CC). Opinions vary regarding the prognosis for this histopathological type compared with the more common squamous cervical cancer (SCC). The effect of radiotherapy has been questioned.

Material and methods: During the period 1914-2004 18,400 cases of CC were treated at Radiumhemmet Stockholm of which 1532 cases were diagnosed as AC or adenosquamous cancer. This series is analysed during the whole period with respect to trends in the proportion out of the total series of CC, trends in stage and age-distribution and in survival by stage and treatment period compared with the SCC.

Results: The proportion of AC cases increased from 4% to 25%. The stage-distribution gradually shifted towards earlier stages. These changes as well as a shift towards higher mean age for the AC cases compared to that of the SCC cases fit an effect of screening activities in action after 1960. Long-term actuarial survival for AC corrected for intercurrent deaths improved by decades of treatment years but is still inferior to that of SCC.

Conclusions:

· The proportion of AC cases increased more than 5 times.

· The stage distribution gradually improved.

· Survival improved by each decade but is still worse than for the SCC cases.
IDENTIFICATION OF A GENE-EXPRESSION SIGNATURE FOR PREDICTING LYMPH NODE METASTASIS IN EARLY STAGE PATIENTS WITH CERVICAL CARCINOMA


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Background and aims: Pelvic lymph node metastasis (PLNM) is an important prognostic factor for cervical carcinoma. The aim of this study was to identify a gene-expression signature that could predict PLNM for cervical carcinoma.

Methods: A total of 88 cervical carcinoma patients with (n = 23) and without (n = 65) PLNM were randomly divided into a training group or a test group. An oligonucleotide microarray containing 1440 probes for human cancer-related genes was fabricated in house and used to detect the gene expression of cervical carcinoma. A gene-expression signature for predicting the PLNM in cervical carcinoma was identified in the training group and validated in the test group. The gene expression level detected in microarray was verified by quantitative reverse transcription polymerase chain reaction (qRT-PCR).

Results: A gene-expression signature for predicting PLNM was developed in patients from the training group, including 11 genes: RPL35, TMSB10, YWHAZ, BTD, LDHA, GUSB, SOD2, NR3C2, FN3K, XRCC4, and WNT2. In the test group, the signature's accuracy, sensitivity, specificity, positive predictive value and negative predictive value were 91%, 90.9%, 93.9%, 83.3% and 96.9% in predicting PLNM, respectively. The expression levels of 5 genes contained in the signature were confirmed by qRT-PCR. A multivariate regression model demonstrated that patients with high 11-gene score were associated with a 33-fold increase in risk for PLNM, compared to those with low score.

Conclusions: This study identified an 11-gene signature for predicting PLNM in cervical carcinoma and may help physician in planning the adjuvant therapies for patients.
MESONEPHRIC ADENOCARCINOMA OF THE CERVIX WITH SPINDLE CELL DIFFERENTIATION: A CASE REPORT

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Mesonephric adenocarcinoma of the cervix are rare, accounting for only about %2-3 of all primary adenocarcinomas. Only 33 cases have been reported so far in english medical literature. A very rare case of mesonephric adenocarcinoma with spindle cell differentiation and glandular component in the uterine cervix of a 50-year-old woman will be discussed. The patient presented with bleeding and gynecologic examination revealed a cervical mass. She underwent total abdominal hysterectomy, bilateral salpingooforectomy, bilateral pelvic lymphadenectomy, appendectomy and peritoneal fluid sampling. Tumor was resected with a surgical margin of 2 cm. Macroscopically the lesion was 4-5 cm, exophytic, almost circumferential, whitish yellow, friable mass in the uterine cervix. Microscopically; a biphasic pattern was seen, with endometrioid-appearing glands sepaerated by spindle cells. The tumor involved the entire cervix with varying depths of penetration. Immunohistochemically, the tumor was positive for vimentin, EMA (epithelial membrane antigen) and CD 10. After surgery the patient received concomitant chemoradiotherapy (cisplatin + external beam radiotherapy + brachytherapy). She was alive and disease-free at 18 months after surgery.

Little is known regarding optimal therapy or prognosis of mesonephric adenocarcinoma of the cervix, with some suggesting an indolent course with a propensity for multiple recurrences, and others an associated aggressive clinical course. Because of the absence of sufficient data to recommend a particular course of therapy for this uncommon disease, it would be reasonable and appropriate to manage patients with mesonephric adenocarcinoma of the cervix according to current guidelines for cervical adenocarcinoma of similar stage and pathologic findings.
THE COLPOSCOPICT MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA DURING PREGNANCY IN R.MACEDONIA

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Aims: Should colposcopy be delayed until 6 weeks postpartum in pregnant patients with atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL) cytology according to the incidence of cervical intraepithelial neoplasia (CIN) 2,3 in pregnant patients referred to our university clinic.

Methods: On 312 pregnant women with abnormal cytology, colposcopy was performed at the University Clinic for Gynecology and Obstetrics in Skopje, R. Macedonia

Results: 312 pregnant patients were identified. The most common cytology was LSIL (40.8%), then ASC-US (32.6%), and HSIL (12.8%). 69 patients (22%) underwent cervical biopsy on their initial colposcopy. 21 had CIN 1, 14 patients had CIN 2, and 11 patients had CIN 3. 22 patients (32%) had no evidence of CIN on biopsy. There were no cases of invasive cervical cancer identified. Of the 234 patients with ASC-US and LSIL cytology, 10 of 39 patients who had a cervical biopsy had CIN 2,3. Of the 128 patients with HSIL, 16 of 30 patients who had a cervical biopsy had CIN 2,3. Repeat colposcopy in the third trimester was performed on 24 patients. Only 1 of 7 patients with a repeat biopsy had CIN 2,3.

Conclusions: Pregnant patients with ASC-US or LSIL cytology rarely have colposcopic findings of CIN 2,3 at their initial colposcopy; therefore, it is reasonable to delay the initial colposcopy in patients with ASC-US and LSIL until 6 weeks postpartum.
SHORT-TERM RESPONSE TO NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADICAL SURGERY IN PATIENTS WITH LOCALLY ADVANCED UTERINE CERVIX CANCER. CASE SERIES

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Objective: To evaluate the short-term response to neoadjuvant multidrug chemotherapy (NMCh) with chemoembolization of uterine arteries (HEUA) followed by radical surgery in patients with locally advanced uterine cervix cancer (LA UCC).

Methods and results:

Patient population: The study included 54 newly diagnosed patients (LA UCC stage IIb (T2bN0-1M0) - 41 (75.9%), stage IIIb (T3bN0-1M0) - 13 (24.1%) patients), median age of 44.8 years (24-60 years). Forty eight patients (88.9%) had a squamous-cell carcinoma and 6 (11.1%) patients had adenocarcinomas.

Treatment: We started the treatment with two NMCh courses administered 3-4 weeks apart: intravenous cisplatin 70 mg/m (day 1) followed by bolus of gemcitabine in lipiodol 500 mg/m² (day 3). The response was evaluated 3-4 weeks following the completion of second course on the basis of clinical evaluation and MRI findings.

Following 1 courses of the NMCh surgery was performed in 37 of 54 patients (32 with T2b, 5 with T3b). After additional chemoradiotherapy, surgical treatment was administered to additional 11 patients (6 with T2b and 5 with T3b). Type III hysterectomy was performed in 43 patients and anterior exenteration of the pelvis in 3 patients. Resection of ureteral segments with formation of ureteroneocystanastomosis was done in 7 of 43 cases.

Conclusions: Administration of the two courses of NMCh with HEUA made it possible to perform surgical interventions in 68.5% of LA UCC patients. After additional chemoradiotherapy the total resectability rate in this population reached 88.9% with urinary tract surgery combined with anterior pelvic exenteration in 20.8% of the cases.
CHORIOCARCINOMATOSIS DEDIFFERENTIATION FROM ADENOCARCINOMA OF THE UTERINE CERVIX: A CASE REPORT

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Aim: Choriocarcinomatosis dedifferentiation from adenocarcinoma of the uterine cervix is a very rare neoplasm. The prognosis of this tumor is extremely poor, despite chemotherapy and surgery. In the present study, we report a 45-year-old woman with Choriocarcinomatosis dedifferentiation from adenocarcinoma of the uterine cervix.

Method: A 45-year-old woman presented with intermittent vaginal spotting, which had persisted for 4 months, also had no sexual contact during 7 months. Pelvic examination revealed a 7x6-cm exophytic friable mass in the cervix. Histologically, a cervical biopsy sample showed a poorly differentiated invasive squamous cell carcinoma. Additionally, PET/CT revealed an right lower lobe nodule and left ischial bone metastasis. After written informed consent obtained, she was started on palliative chemotherapy with paclitaxel 175 mg/m² plus cisplatin 75 mg/m².

Result: Pelvic examination after the third cycle of palliative chemotherapy showed an subjective no change of tumor size, and she complaint of continuous vaginal bleeding. After extensive discussion, the patient underwent radical hysterectomy with pelvic lymph node dissection. Histologic examination demonstrated adenocarcinoma with choriocarcinoma component with clear vaginal resection margins and a metastasis was found in one left external iliac nodes. In a laboratory exam, serum ß-hCG was 11924.0 mIU/ml. The patient recovered well and received one cycle of EMA-CO chemotherapy.

Conclusions: Choriocarcinomatosis dedifferentiation from adenocarcinoma of the uterine cervix is extremely rare. While the prognosis for patients with such a tumor is generally poor, aggressive EMA-CO combination chemotherapy may be beneficial.
THE EFFECT OF CISPLATIN WITH GREEN TEA POLYPHENOL IN THE HUMAN UTERINE CERVICAL CANCER CELL LINES

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Objective: Tea polyphenol has been shown to have anti-tumor properties in a wide variety of experimental systems. In this study, we evaluated TP as a biochemical modulator on the cytotoxic effects of cisplatin in cancer.

Methods: HeLa cells and epigallocatechin galate and polyphenon were used for these experiment. Western blot method were employed to detect the influence of EGCG and polyphenon on the expressions of p53, caspase 3, caspase8 and Noxa genes. The cell viability was determined using the MTT assay.

Results: The viability of the HeLa cells was decreased to 34% at a 12 ug/mL concentration of cisplatin, and to 11% above 25 ug/mL as measured by the MTT assay. However, in the co-treatment with EGCG(50 ug/mL), the cell viability decreased to 47% at 4 ug/mL of cislatin and to 15% at 6 ug/mL of cisplatin in HeLa cells, and in the co-treatment with polyphenon(50 ug/mL), the cell viability decreased to 51% at 4 ug/mL of cislatin and to 11% at 6 ug/mL of cisplatin in HeLa cells. The levels of p53, caspase-3, Noxa and caspase-8 in HeLa cells were increased by EGCG or polyphenon treatment.

Conclusion: These experiments showed that TP has a potentiating effect on cisplatin-induced cytotoxicity of HeLa cells. The synergistic activity of TP might be due to the increased caspase-3 by means of its influence on anti-neoplastic activity of cisplatin. So we conclude that in the co-treatment with TP, effects of cisplatin might be improved without increasing concentration of cisplatin.
SIGNIFICANCE OF PRETREATMENT SERUM CYFRA 21-1 LEVELS AS AN INDEPENDENT PROGNOSTIC FACTOR IN CARCINOMA OF THE UTERINE CERVIX

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Objective: Cyfra 21-1 is abundant in the serum of many patients with malignant tumors. Our purpose was to determine whether pretreatment serum Cyfra 21-1 levels serves as a prognostic indicator in patients with uterine cervix carcinoma, with reference to squamous-cell-carcinoma-related antigen (SCC-Ag).

Methods: Pretreatment serum SCC Ag and Cyfra 21-1 levels of 506 cervical cancer patients were measured. Clinical performance was evaluated by their receiver operating characteristic curves. Prognostic power of the pretreatment variables was assessed using Cox regression analysis.

Results: There was significant relationship between pre-treatment serum SCC Ag/Cyfra 21-1 levels and age, advanced FIGO stage, large tumor size, LN metastasis, and deep stromal invasion. Advanced FIGO stage ($P<0.001$), large tumor size (>4cm, $P<0.001$), elevated pretreatment SCC Ag ($\geq 1.95$ ng/mL, $P<0.001$) and Cyfra 21-1 ($\geq 2.95$ ng/mL, $P<0.001$) levels significantly decreased 5-year DFS by univariate analysis. Stepwise Cox regression analysis showed that pretreatment Cyfra 21-1 ($P=0.015$) was the only independent prognostic factor for disease-free survival. Pretreatment SCC Ag levels showed marginal significance ($P=0.053$). Advanced FIGO stage ($P<0.001$), large tumor size ($P<0.001$), age under 50 years ($P=0.037$) and elevated pretreatment SCC Ag ($P=0.024$), and Cyfra 21-1 ($P<0.001$) levels significantly decreased 5-year overall survival rates by univariate analysis. Stepwise Cox regression analysis showed advanced FIGO stage ($P=0.002$), large tumor size ($P=0.013$), age under 50 years old ($P=0.006$) were independent prognostic factors for overall survival.

Conclusion: Pretreatment Cyfra 21-1 levels significantly correlates with disease-free survival, but not with overall survival.
ROBOT-ASSISTED LAPAROSCOPIC RADICAL TRACHELECTOMY AND BILATERAL PELVIC LYMPHADENECTOMY IN EARLY STAGE CERVICAL CANCER: THE FIRST CASE REPORT IN KOREA

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Radical trachelectomy is a fertility preserving alternative to radical hysterectomy for women with early stage cervical cancer. Radical trachelectomy requires sophisticated surgical skills, including vaginal ligation of the descending branch of uterine artery. A thirty-four year old woman was diagnosed with cervical adenocarcinoma on punch biopsy. About 1.5 x 1.0 cm sized tumor was localized at the right upper lip of the uterine cervix. Loop electrosurgical excision procedure was performed prior to trachelectomy in an attempt to prevent the vaginal cuff from cancer seeding. After bilateral pelvic lymphadenectomy, robot-assisted laparoscopic radical trachelectomy was performed using only four trocars, including three robotic arms and one assistant trocar. Preservation of bilateral uterine arteries was feasible due to three-dimensional image and increased precision provided by the robotic system. Operation time was 480 minutes and there were no preoperative or postoperative complications. Robot-assisted laparoscopic radical trachelectomy, which holds the advantages of both laparotomy and laparoscopy, is a preferable treatment option for young women who wish to preserve fertility.
HUMAN PAPILLOMAVIRUS GENOTYPE DISTRIBUTION IN CERVICAL INTRAEPITHELIAL NEOPLASIA AND INVASIVE CANCERS IN HONG KONG

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Background: At least 15 types of human papillomavirus (HPV) have a potential to cause cervical cancer. This study examined the distribution HPV types among cervical intraepithelial neoplasia (CIN) and invasive cervical cancers (ICC) in Hong Kong.

Subjects and methods: Cervical samples collected from 2790 women including 769 aged 16-84 years with CIN 1, 805 aged 13-78 years with CIN2, 773 aged 19-83 years with CIN 3, 339 aged 21-85 years with squamous cell carcinoma (SCC), and 105 aged 32-86 years with adeno/adenosquamous carcinoma (ADC) were tested by Linear Array HPV Genotyping kit (Roche, CA).

Results: The HPV positive rates were: 79.2% for CIN1, 86.0% for CIN2, 84.2% for CIN3, 95.9% for SCC, and 88.6% for ADC. Proportions of positive samples harbouring >1 HPV type were: 29.4% for CIN1, 27.0% for CIN2, 26.5% for CIN3, 19.1% for SCC, and 20.4% for ADC. HPV16, 18, 52 and 58 were most commonly found (Fig. 1 and 2).

Conclusions: This study provides information necessary for population-specific vaccine cost-effectiveness assessment, and serves as a baseline for monitoring any type replacement after long-term widespread vaccination.

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PRE-OPERATIVE DIAGNOSIS AND THE MANAGEMENT OF MINIMAL DEVIATION ADENOCARCINOMA (MDA) AND LOBULAR ENDOCERVICAL GLANDULAR HYPERPLASIA (LEGH): A MULTI-CENTER, RETROSPECTIVE STUDY

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To improve the pre-operative diagnosis and management of minimal deviation adenocarcinoma (MDA) and lobular endocervical glandular hyperplasia (LEGH), a multicenter, retrospective study was performed.

A total of 112 cases were collected from 24 hospitals. The pathological diagnosis in each case was re-examined by a central review panel, which identified 54 cases of LEGH, 6 cases of MDA, 11 cases of adenocarcinoma. Diagnostic potential of magnetic resonance imaging (MRI), a Papanicolaou smear and the detection of gastric mucin for these patients was evaluated.

Papanicolaou smears of MDA or LEGH patients included NILM and various atypical cells. Gastric mucin detected by the latex agglutinin assay or Pap smears was frequently noted in LEGH cases. The diagnostic accuracy of MRI-based diagnosis for benign or malignant disease was 86.9% (40/46) and 66.7% (10/15), respectively, with an overall rate of 82.0% (50/61). Moreover, cystic structure on MRI with negative cytology and gastric mucin was suggestive of NC (correct ratio: 2/2, 100%). Cystic structure with inner solid parts on MRI with mild glandular atypia and gastric mucin strongly suggested LEGH (24/26, 92%). Solid structure on MRI with atypical glandular cells was indicative of MDA or adenocarcinoma (5/5, 100%). Of the 6 MDA, three had recurred, necessitating radical surgery. In contrast, no LEGH patients showed recurrence irrespective of the type of surgery.

The combination of MRI, a Pap smear and the detection of gastric mucin may improve the precision of pre-operative diagnosis. Patients suspected of having LEGH may need to be treated with less aggressive methods.
**DOES THE SIZE-SUBDIVISION OF STAGE IIA CERVICAL CANCER PREDICT THE PROGNOSIS? A MULTICENTER RETROSPECTIVE STUDY**

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**Background and aims:** In the revised FIGO staging system, stage IIA cervical cancer is subdivided into stage IIA1 and IIA2 by tumor diameter (4 cm). The aim of this study was to evaluate the validity of stage IIA sub-staging.

**Methods:** We reviewed 102 FIGO stage IIA cervical cancer patients who were treated by hysterectomy (N=73, Group S) or radiotherapy (N=29, Group R) between 1996 and 2006. We performed MRI for 89.2% of the patients to assess tumor size. Associations between various variables and 5-year-overall survival (5Y-OS) were investigated by uni- and multivariate analyses using the Kaplan-Meier product limit method.

**Results:** The substage distribution of the study subjects was as follows: 73 stage IIA1 (Group S, N=48: Group R, N=25) and 29 IIA2 (Group S, N=25: Group R, N=4). Interestingly, women with IIA2 tumors were significantly younger than those with IIA1 tumors (the mean age: 49.2 years vs. 58.8 years, P=0.02). The median follow-up period was 62.2 months and their 5Y-OS was 81.1%. Tumor size was significantly associated with 5Y-OS in both Group S and Group R (P= 0.0001 and 0.0005, respectively). When the analysis was confined to the Group S patients, lymph-vascular space involvement, lymph-node metastasis, parametrial involvement, deep stromal invasion and tumor size were significantly associated with 5Y-OS. However, the multivariate analysis of these variables revealed that tumor size was an independent prognostic factor.

**Conclusions:** Our data suggested that the revised FIGO staging, namely size-subdivision of 4 cm, is appropriate in estimating the prognosis of stage IIA cervical cancer.
HPV TYPE DISTRIBUTION IN INVASIVE CERVICAL CANCER AND HIGH-GRADE CERVICAL LESIONS IN MALAYSIA

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Background: Implementation of vaccination against oncogenic HPV types together with cervical screening is expected to significantly reduce the burden of cervical cancer. To estimate the potential impact of HPV vaccines in Malaysia, data on HPV type distribution in cervical cancer and high-grade pre-invasive cervical lesions are needed.

Objectives: To evaluate the prevalence of HPV-16, -18, and other high-risk HPV types in Malaysian women with invasive cervical cancer (ICC), cervical intraepithelial neoplasia (CIN) II/III or cervical adenocarcinoma-in-situ (AIS).

Methods: Malaysian women >21 years old diagnosed with ICC or CIN II/III/AIS were prospectively enrolled. Cervical specimens collected during routine clinical procedures were reviewed to confirm the presence of lesion and tested for HPV DNA.

Results: HPV DNA was detected in 96.0% (97/101) of ICC specimens and 95.9% (70/73) of CIN II/III/AIS specimens. Among ICC patients, 85.1% harboured single HPV type infection, HPV-16 (41.9%), -18 (27.9%), and -45/52 (8.1% each) were the most frequently identified types. These types were also the commonest HPV types in squamous cell carcinoma. In adenocarcinoma/adenosquamous carcinoma with single HPV infection, prevalence of HPV-18 (68.4%) and -45 (15.8%) surpassed the prevalence of HPV-16 (10.5%). Among CIN II/III/AIS patients, 68.5% had single HPV type infection, HPV-16 (44.0%), -52 (22.0%), and -18/58 (8.0% each) were the most prevalent types.

Conclusions: HPV-16, -18, and -45 were detected in the majority of Malaysian women with ICC in this study. Vaccination against oncogenic HPV types including and beyond HPV-16/18 is expected to significantly reduce the incidence of cervical cancer in Malaysia [Study ID: 110425].
RADICAL ABDOMINAL TRACHELECTOMY IN A FOUR AND HALF YEAR OLD GIRL FOR CLEAR CELL ADENOCARCINOMA OF CERVIX - ACCEPTABLE SURGICAL APPROACH

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Introduction: Clear cell adenocarcinoma of cervix, is a very rare tumor in Pediatric Population. Historically the recommended treatment is Radical Hysterectomy + Bilateral Pelvic node dissection, but this result in permanent Infertility. There has been adequate data on feasibility and Oncological safety of Radical Trachelectomy, which is an established surgery for adult women with carcinoma cervix who wish to retain fertility. There have been case reports in literature, where Radical Trachelectomy has been performed in Young girls with clear cell adenocarcinoma of cervix. We report a case of a very young girl with Clear Cell adenocarcinoma of Cervix treated with Radical Trachelectomy

Case history: A four and half year old girl presented with p/v bleeding. During evaluation by Examination under anesthesia + Cystoscopy + Vaginoscopy, she was found to have a 2 x 2 cm cervical mass, Vagina/Parametrium/rectum was free. Biopsy report: clear cell adenocarcinoma of cervix. MRI evaluation of abdomen and pelvis showed no lymphadenopathy. After parental counseling she underwent radical Trachelectomy + Bilateral pelvic node dissection. Intraoperative frozen section confirmed negative nodes and negative vaginal/Parametrial and proximal cut margins. After evaluating final histopathology report she was kept under close observation. 14 months post surgery patient is disease free

Conclusions: To our knowledge, this is amongst the youngest patient to undergo Radical Trachelectomy for clear cell adenocarcinoma of cervix. This fertility sparing approach is safe and feasible in carefully selected cases.
HIGH-RISK GROUP FOR LOCOREGIONAL RECURRENT IN PATIENTS WITH STAGE IB-IIB SQUAMOUS CELL CARCINOMA OF THE CERVIX TREATED WITH CONCURRENT CHEMORADIOTHERAPY

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Objectives: To identify predictive factors for locoregional recurrence in patients with cervical cancer treated with concurrent chemoradiotherapy (CCRT).

Methods: We analyzed 123 patients with stage IB-IIB squamous cell carcinoma of the cervix treated with CCRT between 1997 and 2007. Eligibility for CCRT included tumor size>4cm and/or pelvic lymph node enlargement. CCRT consisted of external beam radiotherapy (50 Gy/25 fractions), high-dose rate intracavitary brachytherapy (18 Gy/3 fractions), and cisplatin 20 mg/m² for 5 days every 3 weeks.

Results: The median age and follow-up period were 47 years and 51 months, respectively. The 5-year OS and DFS of the patients were 82.7% and 74.3%, respectively. Thirty of 123 patients had recurrent tumor, in which 15 patients had distant failure, two patients had both distant and locoregional failure, and the remaining 13 patients had locoregional recurrence. Tumor size (≥5.2 cm) and age (< 48 years) were independent predictive factors for locoregional recurrence by multivariate analysis [OR (95% CI); 5.8 (0.12-1.46), p=0.01, and 9.3 (0.34-2.60), p=0.002, respectively]. Based on these two factors, the patients could be divided into low-risk (n=91) and high-risk (n=32) groups for locoregional recurrence. The 5-year DFS for the low-risk group was 95.3%, which was significantly better than the high-risk group (65.5%, p< 0.0001). Locoregional recurrence occurred in 10 of 32 high-risk patients, and there were only 4 locoregional recurrences in the 91 low-risk patients.

Conclusions: To improve locoregional control in the high-risk patients, it may be worthwhile to consider CCRT using new radiosensitizing agents, adjuvant hysterectomy or adjuvant chemotherapy.
THE STUDY ON EFFICACY OF CHEMOTHERAPY IN PATIENTS WITH ADVANCED CERVICAL CANCER AFTER TREATMENT FAILURE - PILOT STUDY

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Aim: The aim of the study is to create an optimal chemotherapy schedule in patients with recurrent cervical cancer, as well as to evaluate response to the treatment and its toxicity.

Material and methods: 114 patients, aged 28-69 years (average 51.1), diagnosed with squamous cell cervical cancer with no response to the primary treatment (radiochemotherapy) or recurrent disease (proved in CT or MRI or biopsy), were treated in our clinic with chemotherapy.

The patients were divided into four groups:

I - 26 patients - Cisplatin + 5-Fluorouracil

II - 22 patients - Cisplatin + Topotecan

III - 30 patients - Cisplatin + Etoposide

IV - 36 patients - Cisplatin + Mitomycin C + Ifosfamide

Results: All patients received at least 4 cycles of chemotherapy. In 11 patients (9.6%) chemotherapy was terminated prematurely due to haematological toxicity, respectively in groups: 7.7%, 9.1%, 10%, 11.1%.

To evaluate the efficacy of the treatment we used average progression-free survival (PFS) and complete response (CR):

I. group - PFS = 6.7 months, CR - 7.7%

II. group - PFS = 10.5 months, CR - 18.2%

III. group - PFS = 8.6 months, CR - 20%

IV. group - PFS = 6.8 months, CR - 22.2%

Conclusion: Due to unsatisfying results we decided to close the recruitment to the I group of patients.

Low toxicity and results in rest of the groups encourage us to continue the study to establish the optimal chemotherapy schedule.
CISPLATIN AND ETOPOSIDE AS NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH STAGES IIB-IIIB CERVICAL CANCER: A PHASE II STUDY

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To evaluate the efficacy of cisplatin and etoposide as neoadjuvant chemotherapy in patients with advanced stage (stage IIB-IIIB) cervix cancer.

73 patients with advanced cervical cancer who were treated in Comprehensive Gynecologic Cancer Center, CHA University were enrolled. These patients received neoadjuvant chemotherapy using cisplatin and etoposide followed by radical hysterectomy with pelvic and paraaortic lymph node dissection. According to pathologic results, they were treated with concurrent chemoradiation or adjuvant chemotherapy. We analyzed the response of neoadjuvant chemotherapy, overall survival, and prognostic factors.

Of 73 patients, fifty-five had stage IIB, 2 had stage IIIA, and 16 had stage IIIB. The median age was 55 years (range 34-70), and most patients had squamous cell carcinomas (86%). A total of 280 courses of chemotherapy were administered. Objective responses of neoadjuvant chemotherapy occurred in 67 patients (92%); of these, 8 (11%) were complete and 59 (81%) were partial. Six patients (8%) showed no response to chemotherapy. The overall resectability rate was 89% (65/73). The analysis of the surgical specimens showed complete pathological response in 7 of 65 patients (11%). Microscopic residual disease was found in 8 (12%) and macroscopic pathologic response was found in 50 of 65 patients (77%). 48 patients (73.8%) received adjuvant chemoradiation. For a median follow up of 43 months (range, 5-80), the 5-year survival rate (5YSR) was 82% and 3-year disease-free survival rate (3YDFS) was 76%. In analysis of prognostic factors, stage, parametrial involvement, positive surgical margin and lymph node metastasis were statistically significant (p< 0.05).
APPLICATION OF THE RNA-BASED HPV TEST FOR DETERMINATION OF Е6/Е7 ONCOGENE EXPRESSION IN THE DIAGNOSTICS OF CERVICAL EPITHELIAL CHANGES

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Aim: Our purpose was to investigate the diagnostic value of the RNA-based HPV test (NucliSENS EasyQ™ HPV) which utilizes NASBA technology for determination of the expression of Е6/Е7 of five high-risk HPV types (16, 18, 31, 33 and 45).

Methods: Two hundred women aged 16 to 61 (mean 34.44) were prospectively studied. All of the women were subject to colposcopy, cytology and target biopsy. PCR DNA typing for 12 high-risk HPVss and RNA typing for Е6/Е7 oncogenes of five high-risk HPV were performed in parallel with a diagnostic kit NucliSens HPV v1.0 (bioMerieux).

Results: The colposcopy showed 119 normal and 81 abnormal findings (mild in 70 and heavy in 11). Cytological results were normal and non-neoplastic in 167, low-grade in 30 and high-grade in 3 women. The histological examination showed normal and inflammatory changes in 50, HPV findings in 94, low grade CIN in 35 and high grade CIN in 21 patients. DNA tests were positive in 148 (74%) women (60 with one and the rest with 2 and more genotypes). A positive RNA-NASBA test with one genotype was found in 23 women. The comparison of the two typing tests established a full correlation between the detected by the PCR high-risk type HPV and the presence of Е6/Е7 mRNA transcripts from the same HPV genotype.

Conclusion: Our results confirmed the high diagnostic possibilities of NASBA technology. This gave women with precancerous lesions of the cervix an opportunity to receive more precise diagnostics. (Grant TK 55/2009, Ministry of Education and Science)
CLEAR CELL ADENOCARCINOMA OF THE CERVIX ASSOCIATED WITH RUDIMENTARY UTERUS IN AN 11 YEARS OLD GIRL WITHOUT PRE-NATAL DES EXPOSURE

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Background: Clear cell adenocarcinoma accounts for 3 to 10% of primary adenocarcinoma of the cervix. However, cervical clear cell adenocarcinoma in adolescent is rare especially without maternal DES exposure during pregnancy. We would like to report a case and management of an adolescent diagnosed with cervical clear cell adenocarcinoma associated with rudimentary uterus.

Case report: An 11 years old girl presented with history of intermittent bloodstained discharge for one year. Physical examination revealed palpable 14 weeks size of pelvic mass with visible tissue protruding through introitus. MRI showed a huge mass arising from the cervix of a rudimentary uterus. The cervical mass appeared to be pushing the pelvic organ abdominally. There was no evidence of organomegaly, enlarged lymph nodes with normal appearance of upper and lower urinary tracts. The biopsy confirmed to be clear cell adenocarcinoma of cervix stage IB2. She underwent radical abdominal hysterectomy and bilateral pelvic lymph node dissection. Histological examination revealed that lymph nodes and para-cervical tissues were all free of tumor metastasis except an isolated tumor nodule present at vaginal cuff margin. She was subsequently treated with vagina vault radiation and followed up with pelvic examination under anesthesia, cytology and CT imaging.

Conclusion: We reported an extremely rare case of an adolescent cervical clear cell adenocarcinoma with rudimentary uterus in the absent of DES exposure. Literature reviews on similar cases are scarce with no consensus on optimum management. Long term follow-up will ensure the clinicians better idea on treatment, survival rate and subsequent patient counseling.
EVALUATION OF TYPE II RADICAL HYSTERECTOMY IN THE TREATMENT OF 960 PATIENTS WITH STAGE IB-IIB CERVICAL CARCINOMA

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Background and aims: Several studies have suggested that type II and type III radical surgeries are equally effective in treating stage IB-IIA cervical carcinomas. Whether type II radical hysterectomy is an effective treatment for stage IB-IIB cervical carcinoma is currently unclear. The aim of this study was to evaluate the treatment efficiency, clinicopathological features, and prognostic factors of patients with stage IB-IIB cervical cancer who underwent type II radical hysterectomies.


Results: Univariate analysis showed that histological type ($P = 0.003$), clinical stage ($P < 0.001$), pre-treatment squamous cell carcinoma antigen level ($P = 0.007$), depth of cervical invasion ($P < 0.001$), and number of pelvic lymph node metastases ($P < 0.001$) were associated with clinical outcome. Parametrial margin involvement ($P < 0.001$, 95% CI: 1.641-4.721), pelvic lymph node metastasis ($P < 0.001$, 95% CI: 2.055-5.062), and recurrence ($P < 0.001$, 95% CI: 3.005-7.006) were independent prognosis factors. The 5-year OS rates for stage IB-IIB patients were 87.7% and 74.1%, respectively, resulting in an OS rate of 84.3%. The overall recurrence rate was 14.4%. Adjuvant radiotherapy and chemotherapy improved the 5-year OS of stage IIB patients with high risk factors.

Conclusions: Type II radical hysterectomy has a better treatment efficiency for patients with stage IB-IIB cervical carcinoma. Adjuvant therapy improves the treatment efficiency of stage IIA-IIB patients associated with high risk factors.
PROGNOSTIC FACTORS IN NODE-POSITIVE STAGE IB-IIB CERVICAL CANCER PATIENTS TREATED BY TYPE II SURGERY

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Background and aims: Type II and III radical hysterectomies are equally effective in treating stage IB-IIA cervical carcinomas. However, it has not been demonstrated whether type II radical hysterectomies are a successful treatment strategy for pelvic lymph node metastasis (PLNM) in patients with stage IB-IIB cervical carcinoma. The aim of this study was to investigate the treatment efficiency and prognostic factors for patients with stage IB-IIB cervical carcinoma and PLNM who underwent a type II radical hysterectomy.

Methods: 288 patients with stage IB-IIB cervical carcinoma and confirmed PLNM underwent a type II radical hysterectomy between 1995 and 2005 were enrolled in our study.

Results: The 5-year overall survival (OS) rate for the 288 patients was 65.6%. Histology and parametrial margin involvement were independent prognostic factors for PLNM patients. Five-year OS and disease-free survival (DFS) rates for the low-risk group (72.5% and 61.5%, respectively) were significantly higher than those for the high-risk group (47.5% and 42.1%, respectively). In the low-risk group, the 5-year OS and DFS rates for patients that did not receive adjuvant therapy (60.3% and 50.5%, respectively) were lower than the rates for patients that received adjuvant radiotherapy (78.1% and 65%, respectively) versus radio-chemotherapy (72.8% and 63%, respectively). Adjuvant therapy improved the 5-year OS and DFS of patients in the high-risk group.

Conclusions: Type II radical hysterectomy is an adequate treatment for PLNM patients with stage IB-IIB cervical cancer in combination with appropriate adjuvant therapy. Histology and parametrial margin involvement are independent prognostic factors for PLNM patients.
SMALL CELL CARCINOMA OF THE CERVIX (SCCC)
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Background: Small cell cancer of the cervix is a rare and highly malignant sub-type of cervical cancer with a poor prognosis.

Methods and results: We performed a retrospective analysis of all SCCC patients treated in two cancer centres (Beatson, Glasgow and UCH, London) between 2000-2009. All cases were reviewed by the network pathologists and discussed at local Multi-disciplinary meetings. Twenty-nine eligible patients were identified with a median age at diagnosis of 50 (range: 22-86). Eight patients had FIGO stage 1b, 1 stage 2A, 11 stage 2b, 1 stage 3b and 8 with stage 4 disease. Thirteen patients underwent surgery (radical hysterectomy and pelvic node dissection = 11, vaginal hysterectomy =2). Twenty-five patients received chemotherapy (platinum plus etoposide = 20, platinum plus paclitaxel = 2, both regimens =2, gemcitabine and carboplatin=1). Fifteen patients received radiotherapy and fourteen patients received brachytherapy (11 patients had both radiotherapy and brachytherapy). Two patients were too unwell to receive any treatment and died shortly after diagnosis. The majority of patients who relapsed developed distant metastases (n=10) with 4 patients having local failures. The one-year and two-year relapse-free survival for all patients was 37% (95%CI: 19-55%) and 29% (95%CI: 13-47%) respectively. Eleven patients proceeded to salvage therapy after relapse. The one-year survival rate was 51% (95%CI: 31-68%) and 2-year survival rate was 34% (95%CI: 17-52%).

Conclusion: The best treatment for SCCC remains undefined but even with multi-modal therapy survival is poor and further study of the biology of these tumours is needed to find better therapies.
REDUCTION OF CIN, EGL, ABNORMAL PAP TESTS AND CERVICAL PROCEDURES WITH GARDASIL® VACCINATION

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Background and aims: Gardasil, the quadrivalent HPV6/11/16/18 vaccine is up to 100% efficacious in preventing HPV16/18-related CIN2/3 and AIS. We report the impact on the incidence of any CIN2/3 or worse, external genital lesions (genital warts, VIN1-3, or VaIN1-3), abnormal Pap tests, and procedures, regardless of causal HPV type.

Methods: A total of 17,622 women were enrolled in two Phase 3, randomized trials (FUTURE I and II). Gardasil or placebo was given at Day 1, Month 2 and 6. Pap testing occurred at Day 1 and every 6-12 months for up to 48 months. Colposcopy referral was Pap algorithm/HPV test-based. Definitive therapy referral was algorithm based, using accepted standards of care. We estimated the number of events prevented annually per 100,000 vaccinated women, in terms of risk difference in three populations: 1) unexposed: DNA negative at baseline to any of 14 HPV types and seronegative to HPV6/11/16/18; approximating sexually naïve females; 2) mixed HPV-exposed and unexposed; 3) previously HPV exposed (not shown).

Results: After an average follow-up of 3.6 years, significant reductions in the number of CIN lesions (~700-1000 cases prevented), abnormal Pap tests (~1300-1500 cases prevented), colposcopy (~1300 cases prevented), cervical biopsy (~1000-1300 cases prevented), and definitive therapy (~600 cases prevented) were observed in all three populations.

Conclusions: Our data suggest that we could expect to have similar public health impacts in terms of disease reduction in the years immediately following vaccination in women irrespective of their exposure to HPV.
RECENTLY URODYNAMICS CHANGES IN THE PATIENTS WITH CERVICAL CANCER BETWEEN THE PRE-AND POST RADICAL HYSTERECTOMY

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Objective: To evaluate the recently urodynamics changes before and after radical hysterectomy, and to investigate the reasons of postoperative patients with urinary retention.

Methods: 87 patients with cervical carcinoma in FIGO stage I₂-IIₐ were received radical hysterectomy. All patients were compared pre-and post-operational urodynamics changes by using LABORIE Urodynamic System.

Results: Data from the urodynamics analysis performed in 10—14 days after radical hysterectomy have shown that the average first sensation volume (133.8±4.2 vs 100.5±3.8, P=0.032) and residual urine volume (89.0±18.8 vs 10.5±5.8, P=0.037) were increased, while the maximum flow rate of natural(Qmax) (10.5±2.3 vs 22.8±4.1, P=0.001) and the bladder compliance(20.7±12.6 vs 54.2±36, P=0.037) were decreased. Some post radical hysterectomy patients were observed with urinary retention and bladder outlet obstruction accompany with maximum Watts Factor(WFₘₐₓ) (73.6±17.0 vs 53.5±15.11, P=0.003) and the time of urination (74.3±23.9 vs 46.1±16.6, P=0.001) were increased.

Conclusion: Radical hysterectomy result in the recently urodynamics changes, while urodynamics analysis may provide some method to direct the treatment of bladder dysfunction after operation.
THE PLACE OF RADICAL SURGERY IN ADVANCED STAGES CERVICAL CANCER

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Aims: The place of radical surgery in advanced stages (IB2 or above) cervical cancer is still debatable.

Materials and methods: We've studied 28 patients with advanced cervical cancer in which we performed radical hysterectomy Piver 3 with pelvic and paraaortic lymphadenectomy. The final pre- or intraoperative staging was IB2 for one patient, IIB in 20, IIIB (T1BT2BN1M0) in 6 and IVB (T2BN0M1 - ovarian metastases and ascites) in one. Twenty patients initially staged as IIB suffered neoadjuvant radiochemotherapy followed by surgery 4-6 weeks after completion of therapy; all the rest of the patients received postoperative adjuvant chemoradiation.

Results: Intraoperative complications occurred in 3 patients (vascular injuries). Postoperatively, complications occurred in 5 (17.8%): 2 transient acute renal failures, 2 paralytic ileus and one wound seroma. The median number of removed pelvic and paraaortic lymph nodes was 22.0 and 8.9, respectively. We found pelvic and paraaortic lymph nodes metastases in 10 (35.7%), and respectively 3 patients (10.7%). All 3 patients with paraaortic metastases were positive also for pelvic lymph nodes. Follow-up was between 4 and 42 months. At present, 5 patients are dead and 23 alive, 22 without and one with a vaginal recurrence.

Conclusions: The radical surgery in advanced stages cervical cancer represents a feasible technique, with a relatively low rate of intraoperative complications. Postoperative complications look to be generated but the prolonged duration of surgery, but also by the retroperitoneal dissection. Its therapeutic role in terms of survival is not conclusive and could be established in the next future.
UTILIZATION OF IMMUNOHISTOCHEMICAL STUDIES IN DIFFERENTIATING SUPERFICILY INVASIVE OR MICROINVASIVE SQUAMOUS CELL CARCINOMA OF UTERINE CERVIX FROM CARCINOMA IN-SITU (CIS)

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Background: The distinction of superficially invasive (SQCC)/ microinvasive squamous cell carcinoma (MIC) of uterine cervix from carcinoma in-situ (CIS) may be difficult in the presence of an obscuring inflammatory infiltrate. We studied the stromal/ fibroblastic reaction and stromal expression of CD34 and SMA in (LEEP) samples of cervix in MIC and CIS for the distinction of features of invasion.

Design: The pathology archive at UHN was searched between 2001-2009 and 50 cases, 19 SQCC/MIC, 21 CIS and 10 biopsy sites were retrieved. 3 Pathologists reviewed the H&E slides to confirm the presence and type of invasion (single focus vs. multiple foci), presence or absence of inflammation, type of inflammatory cells (eosinophils, plasma cells or lymphocytes) and fibroblastic response. CD34 and SMA were used on formalin-fixed, paraffin-embedded tissue.

Result: The patients’ age ranged from 21-66 years (mean: 37). Moderate to marked fibroblastic reaction was seen in 8/19 patients with MIC and 5/21 CIS. CD34 was expressed in 1/19 MIC and 15/21 CIS, and moderate or strong SMA staining was noted in 6/19 MIC and 6/21 CIS. Chi-Square statistical analysis showed significant difference for fibroblastic reaction between MIC and CIS (p<0.001) and CD34 expression (p<0.001) with little difference for SMA expression (p=0.442)

Conclusion: We demonstrated that loss of CD34 expression, in conjunction with utilization of SMA may have a value in predicting early stromal invasion in CIS. Analysis of a larger series may be necessary to confirm the clinical significance of our findings and their potential for targeted therapy.
EFFICACY OF GARDASIL® AGAINST PERSISTENT INFECTION OR DISEASE IN WOMEN WITH PRIOR VACCINE HPV TYPE INFECTION

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**Background and aims:** In the quadrivalent HPV (types 6/11/16/18) vaccine (Gardasil) clinical program, at vaccination 15% of women showed past cleared infection with one or more vaccine HPV types (seropositive and DNA negative). Analyses in women aged 16-26 demonstrated that no women seropositive and DNA negative for a vaccine type at enrollment were diagnosed with disease related to the previously cleared HPV type. Fifteen placebo subjects developed disease related to previously cleared vaccine types. Vaccination may prevent recurrence or reactivation of infection or disease. Here we present data for women aged 24-45.

**Methods:** 3819 women aged 24 to 45 with no history of cervical disease in the past 5 years, LEEP, hysterectomy, or genital warts were enrolled in an international randomized trial. Women received either Gardasil or placebo at Day 1, Month 2 and 6. Pap testing, genital inspection and cervicovaginal sampling were conducted every 6 months. Analyses were performed in women who were seropositive and negative to ≥1 vaccine HPV type at enrollment. Mean follow-up time per subject was 3.8 years.

**Results:** Persistent infection with vaccine HPV types occurred in 5 vaccine and 15 placebo subjects. No cases of CIN or EGL occurred. Vaccine efficacy against persistent infection was 66.8% (95% CI: 3.8, 90.5), and was 81.3% (95% CI: 14.4, 98.0) in women aged 35-45 (11 placebo, 2 vaccine cases).

**Conclusions:** Vaccination with Gardasil is associated with a lower incidence of reactivation/recurrence of persistent infection related to vaccine HPV types in women aged 24-45.
RADICAL HYSTERECTOMY FOR IRRADIATED CERVICAL CANCER - HOW RADICAL THE PROCEDURE SHOULD BE IN THESE PATIENTS?

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Objectives: To establish the extension of radical surgery in preirradiated cervical carcinoma patients.

Material and methods: This retrospective study included cervical cancer patients diagnosed in "Dr. Ion Cantacuzino" Clinical Hospital, during 2006-2009. After cervical biopsy, patients were referred for preoperative radiotherapy. After radiotherapy, patients were clinically reexamined to establish the feasibility for surgery. Radiotherapy effectiveness and the need for extensive radical hysterectomy were assessed by comparison with pathological results.

Results: Of 87 irradiated cervical cancer patients, 48 were submitted to radical hysterectomy. Initial stage distribution was: IA-6.4%; IB-17.0%; IIA-6.4%; IIB-59.6%; IIIB-10.6%. Restaging postradiotherapy (postRT) showed 76.74% stage I and 23.25% stage IIB cases, with minimal pericervical infiltration.

Carcinomatous cells were present on:
- cervix in 52.78% postRT stage I patients, versus 41.67% postRT stage IIB; p=0.5052.
- corpus uteri in 5.56% postRT stage I patients, versus 33.33% stage IIB; p=0.0196.
- vagina in 2.78% postRT stage I patients, versus 16.67% postRT stage IIB; p=0.0852.
- parametrial tissues in 2.78% postRT stage I patients, versus 25% postRT stage IIB; p=0.0268.
- lymph nodes in 5.56% postRT stage I, versus 16.67% postRT stage IIB patients; p=0.2589.

Piver II radical hysterectomy was performed in 83.33% postRT stage I patients, versus 75% postRT stage II; Piver III was performed on the rest of patients; p=0.5318.

Major postoperative complication occurred in 55.56% cases after Piver III hysterectomy, versus 5.13% after Piver II; p=0.0006.

Conclusion: Piver II hysterectomy provides adequate resection in cervical carcinoma patients responsive to radiotherapy, without major postoperative complication associated with the more radical Piver III hysterectomy.
CASE REPORT. FANCONI'S ANAEMIA AND CERVICAL CANCER

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A 30 year old lady presented to the Colposcopy Department of the Whittington Hospital, London with a severely dyskaryotic smear. She complained of postcoital bleeding. In her medical history she was diagnosed with Fanconi's congenital aplastic anaemia. She underwent bone marrow transplantation with adjuvant radiotherapy and chemotherapy 14 years ago. She has been in remission since treatment, but is possibly infertile.

Colposcopy at presentation was unsatisfactory (transformation zone type3). A high grade lesion with coarse mosaic, coarse punctuation, gland openings, but no abnormal vessels was seen. She was admitted for an urgent excisional laser cone biopsy in theatre under general anaesthesia. The subsequent cone biopsy, measuring 20x15x10 mm, confirmed the presence of multifocal squamous cell carcinoma of cervix FIGO stage IA-1, with multiple crypt involvement and a maximum depth of invasion of 1.1 mm. The excision margins were complete.

Fanconi's anaemia is a rare chromosomal instability disorder (1 in 350000) with a very high risk of developing squamous-cell carcinoma of the lower female genital tract. The cumulative incidence of solid tumours by age 45 is about 30%, which continues to rise with patient’s age. In this group of women it has been suggested that human papillomavirus (HPV) infections were most likely to persist and progress to cervical intraepithelial neoplasia grade 3 (CIN3) and cancer. Vigilance and prompt referral to the appropriate centre for further investigations will allow early diagnosis and treatment of precancerous lesions of the cervix and overall improve the chances of survival in this cohort of patients.
LONG-TERM OVERALL SURVIVAL OF PATIENTS WITH CERVICAL CARCINOMA IB2 - IIB TREATED BY SURGERY ALONE OR WITH ADJUVANT RADIO-/CHEMOTHERAPY

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Objective: To evaluate retrospectively cervical carcinoma patients (stage Ib2 - Iib) treated with radical hysterectomy alone, or with radical hysterectomy and postoperative radiation or chemoradiation by conducting a 10 year follow-up.

Methods: Between 1995 and 1999, 112 cervical cancer patients stage Ib2 -Iib treated with Surgery; radical hysterectomy with pelvic / and paraaortic lymphadenectomy alone (35 patients) or surgery followed by radiation (32 patients) or surgery followed by chemoradiation with cisplatin (45 patients).

After the therapy, patients were followed for more than 10 years. Ten-year survival rates were evaluated. During the 10 year follow up, 7 patients were lost.

Results: Overall 10-year survival rates were 61% for the surgery group, 69% for the surgery and radiation group, 75% for the last group (surgery and chemoradiation).

Initial tumor size was not a risk factor for recurrence. Lymph node metastasis, parametrial involvement, deep stromal invasion and positive margins were significant risk factors for recurrence. The progression-free interval (PFI) for patients with lymph node metastases was not significantly lower in the Chemoradiation group than the other groups.

Conclusion: Lymph node metastasis is the most significant independent risk factor for recurrence. The postoperative chemoradiation improves the long term Overall survival but not the PFI of bulky and locally advanced cervical cancer patients.
OVARIAN TRANSPOSITION FOR THE PRESERVATION OF OVARIAN FUNCTION IN YOUNG PATIENTS WITH CERVICAL CARCINOMA

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Introduction: Ovarian transposition into the paracolic gutters is done with the aim of shielding the ovary from radiation therapy. There is ongoing debate about the effectiveness of ovarian transposition with reported failure rates varying between 12 to 90%.

Objective: Analyze the effectiveness of ovarian transposition for the preservation of ovarian function in women submitted to surgery for cervical cancer.

Materials and methods: Retrospective study. Group 1 (G1): all women submitted to radical hysterectomy for cervical carcinoma with conservation and transposition of the ovaries, between 01.2004 to 09.2009, with or without pelvic radiation after the surgery. Group 2 (G2-Control group): women submitted to radical hysterectomy for cervical carcinoma without conservation of the ovaries (chosen aleatorily). The ovarian function was clinically analyzed.

Results: 22 patients in G1; 22 patients in G2. 8 lost to follow up. 36 women analyzed (19-G1;17-G2). Mean age: 38 (31-46) in G1 and 44,6 (37-49) in G2. 33% (12) submitted to radiation therapy, 26% (5) in G1 and 41% (7) in G2. Preservation of ovarian function was achieved in 63,2% (12) in G1. In G2, 70,6% (n=7) become climacteric. For patients treated exclusively by surgery 21,5% (3) become climacteric in G1 and 70% (7) in G2 (p=0.04). For patients treated by postoperative external radiation therapy 80% (4) in G1 and 71% (5) in G2 (p=1) become climacteric.

Conclusion: Ovarian transposition is safe, is effective in young women treated with surgery for cervical carcinoma. It doesn't seem to be effective if radiation pelvic therapy is performed. Risk of metastasis is low. Laboratory follow up tests for ovarian function should be performed to acquire results.
COMPARISON WEEKLY CISPLATIN THERAPY WITH TRIWEEKLY COMBINATION CHEMOTHERAPY AS ADJUVANT CONCURRENT CHEMORADIATION AFTER RADICAL HYSTERECTOMY IN CERVICAL CANCER

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Objective: We evaluated two chemotherapy methods used with radiotherapy (RT) as adjuvant therapy after radical hysterectomy in cervical cancer.

Methods: IB-IIA cervical cancer patients who underwent radical hysterectomy and pelvic lymph node dissection and followed by adjuvant concurrent chemoradiation therapy due to pathologic risk factors were retrospectively recruited. Adjuvant treatment modalities were concurrent chemoradiation with weekly cisplatin chemotherapy or triweekly combination chemotherapy. Clinicopathologic factors, recurrent site, disease free survival (DFS), overall survival (OS) and side effect between weekly cisplatin group and triweekly combination group were analyzed.

Results: One hundred patients received triweekly combination chemotherapy with RT and 40 patients had weekly cisplatin chemotherapy with RT as adjuvant treatment. There was no significant difference between two groups. Twenty-one of 100 patients (21.0%) were recurred in combination chemotherapy group and five of 40 patients (12.5%) were recurred in weekly cisplatin group (p=0.243). Of recurrence site, 100% (5/5) in the weekly cisplatin group and 61.9% (13/21) in the combination chemotherapy group were extra-pelvic (p=0.281). DFS was 87.5% for patients treated with weekly cisplatin chemotherapy and 79% for those treated with triweekly combination chemotherapy (p=0.2886). OS was 90.0% and 88.0% for the same treatment groups (p=0.8273). Leukopenia, neutropenia, thrombocytopenia, anemia and hepatopathy were more common and more severe on the triweekly combination chemotherapy group (p=0.000) (p=0.000) (p=0.013) (p=0.001) (p=0.003).

Conclusions: Weekly cisplatin therapy as adjuvant concurrent chemoradiation after radical hysterectomy in cervical cancer had a similar therapeutic effect and less side effect compared to the triweekly combination chemotherapy.
RISK FACTORS FOR DELAYED DIAGNOSIS OF CERVICAL CANCER ACCORDING TO A MULTIVARIATE HIERARCHICAL MODEL

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Background: Cervical cancer (CC) represents a major public health problem and delayed diagnosis is frequently done. Studies related to delayed diagnosis of CC are rare in the literature.

Aims: To evaluate the risk factors associated with delayed diagnosis of CC according to a multivariate hierarchical model.

Methods: Women from two Brazilian centers for cancer treatment were invited to answer a questionnaire (132 questions) on risk factors related to delayed diagnosis of CC (104 women with cervical intraepithelial neoplasia and 74 with CC). The risk factors were grouped into three hierarchical layers for multivariate analysis.

Results: The risk factors for delayed diagnosis of CC were: age ≥ 35 years (35 - 44 years: OR = 5.0, P = 0.046; ≥ 45 years: OR = 13.0, P = 0.001), women who did not know the difference between Pap smear test and gynecologic examination (OR = 2.4, P = 0.014), women who did not know the importance of the Pap smear test (OR = 3.7, P = 0.032), history of previous tubal ligation (OR = 2.4, P = 0.045) and absence of gynecologic symptoms (OR = 3.4, P = 0.002). History of previous treatment for sexually transmitted disease represented a protective factor for delayed diagnosis (OR = 0.3, P = 0.028).

Conclusions: The absence of symptoms, poor knowledge about cancer prevention and increasing age were risk factors for delayed diagnosis of CC. Tubal ligation can generate a false sense of security to women regarding the prevention of sexually transmitted diseases and CC.
DELAYED DIAGNOSIS OF CERVICAL CANCER: IS IT POSSIBLE TO DEFINE RISK GROUPS?
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Background: Although the cervical cancer is an easily preventable disease through Pap smear, most of the cases are diagnosed in advanced stages in Brazil.

Aims: To classify women into risk groups for delayed diagnosis of cervical cancer.

Methods: This study included 104 women with cervical intraepithelial neoplasia and 74 with cervical cancer from two Brazilian centers for cancer treatment. The women were invited to answer a questionnaire (132 questions) on risk factors related to delayed diagnosis of cervical cancer. The risk factors were assessed by means of a multivariate hierarchical model. According to this model, the risk factors were: age ≥ 35 years, poor knowledge about the difference between Pap smear test and gynecologic examination, poor knowledge about the importance of the Pap smear, history of previous tubal ligation, absence of gynecologic symptoms and absence of history of previous treatment for sexually transmitted disease. The number of risk factors per woman was calculated. Women were divided into four risk groups for delayed diagnosis of cervical cancer: low risk (no factors), intermediate risk (1 or 2 factors), high risk (3 or 4 factors) and very high risk (5 or 6 factors).

Results: The prevalence rates of cervical cancer were 0%, 21%, 49% and 95% (chi-square test: P < 0.001) respectively for low, intermediate, high and very high risk groups.

Conclusions: These risk groups seem to predict the likelihood of delayed diagnosis of cervical cancer. The greater the number of factors, the greater the likelihood.
REASONS FOR NOT PERFORMING PAP SMEAR: A COMPARISON STUDY BETWEEN WOMEN WITH CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER

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Background: Pap smear is recommended for cervical cancer screening. Despite this recommendation, Pap smear coverage rates are still low in developing countries. The reasons for not performing Pap smear are not clearly understood.

Aims: To compare the reasons for not performing Pap smear between women with cervical intraepithelial neoplasia and cervical cancer.

Methods: Women from two Brazilian centers for cancer treatment were invited to answer a questionnaire (20 questions) about the reasons for not performing Pap smear (104 women with cervical intraepithelial neoplasia and 74 with cervical cancer). The two groups were compared by means of chi-square test.

Results: Women with cervical cancer indicated more frequently the following reasons for not performing Pap smear: absence of symptoms (68.9% vs. 33.8%, P < 0.001), lack of knowledge about the necessity of performing the Pap smear (27.0% vs. 11.5%, P = 0.008), absence of prior orientation (25.7% vs. 11.5%, P = 0.014), disbelief in Pap smear (25.7% vs. 11.5%, P = 0.002), lack of time (40.5% vs. 23.1%, P = 0.012), financial difficulty (28.4% vs. 12.5%, P = 0.008), shame (28.4% vs. 15.4%, P = 0.035), belief that it is not necessary at that age (16.2% vs. 4.8%, P = 0.011) and fear of contracting diseases during the gynecologic examination (8.1% vs. 1.0%, P = 0.021).

Conclusions: Reasons for not performing Pap smear were more common among women with cervical cancer. Nevertheless, all the indicated reasons are related to a poor knowledge about cervical cancer screening and Pap smear.
IDENTIFICATION OF HEAT SHOCK PROTEIN 27 EXPRESSION IN SQUAMOUS NEOPLASIA OF THE UTERINE CERVIX

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Background and aims: Using proteomic methods, we have previously established that heat shock protein 27 (hsp27) may be a marker of both cervical intraepithelial neoplasia (CIN) and squamous cell carcinoma (SCC). However, the histologic distribution of hsp27 has not yet been explicitly defined. The aim of our present study was to evaluate the expression pattern of hsp27 in a broad range of normal cervical tissues in addition to potentially premalignant and malignant lesions of the cervical mucosa.

Methods: Immunohistochemical analyses were performed using formalin-fixed, paraffin-embedded tissue sections of normal mucosa (n= 53), CIN 1-3 (n=90), and SCC (n= 21), in addition to biopsy and hysterectomy specimens, to evaluate the expression patterns of hsp27. The results were expressed as the percentage of positively stained cells relative to the total cell number. The scoring system used for the staining results was as follows: 0 (0%), 1 (1-10%), 2 (11-90%), and 3 (91-100%).

Results: Our immunohistochemical staining results revealed that the expression of hsp27 is detectable not only in SCC but also in CIN1-3 at levels that are significantly higher than in normal mucosa ($P < 0.05$). Moreover, the hsp27 expression levels in CIN3 and SCC were significantly higher than those in CIN1 ($P < 0.05$). Additionally, hsp27 strongly localized at the boundary area in both the tumor and the non-tumor cells.

Conclusion: Our present data show that hsp27 may be involved in tumor development and in the progression from a cervical intraepithelial neoplasia to a squamous cell carcinoma.
KNOWLEDGE ABOUT PAP SMEAR AND HUMAN PAPILLOMAVIRUS AMONG WOMEN WITH CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER

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Background: Cervical cancer is a disease related to HPV infection and can be easily prevented through Pap smear. In developing countries the cervical cancer screening programs are still ineffective in controlling the disease. This difficulty may be related to a poor knowledge about HPV and Pap smear.

Aims: To compare the knowledge about Pap smear and HPV between women with cervical intraepithelial neoplasia and cervical cancer.

Methods: Women from two Brazilian centers for cancer treatment were invited to answer a questionnaire about Pap smear (11 questions) and HPV (3 questions). The sample was composed by 104 women with cervical intraepithelial neoplasia and 74 with cervical cancer. Comparisons were made by means of chi-square test.

Results: In comparison to women with cervical intraepithelial neoplasia, those with cervical cancer most often: did not know what the Pap smear is (32.4% vs. 14.4%, P=0.004), did not know the difference between Pap smear and gynecologic examination (56.8% vs. 36.5%, P=0.008), did not know the importance of Pap smear (21.6% vs. 4.8%, P=0.001), believed that Pap smear is a pregnancy test (59.5% vs. 42.3%, P=0.024), have never heard about HPV before (64.9% vs. 44.2%; P=0.007), have never heard about HPV vaccine before (77.0% vs. 59.6%, P=0.015) and did not know what diseases are HPV-related (78.4% vs. 50.0%).

Conclusions: The study revealed that there was insufficient or misleading information about the Pap smear and HPV among those women with cervical cancer.
ATYPICAL GLANDULAR CELLS DIAGNOSED DURING PREGNANCY AND POSTPARTUM PERIOD - A RETROSPECTIVE REVIEW

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Aims: The objective of the study was to determine the incidence and clinical significance of atypical glandular cells (AGC) or atypical glandular cells of undetermined significance (AGUS) diagnosed in pregnant and postpartum women.

Methods: Smears having a diagnosis of AGC or AGUS, taken from pregnant and postpartum (within 6 weeks after delivery) women between 1995 and 2008 were reviewed and subclassified according to the Bethesda 2001 classification. Case records were then reviewed and a second cytology review was performed after disclosure of the follow up data.

Results: Among 91,133 smears taken from pregnant and postpartum women, 70 had AGC or AGUS (0.07%) diagnosed. Follow up data was available in 40 cases with mean duration of follow up being 43 months. Among the 40 patients with follow up data, nineteen smears had coexisting squamous abnormalities. Thirty patients had a positive pathology, including 18 (45%) cervical intraepithelial neoplasia III (CIN III), four (10%) cervical adenocarcinoma-in-situ, three (7.5%) squamous cell carcinoma of cervix, four (10%) condylomas and one (2.5%) hydatidiform mole. On review, 24 out of 32 smears with AGC ‘NOS’ had a significant pathology.

Conclusions: AGC found on cervical smears during pregnancy and postpartum period is uncommon. However, the chance of having a significant cervical pathology is high and colposcopy should be performed.
ANEMIA IN PATIENTS WITH EARLY CERVICAL CANCER: ASSOCIATION WITH PELVIC LYMPH NODE METASTASIS AND POOR OVERALL SURVIVAL

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Objectives: Anemia is a common finding in cervical cancer patients, but the role of pre-treatment anemia is less clear-cut in early cervical cancer patients treated surgically. We investigated whether there is a correlation between anemia, other clinicopathologic variables, and survival.

Methods: A total of 303 patients diagnosed with stage IA-IIA cervical carcinoma by the criteria of International Federation of Gynecology and Obstetrics and treated with surgery were analysed. Anemia was defined in terms of hemoglobin concentration less than 110g/L. we evaluated the relationships among pre-treatment hemoglobin concentration and anemia presence, clinicopathologic features and prognosis in cervical cancer patients.

Results: The prevalence of anemia in our patients was 24.4%(n=74). Anemia presence and hemoglobin concentration were significantly associated with FIGO stage (P < 0.001), tumor diameter (P=0.029) and pelvic lymph node metastasis (P < 0.001). The optimal hemoglobin threshold value was 118g/L for discriminating cancers metastasizing to pelvic lymph nodes. The 5-year overall survival(OS) for anemic and non-anemic patients were 76% and 88% respectively (P =0.011). Using multivariate analysis, anemia lymph vascular space invasion (LVSI) and pelvic lymph nodes metastasis were significant and independent prognostic factors of OS in early cervical cancer patients treated with surgery.

Conclusion: Pre-treatment anemia is associated with pelvic lymph node metastasis and poor overall survival in patients with early stage cervical cancer.
THE VALUE OF CONIZATION FOR POSTMENOPAUSAL WOMEN WITH HIGH GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA

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Background: The standard treatment for high grade cervical intraepithelial neoplasia (CIN) consists of ablation and excision, but in postmenopause the correct management is still debated.

Aim: To investigate the value of conization in the diagnose and treatment for postmenopausal women with high grade CIN.

Methods: The postmenopausal patients diagnosed as CINII-III by biopsy and conization (LEEP or cold knife conization) selected as the primary treatment method were analyzed retrospectively, premenopausal patients were selected randomize as the control. 101 cases of postmenopausal patients and 202 cases of premenopausal patients were enrolled.

Results: The mean age of postmenopausal women was 56.0y, the premenopausal patients was 36.0y. The cytologic abnormalities (≥ASCUS) has no significant difference between two groups (75.0% vs 79.8%, p=0.036), also the positive rate of HPV test (HC-II) (89.5% vs 86.4%, p =0.812). The satisfactory rate of colposcopy was significantly lower in postmenopausal patients (23.2% vs 68.9%, p =0.001). The positive margin rate of conization was significantly higher in postmenopausal patients (20.8% vs 10.9%, p=0.020). After conization, 10 cases of postmenopausal and 2 cases of premenopausal women were diagnosed as cervical cancer relatively.

Conclusions: The cytology and HR-HPV test may have the same value of diagnose for postmenopausal with high grade CIN lesion. The therapy value of conization was relatively lower for postmenopausal patients, but cervical carcinoma could be found.
UNCLEAR RESECTION MARGIN IN CONIZATION AS RECURRENCE MARKER IN CERVICAL CARCINOMA IN SITU IN SOUTH KOREA

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Background: In most cases, the lesions are completely removed by conization, however, involvement of the resection margins by CIS may occur. This has always represented a problem to the pathologist as well as to the gynecologist when planning follow-up and further therapy.

Aims: The aim of this study was to evaluate unclear resection margin in conization specimens as recurrence marker by investigating the statistical association of the risk of recurrence between clear and unclear resection margins.

Methods: medical and histopathological record review.

Results: 136 patients visited our dept. and treated by LLETZ and conization due to CIS during recent 10 years were enrolled in this study. 79 (58.1%) patients had clear margins in the primary operation specimens and 57(41.9%) patient's margins were involved by dysplasia. There were 16 recurrences. When univariate analysis was performed to investigate the statistical relation between the resection margins and recurrences, there was significant correlation (P = 0.03, P < 0.05) Median follow up duration was 22 months.

Conclusions: In our study, the relation between unclear resection margin and relapse was statistically significant. According to the literature, unclear resection margin is not an optimal recurrence marker. However, our study shows new trend in prognosis of CIS. This means resection margins could been used by recurrence marker. Our study samples are small, so further investment would be necessary.
DETECTION OF TERC AMPLIFICATION IN CERVICAL EPITHELIAL CELLS FOR THE DIAGNOSIS OF HIGH-GRADE CERVICAL LESIONS AND INVASIVE CANCER

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Since telomerase activation is a relatively early event in cervical carcinogenesis, expression of the human telomerase RNA gene, TERC, has the potential to serve as a biomarker for the diagnosis and prognosis of cervical neoplasias. To determine the role of TERC in cervical carcinoma, amplification of TERC was evaluated in liquid-based cervical cytological preparations and compared with the differential diagnosis of the samples analyzed. In total, 83 research centers participated and 7786 cases were enrolled. TERC amplification was detected using a dual-color fluorescence in situ hybridization (FISH) probe set, and these results were compared with cytological and histological results, testing for high-risk human papillomavirus (HPV) DNA, and patient age. TERC amplification was found to be greater in more advanced cases of cervical carcinogenesis. The sensitivity and specificity of TERC amplification in evaluating CIN2+ was respectively 80.7% and 83.8%. Moreover, Youden's index value (64.5%, 95%CI: 61.4-67.6%) and area under the receiver operating characteristic (ROC) curve (82.3%, 95%CI: 80.5-84.1%) of samples with TERC amplification were found to be greater than the same values calculated for cytology and high-risk HPV analyses of the same samples. Therefore, TERC amplification, represents a valuable genetic biomarker, that in combination with an evaluation of cytology or HPV testing, can achieve higher sensitivity and specificity in distinguishing high-grade cervical lesions and invasive cancers from low-grade lesions.

Acknowledgment: We wish to show our thanks to all research centers for kindly providing data.
COMPARISON OF THE EXPRESSION OF THE P16 AND Ki-67 BETWEEN CERVICAL SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA

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Objective: To evaluate the p16 and Ki-67 expressions in cervical adenocarcinoma, we examined the p16 and Ki-67 expressions in cervical squamous cell carcinoma and adenocarcinoma.

Method: Immunohistochemical staining for p16 and Ki-67 was performed in 30 squamous cell carcinoma, 30 adenocarcinoma and 20 controls. A score was given as follows: 0 points for 0% reactivity, 1 point for 1-10% reactivity, 2 points for 11-50% reactivity, 3 points for 51-80% reactivity, and 4 points were for 81-100% reactivity.

Result: There were significant differences in p16 (p=0.00) and Ki-67 (p=0.00) expression status between control, squamous cell carcinoma and adenocarcinoma.

As for p16 expression, the entire squamous cell carcinoma patient showed 4 point. But, in adenocarcinoma patients, p16 expressions were as follows: 4 point, 25 patients; 2 point, 1 patient; 0 point, 4 patients. In squamous cell carcinoma patients, Ki-67 expressions were as follows: 3 point, 7 patients; 2 point, 23 patients. But, in adenocarcinoma patients, Ki-67 expressions were as follows: 3 point, 1 patient; 2 point, 28 patients; 1 point, 1 patient.

There were significant differences in expression status of p16 (p=0.023) and Ki-67 (p=0.014) between squamous cell carcinoma and adenocarcinoma.

Conclusion: p16 and Ki-67 expressions of cervical adenocarcinoma were significantly lower than those of cervical squamous cell carcinoma.
OUTCOME OF EXTENDED FIELD RADIOTHERAPY FOR CERVICAL CANCER PATIENTS WITH PARA-AORTIC LYMPH NODES AT DIAGNOSIS - NCCS EXPERIENCE

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**Aim:** Para-Aortic nodal involvement at presentation in cervical cancer is not uncommon. We report survival outcome and patterns of failure in our patients treated radically.

**Methods:** We reviewed 18 cervical cancer patients with para-aortic node involvement on CT, treated with extended field radiotherapy with or without chemotherapy between March 2003 and November 2007. Treatment data, toxicities and patterns of relapse were recorded. Overall (OS) and disease free (DFS) survival were analysed using Kaplan-Meier method.

**Results:** 88% had squamous cell carcinoma, 22% were FIGO 2B and 50% 3B. 8 patients (44%) received chemotherapy. Median follow-up was 30 months (6 to 81 months), median OS 42.3 months (95% CI, 7.05 - 77.55 months) and median DFS 15.8 months (95% CI, 7.9 - 23.6 months). 36-months OS and DFS were 52.5% and 23.5% respectively. Mean para-aortic dose was 51.8 Gy (45 - 64 Gy). 12 (66%) patients achieved complete resolution (CR); 1 (8%) subsequently recurred in-field as first site of relapse, 4 (33%) developed distant metastases, 3 (25%) relapsed both distantly and in-field while 4 (33%) patients remain disease free at last follow up. 1 patient had late grade 3 gastrointestinal toxicity.

**Conclusions:** Extended field radiotherapy with or without chemotherapy can achieve long term disease-control in approximately a quarter of patients, and is well tolerated. Many however eventually relapse at distant sites, underlying the need for effective systemic therapy.
DIGITAL CERVICOGRAPHY AS AN ADJUNCT TO COLPOSCOPY

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**Introduction:** Visual screening methods for cervical intraepithelial neoplasia such as direct visual inspection and cervicographs have been shown, in several studies, to have low specificity and sensitivity. However, most of these studies used lower resolution photographs. Some used digital photography in conjunction with cervical smears. To our knowledge, there are no published studies using digitally captured and electronically stored images at colposcopy for assessing the degree of correlation with cytology and histology.

**Aim:**

1. To assess the degree of correlation between electronically stored high resolution digital cervicographs, cytology and histology.
2. To evaluate the agreement between different colposcopists.
3. To assess the usefulness of cervicographs as an adjunct for training.

**Methodology:** 40 cases were randomly selected retrospectively and stored images on View point system were interpreted by 5 accredited colposcopists of different grades separately. They were blinded to the original colposcopic impression, cytology and biopsy results. Weighted kappa statistic (Fleiss and Cohen, 1973) was used to assess the concordance in the ratings between cytology, original colposcopy impression and five different colposcopist impression.

**Results:** Results of the 41 cases included in the study, 22 had high grade smear, 13 were low grade and, 5 normal.

- There was *fair* correlation between recent cytology however *moderate* correlation with histology overall colposcopic impression of grade of disease.

- There was more correlation between senior colposcopists on the overall colposcopic grade of the lesion. There was *greater* agreement on overall grade with normal & high grade lesions compared to low grade lesions, although the overall correlation was moderate.
THE 10-YEARS FOLLOW-UP RESULTS OF LOOP CONIZATION WITH RIGHT-ANGLED TRIANGULAR SHAPED EXCISOR IN PATIENTS WITH CIN 3

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Objective: To preserve the uterus in patients with CIN 3 (CIS), the patients were followed up to evaluate the therapeutic value of conization using right-angled triangular shape loop cone biopsy excisor that is known easy to excise of deep cervical tissue and to preserve in a better cervical shape.

Methods: A retrospective review of 126 patients was performed who underwent therapeutic cervical conization for CIN 3 (CIS) by using right-angled triangular shape loop cone biopsy excisor from January, 2000 to December 2009. Among 126 patients who had therapeutic conization, fourteen of them who wanted to preserve the fertility was involved resection margin at cone biopsy.

Results: The mean duration of follow-up patients who had conization for therapeutic purpose was 48.8 months (range 6-120). Their mean age was 38.9 years old and mean parity was 1.3. Ten of 126 patients had CIN 3 (CIS) on exocervix and four of 126 patients had CIN 3 (CIS) on endocervix. During the followed up period, only two person (2/126) had relapse of CIN 3 (CIS), hence, a simple hysterectomy was done.

Conclusion: Right-angled triangular shape loop cone biopsy excisor is more effective low rate of margin positive and recurrent rate in conservative treatment in CIN 3 (CIS) patients who want to preserve uterus or fertility.
CHEMORADIOSENSITIZATION OF BRACHYTHERAPY IN CARCINOMA OF UTERINE CERVIX: THE FRINGE EFFECTS IN ADVANCE DISEASE

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Background: 80 percent of Indian cancer cervix patients report in bulky stage II /stage III / stage IV with dismal cure rates. Carcinoma of uterine cervix afflicts middle aged in her prime of life. Conventional treatments have not been able to give long-term survivals for early stages even after the ‘megarads’ delivery in the core by brachytherapy. The culprits must be the under dosed peripheral fringed areas or radio- resistant hypoxic cells.

Aims:

- To improve disease free and cure rates in late stage cancer of uterine cervix patient assigned for radical/ palliative radiation.
- To evolve betterment of quality of life and long term survival for stage III cervical cancer.
- To provide prolonged palliation/cure in stage IV A disease.
- To find out an answer to the biological behaviour and patterns of recurrence in these cases.

Methods: Post teleradiation Chemosensitized brachytherapy was tried for the first time in the world through a multiarm trial. Study group(n=40) received 5-FU, Cis-platinum, and Bleomycin infusions over 17-20 hours when patient was receiving MDR brachytherapy. The controls (n=40) received only brachytherapy.

Results: Complete primary and complete parametrium response was observed in 36/40 and 30/40 patients respectively in study group on five year survival data. The control group showed primary and parametrium complete response in only 8/40 and 4/40 subjects respectively.

Conclusion: This hallmark observation in the treatment of cervical cancer through chemoradiosensitization of post-teleradiation brachytherapy with long term survival further advocates for future ideal modality of treatment with better response rates in these patients.
PHASE II STUDY ON TOPOTECAN(T)/CISPLATIN (C) COMBINATION REGIMEN FOR TREATMENT OF PERSISTENT, RECURRENT OR ADVANCED CERVICAL CARCINOMA IN CHINESE POPULATION

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Background: T/C regimen has been proven to be effective for advanced cervical cancer with nonoverlapping toxicity. This multicenter phase II study is to explore the efficacy and safety of the T/C in Chinese population.

Method: Planned 40 patients in total with stage IVB, recurrent or persistent carcinoma of cervix will be enrolled to receive topotecan 0.75 mg/m2/d d1-3 followed by cisplatin 50 mg/m2 on d3 every 3 weeks for 6 cycles at maximum. Overall response is primary endpoint according to RECIST1.0, toxicity profile and clinical benefit rate are secondary endpoints.

Result: From Mar 09 to Apr 10, 20 patients with FIGO stage IIA-IVB cervical cancer, ECOG PS 0-1, systemic chemotherapy naïve have been recruited, median age 44yrs (30-65yrs), 66% pts received radiotherapy. Efficacy: Within 15 patients evaluable, 46 cycles of this chemotherapy were administered, 6 patients (40%) had partial response, 4 patients (26.7%) had progressive disease. Safety: 8 patients appeared neutropenia, 5 patients belong to Grade1/2, 3 patients (20%) had G3 neutropenia, 6 patients received supportive G-CSF treatment; only one appeared thrombocytopenia, which was G4, no G1-3 thrombocytopenia observed. For non-hematotoxicity, although 66% patients received anti-emetics, 2 patients without this supportive care had G3/4 vomit, no other side effect was observed during the study.

Conclusion: In this interim analysis, topotecan plus cisplatin seems to be tolerable and demonstrates a comparable response rate with previous study for Chinese cervical cancer patients, it allows to continue study enrolment. Planned study recruitment will be closed by this year end.
THE EFFICACY OF CONCURRENT CISPLATIN AND 5-FLUOROURACIL CHEMOTHERAPY AND RADIATION THERAPY FOR LOCALLY ADVANCED CANCER OF THE UTERINE CERVIX

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Objective: To evaluate the efficacy of concurrent chemoradiation (CCRT) using 5-fluorouracil (5-FU) and cisplatin for locally advanced cervical cancer.

Methods: We reviewed the medical records of 57 patients with locally advanced cervical cancer (stage IIB-IVA and bulky IB2-IIA tumor) who underwent the CCRT at Dong-A University Hospital from January 1997 to June 2007. The CCRT consisted of 5-FU, cisplatin and pelvic radiation. Every three weeks, 75 mg/m² cisplatin was administered on the first day of each cycle and 5-FU was infused at the dose of 1,000 mg/m²/d from the second day to the fifth day of each cycle. Radiation was administered to the pelvis at a daily dose of 1.8 Gy for five days per week until a medium accumulated dose reached to 50.4 Gy. If necessary, the radiation field was extended to include paraaortic lymph nodes.

Consolidation chemotherapy was performed using 5-FU and cisplatin.

Results: Fifty-seven patients were enrolled and the median follow-up duration was 53 months (range 7-120 months).

The overall response rate was 91.5% (74% complete response and 17.5% partial response). The 5-year overall survival and 3-year progression free survival rates were 69.4% and 74.9%, respectively. During the follow-up period (median 23 months, range 7-60 months), fourteen patients were diagnosed as recurrent disease.

Conclusion: CCRT with 5-FU and cisplatin which is the primary treatment for patients with locally advanced cervical cancer was effective and well tolerated.
ANALYSIS OF PROGNOSIS IN CERVICAL CANCER PATIENTS WITH INTERMEDIATE RISK FACTORS

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Objectives: To analyze prognosis of patients with intermediate risk factors of early stage cervical cancer.

Methods: From 1988 to 2006, we analyzed 387 FIGO stage Ib-IIa cervical cancer patients with intermediate-risk factors. Intermediate-risk factors were defined as follows: large tumor size (≥2cm), deep stromal invasion (invasion to middle or deep one third) and lymphovascular space involvement.

Results: 88 patients had no intermediate-risk factor, 134 patients had one intermediate-risk factor, 115 patients had two intermediate-risk factors and 50 patients had three intermediate-risk factors. In univariate analysis of 5-year survival rate, tumor size, deep stromal invasion and lymphovascular space involvement were statistically significant (respectively, P=0.0219, P<0.0001, P=0.0105). In multivariate analysis, deep stromal invasion was the only significant prognostic factor (P=0.0073). The more number of intermediate-risk factor, 5-year survival was decreased (P<0.0001). There was no significant difference of 5-year survival rate between patients with no intermediate-risk factor and patients with one intermediate-risk factor (100% vs 97.7%, P=0.1077). But, 5-year survival rate of patients with two or three intermediate-risk factors were decreased (respectively, 100% vs 92% P=0.0002, 100% vs 93.2% P<0.0001). There were 146 patients of postoperative adjuvant therapy, 107 of them received radiation therapy and others were performed concurrent chemoradiation therapy. But there was no significant difference of 5-year survival rate (93.7% vs 93.8% P=0.4462).

Conclusions: More than two intermediate-risk factors were related to survival. However, there was no significant difference of prognosis between postoperative radiation therapy and concurrent chemoradiation therapy.
PREVALENCE OF HPV IN WOMEN WITH NORMAL CERVICAL CYTOLOGY AND CERVICAL NEOPLASIA AND COFACTORS PLAYING ROLE IN CERVICAL CARCINOGENESIS

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Objective: To examine the prevalence of human papillomavirus (HPV) DNA in cervical samples among women with normal and abnormal cervical cytology from Izmir, Turkey and the relationship between the emergence of cytological abnormalities and the presence of HPV DNA and cofactors.

Materials and methods: Six hundred and forty-two women provided cervical samples for the detection of HPV by PCR-based assays. Age, number of term births, the age at first sexual intercourse, contraceptive method, the existence or history of warts, smoking habit, number of sexual partners, the history of sexually transmitted diseases and the history of circumcision of male sexual partners were recorded.

Results: Patients with cervical cancer, ASCUS, ASC-H, LGSIL and HGSIL carry HPV DNA and especially high risk HPV DNA with a high rate. Smoking, number of sexual partners, history of sexually transmitted diseases and genital warts were related with the prevalence of HPV DNA, meanwhile only the history of sexually transmitted diseases was related with malign transformation. Also we found that the use of barrier methods can't protect from transmission of HPV but might protect from malign transformation.

Discussion: Not all women who were infected with HPV develop premalignant or malignant transformation. A number of cofactors must be effective in predicting which women have a tendency to develop premalignant or malignant lesions. Determining the prevalence of HPV in the population and the cofactors which are important for cervical carcinogenesis will help in improving the strategies for prevention of cervical cancer which is a disease with high rates of morbidity and mortality.
DUTCH ALGORITHM FOR FOLLOW-UP AFTER TREATMENT FOR CERVICAL INTRAEPITHELIAL NEOPLASIA; EFFECTIVE TO PREDICT RECURRENCES UP TO 7.5 YEARS AFTER TREATMENT

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Background and aims: In the Netherlands women treated for high-grade cervical intraepithelial neoplasia (CIN) are monitored for recurrence (rCIN) using cytology. After three subsequent negative smears women return to the population-based screening program. We evaluate this policy and describe the long-term cumulative incidence of rCIN3+.

Methods: In three hospitals 440 women with CIN2/3 were treated between 1988 and 2004. They were monitored by cytological screening until the study cut-off point in December 2009.

Results: The median follow-up was 7.5 years. During follow-up 39/440 (8.9%) developed rCIN3+ of whom 26 within 2 years of treatment (Figure 1). To predict rCIN3+ after the first two years, women with three consecutive negative smears had a significantly lower risk to develop CIN3+ after the first two years of follow-up than those who did not have three negative smears (1/257, 0.4% versus 12/157, 7.6%; p<0.001, Figure 2).

Conclusions: Women treated for CIN2/3 in the Netherlands have a risk of only 9.9% to develop rCIN3+. Women with three consecutive negative smears within 2 years should be referred to the 5-yearly population-based screening program as their risk for rCIN3+ is lower than the risk in the general population.

[Fig1: Cumulative incidence of recurrent CIN3+]  
[Fig2: Cum. inc. rCIN3+, triple negative cytology]
SIGNIFICANCE OF HUMAN PAPILLOMAVIRUS DNA TYPE IN CERVICAL ADENOCARCINOMA BY HPV DNA CHIP


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Objectives: The role of human papilloma virus(HPV) infection in the development of cervical carcinoma is well established, however the prevalence of HPV DNA in cervical adenocarcinoma varies from study to study. This study was designed to determine the possible impact of status of HPV infection on the survival of patients with cervical adenocarcinoma.

Methods: The clinical data of 87 patients with adenocarcinoma of cervix that were diagnosed at department of gynecologic oncology, School of medicine, Keimyung University, from 1999 to 2008 were reviewed and classified according to the WHO classification. For 87 cases, HPV typing was performed with PCR based HPV typing using microdissected paraffin-embedded archival tissue.

Results: The overall prevalence of HPV infection in cervical adenocarcinoma was 68.9% (60 cases). 90% were positive for either HPV 18 (n=34, 56%) or HPV 16 (n=20, 33%) or both (n=3, 5%). Of other single HPV types detected, HPV 45 accounted for 2 cases (3.3%) and HPV 52 was found in one case (1.6%). The status of HPV infection had no impact on patient survival, and could not be correlated with any of the analyzed clinicopathologic parameters. Multivariate analysis confirmed clinical stage and pathologic grade as significantly associated with survival.

Conclusions: Mostly HPV 16 and HPV 18, is highly associated with most of the cervical adenocarcinomas. The status of HPV infection had no impact on patient survival, and could not be correlated with any of the analyzed clinicopathologic parameters.
THE FIRST 18 MONTHS OF INTRACAVITARY HDR BRACHYTHERAPY FOR GYNAECOLOGICAL MALIGNANCIES AT THE BEATSON WEST OF SCOTLAND CANCER CENTRE

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Background In June 2007 we converted from MDR Brachytherapy for Gynaecological malignancies to GammaMed HDR. The switch to HDR has major resource implications. We adopted ABS dose guidelines and used 30Gy in 5 insertions as standard dose. Aims We treated 109 patients with HDR intracavitary insertions. Our aims were to monitor not only feasibility but also immediate and late complications to ensure we were not encountering unexpectedly high levels of toxicity. Methods Patients were identified from the Varian Aria data base and case notes for follow up assessment. Results All were treated with radical intent following external beam radiotherapy and 91% with concomitant cisplatin chemotherapy. Of these 98 had cervical cancers, 11 endometrial cancers and 3 vaginal cancers. We were able to deliver 30Gy/5 fraction delivered twice weekly to 70 (63%) the remainder received shorter courses due to anaesthetic fitness (37) or patient request (2). 1 received no treatment as she was unable to tolerate the applicators, 12 received 2 fractions, 22 received 3 fractions, 5 received 4 fractions. Overall follow-up ranged from 15 to 34 months, during this time we encountered 14 immediate and 9 significant late treatment related complications. Conclusions In our experience switching to HDR required a large amount of preparation by all staff members involved, response are comparable with prior MDR with no change in complications seen. This audit will be repeated in 2 years for completeness for long term toxicities, disease free and overall survival.
A CASE REPORT OF EMBRYONAL RHABDOMYOSARCOMA OF THE UTERINE CERVIX IN A PREGNANT WOMEN

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Introduction: Embryonal rhabdomyosarcoma (ERMS) is extremely rare malignant tumor of uterine cervix. The incidence of these tumors in pregnant women is undefined, only a few numbers of reports have been published. RMS which is most common in early childhood has a second peak of occurrence between 14 and 18 years of age. Common sites of presentation are the orbit, others are head and neck sites, extremities, trunk, and genitourinary organs.

Case: We present a case of a 30 year old pregnant woman who presented with bleeding and a mass protruding from vagina in 30th gestational weeks. On examination, there was a hyperemic, protruding mass which was measured in 5x7 cm diameter. She underwent polypectomy and pathology result came up as botryoid type embryonal rhabdomyosarcoma. After fetal lung maturation at 35th gestational weeks pregnancy was ended by cesarean section. On 27th day of postoperative period, she underwent radical hysterectomy, pelvic-paraortic lymph nod dissection and ovarian transposition. Final pathology result was ERMS at microscopic size on cervical surface and lymph nodes were negative. Postoperative adjuvant chemotherapy (vincristine and actinomycine D) was given according to pediatric protocol. At 15th months control, the patient has no evidence of disease.

Conclusion: Even though EMRS in pregnancy is very rare condition, malignancy should be considered at vaginal bleeding in the pregnancy period.
HRHPV-TESTING IN A UNIVERSITY OUTPATIENT CLINIC: SHORTCOMINGS AND RECOMMENDATIONS

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Objective: To study whether applying hrHPV-testing in a gynaecological outpatient clinic leads to better detection of high-grade cervical intraepithelial neoplasia (CIN2+) lesions.

Methods: This study was designed as an observational cohort study. In the first six months of 2007, 1149 consecutive women visiting the gynaecological outpatient clinic of a university hospital were simultaneously tested for hrHPV and by cytology. Data on previous history, referral reason and CIN2+ yield after 18 months of follow-up were retrieved passively through the Dutch nationwide registry of histo- and cytopathology (PALGA) and the hospital information system. We identified three groups: women with presumed cervix pathology (group 1), women with presumed endometrial pathology (group 2) and miscellaneous (group 3). The main outcome measure was histological confirmed cases of high-grade cervical disease.

Results: The prevalence of hrHPV infection was 21.0% (range:11.6% (group 2) to 30.8% (group 1). The 18 month risk of CIN2+ adjusted for the number of performed colposcopies was 6.0% in the total group. HrHPV positive women with normal cytology at intake had a substantial risk to develop CIN2+ lesions within 18 months (adjusted risk:16.3%). HrHPV-testing detected more CIN2+ lesions than sole cytology (adjusted relative detection rate: 1.42 (95%CI 1.05-1.92)).

Conclusions: The excess risks of CIN2+ in hrHPV-positive gynaecologic outpatients and the better detection of CIN2+ by hrHPV-testing argue for implementation of hrHPV-testing for early detection of high-grade CIN. Gynaecologists should be informed about the risk of hrHPV positive women with normal cytology and consequently the need of follow-up given their significant risk of CIN2+. 
PREVALENCE OF ONCOGENIC HPV 16, 18 IN WOMEN ATTENDING A COLPOSCOPY CLINIC

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Aim: To find out the prevalence of most common oncogenic types of HPV 16 and 18 from cervical scraping / tissue sampling among women attending colposcopy clinic in a public hospital, with reference to early detection of cancer cervix.

Methodology: The study group was, a 140 women attending colposcopy clinic successively. 46 women were selected by random sampling and informed consent . 23 women had cervical scraping [Group A], 15 women tissue sampling [Group B ] and eight women both cervical scraping and tissue samples [Group C] taken for detecting HPV 16,18 by PCR. Cervical biopsy was taken for 46 women.

Results: Group A had Chronic cervicitis 15, LSIL 4, HSIL 2, and Cancer cervix 2 . HPV 16, 18 negative in all.

Group B had LSIL 1 chronic cervicitis 14. HPV 16 detected in one LSIL and one chronic cervicitis., HPV 18 in five chronic cervicitis.

Group C Tissue sampling was positive for HPV 16 in LSIL 2, HSIL 2, and chronic cervicitis 3, and HPV 16, 18 positive in one chronic cervicitis.

Cervical scraping was 100% false negative, indicating exploration of validation.

Conclusion: The results from Tissue samples had high sensitivity, poor specificity, and showed prevalence of HPV 16 in 39 % and HPV 18 in 26 % of women, attending colposcopy clinic.

Highly sensitive HPV tests , colposcopy and biopsy are the most important diagnostic tools in early detection and prevention of cancer cervix in public referral hospitals.
DISTRIBUTION OF HUMAN PAPILLOMA VIRUS TYPES IN TURKISH WOMEN

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Background and aims: Since oncogenic types of Human Papilloma Virus (HPV) are associated with a higher risk of cancer and certain types can be controlled by a vaccine, a study is performed to determine the HPV genotype distribution among Turkish women.

Methods: The study included patients with abnormal cytology between 2002 and 2009 in Hacettepe University Hospital. The results of 1,797 consecutive cervical samples were analyzed retrospectively. Post polymerase chain reaction (PCR) HPV DNA strip detection with hybrid capture technology and post PCR DNA sequencing tests were used to determine the type of HPV.

Results: HPV was detected in 404 (%22.4) of 1797 samples studied. In 194 cases, results were available as high-risk HPV in 50 patients, low-risk HPV in 14 patients and undetermined type of HPV in 130 patients. In the remaining 210 cases analyzed via PCR DNA sequencing, 23 different HPV types were detected. The most frequent genotype was HPV 16 which was observed in 103 cases (49.04%). The following common types were HPV 51 (19.5%), HPV 31 (17.1%), HPV 33 (7.6%), HPV 68 (5.2%), HPV 18 (4.7%), HPV 56 (2.8%), HPV 39 (2.8%) and HPV 52 (2.8%).

Conclusions: HPV 16 is the most common genotype observed among Turkish women with abnormal cytology. It suggests that HPV vaccination may be useful for prevention of cervical cancer in this population.
CAPACITY OF HEALTH PROFESSIONALS IN CERVICAL CANCER SCREENING IN GOMA/DRC

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**Overview:** Cancer is now the leading cause of death worldwide. 28 million of people live with cancer in the world and 8 million die/year by the disease. In DRC, cancer killed approximately 33,000 people in 2005 and cervical cancer was the killer no1 among women and prostate cancer among men. If nothing is done now, this figure will reach 65,000 in 2030. *Source: WHO Infobase.*

**Objectives:** To know the degree of understanding and competency of health professionals (doctors and nurses) in screening methods (VIA and VILI) to make sure that the screening can be initiated without any difficulty. To measure also their capacity of using cryotherapy for treatment of precancerous lesions.

**Method:** We used STEPS Method of WHO, especially Step1 using questionnaire and interview of 50 doctors (general practitioners) and 500 nurses in the city of Goma.

**Results:** We found that: a. 85% of doctors never understand about VIA and VILI methods and 98% of nurses are too. c. 5% of doctors know the substances used for VIA and for VILI but don’t know they are used and 1% of doctors are too. d. 10% of doctors give an education message to their patients (avoid genital infections) and 2% of nurses do too. e. 10% of doctors are aware of HPV vaccine to prevent cervical cancer and no nurse knows that. f. No health professional (doctors or nurses) knows that precancerous lesions can be treated and no one knows how to use cryotherapy. g. No health institution in Goma has a screening service.

**Conclusions:** Health professionals in city of Goma don't have sufficient skills in cervical cancer screening. This constitutes a need for training in this area and it is also a challenge to availability of the service.
CONFORMAL TECHNIQUES LEAD TO A HIGH COMPLETION RATE OF EXTERNAL BEAM RADIATION FOR CERVIX CARCINOMA IN A DEVELOPING WORLD SETTING

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Introduction: Access to good quality oncology care in Africa is beset by many challenges. To improve outcomes for cervix carcinoma patients referred for radical treatment at a public hospital in South Africa, CT-planned conformal external beam radiotherapy (EBRT) was instituted on an 18 megavoltage (MV) linear accelerator. This technique allows shielding of organs at risk with a multi-leaf collimator and skin sparing with the use of high energy, with a presumed reduction in toxicity.

Objectives: Primary end point

• determine the percentage of patients completing a minimum of 45Gy EBRT

Secondary end point

• overall treatment time.

Methods: A retrospective analysis was made of all Stage Ib-IIIb patients referred to radiation oncology from June 2007 to December 2009. Patient demographics, stage, and investigations were recorded. Treatment parameters were noted. Descriptive statistics were used.

Results: Of the initial 339 patients referred, 26 patients (7.7%) did not attend. 32 patients (10.2%) were treated with palliative intent.

282 patients were treated with radical intent. 241 patients (85.4%) completed a minimum of 45 Gy EBRT and 18Gy HDR brachytherapy. 20 patients (7.1%) completed a minimum of 45Gy and an EBRT boost. 6 patients completed EBRT only. In total 267 patients (94.6%) completed the intended minimum dose of EBRT. Average overall treatment time was 41 days (range 35-77).

Conclusion: With the use of conformal planning and high energy MV, a very high percentage of cervix carcinoma patients completed EBRT. The overall treatment time was equivalent to international standards. Impact on survival will be follow up in this cohort.
Prognostic Factors for Improved Survival in FIGO Stage IVB Cervical Cancer


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Background: Prognostic factors for FIGO stage IVB cervical cancer have not been well-known because it was rare. Thus, we sought to evaluate prognostic factors for improving clinical outcomes in the disease.

Methods: Among 2,322 patients with cervical cancer between January 2000 and March 2010, 43 (1.9%) had FIGO stage IVB disease. After we excluded 13 patients due to insufficient data, 30 (1.3%) were enrolled, who received chemotherapy alone or concurrent chemoradiation (CCR) using platinum agents. Distant metastasis defining FIGO stage IVB disease included extra-peritoneal lymph node, lung, liver parenchyme and bone metastases.

Results: The median follow up was 17.5 months (1.8 to 100.1 months). Among all patients, 17 (56.7%) and 13 (43.3%) underwent chemotherapy alone and CCR, and 15 (50%) received taxane- and platinum- based chemotherapy. Complete response (CR) and partial response (PR) were 23.3% and 40% (CR, n=7 vs. 0; PR, n=4 vs. 8 in CCR and chemotherapy alone; p< 0.05). Squamous cell carcinoma was only a favorable factor for progression-free survival (adjusted HR, 0.15; 95% CI, 0.02 to 0.88), whereas CCR (adjusted HR, 0.02; 95% CI, 0.01 to 0.39), taxane- and platinum-based chemotherapy (adjusted HR, 0.12; 95% CI, 0.02 to 0.93) and ≥6 cycles of chemotherapy (adjusted HR, 0.10; 95% CI, 0.02 to 0.52) were prognostic factors for improved overall survival on multivariate analyses.

Conclusions: These findings suggest that squamous cell carcinoma, CCR, taxane- and platinum-based chemotherapy and ≥6 cycles of chemotherapy may be associated with improved progression-free and overall survivals in FIGO stage IVB cervical cancer.
QUICK COURSES OF NEOADJUVANT CHEMOTHERAPY IN FIGO STAGE IB2 AND IIA2 CERVICAL CANCER PATIENTS WITH CISPLATIN AND IRINOTECAN

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Background: Cervical cancer is the most common gynaecological cancer site in Kazakhstan with more than 12 hundred cases diagnosed annually. Radical hysterectomy is advantageous in patients with early stages of cervical cancer. Despite the previous randomized trials, there has been no consensus on the best treatment strategy for patients with bulky early disease.

Aim of this study was to evaluate the possibility of metronomic chemotherapy with cisplatin and irinotecan in terms of local tumor control and toxicity.

Methods: 11 patients with bulky FIGO stage Ib2 and Ila2 cervical cancer were evaluated. Median age of patients was 46.3±6.7 years. NACT scheme was cisplatin 60 mg/m² on the 1st day and irinotecan 60 mg/m² on day 1, 8, 15. 10 days after completion on NACT all patients underwent type III radical hysterectomy.

Results: We registered decreasing of tumor volume in all patients. The median tumor volume after NACT regressed to 72.8±5.6%. Overall clinical response registered in 81.8% of cases with 9.1% of complete responses. Tumor regression less than 50% was found in 2 patients (18.2%).

We did not observe toxicity reactions more than grade 2. The most common toxicity was gastrointestinal: nausea and vomiting, and diarrhea were seen in 72.7% of cases. Anemia and leucopenia registered in 36.7% and 18.2%, respectively.

Conclusion: Metronomic chemotherapy with cisplatin and irinotecan can be used safely in patients with bulky cervical cancer stages Ib2 and Ila2 before surgery, but further studies still needed to evaluate the effectiveness of this treatment strategy.
HIGH DOSE - DENSITY NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SIMPLE TRACHELECTOMY. ONCOLOGICAL AND PREGNANCY RESULTS

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Objective: In our prospective study were included fifteen patients with early stage cervical cancer that do not fulfill standard criteria for fertility-sparing surgery (tumor more than 2 cm in the biggest diameter or infiltrating more than half of stroma). All women had strong desire to save fertility.

Patients and methods: All patients received three cycles of dose-density neoadjuvant chemotherapy (NAC) at a 10-day interval: cisplatin plus ifosfamide in squamous cell cancer or plus doxorubicin in adenocarcinoma with good tolerance. After NAC, they underwent laparoscopic pelvic lymphadenectomy and vaginal simple trachelectomy. Sentinel lymph node (SLN) mapping was performed in all cases.

Results: Five patients had no residual tumor, six had only microscopic residual disease and four had macroscopic residual disease. Four women lost fertility (radical hysterectomy - 1 decision of patient, 1positive endocervical margins, 1 positive SLN, 1 endocervical recurrence). Seven women delivered babies (one premature six term delivery); one woman is pregnant 3rd trimester. Three women had recurrence, (two endocervical and they are after radical hysterectomy without evidence of disease, one with recurrence in ovary died of disease).

Conclusion: NAC followed by fertility-sparing surgery seems to be feasible treatment for women with tumor bigger than 2 cm or infiltrated more than half of the stroma.

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QUALITY OF LIFE OF CERVICAL CANCER SURVIVORS: A POPULATION-BASED CROSS-SECTIONAL STUDY IN THE SOUTH OF THE NETHERLANDS

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Background: Quality of life (QoL) is an important outcome measure following cancer treatment. This study analyzed the QoL of cervical cancer survivors 2-10 years after primary diagnosis.


Results: Medical records of 236 patients were reviewed of whom 130 patients were still alive. 18 patients were not available for the survey (severe illness, moved away, language problem). 54 (48.2%) of the remaining 112 survivors responded. Patients underwent radical surgery (with or without adjuvant radiotherapy), radiotherapy only or radiotherapy combined with chemotherapy or hyperthermia as a curative treatment. Non-respondents were significantly older ($p=.026$). No other differences were observed between respondents and non-respondents regarding year of diagnosis, FIGO-stage, co-morbidity, tumor size and treatment modality. QoL was generally good: 81.1% scored 5, 6 or 7 on a global QoL-scale ranging from 1 (very poor) to 7 (excellent). Patients with ≥1 treatment-related late complication had worse global health/QoL, role functioning (work/hobbies) and experienced more nausea/vomiting, pain and appetite loss (all $p=< .050$). Patients aged < 50 years at diagnosis had significantly ($p=.036$) more problems with emotional functioning (feeling tensed, worried, irradiated and/or depressed). QoL of the different treatment groups seemed comparable. However, the groups were too small to be able to detect statistically significant differences.

Conclusions: Younger patients and patients with treatment-related complications had worse emotional functioning and overall QoL, respectively. QoL of patients who underwent different treatment modalities was comparable.
TELECERVICOGRAPHY FOR CERVICAL CANCER SCREENING

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The Papanicolaou smear is the standard screening tool for cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC). High false negative rates of Pap smear have been criticized. Telecervicography has been recently developed as a remote cervical cancer screening test.

The purpose of this study was to evaluate the performance of Telecervicography compared with cytology for the detection of CIN and ICC.

Cervical cytology and Telecervicography were performed on 3065 women at the Gynecological Cancer Clinic at Konkuk University Hospital between August 2005 and January 2010. Telecervicography was performed with a TeleCervico (National Testing Laboratories, Seoul, Korea). Of the 3065 women, 863 women were eligible for analysis. The mean age of the women was 48 years. Histologic evidence was obtained on all women. The sensitivity, specificity, likelihood ratios (LR), were compared to that of cytology. The sensitivity, specificity, and positive LR of the cytologic test were 57% (95% CI 51%-62%), 93% (95% CI 91%-95%), and 8.2 (95% CI 5.9-11.2), respectively; for Telecervicography were 92% (95% CI 88%-95%), 87% (95% CI 84%-89%), and 6.9 (95% CI 5.6-8.5), respectively. When cytology test was performed in conjunction with Telecervicography, the sensitivity and specificity were 95% (95% CI 92%-97%) and 83% (95% CI 80%-86%), respectively.

The sensitivity of Telecervicography was higher in comparison with cytology in the detection of CIN or ICC, as was the higher specificity for cytology. Two tests combined will increase the sensitivity, but the specificity remains low. Telecervicography can be considered as a useful complimentary tool to cytology.
Minimal deviation adenocarcinoma of the uterine cervix evolved from lobular endocervical glandular hyperplasia after five years from initial diagnosis

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This case is a 39 years old woman. Watery discharge appears from 33 years old. In an image, uterine cervix showed a cystic lesion, and we underwent a deep biopsy and had a diagnosis of lobular endocervical glandular hyperplasia (LEGH). We offered hysterectomy to her because adenocarcinoma in situ slightly combined in LEGH, but she refused. Thereafter, she got pregnant by in vitro fertilization and gave birth by cesarean section at 36 years old. She got pregnant with the second-born at 38 years old spontaneously. However, she had premature rupture of membranes at 31 gestational weeks, and underwent a cesarean section. A papillary lesion appeared in external os at puerperium six months. It had a diagnosis of serous adenocarcinoma (p53 positive). We underwent radical hysterectomy because of diagnosis with stage IIa cervical cancer. Macroscopically there was a cystic lesion in the uterine isthmus, but not clearly formed mass lesion. Microscopically the cystic lesion was diagnosed LEGH. There was minimal deviation adenocarcinoma (MDA) in the neighborhood of LEGH, and there was common adenocarcinoma in external os. Without tumorigenesis, the poor differentiated serous adenocarcinoma was infiltrated more than one-third vagina wall in continuity. Pathological stage was pT3aN1M0.

LEGH has difficult differential diagnosis with MDA, and the biological dynamics of LEGH still have many any questions. We experienced a rear case that MDA and poor differentiated serous adenocarcinoma of the uterine cervix evolved from LEGH after five years from initial diagnosis.
A PHASE I STUDY OF CONCURRENT CISPLATIN CHEMOTHERAPY IN PATIENTS WITH CARCINOMA OF THE CERVIX RECEIVING PELVIC RADIOTherAPY

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Purpose: To evaluate the maximum tolerated dose (MTD) of weekly cisplatin in a sample population of South African patients with cervical carcinoma, when given in combination with a radical course of pelvic irradiation.

Patients and methods: Patients with carcinoma of the cervix stage IB2 - IIIB received up to 6 cycles of cisplatin at weekly intervals. Groups consisting of 3 patients each were treated at each of the 3 predetermined dose levels of cisplatin (20, 25, and 30 mg/m²).

Results: Eighteen patients were treated and evaluated for toxicity. All the patients who received 20 mg/m² (n=3) and 25 mg/m² (n=3) cisplatin had no dose limiting toxicity (DLT). Four of the 12 patients, who were given cisplatin 30 mg/m² experienced DLT with rising serum creatinine and declining creatinine clearance. The minimum creatinine clearance was 22 ml/min. The highest serum creatinine was 174 µmol/l.

Conclusions: This study showed that a weekly dose of 25 mg/m² of cisplatin was the MTD when used in combination with pelvic irradiation for this sample of patients. This dose is lower than the recommended dose of cisplatin 40 mg/m²/week. It is recommended that the dose of cisplatin when used with concomitant radiation therapy be reduced to 25 to 30 mg/m² for patients from developing countries.
CERVICAL CANCER CURE FRACTIONS IN RELATION TO SCREENING. FURTHER EVIDENCE FROM THE SWEDISH NATIONWIDE AUDIT

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Cervical screening reduces the incidence of cervical cancer but also detects invasive disease at early stages. It is not known to what extent this also implies better chances of cure.

Methods: A cohort of all cervical cancer cases in Sweden diagnosed 1999-2001 (n=1230) was followed prospectively until 2008, and the cure fraction, a measure of survival not affected by lead time bias, was estimated for different screening histories, mode of detection, and stratified by age at cancer diagnosis, histopathological type and FIGO stage.

Results: Overall cure fraction was 68%(CI 64-71), under age 65 it was 75%(72-78), and above age 65 43%(36-50). 52% of lethal cancers were diagnosed after the age of 65. 82% of women who died had overdue or no smear. Cure fraction for screen-detected cervical cancer cases in ages 23-65 was 90%(73-97), for symptomatic cancers 67%(62-71). Symptomatic interval cancer had a cure rate of 74%(68-79), symptomatic cases with a overdue or missing smear 60%(54-66). Cure fraction was well related to FIGO Stage and was equal for all histopathological types except small cell carcinomas.

Conclusion: Early stage detection of invasive cervical cancer in screening implies improved cure for squamous cancer as well as for adenocarcinoma. These findings are unaffected by lead time or length bias. Few deaths remain be prevented among regularly screened women. Any further reduction of death in cervical cancer will require excellent organization to detect the last few cases among participants and to cover more under-screened women in the population.
NEO-ADJUVANT CHEMOTHERAPY (NACT) IN LOCALLY ADVANCED CERVICAL CANCER: WEST OF SCOTLAND EXPERIENCE

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Neo-adjuvant chemotherapy in locally advanced cervical cancer (LACC) can improve response rates although survival benefit remains unproven. We assessed efficacy and tolerability of 3-weekly Cisplatin and Paclitaxel in LACC. Retrospective data were obtained from case notes of 58 patients who underwent NACT from 01/11/2007 to 31/12/2009. Patients with bulky Stage 2B and above or with significant nodal involvement received NACT comprising of Cisplatin 50-70 mg/m² and Paclitaxel 175 mg/m² given 3 weekly. After 3 cycles, depending on response, patients continued to six cycles followed by radiation or switched to concomitant chemo-radiation (CCRT). The median follow up was 20 months. The number of chemotherapy cycles delivered were 6, 5, 4 and 3 or less in 23 (40%), 8 (13%), 11 (19%), 15 (26%) patients respectively. Partial response/stable disease was noted in 53 (92%) patients whilst 5 (9%) progressed on chemotherapy. 5 (9%) patients developed grade 3 myelotoxicity and 3 patients had grade 3 vomiting. Grade 1/2 nausea, vomiting and peripheral neuropathy were the major side effects. 16 (26%) patients have died at the time of the analysis. Those receiving 6 cycles were less likely to receive or complete CCRT due to myelosuppression and neuropathy but in those receiving 3 cycles CCRT was effectively delivered. Neo-adjuvant chemotherapy has shown improved response rate in early trials. Our results do show better tolerability of NACT with 92% response rate and grade 3-4 toxicity observed in 13% patients. Data on survival are premature. Future trials will investigate shorter dose dense induction prior to CCRT.
CHROMOSOME 3Q 26 REGION GAIN CAN SAFELY IDENTIFY WOMEN LESS LIKELY TO PROGRESS FROM LGSIL TO HGSIL

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Objective: To determine the value of genetic instability of chromosome 3q 26 region gain in predicting which low grade squamous intraepithelial lesions (LGSIL) will progress to higher grade dysplasia (HGSIL).

Methods: LGSIL and ASCUS liquid cytology specimens from 40 consecutive women were examined using FISH technology for the detection of 3q26 region gain. All women at an initial visit underwent colposcopy. Biopsies were obtained and histological confirmation of LGSIL/≤CIN II was available in all cases. Women were reevaluated 12-22 months after their first exam, with liquid cytology, colposcopy and biopsies in all cases. FISH status for 3q26 gain at initial LGSIL/ASCUS specimens was correlated with second visit results.

Results: Overall, 10 (25%) patients were considered FISH positive for 3q26 region gain and 30 (75%) were FISH negative. Three out of ten positive patients (33.3%) progressed to HGSIL/≥CIN II during follow up, while negative patients had no progression (none out of 30, i.e.: 0%). The ability of 3q26 gain to predict progression has a Sensitivity, Specificity, Positive and Negative Predictive Value of 100%, 81.1%, 30% and 100% respectively.

Conclusion: In this first prospective study, the genetic instability of 3q26 region gain detected in LGSIL cytology specimens seems to adequately predict which LGSIL will not progress to HGSIL. Thus, 3q26 gain may be used in stratifying patients risk of progression and maybe alter their management reducing cost of follow up. Larger studies with longer follow up are needed in order to verify these data.
90-YEARS EXPERIENCE OF CARCINOMA OF THE UTERINE CERVIX AT RADIUMHEMMET. DISTRIBUTION BY AGE, STAGE AND HISTOPATHOLOGY

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Objective: To analyze time trends in age, stage and histopathology distribution in to our knowledge the largest series in the literature of invasive cervical carcinoma (CC) cases.

Methods: Retrospective study comprising 18472 women treated 1914-2004 at Radiumhemmet, Stockholm.

Results: During the 90-year study period, the annual number of cases increased to over 400 cases until 1965, thereafter a gradual drop was seen to less than 100 cases in 2004. A pronounced shift towards earlier stages at diagnosis was noted. The mean age at diagnosis increased in all stages, but predominantly in advanced stages. In stage I and stage IV the mean age increased with 4.3 years (8.6%) and 14.3 years (21.8%) respectively. The mean age at diagnosis increased more for squamous cell carcinoma cases (SCC) than for adenocarcinoma (AC) cases. A reduction of SCC cases and an increase of AC cases were observed with 22% respectively.

Conclusions: A considerably drop in the number of cases referred for treatment and a change in the distribution by age, stage and histopathology was noted. These changes are probably connected with:

(1) that Sweden during this 90 year period underwent a great change from a poor agriculture country to a highly industrialized state,

(2) socioeconomic change with increased welfare, knowledge in medical science and availability of health care,

(3) the introduction of screening programmes for CC in the 1960s and

(4) a change in the riskfactors for CC (changed sexual behaviour, introduction of contraceptive pills, easier spread of viral infections and changed smoking habits).
NEO-ADJUVANT CHEMOTHERAPY FOLLOWED BY CONISATION IN PATIENTS WITH STAGE IB1 CERVICAL CANCER AND CHILD WISH

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Objectives: To assess safety of neoadjuvant chemotherapy and conisation in patients with stage Ib1 cervical cancer and child wish.

Methods: From April 2004 until May 2010, 9 women with stage Ib1 cervical cancer (tumor size < 3 cm) were included. Median age was 36 year (range 27-39 years). All women underwent a pelvic lymphadenectomy prior to neoadjuvant chemotherapy. The first 2 patients received 3 courses of TIP (Paclitaxel 175 mg/m2, Ifosfamide 5000 mg/m2, cisplatinum 75 mg/m2, q3w); 5 women received Paclitaxel/Carboplatin dose dense (Paclitaxel 90 mg/m2, carboplatin AUC 4 on day 1 and 8, q3wk); 2 women received 9 courses of Paclitaxel 60 mg/m2, carboplatin AUC 2.7 weekly). 3-6 weeks after the last chemotherapy a conisation was performed.

Results: Adenocarcinoma was present in 5 and squamous cell carcinoma in 4 patients. Eight women had negative pelvic lymph nodes and one had 1 micrometastasis. Pathological examination after neoadjuvant chemotherapy showed: pathological complete remission (n=5); microscopic residual tumor (n=1) and invasive tumor of 6 mm (n=1) and 15mm (n=1). The last patient underwent a radical hysterectomy. One patient is currently still receiving chemotherapy. After a median follow-up of 23 months (range 8-77 months) no relapses were observed. Five women attempted to conceive: 4 pregnancies occurred of which 2 normal babies were born at 40 weeks pregnancy. One patient is currently 33 weeks pregnant and 1 patient had a first trimester miscarriage.

Conclusions: Neoadjuvant chemotherapy resulted in a high response rate and no recurrences. After conisation no preterm deliveries were observed.
EPIDEMIOLOGICAL FACTORS ASSOCIATED WITH CERVICAL CANCER: A 15-YEAR REVIEW OF CASES

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Introduction: The incidence of cervical cancer has fallen since the introduction of the NHS Cervical Screening Programme in 1988, however, over the past 10 years there has been a steady reduction in the number of women attending for screening.


Results: 1507 women were diagnosed during the 15-year study period. The number of cases fell by 18.5% between 1995-1999 (561) and 2000-2004 (457) but rose by 7.0% in the 2005-2009 period (489). Age-standardised incidence rates demonstrated no significant difference between the first and last cohort (11.2-9.57 per 100,000 population, 95% CI 10.25-12.15 and 8.70-10.44 respectively). There was no difference in the median age at diagnosis or age distribution between the three time periods. The disease distribution by socio-economic status did not alter, with the majority of women belonging to the most deprived socio-economic group (52.2%, 53.0% and 51.7%). The percentage of squamous tumours did not change (70.8%, 70.5% and 70.3%), however, there was a reduction in the percentage of microinvasive as compared to frankly invasive squamous cancers (34.3%, 22.7% and 16.2%).

Conclusions: Despite a comprehensive cervical screening programme there has been only a non-significant reduction in the incidence of cervical cancer over the past 15 years suggesting that the existing programme may have reached its maximum efficiency. The reduction in microinvasive disease is probably a reflection of better diagnosis and treatment of pre-neoplastic cervical lesions via screening.
PHOTODYNAMIC THERAPY FOR PRECANCER AND EARLY STAGE CANCER OF THE UTERINE CERVIX WITH FERTILITY PRESERVATION

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The number of the patient with dysplasia and CIS of the uterine cervix has been increasing recently, especially in the younger ages who need fertility preservation. Although cervical conization is standard therapy for dysplasia and CIS, the significant increase in the obstetrical risks such as premature delivery after conization has been reported. On the other hand, PDT is an excellent procedure to treat CIN3 by photochemical reaction generated by laser irradiation to the lesion after injection of tumor-specific photosensitizer. We have developed protocol and applied PDT to CIN3 and early stage cervical cancer since 1989. PDT was performed for 520 cases (146 dysplasia, 342 CIS, 4 AIS, 24 MIC, 1 MIAC, 2 invasive SCC, and 1 invasive adenoca.) 97%(503/520) of PDT cases were CR by the single PDT procedure. CR rates for dysplasia, CIS, MIC were 99%, 97%, and 92%, respectively.

As a retrospective cohort study, two kinds of uterine preservation therapy (PDT and conization) for dysplasia, CIS and early stage cervical cancer were compared with respect to cure rate and fertility after therapy. Although cure rate by PDT is nearly equal to that by conization, pregnancy rate and delivery rate after PDT were significantly higher, and premature delivery rate after PDT was lower than those after conization. Especially, cumulative delivery rate curve of PDT cohort was significantly higher than that of conization cohort (p=0.009, Log-Rank test). These data suggested that PDT for CIN3 and early stage cervical cancer might be superior therapy for fertility preservation as compared to conization.
A PROSPECTIVE EVALUATION OF SEE AND TREAT IN WOMEN WITH ABNORMAL VAGINAL CYTOLOGY: IS THIS AN APPROPRIATE MANAGEMENT PROTOCOL

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Aim: To evaluate the correlation between vaginal cytology and final pathology results in patients having abnormal cytology who have undergone LEEP and endocervical curettage (ECC), and to investigate whether or not this is an appropriate management protocol for those patients

Methods: Women presented with abnormal vaginal cytology (ASC-US, LSIL, ASC-H, HSIL) to our clinic were evaluated for inclusion in a see and treat protocol. All patients were subjected to colposcopic examination. LEEP and ECC were done to all patients having abnormal colposcopic impression and unsatisfactory colposcopic evaluation.

Result: To date, 211 patients have been enrolled in this study. The incidence of ASCUS, LSIL, ASC-H and HSIL were 12%, 49%, 8% and 31%, prospectively. There was higher incidence of ≥ CIN II lesions in patients with ASC-H and HSIL Pap. result. Overtreatment was prevalent in patients with ASCUS/LSIL. However, only 2% of patients with ASC-H and HSIL have negative final pathology result. Thirty one patients had positive surgical margin and 9 patients had positive ECC. The rate of positive surgical margin (7% vs 30%) and ECC (1% vs 7%) was much higher in patients having ≥ CIN II. The rate of hemorrhage required intervention was 3% and recurrence rate was 3%.

Conclusion: The use of see and treat protocol for patients having ASC-H and HSIL vaginal cytology results may be an acceptable treatment option because of a high incidence ≥CIN II lesions with low recurrence and complication rate. Also ECC should be done together with LEEP to all those patients.
SQUAMOUS CELL CARCINOMA IN SITU WITH INTRAEPITHELIAL SPREAD TO THE UPPER GENITAL TRACT AND INVASION OF OVARIES - CASE REPORT

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Introduction: Squamous cell carcinoma in situ of the uterine cervix with contiguous intraepithelial spread to the endometrium, fallopian tube, and ovary is an extremely rare clinical entity.

Case report: We report a case of a 66-year-old woman, who was found to have malignant squamous cells on a cervical smear, underwent a cervical biopsy with D&C followed by a conisation biopsy and finally hysterectomy with bilateral salpingo-oophorectomy. No grossly visible tumor was present in the uterus, both ovaries, and tubes. The microscopic examination revealed squamous cell carcinoma of the uterine cervix in situ with a contiguous intraepithelial spread to the endometrium, tubes, and ovaries, with a focal invasion to the parenchyma of both ovaries.

PCR analysis for high-risk human papillomavirus (HR-HPV) infection revealed HPV 16 positivity all in cervix, endometrium, fallopian tubes, and ovaries. Loss of heterozygosity (LOH) analysis with a panel of microsatellite markers detected a homogeneous LOH pattern on 6p and 6q throughout all microdissected lesions.

The patient was administered adjuvant radiotherapy. She has no signs of the disease six years after the diagnosis.

Conclusion: We report an extremely rare case of squamous cell carcinoma in situ with contiguous intraepithelial spread to the upper genital tract and invasion of ovaries. We conclude that homogeneous LOH patterns throughout the cervix, endometrium, fallopian tubes, and ovaries are suggestive for monoclonal process originating in the cervix.
DELAYED TYPE HYPERSENSITIVITY SKIN TEST TO HUMAN PAPILLOMAVIRUS 16 SPECIFIC ANTIGENS IN HEALTHY SUBJECTS AND CERVICAL CANCER PATIENTS IN INDONESIA

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In this study performed in Indonesia, immune responses to the human papillomavirus (HPV) type 16, in healthy women and cervical cancer patients were challenged and objectified.

In 43 healthy individuals and 39 cervical cancer patients a Delayed Type Hypersensitivity (DTH) test with synthetic antigens of the most immunogenic regions of HPV 16 E2, E6 and E7 were injected intracutaneously in the upper arm. Skin reactions were examined, and pre and post challenge, the production of interferon-gamma by peripheral mononuclear blood cells (PMBC's) was quantified using ELISPOT. Results of the DTH skin test and the Elispot were compared between healthy women and patients.

Significantly more healthy donors (26.2%) showed skin reactions than did cervical cancer patients (5.4%) (Fisher’s exact test p=0.01), no side effects besides itching were reported. The ELISPOT showed induced interferon gamma production in 48.4% of the healthy individuals and in 48.0% of the patients.

In this study, the DTH skin test has proven to be feasible and safe. Cervical cancer patients were significantly less capable of showing a positive skin reaction than healthy individuals. The skin test could therefore be used to identify women at risk for developing cervical cancer in areas where medical resources are low and the access to specialized health care is limited. As an induced immune response after DTH skin test was detected by IFN γELISPOT in almost 50% of the healthy individuals and patients, subcutaneous administration of HPV peptides could be explored in future therapeutic vaccination strategies.
ANALYSIS OF ROUTINE FOLLOW-UP AFTER PRIMARY TREATMENT FOR CERVICAL CANCER IN STAGES IA, IB AND IIA

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Objective: Evaluate of effectiveness of follow-up after primary treatment for cervical cancer.

Design: Retrospective analysis.

Setting: Department of Obstetrics and Gynecology Faculty Hospital and Constantine the Philosopher University Nitra, Slovakia.

Methods: We retrospectively analyzed 113 patients who have undergone surgical treatment for cervical cancer between 2001 and 2009 at the Faculty Hospital Nitra and they received chemoradiotherapy after evaluation of risk factors. Monitoring after primary treatment consisted of general physical examination, gynecological examination, vaginal and abdominal ultrasonography, chest X-ray and determining the level of SCCA. The examinations were performed by oncogynecologist and clinical oncologist every 3 months after primary treatment. We compared the survival of patients with symptomatic and asymptomatic recurrences.

Results: The recurrences were observed in 17 (15%) patients. The median survival following the detection of recurrence was 11 months (range 4-22). The median survival of asymptomatic patients was 12 months (range 10-16) and symptomatic patients was 10.5 months (range 4-22). All patients died within 2 years after detection of recurrences.

The differences in survival of symptomatic and asymptomatic patients were not significant (p=0.616).

Conclusion: Regular surveillance after primary treatment of cervical cancer in the rigid intervals and diagnosis of recurrences in the asymptomatic patients does not improve survival compared with symptomatic patients. It is necessary to re-evaluate the algorithm of follow-up not only in terms of survival but also in terms of economic consequences and quality of life.
SHOULD WOMEN WITH POSTCOITAL BLEEDING BE REFERRED FOR COLPOSCOPY?
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**Background:** Postcoital bleeding (PCB) is an unpleasant symptom and distressing to both patient and partner. Although PCB is benign, it is considered as a cardinal symptom of cervical cancer. Currently there are no national guidelines for the management of PCB to ensure good medical practice. The main aim of investigating these women is to exclude serious cervical pathology, particularly cervical cancer.

**Aim:** To determine the risk of finding significant cervical pathology; particularly cervical cancer in women referred to the colposcopy clinic primarily because of postcoital bleeding.

**Methods:** Retrospective study of 54 case notes in a District General Hospital in UK from 2008-2010.

**Results:** Majority (72%) of the women were in the age group between 25-40 years but 24% were less than 25 years of age and hence not had the cervical smears before the referral. 30% had associated intermenstrual bleeding (IMB). 70% were on hormonal contraception of which 53% had cervical ectropion and 44% had IMB. Two patients were referred with severe dyskaryosis. 22/54 (41%) had cervical ectropion. 3/54 patients had CIN, out of which 2/54 had high grade disease-Squamous cell carcinoma-Stage 1A1. (treated with Conization) at the age of 23yrs & 26 yrs.

**Conclusion:** Persistent PCB particularly associated with intermenstrual bleeding should still raise suspicion of cancer and referral to Colposcopy specially in young women who never has had cervical smears. Though cervical ectropion, infection and hormonal contraception related bleeding are common causes but early detection of cervical cancer gives an opportunity to fertility preserving treatment. Future research is necessary to have a structured approach.
RECREATION BLOOD SUPPLY OF UTERI AFTER RADICAL TRACHELECTOMY

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The problem of preserving reproductive function of oncology patients has high level of significance.

To detect early circulatory disorders uterus after radical trachelectomy, we analyzed the ultrasonographic signs of blood flow recovery in 4 patients with cervical cancer T1aN0M0 maximum dimensions of the tumor from 0.6 to 1.8 cm. The analysis revealed the features of the development of collateral vessels after surgery, as an important criterion for predicting the development of insufficiency of blood supply. These changes lead to infertility, amenorrhea or dysmenorrhea, which are observed in every fourth patient was operated. In our cases, these violations were not related to surgical technique, and dependent on individual anatomical features of blood supply to the uterus.

The age of patients from 28 to 33 years. In stage Ia echographic signs of Education is not revealed. When the energy flow mapping the distribution of color loci was peripheral, chaotic, with different color intensity, the number of them around the uterus was 12-15. Clear contours bounding the region of surgery, was not determined, but visualized boundary area with broken homogeneity and heterogeneity echostructure. Qualitative assessment of organ blood flow was characterized by a gradual increase in the number of displayable colors loci identified in the external uterine (a place to vascular surgery), which is indicative of a sign of collateral circulation and prognosis of functional completeness of the uterus. It shoud be noted that in order to indentify the detailed ultrasonographic signs.

Features of the restoration of blood supply. further accumulation of material.
DISCRIMINATION OF CERVICAL NEOPLASIAS USING AUTOMATED IMAGE ANALYSIS

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Background and aim: A digital colposcopic imaging system with computer aided detection has the potential to assist colposcopists by providing an objective and quantifiable assessment of disease during colposcopic examinations. The aim of this study is to examine the accuracy of an automated cervical image analysis system to differentiate high-grade cervical lesions (≥CIN2, cervical intraepithelial neoplasia) from normal and low-grade lesions.

Methods: A convenience sample of 99 women underwent colposcopy and electrosurgical loop excision procedures. Stereoscopic digital cervical images were acquired throughout the colposcopic examination and after excision. Cervical images were analyzed using multi-step algorithms designed to analyze cervical anatomy, acetowhite epithelium and blood vessels. Linear discriminant analysis was applied to differentiate high-grade lesions from normal and low-grade lesions. Sensitivity and specificity were calculated using cervical image annotations and histopathology as the criterion standards.

Results: The automated image analysis system had a sensitivity and specificity of 92% and 89%, respectively, in discriminating high-grade lesions (≥CIN2) from normal and low-grade lesions. The receiver operating characteristics area under the curve was 0.94. For comparison, the colposcopic impression had a sensitivity and specificity of 92% and 33%, respectively, compared with histology.

Conclusions: We conclude that a computer-based image analysis system that detects and discriminates cervical cancer precursors from less severe neoplasias may be a useful adjunct for colposcopy.
EXPRESSION OF LYMPHANGIOGENESIS PATHWAY GENES IN CERVICAL NEOPLASIA

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Background: The purpose of this study was to examine the presence "lymphangiogenic phenotype" of cervical cancer as well as the rate of mRNA VEGFC, VEGFD, VEGFR3 expression.

Materials: Cervix tissue samples from 38 patients ( IB - 10, IIB - 15, IIIB - 13 patient) were investigated by QRT-PCR and QPCR technique. Normal cervix samples (10 patients) were removed during hysterectomy for other than cervical pathology reasons.

Methods: The method used for quantititative determination of the numbers of mRNA copies of selected genes was the QRT-PCR and QPCR technique, with the use of an ABI PRISM 7700 (TaqMan) sequence detector. The nucleotide sequence for starters and probes for quantitative RT-PCR was designed with the use of the Primer Express Version 1.0 ABI PRISM sowtware.

Results: The observation of VEGF-C expression in cervical cancer revealed its growing tendency in particular clinical stages, although the differences between groups were not always statistically significant. Statistically significant differences were found between control group and the group of II FIGO stage, between control group and III FIGO stage group, between I and III clinical stage group. The number of VEGF-D mRNA copies in control group significantly differed from values acquired in all clinical cancer stages. There was also a significant difference between II and III FIGO stage group. The level of VEGFR-3 expression in III degree of FIGO stage was considerably higher than in I and II degree.

Conclusion: Expression of VEGFC, VEGFD and VEGFR3 has been determined lymphangiogenic activity of cervical squamous cancer.
KNOWLEDGE OF AND ATTITUDES TO CERVICAL CANCER SCREENING AMONG CAMEROONIAN HEALTHCARE PROFESSIONALS

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Objectives: To evaluate knowledge of and attitudes to cervical cancer among Cameroonian healthcare professionals

Methods: Anonymous questionnaire survey regarding cervical cancer epidemiology, its natural history, relation to HPV and the various screening methods available.

Between 1 June and 30 June 2009, 850 questionnaires were distributed in Yaoundé, Cameroon.

Results: 401 questionnaires were collected (medical students (n=71), nursing and midwifery students (n=38), general practitioners and pediatricians (n=45), gynecologists (n=13), nurses (n=214) and midwives (n=20)). The average age of the respondents was 37 years. Most of the healthcare professionals are aware that cervical cancer is a major public health concern (86%) about which the general public is ill-informed (75%). The vast majority (90%) believe that early screening helps prevent cervical cancer, but 59% of the women surveyed never underwent (or not in the five last years) regular gynecological examinations. The link between HPV and cervical cancer is understood (70%) as is the fact that HPV is sexually transmitted. Knowledge about the vaccine is still lacking, but most healthcare professionals (75%) would encourage young women to be vaccinated.

Conclusion: Most healthcare professionals are aware of the causes of cervical cancer and are familiar with the screening methods. They will be important actors in the screening campaigns to be set up in the near future.

Keywords: Cameroon, health professionals, knowledge assessment, screening and prevention, HPV, cervical cancer.
FOLLOW-UP CYTOLOGY IN WOMEN THAT UNDERWENT LOOP EXCISION OF THE CERVIX: MANAGEMENT OF DYSKARYOTIC SMEARS AFTER TREATMENT

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Aim: The aim of this study is to assess the outcome of investigation for women with abnormal cervical cytology following loop excision.

Methods: This retrospective study was conducted over a 12-months period in a gynaecological oncology centre in the United Kingdom. Women following loop excision of the cervix had follow-up cytology according to national guidance 6 to 8 months after the treatment. Women with abnormal cervical cytology were reviewed in the colposcopy clinic for further investigation. We recorded the investigation performed and the outcome.

Results: 464 patients that underwent loop excision of the cervix had a smear test performed at 6-8 months following treatment. 421 (91%) patients had no dyskaryosis on cytology. Mild dyskaryosis was found in 21 cases. Cervical biopsy was performed in 17 (81%) women with mild dyskaryosis and showed only one (4.5%) case of high-grade CIN. 14 women were found to have moderate dyskaryosis on follow-up cytology: 10 women had a repeat loop excision, 3 women underwent a simple hysterectomy and 1 woman had cervical biopsy; 10 (71.4%) cases of high-grade CIN were found. 8 women had severe dyskaryosis: 6 of them underwent a repeat loop excision, 1 woman had a simple hysterectomy and 1 woman had cervical biopsy; 6 (75%) cases of high-grade CIN were found in this group.

Conclusion: Moderate or severe dyskaryosis on follow-up cytology after loop excision of the cervix are highly predictive of persistence of high-grade CIN and a repeat excision should be recommended.
EXPRESSION OF METASTATIC PATHWAY GENES IN CERVICAL NEOPLASIA

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Background: The aim of this study was the selection of genes taking part in molecular pathway of metastases and identifying genes showing more than 2-fold difference in their expression in normal cervix and cervical cancer using microarray technique.

Materials: Cervix tissue samples from 32 patients (invasive cancer stages Ib-IIb) with histopathologically confirmed malignancy were investigated by oligonucleotide microarray (Affymetrix) contained 22,283 genes. Normal cervix samples (12 patients) were removed during hysterectomy for other than cervical pathology reasons.

Methods: Tissues samples were homogenized (Polytron). Total RNA was isolated using TRIzol reagent (Gibco BRL) and purified by using RNeasy Mini Kit (Qiagen). RNA was turned back into DNA (cDNA) which was the matrix for synthesis of biotinilised cRNA. The marked cRNA was purified by using RNeasy Mini Kit (Qiagen), fragmented and hybridized with microarray HG_U133A (Affymetrix) according to the manufacturer’s protocol.

Results: From oligonucleotide microarray (Affymetrix) contained 22,283 genes we chose 119 human transcripts that correspond with metastases. Our results showed that normal cervical tissues were segregated from cancer samples using 10 genes (COX-1, VEGFA, PLA2G3, MMP9, BCL3, PLAU, PTGS2, TGFB1, ECGF1, EDN1) associated with metastatic process whose expressions were significantly different between these specimens (more than 2-fold difference). The number of NFKBIA, FGFR1,CEACAM1, MMP2 and VCAM1 mRNA copies was significantly lower in all cervical cancer subgroups in comparison to the control group.

Conclusion: Gene expression profiling by oligonucleotide microarray may be useful for further molecular classification of cancer progression and prediction of metastases.
NEOADJUVANT CHEMOTHERAPY FOR INVASIVE CERVICAL CANCER DURING PREGNANCY: REPORT OF NINE CASES

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Introduction: cervical cancer complicates 1 to 10/10000 pregnancies. Chemotherapy might be administered in cervical cancer (CC) pregnant patients in order to obtain stabilization of the neoplastic disease, delaying delivery until fetal viability and maturity are reached.

Patients and methods: pregnant patients with CC treated in our centre with neoadjuvant chemotherapy followed by radical surgery were considered for this analysis.

Results: between 1994 and 2009 9 pregnant patients with invasive CC were treated in our centre. Median gestational age at diagnosis was 18 weeks (range 12-26). FIGO stage was Ib2 in 5 patients and Ib1 in 4, histology was squamous in 7 cases and adenocarcinoma in 2. All patients received cisplatin 75 mg/m² as neoadjuvant chemotherapy every 3 weeks. Median number of cycles received was 4 (range 2-6). 2 patients received second-line chemotherapy due to progressive disease. Between 30 and 36 gestational week all patients underwent cesarean section with radical hysterectomy and pelvic lymphadenectomy. Three patients received adjuvant radio-chemotherapy for positive lymphnodes (2) and for close resection margins (1). Three patients had a pelvic relapse. Two of these died for progressive disease after 27 months. Another patients had a lymphnode relapse, was treated with radio-chemotherapy and is alive after 91 months. No fetal adverse effects were observed and neonatal outcome was good in all cases.

Conclusion: Use of neoadjuvant chemotherapy for locally advanced cervical cancer in pregnancy could be considered as a therapeutic option in women who desire continuation of pregnancy. This approach was not associated with adverse perinatal outcome.
SYSTEMATIC LITERATURE REVIEW, A RANDOMISED TRIAL AND A PREFERENCE TRIAL CHALLENGING THE PRACTICE OF VAGINAL DILATION DURING RADIOTHERAPY

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Background: Vaginal dilation is recommended during pelvic radiotherapy by UK guidelines, numerous authors and the Cochrane library. A survey shows that these guidelines are followed by 97% of British gynaecological radiotherapy units during brachytherapy and 73% promote dilation for external beam radiotherapy.

Methodology: We challenged the basis for these guidelines by systematically examining of all of the literature. We tested dilation against vibration in a randomised trial and correlated dilation frequency with outcome in a preference trial.

Result: There are only 6 papers with any data relating vaginal function to dilation with radiotherapy. No paper contained any data to show that the practice reduces scarring and stenosis. This literature review prompted us to design a tool to measure vaginal length, elasticity and viscosity before, during and after radiotherapy. 18 women were randomly allocated a vibrating or static dilator as adjuvant treatment during radiotherapy. There was no difference in vaginal length, elasticity or viscosity comparing vibration with conventional dilation. Sexual function and LENT SOMA scores were also similar in the two randomly allocated groups. A preference trial measuring vaginal length, elasticity and viscosity also failed to show any advantage to dilation in 16 women who chose to dilate compared to with those who declined.

Conclusion: There is evidence of rare but serious harm from dilation during radiotherapy, dilation is occasionally psychologically traumatic, it absorbs resources, it is scientifically illogical and there is no scientific justification for the practice. We criticise the practice of vaginal dilation in the acute phase of treatment.
EXPRESSION OF ANGIOGENESIS AND LYMPHANGIOGENESIS PATHWAY GENES IN CERVICAL NEOPLASIA


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Background: The key role in process of angiogenesis and lymphangiogenesis plays the family of the vascular endothelial growth factor - VEGF. Additionally, it has been proved that VEGF-C and VEGF-D lymphangiogenic molecules may also activate VEGFR-2 receptor which is the main signal transductor for angiogenesis process. The aim of this study was to estimate the correlation between VEGF-C, VEGF-D expression and mRNA concentration of VEGFR-2 and VEGFR-3 receptors. The last aim was to compare mRNA concentration of VEGFR-2 and VEGFR-3.

Materials: Molecular analysis was performed in 56 women with cervical cancer (15 in IB clinical stage, 21 in II and 20 in III). The control group consisted of 10 patients who underwent uterus removal on other than malignant neoplastic disease reason.

Methods: the method used for quantitative determination of the numbers of mRNA copies of selected genes was the QRT-PCR and QPCR technique, with the use of an ABI PRISM 7700 (TaqMan) sequence detector. The nucleotide sequence for starters and probes for quantitative RT-PCR was designed with the use of the Primer Express Version 1.0 ABI PRISM software.

Results: Positive correlation was found between VEGFR-3 expression and mRNA concentrations of VEGF-C and VEGF-D, indicating that there is positive feedback in prolymphangiogenic molecules system. Moreover, comparing mRNA concentration of VEGFR-3 to the number of VEGFR-2 mRNA copies in particular cancer groups a significant difference was stated to the advantage of VEGFR-3.

Conclusion: This observation indicates that lymphangiogenesis dominates angiogenesis in planoeplthelial cervical cancer in IB-IIIB clinical stages.
EXPRESSION OF HPV L1 CAPSID PROTEIN AND HPV GENOTYPES IN LIQUID-BASED CYTOLOGY SAMPLES

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Objective: The aim of the study is to investigate the expression rate of human papillomavirus(HPV) L1 capsid protein and HPV genotypes by cervical intraepithelial neoplasia(CIN).

Methods: Immunohistochemical stain for HPV L1 capsid protein and HPV genotypes were performed on liquid-based cytology(LBC) specimen in 675 women who had been confirmed by histology.

Results: L1 capsid protein was positive in 57% of CIN 1, 2 and 34% of CIN 3, but 6% of cancer. The relation between L1 capsid protein and HPV 16, HPV 16/L1(+) cases represented 62%, 54%, 34%, 2% of CIN 1, 2, 3 and cancer. HPV 16/L1(-) cases represented 38%, 46%, 66%, 98% of CIN 1, 2, 3 and cancer, respectively(CIN 1&2:CIN3&cancer, p< 0.001).

Conclusions: Expression of L1 capsid protein decreased with lesion progression from CIN 1 to CIN 3 and cervix cancer. The combination of L1 capsid protein and HPV 16 in LBC appears to be useful prognostic marker.
NEOADJUVANT CHEMOTHERAPY (NCH) FOLLOWED BY ABDOMINAL RADICAL TRACHELECTOMY (ART) SPARING THE UTERINE ARTERIES (SUA) FOR INVASIVE CERVICAL CARCINOMA (CC)

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Objectives: To analyze the possible role of NCH prior a surgical fertility sparing procedure.

Materials: Three patients of 23, 24 and 31 years old, stages Ib1, with clinical central tumor (CCT) = 3 cm, underwent platinum based NCH, with four cycles of this scheme: Cis-platin 50 mg/m2/days 2-3, Paclitaxel 175 mg/m2/days 1, 5-Fluorouracil 800mg/m2/days 1-2-3. They were staged under FIGO´s staging system. MNR scan and hysteroscopy were performed before and after NCH as presurgical staging studies, in order to evaluate the clinical response and the possible surgical free margins. The ART-SUA was performed 1 month after the last cycle of NCH. Clinical(CR) and pathological response (PR), toxicity, feasibility of the surgical procedure, pregnancies, and relapses were analyzed.

Results: The surgical procedure could be performed in all cases. The NCH was well tolerated in the three patients. Toxicity: Hematologic, grade 1; Alopecia, grade 2. CR: > 50%. Two cases with complete response by NMR. Hysteroscopy confirmed the endocervical status after NCH. PR: case 1: tumor size : 15 by 9 mm; case 2: 10 by 6 mm; and one case of complete PR. All cases had free margins at the top of the cervical stump. Follow-up: 6 - 24 months. Up to now, no pregnancies and no relapses were registered.

Conclusions: With this modality of performing less radical treatments, NCH has to be taken into account as a possible option for selected patients with FIGO stage IB1 CCT > 2 cm who have not fulfilled their maternity yet.
LASER ABLATION VERSUS DIATHERMY LOOP EXCISION (LLETZ) FOR THE TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA: SHORT AND LONG TERM OUTCOMES

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**Aim:** To determine the short and long term affects of 2 alternative treatment options for CIN.

**Design:** Retrospective cohort analysis

**Setting:** District General Hospital, UK

**Methods:** Clinical details and study data are retrieved from colposcopy database. Pregnancy data were obtained from individual patient file review. Those who had previous knife conisation or more than 1 previous treatment were excluded from the study.

Main outcome measures: Short term parameters- negative first post treatment smear, need for repeat treatment or smear. Long term parameters- recurrence of abnormal smear, late miscarriages and preterm delivery as a result of cervical incompetence, cervical stenosis and its sequelae.

**Results:** 46 patients underwent LLETZ and 22 had laser ablation. In LLETZ 37 (80.43%) had negative smear after treatment, 4(8.69%) had repeat LLETZ, 3(6.52%) had repeat colposcopy visits and 1 underwent hysterectomy for Stage 1a1 cervical cancer. 5(10.87%) patients had further interval abnormal smears and 3 required treatment. There were 3 (60%) term pregnancies, 1(20%) late miscarriage and 1(20%) preterm delivery. 1 patient had hematometra due to cervical stenosis.

In laser group, 15 had negative smear after treatment (68.18%), 1 had repeat Laser (4.55%), 5 had repeat colposcopy visits (22.73%). 2(9.09%) patients had further abnormal interval smears and none required treatment. 4 (80%) patients had term pregnancies. One (20%) delivered at 36 weeks.

**Conclusions:** Although laser ablation is associated with higher number of positive post treatment smears, repeat treatment rate is lower than LLETZ. Recurrence rate of interval smear abnormalities is similar.
TREATMENT OF METASTATIC CERVICAL CANCER WITH PACLITAXEL AND CISPLATIN - A SINGLE CENTRE EXPERIENCE

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Introduction: Metastatic cervical cancer (MCC) remains an incurable disease. Different treatment approaches were experienced in the last years with low response rates and short survival benefit.

Aims: To review IPOP clinical experience on MCC treated with paclitaxel and cisplatin (PC).

Methods: Retrospective study of pts treated with PC for MCC was conducted using clinical records to obtain information on pts and disease characteristics, patterns of treatment, response obtained and toxicity. SPSS was used for statistical analysis.

Results: A total number of 51 pts were evaluated. The median age at diagnosis was 47 years. Histology: 76% squamous type and 17.6% adenocarcinomas. Stage I (FIGO) was found in 30% pts, II in 40%, III in 14% and IV in 16%. The initial treatment was surgery for 27.5%, chemotherapy and radiotherapy in 42.9%, radiotherapy alone 52.4%. Eleven pts (21.6%) presented completed response, 18 (35.3%) partial response, 4 (7.8%) stable disease and 18 (35.3%) had progressive disease. Five years overall survival was 46.1%. Median disease free survival was 18 months. Median time to progression since PC was 7 months. Toxicity grade ≥3: anemia 3.6%, hypomagnesemia 2.2%, neutropenia 1.5%, nausea/vomiting 1%, peripheral neuropathy 0.7%.

Conclusion: Response rate and overall survival in this set of patients treated with PC corroborate published data and are similar to other systemic treatment options for MCC. The low toxicity profile makes this treatment attractive.
CONCURRENT CHEMORADIATION WITH GEMCITABINE AS SINGLE AGENT FOR LOCALLY ADVANCED CERVICAL CANCER IN PATIENTS 60 YEARS OR OLDER

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Background: Concurrent chemoradiation is the standard treatment in locally advanced cervical cancer. Age is considered a prognostic factor for survival and can be limiting factor for adequate radical treatment. Our purpose was to evaluate the use of gemcitabine as single agent in the treatment of locally advanced cervical cancer in older patients.

Patients and methods: A retrospective review of clinical charts of patients 60 years of age and older treated with concurrent chemoradiation for locally advanced cervical cancer and weekly administered gemcitabine (125 mg/m²) as single agent. Variables of evaluation were response rate, treatment associated toxicity, disease-free survival and overall survival.

Results: Twenty-six patients were evaluated, mean age 74 yo (Range 60-88). Clinical stage IIB accounted for 61.5% of cases. Diabetes mellitus was present in 46.1% of patients and hypertension in 61.5%. Response rate was complete in 21 cases (91.3%), partial in 4.3%, two cases had progression of disease and two patients were lost of follow-up. Most common toxic events were lymphopenia grade 3 (10.43%) and asthenia grade 2 (20.8%). Grade 3 hematologic toxicity, per cycle, anemia 0.86%, neutropenia (1.7%), and lymphopenia (10.43%). Non-hematologic toxicity were hyperglucemia (9.5%), asthenia (4.3%) and diarrhea. Disease free survival at 36 months was 80% and overall survival 16.2. During follow-up three patients had recurrent disease (13%).

Conclusion: Concurrent chemoradiation with weekly gemcitabine followed by brachytherapy is highly efficacious and well tolerated. Age does not seem to be a limiting factor for the treatment of this neoplasm with this modality.
SIGNIFICANCE OF NUMBERS OF METASTATIC AND RESECTED LYMPH NODES IN IB1 TO IIA CERVICAL CANCER: PRIMARY SURGERY VS. NEOADJUVANT CHEMOTHERAPY

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Background: To compare the significance of the numbers of metastatic lymph nodes (MLN) and resected lymph nodes (RLN) between primary surgical treatment (PST) and neoajduvant chemotherapy before surgery (NCS) in FIGO stage IB1 to IIA cervical cancer.

Methods: We reviewed 451 patients treated with PST and 73 treated with NCS between 2000 and 2008. Adjuvant treatment was performed for ≥2 intermediate- or ≥1 high-risk factors.

Results: The extent of lymphadenectomy and the number of RLN were not different between PST and NCS, whereas the number of MLN was more in PST than NCS (mean, 1.6 vs. 1.3; p=0.02). Although the number of MLN was not associated with survival in NCS, its increase (0, 1-2 and ≥3 of MLN) was related with poor progression-free (mean, 100.8 vs. 87.6 vs. 57.7 months) and overall survivals (mean, 106.2 vs. 95.4 vs. 77.5 months) in PST (p< 0.01). Furthermore, ≥20 of RLN was associated with improved progression-free survival (mean, 77.9 vs. 57.2 months) in only patients with MLN who underwent PST (p< 0.05). The increase of MLN was related with the increased of distant recurrence in PST (44% vs. 72.7% vs. 78.6 % in 0, 1-2 and ≥3 of MLN; p=0.02) despite no association in NCS.

Conclusions: The number of MLD may be more important to predict poor survival and distant recurrence in PST than NCS. Moreover, ≥20 of RLN may be associated with improved progression-free survival in patients with MLN who underwent PST, suggesting the benefit of systematic lymphadenectomy in the patients.
THE IMPACT OF CERVICAL CANCER TREATMENT ON SEXUAL FUNCTION AND INTIMATE RELATIONSHIPS: A CRYING SHAME

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Cervical cancer primarily affects economically disenfranchised women and is the largest cancer killer of women in underdeveloped regions. Although cure is possible, treatment complications significantly impact social and sexual functioning. Complications include infertility, early menopause, nerve and bone damage (spinal stenosis, neuropathic pain), urinary and bowel complications (loss of sensation, obstruction, incontinence, pain, fistulas allowing stool and urine to leak vaginally), vaginal changes (inflammation, shortening, stenosis, dryness), pain with intercourse, and loss of desire. The aims of this study were to explore the impact of cervical cancer treatment on sexual function and intimacy and to assess needed support for promoting satisfaction in and survival of current relationships and courage to engage in new ones.

Twenty in-depth interviews were conducted with women and male partners, in the Midwest US, to explore physical complications, behavioral and emotional responses, and relationship dynamics related to sexual changes. Narrative analysis was used to identify themes and situate them within real life context.

Women told of isolation, physical and emotional pain, and fear of intimacy since treatment. None had been informed of the extent of damage that might occur. None were invited to talk about sexual issues or offered help beyond dilators and lubricant by health care providers. Comments revealed that many providers did not understand potential complications, or how to assess or intervene.

Findings indicate need for cancer survivorship curricula in healthcare education; sexual rehabilitation and communication skills interventions for patients and partners; cross cultural study; and consideration of the social consequences of “cure.”
LOCALLY ADVANCED RECURRENT CERVICAL CANCERS - THE WAY OUT

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\textbf{Method:} The study retrospectively analysed data of 22 patients who underwent exenteration surgery (12 anterior, 3 posterior, 7 total) in a single unit in the Department of Surgical Oncology at the MNJ Institute of Oncology and RCC (02/2006 to 12/2009). All patients received prior chemo radio therapy, 3 underwent previous surgery. 3 had vesico vaginal fistula preoperatively. Exenteration surgery with curative intent was attempted only after laparoscopy and trial dissection and the immediate post operative outcome analysed.

\textbf{Results:} Postoperative mortality was 1(4.5\%), and major morbidities were seen in 5 patients (22.7\%) (Sepsis, stomal leak, severe electrolyte imbalance). All surviving patients were disease free at the last follow up (3 months to 49 months). Immediate postoperative outcome was better in young well preserved patients. There was no significant correlation with the time interval between primary treatment and recurrence, type of exenteration, the histological type, metastatic spread to pelvic lymph nodes, or pre operative vesico vaginal fistula. Careful case selection with trial dissection ensured 100\% tumour free margins.

\textbf{Conclusion:} Pelvic exenteration has an acceptable immediate postoperative outcome, justifying it as a therapeutic option in locally advanced recurrent cervical cancer. There should be a change in the perception of this surgery as a morbid, high risk mutilating surgery to an effective therapeutic tool in carefully selected patients.

Locally advanced recurrent cervical cancers remains a therapeutic challenge in India. This retrospective study aims to describe our immediate results of pelvic exenteration surgery for locally advanced recurrent cervical cancers post chemo radiation.
HPV GENOTYPES PREDICT SURVIVAL BENEFIT FROM CONCURRENT CHEMOTHERAPY AND RADIOTHERAPY IN ADVANCED SQUAMOUS CELL CARCINOMA OF CERVIX

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Purpose: To study the prognostic value of the genotypes of HPV in patients with advanced cervical cancer after radiotherapy with/without concurrent chemotherapy.

Materials and methods: 327 patients with advanced squamous cell carcinoma of cervix, which was defined as FIGO III/IVA or positive lymph nodes, between August 1993 and May 2000 were eligible for this study. HPV genotyping was determined by Easychip® HPV Blot membrane, which detects 38 types of HPV.

Results: A total of 22 HPV genotypes were detected and only 4 patients (1.2%) had negative HPV tumors. HPV16, 58, 18, 33 were the four leading genotypes. Concurrent chemoradiotherapy (CCRT) significantly improves the final overall survival outcome in this cohort and has the same trend for disease-specific survival. Further analysis compared the survival differences between chemo (+) and chemo (-) groups for each leading HPV type. The results of Cox regression analysis showed that in advanced cervical cancer patients with HPV18 or HPV58 infections, cisplatin-based chemotherapy improves disease-specific survival. However, no survival benefit of chemotherapy could be demonstrated in patients with HPV16.

Conclusions: CCRT is of better benefit to cervical cancer patients with HPV18 and HPV58 infections. HPV genotypes could be a useful biomarker to personalize the optimal treatment for patients with advanced cervical cancer. However, the underlining mechanisms of this effect still need further studies.
CORRELATION BETWEEN IMMUNOCYTOCHEMISTRY OF HPV L1 CAPSID PROTEIN AND BEHAVIOR OF LOW GRADE CERVICAL CYTOLOGY IN KOREAN WOMEN

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Aim: The aim of this study was to evaluate the behavior of low grade cervical cytology in Korean women infected with human papillomavirus (HPV) according to the results of immunocytochemistry of HPV L1 capsid protein.

Methods: From January 2006 to December 2007, a total of 353 immunocytochemistry stains in low grade cytology infected with HPV were performed. As a result of exclusions, the evaluable study objects were 318 patients. The study population was followed up in 4-6 months intervals. Regression, persistence, and progression of cytology of 318 cases were investigated with the results of HPV L1 immunocytochemistry.

Results: Low grade cervical cytology of 137 cases showed HPV L1 capsid negative in immunocytochemistry; of these, 38 (27.7%) progressed to high grade lesion, 50 (36.5%) persisted, and 49 (35.8%) cases regressed to normal cytology. Whereas, 181 low grade cervical cytology cases expressed HPV L1 capsid positive; of these, 15 (8.3%) progressed to high grade lesion, 74 (40.9%) persisted, and 92 (50.8%) cases regressed to normal cytology. Immunocytochemistry results of the HPV L1 protein shows a linear association with the progression or regression behavior of low grade cervical cytology infected with HPV (linear by linear association test, P < 0.05).

Conclusions: The immunocytochemistry expression of HPV L1 protein was significantly related with biologic pattern of LSIL in Korean women. Hence, the immunostaining of HPV L1 is helpful to provide further information for low grade cytology.
AGE-SPECIFIC HPV PREVALENCE AND GENOTYPE DISTRIBUTION IN WOMEN WITH NORMAL CERVICAL CYTOLOGY: AN ANALYSIS OF TWO PERIOD COHORTS

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Human papillomavirus (HPV) prevalence rates and genotype distribution among women with normal cervical cytology differ widely across different populations. A population-based HPV genotyping study among female residents (age >= 30 years) of Taoyuan, Taiwan was conducted between 2004 and 2005 and reported previously (2004 cohort). Between 2008 and 2009, those who did not belong to the 2004 cohort were invited. After signing informed consent, every participant had a Pap smear, structured questionnaire, and a HPV testing. Those who had been accrued in the 2004 cohort (n = 135) were excluded in analysis of the 2008 cohort. Of the 5026 women (2008 cohort), 118 (2.35%) had a cytology results of >= atypical squamous cell of undetermined significance. The remaining 4,908 women had a normal cytology. Among the 2008 cohort and 2004+2008 cohort (n = 9816) with normal cytology, the overall HPV prevalence rates were 13.4% (95% confidence interval [CI] 12.4%-14.3%) and 11.0% (95% CI 10.5%-11.6%), respectively. The five most prevalent types, HPV-52, -53, -70, -18, and -58, in the 2008 cohort were the same as the 2004 cohort despite some changes in their ranking. Although distributions of demographic parameters (age, menopausal status, and use of Pap, hormone and oral contraceptives) were significantly different between the 2004 and 2008 cohorts, overall HPV prevalence and multiple infections were positively correlated with age in the 2004+2008 cohorts. Type-specific prevalence rates were positively correlated with age in the top-5 types, except HPV-18 and -52 in the 2008 cohort.
COMBINATION OF IRINOTECAN AND NEDAPLATIN FOR RECURRENT CERVICAL CANCER

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Objectives: There is no standard chemotherapeutic regimen against recurrent cervical cancer. In our institute, combination chemotherapy of irinotecan and nedaplatin was administered for recurrent cervical cancer patients, and the efficacy and side effect of this regimen were evaluated.

Methods: Irinotecan 60mg/m² (day1,8,15) and nedaplatin 80 mg/m² (day1) were administered every 4 weeks. As the main evaluation criteria, the primary endpoint is progression-free survival (PFS), and secondary endpoints are adverse events, completion rates, effective rates, and overall survival (OS).

Results: Histology of evaluated eighteen cases (median age:57 years old) were all squamous cell carcinomas, and completion rates was 72.2%. There were 3 cases of complete response, 2 of partial response, 5 of stable disease, and 7 of progressive disease. Effective rates was 29.4%, and median progression-free survival was 5.5 months, and median overall survival time was 7.5 months. Grade3 or more of adverse events were leukopenia, neutropenia, anemia, thrombocytopenia, nausea, and confusion.

Conclusion: In our study, irinotecan and nedaplatin seemed to be useful for extending PFS and be safe for recurrent cervical cancer patients.
HUMAN PAPILLOMAVIRUS GENOTYPE IN CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2 AND 3 OF TAIWANESE WOMEN

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We aimed to assess the distribution of human papillomavirus (HPV) genotypes in high-grade cervical lesions in Taiwan. The study included 1086 paraffin-embedded, formaldehyde-fixed cervical intraepithelial neoplasia (CIN) 2/3 specimens. HPV genotyping was performed using polymerase chain reaction (PCR)-based methods. Multiple HPV types were validated by E6 type-specific PCR, direct sequencing, and/or real-time PCR. HPV DNA was detected in 995 (91.6%) specimens, and multiple HPV types were identified in 192 (19.3%) samples. The leading HPV types were HPV16 (24%), HPV52 (20%), HPV58 (20%), HPV33 (13%), HPV31 (8%), and HPV18 (4.6%). While the leading 6 types consisted of 87.6%, HPV16 or 18 comprised only 30.9%. The prevalence of different HPV types showed a significant association with age. In women older than 50 years, HPV16 and 18 comprised 21.3% (83/389) while HPV52, 58 and 33 represented 55.5% (216/389). In women aged less than 50 years, HPV16 and 18 comprised 32.1% (224/697, P < 0.0001), while HPV 52, 58 and 33 represented 47.9% (334/697, P = 0.02). The distribution of HPV genotypes was compared with previously reported findings for Taiwanese women with cervical cancer (CC). The overall HPV16 positivity rate was significantly higher in CC than in CIN 2/3 (odds ratio: 2.14, 95% CI: 1.91-2.40). In addition, HPV18, 39, and 45 were significantly overrepresented in CC, while HPV52, 58, 33, 31, 35, 51, and 53 were underrepresented. We concluded that an effective vaccine against the most common HPV types could prevent a significant proportion of cervical cancer cases that occur in Taiwan.
CONCURRENT PARAMETRIAL BOOST DURING PELVIC RADIATION FOR LOCALLY ADVANCED CARCINOMA CERVIX: LATE EFFECTS AND SURVIVAL

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Background: locally advanced carcinoma cervix is treated with external beam radiotherapy with concurrent cisplatin followed by brachytherapy. Many of these patients require additional parametrial boost during their treatment. At low resource centres, machine time is limited due to heavy load so we offered concurrent parametrial boost with whole pelvic radiation and examined the acute and late side effects. The acute effects were presented as poster in IGCS meeting 2008.

Materials and methods: 35 patients with locally advanced carcinoma cervix treated at our institution between February 2008-May 2009 were followed up. All patients were treated with 48-50Gy at 2 Gy per fraction external beam radiotherapy to pelvis via four field technique with concurrent weekly cisplatin. Concurrent parametrial boost was delivered at 0.40Gy per day midline dose with AP/PA field to total 9-10Gy. LDR brachytherapy was delivered after 1 week of completion of EBRT. Chronic side effects and survival was analysed.

Results: Median age 44 years (range 23-73). Stage: IIB 63%(22), IIIA/B 17%(6) and IVA 20%(7). Parametrial involvement was unilateral in 54 % (19) and bilateral 46%(16). At 2.3 years, Kaplan-meier estimated overall survival is 58%. Incidence of chronic cystitis was 0% and proctitis was 6%(2). OS for stage IIB at 2.3 years is 57%, stage III 44% and stage IV 42%.

Conclusion: Concurrent parametrial boost during pelvic radiation for locally advanced carcinoma cervix has acceptable long term side effects without compromising survival. This approach can be applied in low resource centers to save machine time.
POSTOPERATIVE BLADDER FUNCTION OF NERVE-SPARING RADICAL HYSTERECTOMY NAVIGATED BY INTRAOPERATIVE ELECTRO NERVE STIMULATION


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Background: To preserve the bladder function after Piver type IV radical hysterectomy, nerve-sparing technique is going to be a popular procedure recently. However it is still difficult to identify the autonomic nerves including the vesicle branches of the pelvic plexus from uterine cervical supporting tissue.

Aims: To evaluate the availabilities of intraoperative electro-nerve stimulation for detection of autonomic nerves as a procedure of preserving the post-operative bladder function.

Methods: Forty-one patients received nerve-sparing radical hysterectomies and carried out intraoperative electro-nerve stimulation. The patients were classified into two groups depending on the response of electro-nerve stimulation; group A(n=30) with bladder contraction and group B(n=11) without contraction. Two groups were compared on parameters of bladder function estimated by urodynamic study at the point of pre-operation and 1,3,6,12 months after the operation respectively. Urodynamic parameters were compliance at the moment of strong desire to void(Cves), maximum flow rate(MFR), abdominal pressure during the voiding phase(Pabd), detrusor contraction pressure at maximum flow(Pdet), residual urine volume(RU) and bladder sensation.

Results: At the point of 12 months post hysterectomy, the average values of bladder function parameters are shown in parenthesis(group A,group B) respectively; Cves(ml/cmH2O)(89.1,44.3), MFR(ml/sec)(17.5,22.7), Pabd(cmH2O)(4.8,8.5), Pdet(cmH2O)(19.9,27.6), RU(ml)(15.2,77.4).Regarding to post operative Cves, group A showed better compared with group B(P=0.04).Decrease of bladder sensation was shown in 9 cases of 41 patients and group A(n=4) showed more preserved bladder sensation compared with group B(n=5),significantly(p=0.04).

Conclusions: During the nerve-sparing radical hysterectomy, confirmation of detrusor muscle contraction following intraoperative electro-stimulation is a useful technique to predict post-operative bladder function.
INCREASED AWARENESS OF THE HUMAN PAPILLOMAVIRUS DOES NOT INCREASE VACCINE ACCEPTANCE IN YOUNG ADULTS

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Background and objectives: Most studies report an HPV vaccine acceptance of 50-80%, despite a low awareness of the Human Papillomavirus (HPV). This study was performed to investigate the knowledge of young adults about HPV, related to vaccine acceptance before and after the implementation of the HPV vaccine in the national vaccination program.

Methods: 698 male and female students aged 18-25 years were recruited at university faculties and non-university college and interviewed about HPV, cervical carcinoma and HPV vaccine acceptance. These results were compared with our study results conducted in 2005, before the introduction of the HPV vaccine.

Results: Of all participants 46.6% had ever heard of HPV, and 99.6% had heard of cervical carcinoma. Women and students from the medical faculty were significantly more aware of HPV and had a better knowledge of the national cervical screening program. Compared to 2005, knowledge on HPV and cervical carcinoma significantly increased, but acceptance of a “catch-up” HPV vaccination in women decreased from 61% to 51% (p < 0.01). However, acceptance of the HPV vaccination for 12-year old girls increased from 43% to 79% (p < 0.01).

Conclusions: After media attention and the implementation of the HPV vaccine in the national vaccination program, the knowledge about HPV and cervical carcinoma has increased. Despite this increase, the acceptance of a “catch-up” HPV vaccination in this age group decreased. However, HPV vaccination for 12-year old girls is now increasingly accepted. This might be due to the vaccine implementation strategies, focussing on 12-16 year old girls.
A CASE - SUCCESSFUL TREATMENT OF ADENOCARCINOMA (IB2) IN THE UTERINE CERVIX WITH CONCURRENT CHEMO-PHOTODYNAMIC THERAPY (CCPDT)

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Background: Photodynamic Therapy (PDT) has been applied on the treatment of cancer patients. We tried to use CCPDT on Cervical cancer patient and we here report the successful case of it.

Diagnosis and treatment: The patient was 46 years old with cervical polyp. Polypectomy was done and the specimen was revealed with endocervical adenocarcinoma with positive resection margin and the clinical stage was Ib2.

Photosensitizer Photofrin® (porfimer sodium, Axcan Pharma Inc., Canada) 136mg was injected 48 hrs before PDT and Carplan® (Carboplatin, Dong-A Pharm Inc., Korea) 128mg was injected 3 hrs prior to PDT. Then, 632 nm Lazer light was applied on the lesion.

Result: No cancer cell was seen in the 4 consecutive cytologic tests for 8 months and punch biopsy on the positive margin was negative. Finally, the patient was confirmed the negative for cancer through the negative histologic findings after Radical hysterectomy with Para-aortic & pelvic lymph node dissection 10 months after CCPDT.

Conclusion: Thereby, we are reporting a successful treatment of endocervical adenocarcinoma (Ib2) which showed no cancer after CCPDT.
CERVICAL INTRAEPITHELIAL NEOPLASIA AND NORMAL EPITHELIUM: CORRELATIONS BETWEEN EXPRESSION OF TUMOR MARKERS, AND HORMONAL CONTRACEPTIVES, SEX HORMONE LEVELS AND SMOKING

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Introduction: Smoking and oral contraceptive (OC) use has since several decades emerged as epidemiological risk factors for cervical neoplasia, but little is known about biological mechanisms, if any.

Methods: 228 women with cervical biopsies ranging from normal epithelium to carcinoma in situ (CIN III) were recruited. Expression of eleven tumor markers, with relevance in cervical neoplasia were included. Use of combined OCs and progestogen-only contraceptives were identified, serum estradiol and progesterone were measured, and smoking habits and serum cotinine were included.

Results: Hormonal contraceptives: An overexpression of Cox-2 was observed in all OC users. Interleukin 10 was underexpressed only in women with CIN. p53 and epidermal growth factor receptor (EGFR) expression differed from non-users when only medicated intrauterine device users were analysed. Systemic progestogen-only use did not correlate to expression of any tumor marker.

Serum hormones: In normal epithelium, low progesterone levels correlated to expression of EGFR and CD4+. High progesterone levels in CIN correlated to expression of retinoblastoma protein (Rb), p16 and COX-2. Expression of COX-2 and CD4+ correlated to serum estradiol levels in CIN.

Smoking: The tumor suppressors p53 and FHIT, and the immunologic marker interleukin-10 were under-, and Cox-2 and Ki-67 were over-expressed, in smokers with CIN.

Conclusion: The study shows molecular alterations never or rarely studied previously in users of hormonal contraceptives, serum sex hormone levels, and in smokers, in CIN and in normal cervical epithelium. This indicates biological events that could explain previous epidemiological findings.
BURDEN OF FEMALE GYNAECOLOGICAL CANCERS IN CENTRAL ITALY

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The estimation of cancer burden is helpful to set up priorities for disease control.

The purpose of this study was to analyse incidence and mortality gynaecological cancer in Umbria Region (Italy), from 1978 to 2008.

Mortality data were derived from the National Institute of Statistics, while incidence data were provided by the Umbrian Population-Based Cancer Registry. Age-standardised mortality and incidence rates were calculated. Mortality trends were analysed by joinpoint regression model.

While the incidence rate of endometrial and ovarian cancers unchanged, the incidence rate of cervical cancer decreased (9.2-4.6 per 100,000), (Table 1).

Table 1. Age-standardised (Italy 1991) incidence rates, per 100,000 inhabitants, by cancer sites.

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<tr>
<td>Uterus n.s. (C55)</td>
<td>3.7</td>
<td>0.3</td>
<td>0.8</td>
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<tr>
<td>Cervix uteri (C53)</td>
<td>12.6</td>
<td>7.5</td>
<td>7.3</td>
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<tr>
<td>Corpus uteri (C54)</td>
<td>18.3</td>
<td>20.3</td>
<td>21.7</td>
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<tr>
<td>Ovary (C56)</td>
<td>11.6</td>
<td>15.9</td>
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[Table 1]

Figure 1 shows incidence and mortality trends for total uterus.

[Joinpoint regression analysis relative to the mort]

The dramatic decrease in cervical cancer incidence is probably due to the effectiveness of cervical screening and in general to good accessibility to services. Nevertheless, Cancer Registry is important for monitoring and evaluating the quality of healthcare delivery. Instead, the continuous decline of mortality rates over the time period is largely linked to early and specific clinical diagnosis and multidisciplinary treatment.
EVALUATION OF PATHOLOGICAL RESPONSE (PR) AS A NEW PROGNOSTIC PARAMETER AFTER NEOADJUVANT CHEMORADIATION PLUS RADICAL SURGERY FOR ADVANCED CERVICAL CANCER

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Background and aims: Neoadjuvant CT-RT followed by radical surgery resulted in a high rate of complete pathological response and favorable clinical outcome in advanced cervical cancer. The aim of this study was to investigate the correlation of residual neoplastic tissue (pR) with age, hystotype, depth of invasion, presence of metastatic lymph nodes, distant metastasis and clinical outcome, following CT-RT plus radical surgery in patients with stage IB-III cervical cancer.

Methods: The study group included 72 women with a histological diagnosis of advanced cervical carcinoma (62 squamous, 10 not squamous) receiving a platinum-based chemotherapy concomitant with external beam radiotherapy followed by radical surgery. According to findings previously reported from our group, the study population was divided in three groups: No Response (pR2): persistence of tumor bulk with macroscopical residual > 0.3 cm; Partial Response (pR1): persistence of one or more microscopical residual; Complete response (pR0): absence of neoplastic cells invading stromal tissue.

Results: We observed neoplastic masses (pR2) in 25 cases (35%), single or multiple microscopic neoplastic residual (pR1) in 18 cases (25%), and no invasive neoplastic cells (pR0) in 29 cases (40%). pR0 was more frequent in SCC tumors compared to NSCC (45% vs 10%; p=0.0314) and correlated with negative lymph nodes (p=0.02) and absence of distant metastases (p=0.003). Moreover, at univariate analysis, patients with pR0 or pR1 showed better prognosis compared with patients with pR2 (5-years OS 90% and 82% respectively vs 52%; p=.004).

Conclusions: pR could represent a putative prognostic parameter in the management of advanced cervical cancer.
THE IMPACT OF LYMPH NODE DENSITY ON SURVIVAL OF CERVICAL CANCER PATIENTS

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Objective: To evaluate the prognostic value of lymph node density (LND) in patients with lymph node positive cervical cancer.

Methods: A total of 88 consecutive patients were included in our study. Patients were treated with cisplatin-based concomitant chemoradiotherapy, after surgical staging was performed at the Medical University of Vienna. LND, i.e., the ratio of positive lymph nodes to the total number of lymph nodes removed, was assessed pathologically. Patients were stratified into two groups according to LND: patients with LND ≤ 10% and patients with LND >10%. LND was correlated with clinico-pathological parameters by chi-square tests. Univariate log-rank tests and multivariate Cox-Regression models were used to evaluate the association between LND and survival.

Results: Patient characteristics are provided in Table1. A significant correlation between LND and FIGO stage (p=0.03), but not patients' age (p=0.2), histological grade (p=0.8), and histological type (p=0.5), was observed. In a univariate survival analysis LND (p=0.01; p=0.01), FIGO stage (p=0.01; p=0.008), and histological grade (p=0.03; p=0.04) were associated with disease-free and overall survival, respectively. Patients with LND >10% had impaired disease-free and overall survival rates compared to patients with LND ≤ 10%. In a multivariate regression model, LND (p=0.01; p< 0.05) and FIGO stage (p=0.002; p=0.002) were independent predictors of disease-free and overall survival, respectively (Table 2).

Conclusions: LND >10% is associated with an impaired disease-free and overall survival. LND may be used as an independent prognostic parameter in patients with lymph node positive cervical cancer.
THE CURRENT APPROACHES TO THE TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER

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Aims: To improved treatment of locally advanced cervical cancer with the use chemoradiotherapy and subsequent surgical intervention.

Methods: During the period from 2006 to 2010 62 patients were treated against locally advanced cervical cancer (T1b-3bN0-1M0) according to combinative methods of therapy. Squamous cell carcinoma was detected in 88.7% of cases, adenocarcinoma-in 6.5%, adenosquamous-in 4.8 %. A laparoscopic ovarian transposition was done in the first stage to patients in reproductive age (40.3%). Preoperative chemoradiotherapy treatment was performed according to the schedule as follows: 5FU 250 mg/m² for 5 days, and then CDDP 20 mg/m² for 3 days accompanied by the remote pelvic irradiation under dynamic fractionation to 30Gy, and brachytherapy 10Gy. The Wertheim-Meigs surgery was performed after 3-4 weeks.

Results: The chemoradiotherapy carried out without interruption in 85% of the patients. Local radioreactions of 1-2 degrees were detected in 28.8% of patients, anemia of I-II degrees-in 27.4%, leukopenia II-in 9.7% and degree IV in 1.6%. Therapeutic pathomorphos of III-IV degrees was remarked in 61.2%. Chemoradiotherapy had not effect on the duration of operation and volume of blood loss. There were no differences observed during the post operative periods.

Conclusion: The combined approach to the treatment of locally advanced cervical cancer may improve resectability of neoplastic process, has no influence on the technical facilities to perform the surgical intervention, and does not significantly aggravate the postoperative time.
EARLY EVALUATION OF RESPONSE TO CHEMORADIATION FOR ADVANCED CERVICAL CANCER BY DIFFUSION AND PERFUSION MRI: A PILOT STUDY

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Background and aims: Oxygen intratumoral interstitial pressure is an independent predictive factor of response to radiation in advanced cervical cancer. This variable requires invasive procedures to be measured and suffers suboptimal reproducibility. Diffusion (DWI) and perfusion (DCE) magnetic resonance imaging are quantitative non-invasive techniques able to assess tumour microenvironment, interstitial fluid pressure and microvascularisation. The purpose of this study is to determine whether apparent diffusion coefficients (ADCs) obtained with diffusion imaging and volume transfer constants (Ktrans) obtained with perfusion MRI are accurate parameters for prediction and evaluation of cervical cancer treatment response.

Methods: DWI and DCE MRI datasets are prospectively collected for 10 consecutive patients suffering FIGO 1B2 and 2B cervical cancers before, during (at 20 Gy and 45 Gy) and after completion of treatment. Gold standard for evaluation of response is clinical examination under anaesthetics and MRI tumour volume reduction using RECIST criteria. Predictive value of DWI and DCE MRI variables was calculated using the t Student statistical test.

Results and conclusion: ADC and Ktrans mean values and voxel by voxel distribution of these parameters are early indicators of tumours response to chemoradiation.
SMALL CELL NEUROENDOCRINE CARCINOMA OF THE CERVIX: RESULT AND TYPES OF RECURRENCE


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Objective: To analyze the sites of relapse and overall survival in women with neuroendocrine marker-positive small cell carcinoma of the cervix.

Methods: The records of all women who had their initial treatment for cervical cancer at Samsung Medical Center between 1994 and 2008 were reviewed. 17 patients had stages IB1-IIIB cancers that were originally described as “small cell”. Of these, 15 were found to have small cell carcinoma as indicated by positive staining for chromogranin or synaptophysin. Local treatment consisted of a radical hysterectomy in 13 patients and radiation therapy in two. of these 13, 6 patients received postoperative radiation therapy. 14 patients received chemotherapy as part of their initial treatment. The median follow-up for surviving patients was 32 months (range, 2-104 months).

Results: Five (33.3%) of the 15 patients had a relapse. The median time to first relapse from the initiation of treatment was 8 months (range, 7-15 months). Most patients developed hematogenous distant metastases before their death. 5 of 8 patients who were treated with radiation therapy or CCRT had a recurrence above the radiation fields in the paraaortic lymph nodes. No patient had brain metastases as the sole site of first recurrence. One patient developed brain metastases concurrently with lung metastases. The overall survival rate was 20% at 5 years.

Conclusion: Patients with small cell cervical cancer have a poor prognosis. Their course is frequently characterized by the development of widespread hematogenous metastases; locoregional recurrence is also frequent. Brain metastases were seen only in patients who also had distant metastases.
IMPLEMENTATION OF RADICAL HYSTERECTOMY (RH) IN WESTERN KENYA (WK): AN EDUCATIONAL PILOT PROJECT

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Background: A VIA-based screening program was started in 2009 for HIV-affected women in Western Kenya (WK), identifying some stage 1 cervical cancers (CC). Gynaecologists in WK have no prior training in RH surgery, and in WK access to radiation therapy is limited. This pilot was conducted to facilitate gynaecologists’ attainment of the knowledge and skills to safely perform RH in their own context.

Methods: The Society of Gynecologic Oncology of Canada (GOC) developed an educational program which includes modules on anatomy, on indications for, and complications of RH. The program also facilitates database-based longitudinal assessment of these patients. We administered the program in WK using a GOC surgical mentor and training included intraoperative instruction. Evaluations included pre/post tests of participants’ knowledge, qualitative feedback of participants’ experience, and objective evaluation of their surgical skills.

Results: Two Kenyan gynaecologists were trained to perform RH. Participants’ knowledge and surgical skills improved as measured by pre/post tests and intraoperative evaluation. Participants indicated a high level of satisfaction with the program. After completing all modules and 6 RH with the mentor, they independently successfully performed a 7th RH.

Discussion: Treatment for early stage CC should be available to support screening in low resource countries. We developed and evaluated an educational program that successfully taught 2 Kenyan gynaecologists to safely perform RH in their own context. This pilot demonstrates it is possible to teach RH in a short period of time in a low resource setting. The benefit to patients with early stage CC is immense.
PELVIC EXENTERATION AFTER CENTRAL POST RADIATION RECURRENT FOR CERVICAL CANCER

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Pelvic exenteration is an option that may be applicable as a component in the current multidisciplinary approach to extensive pelvic malignancy. Pelvic exenteration may be indicated for primary tumors, locally recurrent malignancies as salvage surgery, or, in rare cases, as a palliative procedure. Compared to other pelvic malignancies, cancer of the uterine cervix has a propensity to present with locally aggressive disease confined to central pelvis without systemic metastases and, therefore, is the most common tumor amenable to resection by pelvic exenteration.

In this work we analyzed three patients with central recurrent disease of cervical cancer who submitted to this procedure for local control of disease and leaving the patients with satisfactory functional status. The patients had the tumor confined to the pelvis with macroscopic invasion of the bladder, rectum and vagina. They had pain, urinary infection and necrotic vaginal ulceration. The age of patients were 55, 63 and 50 years old. In preoperative evaluation we submitted the patients of an extensive radiographic evaluation, to include CT of the chest, abdomen, and pelvis, MRI of the pelvis; and PET. These studies not only determine the presence of metastatic disease but also assist in planning the operation.

All patients were resectable with adequate marginal clearance and can be performed leaving the patients with satisfactory functional status.
BONE METASTASIS FROM CERVICAL CANCER: 20-YEAR EXPERIENCES

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Objectives: To identify clinical characteristics of patients with bone metastasis from cervical cancer.

Methods: We reviewed medical records of patients with bone metastasis diagnosed by radiographic or pathologic exam at the Asan Medical Center between 1989 and 2008.

Results: Eighty-four patients with bone metastasis were identified. The median age was 50 (range, 27-83). 34 patients (40.5%) had FIGO stage I disease, 29 (24.5%) had stage II, 6 (7.1%) had stage III, and 15 (17.9%) had stage IV disease. In histology, squamous cell type was most common (66.7%). Twelve patients (14.3%) had bone metastasis at the time of initial diagnosis. 27 (32.2%) had fracture at diagnosis or during treatment. 63 (75%) had metastasis in the axial bone, 7 (8.3%) in the peripheral bone, and 14 (17%) in both. 34 (40.5%) had only one metastatic bone lesion at diagnosis. 74 (88.1%) had surgery, radiation, chemotherapy, or combination therapies for bone metastasis. And 12 (14.3%) showed complete or partial remission after therapy. 38 patients (45.2%) died during follow-up. Median OS from initial diagnosis was 41 months (95% CI, 21.18-60.82). Median OS from the time of diagnosis of bone metastasis was 11 months (95% CI, 7.04-14.96).

In univariate analysis, patients received any treatment or had metastasis in only one bone showed better in OS after the diagnosis of bone metastasis (Fig 1, 2).

Conclusions: Bone metastasis from cervical cancer is devastating. Multimodal therapy may increase the overall survival after the diagnosis of bone metastasis.

[OS in patients with or without treatment]

[OS by number of involved bone]
RADICAL HYSTERECTOMY FOLLOWING INTENSITY-MODULATED ARC THERAPY (IMAT) ± CISPLATIN IN THE MULTIMODALITY TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER

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Background & aims: To evaluate radical hysterectomy (RH) after IMAT ± Cisplatin in irresectable cervical cancer.

Methods: 34 patients entered this study (FIGO IB:1; IIB:21; IIIA:4; IIIB:6; IVA:2)

Pretreatment investigations included MRI and 18FDG-PET. Respectively 60, 56 and 45 Gy was delivered to the visible tumor, clinical target volume (uterus, cervix, uterus, vagina, parametria) and elective lymph nodes. Response was evaluated clinically and with imaging. If considered irresectable, a brachytherapeutic (BT) boost was performed.

Results: One patient developed grade 3 acute hematologic toxicity (WBC >1000–< 2000/uL) and 1 patient developed late grade 3 intestinal toxicity (BT group). There was no late grade 3 toxicity in the RH group. One patient died of cardiac arrest before evaluation of resectability.

IMAT resulted in resectability in 27/33 patients (81%). Class II RH was performed in 25 patients and extrafascial RH in 2. Pathologic complete remission, microscopic and macroscopic rest was obtained in 12, 14 and 1 patients respectively.

26/27 patients had negative resection margins. Median number of nodes removed was 11. Median hospital stay = 10 days; blood transfusion was needed in 3 patients. Post-surgical complications included cystitis, temporary paresis of the upper limb (n=1), deep venous thrombosis (n=2) and large lymphocelees (n=4) leading to lymph edema (n=4) and hydronephrosis (n=1). There were no re-interventions, no fistulas nor mortality.

At a median follow-up of 17 months, pelvic control is achieved in 26/27. Two patients metastasized.

Conclusions: Hysterectomy after IMAT ± cisplatin is feasible, has low toxicity and results in excellent local control rates.
CASE-CONTROL ANALYSIS OF DIETARY FOLATE AND RISK OF PRECANCEROUS CERVIX LESION: A PILOT STUDY

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An increasing number of studies are focusing on the potential association between dietary folate intake and risk of various cancers. The aim of present pilot study was to investigate the relationship between precancerous cervix lesion and circulating concentrations of folate.

Using an ongoing case-control study were assessed dietary folate in 30 incident precancerous cervix lesion and 31 healthy control subjects. Furthermore we analysed circulating concentrations of vitamin B12 and homocystein in all case and control.

Folate levels of the patients with precancerous cervix lesion were higher than control group (p<0.028). There is no significant difference between vitamin B12 and homocystein levels in two groups.

The causes of precancerous cervix lesion are multi-factorial and still unclear. However, high serum folate levels might be considered, as a predisposing factor in patients with precancerous cervix lesion. This is the pilot study and further investigations with larger groups has planned and designed.
RECURRENT CERVICAL CARCINOMA AFTER PRIMARY LAPAROSCOPIC RADICAL SURGERY

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Objective: This study was undertaken to investigate the patient in recurrent cervical carcinoma who had undergone a primary laparoscopic radical hysterectomy and pelvic lymphadenectomy.

Study design: A retrospective analysis of 174 patients that were performed laparoscopic radical hysterectomy. The numbers of recurrent cervical carcinoma after radical hysterectomy and pelvic lymphadenectomy for stage IB to IIA disease at a single institution was performed to evaluate clinicopathologic parameters, time to recurrence, pattern of failure.

Results: Total 12 patients recurrent. The recurrent rate is 6.9%. Nine patients were death after recurrent and 3 patients still alive.

Most of the recurrent patients had positive pelvic lymph node metastasis or positive vaginal involved or positive LVSI initially. There is no unusually metastasis patent in the patients received laparoscopic radical hysterectomy.

Conclusions: Laparoscopic radical hysterectomy has a similar recurrence rate as radical hysterectomy. Positive pelvic lymph node metastasis or positive vaginal involved or positive LVSI has higher recurrent possibility.
POSTOPERATIVE MORBIDITY AFTER NERVE-SPARING RADICAL HYSTERECTOMY

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Conventional radical hysterectomy (RH) is associated with significant late morbidity. The most frequent is bladder dysfunction and there are controversial data about sexual functions and anorectal dysfunctions. Nerve-sparing (NS) modification of RH has been developed in order to reduce surgical treatment related morbidity.

Although the NS modification technique has not become fully standardized, preservation of both the hypogastric plexus and the splanchnic nerves is currently mostly recognized as main principle.

Objective: The aim of this study was to evaluate potential difference in postoperative morbidity in patients treated with nerve-sparing and classical radical hysterectomy for cervical carcinoma.

Method: In this study we evaluate, using specifically designed questionnaire, three main areas of postoperative morbidity: bladder, sexual and anorectal dysfunction. Patients treated with postoperative radio therapy were excluded from this study.

Results: 23 patients with NS RH and 44 with RH (20 type C and 24 type D) were analyzed 5 months after surgery. Bladder dysfunction occurred in 4% of patients with NS RH and 25% of patients with RH. Anorectal dysfunction were present in 6% of patients with NS RH and 23% of patients with RH. There were no significant differences in occurrences of sexual dysfunction in this two groups of patients.

Conclusions: Results of our study implicated that incidence of complications resulted from disturbances of autonomic pelvic nerves were significantly lower in patients with NS RH in comparison with RH. This surgical strategy deserves consideration in the vision of improving both cure and quality of life in cervical cancer patients.
CERVICAL INTRAEPITHELIAL NEOPLASIA IN THE “DR. SALVATOR VUIA” CLINICAL OBSTETRICS AND GYNECOLOGY HOSPITAL ARAD DURING THE 2000-2009 PERIOD

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Our study concerning the incidence of Cervical Intraepithelial Neoplasia (CIN) covers the 2000-2009 time span, the data being collected from the Histopathology Exams (HPE) registers. During this period, 83,006 Ob-Gyn patients were admitted in our hospital and 16,063 HPEs were performed (19.35% of all patients). CIN lesions were discovered in 1256 cases and Cervical Intraglandular Dysplasia (CIGD) in 53 cases.

CIN I, CIN II and CIN III lesions represented 65.92% (828 cases), 19.67% (247 cases), and 14.41% (181 cases) of the total CIN cases, respectively.

The mean patients' age was 44.65± 9.83 years for all cervical dysplasia cases, 44.58± 9.75 years for all CIN cases, 43.81±9.22 years, 46.50±10.17, and 45.46±11.05 years for CIN I, CIN II, and CIN III, respectively. The mean patients' age for the CIG case was 46.45 ± 11.63 years.

Early detection of CIN lesions through adequate clinical and paraclinical exams is of utmost importance for preventing cervical cancer, which remains a serious and frequent health problem in Romania.
NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED CERVICAL CARCINOMA AT IIB- IIIB STAGES

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Methods and material: 78 women with locally advanced cervical carcinoma (CC) were treated with preoperative chemotherapy with following surgical intervention and combined radiotherapy at period from 2003 to 2008.

At the first stage all the patients received neoadjuvant chemotherapy (NACT) with following regimen: paclitaxel 135 mg/m\(^2\), cisplatin 75 mg/m\(^2\) or carboplatin AUC5. In 6 women (10,3%) with unresectable CC combined radiotherapy was performed because of inefficiency of treatment at the first stage. In other 72 patients (92,3%) hysterectomy III type and following radiotherapy was conducted.

Results and discussion: Sonography against background of the NACT showed reduction of uterus cervix volume after the first course in patients with IIb stage by 30,2% (from 49,6 см\(^3\) to 34,8 см\(^3\)), IIIa-b stage 38,9% (с 67.5 до 39,3 см\(^3\)). The most decreasing of uterus cervix volume was observed after the first course of therapy. After two courses of therapy reducing of primary volume by 41,7% at IIb stage and by 52,5 % at III stage is achieved. Results of our work are encouraging: at present 49 patients (62,8%) are alive and did not have recurrence of disease.

Recidiv 20 patients (25,6%), 11 (14,1%) were died. 24 (63,2%) from 38 women with IIIb stage stay alive 1-3 years without recurrences. Progression of disease in patients with III b was noted in 26,3 %.

Conclusion: We determine that including of (NACT) in complex treatment of women with locally advanced cervical carcinoma allows respectability in 92,3% with level of radical surgical intervention - 73,6 %.
CERVICAL CANCER IN THE “DR. SALVATOR VUIA” CLINICAL OBSTETRICS AND GYNECOLOGY HOSPITAL ARAD DURING THE 2000-2009 PERIOD

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Our study concerning the incidence of cervical cancer covers the 2000-2009 time span, the data being collected from the Histopathology Exams (HPE) registers. During this period, 83,006 Ob-Gyn patients were admitted in our hospital and 16,063 HPEs were performed (19.35% of all patients).

Cervical cancer represented 58.83% (733 cases) of the 1246 overall genital cancer cases. The fragments sent to the histopathology departments were obtained by biopsies in 679 cases (92.63%) and from surgical specimens in 54 cases (7.37%).

All but two patient had different type of carcinomas (99.72%), with the sole exception of a carcinoma-sarcoma combination and a neoplasia with neuroendocrine cells (each case representing 0.14% of all cervical cancers). There were 16 cases (2.18%) of microinvasive carcinomas combined with CIN lesions and 3 cases of CIN III combined with in situ carcinoma (0.41%). The mean patients’ age in case of cervical cancer was 52.90 ±12.97 years.

Early detection of CIN lesions through adequate clinical and paraclinical exams is of utmost importance for preventing cervical cancer, which remains a serious and frequent health problem in Romania.
EVALUATION OF COLD KNIFE CONIZATION IN DIAGNOSIS AND TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA III, A 301 CASES REVIEW

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Objective: To evaluate ThinPrep Cytology Test (TCT), human papillomavirus (HPV) test, colposcopy with biopsy and cold knife conization (CKC) in diagnosis and treatment of cervical intraepithelial neoplasm (CIN) III.

Methods: A retrospective analysis on the clinical data was conducted in 301 women with CIN III, who underwent CKC from January 2000 to October 2008. They all had liquid cytology test (TCT), histopathological examination of multiphase biopsies under colposcopy; and 229 of them had HPV-DNA test by Hybrid Capture II (hc2).

Results: TCT impression turned out to be HSIL in 113 cases (37.54%), LSIL in 76 (25.25%), ASCUS in 92 (30.56%) and normal in 20 cases (6.64%). Hc2 showed positive result in 213 (93.01%) out of the 229 cases detected by HPV test and negative in 16 (6.69%). After CKC, histopathological diagnosis were CIN III in 188 (62.48%) cases and 6 (2.99%) of them were with positive margins. In the 15 (4.98%) of early invasive carcinoma, 12 with I a1 were followed up without any further treatment; another one with I a1 and two with I a2 underwent extensive hysterectomy and lymphorectomy. All patients were followed up and no recurrence was observed.

Conclusions: The combination of TCT, HPV test, and colposcopy with multiple biopsies is valuable in screening and diagnosis of cervical lesions. CKC is an essential approach to avoid miss-diagnosis of early invasive cervical carcinoma, and an effective treatment of both CIN III and cervical carcinoma I a1.
PRIMARY SCREENING FOR CERVICAL CANCER IN CAMEROON: PRELIMINARY RESULTS COMPARING SELF- VS CLINICIAN-COLLECTED SPECIMENS FOR HPV DETECTION

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Introduction: Cervical cancer screening by cytology in low resource setting is difficult to implement due to logistical problem as "speculum collected specimen". Self-collection of High-Risk Human Papillomavirus (HR-HPV) may become a valuable screening test. We report here preliminary data.

Objective: Our aim was to determine the agreement between self- and clinician-collected samples for HR-HPV to detect cervical pre-cancer and cancer.

Material and methods: Since July 2009, we have initiated cervical cancer screening with visual inspection with acid acetic (VIA), cytology and HPV testing. Two hundred sixteen patients aged between 30-65 years old have been included. Women collected a vaginal self-sampling for HPV test before undergoing screening with clinician-collected HPV test, VIA and cytology. The HPV test was performed with Abott Real Time High Risk HPV test. Kappa (K) test was used to determine the concordance between self- and clinician-collected HPV tests.

Results: Data were completed for 169 patients. The HR-HPV prevalence was of 22.5%. Self-collected HPV tests were positive for 33 patients (19.5%) and 29 (17.2%) for clinician-collected samples. Global concordance was of 91.7% (K=0.72). Abnormal cytology was identified in 7.8 % women. HPV tests were positive in 44.4% of patients with abnormal cytology (ASC-US or more). A 100% concordance was observed between self-and clinician-collected samples in patients with abnormal cytology.

Conclusion: Preliminary data suggest that self-collected are as sensitive as clinician-collected samples to detect HR-HPV infection. Complete data will be needed to confirm these results.
VARIATIONS IN RECURRENCE PATTERN OF STAGE IB CERVICAL CANCER ACCORDING TO LYMPH NODE INVOLVEMENT

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Introduction: In this study we investigated the variations in recurrence pattern of stage IB cervix cancer according to the lymph node involvement.

Methods: We revised 170 patients who had undergone type III radical hysterectomy and systematic retroperitoneal lymphadenectomy in between 1993-2007.

Results: Among the patients in study group 115 of them didn’t have lymph node metastases and 55 of them did have. Twenty-seven patients developed recurrence. Twelve patients of them were in lymph node negative group and 15 patients were in lymph node positive group. The ratio of recurrence was higher in the lymph node positive group (27.3% vs 10.4%, p=0.011). Recurrence was detected in only the pelvic region in 9 of 12 patients with lymph node negative group and in 7 of 15 patients with lymph node negative group. The recurrence pattern wasn’t changed by according to lymph node involvement. However distant recurrence was more common in lymph node positive group (53.3% vs 25%, p=0.137). In addition to, 6 of 7 patients with pulmonary recurrence were in lymph node positive group. And also the recurrence in upper abdomen was only observed in lymph node positive group.

Discussion: This study suggests that the presence of lymph node involvement in stage IB cervix cancer statistically does not affect whether the recurrence is local or distant. However it is observed that in lymph node positive group the distant recurrence was more frequent.
UTILIZING VARIAN ECLIPSE CONTOUR FUNCTION TO GENERATE A COMPOSITE PLAN FROM EXTERNAL BEAM AND BRACHYTHERAPY PLANS FOR CERVICAL CARCINOMA

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Purpose: As there is no commercial application allowing composite gynecologic planning, this study describes a unique method of dosimetrically combining dose from external radiation and brachytherapy. This composite plan allows more accurate nodal and parametrial dose planning.

Materials and methods: Utilizing the “Isodose to Contour” function in Eclipse, the isodose distribution from the HDR implant is overlaid onto the external plan. Initially, the implant CT data set is registered by bony anatomy to the external beam data set. The tandem volume is created by contouring it on the HDR CT. Since the HDR isodose distribution is generally a symmetric cylinder, radial measurements are taken of the doses of interest to be overlaid for the composite. With the contouring margin tool, the doses of interest are recreated by expanding the contoured tandem by the known radial measurements. Because the HDR CT is registered to the external beam CT, one can overlay the HDR isodose distribution on the external beam isodose distribution. Adding the isodose lines where they cross from each plan allows an estimation of the composite dose and the boost is planned from this composite.

Results: The composite dose gives the physician adequate information to design a boost plan targeting underdosed regions and conforming to isodose lines from the brachytherapy. After boost planning is completed, one can generate a rough composite of all plans.

Conclusion: This composite dose technique allows the physician to design boost and nodal radiation more accurately.
FEASIBILITY OF DYNAMIC ADAPTIVE RADIOTHERAPY FOR CERVICAL CARCINOMA

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Purpose: The purpose of this study was to evaluate the feasibility of a novel dynamic adaptive radiotherapy treatment for cervical carcinoma.

Materials and methods: Ten patients at the University of California, San Diego with malignant neoplasm of the cervix were selected for this study. Upon selection, each patient underwent a CT scan with a full and empty bladder. These scans determined the ITV created with traditional treatment margins. Four treatment plans were subsequently generated: one each with a central, posteriorly, and anteriorly situated PTV to account for organ motion. The fourth plan was "PTV chaos" with typical large margins. All plans were optimized to the "chaos" volume, treating each patient traditionally; however, the radiation therapists chose one of four treatment plans daily depending on the anatomy viewed on pretreatment CBCT. Choices were recorded and compared to treating physician choices.

Results: The therapists and the treating physician had a 44% agreement on chosen plans. However, upon secondary inspection, it was found that the physician deemed 90% of the therapists' picks as acceptable, although not ideal choices. Further data is being collected including data from multiple physicians (inter-user variability) and multiple therapists (untrained and highly trained).

Conclusions: Preliminary data demonstrates that therapists have difficulty picking the most appropriate treatment volume sparing the most vulnerable organs. However, therapists, even when minimally trained, chose treatment volumes that covered the target.
THE PARTICIPATION OF METALLOTHIONEIN-POSITIVE STROMAL FIBROBLASTS IN THE DEVELOPMENT AND PROGRESSION CARCINOMAS OF SQUAMOUS ORIGIN

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Introduction: The activated fibroblasts of tumor microenvironment called carcinoma-associated fibroblasts (CAFs), are an important element, that participate in tumor development. In malignant neoplasms, the number of CAFs often increases significantly. CAFs help to determine whether the neighboring cancer cells proliferate, infiltrate the surrounding tissue, or metastasize to distant organs. Metallothionein (MT) has been shown to have a protective influence on apoptosis and the expression of MT by tumor cells plays an important and complex role.

Aim: The aim of the study was to determine the importance of MT expression by stromal fibroblasts in the microenvironments in carcinomas of squamous cell origin.

Method: Tissue samples for immunohistochemical staining were derived from 50 patients with squamous cell carcinoma of the uterine cervix. Immunoreactivity of MT in tumor tissue samples and tumor stroma was determined.

Results: MT immunoreactivity was observed in both tumor cells and also identified in the microenvironments of tumor. The MT immunoreactivity was detected on the fibroblasts of the stroma of tumor. The number of MT positive fibroblasts diminished as the distance from the tumor tissue increased. An accumulation of MT positive cells around the cancer nest in affected patients correlated with certain clinicopathological features, such as an advancement of the disease, the presence of lymph nodes metastases, and a poor prognosis for the case.

Conclusion: It seems that the presence of MT immunoreactivity in the fibroblasts of the tumor microenvironment may be a marker of both remodeled fibroblasts (i.e., CAFs) and a remodeled tumor microenvironment.
OVARIAN TRANSPOSITION IN CERVICAL CANCER

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Introduction: There is inconsistent data about the role of ovarian transposition in protecting gonadal function in premenopausal women treated with pelvic radiation therapy (RT), with reported failure rates varying between 12 to 90%.

Methods: Retrospective study of women submitted to surgical treatment for cervical cancer with ovarian preservation, between January 2004 to September 2009. Ovarian function was clinically analyzed.

Results: Twenty-five premenopausal women were included. Mean age was 39 years (31-49). In 84% of them (n=21), both ovaries were transposed (group 1); in one case unilateral ooforectomy was performed because of an ovarian cyst and in 3 women (12%) the ovaries were preserved without transposition (group 2). Only 8 patients (32%) received postoperative RT, all but 1 were in group 1. Three women were lost to follow-up. Of the 22 patients left, 68% (n=15) retained ovarian function. Only 2 of the non-climacteric patients (13%) received RT. Four (57%) of the climacteric patients (n=7, 32%) received RT. Eighteen percent of our followed patients developed chronic pelvic pain (n=1) and benign ovarian lesions (n=3), two of them were climacteric and had subsequent ooforectomy. Therefore, only 13 patients (59%) retained ovarian function with no problems.

Conclusions: Our work shows an ovarian failure rate of 32% and 8% incidence of complications. Pelvic RT was the most important failure factor. Almost 60% of the patients retained ovarian function with no subsequent problems. Ovarian transposition seems to be a safe procedure and should be offered to all premenopausal women with early stage cervical cancer with macroscopically normal ovaries.
KNOWLEDGE OF HPV AND CERVICAL CANCER AMONG HIV POSITIVE WOMEN IN LAGOS-NIGERIA

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Background: Cervical cancer is the most common cancer among women in parts of Africa. HIV is a known co-factor that enhances the oncogenic potential of HPV. In Nigeria there are about 4.5 million people living with HIV/AIDS, about 60% are women. The objective of this study was to determine the knowledge of HIV positive women on HPV and cervical cancer.

Material and methods: 200 women who attended an HIV clinic in Lagos in January 2010 and who consented to participate in the study were randomly selected. They were given self administered questionnaire. The questionnaire sought to determine their sociodemographic characteristics, their knowledge of HPV, cervical cancer and the HPV vaccine.

Results: 183 completed the questionnaire. The mean age was 33.0±6.1 years (range 23-52 years). 32.1% had had post secondary school education and 29.5% were single. 117 (71.1%) had never been on form of contraception. HIV diagnosis was made in 127 (69.3%) during severe illness. 58.1% never heard of cervical cancer. 74.4% had never had any form of cervical cancer screening. About 90% have never heard of HPV and 92.3% did not know that HPV causes cervical cancer, 82.1% didn’t know that HPV is contacted by sexual intercourse and only 17.1% knew cervical cancer can be prevented by a vaccine.

Conclusion: The overall knowledge of cervical cancer and HPV was very poor. There is need to improve the knowledge of this disease among this population. Cervical cancer screening should be made available and a little or no cost to them.
PRIMARY MALIGNANT MELANOMA OF THE UTERINE CERVIX - A CASE REPORT

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Introduction: Malignant melanoma (MM) represents 1% of all cancers and has an incidence of 3-7% in the female genital tract, the majority of cases being reported in the vulva and vagina. Primary MM of the cervix is very seldom encountered. The literature reviews have been based exclusively on case reports, which create many controversies in what refers to diagnosis and management.

Case report: Our patient is a 75 year old white female who had a 1-month history of vaginal bleeding due to a bleeding cervical lesion, being referred to our institution. Gynecological examination revealed a 1.5 cm exophytic cervical lesion, ulcerated and hemorrhagic. Incisional biopsy was taken and sent for histopathological examination, which revealed a MM of the cervix, confirmed by immunohistochemistry. Exclusion of the primitive tumor in other sites as in the skin, eye, oropharynx and anorectal, was made. The tumor was stage IB1 of the International Federation of Gynecology and Obstetrics (FIGO) classification and the patient underwent a radical hysterectomy with bilateral adnexectomy and pelvic lymphadenectomy. The post-operative course was uneventful. Three months and a half later, the patient was admitted in our emergency room complaining of general weakness and the toraco-abdomino-pelvic CT showed hepatic metastization. She initiated chemoradiotherapy and died three months later.

Discussion and conclusion: Although the diagnosis was made in an early disease stage, the prognosis was very poor, allowing to conclude that this rare entity has undoubtfully an unpredictable and poor prognosis, with no cases of cure described until today.
IB1 INVASIVE CERVICAL CANCER MANAGEMENT IN PREGNANCY

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Objective: Case report presenting management of cervical invasive cancer in successful pregnancy.

Aims: 35 years old patient referred with high grade cervical lesion in the 12th week of pregnancy. Suspect colposcopy and cone biopsy proved invasive squamous cell cervical cancer IB1 (12x4mm). Pregnancy continuing was strong desired.

Methods: Pelvic systematic lymphadenectomy by open laparotomy, simple vaginal trachelectomy and cerclage were performed in the 16th week.

Results: 23 negative lymph nodes, residual squamous cancer pT1b1N0M0,gr.III. Caesarian section delivery in 36+1 week was followed by immediate hysterectomy. No residual disease.

Conclusion - discussion: There isn't standard protocol for cervical cancer management in volitional pregnancy. Actually published data shows very good prognosis for cervical cancer patients with lesion less than 20 mm and less than half of cervical stroma. There is limited effect or almost no benefit of parametrial resection for cervical cancer patients with small volume tumor with negative nodes. Our published data of fertility sparing protocol LAP I - laparoscopic sentinel node detection with laparoscopic lymphadenectomy followed by simple vaginal trachelectomy showed superiority of this protocol in selected group of patients. Published paper about radical abdominal trachelectomy in pregnancy has 60% failure abortion. Vaginal approach for trachelectomy is more favor for concurrent pregnancy and in selected group of patients is effective as a standard treatment. Approach for lymphadenectomy depends on surgeon’s technical skills and size of pregnancy. Sentinel node identification wasn’t due to pregnancy possible. Described management of concrete example is evidence based and effective from obstetrical and oncological point of view.
IMPACT INDICATORS OF CERVICAL CANCER

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Background: Cervical cancer is a major cause of loss in women of fertile age and economically active, also affects entire families and society. Hence the need to objectively evaluate the health status of women with cervical cancer and have valid and reliable data about the impact of this disease on society.

Methods: We found crude rates and age-specific standardized rates using as numerator cases of cervical cancer collected by the Population Based Cancer Registry of Arequipa, Peru from 2004 to 2007 and as denominators the female population of Arequipa. In the calculation of life expectancy was used the method of Reed - Merrell modified and the calculation of potential years of life lost was used Measurement Index Potential Years of Life Lost.

Results: The mortality crude rate from cervical cancer is 7/100,000 women, being the fourth leading cause of cancer death in women. The mortality median age was 50 years. The Potential Years of Life Lost amounted to large social and economic losses for the people of Arequipa, making a total of 1819.5 years of life lost of which 1901.7 were economically productive ages, consolidating a total economic loss for the Arequipa region of USD 4´648,600.00.

Conclusions: The indicators of the impact of cervical cancer presented, provide a manageable amount of relevant and timely information that allows prioritizing within health problems.
IN VITRO ANTITUMOR EFFECTS OF HIV-PROTEASE INHIBITORS IN CERVICAL CANCER CELLS

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Introduction: Despite the use of screening programs and therapy, invasive cervical cancer (ICC) remains the fifth most deadly cancer among women worldwide. The main risk factor in the development of ICC is infection with human papillomavirus type 16 (HPV-16). New therapies are still needed. Recent data indicate that HIV-protease inhibitors reduced incidence of HIV-associated tumors including cervical cancer, affecting directly tumor cell metabolism. The aim of this study was to evaluate the effects of HIV-protease inhibitors Indinavir and Saquinavir on ICC-cell proliferation, migration and invasion.

Methods: ICC-cell cultures were obtained from patients affected by ICC. The epithelial purity of ICC-cell lines was checked by immunocytochemical staining with antibody against pancytokeratin and EMA. HPV type was assessed using the Linear Array HPV genotyping test. Cells were exposed to Indinavir and Saquinavir, both 10 microM for 4 days. The BD BioCoat Tumor Invasion System was used for Cell-Invasion and Cell-Migration assays. For proliferation assay, the number of cells was evaluated by crystal violet dye uptake assay.

Results: We selected three established ICC-cell lines infected by HPV-16 and CaSki cell as HPV-16 ICC model. The treatment with Saquinavir inhibited the migration and proliferation in all ICC-cell lines and inhibited the invasion in three of them, but not in Caski cells. These effects were not observed with Indinavir.

Discussion: The present data indicated anti-proliferative, anti-migration and anti-invasive effects of Saquinavir. Probably we did not found any inhibitory effect on invasion of CaSki cells because it represents an in vitro model of heavily deregulated ICC.
ESTROGEN METABOLITES IN PATIENTS WITH VIRUS-ASSOCIATED CERVICAL CANCER
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The purpose of the study was to determine the level of urinary estrogen metabolites in patients with cervical cancer.

Materials and methods: The study included 26 patients with stage I-IV cervical cancer. The level of urinary estrogen metabolites was assessed using ESTRAMET enzyme immunoassay kit (Mirax-Pharma).

Results: The median age of the patients was 45.6±14.3 years. Stage I cervical cancer was diagnosed in 23.1% of patients, IIb in 38.5%, IIIb in 30.8%, and IV in 7.7%. Histological examination confirmed squamous cell cervical cancer in 88.5% of cases, granular-squamous cancer in 7.7% and adenocarcinoma in 3.8%. Moderately-differentiated squamous cell cervical cancer was diagnosed in 48.8% of cases and poorly-differentiated cancer was revealed in 70%. HPV-infection type 16 was identified in 70% of cases, type 18 in 15% and mixed HPV types were detected in 23% of cases. The level of metabolite 2OHE1 in urine was lower in cervical cancer patients than in healthy women (8.95±2.9 ng/mg versus 19.7±1.2 ng/mg). The level of metabolite 16OHE1 was 14.95±4.4 ng/mg in cervical cancer women and 15.2±2.4 ng/mg in healthy women. Estrogen metabolite 2/16 ratio was significantly lower in cervical cancer patients than in healthy women (0.7±0.15 versus 1.67±0.24).

Conclusion: Changes in estrogen metabolite 2OHE1/16OHE1 ratio towards predominance of the “aggressive” metabolite 16OHE1, which contributes to the induction of such mechanisms of estrogen-dependent carcinogenesis as enhancement of cell proliferation and genotoxic damage to hereditary apparatus, allow to consider cervical cancer as estrogen-dependent tumor and the determination of estrogen metabolite level as a new diagnostic criterion.
PROGNOSTIC VALUE OF PRETREATMENT SCCAg AND CYTOKINE SERUM CONCENTRATION IN CERVICAL SQUAMOUS CELL CANCER PATIENTS

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**Aim:** The purpose of this study was to determine the prognostic significance of pretreatment serum tumour marker SCCAg and cytokines: IL-6, VEGF, sTNF RI concentration in cervical squamous cell cancer patients, in aspect of the disease-free survival (DFS).

**Methods:** The study comprised 72 previously untreated patients with cervical squamous cell carcinoma. All tumors were verified histologically and staged according to the FIGO classification. Serum concentrations of SCCAg were determined, using the Abbott instruments system and of cytokines, by the ELISA of R&D. For the statistical analyses, the Mann-Whitney test, the Kaplan-Meier method and Cox's regression model, were applied.

**Results:** In the study group, serum SCCAg, IL-6, VEGF and sTNF RI levels were found to be elevated in 60%, 60%, 54% and 86% respectively. During the 5-year's follow-up, in 26 patients the recurrent disease was confirmed and in 46 patients remission of the disease. The examined pretreatment serum SCCAg and cytokines (except sTNF RI) concentration, were significantly higher in patients, who developed recurrent disease. In univariate analysis, SCCAg (p< 0,0004), IL-6 (p< 0,0001), VEGF (p< 0,003), sTNF RI (p< 0,015), clinical stage and histological grade were considered factors of poor prognosis. So far, multivariate analysis has proven that SCCAg and IL-6, apart from stage and grade, were the independent prognostic factors of the DFS.

**Conclusions:** Our results have demonstrated, that elevated pre-treatment serum SCCAg and IL-6 concentration, proved to be an independent prognostic factors of poor DFS in squamous cell cervical cancer patients.
HUMAN PAPILLOMAVIRUS PREVALENCE AND TYPE DISTRIBUTION IN CERVICAL ADENOCARCINOMA: RESULTS FROM A MULTINATIONAL EPIDEMIOLOGICAL STUDY IN EUROPE

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A study of human papillomavirus (HPV) infection in invasive cervical cancer (ICC) assessed the prevalence of HPV types in invasive cervical adenocarcinoma (ADC) and squamous cell carcinoma (SCC) in 12 European countries.

Formalin-fixed, paraffin-embedded specimens from women ≥18yrs with ICC were HPV-DNAtyped by PCR for 14 high-risk HPV types and histopathological review including blinded expert review of HPV+/- ADC.

Agreement between original and expert diagnoses was 80.1% for ADC (85% for HPV+ ADC and 57% for HPV- ADC). New expert diagnoses for HPV- cases included non-cervical ADC and histological subtypes of cervical ADC considered unrelated to HPV. Following expert review, ADC cases, described in analysis, included most commonly mucinous ADC (86.0%), clear cell ADC (6.9%), minimal deviation ADC (1.7%) and serous ADC of cervix (5.4%). ADC accounted for 13.4% of all ICC (n=3162). Median age for ADC was 45yrs. Overall HPV+ rate was 94.2% for SCC, 81.3% for ADC, and 90.4% for mucinous ADC. A single HPV type was found in 93.3% of HPV+ ADC, predominantly HPV16 (54.2%), HPV18 (40.4%) and HPV45 (8.3%). Of 17 multiply infected women with ADC, 15 had been infected with HPV16, HPV18 or HPV45. Women diagnosed with ADC and single HPV16/18/45 infections were younger than those infected with other single HPV types (42/43/44yrs versus 56yrs, respectively). HPV16/18/45-related ADC occurs at an earlier age than HPV-16/18/45-related SCC, and accounts for 98.1% of all single HPV infected ADC.

Implementation of a HPV16/18 vaccine including HPV45 cross-protection would reduce the burden of ADC [Study ID: 108288/108920].
THE GENE AMPLIFICATION OF HUMAN TELOMERASE (HTERC) IN CARCINOMA OF THE UTERINE CERVIX

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Background and aims: Tumors are frequently characterized by series of cytogenetic abnormalities. The amplification of gene hTERC (3q26) was the most consistent chromosomal abnormality found in carcinoma of the uterine cervix. Gene hTERC is localised in the long arm of chromosome 3 (3q), whose region contains the gene for RNA component of human telomerase.

Methods: The amplification of the gene hTERC (3q) was detected by two methods - interphase fluorescent in situ hybridization (FISH) and comparative genome hybridization (CGH) in our study. Patients have follow up 3 years.

Results: 23 women are currently in our file with the carcinoma of the uterine cervix. Gain of hTERC gene was found in 11 patients (48%) - in the group of adenocarcinoma 4%, in the group of spinocelullar carcinoma 44%. From 3 cases of cancer recurrent 2 women had the positive amplification with the significant level about 30%. Women with the detection of amplification of gene hTERC had positive lymph vascular space involvement in 64% and Human papillomavirus infection in 100%. 4 patients with lymph nodal metastases had proven the amplification in 75%.

Conclusions: Actual results indicate the amplification of gene hTERC (3q26) could predict worse prognosis of women with carcinoma of the uterine cervix. It should be included into the therapeutic management in the future. We could theoretically prefer intensive dispensarisation of patients and aggressive therapy of the cervical cancer with positive amplifications of gene hTERC (3q26).

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DETECTION OF ONCOGENIC TYPES OF HUMAN PAPILLOMAVIRUS (HPV) IN CASES OF LOW GRADE INTRAEPITHELIAL LESION (LSIL) WITH THE MICROARRAYS METHOD

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Background and aims: The study population consisted of 1169 women who proceeded to the outpatient clinic of the Saint Savas Hospital for their annual gynecological check-up and Test Papanikolaou during 2007-2008. The aim of the study was the detection and determination of the prevalence of the high-risk HPV types in low grade intraepithelial lesions of the uterine cervix (LSIL).

Methods: The presence of 17 oncogenic HPV types was examined using the Microarrays technique.

Results: LSIL was diagnosed in 333 out of 1169 Pap smears in our study. HPV 16 was the most frequently detected type (24,9% of LSIL cases), followed by HPV 51 which was detected in 18,6% . Type HPV 33 was found in 14,4%, HPV 56 in 12,3% and HPV 31 in 11,4% of LSIL cases.

Conclusions: HPV types 16 and 51 are the most frequently found in LSIL in our study, however types 33, 56 and 31 are also often detected. Of special significance is the increased detection of HPV type 51. The high percentage of high-risk HPV types among our population indicates the necessity for more careful monitoring of all women diagnosed with LSIL in their Pap smear.
E6 AND E7 MRNA EXPRESSION AND HPV DNA TESTING IN CERVICAL SMEARS. COMPARISON AND CORRELATION WITH THE CERVICAL CYTOLOGY

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Background and aims: High risk HPV types 16, 18, 31, 33 and 45 constitute the main cause of severe cervical lesions, which can be detected in Test Papanikolaou. The aim of our study is the comparison between the HPV DNA testing and the expression of mRNA E6 and E7 viral oncoproteins in 731 women who were examined in Saint Savas Hospital.

Methods: Cervical smears obtained from 731 patients were analyzed for HPV DNA typing using Microarrays. The presence of E6/E7 was identified using the Nuclisens EasyQ NASBA method.

Results: Normal cytology was diagnosed in 79% of the samples, ASCUS was found in 2% of our population, LSIL in 17% and HSIL was identified in 2%. According to MA testing, 32% of the samples were found positive, while 12% of our population was mRNA positive. The prevalence of E6/E7 mRNA was 19% in women aged 15-26, 21% in women 26-35 years old, 15% in the age group 35-48 and 6% in women over 48 years old. HPV16 was found in 7.7% of the population, HPV18 in 4.2%. HPV33 was detected in 2.6% of our sample, HPV31 in 2.5% and HPV45 in 1.4%.

Conclusions: Comparing the two methods, negative MA/ negative mRNA was found in 461 cases (63.1%), positive MA/ positive mRNA in 89 (12.2%), negative MA/ positive mRNA in 33 (4.5%) and positive MA/ negative mRNA in 148 cases (20.2%). Different MA/ Mrna ratio was found in each cytological group.
HPV INFECTION IN MENOPAUSE: AN EPIDEMIOLOGICAL STUDY

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Background and aims: The epidemiological study of HPV infection in menopausal women and the evaluation of the progress of the disease in that group.

Methods: We studied cervical smears of 168 women, aged 48 to 60 years-old, who proceeded to the Outpatient Clinic in Saint Savvas Hospital in order to have their annual gynecological check-up. All the women in our study were in menopause at least for 18 months. For the HPV typing we used the Microarrays method.

Results: The overall prevalence of HPV infection in this age group is 55%, regardless of cytological results in Test Papanikolaou. The most frequently detected high-risk type was HPV 16, while among the low-risk types, in highest prevalence was HPV 42, followed by HPV 6. An interesting finding is the high percentage of HPV infection in samples with normal Test Papanikolaou.

Conclusions: The overall high prevalence of HPV infection in menopausal women in our study is indicative of the increasing frequency of the virus in this age group. Since menopausal women nowadays constitute a numerous group, further investigation and evaluation should take place in order to clarify the biological behaviour of the infection, as well as parameters which possibly have a role in the progress of the infection.
NERVE-SPARING RADICAL HYSTERECTOMY FOR UTERINECERVICAL CANCER

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Objective: The objective of this study is to investigate the therapeutic efficacy of nerve-sparing radical hysterectomy for cervical cancer and to assess postsurgical bladder function.

Methods: A nerve-sparing radical hysterectomy was carried out on 4 patients with stage 1b1 uterine cervical cancer. Nerve-sparing radical hysterectomy is a technique for preserving the autonomic nerve systematically, including the hypogastric nerves, pelvic splanchnic nerves, and pelvic plexus and its vesical branches, based on anatomic considerations. The nerve-sparing procedure was successfully completed in all patients in the study. Postoperative assessment of bladder function consisted of

(a) the time to establish complete self urination (residual urine volume less than 50 ml),

(b) the sensation of bladder fullness, and

(c) the satisfaction of micturition. Operation time, blood loss volume, and complications were analyzed.

Results: Urinary functions:

(a) Mean time to establish complete self urination was 6.6 days,

(b) the sensation of bladder fullness was kept in all patients,

(c) all patients reported satisfaction of micturition at the time of discharge.

Mean operation time was 7h 40min. Mean blood loss was 1635g. No serious complications occurred after surgery.

Conclusions: The surgical technique performed in this study is effective for preserving bladder function. The quality of life could be improved for patients with cervical cancer who were treated with a nerve-sparing radical hysterectomy. Further studies will be necessary to assess the efficacy of nerve-sparing radical hysterectomy in randomized trials.
PROGNOSTIC VALUE OF PODOPLANIN EXPRESSION IN THE INTRATUMORAL STROMA OF UTERINE CERVICAL CARCINOMAS

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Background: The microenvironment of cancer plays a critical role in its progression. Many components of the intratumoral stroma (ITS) have been investigated in relation to tumor progression, including the composition of the extracellular matrix, microvessel density, and the epithelial mesenchymal transition. Previous studies have shown that up-regulation of podoplanin has a role in tumor invasion, probably related to collective cell migration. Little is known about its expression and significance in uterine cervical carcinoma.

Aim: Our objective was to investigate the clinicopathological significance of podoplanin expression in the ITS of uterine cervical cancer.

Methods: We selected patients with clinical stage I and IIA uterine cervical carcinomas (n = 143) that underwent surgery between 2000 and 2007. Clinicopathological data were obtained from patient medical records and all slides were reviewed. Immunodetection of podoplanin was performed on histological sections from tissue microarrays blocks using the monoclonal antibody D2-40. A multinomial logistic regression model was adjusted to evaluate the association between podoplanin expression and classical prognostic factors.

Results: Twenty-seven cases (18.8%) contained ITS fibroblasts that positively stained for podoplanin. There was no association between podoplanin expression and age, clinical stage, tumor size, histologic type, depth of infiltration, or vascular involvement. Expression of podoplanin was only associated negatively with nodal metastasis and death.

Conclusions: These results suggest that podoplanin is an important component of the stromal microenvironment in uterine cervical carcinomas and represents a favorable prognostic factor.
KNOWLEDGE OF HUMAN PAPILLOMA VIRUS INFECTION AND ACCEPTANCE OF HUMAN PAPILLOMA VIRUS VACCINE AMONG WOMEN SEEN IN A COLPOSCOPIC CLINIC

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Background and aims: This study has accessed colposcopic patients' knowledge of human papilloma virus (HPV) infection and acceptance of HPV vaccine.

Methods: Between December 2009 to May 2010, 401 women attending Ramathibodi Hospital colposcopy clinic, Mahidol University, Bangkok, Thailand for the evaluation of abnormal Pap's smears or previously diagnosed cervical intraepithelial neoplasia participated in a questionnaire survey. The questionnaires composed of 3 sections: the demographic characteristics, 10 items of knowledge in HPV infection and the acceptance towards HPV vaccine.

Results: The Pap's smear results of 401 women, 257 women (64.1%) presented with ASCUS or LSIL, 126 women (31.4%) with HSIL or Cancer. In terms of knowledge about HPV infection, 224 women (55.9%) had ever heard about HPV. Two hundred and twelve in 401 women (55.9%) knew that HPV is one of the causes of cervical cancer and 52.6% knew that it causes cervical intraepithelial neoplasia. The median score of knowledge about HPV infection was 4 (range, 0-10). The factors associated with HPV infection knowledge's scores were age (p=0.02), patients' education (p< 0.001), number of sexual partner (p=0.01), parity (0.0049), personal and household income (p=0.0002 and p=0.0118, respectively). Acceptance of HPV vaccine were 86.9%. Women who were younger than 45 years old, had no childbirth, had household's income more than 30,000 Bahts, singer, had more than one sexual partners, whose knowledge of HPV infection's score >4 were associated with more vaccine acceptance.

Conclusions: Although the knowledge scores were associated with the acceptability of HPV vaccine, this demonstrates a significant lack of knowledge about HPV infection in the abnormal Pap's smear patients.
HYBRID IMAGING BY SPECT/CT FOR SENTINEL LYMPH NODE DETECTION IN PATIENTS WITH CANCER OF THE UTERINE CERVIX

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Introduction: Conventional lymphoscintigraphy provides planar images with little spatial information on location of pelvic sentinel lymph nodes (SLN). SPECT has better spatial resolution and may improve preoperative SLN anatomical localization. Aim of the study was to assess SPECT/CT utility on SLN detection in cervical cancer patients.

Methods: Stage IA-IB1 cervical cancer patients undergoing pre-operative SPECT/CT for SLN detection and operated at Claudius Regaud Cancer Center were analysed. A combined technique (radiotracer and blue dye) was used. Patients underwent laparoscopic sentinel node biopsy followed by full pelvic dissection.

Results: 41 patients were included. A 100% SLN detection rate was achieved. At least one SLN was clearly visualized by SPECT/CT in 39 of 41 patients (95%) and full anatomic concordance with intraoperative anatomical location of SLN was found in 37 of the 39 patients with at least one SLN identified by SPECT/CT (95%). Location of removed SLN included the external and internal iliac area in 89% patients, the common iliac area in 11%, and the infra-mesenteric paraaortic area in 1%. No SLN was found in the infrarenal paraaortic region. Lymph node involvement was identified in 5 patients (12.1%). SLN correctly predicted lymph node involvement in 100% patients. However, SPECT/CT failed to identify 1 of the 5 metastatic SLN.

Discussion: SPECT/CT hybrid does not improve SLN detection rate but accurately detects preoperative SLN topography, improving surgical approach to patients with cervical cancer staging. Diagnostic quality of anatomic landmarks of CT images of SPECT/CT could be improved by the use of contrast injected CT.
MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 3 AND MICRO-INVASIVE CARCINOMA OF CERVIX: ANALYSIS OF 83 CASES


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Objectives: To analyze the clinicopathologic characteristics and treatment modalities of patients with cervical intraepithelial neoplasia grade 3 (CIN3) and cervical micro-invasive carcinoma (MIC).

Methods: Clinical and pathologic features of 83 cases of patient with conization diagnosed CIN3 or MIC were retrospectively analyzed. Patients’ mean age was 40.5 years and the common cytological screening result was high-grade squamous intraepithelial lesion. Colposcopic biopsy results included CIN3 (65 cases), suspected invasive carcinoma (16 cases), and discrepancy between cytology and histology (2 cases).

Results: Based on the pathological examination of conization samples, 52 patients were diagnosed as CIN3 (CIN3 group) and 31 as MIC. In patients with MIC, 23 patients were Ia1 (Ia1 group) and 8 were Ia2 (Ia2 group). In CIN3 group, 29 patients (55.8%) received close follow-up as post-conization treatment, 23 patients (44.2%) underwent hysterectomy. In Ia1 group, 3 patients managed by close follow-up, 19 patients (82.6%) received hysterectomy, and 1 received repeat conization. All 8 patients with Ia2 cervical carcinoma received radical hysterectomy. No disease recurrence was found during the follow-up.

Conclusions: For CIN3 and MIC patients, colposcopic-directed biopsy has important suggestive value, but conization is necessary for the definite diagnosis. For young women with CIN3, conization served as the final treatment for reserving fertility. For women with Ia1 cervical carcinoma, hysterectomy is recommended except in women with strong desire for child-bearing, with negative resection margin and well follow-up condition. For women with Ia2 cervical carcinoma, radical hysterectomy is recommended, while radical trachelectomy is strictly indicated in patients with extremely strong desire for child-bearing.
KNOWLEDGE OF TAIWANESE WOMEN SEEKING HPV VACCINATION

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In Taiwan, human papillomavirus (HPV) vaccine is recommended to women aged 9 to 26 years. The purpose of this study was to examine health beliefs among women aged 9-26 years and women aged over 26 years who seek HPV vaccination. Subjects were recruited from three hospitals in southern Taiwan. One hundred and eighty-nine women with initiated HPV vaccination completed a questionnaire of health belief. 38% (n = 72) of the women with initiating vaccine were over the age of 26 years. Health beliefs about HPV vaccination were different between women aged 18 to 26 years and women aged over 26 years. Women aged 18-26 years were more likely than women aged over 26 years to concern the cost and availability. Recommendations from others are main reasons for young adult women to initiate HPV vaccination; while self-awareness at high risk for cervical cancer and personal gynecologic diseases are main reasons for adult women to initiate HPV vaccination. Media plays an important role to trigger women to seek HPV vaccination.
A PHASE I/II STUDY OF CISPLATIN AND RADIATION IN COMBINATION WITH SORAFENIB IN CERVICAL CANCER

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This is a single-arm, open-label, phase I/II trial in patients with early stage epithelial carcinoma of the cervix. Sorafenib (S) is a dual kinase inhibitor with anti-VEGF properties that may increase the affect of chemotherapy and radiation on tumor cells. In the phase I component, patients were divided into low risk (tumor size ≤5 cm and either radiographically node negative or only para-aortic node positive) or high risk (tumor > 5 cm or remote node positive). All patients received conventional treatment with radiation and chemotherapy (RT-CT) but the low risk/para-aortic groups received S alone in escalating doses for at least 1 week prior to the start of (RT-CT), while the high risk patients received S alone in escalating dose for at least 1 week prior to the start of RT-CT, as well as concurrently with RT-CT. Twelve patients were enrolled on the study. No DLTs were experienced in the low risk group at dose level 1:200 mg PO BID of S, or dose level 2:400 mg PO BID of S. Accrual continues at dose level 1 to expand for a total of 6 patients. Two DLTs were experienced in the high risk dose level 1:200 mg PO BID of S group (grade 3 anal mucositis and a grade 3 vesico-recto-vaginal fistula). Accrual continues at dose level 1:200 mg PO BID of S. Most common toxicities of any grade include diarrhea (82%), lymphopenia (82%), and nausea (82%). Most common grade 3 or greater toxicities include lymphopenia (73%), leucopenia (18%), and thrombocytopenia (18%).
THE EFFECT OF HPV 16/18 E6 ON TERT PROMOTER METHYLATION IN CERVICAL CANCER CELLS

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Objective: HPV oncoprotein E6 activates telomerase reverse transcriptase (TERT) expression and causes cellular immortalization. But it remains unclear if E6 could affect TERT transcription by DNA methylation. In this study we explored the methylation status of TERT promoter in cervical cancer cell lines and the changes of it after E6 was being silenced by RNAi.

Methods: Three kinds of cervical cell lines, HPV16 positive Caski and Siha, along with HPV18 positive Hela, were taken to analyze the methylation status of TERT promoters by methylation-specific polymerase chain reaction (MSP) and bisulfite sequencing (BS). Stealth RNAi was transiently transfected to these cell lines to silence the HPV16/18 E6 genes, and then the changes of mRNA level of TERT and the status of promoter methylation were examined.

Results: Hypomethylation status around the transcription start site (-156~+162bp) of TERT was related to its transcription. After transfection with Stealth RNAi, the levels of HPV16/18 E6 and TERT mRNA were greatly decreased. The methylated CpG around the transcription start sites in Caski and Siha cells were statistically increased (respectively P=0.016, P< 0.001). But there were no significant difference in Hela cells (P=0.128).

Conclusions: Hypomethylated CpG in -156~+162bp around the transcription start site allow for the expression of TERT in cervical cancer cells. HPV16 E6 can promote TERT transcription through demethylating the DNA sequence around the transcription start site of TERT in cervical squamous cancer cells.
QUALITY OF LIFE AND COST OF TREATMENT IN CERVICAL CANCER AND HPV RELATED DISEASE IN THAILAND

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Background: Cervical cancer is the second most common cancer in women worldwide and is a leading cause of cancer-related death in women in developing countries including Thailand which cervical cancer is still the most common female cancer for decades. We aim to evaluate patient's health related quality of life (QoL) and health care resource utilization associated with cervical cancer, cervical intraepithelial neoplasia (CIN) and genital wart.

Methods: QoL was obtained by using Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire. Costs from provider perspective were the unit cost at King Chulalongkorn Memorial Hospital. We developed a mutually exclusive state-transition Markov model to portray the algorithm of treatment of various stages of cervical cancer, CIN and genital wart by tracking a hypothetical lifetime cohort of 12-year-old girls.

Results: The global QoL was 78.08 (95%CI=76.4,79.8). The subscale score were as followings: physical well-being 81.9 (95%CI=79.6,84.3), social well-being 72.5 (95%CI=70.1,74.9), emotional well-being, 78.7 (95%CI=76.3,81.2), functional well-being 79.3 (95%CI=76.9,81.7). There were no significant differences between stages of diseases and global QoL or subscales. The estimated mean direct cost per a patient with cervical cancer stage IA1, IA2-IIA, IIB-IVA, IVB, CIN1, CIN2/3 and genital wart were $1277, $3020, $12506, $10019, $167, $1551 and $111, respectively.

Conclusion: Our study shows that the impact of QoL on CIN or genital wart did not differ from cervical cancer. However, the cost of treatment was burdensome to the country. The national policy to help reduce this burden and further researches to evaluate the impact is expected.
A CASE OF CERVICAL CANCER METASTATIC TO THE SMALL INTESTINE 4 MONTHS AFTER INITIAL SURGERY


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Background: The metastasis of cervical cancer to the intestine remains infrequent. Herein, we report an unusual case of cervical cancer that metastasized to the small intestine.

Case report: A patient was a 41-year-old woman with stage IIb cervical cancer. She underwent radical hysterectomy with pelvic lymphadenectomy. Pathological examination revealed squamous cell carcinoma. She was treated with concurrent chemoradiotherapy (CCRT). Three months postoperation, laboratory profile demonstrated elevated serum SCC levels of 31.6 ng/mL and severe anemia. She had persistent bloody stool, but an enhanced computed tomography (CT) of the abdomen and upper and lower endoscopy failed to detect any definite intestinal lesions. Based on the diagnosis of recurrence of unknown origin, she received chemotherapy with paclitaxel and carboplatin. She had fever and high white blood cell and C-reactive protein immediately after chemotherapy. A position emission tomography and CT demonstrated strong 19F-fluorodeoxyglucose accumulation in the small intestine, indicating the metastasis to this site. She underwent the resection of the small intestine, and pathology confirmed the metastasis of cervical cancer to the small intestine. She was given additional chemotherapy with docetaxel and carboplatin.

Results: This case emphasizes that although rare, the metastatic cervical cancer to the small intestine should be considered when the patient has persistent bloody stool with elevated serum SCC after treatment of cervical cancer.
MULTI-INSTITUTIONAL PHASE II CLINICAL STUDY OF CONCURRENT CHEMORADIOThERAPY FOR LOCALLY ADVANCED CERVICAL CANCER IN EAST AND SOUTHEAST ASIA

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Purpose: To evaluate the toxicity and efficacy of concurrent chemoradiotherapy using weekly cisplatin for patients with locally advanced cervical cancer in East and Southeast Asia, a multi-institutional Phase II clinical study was conducted among eight Asian countries.

Materials and methods: Between April 2003 and March 2006, 120 patients (60 with bulky Stage IIB and 60 with Stage IIIB) with previously untreated squamous cell carcinoma of the cervix were enrolled in the present study. Radiotherapy consisted of pelvic external beam radiotherapy (total dose, 50 Gy) and either high-dose-rate or low-dose-rate intracavitary brachytherapy according to institutional practice. The planned Point A dose was 24-28 Gy in four fractions for high-dose-rate-intracavitary brachytherapy and 40-45 Gy in one to two fractions for low-dose-rate-intracavitary brachytherapy. Five cycles of weekly cisplatin (40 mg/m²) were administered during the radiotherapy course.

Results: All patients were eligible for the study. The median follow-up was 27.3 months. Of the 120 patients, 100 (83%) received four or five cycles of chemotherapy. Acute Grade 3 leukopenia was observed in 21% of the patients, and Grade 3 gastrointestinal toxicity was observed in 6%. No patient failed to complete the radiotherapy course because of toxicity. The 2-year local control and overall survival rate for all patients was 87.1% and 79.6%, respectively. The 2-year major late rectal and bladder complication rate was 2.5% and 0%, respectively.

Conclusion: The results have suggested that concurrent chemoradiotherapy using weekly cisplatin is feasible and effective for patients with locally advanced cervical cancer in East and Southeast Asia.
CERVICAL ADENOID BASAL CARCINOMA ASSOCIATED WITH INVASIVE SQUAMOUS CELL CARCINOMA: A REPORT OF RARE CO-EXISTENCE AND REVIEW OF LITERATURE

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In the spectrum of basaloid lesions of uterine cervix, adenoid basal carcinoma (ABC) is a rare histologic type, associated with an indolent course and exceptionally good prognosis. Histologically, it resembles other aggressive tumors like adenoid cystic carcinoma (ACC) and rarely can harbor other associated malignancies such as squamous cell carcinoma (SCC), adenosquamous cell carcinoma, small cell (neuroendocrine) carcinoma or carcinosarcoma. The prognosis of pure ABC differs markedly from ACC or if there is an associated malignancy, making an adequate biopsy essential to provide sufficient yield for a clear diagnosis and therapeutic planning. We report a 64-year old asymptomatic lady with an abnormal screening cervical cytology, who underwent a conization to reveal an ABC with overlying microinvasive SCC. Doubtful resection margins led us to propose a radical hysterectomy with adnexectomy with pelvic and para-aortic lymph node dissection. Subsequent histopathological examination showed a true invasive SCC co-existing with ABC, with invasion of the parametrium for which post-operative chemoradiation was prescribed. A literature review revealed 11 previously reported cases of co-existing invasive SCC with ABC. The prognosis of these patients appears to depend on the invasive SCC component. Our case report reiterates the importance of adequate cone biopsy, thorough histological examination and careful interpretation to cover the possibility of a co-existent malignancy. Besides, it presents an argument in favor of radical surgery for the treatment of indefinite lesions, even with inactive clinical features and no distinctly invasive component is demonstrated on initial diagnosis.

Keywords: Adenoid basal carcinoma, squamous cell carcinoma, uterine cervix
EFFECT OF PERI-OPERATIVE BLOOD TRANSFUSION ON THE PROGNOSIS OF EARLY-STAGE CERVICAL CANCER

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Objective: The aim of the present study is to show a correlation between use of blood transfusions and long-term prognosis of patients undergoing surgery for early-stage cervical cancer.

Methods: A total of 157 patients operated at our department for cervical cancer in the period 1995-2008 were retrospectively analyzed. We considered 85 women who underwent radical hysterectomy type 3 of Piver and pelvic lymphadenectomy for FIGO stage IA1-IB1.

Results: We compared women who did not need blood transfusion (n=59), patients undergoing homologous blood donation (n=15) and patients who received allogeneic transfusion (n=11). Age, BMI, FIGO stage, nodal status and co-morbidities were similar among the 3 groups. Median (range) estimated blood loss was 200 (50-600), 600 (350-1100) and 700 (400-1500) mL in the no blood transfusion, autologous blood transfusion, and allogeneic blood transfusion groups, respectively. The mean number of units transfused (2) was the same in both transfused groups of patients. After a median follow-up of 52.4 (4-176.6) months, 5 (45.4%) recurrences were observed in patients who received allogeneic blood transfusions vs. 1 (6.6%) in those who received homologous transfusion (p=0.05) and 2 (3.4%) in patients not transfused (p=0.002). The recurrence rate was similar between the homologous transfusion group and the not-transfused group (p=0.37).

Conclusions: The results suggest that the use of allogeneic but not homologous blood transfusion worsens the prognosis of early-stage cervical cancer, maybe due to a transitory immunodepression that promote the spread of neoplastic cells during surgery.
EMBRYONAL RHABDOMYOSARCOMA OF THE UTERINE CERVIX: A CASE REPORT AND REVIEW OF THE LITERATURE

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Embryonal rhabdomyosarcoma (ERMS) is a highly malignant tumor arising from embryonal mesenchyma and is the most common pediatric soft tissue sarcoma. ERMS of the female genital tract usually occurs in the vagina during childhood. In adults, the ERMS of the uterine cervix is especially rare.

We present the case of a 34-year-old woman diagnosed with an ERMS of the cervix, without evidence of distant disease, who was treated by total hysterectomy and bilateral salpingo-oophorectomy, followed by 4 cycles of IVAdo (ifosfamide- vincristine- actinomycin and doxorubicin) and 3 cycles of IVA (ifosfamide- vincristine- actinomycin) chemotherapy. The patient showed no evidence of recurrence 18 months following initial diagnosis and 12 months after the end of treatment.

A review of the literature demonstrates that a multimodality approach to therapy (surgery, adjuvant chemotherapy and in selected cases radiation therapy) of ERMS of the uterine cervix, can offer a long-term survival and should be considered for the treatment.

Embryonal rhabdomyosarcoma of the cervix is rare, but the awareness of this uncommon type of tumor in this localisation is very important to avoid misdiagnosis.
NEOADJUVANT CHEMOTHERAPY FOR BULKY CERVICAL CANCER: ÇUKUROVA EXPERIENCE

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Although the treatment of invasive cervical cancer is affected by the stage of the disease, there is no standard management of stage Ib - IIA cervical carcinoma. Treatment of bulky stage Ib2 tumors (primary tumors greater than 4 cm) is difficult and whatever primary treatment is chosen, the recurrence rate is higher when compared to stage Ib1 disease. Chemotherapy has the potential to dramatically shrink some tumors and most neoadjuvant chemotherapy trials have shown high rates of initial response. So, neoadjuvant chemotherapy followed by radical surgery has emerged as a possible alternative to conventional chemo-radiation, which may improve a survival in patients with stage Ib2 disease. From 2004 to 2009, 24 patients were enrolled the study while 17 patients were completed the inclusion criteria. All eligible patients had radical surgery after NACT. Following neoadjuvant treatment, pathological complete response was observed in 3 cases. At the follow-up period, 9 patients experienced the disease progression and 7 of 9 patients had died. In the current study, we will analyze the role of neoadjuvant chemotherapy followed by surgery in 17 patients with bulky cervical tumor as an alternative option treatment to the Standard surgery fallowed by chemoradiation for bulky cervical cancer.
COMPUTER-ASSISTED ASSESSMENT OF LYMPHANGIOGENESIS IN THE TRANSFORMATION ZONE OF NORMAL CERVIX THROUGH TO EARLY CERVICAL CANCER

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Background and objective: Lymphangiogenesis is reported to be triggered when high grade lesions of the cervix (HGSIL) progress to invasive carcinoma. We aimed at verifying the lymphangiogenesis pattern in HGSIL and microinvasive lesions in comparison to that observed in normal cervical tissue.

Material and methods: 20 cases of cervical neoplasia (10 CIN3 and 10 FIGO stage 1A1) + 10 cases of normal cervical tissue were reacted with D2-40, an antibody to M2A, a specific lymphatic endothelial marker. Lymphatic vessels (LV) were detected using a colorimetric method with further computer-assisted mathematical morphology post-processing. Whole field of the Transformation Zone (TZ) was assessed from normal squamous tissue through to normal glandular tissue. Respective LV density, morphology and distance to the neoplastic and normal epithelium were measured and compared.

Results: In normal cervical tissue, prominent LV density was already detected under the TZ. In HGSIL, the LV density and caliber were diffusely increased throughout the stroma. In early cervical cancers, LV density and caliber remained elevated but were closely apposed to the invasive tumor bundles.

Conclusions: For the first time, prominent lymphangiogenesis is described under the TZ of normal cervical tissue and appears preexisting to the neoplastic event. A further increase in LV density and caliber is observed through the process of HGSIL development and early stromal invasion.
MICROINVASIVE ADENOCARCINOMA OF THE UTERINE CERVIX SHOULD BE TREATED CONSERVATIVELY

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Background and aims: Lately more and more studies showed that conservative treatment and so preserving fertility, is save in the treatment of microinvasive adenocarcinoma of the uterine cervix. The purpose of this study was to evaluate the treatment and follow up of women with early cervical adenocarcinoma and to evaluate if conservative treatment is justifiable.

Methods: All cases of microinvasive cervical adenocarcinoma in the region of Rotterdam, the Netherlands between 1984-2006 were retrieved. Clinical and pathological data were reviewed and analysed.

Results: 59 patients were identified; 32 had FIGO stage 1A1 and 27 FIGO stage 1A2 cervical adenocarcinoma. The mean age at diagnosis in stage 1A1 was 39 years and stage 1A2 41 years. The mean follow-up was 79.9 month. In stage IA1 47% were treated by conization, another 47% by simple hysterectomy and 6% by radical surgery. In stage IA2 52% was treated by radical surgery, 22% had simple hysterectomy and 26% a conization. In the 16 patients treated by radical hysterectomy with pelvic lymph node dissection, no lymph node metastases were found. Only 2 recurrences (3.3%) were reported, both had stage IA1 disease. Of the 22 women treated by conization, 11 had 18 pregnancies and resulting in 14 live births and 4 spontaneous abortions.

Conclusions: The risk of metastastic and of recurrent disease was very low. Our data support former studies; microinvasive adenocarcinoma of the uterine cervix can be treated by conservative treatment, to spare fertility.
CLINICAL-MORPHOLOGICAL PROGNOSTIC FACTORS OF CERVICAL CANCER IN PATIENTS IB STAGES, TREATED BY SURGERY OR COMBINE THERAPY

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The study of clinical of histological features (age, type of tumor growth- exophytic, endofitic, histology lymth node metastasis, canceromatosys and vascular invasion) was performed in 195 cervical cancer cases IB stage treated from 2001 to 2004 years in Lviv regional oncolodical hospital. The prognostic significance of these parameters for overall and five year survival rate was demonstrated by multivariate Cox regression analysis and by Kaplan-Mayer method. Was performed that young age of patients (less then 30 years), endofitic type of tumor growth, the carcinomatosis and lymth node metastasis in postoperative tissue are indicators of unfavorable prognosis for overall survival, five year survival. It could be considered to give more agressive neoaduvant therape in those cases.
MANAGEMENT OF LOW GRADE SMEAR WITH PROVEN NORMAL COLPOSCOPY

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Introduction: Women referred with mild dyskaryosis or less who have a normal colposcopy are at low risk of developing cervical cancer. Their management is best determined by cytology follow up.

Aim: To review if we are adherent with national policy for low grade smear. Can we reduce the number of unnecessary visits to colposcopy?

Methods This is a retrospective study from January 2007 to June 2007. We used the Colposcopy data base and EPR system in order to generate our patient group.

Results: We identified 72 patients who were new referral for mild dyskaryosis. 10 patients (14%) had a normal colposcopy. From this normal colposcopy group, 8 of them (80%) resolved to negative smear during follow up period, although their colposcopy visits ranged from 2 to 5 visits. 1 patient (10%) continued to have a low grade lesion up to 18 months requiring treatment after biopsy had confirmed CIN 1 (5 visits). Another patient progressed to moderate smear in 6 months time requiring treatment but the histology concluded CIN1 (3 visits).

Conclusion: In view of these findings it is safe to discharge them back to GP for follow up cytology unless repeat smears show persistent mild grade dyskaryosis. This in turn reduces the number of colposcopy clinic visits. Frequent visits to colposcopy increases anxiety, risk of default and above all the cost of attendance per visit.
THE ROLE OF CIRCULATING ANTIOXIDANTS ON HIGH RISK HUMAN PAPILLOMAVIRUSES INFECTION AND CERVICAL CARCINOGENESIS

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Objective: To evaluate the role of diet and circulating antioxidants on high risk human papillomaviruses (HPV) and cervical carcinogenesis.

Materials and methods: The National Cancer Center of Korea (NCC) recruited 1,096 women, aged 18-65, to participate in a HPV cohort study from March 2006 up to present. For this analysis, we included 316 HPV-positive. All women were examined using liquid based cytology and HPV DNA testing (Hybrid Capture 2) as well as colposcopic biopsy were taken when necessary. Information on non-dietary (alcohol, smoking habits) risk factors and intake of nutrients from specific dietary sources as well as nutritional supplements were recorded. Laboratory assays included serum retinol, β-carotene, lycopene, zeaxanthin+lutein, α-tocopherol, and γ-tocopherol.

Results: When the HPV DNA load and the diagnosis of cervical dysplasia were considered together in the HPV-positive women, high viral load (>500) was associated with an increased risk of CIN I (OR 3.37, 95% CI, 1.49-7.60) and CIN II/III (OR 2.64, 95% CI, 1.06-6.59). The Lowest circulating levels of lycopene were associated with moderate and severe cervical dysplasia in HPV positive women (p=0.005). The Lowest circulating levels of retinol were inversely associated with moderate and severe cervical dysplasia in HPV positive women (p=0.012).

Conclusion: Lycopene in women at risk for a new infection or already infected with high risk HPV appeared to have a protective role in the prevention of progression of cervical carcinogenesis.

Keywords: HPV, Viral load, Cervical dysplasia, Lycopene, Retinol
THE EFFICACY OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIOThERAPY AND CONCURRENCY HYPERTHERMIA IN PATIENTS WITH ADVANCED-STAGE CERVICAL CANCER

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Objective: To evaluate the efficacy of neoadjuvant chemotherapy, followed by radiotherapy and concurrent hyperthermia (triple therapy) for patients with advanced-stage cervical cancer.

Methods: From our hyperthermia database 43 patients were selected, who were treated from 1996 to 2010 with triple therapy, because of large primary tumors (>6 cm) or para-aortic lymph node metastases.

All received platinum-based chemotherapy followed by full-dose radiotherapy, brachytherapy and 5 hyperthermia treatments. Response was evaluated by gynecologic examination and CT-scan. Time-event variables were estimated using the Kaplan Meier method.

Results: Mean age of the patients was 50.4 years (range 29-80), Median tumor size was 5.9 cm (range 3.5-8.0), positive lymph nodes were present in 90.7%. Treatment was completed in 40 patients. Median follow-up time was 20 months (range 0-102). Two patients achieved complete response after chemotherapy. The complete response rate after completion of triple therapy was 75% (95% CI 62-88%), with an overall survival of 60% (95% CI 36-83%) at 12 months.

Fifteen patients (34.9%) had an acute coagulation complication due to chemotherapy. The number of grade 3 and 4 hematological-, nephrogenic and urologic complications each did not exceed 10%.

Conclusion: The triple therapy seems effective in the treatment of advanced-stage high risk cervical cancer. However, in view of the high percentage of acute coagulation complications the use of preventive anti-coagulantia seems indicated during the treatment period. We plan to conduct a phase II trial for prospective corroboration.

Keywords: Advanced-staged cervical cancer, neoadjuvant chemotherapy, radiotherapy and hyperthermia.
SEXUAL DYSFUNCTION: A CLINIC FOR INFORMATION, INTERVENTION AND REHABILITATION

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After gynaecological cancer and following treatments, sexual dysfunction is a symptom that distresses a great proportion of women. The impact on sexual function after treatment can be of physical, psychological and social origin. Treatment can cause changes in mucous membranes and supporting tissues and nerve-, vascular and hormonal factors are all involved. Women report insufficient lubrication, vaginal shortness, inelasticity, and dyspareunia. From the psychological aspect, the disease- and treatment-induced morbidity can affect the sexual function and libido as well as a impaired self image and feelings of mutilated femininity. Socially, studies have shown that primary women with a history of cervical cancer has a higher incidens of divorce and separation. Women also report difficulties in meeting new partners due to sexual dysfunction and as earlier mentioned impaired self image.

Information about sexual dysfunction is often the most important issue when patients are asked about what side-effects they want more information about. By giving the patient and her partner the opportunity to discuss sexual issues early in the course of treatment, the impact of disease and treatment on the sexual function can be less severe.
PATHWAYS INVOLVED IN CERVICAL CLEAR CELL ADENOCARCINOMA

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Background and aims: Clear cell adenocarcinoma (CCAC) of the cervix and vagina are relatively rare. Our aim was to elucidate pathways involved in its carcinogenesis. Next to established causes as intra-uterine exposure to diethylstilbestrol (DES), these included also disruption of the p16INK4A/cyclin D/Rb pathway by high-risk human papillomavirus (hrHPV) or by BMI-1 overexpression.

Methods: From the Central Netherlands Registry for CCAC, tumour samples from four centers were collected and tested for hrHPV, and stained for p16INK4A, p53, MIB-1 and BMI-1. DES-exposure was collected from patient files and defined as exposed, unknown and non-exposed.

Results: A total of 28 women with a median age of 29 years were included and followed for a median of 137 months. The 10-years survival was 82.1%. The 15(53.5%) DES-exposed women developed CCAC at a younger age than non-exposed women (21 versus 35 years, p< 0.001) and had a better 5-years survival (100% versus 60%, p=0.017). The DES-exposed tumours were hrHPV-positive in 5 cases (33.3%). Of the remaining 13 women, 8(61.5%) were hrHPV-positive, however only 3 tumours showed diffuse increased expression of p16, and diminished expression of p53, characteristic for hrHPV-mediated carcinogenesis. BMI-1 staining was increased in four (30.7%) of the non-DES-exposed samples, but none of them displayed reduction of both p53 and p16 associated with BMI-1-associated carcinogenesis.

Conclusion: Pathways involved in the development of CCAC include intra-uterine DES-exposure (53.5%) and hrHPV-mediated carcinogenesis (10.7%). BMI-1-associated carcinogenesis could not be confirmed in this study. Therefore, one third of all CCAC remains to be elucidated by other pathways.
DETECTION OF NODAL METASTASES IN CERVICAL CANCER - COMPARISON OF PET AND SENTINEL NODE BIOPSY

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The incidence of cervical cancer vary widely throughout the world. Globally, cervical cancer afflict more than 400 000 women and cause about 250 000 deaths annually. Lymph node metastases are one of the most important prognostic factors and the knowledge of lymph node status is necessary for management of adjuvant treatment. The importance of ultrastaging and accurate detection of positive lymph nodes is underscored by the potential success of chemoradiation. Cervical cancer is a good target for lymphatic mapping due to possibility to inject tracer into the cervix and recent data are encouraging. FDG-PET is non-invasive procedure, but the possibility of micrometastases detection is limited.

Background and aims: The purpose of our study is to compare the sentinel lymph node procedure and PET in lymph node metastases detection in cervical cancer.

Methods: Between January 2004 and May 2010 forty patients with cervical cancer were included into the study.

Conclusions: Sentinel lymph node biopsy in cervical cancer is feasible for ultrastaging and lymph node status clarification. FDG PET is a sensitive method in lymph node involvement detection, but it is limited in micrometastases identification.
CHRONIC MYELOGENOUS LEUKEMIA IN A PATIENT WITH ADVANCED STAGE ADENOSQUAMOUS CARCINOMA OF THE CERVIX: A RARE COMBINATION OF CONCURRENT MALIGNANCIES

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There is substantial literature on secondary leukemias occurring after pelvic radiation for cervical cancer. The case at hand is a rare occurrence of an untreated cervical cancer together with chronic myelogenous leukemia. This report aims to discuss the special considerations for treatment of advanced cervical cancer in the presence of CML.

A 55-year old multigravid presented with postmenopausal vaginal bleeding. Physical examination and other diagnostics pointed to a Stage IVB cervical cancer with pulmonary metastases. There was splenomegaly. White blood cell count was elevated at 268 x 10⁹/L. Bone marrow biopsy showed a markedly hypercellular marrow, marked granulocytic hyperplasia, and severe myelofibrosis consistent with CML. BCR/ABL FISH assay showed 73.7% fusion genes detected.

Treatment for cervical cancer consisted of external pelvic beam radiation concomitant with low-dose weekly cisplatin-paclitaxel chemotherapy. Cytoreduction using hydroxyurea was given for CML. To an already challenged bone marrow, chemoradiation for cervical cancer was expected to exaggerate myelosuppression. Treatment was affected by anemia, eventual neutropenia, thrombocytopenia, pulmonary infection, and severe electrolyte imbalance. Maintaining high haemoglobin levels was difficult as transfusion might aggravate the hyperviscosity associated with the leukemic state while erythropoietin might enhance thrombosis in an already hypercoagulable state. Documentation of infection was stringent as response parameters were wanting. Hydroxyurea was started aimed also at decreasing the risk of thrombosis once chemoradiation commences. Despite treatment, there was limited response in the cervical lesion. The pulmonary lesions progressed. She eventually succumbed to complications of acute respiratory distress syndrome from pneumonia and pulmonary metastasis three months from the diagnosis.
DETECTION OF HPV TYPE 16 AND 18 BY REAL TIME PCR IN WOMEN WITH GENITAL WARTS IN SOUTH OF IRAN

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Background: The purpose of this study was to find human papilloma viruses (HPV) type-distribution especially high-risk types in the patients with anogenital warts in our region (Fars, Iran). It might be essential for determining which types of HPVs should be included in new second-generation vaccines targeted to cancer prevention programs.

Materials and methods: We performed a cross sectional study to detect HPV-16 and HPV-18, as two important high risk HPV types, in peripheral blood and exophytic tissue of patients with external genital wart by Real-time polymerase chain reaction (PCR) method.

Results: In this study, Seventy-nine women were enrolled. HPV-16 and -18 were detected in 17.7% of participants. HPV16 and HPV18 were detected in 2.5% and 16.5%, respectively, that is dissimilar to other report in the worlds..

Conclusion: The type of HPV positivity in the patients with general warts varies depending on the geographic area evaluated. In previous studies HPV 16 was one of the less common HPV types seen in genital warts and HPV 18 was very rare in the other geographic area. But in our study HPV 18 is more common than HPV 16. So based on the results, this type of HPV should be considered in vaccines to cancer prevention programs in this geographic area.
IS RADICAL TREATMENT INDICATED FOR EARLY INVASIVE CERVICAL ADENOCARCINOMA?

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Objective: To analyze the prognosis and complications of treatment in patients with Early Invasive Adenocarcinoma of the Cervix, FIGO stage 1A1 and 1A2.

Methods: Retrospective chart review, including a central pathology review, of 54 patients treated for early invasive adenocarcinoma of the cervix at the Juravinski Cancer Center in Hamilton, Ontario, Canada, from 1985 to June 2009.

Results: Of 54 patients, 49 patients (91%) had FIGO stage 1A1 and 5 patients (9%) had stage 1A2 adenocarcinoma of the cervix. 48 patients (88.5%) underwent radical hysterectomy including bilateral pelvic lymph node dissection, and 6 patients (11.5%) underwent conization only. No lymph nodes metastases were found in the radical hysterectomy group. No lymphovascular invasion (LVI) was identified in any of the patients. For one case, LVI was indeterminate. No recurrences were encountered (mean follow up 7 years) for the entire cohort.

Radical surgery was associated with a 45% complication rate, ranging from transient bladder or sexual dysfunction to neuropathy.

Conclusions: Lymph nodes metastases and recurrences appear to be rare in this patient cohort. As for its counterpart microinvasive squamous cell carcinoma, conization may be an acceptable mode of treatment for FIGO stage 1A adenocarcinoma of the cervix.
THE VALUE OF COLPOSCOPY IN SCREENING CERVICAL INTRAEPITHELIAL NEOPLASIA

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The Papanicolaou smear is the primary screening tool for cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC). False negative rates of Pap smear have been reported as high as 50%. Recent articles suggest that the use of colposcopy in addition to the Pap smear might improve the accuracy of CIN and ICC detection. However, colposcopic screening has not been practical because of its cost and the necessity of expertise in the evaluation of colposcopic findings. Because cervical cancer can be prevented by simple treatment of CIN, combined cytology and screening colposcopy is considered to be an important screening tool for CIN. The present study compared the usefulness of Pap smear with colposcopy in screening for CIN. Two hundred and forty-three patients were evaluated with cytology, colposcopy, and colposcopically directed biopsy. CIN and human papillomavirus infection were diagnosed by biopsy. We excluded patients with a history of an abnormal Pap smear within the past 12 months, or a history of abnormal vaginal bleeding. Fifteen patients (6.2%) had CIN lesions diagnosed by colposcopically directed biopsies. In 13 patients condylomatous lesions were found, in 7 patients CIN I, in 3 CIN II, and in 5 patients CIN III were diagnosed. Sensitivity and specificity rates of Pap smear were 66.7% and 97.8%, respectively. The corresponding figures for colposcopy were 80.0% and 98.2%. The combination of both methods led to optimal sensitivity and specificity (100%, respectively) Screening colposcopy is a valuable supplementary strategy for the detection of CIN, otherwise not detected with Pap smears.
CONSERVATIVE SURGERY OF CARCINOMA OF THE CERVIX

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Cancer of the cervix is the second most common female cancer with more than half a million cases per year worldwide. Traditionally, the treatment for invasive cervical carcinoma that progresses beyond microinvasion has been radical hysterectomy. Long term experience of radical surgery has shown that there are excellent results in terms of survival and quality of life, but it always diminishes the chances of future childbearing. We present a new approach to fertility sparing surgery: abdominal radical trachelectomy.

Objective: Analysis and discussion of current experience with abdominal radical trachelectomy as the treatment for early stages of cervical cancer in fertile woman.

Methods: Presentation of 4 cases of open abdominal trachelectomies with pelvic lymphadenectomy. All procedures were indicated for cervical cancer IB1 epidermoid carcinoma GII. Frozen section of pelvic nodes an a slice upper margin of cervix revealed no metastasis on infiltration. The total number of lymphnodes removed was 20 - 25 pelvic nodes, all negative for malignancy. There were no complications or blood transfusions. The patients were 19, 25, 29 and 33 years old. Two of them had one child and the other 2 didn’t have any children.

Results: All patients that were submitted to this procedure had normal menstrual cycles. One got pregnant and had a premature child and the other three use oral contraceptives and condoms because they don't have a partner yet.

Conclusion: Abdominal radical trachelectomy may be suitable for women with early stage invasive carcinoma of the cervix who strongly desire to have children.
PRIMARY CERVICAL MALIGNANT MELANOMA: A CASE REPORT

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Background and objectives: Primary cervical malignant melanoma is an uncommon disease, and it is important to exclude a metastatic lesion. This case reports a rare and aggressive entity, in a 37-year-old young patient and shows us the pattern of development, management, spread and follow-up of the illness.

Methods: A case report of a patient with malignant melanoma initially diagnosed as H-SIL/CIN 3 lesion, followed for thirteen months all they long. The medical literature is reviewed.

Results: This disease, initially diagnosed for Cervicitis, L-SIL / CIN 1, H-SIL / CIN 3, Malignant Poorly Differentiated Neoplastic and Malignant Melanoma. The definitive diagnose were performed by immunohistochemical staining reactions. She underwent two surgical procedures like LETTZ after than RADICAL HYSTERECTOMY, RADICAL PARAMETRECTOMY UPPER VAGYNECTOMY AND PELVIC LYMPHADENECTOMY.

Conclusions: Cervical Malignant Melanoma is a very aggressive pathology, mainly in the young patients. It has a worse prognostic and liver and lungs metastatic spread can to occur earlier. This patient disease progressed fast and at this time she presents lung and liver metastasis.
DETECTION OF BIOMARKERS FOR HPV INFECTION AND CERVICAL DYSPLASIA WITH GMR SENSOR- AND HIGH MAGNETIC MOMENT NANOPARTICLE DEVICE

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Background: HPV DNA results in malignant transformation of cervical cells by integrating into host cell DNA and leading to unregulated expression of onco-proteins E6 and E7. Tests that identify downstream effects of high-risk HPV integration will improve the positive predictive value of screening strategies. Giant magnetoresistive (GMR) sensors and magnetic nanoparticles based detection can quantify low concentrations of proteins. Our objective was to use a GMR sensor- and high magnetic moment nanoparticle-based protein detection platform to quantify HPV 16 E7 protein in cervical cell lines as a biomarker for HPV 16 infection.

Methods: Cervical cell lines known to be HPV 16 positive (HPV immortalized benign vaginal epithelial and endocervical cells, CaSki, and SiHa), and an HPV 16 negative cell line (HEK) were cultured and lysed. Protein quantification of HPV 16 E7 was estimated by Western Blot, and GMR sensor- and high magnetic moment nanoparticle-based protein detection was used for quantification.

Results: GMR sensor- and high magnetic moment nanoparticle-based detection device confirmed the quantification of HPV 16 E7 proteins in all HPV 16 positive cell lines and did not detect E7 in the HPV 16 negative HEK cell line. These results were consistent with the estimations from Western Blots.

Conclusion: GMR sensor- and high magnetic moment nanoparticle-based protein detection is feasible for quantification of HPV 16 E7. A GMR detection platform may be a feasible low cost, handheld, point-of-care method which improves the specificity and positive predictive value of current molecular and cytological screening.
INSUFFICIENT ACCURACY OF LEEP SPECIMENS FOR PREDICTION OF LYMPH-VASCULAR SPACE INVASION FOUND AT HYSTERECTOMY IN EARLY-STAGE CERVICAL CANCER

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Objectives: The aim of this study was to determine whether loop electrical excision procedure (LEEP) specimens can predict the lymph-vascular space invasion (LVSI) seen at hysterectomy specimens for early-stage cervical cancer.

Patients and methods: A retrospective review of pathologic data from patients who underwent LEEP before radical hysterectomy for early-stage cervical cancer between 2008 and 2010 was performed. Pathologic variables, including LVSI, depth of invasion, tumor size and marginal status, were collected from both LEEP and hysterectomy specimens. Data were analyzed using chi-square test.

Results: During the study period, 44 patients with stage IA2-IIA cervical cancer who underwent LEEP before hysterectomy were identified. Of these, 13 patients with no residual disease in hysterectomy specimens and 1 patient with insufficient pathologic data were excluded. Negative predictive value of LEEP for the detection of LVSI was 0.76, indicating false negative rate of 24%. In LEEP specimens with negative LVSI, marginal status was not associated with positive LVSI found at hysterectomy specimens ($P=.687$). Invasion depth ($P=.865$) and tumor size ($P=.597$) were also not associated with false negative LVSI in LEEP specimens.

Conclusion: LEEP specimens lack sufficient predictive accuracy for the detection of LVSI in hysterectomy specimens. These results indicate that decision on less radical surgery based on absence of LVSI in LEEP specimens may not be safe.
PREVALENCE OF CHLAMYDIA TRACHOMATIS IN WOMEN WITH NORMAL AND ABNORMAL PAP SMEARS IN LAGOS-NIGERIA

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Objective: To determine the association between Chlamydia trachomatis and abnormal Pap smear.

Methods: Consenting ninety women, 30 with abnormal Pap smear (cases) and 60 with normal cervical smear (controls) were interviewed using a structured form to obtain sociodemographic data. Cervical smear and endocervical swab were taken from each woman for cytology and Chlamydia trachomatis test using genomic detection test, respectively.

Results: The mean age of the cases was 37.5±5.6 years and 41.8±8.5 years for the controls. The prevalence of C. trachomatis in the study population (n=90 women) was 27.7%; with majority of the women in reproductive age group. The prevalence of C. trachomatis decreased with age (X² for trends=16.53, df = 5, p=0.05). There was no statistically significant association between age and prevalence of C. trachomatis among women with abnormal smear (X² = 1.76, df = 4, p = 0.780).

The prevalence of C. trachomatis in women with abnormal cervical smear was 50 %(15/30) compared with women with normal cytology 16.7 %(10/60) and this difference was statistically significant (X² = 10.95, p = 0.001). There was however, no statistical association between the prevalence of C. trachomatis and cervical cytological types (X² = 1.892, p = 0.595).

Conclusion: The findings in this study shows that C. trachomatis is significantly associated with abnormal cervical smear in Lagos.
CERVICAL CARCINOMA AFTER KIDNEY TRANSPLANTATION
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Renal transplantation and its required immunosuppression are a well-documented risk factor for the development of both epithelial and nonepithelial cancers. The risk of cervical carcinoma has been estimated to be 3 to 16 times higher for renal transplant recipients than for the general population. Cervical carcinomas represent approximately 3% of all malignancies among transplant recipients.

A 37-year-old female was referred to the Oncology Institute of Vojvodina in September 2009, with diagnosis of cervical cancer. She was maintained on hemodialysis with chronic renal insufficiency and received a mother’s donor kidney transplant in June 2007.

The transplant-associated immunosuppressive regimens contained CellCept (mycophenolate mofetil), Prograf (tacrolimus), and prednisone.

Twenty-five months after renal transplantation, in July 2009, she presented with postcoital bleeding. The cervical biopsy was taken and which confirmed invasive cervical carcinoma stage Figo III b. Therapeutical treatment in this patient should take into consideration her renal function and the effects of immunosuppressive agents and special reference to the pelvic kidney localization.

She was treated with three-dimensional conformal radiotherapy in September 2009, with irradiation technique consisted of 46 Gy in 23 Gy fractions. Patient was subjected to magnetic resonance imaging. Graft function was monitored by creatinine clearance. During nine-months follow-up period, her performance status is ECOG 0.

Many complications after renal transplantation can be prevented if they are detected early. Guidelines have been developed for the prevention of diseases in the general population, but there are no comprehensive guidelines for the prevention of diseases and complications after renal transplantation.
CLINICAL IMPACT OF BRACHYTHERAPY DOSE RATE AND PLANIMETRY IN THE TREATMENT OF ADVANCED CERVICAL CANCER (ACC)

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Objective: To compare the outcome of patients treated for ACC by concomittant chemoradiation (cCRT) using either a Low Dose Rate Brachytherapy (LDR Br) with dose calculated to point A or a Pulse Dose Rate Brachytherapy (PDR Br) with 3D MRI dosimetry.

Methods: From april 2005 to july 2009, 55 patients with advanced cervical cancer were consecutively treated in our unit. External beam radiation was delivered with a 4-field box technique to a dose of 45 to 50.4Gy in 28 fractions with concomittant radiosensitizing weekly cisplatin. Brachytherapy was then performed using LDRBr for the first 17 patients. PDRBr was delivered to the following 38 patients. Prescribed total dose was 80-85Gy. Treatment toxicity and disease relapse rates were prospectively assessed. Kaplan Meier survival curves were generated. Log rank test and Cox regression analysis allowed uni- and multivariate analysis of tumor and treatment related variables.

Results: FIGO stages were equally distributed in both groups. Acute urological or enteric > grade 2 toxicity was more frequent with PDR Brachytherapy. After a mean follow-up of 21 months, central pelvic control rate was respectively 94.8% (PDRBr) and 82.4% (LDRBr) (p=0.16). Disease free survival at 32 months were 88.4% (PDRBr) and 62.5% (LDRBr) (p=0.04).

Conclusions: For patients with advanced cervical cancer treated by chemoradiation, Pulse Dose Rate Brachytherapy with 3D MRI dosimetry appears to improve the central pelvic control rate with a positive impact on disease free survival at the cost of an increase in acute toxicity when compared to LDR Brachytherapy.
OVARIAN CRYOPRESERVATION WITH SLOW-FREEZING FOLLOWED BY RE-IMPLANTATION RESTORES OESTROGEN PRODUCTION AFTER GONADOTOXIC RADIOTHERAPY TO THE PELVIS

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Background: Ovarian function plays a key role in the regulation of sexual development, the regulation of normal menstrual function and peripheral hormone effects on bone and other tissues. Chemotherapy is often very toxic to ovaries. Radiotherapy, even in low doses of 10 to 15 Gray will deplete the number of primordial follicles and will cause premature ovarian failure. Ovarian tissue cryopreservation and re-implantation after toxic cancer treatment may safeguard hormonal function.

Methods: 13 Pre-menopausal patients with locally advanced cervical squamous carcinoma had pre-radiotherapy bilateral laparoscopic oophorectomy. Ovarian dissection was performed to remove the cortex and the ovarian cortex then divided into small strips. Ovarian tissue cryopreservation was done with a slow freezing protocol. After completion of chemo-radiotherapy, thawed tissue was introduced back into subcutaneous tissue of the upper arm of patients with the aim of restoring ovarian function.

Results: 12 Of 13 patients had evidence of oestrogen production. Length of follow up was between 14 and 25 months after re-implantation. Oestrogen production started more than 6 months after re-implantation in 10 out of 12 cases. Levels of circulating gonadotrophins remained high despite oestrogen production and follicle formation. Oestrogen levels were generally low.

Conclusion: This is the largest reported series of hormonal follow up of cases of re-implantation of ovarian tissue after slow-freezing. Ovarian cryopreservation is a useful technique to safeguard hormonal function (and in certain cases fertility) in children and young women with cancer who are at risk of ovarian failure.
CONCURRENT CHEMORADIOTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED CARCINOMA OF UTERINE CERVIX AND SUPPORT WEEKLY LOW DOSE ERYTHROPOIETIN ALFA

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Purpose: Concurrent chemoradiotherapy has become the standard of the treatment for locally advanced cervical cancers (LA-CC) stage IIB, IIIB, and IVA, at the time of diagnosis. This management increases acute and late toxicities. Anemia is frequent complication of cervix cancer patients. Erythropoietin is used to correct or prevent anemia.

Methods: Between 2000 and 2005, a total of 30 patients with squamous cell LA-CC were treated using external beam radiotherapy and LDR brachytherapy with two cycles of concurrent chemotherapy and two cycles of sequential chemotherapy (cisplatin 50 mg/m² i.v. infusion day 1 and 5-fluorouracil 1000 mg/m² 24 hour continuous infusion days 2-5, every 28 days). Patients received erythropoietin alfa 10 000 IU s.c. once weekly, during concurrent chemotherapy.

Results: The initial FIGO stage was IIB, IIIB, and IVA-B, and 6 patients, respectively. Median age of the patients was 47 years (range, 31-62 years). The 5-year overall survival was 90 % for all stages. The acute hematological toxicity (CTC) consisted of grade 3 leukopenia in seven patients (23 %), grade 4 in three patients (10 %). Grade 2 thrombocytopenia was observed in nine patients (30 %), grade 3 in five patients (17 %). Late toxicity (RTOG/EORTC) consisted of rectal toxicity grade 1, 2 and 3 in three (10 %), five (17 %) and nine (30 %) patients, respectively.

Conclusion: Concurrent chemoradiotherapy with support of weekly low dose erythropoietin alfa followed by sequential chemotherapy was safe and well torelable regimen.
TOPOTECAN IN RECURRENT CERVICAL CANCER: A REPORT OF 10 CASES


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Background: Topotecan (HYCAMTIN™) is an active agent in squamous cell carcinoma of the uterine cervix. In recent GOG phase III studies, intravenous topotecan (0.75 mg/m²) plus cisplatin demonstrated significant progression-free and overall-survival benefits in patients with advanced and recurrent cervical cancer. In the current study we have retrospectively evaluated the safety, tolerability, and efficacy of single agent topotecan in recurrent cervical cancer.

Patients and methods: 12 patients with recurrent carcinoma of the uterine cervix after radical surgery, radiotherapy and two previous lines of chemotherapy (first-line cisplatin and vinorelbine, second-line paclitaxel) were treated with topotecan 3 mg/sqm every 7 days (maximum, 5 mg per dose) diluted in 250 ml of normal saline in a 30-min infusion for progressive disease. Toxicity was evaluated with the CTG criteria and response was evaluated according to the RECIST criteria.

Results: Patients received a mean 5.5 courses (range, 3-18 courses). The most frequently severe adverse events were grade 3 anemia (50%) and grade 4 (8%) along with grade 3 neutropenia (25%). Two patients had grade 4 thrombocytopenia. No complete or partial responses were observed; 3 patients (25%) exhibited disease stabilization as maximum response (two in irradiated sites, and three in lung/mediastinum). Median progression-free interval was 4.5 months and median overall survival was 9 months.

Conclusion: In our experience weekly topotecan regimen used in the current study was well tolerated, and resulted in disease stabilization in 25% of the cases even in this unfavourable setting of cervical cancer patients.
SQUAMOUS CELL CARCINOMA OF UTERINE CERVIX WITH INVASIVE DEPTH LESS THAN 3MM AFTER CONIZATION: IS CONSECUTIVE SIMPLE EXTRAFASSIAL HYSTERECTOMY ENOUGH?

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Introduction: Early stage cervical cancer and cervical intra-epithelial neoplasia (CIN) were observed to be increased recently. Cervical conization surgery is the standard management of high grade CIN and occasionally superficially invasive squamous cell carcinoma (SCC) is coexisted. When T1a1 SCC lesion (defines as stromal invasion< =3mm and lateral extend< =7mm) was observed after conization, consecutive hysterectomy will be advised if fertility is no longer desired. Whether simple extrafascial hysterectomy is enough or not is still questionable if endocervical margin is involved by the dysplastic cells.

Methods: A retrospective charts and pathology review (from January 2002 to December 2009) were carried out after IRB approval in our institute. Fifty-six cases were found to completely fit the following criteria: 1.T1a1 SCC lesion on the conization specimen and 2. consecutive simple extrafascial hysterectomy. They were divided into 2 groups according to the condition of endocervical involvement. The final pathology of hysterectomy was defined as surgical scale “adequate” (no residual lesion, only residual CIN or residual T1a1 SCC lesion) and “inadequate” (residual >= T1a2 SCC lesion).

Results: In the group with endocervical involvement (total 28 cases), 26 cases (92.8%) were adequate. In the group without endocervical involvement (total 28 cases), 28 cases (100%) were also found to be adequate. No significant difference was observed. (Chi-square method, p=0.491)

Conclusion: Simple extrafascial hysterectomy is the adequate scale of hysterectomy for treating the cases with T1a1 cervical SCC proved by conization regardless of endocervical condition. Smaller surgical scale might be the future trend in treating cervical cancer.
CLEAR CELL ADENOCARCINOMA OF THE CERVIX WITHOUT ASSOCIATION IN UTERO DIETHYLSTILBESTROL EXPOSURE: TWO CASES REPORT

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Background: Primary clear cell adenocarcinoma of cervix (CCAC) is usually seen in women with a history of in utero exposure to diethyl acetyl bestrol (DES). We report two cases of clear cell adenocarcinoma of cervix with no history of exposure to DES in embryonic period.

Case report: The first case was a 14-year-old women with complaint of painless vaginal bleeding. There was atypical cells in Pap Smear and a bleeding tumor with 1.5 cm in diameter was found in vagina. She was admitted with a diagnosis of CCAC of the uterine cervix stage Ib2 according to FIGO classification. The second case was a 23-year-old patient with complaint of painless vaginal bleeding. The results of cervical cytology was normal. Evaluation of the punch biopsy sample revealed CCAC. Her clinical exam showed stage IIb according to FIGO classification. Both patients had no history of exposure to DES during embryonic period. The first patient treated with radical abdominal hysterectomy and systematic pelvic lymphadenectomy and for the another one external beam radiotherapy and brachytherapy was performed. There was no any recurrence or metastasis after an 18-24 months follow-up.

Conclusions: Primary clear cell carcinoma of cervix could be unrelated to HPV infection or exposure to DES during embryonic period and in approach to these patients this subject should be considered.

Keywords: Clear cell adenocarcinoma, diethyl acetyl bestrol (DES), Human Papiloma Virus (HPV).
AORTIC METASTASIS OF CERVICAL CARCINOMA - A RARE CASE
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Squamous cell carcinoma of the cervix metastasize mainly by direct local invasion of adjacent tissues and lymphatics and less commonly through blood vessels. The most common sites of lymph node metastases are the internal iliac, obturator, external iliac, and common iliac lymph nodes. Later in the course of the disease, extension to the lateral sacral, paraaortic, and inguinal nodes can occur. Isolated invasion of the sacral, external iliac, and hypogastric nodes may be occasionally observed. Blood-borne metastases to the lung, liver, bone, heart, skin, and brain are generally seen in stage IV tumours or when the local growth has previously been irradiated. We report a rare case of a female patient, age 63, hospitalised and deceased with a massive upper digestive haemorrhage caused by a gastric fistula. The autopsy revealed a large aorta, firstly considered as an aneurism but presented in section as an aortic tumoral mass. The histopathologic examination revealed a carcinomatous mass associated with central necrosis and areas of squamous differentiation, invading the aorta. The history of the patient revealed, seven years before, a squamous cell carcinoma, associated with clear-cell differentiation, previously diagnosed by the same histopathologist. Despite the treatment (combined surgical, chemotherapy and radiotherapy), the patient developed metastatic disease and died with a massive haemorrhage. Whatever the mechanism, lymphatic or hematogenous spread of the tumoral cells, the aortic wall represents an unusual site of metastasis, with an unfavorable prognosis significance.
A FIVE-CYCLE TREATMENT REGIMEN FOR ADVANCED NEUROENDOCRINE CERVICAL CARCINOMA USING PACLITAXEL, CISPLATIN, ETOPOSIDE AND CARBOPLATIN WITH RADIATION IS REVIEWED

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Background: Neuroendocrine carcinoma of the cervix is rare, comprising 3% of cervical neoplasms. Standard combination chemotherapy, although widely accepted, is lacking and gives dismal responses. We used a 5-cycle regimen of paclitaxel, cisplatin, etoposide, carboplatin and radiotherapy, in the treatment of advanced small-cell carcinoma of the cervix.

Methods: A regimen consisting of 5 different cycles where used to induce a complete response in a patient with advanced small-cell carcinoma of the cervix. Cycle A consisted of paclitaxel 175mg/m² and cisplatin 60mg/m² IV; cycle B of cisplatin 60mg/m² and etoposide 75mg/m² IV, followed by etoposide 100mg PO; cycle C of radiotherapy: 40Gy pelvic external beam, 40Gy para-aortics, 1000cGy total HDR vaginal canal boost; cycle D of paclitaxel 175mg/m² and carboplatin AUC 6 IV; and cycle E etoposide 100mg PO and carboplatin AUC 6 IV.

Results: A twenty-five year-old patient presented with a 3cm cervical lesion with histology showing poorly-differentiated carcinoma with neuroendocrine features. Immunostains were strongly positive for synaptophysin, chromogranin, and CD56. PET/CT and laparotomy confirmed bilateral internal iliac and high para-aortic lymphadenopathy. Grade 3 anemia developed during cycle E. Patient experienced a complete response with a follow-up of 12 months.

Conclusion: A standard regimen of chemotherapy and/or radiation is lacking in the treatment of small cell neuroendocrine carcinoma of the cervix. Further multicenter clinical trials to assess this regimen are needed.
VALUE OF HPV DNA TESTING IN PREDICTION OF HIGH-GRADE CERVICAL LESION IN WOMEN WITH ASCUS: REVIEW OF THE LITERATURE

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Objective: The aim of this study was to determine the value of HPV testing in detection of high grade cervical lesion in women with ASCUS.

Results of different studies showed that the probability of ASCUS progression to invasive disease over 6 month and to H SIL over 24 months was 0.06 and 0.25% respectively. The 24 month cumulative incidence of H SIL in women with ASCUS varied between 6 and 9 %. These data indicate that women with ASCUS need further evaluation.

Methods: We analyzed results of 5 studies published between years 2006. and 2009. dealing with issue of HPV DNA testing in women with ASCUS.

Results: 1778 women were analyzed in this studies. Positive HPV DNA testing was significantly associated with L SIL, H SIL or invasive carcinoma. The specificity of HPV DNA testing was 84% and negative predictive value 99.7%. The prevalence of a high-risk HPV infection decreased with age in women with ASCUS.

Conclusion: The HPV DNA testing is useful in prediction of high-grade cervical lesion in women with ASCUS and in formulation of decisions concerning future treatment. Women with HPV DNA negative ASCUS have very low absolute risk of subsequently development of high-grade cervical lesions. HPV testing can be repeated after 12 months when no CIN is found on colposcopy and biopsy.
INTER-OBSERVER VARIABILITY OF FIGO STAGING IN CERVICAL CANCER

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Objective: Treatment planning for cervical cancer is based on FIGO staging. In the FIGO staging system of cervical cancer is staged predominantly by clinical examination, preferably under anesthesia. The stages are defined by progression of disease beyond the cervix to adjacent tissues including vagina, parametria, pelvic sidewalls, sacro-uterine ligaments, bladder and / or rectum. Although widely used the reliability of this staging system in unclear. We therefore assessed the inter-observer variability of examination under anesthesia in cervical cancer.

Methods: Subsequent patients undergoing a staging procedure for primary cervical cancer were enrolled in the study. Three experienced clinicians performed a gynaecological exam under anaesthesia. Tumor size and the involvement of parametria, pelvic sidewalls, vagina, sacro-uterine ligaments, bladder and rectum and FIGO stage were scored as well as treatment proposal.

Results: A total of 56 patients were enrolled. A moderate inter-observer agreement was found among the observers with regard to FIGO stage with respectively a free-marginal Kappa value of 0.581 and a proportion of agreement (pc) of 0.619. An excellent inter-observer agreement was found on the proposed therapy (with a free-marginal Kappa value of 0.944 and pc of 0.963).

Conclusions: This study showed only a moderate inter-observer agreement on clinical staging of patients with cervical cancer. Nevertheless an excellent inter-observer agreement on treatment proposal was found.
IMMUNOHISTOCHEMICAL DETECTION OF P16<sup>INK4A</sup> IN PRECANCEROUS LESIONS AND CERVICAL CARCINOMAS

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**Background:** It is known that HPV infection in cervical carcinogenesis causes a number of alterations in gene or protein expression within the infected host cells. Interaction of HPV oncogenic proteins with cellular regulatory proteins leads to up regulation of p16<sup>INK4A</sup>, which is a biomarker for HPV infection.

**Aims:** To investigate and compare the expression of p16<sup>INK4A</sup> in benign, precancerous and carcinomatous lesions of the cervix.

**Method:** This study reviewed the p16<sup>INK4A</sup> expression in cervical biopsies from 100 patients (normal tissues, n=10; CIN1 cases, n=18; CIN2 cases, n=33; CIN3 cases, n=19, and squamous carcinomas, n=19). The paraffin-embedded blocks were used for the immunohistochemical detection, performed by monoclonal antibody to p16 (DAKO). The p16<sup>INK4A</sup> was scored using the simple protocol (positive vs negative) at cut off staining in more than 10% of epithelial cells.

**Results:** The all cases of benign cervical epithelium were negative for the expression of p16<sup>INK4A</sup>. In opposite, all cases of CIN3 and squamous cervical carcinomas showed significant positivity for p16 staining (p< 0.001). In CIN 1 50% and in CIN2 72.7% cases were positive for p16 (p< 0.01).

**Conclusions:** The p16<sup>INK4A</sup> overexpression is associated with high-grade precancerous lesions and cervical carcinomas and it correlates with grade of CIN. Therefore p16<sup>INK4A</sup> is a biomarker of cervical neoplastic changes and its examination should be incorporated into the standard surgical pathology practice when assessing cervical lesions.

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CLINICAL IMPLICATIONS OF HUMAN PAPILLOMAVIRUS GENOTYPE IN CERVICAL ADENO-ADENOSQUAMOUS CARCINOMA

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Purpose: Our aims were to evaluate the genotype distribution of human papillomavirus (HPV) and the correlation between HPV parameters and clinicopathological variables and prognosis in cervical adeno-adenosquamous carcinoma (AD/ASC).

Patients and methods: Consecutive patients who received primary treatment for cervical AD/ASC International Federation of Gynecology and Obstetrics (FIGO) stage I-IV between 1993 and 2008 were retrospectively reviewed. SPF1/GP6+ polymerase chain reaction (PCR) followed by reverse-blot detection HPV DNA and E6 type-specific PCR was performed for genotyping.

Results: A total of 250 AD/ASC patients were eligible for analysis. HPV DNA sequences were detected in 98.4% of the specimens. HPV 18 was detected in 48.0%, HPV 16 in 38.4%, and HPV 58 in 8.8% of the samples. Using 1993-2000 data set, HPV16-negativity and HPV58 positivity were significantly related to FIGO stage II-IV, and HPV16-positivity was correlated with younger age. By multivariate analysis, FIGO stage and HPV16-negativity were significantly related to cancer relapse. Age, FIGO stage, and HPV16-negativity were significant predictors for cancer-specific death. HPV16-positivity was significantly associated with good prognosis in those receiving primary RT (P = .0095).

Conclusion: FIGO stage and HPV16-negativity were significant prognostic factors in cervical AD/ASC. The finding that HPV16-status differentially impacted on prognosis depending on method of primary treatment has important clinical implications.
PREVALENCE OF RESIDUAL TUMOR IN SQUAMOUS CELL CARCINOMA (SCC) OF THE UTERINE CERVIX POST RADIATION UNDERGOING ADJUVANT CERVICECTOMY (PRELIMINARY REPORT)

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Objective: To evaluate the prevalence of microscopic residual tumor of the patients with SCC of cervix stage IB2-IIB post concurrent chemoradiation therapy by Loop Electrosurgical Excision Procedure (LEEP).

Methods: From 1 January 2006- 28 February 2010, the patients with SCC of the cervix after radiation for 3 months were enrolled. The patients without visible residual tumor after radiation will undergo LEEP.

Results: Forty patients were enrolled. All patients have undergone adjuvant cervicectomy. This procedure time were less than 20 minutes. Thirty two of the patients had blood loss between minimal blood loss to 30 cc. and maximum blood loss was 300 cc. No other immediate or delayed complication found. For pathology of LEEP, 32 (80%) patients had negative for malignancy, 6 (15%) patients had positive for SCC, 2 (5%) patients had preinvasive lesion. Six patients underwent extrafascial hysterectomy due to the results of SCC from LEEP. After treatment, 3 (7.5%) patients had progressive disease and 8 (20%) patients had recurrent disease. For recurrent disease 6 patients had distant metastases and 2 patients had local recurrence. The median survival was 23 months (3-45). At the last follow up, 31 patients were free of disease and 9 patients died of disease.

Conclusion: The procedure is feasible in this group of the patients without serious complication.
PELVIC EXENTERATION IN THE MANAGEMENT OF LOCALLY ADVANCED UTERINE CERVIX CANCER. CASE SERIES

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Objective: Evaluation of survival rates following pelvis exenteration (PE) in uterine cervix cancer (UCC) patients.

Methods: The study included 26 patients with newly diagnosed and recurrent UCC treated from January 2006 through December 2009. Their age ranged from 28 to 62 years (median age of 45.0). Twenty-two patients (84.6%) had squamous-cell carcinoma, 4 (15.4%) had adenocarcinoma. Anterior PE was performed in 84.6% of the cases (22 patients), posterior PE - in one, total PE - in 3 (11.5%).

Results: Radical surgical interventions were performed in 69.2% of the cases (18 patients), the operation was nonradical in 30.8% (8 cases). There was no intra- or postoperative lethality. Overall survival at 12 months was 52.2±10.4%, at 24 months - 37.3±11.6%. Median for survival time was 10.0±5.6 months.

Survival of radically operated patients at 12 months was 63.6±11.8%, at 24 months - 45.5±13.8% (p>0.05); survival of patients with no metastasis in pelvic lymph nodes: at 12 months - 76.0±12.1%, at 24 months - 63.3±15.3% (p>0.01).

Poor survival was registered in nonradically operated patients and in patients with metastatic pelvic lymph nodes. Median for survival time in those subgroups was 5.0±0.8 months and 6.0±0.7 months respectively.

The highest survival rates were recorded in patients with no tumor metastases in pelvic lymph nodes who had undergone radical surgical intervention: at 12 months - 88.9±10.5%, at 24 months - 77.8±13.9%). These patients survived more than 3 years on the average.

Conclusion: Careful selection of candidates for PE is necessary to achieve optimal cost/benefit treatment ratio.
FACTORS INFLUENCING HPV VACCINATION UPTAKE AMONGST YOUNG WOMEN FOLLOWING A NATIONAL VACCINATION PROGRAM

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Aims: In 2007, a HPV vaccine was introduced in Australia to prevent cervical cancer and genital warts amongst women aged 12-26 years via school- and population-based programs. The current study aimed to: i) investigate knowledge, self-efficacy, facilitators, impediments, outcome expectations, and goals of HPV vaccine recipients and non-recipients; and ii) explore vaccination decision-making and post-vaccination sexual attitudes of school- and population-based recipients.

Method: 161 female university students (102 recipients and 59 non-recipients) under the age of 26 completed purpose-designed questionnaires, informed by a pilot study (n=20) and literature. All scales had moderate-high internal consistency (α=.65 to .92).

Results: Vaccine recipients scored significantly higher than non-recipients on self-efficacy, facilitators, outcome expectations, and goals (all p< .001); and significantly lower on impediments (p< .001). There was a lack of knowledge (mean score of 57%) amongst all participants. Facilitators (p=.010) and impediments (p=.030) were key predictors of vaccine uptake. School-based recipients were significantly less involved in the vaccination decision than population-based recipients (p=.001). The majority of participants were still concerned about sexual health and protection following vaccine receipt.

Conclusions: This study explored factors affecting uptake of the HPV vaccine among one of the first vaccinated cohorts worldwide. Results suggest that health professionals and policy makers need to focus on promoting facilitating factors whilst addressing potential barriers to vaccination. The poor HPV knowledge results and low decisional involvement of many vaccine recipients suggests that health professionals and policy makers should consider more actively involving young women in the informed decision-making process for HPV vaccination.
ARE HR-HPV TYPING AND VIRAL LOAD QUANTIFICATION PREDICTIVE FOR INFECTION PERSISTENCE IN WOMEN UNDER 30 WITH NORMAL SMEAR?

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Background and aim: Persistence of high-risk HPV (HR-HPV) infection is a strong risk factor of premalignant cervical lesions. The aim of this study was to evaluate if HR-HPV typing and quantification are predictive for infection persistence in women under 30 with normal cervical smear.

Materials and methods: Patients under 30 being HR-HPV positive while having a normal cervical smear were included. HR-HPV type 16, 18, 31 and 33 infections were detected and quantified using duplex real-time PCR. Included patients were offered for a second smear and HR-HPV detection and quantification within a year interval.

Results: HR-HPV was identified in 43 (21.9%) of 199 included women. HPV 16 was the most frequent (51.2%), followed by 18 (25.6%), 33 (18.6%) and 31 (13.9%). Mean HR-HPV viral load was $1.9 \times 10^6$ copies per millions cells without significant difference between types. 39 women attended for a second smear within a mean delay of 11.7 months. HR-HPV infection persistence was identified in 20 patients and 5 were diagnosed with CIN1+. HR-HPV viral load was not significantly associated with HR-HPV infection persistence or CIN1+ occurrence. Only HPV16 infection was significantly more likely to persist and to develop CIN1+: 91.7% vs. 33.1% (p=0.001) and 33.3% vs. 3.7% (p=0.025), respectively.

Conclusion: In women under 30 with normal smear, HR-HPV viral load is commonly high and is not predictive of infection persistence within a year interval. HPV16 positive women are significantly more likely to have persistent infection and to develop CIN1+ and should be monitored carefully.
EFFICACY OF THE HPV-16/18 AS04-ADJUVANT VACCINE IN WOMEN ACCORDING TO THEIR INITIAL DNA AND SEROSTATUS: PATRICIA END-OF-STUDY RESULTS


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Objectives: The AS04-adjuvanted human papillomavirus (HPV)-16/18 vaccine shows high prophylactic vaccine efficacy (VE) against cervical intraepithelial neoplasia (CIN)2+ associated with HPV-16/18. We report VE stratified by initial cervical DNA/serostatus from the PATRICIA (NCT00122681) end-of-study analysis.

Methods: Women aged 15-25 years, irrespective of baseline HPV DNA status, serostatus, or cytology, were randomised to receive HPV-16/18 vaccine (n=9,319) or hepatitis A vaccine (n=9,325) at Months 0, 1 and 6. Cervical samples were collected every 6 months for HPV DNA typing; gynaecological and cytopathological examinations were performed annually. VE is reported for the total vaccinated cohort (women receiving ≥1 vaccine dose). Results: At baseline, 5.4% women were DNA-positive for HPV-16, 2.3% for HPV-18, and 0.5% for HPV-16/18; 13.9% women were DNA-negative but seropositive for HPV-16, and 10.6% for HPV-18. VE against CIN2+ at end-of-study by baseline DNA/serostatus is shown below.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Baseline HPV serostatus and/or DNA status</th>
<th>VE against CIN2+ associated with HPV-16 and/or HPV-18 detected in the lesion % (95% CI)</th>
<th>VE against CIN2+ associated with HPV-16 and/or HPV-18 detected in the lesion % (95% CI) (Type Assignment Algorithm [TAA, assigns probable HPV causality in lesions with multiple HPV types])</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16/18 CIN2+</td>
<td>DNA-negative and seronegative</td>
<td>95.6 (90.2-98.4;p&lt;0.0001)</td>
<td>98.5 (94.3-99.8;p&lt;0.0001)</td>
</tr>
<tr>
<td>HPV-16/18 CIN2+</td>
<td>DNA-negative, regardless of serological status at baseline</td>
<td>93.4 (87.5-96.9;p&lt;0.0001)</td>
<td>97.2 (92.7-99.3;p&lt;0.0001)</td>
</tr>
<tr>
<td>HPV-16/18 CIN2+</td>
<td>DNA-negative and seropositive for HPV-16 and/or HPV-18</td>
<td>65.3 (&lt;0-91.8;p=0.0770)</td>
<td>81.1 (13.3-98.0;p&lt;0.0225)</td>
</tr>
<tr>
<td>HPV-16/18 CIN2+</td>
<td>DNA-negative for the type considered but DNA positive for the other vaccine type, regardless of serostatus</td>
<td>91.8 (43.8-99.8;p=0.0023)</td>
<td>100 (54.4-100;p=0.0012)</td>
</tr>
<tr>
<td>HPV-16 CIN2+</td>
<td>DNA-positive for HPV-16/DNA-negative for HPV-18, regardless of serostatus</td>
<td>84.4 (&lt;0-99.7;p=0.0644)</td>
<td>100 (&lt;0-100;p=0.0284)</td>
</tr>
<tr>
<td>HPV-18 CIN2+</td>
<td>DNA-positive for HPV-16/DNA-negative for HPV-18, regardless of serostatus</td>
<td>100 (3.4-100;p=0.0226)</td>
<td>100 (&lt;0-100;p=0.0484)</td>
</tr>
</tbody>
</table>

Conclusions: The vaccine demonstrated high efficacy against CIN2+ associated with HPV-16/18 in HPV-16/18 DNA-negative women, even those seropositive for HPV-16 and/or -18. Women currently infected (DNA-positive) with one vaccine HPV type were protected against the other vaccine type, if DNA-negative for that type.

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CONFORMAL RADIOTHERAPY IN CERVICAL CANCER: THE EFFECT OF HIV INFECTION ON COMPLETION RATE AND RESPONSE

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Background: Cervical cancer is an AIDS defining illness and one of the most common cancers in HIV infected woman. Conformal CT planned external beam radiotherapy (EBRT) on an 18MV LINAC, concurrent weekly chemotherapy, and high dose rate (HDR) brachytherapy is the standard of care if the CD4 is greater than 200.

Objectives: To determine the effect of HIV infection on completion rate and response to standard radical chemoradiation.

Methods: A retrospective analysis of all FIGO Stage Ib- IIIb cervix carcinoma patients treated with radical intent in an 18 month period. Patient demographics, staging, treatment regime and response at EUA were documented. Statistical analysis was performed with the chi-squared test (p< 0.05 significant).

Results: 282 patients were treated with radical intent, 38 patients were HIV positive (13.4%). The mean age of the HIV positive group (41 years) was significantly younger than the HIV negative group (51 years) (p< 0.01). There was a significant reduction in completion rate for the HIV positive group; 73.7% vs. 87.3% of the HIV negative cohort completed a minimum of 45 Gy EBRT and 18Gy HDR brachytherapy (p=0.03). A complete response at time of the first brachytherapy insertion was achieved in only 12.2% of the HIV positive group, and in 33% HIV negative patients (p=0.01)

Conclusion: Analysis of this patient cohort demonstrates the co-existence of HIV infection significantly affected the response rate to radiotherapy, and lead to a reduced completion rate of EBRT and HDR brachytherapy. This cohort will be followed up to establish survival outcomes.
CERVICAL INTRAEPITHELIAL NEOPLASIA IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS


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Objectives: To study the prevalence of cervical intraepithelial neoplasia in women diagnosed with SLE submitted or not to immunosuppression therapy.

Methods: 95 SLE patients including 43 who were under immunosuppressive therapy continuously for at least 1 year was compared with 120 age- and sociocultural-paired women (control group) submitted to routine cervical cytopathology screening.

Results: The prevalence of atypical squamous cells of undetermined significance, low-grade and high-grade intraepithelial lesions were significantly increased in SLE patients (13.5%, 6.4%, and 2.8%, respectively) compared with controls (3.7%, 1.3%, 0.5%, respectively, P< 0.001). Multivariate analysis showed that SLE women had a 8-fold higher prevalence of cervical intraepithelial neoplasia (OR: 7.23, 95% IC: 3.40-15.38) and an 12-fold higher prevalence of high grade cervical intraepithelial neoplasia (OR: 11.36, 95% IC: 2.57-50.10) compared with controls. SLE patients with long-term use of immunospressors presented even higher prevalence of low-grade and high-grade intraepithelial lesions in comparison with those without long-term use of these agents (67.8% vs. 32.3%, P = 0.03).

Conclusions: SLE patients, especially those exposed to long-term immunosuppression, have increased risks of presenting cervical intraepithelial neoplasia comparing to the general population. They should be followed up more stringent.
A RARE CASE OF RENAL CELL CARCINOMA METASTAZING TO THE UTERINE CERVIX

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Objectives: In rare cases secondary metastatic tumours originating from other organs can be found in the uterine cervix. To the best of our knowledge only four cases have been previously reported in the literature.

Methods: A 65 year old woman was admitted with complaint of abnormal vaginal bleeding. Nine weeks earlier, she had a left sided nephrectomy for renal cell carcinoma as well as removal of the left renal vein. Metastatic workup at that stage was within normal limits. Histology showed multiple nodules of renal cell carcinoma which appears confined to the kidney and hilar vessels. Biopsies of the cervical lesion confirmed metastatic renal cell carcinoma. A thorough diagnostic workup followed, including physical and pelvic examination, pelvic ultrasound, magnetic resonance imaging of the pelvis and upper abdomen, showing that the metastatic tumour was confirmed to the uterine cervix. Radical hysterectomy with bilateral salpingo oophorectomy and pelvic lymphnodes resection followed.

Results: Pathologic examination confirmed tumour present in cervix and upper 1cm of the vagina. Microscopic and immunohistochemical analysis confirmed that the tumour was metastatic, originating from the primary renal cell carcinoma. Post operatively the patient refused chemotherapy and only received whole pelvic radiation and three years later remains disease free and in good general condition.

Conclusion: Due to the rarity of this condition, treatment of renal cell carcinoma metastatic to the uterine cervix should be individualized. Surgical therapy should be considered in carefully selected cases.
RADICAL ABDOMINAL TRACHELECTOMY FOR CERVICAL MALIGNANCIES: SURGICAL, ONCOLOGICAL AND FERTILITY OUTCOMES IN 60 PATIENTS

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Objective: To report our experience of radical abdominal trachelectomy (RAT) for 60 patients with cervical malignancies.

Methods: We conducted a retrospective review of a prospectively maintained database of patients undergoing fertility-sparing radical abdominal trachelectomy for cervical malignancies at our institution from 04/2004 to 05/2010.

Results: Sixty patients with malignant cervical tumors (58 adult patients with invasive cervical carcinoma and two pediatric patients with botryoid sarcoma) underwent RAT. Two patients were supplemented with radical hysterectomy due to unfavorable intraoperative pathological findings. Twelve patients with pathologic risk factors received adjuvant therapy, including two patients who received postoperative radiochemotherapy and thus lost their fertility. Among 54 patients who were theoretically able to conceive, only 9 (16.67%) attempted to get pregnant. One of them conceived naturally and delivered by cesarean section after 39 weeks. Our preliminary data of a survey in 28 patients suggested that social-familial factors could influence the reproductive outcomes a lot. No recurrences were observed at a median follow-up of 25 months. The main perioperative complication was postoperative cervical stenosis (5/60).

Conclusions: RAT appeared to be a proper option for patients with cervical malignancies who wanted to preserve fertility but were thought to be poor candidates for RVT. Installation of a tailed T-IUD may be an effective means of preventing postoperative cervical stenosis. The issues influencing the reproductive outcomes require further investigation.
OBESITY: A PREDICTIVE FACTOR OF SIGNIFICANT DISEASE FOLLOWING A DIAGNOSIS OF CERVICAL GLANDULAR DYSKARYOSIS?

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Introduction: Obesity is considered an important cause of several malignancies. Whilst its role in increasing the risk of cervical adenocarcinoma is well documented, its role in the risk of significant disease following a smear reported as cervical glandular dyskaryosis has been identified in a small retrospective study. With rising incidence of obesity and improved screening methods, the incidence of cervical glandular dyskaryosis has risen in the UK with significant disease outcomes. This leads to an increase in use of diagnostic and therapeutic resources and manpower.

Objectives: To determine whether obesity should be considered as a predictive factor of significant disease following a diagnosis of cervical glandular dyskaryosis?

Methods: A review of available literature and results of studies presented at an international meeting.

Results: A rising incidence was observed in other studies with data collected over significant time periods (4 - 10 yrs) at a recent scientific meeting- British Society for Colposcopy and Cervical Pathology. Adedipe et al (2009) identified an incidence of 0.601% (higher than quoted) and a positive predictive value of cervical smears in identifying disease in a general population at 57.1%, which rose to 75% within the subgroup of women with BMI>25.

Conclusion: A BMI> 25 should be recognized formally as a significant predictive factor for presence of disease following cervical glandular dyskaryosis. This aids the clinician's ability to deliver care. More research is needed into identifying the type of obesity (as determined by waist -hip ratio) and time-period of obesity that is associated with significant disease.
FACTORS AFFECTING THE FORMATION AND PROGRESSION OF CERVICAL DYSPLASIAS AND CARCINOMAS

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In the formation of cervical neoplasias the most important risk factor is high-risk HPV infection, but its effect is influenced/modified by several other factors. In the present study we investigated the effect of low-penetrance genetic factors on the risk of cervical cancer formation in HPV infected patients.

First, effect of allelic polymorphisms of X-ray cross complementing 1, glutathione-S-transferase M1 and T1, p53 and dopamine-receptor D2 genes was studied on the risk cervical dysplasia formation in participants infected with HPV-16. During the 8 years observation period 36 participants developed a cervical dysplasia, while 38 remained symptom- and disease free. From the studied polymorphisms, the GSTM1 affected the risk of dysplasia, among the symptom free participants the prevalence of 0-genotype was 38.9%, while in the dysplasia group it was 63.2% (p< 0.05).

In the second part of the study the effect of the same polymorphisms was studied on the progression of cervical intraepithelial neoplasia or invasive cervical cancer. 205 patients with CIN or cervical cancer were followed for at least 7 years. All the patients received the necessary therapy, according to their tumor status. By the end of the study 148 patients were symptom-free, 43 showed progression and 14 patients died. Significant difference (p< 0.05) was found in the distribution of GSTM1 (0-genotype: 63.2% vs. 52.7%), GSTT1 (0-genotype: 45.6% vs. 30.4%) and XRCC1 alleles (AA-homozygotes: 93% vs. 81.8%) between the groups with and without disease-progression.

Conclusion: Low-penetrance genetic factors modify the risk of tumor formation and progression in HPV infected persons.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

HPV SUBTYPES IN PATIENTS WITH CYTOLOGICAL ABNORMALITIES IN GAZI UNIVERSITY OUTPATIENT CLINIC

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\textbf{Aim}: Cervical cancer is an important global health problem. Human papillomavirus (HPV) infection is found to be associated with cervical cancer. The aim of this study is to find distribution of HPV types in patients with abnormal cytology.

\textbf{Materials and methods}: The women admitting to the gynecology outpatient clinic of Gazi University Hospital between April 2007 and June 2010 were included to this study. All cervical samples were analyzed for HPV DNA typing via PCR.

\textbf{Results}: Overall 892 patients were included to this study. HPV DNA was positive in 134\% (15.02\%) of this patients. 23\% (17.16\%) of this patients are detected to have abnormal cytologies. 21.7\% of the patients with abnormal cytology were determined as ASCUS, 8.7\% as ASCH, 56.5\% as LSIL, 8.7\% as HSIL. In ASCUS group 80\% of patients had HPV type 16, 20\% had HPV type 11. In ASCH group 50\% of patients were positive for HPV type 16, other 50\% were positive for HPV type 52. In LSIL group 38\% of patients had HPV type 16, 7.6\% had HPV type 11, 7.6\% had HPV type 42, 7.6\% had HPV type 68, 30\% had HPV type 18 and 7.6\% had HPV type 52. All the patients with HSIL were found infected with HPV type 16.

\textbf{Conclusion}: This findings showed that the most frequent subtype of HPV in patients with abnormal cytology was HPV type 16 (56.5\%). LSIL is the most frequently seen cytological abnormality in HPV type 16 positive patients.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

USEFULNESS OF FDG-PET SCAN IN CERVICAL SMALL CELL CARCINOMA


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Small cell carcinoma of the uterine cervix is an uncommon tumor and is associated with early metastasis and high mortality even in patients with early stage disease.

This tumor also features a tendency of early distant metastasis, resulting in treatment failure in most cases. Rapid disease progression, during or immediate after treatment, has been observed in some patients. Detection of early metastasis for cervical cancer by convention image studies, including computed tomography (CT) or magnetic resonance image (MRI) is not sensitive. Therefore, a more sensitive whole-body imaging, with the potential of detecting insidious metastatic lesion at diagnosis, is urgently demanding in the management of small cell cervical cancer.

18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) has been accepted for staging of small cell and non-small cell lung cancers, breast cancer, colorectal cancer, head and neck cancer, and cervical cancer, but not in small cell cervical cancer. We conduct a phase II study to investigate the additional benefit after adding FDG-PET as a pretreatment survey in patients with newly diagnosed small cell cervical cancer.

Between May 2001 and December 2008, a total of 28 patients with newly diagnosed small cell cervical cancer were enrolled (Table 1). Their median age was 54 (range 25-81) years. New lesions found by FDG-PET scan, compared to MRI or CT, were listed in Table 1. In 3 cases, treatment principles were changed due to new findings of PET scan. However, there are no statistically significant difference in terms of progression free survival and overall survival.
RAMAN SPECTROSCOPY - A NOVEL TOOL FOR CERVICAL CANCER SCREENING

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Cervical cancer is the second most common cancer in women worldwide and if detected early is almost 100% curable. As current screening methods such as the Pap test, are highly subjective and in many cases show low sensitivity and specificity, new supportive techniques are desirable to improve the quality of cervical cancer screening.

The aim of this study was to investigate the potential of Raman spectroscopy to detect biochemical changes in cervical smear samples and four cervical cancer cell lines with different HPV copy number.

The Raman spectra showed differences between the biochemical composition of superficial epithelial cells, navicular cells and polymorphs, as well as between the nucleus and cytoplasm of superficial squamous epithelial cells. The main variations observed between the cell types were in the glycogen, protein and nucleic acid levels. In the abnormal cervical cells, a significant increase in the nuclear activity was observed, as indicated by an increase in the intensity of peaks assigned to nucleic acids. The cervical cell lines showed distinct differences in their Raman spectra corresponding to protein, nucleic acid and lipid levels. Principal Component Analysis (PCA) successfully discriminated different classes of cervical cells, cell regions, and normal from abnormal cells. In addition, the cervical cell lines were discriminated by PCA based on their HPV copy number.

The results show that Raman spectroscopy can be used for identification and discrimination of normal and abnormal cervical cells. Moreover, HPV positive and negative cell lines could be discriminated based on their biochemical fingerprint.
THE PREVALENCE OF HPV INFECTION IN GAZI UNIVERSITY OUTPATIENT CLINIC

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Aim: Importance of human papilloma virus (HPV) in the carcinogenesis of cervix is one of the most striking development in modern science with the advent of efficient prophylactic vaccine against the unique disease. To determine nation-wide strategies, prevalance of HPV for that population should be determined. Data concerning the prevalance of HPV infections in Turkey are insufficient. This study aims to find prevalance of HPV infections in Turkish women subpopulation.

Materials and methods: The women admitting to the general gynecology outpatient clinic of Gazi University Hospital between April 2007 and June 2010 were included to this study. The patients referred for abnormal smear were not included to detect true prevalance of general population. All cervical samples were analyzed for HPV DNA typing via PCR.

Results: Total of 892 patients were included in this study. HPV DNA was positive in 15% (134) of the patients. 4.7% of the patients had HPV type 16; 1.5% had type 18; 0.5% had type 31; 1% had type 53; 1.4 % had type 6; 0.8 % had type 11; 50.2% had type 68; 0.2 % had type 52; 0.2% had type 56; 0.2% had type 35; 0.1 % had type 42.

Conclusion: This results showed that the prevalance of HPV infections in our subpopulation (15.02 %) is higher than expected. Most frequent type is detected as HPV type 16 ( 4.7 %). Our goal is to improve the awareness of Turkish women about HPV infections and the importance of prophylactic vaccination.
TAMPON SAMPLING DETECTS CERVICAL CANCER:

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Background: Cervical cancer incidence rates in South Africa are extremely high and the national screening policy has not been implemented due to various reasons. Self-collected samples will obviate the need for trained personnel and instrumentation, but yields inferior cytology results. This study was done to prove the principle of tampon collection to detect high risk HPV DNA (hrHPV) in patients with cervical cancer.

Method: In this prospective descriptive study tampons were self-inserted by patients with newly diagnosed cervical cancer. After three hours it was removed and put into phosphate buffer solution (PBS). Consensus PCR test was done to detect hrHPV and genotyping was done on positive specimens.

Results: One hundred and one patients with cervical cancer (squamous type in 97, adeno- or adenosquamous in 3 and small cell carcinoma in 1) were tested for hrHPV. Only seven specimens tested negative and hrHPV was detected in 94 of the specimens of patients with cervical cancer. Of the positive patients, 50% tested positive for HPV16, 41% had only one viral type, 21% were positive for HPV18 and 31% had three or more viral types positive.

Conclusion: This study demonstrates that tampon collection and DNA based testing is feasible in our context. Our study shows a very high sensitivity of this self-collected test for cervical cancer (94%). Multiple viral types was a common finding. HPV16 only explained 50% of cervical cancers in our study.
VILLOGLANDULAR ADENOCARCINOMA OF THE UTERINE CERVIX
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Introduction: The villoglandular adenocarcinoma of uterine cervix is a rare neoplasia, with histological and clinical differences to other types of cervical adenocarcinomas. Until 1994 it was not incorporated inside the types of cervical carcinoma for the World Health Organization (WHO).

Objectives: Clinical and pathology study of villoglandular adenocarcinoma of uterine cervix.

Material and methods: Retrospective study of cases of this type of tumor diagnosed and treated in this service since 2002 until 2009.

Results: There have been diagnosed four cases of cervical villoglandular adenocarcinoma; three of the cases had good outcome and patients are free of disease, whereas one of the cases has filed a torpid evolution and continues even in treatment.

Discussion: The villoglandular adenocarcinoma of the uterine cervix usually affects young patients. The treatment of this type of tumors must be conservative, if the patient wants to preserve the fertility, due to its favorable evolution. The microscopic finds are typical and include: exofitic growth, surface with papilar aspect and small to moderated nuclear atipia.
PARA-AORTIC LYMPH NODE (PAN) INVOLVEMENT IN STAGE IB-IIA CERVICAL CARCINOMA: THE FREQUENCY AND THE ASSOCIATED RISK FACTORS

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Objective: To determine the frequency of para-aortic lymph node (PAN) involvement in stage IB-IIA cervical carcinoma and to identify the high-risk factors for PAN metastasis.

Methods: From 2005 to 2010, 466 patients with Stages IB-IIA cervical carcinoma who underwent radical hysterectomy and systematic pelvic and PAN dissection were investigated retrospectively.

Results: A median of 7 PAN were removed per patient. The frequency of PAN involvement was 12.7% for 466 patients and was 6.2%, 9.8%, 16.1% and 23.9% in FIGO stage IB1, IB2, IIA1 and IIA2, respectively. The frequency of PAN metastasis was associated significantly with FIGO Stage, tumor size, lymph vascular space invasion (LVSI), parametrial invasion and pelvic lymph node metastasis. In a multivariate analysis, tumor size>3cm (P=0.022), more than 3 pelvic nodal involvement (P=0.027) and common iliac lymph node involvement (P<0.001) were independent factors for PAN metastasis. By using a receiver operating characteristic (ROC) curve, we found the optimal cut off point of tumor size to predict PAN metastasis was 3cm (sensitivity, 94.6%; specificity, 31.1%). The mean operating time for para-aortic lymphadenectomy was 30 min (20-45min) and the median blood loss during the overall surgical procedure was 400 ml (100-1450 ml). The rate of surgical complications was 7.6%, but no surgery-related death occurred.

Conclusion: PAN dissection is safe and beneficial for certain group of patients with cervical cancer. It is recommended that PAN dissection should be routinely done for the IB-IIA cervical cancer patients whose tumor size is no less than 3cm.
DIAGNOSTIC CERVICAL BIOPSY AND SUBSEQUENT HPV ACQUISITION

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Objective: To analyze the association of the number of biopsies taken at enrollment with subsequent human papillomavirus (HPV) infections detected at the 6-th and 12-th month follow-ups.

Methods: The study included 455 patients who underwent colposcopy and diagnostic biopsy for histological analysis after cytological finding of mild cervical intraepithelial neoplasia. Polymerase chain reaction was used in HPV genotyping and it was performed for every patient at the enrollment of the study and afterwards at month 6 and month 12. Our analysis considered each woman’s possible acquisition of new subsequent HPV genotype according to the number of biopsies.

Results: The average acquisition of a new HPV genotype at month 6 for women with zero, one, and two or more biopsies was 1.81%, 1.69%, and 1.98%, respectively. At month 12 the HPV acquisition was 2.63%, 2.15%, 2.98%. In a logistic regression model with adjustment for age, baseline HPV status, and having a new sexual partner at month 6 follow-up and month 12 follow-up, two or more biopsies (compared with one biopsy) was not associated with acquiring new HPV genotype (odds ratio 1.0, 95% confidence interval 0.75-1.3).

Conclusion: Multiple biopsies compared with a single biopsy did not increase the likelihood of acquiring new HPV infections.
P16$^{INK4A}$ IMMUNOPROFILING OF SQUAMOUS LESIONS OF THE UTERINE CERVIX WITH LIMITED DIAGNOSTIC REPRODUCIBILITY

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Objectives: The impact of p16$^{INK4A}$ immunohistochemistry on the histopathologic classification of cervical squamous lesions with the limited diagnostic reproducibility (CIN I and atypical immature squamous metaplasia; AIM) was analyzed.

Material and methods: The total of 200 cervical biopsies was divided into groups of CIN I (n=29), CIN II (n=48), CIN III (n=32), squamous metaplasia (M; n=51), squamous metaplasia with histologic signs of HPV infection (M-HPV; n=16) and AIM (n=24). All samples were analyzed immunohistochemically with p16$^{INK4A}$ antibody. The intensity (strong; weak) and horizontal distribution (focal; diffuse) of immunoreaction were assessed and the most common staining pattern for each group was identified.

Results: The typical immunostaining patterns for p16$^{INK4A}$ were as follows: CIN I - diffuse weak positivity (51.7%), CIN II - diffuse strong positivity (87.5%), CIN III - diffuse strong positivity (93.75%), M-HPV - focal weak positivity (56.3%) and M - negativity (86.3%). AIM was the most heterogeneous group showing typical immunoprofiles of high-grade CIN (25.0%), M-HPV (33.3%) and M (29.2%). The nature of AIM lesions with focal strong immunoreaction (12.5%) is unclear. Significant heterogeneities were observed also in CIN I group which contained lesions with high grade CIN (24.1%) and M-HPV (20.7%) immunoprofiles and in M-HPV group comprising cases with M immunoprofile (43.7%).

Conclusion: p16$^{INK4A}$ immunoprofiling is capable to distinguish cases with a supposed different biologic behavior between lesions classified as CIN I. AIM group may be almost completely stratified into lesions with various precancorous potential.

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LOCALY ADVANCED CERVICAL CANCER TREATMENT WITH CONCURRENT RADIATION AND CISPLATIN IN OUT-OF-PROTOCOL MANAGEMENT: FEASIBILITY AND SURVIVAL

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Introduction: In 1999 and 2000 5 randomized studies, showed that survival rate of patients with cervical cancer treated with radiotherapy alone was lower than with concomitant chemotherapy, and its mortality were reduced in 30% to 50%. According to these results we adopted the treatment with cisplatin chemoradiation as routine management of cases with locally advanced cervical cancer. The aim of this study was to evaluate feasibility and the response rates and overall survival of patients with LAC cancer treated with cisplatin-based chemotherapy during radiation, on an out-of-protocol basis.

Methods: We conducted a retrospective review of 69 consecutive newly diagnosed and previously untreated patients with LAC cancer, who received chemoradiation between June 1999 and July 2003. Treatment consisted in external beam radiation followed by one 137-Cesium intracavitary application. Cisplatin was administered for 6 weeks during external beam radiation.

Results: Overall, treatment was well tolerated, although 52 patients presented some degree of acute adverse toxicity. The most common acute adverse effects were gastrointestinal (65%), hematological (48%), and genitourinary (10%). Survival at 3 years was 61.78% (54.51-69.05), mean 41.80 months (IC 95%: 35.26-48.33). Overall survival after adjusting by FIGO stage IB2-IIa and IIb-IIb was 73.9% and 50.05% respectively (p<0.1839). Overall survival according to stages IB2-IIb and III-IVa changed to 74.8% (67.87-81.73) and 34.91% (21.74-48.08) respectively (p<0.0376).

Conclusion: Results of the present report indicate that adding the weekly regimen of cisplatin to standard pelvic radiation in patients outside research settings is achievable, shows no unexpected toxicity, and is effective.
EQUIVALENT SURVIVAL AND RECURRENCE OUTCOME IN EARLY STAGE INVASIVE ADENOCARCINOMA COMPARED WITH SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX

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Objectives: To evaluate an outcome and determine prognostic factors of the early stage invasive adenocarcinoma compared with squamous cell carcinoma of the uterine cervix following radical hysterectomy.

Material and method: A retrospective study of 316 Thai patients with cervical cancer stage IA2-IIA (120 adenocarcinoma and 196 squamous cell carcinoma) who had undergone radical hysterectomy from January 1, 2000 to December 31, 2006 was done.

Results: With a median follow up of 65.23 months, the estimated 5-year recurrence-free survival and overall survival for patients with adenocarcinoma did not differ from those for patients with squamous cell carcinoma (90.3% vs 93.1% and 90.9% vs 93.5%, respectively). Multivariate analysis identified the significant prognostic variables as cervical stroma invasion and lymphovascular space invasion.

Conclusions: Survival and recurrence were equivalent for surgically treated cervical cancer in patients with either early stage adenocarcinoma or squamous cell carcinoma. Significant independent risk factors for tumor recurrence were positive lymphovascular invasion and middle/outer third cervical stroma invasion.
CERVICAL CARCINOMA IN A HOMOSEXUAL WOMAN: CLINICAL EVIDENCE OF HPV TRANSMISSION AMONG WOMEN

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We report a case of a 51 y.o., G0, with vaginal bleeding, smoker, with no heterosexual intercourse. She is in homosexual, monogamous relationship, had 2 prior female sexual partnerst. Both had prior heterosexual intercourse. On examination, cervix with 3x3 cm mass. Punch biopsy showed Adenocarcinoma, G2. RHBSO BLND was performed. Specimen showed 3x3cm nodular mass on the endocervical canal. Final pathology: G3, invasive squamous cell carcinoma, small cell type FIGO 1B1.

Discussion: HPV prevalence among lesbian and bisexual women ranges from 3.3% to 30%. The prevalence is 19% in those w/o heterosexual sex. The sexual practices between female partners that could account for HPV transmission include digital-vaginal sex, oral sex, and use of insertive sex toys. There are reports of genital HPV on the fingertips of subjects, substantiating the hypothesis that HPV could be introduced intravaginally with digital-vaginal contact between female partners. Our case is a homosexual woman with no history of sexual penetration nor received digital stimulation of the clitoris and vagina or shared sex toys. Patient had history of cunnilingus on her 1\textsuperscript{st} female partner only. Sexual practice is thru clitoral rubbing. General assumptions about sexual practices between women confer a relatively low risk of HPV transmission. Such assumptions presume absence of the mucosal contact present during vaginal-penile sex. The transmission of HPV, however, requires only skin to skin contact, making sexual transmission between women by direct genital-to-genital contact plausible.

Conclusion: We report a case of cervical cancer (thus HPV transmission) in a homosexual woman.
LYMPH NODE HPV-DNA POSITIVITY IN UTERINE CERVICAL CANCERS AND ITS RELATIONSHIP WITH PROGNOSTIC FACTORS

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Objective: To determine the correlation between classic prognostic factors and HPV-DNA positivity in regional lymph nodes of patients with cervical cancer.

Methods: Thirty-seven patients who underwent radical hysterectomy with regional lymph node dissection for early stage (FIGO stage IB) uterine cervical cancer were assessed for HPVDNA status of the regional lymph nodes utilizing polymerase chain reaction (PCR). HPV-DNA presence and types were analyzed in paraffin embedded tissues from all primary tumors and 746 regional lymph nodes. The correlation between HPV-DNA positivity of the lymph nodes and prognostic factors [stage at the time of diagnosis, status of the regional nodes, status of parametria and surgical margins, tumor size, histological type, cervical stromal invasion depth and lymphovascular space invasion (LVI)] was investigated.

Results: Lymph node HPV-DNA positivity increased in larger tumors (p< 0.05). In addition, lymph node metastasis and primary tumor HPV-DNA status were closely correlated with HPV-DNA status of the lymph nodes (p< 0.05). No statistically significant relevance was present between patient age, histological type of tumor, FIGO stage, parametrial and vaginal involvement, cervical stromal invasion depth, lymphovascular space invasion (LVI) and lymph node HPV-DNA positivity.

Conclusions: HPV-DNA in lymph nodes of patients with uterine cervical cancer may have an influence on disease survival and requires further research. Large multicenter clinical trials with long term follow-up periods are needed to address the clinical and prognostic significance of HPV-DNA positivity of regional nodes.
SURGICAL MANAGEMENT OF BULKY (> 4CM) CERVICAL CARCINOMA
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Background: Treatments of bulky stage IB cervical cancer is controversial. The treatment options are definitive concurrent chemoradiation therapy or radical surgery with or without neoadjuvant or adjuvant therapy. The treatment decision is based on the patients’ status and preferences, tumor characteristics, and experiences of clinician.

Objective: To assess the surgico-pathological outcomes of patients who treated for bulky cervical carcinoma

Methods: Between 2006-2010, 42 patients with bulky cervical carcinoma treated with primary type 3 radical hysterectomy and adjuvant treatment based on risk factors were analysed retrospectively.

Results: Mean age of the patients 49.6±10. 83% of the patients was SCC while 17% was non-SCC. Mean tumor diameter was 5.2±1 cm. Mean number of resected lymph nodes were 43±16. LVSI, parametrial involvement, deep stromal invasion were positive in 74%, 24%,43%, respectively. Pelvic and paraaortic LN metastasis was found in 43% and 15% of the patients, respectively. Radiotherapy was used in 65% of the all patients. Recurrences were seen in 26% of the patients and all the recurrences were seen within the pelvis. 44% of the recurrences were seen in vaginal cuff while 56% were seen in other locations within the pelvis. Mean overall and disease free survival was 19.7±10, 17.5±9 months, respectively.

Conclusion: Size of the tumor should not be accepted as a contrindication for the surgery. Radical hysterectomy and adjuvant chemoradiotherapy based on histopathological risk factors is a valid approach for patients with bulky cervical carcinoma. Additinally, one third of the patients can be avoided from radiotherapy with this strategy.
DETECTION OF HPV E6 AND E7 ONCOPROTEINS IN CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) 2/3 AND INVASIVE CANCERS

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Overexpression of HPV E6 and E7 is required to induce and maintain the transformation of cervical epithelium into CIN 2/3 and ultimately, invasive cancers. To demonstrate the expression of HPV E6 and E7 in clinical specimens, HPV recombinant proteins of HPV16 E6, HPV18 E6, HPV16 E7 and HPV18 E7 genes were expressed in E. coli and used as immunogens for generating antiserum. Monoclonal antibodies were screened from hybridoma cell lines and optimized for IHC. Tissue microarrays containing CIN2, CIN3, and squamous cell carcinoma with its corresponding adjacent normal tissues were used to perform IHC using anti-E6, anti-E7, and anti-p16 antibody as well as CISH (L1 probe).

Results: Histologic specimens from 46 cases of CIN2, 48 CIN 3, 22 squamous cell carcinoma and 23 adenocarcinoma were collected. The monoclonal antibodies are not type specific, which may be explained by the similarity of E6 and E7 proteins in oncogenic HPV. A 100 % staining of MAb3, an monoclonal antibody derived from E7 oncoprotein of HPV 16, staining was seen in squamous cell carcinoma, 91 % in adenocarcinoma, 89% in CIN 3 and 77% in CIN 2. MAb7, a monoclonal antibody from HPV 16 E6 protein, showed a 96% sensitivity for squamous cell carcinoma, 71% for adenocarcinoma, 70% for CIN 3 and 61% for CIN 2. Their specificities were 100%.

Conclusion: HPV E6 and E7 oncoprotein expression in invasive cervical cancer and in their precursors was confirmed by immunohistochemical staining of our novel antibodies. It can be teste for their clinical usage.
P16 INK4A EXPRESSION IN PREINVASIVE CERVICAL LESIONS AND INVASIVE SQUAMOUS CELL CARCINOMA, AND ITS CLINICAL VALUE

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Background: Early diagnosis with screening methods is essential for the cervical cancer precursors and invasive cervical neoplasias prevention and early diagnosis. The ideal screening test should distinguish women with non-progressive mild neoplasia from those with oncogenic transformation and at women with risk of developing invasive cancer in order to facilitate decision on therapy and need of follow-up. p16 INK4a is one of the new diagnostic and screening marker.

Objective: To evaluate the p16 INK4a expression in cervical preinvasive neoplasias and invasive squamous cell carcinomas (SCC).

Material & method: The p16 INK4a expression levels, in 55 cases with cervical high grade lesions and 30 patients with invasive squamous cell cervical carcinomas were measured by semiquantitative immunohistochemical method. We also assessed the relationship between p16INK4a and HPV. Presence of HPV was determined PCR method.

Results: Strong and diffuse p16INK4a expression were seen in HSIL and SCC group. Most of the patients with LSIL showed weak expression of p16INK4a. However, p16INK4a was also strong positive in patients with LSIL lesion which was caused by high risk HPV (p< 0.001).

Conclusion: We showed a statistical significant relationship between p16INK4a overexpression in high grade cervical lesions and HPV infection. p16INK4a overexpression might be a useful marker for the prediction of low grade lesion progression into the high grade lesions. However, further studies with larger samples size and longer follow up are needed to reach clear conclusions.
PREDICTORS OF SURGICAL MARGIN POSITIVITY AFTER LEEP

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Background: Positive surgical margins is an unexpected and unwanted outcome of LEEP procedure and it is clinical dilemma for the clinicians and its management is debateful.

Objective: To identify the risk factors for the development of positive surgical margins after LEEP.

Material & method: 391 LEEP procedure performed for abnormal colposcopy findings after different abnormal smear was analysed retrospectively.

Results: There were 391 patients. Mean age of the patients was 38.9± 8.6 (range 20-73). ASCUS, LSIL, HSIL, ASC-H and AGC rates were 46%, 28%, 21%, 4%, 0.5%, respectively. HPV was positive in 29% of the patients. Surgical margins was positive in 17% of the patients.

Mean age of the patients with positive surgical margins was statistically significantly lower in (37 vs. 39,p=0.041) . Higher degree of cytological abnormality (HSIL,AGC) and HPV positivity were found as significant factors for surgical margin positivity after LEEP.

Conclusion: Younger age, HPV positivity and higher degree cytological abnormality was significant risk factors for the development of positive surgical margins after LEEP.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

HPV PREVALENCE IN TURKEY: A MULTICENTER TURKISH GYNECOLOGIC ONCOLOGY GROUP STUDY

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Background: Human Papillomavirus (HPV) is a well-known pathogen for lower genital tract neoplasias, yet little is known regarding HPV prevalence in Turkey. Also, HPV prevalence has not been evaluated by a multicenter study in Turkey.

Objective: To retrospectively evaluate the prevalence of HPV in patient records obtained from members institutions of Turkish Society of Gynecologic Oncology

Methods:Demographic characteristics and data about HPV and cervical cytological abnormalities were evaluated retrospectively collected from the 9 healthcare centers by using a same database.

Results: There were, 30% women with cytologic abnormality and 70% women with normal cytology. Overall HPV positivity was 22%. Multiple HPV prevalence was 2% for whole grp. The overall prevalence of HPV in women with abnormal Pap smears was 49%, while it was 16% in women with normal Pap smears. The most common HPV types in cytologically normal women were as follows; HPV 16 (40%), HPV 18 (12%), HPV 6 (12%) and HPV 11 (6%). The most common HPV types in cytologically abnormal women were as follows; HPV 16 (50%), HPV 18 (10%), HPV 31 (7%) and HPV 45 (6%).

Conclusion: HPV prevalence and type distribution is similar to the Western countries in Turkey. Also, HPV 16 is the most common types in Turkish population.

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WELL DIFFERENTIATED VILLOGLANDULAR ADENOCARCINOMA OF THE CERVICAL CANCER - SHOULD WE DO CONIZATION WITH HYSTEROSCOPY TO DIAGNOSE IT?
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Well differentiated villoglandular adenocarcinoma (WDVGA) is one of rare histological type of cervical cancer. It usually associated with young premenopausal women with favourable prognosis. We present a case of WDVGA of cervical cancer which was diagnosed by conization and hysteroscopy.

A 37 years old lady parity 4 with postcoital bleeding for 2 years. An irregular growth from the cervix with contact bleeding was detected. Excisional biopsy was performed. Histopathological examination showed WDVGA. Colposcopy showed type 1 squamous-columnar junction with no growth seen but positive acetowhite area. Large loop excision of transformation zone (LLETZ) under local analgesia was performed. The result showed no CIN or malignancy changes. Repeat tophat LLETZ with hysteroscopy was performed. There was acetowhite area with no abnormal vessels and the endometrial cavity was normal. The results were secretory endometrium, chronic cervicitis with focal glandular dysplasia. She opted for conservative management with colposcopy surveillance.

WDVGA is a low grade adenocarcinoma of cervical cancer, which often superficially invasive and rarely exhibit lymphovascular invasion. It is associated with OCP use and high-risk types of HPV (type 16 and 18). The definitive diagnosis could only made either by conization or by hysterectomy. This is because villoglandular tumour may be associated with a high-grade lesion or a deeper invasive disease with lymphovascular invasion. Hysteroscopy was performed as WDVGA is a subtype of endometroid adenocarcinoma of endometrial cancer.

We suggest diagnosis of WDVGA of cervical cancer should be made by conization to exclude a deeper invasive disease and by hysteroscopy to exclude endometrial cancer.
RADIATION SENSITIVITY OF CANCER CERVICIS CELLS (C4-I) AND EXTRACELLULAR CYCLIC GMP AS A BIOMARKER OF RADIATION EFFECT

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Treatment of cancer of the uterine cervix is dependent of stage and involves surgery, radiation and chemotherapy. Extracellular cGMP levels have been shown to be reliable marker for therapeutic response and an early prognostic marker for relapse. In the present study C4-I cells (human cell line derived from a carcinoma of the uterine cervix) were exposed to 2, 4, 8 and 12 Gy. Effects on cell densities, cell cycle, apoptosis and extracellular concentrations were determined after 1, 3 and 6 days. The effects were dependent on both radiation dose and time after exposure. The apparent ID50 were 2.8 and 3.2 Gy after 3 and 6 days, respectively. Cell cycle analysis showed a dose- and time dependent increase in the fraction of aneuploid cells but with little effect on apoptosis within this time period. When extracellular cGMP levels were related to remaining cancer cells a clear dose-dependent effect was seen. At day one, three and six the highest radiation dose increased the levels approximately 2, 10 and 30 times above the control.
ADVANCED LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE CERVIX - IS CURE POSSIBLE?

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Introduction: Cervical lymphoepithelial carcinoma is an uncommon tumor and is morphologically similar to the nasopharynx indiferenciated carcinoma.

Material and methods: This case report was based on the analysis of the patient’s medical registers from Hospital Mario Kroeff (HMK), Brazil.

Results: A 32 years old woman went to another hospital for a hysterectomy and bilateral anexectomy with reviewed histopathology data of Lymphoepithelioma-like carcinoma of the cervix. Relaparotomy was intended to complete the suited treatment for cervical carcinoma with parametrectomy and pelvic lymphadenectomy. At surgery we verified an irressecable lymphadenopathy at left internal iliac chain, as shown in a pre operative pelvic tomography. Since the citopatology analysis of a fine needle punctation aspiration of the adenopathy was positive to malignat cells, she was submitted to combinated treatment with pelvic radiotherapy (50Gy/25 Fr) and chemotherapy (CDDP x 5 - 40mg/m²) and posterior braquitherapy (4 x 0,7 Gy) from 16/07/2009 to 06/08/2009. Since months after, a pelvic tomography and a pelvic magnetic resonance shown complete regression of the metastatic site.

Discussion: Lymphoepithelioma-like Carcinoma of the cervix is a rare neoplasm and the incidence is higher in Asia than in the West. The prognosis seems to be better than that of cervical squamous cell carcinoma, generally at early stages at diagnostic and with lower tendency to metastasize to lymph nodes according to data from the medical literature. This case suggest that tumor behavior is less aggressive than other histologic types of cervical cancer and like the nasopharynx tumor is high sensitive to the radiotherapy and chemotherapy.
ON IMPROVING THE EFFICACY OF UTERINE CERVIX CANCER DIAGNOSTICS IN PREGNANT WOMEN IN BELARUS

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The existing initial gynecological evaluation procedure of pregnant women in Belarus leaves a risk to miss the diagnosis of uterine cervix cancer (UCC).

Objective: To study the rates of newly diagnosed UCC in pregnant women and to evaluate the efficacy of initial examination procedure of pregnant women.

Materials and methods: The study included 29 pregnant patients (ages 21-40) newly diagnosed with UCC (stage I-IV), 25 patients with squamous-cell carcinoma and 4 patients with adenocarcinoma. Initial gynecological examination of pregnant women included pelvic exam and a pap smear of uterine cervix.

Results: Our analysis shows that 58.6% of pregnant women diagnosed with UCC had stage I and 41.1% already progressed to stages II-IV. Among patients, 24.1% were in their first trimester, 27.6% were in second trimester, 24.1% were in third trimester and 17.2% after delivery. Additionally, 6.9% of pregnancies were terminated. Pregnant patients diagnosed with UUC also presented with endocervicitis in 65.5%, polyps - in 3.5%, and severe dysplasia or carcinoma-in-situ in 6.9%.

Conclusions: Missed routine diagnostic opportunity of precancerous changes of the cervix is one of the leading causes of UCC diagnosis during pregnancy.

Primary diagnosis of UCC during second and third trimester and after delivery suggests that additional tests are in order during initial pregnancy visit including colposcopy and pap smear from both uterine cervix and cervical canal for cytology and HPV testing.
AUDIT OF OUTCOME OF LLETZ (LARGE LOOP EXCISION OF TRANSFORMATION ZONE) IN A DGH OVER A 7 YEAR PERIOD

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Background: Increasing women in reproductive age undergo LLETZ. Research has revealed that LLETZ increases risk of pregnancy problems. It is in best interest of patient to avoid LLETZ if possible.

Aim: To review appropriateness of LLETZ.


Standards: According to National guidelines-May/2010 proportion of CIN2/3 on treatment at first visit should be >/=90%.

Excision for low grade smears in first visit should be done only if audit recognises CIN2/3 in >/=90%. Biopsy should be undertaken in >95% of moderate/severe dyskaryosis at 1st visit.

Results: Of 2491 lletz done during this period, 10% were negative for CIN. Of these 9.7% were at 1st visit. Negative LLETZ at first visit for low-grade smear and clinical-indication was 67%. All except 2 moderate/severe dyskaryosis had biopsy.

Conclusions: 75% women who underwent LLetz were of reproductive age.

Proportion of CIN was >90% but CIN2/3 on LLETZ for low-grade smear and other clinical-indications at first visit was <90%. (STD >90%).

Moderate/severe dyskaryosis were appropriately managed.

10% of CIN1, 9.5% of CIN2, and 5.6% of CIN3 on punch biopsy, who had LLETZ, had negative results.

Discussion: More than recommended women are undergoing LLETZ at first visit for low-grade smears and clinical-indications. We recommend to do punch biopsy in these women if colposcopy suggests CIN.

20% of patients with CIN1 and CIN2 on punch biopsy had negative LLETZ. Is it advisable to do a study to clinically follow up these women in colposcopy?
SENTRY LYMPH NODE MAPPED BY LYMPHOSCELLINTIGATION AND BLUE DYE FOR CERVICAL CANCER - PRELIMINARY ANALYSIS OF THE FIRST SIX CASES

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Aim: Evaluation of the sentinel lymph node detection, mapped by lymphoscintigraphy and blue dye, in cervical cancer early stages (stages IA1 to IB1).

Patients and Methods: This analysis was based on the preliminary results of a prospective study from the department of Gynecology Oncology in Hospital Mario Kroeff (HMK), Brazil. Six patients were submitted to the injection of 1-2 mCi of technetium-99m-phytate at the cervix six hours prior to surgery and a total of 4 ml of patent blue right after laparotomy. The technique used was injection at the 4 quadrants of the uterine cervix. The lymphoscintigraphy was performed two hours after the injection of the radiopharmaceutical. The surgical technique was laparotomy followed by pelvic lymphadenectomy (below the iliac vessels as it crosses the ureter). To identify the sentinel lymph node, a Neoprobe 2000 was used (2100 model).

Results: Any lymph node identified by either technique was considered a sentinel lymph node. A total of 68 lymph nodes were isolated, 10 of them were the sentinel lymph nodes. 2 of the sentinel lymph nodes were positive for malignancy, and the other 8 were negative. None of the other nodes were positive for malignancy.

Conclusion: The combined technique for mapping sentinel lymph nodes, using patent blue and radiopharmaceutical technetium-99m-phytate is trustable, easy to apply and presents low morbity. There was at least one sentinel lymph node mapped in every one of the 6 cases. The study will go on, and a larger number of cases will help validate this technique.
IS IT NECESSARY TO MAKE CT-PLANNING FOR EACH BRACHYTHERAPY APPLICATION DURING THE TREATMENT OF CERVICAL CANCER?

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Purpose: High dose rate (HDR) intracavitary brachytherapy (BRT) is performed with multiple applications. In this study, we investigated whether CT-planning is required at each application in order to defeat high organs at risk doses and lower target doses.

Methods and materials: The dosimetric and clinical parameters of 37 patients treated with external-beam radiotherapy (ERT) and HDR BRT between January 2007 and February 2010. BRT treatment was delivered with a HDR $^{192}$Ir source afterloading system in four fractions. Initially, a standard treatment plan normalized to Point A was applied and 3D plans were generated for each insertion. Critical organs were contoured (bladder, rectum, sigmoid colon) and dose-volume histograms were created. The maximum dose received by a contiguous 2 cm$^3$ volume (D2cc), determined from the cumulative DVH for each fraction were measured.

Results: When a single plan was used, International Commission on Radiation Units and Measurement (ICRU) reference points and 2 cm$^3$ volumes of bladder and rectum were significantly increased. The sigmoid and small bowel exhibited a more variable increase in dose. Dose-volume parameters (D2cc) for OAR were all augmented; an increase of 5.6 Gy$^3$ for the bladder ($p = 0.02$), 5.4 Gy$^3$ for the rectum ($p = 0.03$), and 0.7 Gy$^3$ for the sigmoid colon ($p = 0.3$) were observed.

Conclusions: A single plan used for an entire course of BT can result in significant increases to OAR doses which may increase the unpredictable toxicities. In order to overcome this problematic issue CT-plan should be performed at each BRT application.
CARCINOGENIC SEXUAL PRACTICES OF THE GERIATRIC PERSONS IN NIGERIA AND PERCEIVED HUMAN PAPPILOMA VIRUS INFECTIONS

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Main risk factor for Cervical Cancer (CC) development is persistence infection with high risk group Human Papilloma Virus (HPV). HPV infection is mostly common Sexually Transmitted Infections (STIs). Since Sexual Behaviour (SB) determines exposure to HPVs. In Nigeria many geriatrics are faced with Reproductive Health challenges including engagement in risky sexual activity. Therefore geriatrics SB needs to be examined to prevent HPV infections leading to CC the second commonest cancer among Nigeria women.

This study was cross-sectional in design, comprising 400-geriatrics selected using multi-stage sampling method. Qualitative and quantitative methods of data collection were implored. The FGDs were recorded on audio-tape and themes developed while questionnaire data were analyzed using chi-square/inferential statistics.

A total of 25.0% of the participants engaged in extra-marital without condom-use. Majority (47.5%) agreed STIs including HPV do not distort sexual practice. Since 50.0% felt condom is not geriatrics. Perceived having sex with adolescent-virgins is an immunity against HPVs. Most (60.3%) opined visiting Traditional healers and herb-use (10.3%) would provide prevention against STIs/HPVs. FGD participants unanimously opined geriatric women who engage in frequent-sex would develop CC because sperm that suppose to flush by menses settles in female’s body. Moreover, they believed female sex organs were tight from adolescence including old-age which shrinks their sex organs, sex therefore, becomes painful and cancerous.

Behavioural antecedents of geriatrics and its perceived carcinogenicity are significant public health problem in Nigeria. There is need to provide health promotion and screening for early detection of CC and HPV to mitigate the problem.
CERVICAL CARCINOMA ONTO A COMPLETELY PROLAPSED UTERUS

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Objective: The development of cervical carcinoma onto a completely prolapsed uterus is a rare condition to deal with, especially into rural communities where the approach to medical centers and services is extremely difficult.

Materials - methods: The clinical characteristics of a 70-years-old patient who was admitted to our outpatient department because of a completely prolapsed uterus associated with a cervical ulcerated lesion and enterocele, are presented. The tumor had an anthocramvoid whitish - gray appearance, length of 14.5 cm and width of 9.5 cm. Upper and lower abdominal computerized tomography scanning revealed no lymphoid or other metastasis.

Results: The treatment performed, under spinal anaesthesia, was modified vaginal hysterectomy, modified colpocleisis and posterior colpopereineorrhaphy, followed by external irradiation. Routine histological study of the uterus revealed the presence of invasive squamous carcinoma. The total operative time was 1 and a half hour. There were no intraoperative or postoperative complications. After 6 days, the patient discharged from our department. Two years after surgery, she is still alive, without any sign of disease.

Conclusions: Once a prolapsed uterus associated with an operable invasive cervical carcinoma is found, vaginal hysterectomy complemented with radiotherapy seems to be an adequate therapeutic option. The final postoperative result depends on the stage of carcinoma, presence or absence of metastasis and surgeon's ability.
POST OPERATIVE COMPLICATIONS IN HIV INFECTED PATIENTS UNDERGOING RADICAL HYSTERECTOMIES FOR CERVICAL CANCER AND THE VARIABLES TO PREDICT THEM

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Background: Early stage invasive cervical cancer is mostly treated with radical hysterectomy, but there are no literature comparing the outcome and complications of surgery in HIV positive patients. Post operative morbidity in HIV positive patients varies between 10 to 90%. Several markers have been used in an attempt to pre operatively predict the patient with the higher risk of adverse outcome post operatively.

Objective: To determine the incidence of complications in the HIV positive patients compared to HIV negative patients and the use of markers to predict them.

Method: Retrospective cohort audit from 1 January 2006 to 31 December 2009.

Results: Of the 153 radical hysterectomies done, only 23(15%) patients were HIV positive. The average age was 39.9 years. 43% were stage 1B1 and 83% had squamous carcinoma. 13 patients developed 20(43%) complications, with the most common UTI (53%), followed by wound sepsis (17%), pneumonia (17%) and vault abscesses (17%). There was no significant difference in the incidence of complications, hospital stay, hemoglobin values and highest temperature compared to HIV negative patients. In the patients with complications the %CD4 count was 17.86% and the WCC 5.5 x 10⁹/L compared to 23.4% and 7.2 x 10⁹/L in those who didn’t develop any. Viral load and albumine was not routinely done. HIV positive patients received more blood products during hospital admission.

Conclusion: Radical hysterectomy can be done in HIV positive patients with same complication rates as HIV negative patients, provided that the %CD4 count is more than 18% and the WCC more than 6 x 10⁹/L.
DOES HIV INFECTION RESTRAIN TREATMENT OPTIONS FOR PATIENTS WITH ADVANCED CERVICAL CANCER?

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Introduction: South Africa lies at the heart of the HIV pandemic. It affects all aspects of life including prevalence and mana management of cervivcal cancer. The research question was whether HIV infection derailed management of cervical cancer.

Methodology: The records of 50 consecutive patients HIV + with cervical cancer were compared with a concurrent group of 50 consecutive patients HIV - with cervical cancer. Standard treatment for advanced stage cervical cancer was given as chemoradiation.

Results: The presentation, staging, management and outcome of both groups were similar with the exceptions of the following:

HIV +: mean age 35 versus 55 in HIV - (p< 0.001)

HIV +: more pretreatment anaemia (40%) versus HIV - (20%) (p=0.02)

HIV +: less comorbid disease (26%) versus HIV - (46%) (p=0.37)

HIV +: More interruptions and incomplete treatment (48% versus HIV - (20%)(p=0.03)

Deaths and survival rates were not significantly different

Discussion and conclusion: Contrary to the expected outcome the findings showed that the two groups were largely the same and that treatment (although a bit more interrupted in HIV + patients) resulted in a comparable outcome. HIV infected status should not be regarded as a deterrent to treatment for cervical cancer.
CYTOLOGIC AND HISTOPATHOLOGIC DIAGNOSTIC MANAGEMENT IN EMBRYONAL Rhabdomyosarcoma of the Uterine Cervix

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Rhabdomyosarcoma (RMS) of the lower genital tract is a rare tumor. It can originate in childhood from the vagina, but in rare cases, RMS can arise in the uterine cervix, with a peak incidence in the 2nd decade. A case of a 21-year-old woman, presenting with vaginal bleeding, is reported. The clinical examination revealed a tumor located at the external os of the uterine cervix. The patient underwent a Pap test, followed by a biopsy and total hysterectomy with bilateral anexectomy. The cytologic exam revealed isolated tumor cells with enlarged irregular nuclei, some of them with sarcomatous differentiation features. As the cytologic aspects only suggested the presence of a high grade cervical lesion or a malignant entity, without the possibility of a precise diagnosis, a biopsy was recommended. The surgical specimens were paraffin-embedded and stained with Hematoxylin and Eosin. Immunohistochemical markers, such as: sarcomeric actin, vimentin and desmin were also performed. The histopathologic examination revealed an embryonal rhabdomyosarcoma, with small and spindle shaped cells, some of them with deep acidophilic cytoplasm; focally anaplastic features, with bizarre nuclear forms were noted. The highly cellular areas alternated with paucicellular regions, with abundant mucoid intercellular material. If the Pap test reveals characteristic cytologic features in cases of pure sarcomas, for rhabdomyosarcoma, it can be only suggested the malignant nature of the lesion, the accurate diagnosis being achieved by histopathologic examination. Despite the advanced diagnostic methods, like immunophenotyping and molecular genetic analysis, rhabdomyosarcoma represents, for pathologists, a challenge of diagnosis and prognosis.
INTERLABORATORY VARIABILITY IN THE ASSESSMENT OF CYTOLOGICAL SAMPLES IN ORGANIZED CERVICAL SCREENING PROGRAMME IN LUBLIN PROVINCE, POLAND

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Organized cervical screening programme with central internet-based electronic database was implemented in Poland in 2007. In Lublin province of Poland, cytological smears have been assessed by 12 cytological labs and reported in the Bethesda System.

The aim of the study was to analyze interlaboratory variability of cytological results obtained in the programme in Lublin province.

From 1st January 2007 until 31st December 2009 within a full 3-year screening interval 141,380 cytological smears were assessed. Smears classified as NILM, ASC-US, ASC-H, LSIL, HSIL and glandular pathology were diagnosed in 134,584 (95.19%), 3,821 (2.7%), 655 (0.46%), 990 (0.7%), 324 (0.23%) and 233 (0.16%) of cases respectively in all labs. Maximum interlaboratory differences for the percentage of diagnoses of NILM, ASC-US, ASC-H, LSIL, HSIL and glandular pathology was 5.07% (92.99%-98.06%), 5.24% (0%-5.24%), 1.79% (0%-1.79%), 3.41% (0.16%-3.56%), 0.45% (0%-0.45%), 0.44% (0%-0.44%) respectively. Rates of abnormal pap results differed significantly between laboratories (χ²=1388.6; p< 0.001). Reports of colposcopic/histological verification of abnormal results were unavailable for the most of women participating in the programme.

Although direct estimation of pap test sensitivity and specificity is not possible for all the cytological laboratories due to the lack of colposcopic/histological reports, profound interlaboratory variability in the assessment of pap smears may indicate potentially insufficient quality of cytological assessments in some laboratories.

External quality control of cytological assessment should be implemented in laboratories working in the organized cervical screening programme in Lublin province of Poland.
SURGICAL TREATMENT, WERTHEIM-MEIGS OF CERVICAL CANCER

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Objectives: The aim of the study was to estimate, distribution by stage of disease and comparison between clinical and postoperative stage of the disease in patients with invasive cervical cancer.

Materials and methods: 218 surgically treated patients with histologically verified invasive cervical cancer were included in the study.

Results: Most of the cases 41.2% were aged between 41-50. Most our cases 68.2% was in I b stage of the disease, 23.5% had II a stage and 8.3% of patients was in II b stage of cervical cancer. Surgically removed lymph nodes were positive in 24.2% cases in I b stage of the disease, 42.3% were positive in stage II a and in even 86.5% patients with II b stage of cervical cancer. Lymph-vascular invasion was present in 59.2% of all cases. In patients with negative lymph nodes we found 41.6% in lymph-vascular invasion which is a bad prognostic factor and was the reason for radiotherapy. Most of our patients had grade 2 (moderately differentiated) cancer - 69.2% then grade 3 (undifferentiated) 20.5% and grade 1 (well differentiated) - 10.3%.

Conclusions: The analysis of patients age shows the trend of increased incidence rate of invasive cervical cancer in younger females. Most surgically treated cases was in I b stage of the disease. Clinical stage higher then surgical was found in 14.1%, while in 21.6% it was lower.
RECURRENT CERVICAL CARCINOMA AFTER ROBOT-ASSISTED LAPAROSCOPIC RADICAL HYSTERECTOMY AND BILATERAL PELVIC LYMPH NODE DISSECTION

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Objective: The purpose of this study was to evaluate the cervical cancer recurrences of robot-assisted laparoscopic radical hysterectomy retrospectively.

Methods: 35 early stage cervical carcinoma cases were underwent robot-assisted laparoscopic radical hysterectomy between November 2005 and December 2009 at our institution. Data prospectively collected including age, body mass index (BMI), stage, estimated blood loss (EBL), perioperative blood transfusions, number of lymph nodes obtained, size of both parametrium and vaginal edge, status of surgical margins, length of hospital stay, intraoperative and postoperative complications and recurrences.

Results: None of the cases required conversion to laparoscopy or laparatomy. The mean age was 44.1 years (range, 32-73 years). The mean BMI was 25.4 kg/m² (range, 19-38). The mean length of hospital stay was 3.8 days (range, 2-6). The mean operation time was 263 minutes (range, 145-530). The mean EBL was 82 ml (range, 25-300 ml). The mean follow-up time was 30 months (range, 6-53 months). The mean number of pelvic lymph nodes was 19.5 (range, 9-35). The mean size of right parametrium, left parametrium and vaginal edge was 2.94 cm (range, 2-5), 3.01 cm (range, 2-5) and 1.68 cm (range, 0-3) retrospectively. 5 patients have developed recurrences minimum 16 months after surgery and one of the patient died due to an progressive disease.

Conclusions: Robot-assisted laparoscopic radical hysterectomy is feasible. We must proceed cautiously if a new modality appears to present an increased recurrence rate comparing with the other conventional modalities. Therefore robot-assisted laparoscopic radical hysterectomy will encourage an protocol setting until oncologic outcome data became available.
BORDERLINE SMEARS: IS THE CURRENT FOLLOW UP STRATEGY ADEQUATE?

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Objectives: To study smear follow up pattern in women with borderline smears and evaluate adequacy of current follow up strategies.

Methods: Retrospective cohort study. Women with borderline smears in 2001 were identified from cytopathology database and followed till 2006. Women were excluded if they had prior abnormal smear history. Progression rates to low grade and high grade disease as well as discharge rates to normal recall were noted. Survival analysis was performed using SPSS. Data was censored for women who did not progress and not completing recommended follow up.

Results: Of 1434 women, 25.6% had previous low grade (LG) histology or smear (mild/borderline) abnormality and 7.7% had previous high grade (HG) disease. 951 women were included for follow up study. Mean age was 38.24 (12.25) years. Median number of follow up smears was 3.0 (range 1-14). 486 women (51.1%) were discharged to normal recall. Loss to follow up rate was 36.7%; 10.2% women continued to have smear follow up at the end of the study period. Overall, out of 600 women with no prior smear abnormalities and completing follow up, 30 (5%) progressed to HG cytology; 75% of disease progression occurred within 48 months.

Conclusion: Regular cytological surveillance till 2 years is justified in women with borderline smears as majority of HG disease will be detected within this interval.
CERVICAL CANCER IN PREGNANCY- IS IT SAFE TO DELAY TREATMENT? EXPERIENCE FROM ST THOMAS’ HOSPITAL

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Background: Cervical carcinoma is the most frequent malignancy diagnosed during pregnancy. Treatment is challenging, as there are implications for the mother and foetus. There is lack of prospective evidence, and the experience of most clinicians is limited.

Aims: To discuss the management of 2 patients treated at our institution, with locally advanced cervical cancer presenting during pregnancy. Both elected to continue the pregnancy, and defer treatment.

Methods: Patient records and the available literature were reviewed, to identify factors to consider when managing these patients.

Results: The patients presented with bulky disease, with stages Ib2 and IIa2 squamous cell cervical carcinoma, and were in the second trimester. Both opted to defer oncological treatment, and underwent delivery at 32 weeks’ gestation. They received chemoradiation followed by intracavitary brachytherapy. At follow up of 24 months and 12 months, both patients were alive without disease recurrence and the children were well.

Conclusions: Locally advanced cervical cancer diagnosed in pregnancy can be managed by radical chemoradiation with sacrifice of the foetus, neoadjuvant chemotherapy whilst awaiting foetal viability, or planned delay with close surveillance. Data on treatment delay is sparse, and the decision depends on clinical stage, nodal status, histological subtype, gestational stage and the patient’s wishes. Patients should be counselled regarding the potential for disease progression during this time. We advocate deferred treatment in selected cases of locally advanced cervical cancer diagnosed after the first trimester, provided that there is close surveillance whilst awaiting foetal maturity, and encourage participation in the current prospective clinical trial.
THE RISK OF PELVIC FRACTURE AFTER RADIOTHERAPY IN PATIENTS WITH CERVICAL CANCER

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Background: Pelvic fractures are although rarely seen after radiotherapy (RT), it mimics the bone metastasis causing pain. In this study we evaluated the incidence and associated risk factors in patients treated with curative-intent radiotherapy for cervical cancer.

Methods: A total of 224 patients with cervical cancer were treated between January 2007 and April 2010, among these, 138 patients having at least one post-treatment computed tomography scan or magnetic resonance imaging study available were analyzed. In patients with bone pain, bone scintigraphy is also acquired in order to rule out bone metastasis. Patients were treated with conventional 1.8Gy doses with a total dose of 50.4Gy to pelvic region.

Results: Median age of patients was 59 years (ranged 29-90 years). Pelvic fractures were noted in 11 of 138 patients (7.9%). Eight patients (72%) were complaining about pain which was the most common presenting symptom. The median time from the completion of radiotherapy to the detection of fractures on imaging studies was 13.2 months (range, 7.1-29.2 months). All but one developed pelvic fractures within 2 years after completion of RT. 8 of 11 patients had co-morbid diseases including obesity and osteoporosis. Also all patients with pelvic fracture were post-menopausal. Patients with pelvic fracture were significantly elder than without fracture (72 years vs. 58 years; p = 0.002).

Conclusions: Pelvic fractures should be ruled-out from bone metastasis with similar clinical findings but different strategies. Since majority of patients were post-menopausal, bone mineral density screening should be considered in these women.
THE IMPORTANCE OF RECTUM DOSES FOR PREDICTING LATE RECTAL TOXICITIES IN PATIENTS TREATED WITH CERVICAL CANCER BRACHYTHERAPY


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Background: Rectal toxicity is a dose-limiting complication during the treatment of gynecological tumors treated with external radiotherapy (ERT) and brachytherapy (BRT). We analyzed the correlation between rectum doses and late rectal complications.

Materials and methods: The clinical and dosimetric data of 53 patients treated with curative cisplatin based ERT (50.4 Gy) and BRT (4x7Gy) were evaluated. Conventional Point A plan (CV) was performed for 32 patients (60%) and conformal BRT plan (CF) was performed for 21 patients (40%). International Commission on Radiation Units and Measurement (ICRU) rectum point dose was measured for conventional plan; maximum dose received by a contiguous 2 cm$^3$ and 5 cm$^3$ volumes (D2cc and D5cc) were evaluated for conformal plan.

Results: With a median follow-up of 18.2 months (8.4-41.2 months), late rectal toxicities were seen in 15 patients (28%). 10 patients treated with CV (31%) and 5 patients with CF (24%) had late rectal toxicities. In CV, ICRU rectum point doses were found to be higher in patients with late toxicity compared to that without rectal toxicity (5.06Gy±1.09Gy vs. 4.14Gy±0.86Gy; p=0.06). Likewise, in CF, D2cc (7.21Gy±1.09Gy vs. 5.65Gy±0.76Gy; p=0.08) and D5cc (6.77Gy±1.45Gy vs. 5.53±0.76; p=0.09) were found to be higher in patients having rectal toxicity compared to no toxicities.

Conclusions: ICRU rectal point dose in conventional plan and D2cc-D5cc in conformal plan were predictors for rectal toxicities. Although the difference was not significant, it was close to the level of significance. Longer follow-up and randomized studies are warranted for better evaluation.
PROGNOSTIC ANALYSIS FOR CERVICAL CANCER PATIENTS WITH PELVIC LYMPH NODE METASTASIS

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Objectives: Lymph node metastasis is an important route by which cervical carcinoma can spread and one of the most important prognostic factors. For the patients with early stage cervical cancer, the 5-year survival rate may exceed 50% with the evidence of lymph node metastasis. The objectives of this study were to evaluate the prognosis for the cervical cancer patients with pelvic lymph node metastasis.

Method: 210 women with stage IB-IIB cervical carcinoma histologically proven involved pelvic nodes were analysed. Univariate and multivariate analyses using the Cox regression model were performed to determine the prognostic significance of some clinicopathologic factors and the expressions of ER, PR, neu, P53, nm23, bcl-2, cyclin D1, TOPOII and GST.

Results: The 5-year overall survival (OS) and disease-free survival (DFS) were 58% and 56% respectively. In a univariate analysis, an old age (≥ 44 years, P = 0.008), stage II disease (P = 0.043), non-squamous cell carcinoma (P < 0.001), parametrium invasion (P = 0.008), lymph vascular space invasion (P = 0.023) and positive nm23 expression (P = 0.017) were associated with significantly decreased survival. The patients with multiple lymph nodes metastases had similar 3-year OS of patients with one lymph node involved (74% vs 75%), but their 5-year OS decreased significantly (54% vs 74%). In the multivariate analysis, non-squamous cell carcinoma and positive nm23 expression were significant and independent prognostic factors of OS.

Conclusion: Non-squamous cell carcinoma and positive nm23 expression are predictive of worse OS for cervical cancer patients with pelvic lymph node metastasis.
FULL-DOSE CHEMORADIATION IN ADVANCED CERVICAL CANCER PRIMARY TREATMENT

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Background: New anti-tumor drugs and technological achievements in radiotherapy (RT) equipment development are definitely important for advanced cervical cancer (ACC) treatment, but long-term results depend on their optimal integration.

Purpose: To evaluate clinical efficacy and safety of two programs of chemoradiation with full-dose chemotherapy.

Patients and methods: 112 pts., 16-67 y.o., T2a-3bN0-1Mo, underwent pelvic irradiation after 78(69.6%) - A or concomitantly 34 (30.4%) - B with full-dose chemotherapy (CHT), cis-carboplatinum, taxans, gemcitabine, 5FU, cyclophosphamide, bleomycin, doxorubicin in 2-4 drug combinations, 2 cycles in 87%. 14 (12.5%) LN-positive pts. received paraaortic irradiation. G-CSF (Leucostim®, Biocard, Russia) 600mcg weekly and erythropoietin (Epostim®, Bio-Progress, Russia) were injected to prevent predicted hematological toxicity. 2D-3D ultrasound was used for HR-CTV monitoring.

Results: No CR, PR > 75% - 12.8%, progression - 17.9% after neoadjuvant CHT. Pre-planned course of RT was completed in 104 (92.8%) [A-74(94.9%), B- 30(88.2%)], with IR-CTV doses lower in A vs B: 62-66Gy - 33 (42.3%) vs 6 (17.6%), 67-70Gy - 31 (39.7%) vs 18 (52.9%), 71-75Gy - in 10(12.8%) vs 8 (23.5%), 76-81Gy - y 4(5.1%) vs 2 (5.8%). Treatment was safe in both groups, more tolerable in A vs B (no breaks: 20(25.6%) vs 2(5.8%); break duration 7±3.4 vs 12.5±5.4 d., toxicity ≥ II grade RTOG in bladder 15.4% vs 23.5%, intestinum 17.1% vs 41.1%, haematological - 32.1% vs 73.5%. 5 year OS 88 (75.9%) [A- 62 (79.8%), B- 23 (67.6%)], DFS 81 (72.3%) [A- 60 (76.9%), B - 21 (62.4%)]

Conclusion: Full-dose chemoradiation is effective and safe for ACC treatment.
MOLECULAR TESTING OF SELF-COLLECTED TAMPONS: A FEASIBLE WAY TO TRIAGE YOUNGER WOMEN AND SCREEN OLDER WOMEN IN THE DEVELOPING WORLD

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Introduction: There is a need to simplify cervical cancer screening in the developing world. Tampon sampling has been shown to render equal results to physician collected cervical samples when tested for high risk human papilloma virus (hrHPV). This method has not been evaluated in our urban population.

Objectives: This study aims to predict the efficacy of molecular cervical cancer screening on self collected tampon samples, HPV type distribution and the incidence of cytological abnormalities in women with high risk HPV.

Methods: We report a prospective descriptive study of 261 patients between the ages 25 and 75 years. HPV DNA genotyping was performed on tampon collected specimens.

Results: The prevalence of high risk HPV DNA positivity was 56%. The incidence was 32% in the youngest group (< 35 years) and 16% in women over 55 years. HPV types 45, 51, 16 and 18 were the most frequent types. The overall incidence of abnormal cytology was 14% and the age group above 55 years had the highest incidence (22%). In patients who were negative for hrHPV, 96% had normal cytology.

Conclusion: We found HPV DNA testing of self collected samples a feasible way to triage women in this population with an excellent negative predictive value. This method was an effective primary screening test for older women with a higher incidence of cytologic abnormalities and a lower incidence of HPV.
NEOADJUVANT REGIONAL INTRAARTERIAL CHEMOTHERAPY WITH THE USE OF IRINOTECAN IN PLATINUM-CONTAINED COMPLEXES IN TREATMENT OF CERVICAL CARCINOMA PATIENTS

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Purpose: To study efficacy of neoadjuvant regional intraarterial chemotherapy with the use of combination of Irinotecan and Platinum derivatives for treatment of cervical carcinoma patients.

Materials and methods: 36 patients with cervical carcinoma of T1b2-T3b stage received intraarterial chemotherapy as the first line therapy: Irinotecan 100 mg/m² and Cisplatin 50mg/m² or Carboplatin AUC 5.

T1 b2 stage was diagnosed in 3 patients, T 2a-b in 11 patients, T 3b in 22 patients.

9 initially inoperable patients with cervical carcinoma of T1b2 - T2a-b stages received neoadjuvant regional intraarterial chemotherapy and as a result they underwent radical surgery. At the second stage of treatment the Vertgame’s surgery was performed for them. 27 patients with T2b - T3b stages underwent combined radiation therapy at the second stage of treatment after regional intraarterial chemotherapy.

Results: Efficacy of intraarterial chemotherapy was evaluated based on gynecologic examination, data of ultrasound monitoring, MRI, morphologic study of medicinal pathomorphism. All patients had clinical tumor regression and hemostatic effect. The complete clinical effect was observed in 7 patients after the given intraarterial chemotherapy, partial effect - in 27 patients, stabilization was noted in 2 patients. In a result of morphologic study after regional intraarterial chemotherapy of medicinal pathomorphism, the first grade was seen in 6 patients, the second grade - in 22 patients, the third grade in 7 and the fourth grade in 1 patients.

Conclusions: The use of neoadjuvant intraarterial chemotherapy with Irinotecan in a combination with Platinum derivatives in cervical carcinoma patients is highly efficient.
BLADDER, ANORECTAL AND SEXUAL FUNCTION AFTER NERVE-SPARING RADICAL HYSTERECTOMY FOR THE TREATMENT OF CERVICAL CANCER; A LONGITUDINAL PROSPECTIVE COHORT STUDY

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Background: Conventional radical hysterectomy (RH) for early stage cervical cancer (CxCa) is associated with significant bladder, anorectal and sexual dysfunction. Nerve-sparing modification of RH (NSRH) has been developed with the aim to reduce surgical treatment related morbidity. The aim of this study was to prospectively assess morbidity in patients after the NSRH compared to the patients after a conventional RH.

Methods: Bladder, anorectal and sexual complaints were assessed by the Gynaecologic Leiden Questionaire (LQ). From 1998 until 2007 patients completed the LQ before, 12 and 24 months after treatment. From 2003 the NSRH was the standard surgical treatment.

Results: Included were 229 women with CxCa of which 123 had had NSRH and 106 a conventional RH. Forty-one percent had adjuvant radiotherapy. Up to 2 years of follow-up, women reported significantly more pelvic visceral and sexual complaints compared with pre-treatment. No significant differences could be demonstrated between the conventional RH and NSRH for any of the complaints with exception of an unexpected finding that a smaller percentage of the women in the NSRH group (37% versus 64%) complained about numbness of the labia (p< 0.001). Up to 2 years adjuvant radiotherapy had a negative impact on lymphedema, urinary incontinence, diarrhoea and narrow vagina.

Conclusion: In the current longitudinal cohort study, treatment for CxCa was associated with worse subjective bladder, anorectal and sexual functioning, irrespective of the surgical procedure used. Adjuvant radiotherapy deteriorated dysfunctions. The results have to be interpreted with caution in view of the study design and method used.
18F-FDG PET/CT AS A SELECTION TOOL FOR SALVAGE SURGERY OR IMAGE-GUIDED RADIOTHERAPY IN PATIENTS WITH RECURRENT OVARIAN CANCER

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**Purpose:** Recent results showed the clinical feasibility of intensity-modulated whole abdominal radiation therapy, which could offer a therapeutic option for consolidation treatment in patients with residual/relapsed ovarian cancer (ROC). To evaluate the additional impact of F-18 FDG PET/CT imaging as a selection tool for salvage surgery or radiotherapy in patients (pts.) with suspected ROC.

**Material/methods:** 110 contrast enhanced whole-body PET/CT examinations of 69 pts. with ROC after first-line therapy were enrolled and analyzed. Studies were interpreted conjointly by two nuclear medicine physicians and two radiologist followed by a presentation of the imaging findings at the tumor board committee and a decision of further therapeutic management of the patients.

**Results:** In 19% of the examinations no recurrence, in 81% a localized focal FDG-uptake (SUV\textsubscript{mean} > 2.0) was visualized (i.e. 25% regional relapse, 75% systemic tumor spread). No correlation between PET findings and CA-125 levels. (p>0.05). No close correlation between tumor volume as detected by PET and CA-125 levels (p > 0.05), in 50% of the pts. pathological PET/CT findings with CA-125 levels < 35 U/ml during median follow-up of 3.5 ys.

**Conclusion:** Our data suggest to use F-18 FDG PET/CT as a selection tool for salvage surgery or high precision radiotherapy in patients with recurrent ovarian cancer; additionally PET/CT is helpful for defining gross tumour volume, either prior to surgery or for radiotherapy planning, i.e. in the determination of the target volume after virtual PET/CT simulation.
WHAT IS THE ADDITIONAL ROLE OF 18F FDG-PET/CT ON THERAPY MANAGEMENT DURING FOLLOW UP IN BREAST CANCER?

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Objective: Detection of distant and regional lymph node metastases with conventional diagnostics (ultrasound, CT, MRI, bone scintigraphy) in patients with breast cancer have a lower sensitivity and specificity as compared to F¹⁸ FDG PET/CT. To analyze the additional role of whole body PET/CT in patients with breast cancer during follow-up, 80 patients were analyzed prospectively.

Material/methods: In addition to conventional diagnostics (CD) F ¹⁸ FDG PET/CT was applied during follow-up. Inclusion criteria: completed first line therapy, rising tumor markers, clinical findings and CD suspicious for relapse. Exclusion criteria: inflammatory breast cancer, time between radiotherapy and PET/CT < 6 months, time interval between surgery and PET/CT < 3 months. Maximal time for follow-up 72 months.

Results: Same diagnostic results (PET vs. CD): 25/80 (31%). Detection of new tumor manifestations by PET: 55/80 (69%). False negative PET result 4/55 (7%) as correlated by histology. Treatment decisions based on PET: palliative intention 49/55 (71%), potentially curative (single distant focus in liver and bone 3/39), salvage therapy 16/55 (29%).

Conclusion: Molecular imaging by whole body F-18 FDG PET/CT as a single diagnostic procedure is a valid, precise and effective method for adequate surveillance of patients after primary breast cancer therapy. It may be used for therapy management (surgery salvage therapy vs. palliative) as well as for radiation treatment.
WHOLE-BODY DIFFUSION-WEIGHTED IMAGING USED IN PREOPERATIVE EVALUATION OF CERVICAL CANCER AND LYMPH NODE METASTASIS - ANALYSIS OF 31 CASES

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Objective: To investigate the feasibility of whole-body diffusion-weighted imaging (WB-DWI) in detecting cervical cancer and distinguishing metastatic lymph nodes from nonmetastatic lymph nodes.

Methods: Between January 2007 and October 2009, 31 patients scheduled for pelvic lymph node dissection/biopsy underwent WB-DWI. We measured mean apparent diffusion coefficient (ADC) of cervical tissue and suspected nodes. A lymph node with an ADC value less than 1.0 ×10⁻³ mm²/s and MR image abnormalities, was considered as a metastatic one. WB-DWI findings were compared with pathologic results as a reference standard.

Results: The mean age of 31 patients was 39.2 (22-54). The mean ADC of cervical cancer (0.94±0.17X10⁻⁶ mm²/s) was significantly lower than that of normal cervical tissue (1.73±0.14X10⁻⁶ mm²/s; p< 0.05). Except for one case with a 0.6cm undetected lesion, the accuracy rate of WB-DWI in detection of cervical cancer was 96.8%. WB-DWI detected metastatic lymph nodes in 11 cases. However, in 2 of them, metastatic lymph nodes were found to be ovarian endometriosis cysts. DWI showed no metastasis in 20 cases, one of which was pathologically confirmed to have one metastatic lymph node (0.74cm). The sensitivity and specificity of WB-DWI in detecting lymph node metastasis were 90.0%, 90.5%, respectively. The positive and negative predictive value were 81.8% and 95.0%, respectively.

Conclusions: Whole-body diffusion-weighted imaging (DWI) is an effective method for detecting cervical cancer and an alternative method for distinguishing metastatic lymph node with high sensitivity and specificity. A further multi-center prospective study is required to verify these results.
EVALUATION OF ROLE OF FDG-PET/CT IN STAGING AND MANAGEMENT OF OVARIAN MALIGNANCIES

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Background: Staging of ovarian cancer is surgicopathological and requires a maximal surgical effort that is often associated with considerable morbidity. Accurate preoperative estimation of staging can help select women who may benefit from neoadjuvant chemotherapy.

Aim: To evaluate the diagnostic accuracy of PET/CT and CECT in staging of ovarian cancer, with surgicopathological findings as the reference standard.

Methods: 20 women aged 20-65 years, with a preoperative diagnosis of ovarian cancer and planned for primary cytoreductive surgery were invited to participate. Exclusion criteria were: Uncontrolled diabetes; pregnant/ lactating; recurrent cancer; contrast allergy. All participants underwent FDG-PET/CT and CECT followed by laparotomy. The surgeon was blinded to the results of imaging till operation findings were declared.

Results: Standardised Uptake Value of primary detected lesions ranged from 3 to 15.8 (mean 8.8; median 7.7) FDG-PET/CT and CECT were concordant with final pathological staging in 79% and 74% cases, respectively. Sensitivity, specificity and accuracy for detection of lymph nodes by FDG-PET/CT were 100%, 81.3% and 85% respectively; of CECT were 50%, 87.5% and 80% respectively. Sensitivity for detection of deposits in omentum, peritoneum, liver surface and undersurface of diaphragm were all 100%. PET additionally correctly upstaged 2 cases from Stage IIIC to Stage IV by detecting metastases to extra-abdominal lymph nodes, liver and lungs.

Conclusions: PET-CT can increase the accuracy of pre-treatment staging of ovarian cancer compared with CECT, thus identifying patients with Stage IIIC-IV disease in whom optimal debulking is not likely, who may benefit from neoadjuvant chemotherapy.
ROLE OF TRANSVAGINAL ULTRASOUND IN THE FOLLOW UP OF PATIENTS TREATED WITH CONSERVATIVE SURGERY FOR OVARIAN BORDERLINE TUMORS

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Objective: Fertility-sparing surgery has been proposed for the treatment of borderline ovarian tumors (BOT). Relapse generally seems to be increased if a fertility sparing approach is chosen: 25% versus 5% in radically operated women. The aim of this study was to assess the diagnostic value of TVS in the follow up of patients submitted to conservative treatment.

Methods: We retrospectively reviewed the data of 31 patients treated for BOT and follow up in 2 institutions. Inclusion criteria were at least 2 scan and a follow up period > 6 months. TVS findings of; ovarian lesions, tumor recurrences, site and sonographic characteristics of recurrences were evaluated. Specific prognostic factors such as; stage, histology, micropapillary subtype, exophytic tumor growth, intraoperative spillage, and route of surgery were analyzed and correlated with TVS findings.

Results: The median duration of follow-up was 59 months (range 6-120) with a mean number of scan of 5.2(2-15). 16 patients had serous, 13 mucinous and 2 serous/mucinous BOT. 4 patients underwent cistectomy (CYS), 18 unilateral salpingo-oophorectomy (USO), and 9 radical surgery (RS). 2 patients in the CYS group (50%), 4 in the USO group (22%), and 1 (11%) in RS showed a lesion at TVS suggestive for recurrence. In all cases the relapse was confirmed by histology. 4 patients had a recurrent borderline tumor exclusively on the remaining ovary, 3 had developed a recurrence on the ovary and pelvic peritoneum.

Conclusions: TVS seems to be a reliable diagnostic tool for the monitoring of young women treated conservatively for BOT.
THREE DIMENSIONAL ULTRASOUND TO ASSESS THE NEO-ADJUVANT CHEMOTHERAPY RESPONSE OF LOCALLY ADVANCED CERVICAL CANCER

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Objective: To estimate the potential role of 3D ultrasound (3D-US) in establishing tumor volume as an assessment of neoadjuvant chemotherapy (NACT) response, in patients with locally advanced cervical carcinoma (LACC).

Methods: A prospectively stored 3D power Doppler volume data from 28 women with a diagnosis of LACC, submitted to 3 cycles of NACT followed by surgery, were examined. MRI was performed before the first cycle of NACT and 10 days before surgery. The 3D-US was performed within 3 days after each cycle. We visualized presence of hydrouretheronefrosis, and enlarged pelvic lymph nodes; we identify tumor with a gray-scale analysis as a hypo-isoechoic lesion with irregular borders. The vessels traversing the tumor were investigated. Vaginal, parametrial, bladder, and rectum infiltration was evaluated. Sections were taken and the volume was computed automatically by the VOCAL software.

Results: At histology, 3 patients had stable disease, 19 had a partial response, and 6 had a complete response. In 1 patient with a partial response, the 3D-US and MRI couldn't both show the residual tumor. The sensibility and specificity of 3D-US regard was 81% and 75% respectively. The sensibility and specificity of MRI-scan was 75% and 57% respectively. At 3D-US, tumor volume reduction was higher between the first and second cycle of NACT than between the second and third with a median volume difference of 9 cm³ (range 20-2) and 1 cm³ (range 13-0.5) respectively.

Conclusion: 3D-US is useful in predicting tumor response to NACT in LACC patients and in identifying the responders to chemotherapy.
THE ROLE OF ULTRASOUND IN PELVIC RELAPSE OF PATIENTS TREATED FOR EPITHELIAL OVARIAN CANCER

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Objective: The aim of this study was to assess the usefulness of transvaginal sonography (TVS) in detecting pelvic relapse of patients optimally treated for epithelial ovarian cancer (EOC).

Methods: A prospective study of patients with EOC pelvic relapse was conducted between January 2006 and January 2009. Eligibility criteria was disease free interval >6 months. Women were submitted to clinical examination, Ca125 level, and TVS every 3 months for 2 years after primary treatment, then at intervals of 6 months. FDG-PET/CT was carried at 6 months intervals for the first 2 years and then each year. The site and sonographic characteristics of recurrences were evaluated.

Results: 18 patients out of 55, had a pelvic relapse. 10 patients had also an extrapelvic recurrence, of which 6 had carcinomatosis. The median follow-up was 16 months(range 6-33), with a mean number of TVS was 5(range1-13). All suspected pelvic recurrences were detected by FDG-PET/CT, except in 5 cases where first diagnosis of relapse was made by TVS, and in 2 cases where the diagnosis was carried out by physical examination. At TVS, the recurrences were solid mass, with irregular margins and abundant vascularisation; the mean diameter was 4.5cm(1-13cm). In 3 cases the TVS was not able to visualize the pelvic recurrence, even though FDG-PET had remarked it. In undetectable cases the mean diameter of the pelvic recurrence was < 0.8cm (0.5-1.2cm).

Conclusion: TVS represents an available diagnostic tool for monitoring the pelvis of EOC patients. TVS was not able to detect lesions < 1cm
RISK OF MALIGNANCY INDEX: HOW FEASIBLE IS IT TO CALCULATE THE SCORE?

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Introduction: Multiple guidelines recommend RMI-based triage of women with a suspicious adnexal mass to a Gynaecologic Oncologist (GO) for primary surgery. This study evaluated the feasibility of RMI-based triage in Canada based on current practices of CA-125 measurement and ultrasound (US) reporting.

Methods: Charts from all patients with an adnexal mass seen in a tertiary centre GO practice from 2005-2009, excluding patients with known ovarian cancer, prophylactic surgery candidates, or those without an US evaluation, were retrospectively reviewed to confirm menopausal status, CA-125, and US results. For each US, each of the 5 RMI morphology features (multilocularity, bilaterality, solid components, ascites, metastases) were classified as “reported/present,” “reported/absent,” or “not reported.” US reports were considered complete only if they reported all 5 features. We compared the proportion of complete US reports from external vs. internal sources (Fisher’s exact test), and determined the proportion of patients for whom an RMI score was calculable.

Results: 369 patients were eligible. CA-125 levels were determined in 53% prior to GO referral (84% overall). US reports were complete in only 7.7% of patients (external-5.9%, internal-10.4%, p=0.08), although some of the remaining US reports contained enough information to reliably assign an RMI US score (external-44.8%, internal-33.3%, p=0.04). An overall RMI score could only be calculated in 35.6% of patients.

Conclusions: The high rate of incomplete US reporting and non-routine measurement of CA-125 renders RMI-based triage for primary surgery by GO inconsistently feasible in the Canadian context. Further studies should explore the potential benefits of synoptic reporting of US and CA-125 results.
ULTRASOUND IN DIAGNOSIS OF NEW AND RECURRENT BORDERLINE OVARIAN TUMORS

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Our aim was to assess the histology of recurrent ovarian masses in patients with conservatively treated borderline ovarian tumors (BOT), to determine the ability of ultrasound to diagnose new and recurring BOT, and to assess differences in ultrasound variables between new and recurrent BOT. The gold standard was the histological diagnosis of the ovarian mass. 20 patients with a history of BOT and an ovarian mass and 93 patients with newly diagnosed BOTs, participating in an international multi-center ultrasound study on ovarian masses (IOTA phase 2), were included. In 17 (85%) patients with a previous BOT, a recurrent BOT was found. In the remaining 3 cases (15%) the recurrent tumor was benign. All recurrent BOT histotypes matched the primary BOT. No BOT recurred as invasive primary tumor or with invasive peritoneal implants. Subjective assessment of ultrasound findings was a better method for identifying BOT in patients with a history of BOT than in patients with newly diagnosed BOT (sensitivity 76% [13/17] vs. 41% [38/93]). Patients with BOT recurrence were younger (median 35 years vs. 53) and had smaller tumors (median 41 mL vs. 548) with more papillations (mean 2.06 vs. 1.44) than patients with newly diagnosed BOT. The early ultrasound diagnosis of recurrence permitted conservative treatment of recurrence in 65% [11/17] patients. In conclusion, BOT history is a strong predictor of BOT in a recurrent ovarian mass. US is highly accurate in diagnosing BOT recurrence and can be used for follow up after fertility sparing procedures where early diagnosis of recurrence is essential for conservative treatment.
ANALGESIC EFFICACY OF FORCED COUGHING VERSUS LOCAL ANESTHESIA DURING CERVICAL PUNCH BIOPSY

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Objective: To compare local anesthesia (LA) and forced coughing (FC) in terms of subjective pain perception during cervical punch biopsy.

Methods: In this randomized, controlled trial, 114 patients (mean age: 38.9±9.0 years) scheduled for colposcopically-directed cervical punch biopsy were randomly assigned into LA (n=39); FC (n=39) and control (n=36) groups. Pain perception during cervical punch biopsies was measured on a 10-cm visual analog scale (VAS) during the insertion of the speculum, injection of the local anesthetic to cervix, the first cervical biopsy taking and the overall pain perceived during the entire procedure. Additionally, age, obstetric history (numbers of gravidity, parity and prior fractional curettage), reproductive stage (pre/postmenopause), indication for the current biopsy and duration of the entire intervention were recorded for each patient.

Results: There was no difference between the experimental groups in terms of age, numbers of gravidity, parity and prior curettage whereas 57.1% of the postmenopausal patients were randomized to the LA group (p=0.036). Pain score obtained during the first cervical biopsy was significantly lower if LA was applied (p=0.016). Groups were similar in other pain sub scores. Duration of the entire procedure was significantly longer (p< 0.001) in LA group, while it was not significantly different in FC patients compared to controls.

Conclusion: In conclusion, LA but not FC provides significant pain relief during cervical biopsy. Based on similarity to control data in terms of pain relief and shortening of the operation, FC per se seems related neither to pain relief nor a faster cervical biopsy.
THE ADDED VALUE OF A SENIOR ADULT ONCOLOGY PROGRAM FOR ELDERLY WOMEN WITH GYNECOLOGIC CANCERS

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Introduction: We successfully applied for national funding to set up a senior adult oncology program, cancer occurring frequently in patients over 70. A mobile team was brought together consisting of a geriatrician, a nursing coordinator, two nurses, a dietician, a clinical pharmacist and a social worker. Expertise of an occupational therapist and a neuropsychologist is readily available.

Objective: Assessing the patient's ageing profile at the time of cancer diagnosis.

Methods: After one year of the program, we report the results of 34 patients, older than 65, treated for pelvic gynecological malignancies. The nurse does the G8 screening to identify potential geriatric problems. If the score is 14 or lower, a comprehensive geriatric assessment (CGA) is completed. Based on the findings of the CGA and the Charlson comorbidity index, the geriatrician determines the profile of the patient and makes recommendations on geriatric issues.

Results: The mean age is 80.6 years. Tumor localization is: ovary (n=4) - cervix (n=12) - uterus (n=14) - vulva (n=4). The patients profiles are: fit (n=16) - vulnerable (n=15) - frail (n=3). Half the patients assessed were either vulnerable or frail. Problems identified were risk of malnutrition, functional decline, depression and a poor social network, factors that influence tolerance of cancer treatment.

Conclusion: Determining the profile of the senior adult at the time of staging of the tumor should be considered good medical practice. It enables the gynecologist to establish a personalized care plan taking into account the fact the patient is robust, vulnerable or frail.
18F-FDG PET CAN IDENTIFY TUMOR RELAPSE IN OVARIAN CANCER PATIENTS (PTS) WITH NEGATIVE SERUM MARKERS LEVELS?

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Non-invasive surveillance procedures in pts with ovarian cancer after primary treatment and NED are still debated and several criticisms have been raised on the reliability of CA 125 as a marker for recurrence. We studied the accuracy of 18-F FDG PET scan (PET) in pts with ovarian cancer after primary treatment. We retrospectively evaluated 62 females during follow-up after surgery + chemotherapy with 130 PET (76PET/CT) and CA 125. In 55 studies PET was performed in pts with negative marker and clinical suspicious of relapse; in the remaining 75, pts presented progressive rising or high CA 125 (NED or negative/doubtful radiological investigations). Sensitivity, specificity, and accuracy of PETs were based on clinical follow-up (all pts) and US/CT/MR scan (44 pts).

About the discordant results, in 12/13 cases PET correctly detected recurrences, in 16/19 PET failed, in 3/19 PET indicated an early response to therapy. PETs showed 7 supra-diaphragmatic district lesions and 25 in liver, lung, bone. PET and CA 125 TP, TN, FP, FN results were 68, 45, 1, 16, and 72, 43, 3, 12 respectively. PET sensitivity was 81%, specificity 98%, accuracy 87%, while PPV and NPV resulted 99% and 74% respectively.

PET is an useful tools to plan the best treatment when CA 125 progressively raises. PET can identify tumor relapse also in pts with negative serum markers levels. PET can fail the detection of very small lesions and serosal (peritoneal/mesenteric) metastases (especially near to physiological intestinal uptake).

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<th>PET+</th>
<th>PET-</th>
<th>TOTAL</th>
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<tr>
<td>CA 125+</td>
<td>56(43%)</td>
<td>19(15%)</td>
<td>75(58%)</td>
</tr>
<tr>
<td>CA 125-</td>
<td>13(10%)</td>
<td>42(32%)</td>
<td>55(42%)</td>
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<tr>
<td>TOTAL</td>
<td>69(53%)</td>
<td>61(47%)</td>
<td>130(100%)</td>
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[Table 1]

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IMAGING APPEARANCES OF RECURRENT CERVIX CANCER FOLLOWING UTERUS CONSERVING SURGERY (TRACHELECTOMY)

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Purpose: The purpose of this exhibit is:

1. To outline the role of MRI in predicting the feasibility for trachelectomy
2. To review the MRI appearances after trachelectomy
3. To gain awareness of the patterns of tumour recurrence post -trachelectomy

Content: We will review the essential criteria on MRI used to predict the feasibility of uterus conserving surgery. The typical MRI appearances after trachelectomy that should be recognised as normal and not recurrent disease will be illustrated. Using supportive data from our own institution, the CT and MRI appearances of recurrent disease following trachelectomy with clinico-pathological correlation will be described.

Summary: The major teaching points of this exhibit are:

1. MRI is an invaluable tool in assessing feasibility for fertility preserving surgery
2. Understanding the typical MRI appearances after trachelectomy are important to avoid misinterpretation
3. MRI surveillance is important to detect recurrence
4. Recurrence can be either local or distal and imaging follow up should be tailored accordingly
UTERINE GIANT TUMOR-DIFFERENTIAL DIAGNOSIS DILEMMA AND MANAGEMENT: A CASE REPORT SERIES

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Introduction: Giant tumors of the uterus are uncommon, particularly in developed countries. Large uterine tumors may compress the urinary bladder and ureters with great potential for renal damage if not treated. When pelvic mass is discovered, careful examination and radiographic imaging are imperative to arrive at the correct diagnosis.

Case report: Three postmenopausal female patients, age 69, 57, and 43 were treated at the Oncology Institute of Vojvodina because of huge abdominal tumor. Abdominal distension, pelvic discomfort, disturbed bowel movement, constipation, and urinary symptoms were the main symptoms. Preoperatively all three patients were examined by US and CT or MRI. In first patient, CT of abdomen and small pelvis confirmed tumor mass which completed whole abdominal space without signs of infiltration in surrounding structures. In other two patients, MRI showed tumor mass which completed whole abdominal space with compression of left urether and kidney, and combination of paraaortic and paraaortal lymphadenomegaly. Abdominal hysterectomy with bilateral salpingo-oophorectomy were performed in all three cases. Evacuated tumors were 18 kg, 5.5 kg, and 3 kg weight and 40 cm, 26 cm, and 23 cm in length. The histological examination verified a degenerated uterine leiomyoma with cystic lesions and necrosis, with no evidence of malignancy.

Discussion: In similar cases it’s necessary to exclude other abdominal tumors such as sarcoma, malignant and benign ovarian tumors, retroperitoneal leiomyosis, schwannoma, and intestinal tumors. The atypical appearances that follow degenerative changes are common in huge tumor mass and may cause confusion during diagnostic procedure. Definitive diagnosis could be confirmed only by detail pathological examination of removed tumor. Surgical complication may be very serious in their nature, and those cases should be treated only by experienced and well-trained surgeons.
FDG-PET/CT FINDINGS IN CORRELATION WITH LAPAROSCOPY IN ADVANCED OVARIAN CANCER STAGING: USEFULNESS AND LIMITS

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Objective: The aim of the study is to assess the value of PET/CT scan findings compared to laparoscopy to predict optimal cytoreduction in advanced ovarian cancer.

Methods: Prospective analyses of forty cases with advanced ovarian cancer submitted to diagnostic laparoscopy and PET-CT scan in University teaching Hospital, Department of Gynecology. Patients were submitted to diagnostic laparoscopy. The diffusion of ovarian cancer was reported on an abdominal sketch and it was assessed in 9 different areas. All patients were submitted to PET-CT scan with the same assessment procedure.

Results: Three hundred sixty quadrants were evaluated. In 14/360 areas (3.8%), surgical evaluation was not possible because of widespread adhesions. Negative laparoscopic findings and negative PET/CT data were observed in 26/346 areas (7.5%), while positive laparoscopic findings and positive PET/CT data were observed in 243/346 areas (70.2%); therefore true results were confirmed in 269 areas (out of 346 laparoscopic evaluable sites: 77.7%). False results were observed in 22.3% of cases, because of 12/346 false positive PET/CT results and 65 false negative PET/CT findings. False positive PET/CT findings were evenly present in all quadrants. False negative PET/CT findings were present in 31 out 109 (28.4%) explorable upper abdominal areas. Final analysis sensitivity and specificity for PET/TC scan was 78.9% and 68.4%, respectively.

Conclusions: Our results suggest that laparoscopy is the gold standard for assessing the abdominal spread of advanced ovarian cancer; PET/CT can not be considered a valid alternative tool to predict optimal cytoreduction in advanced ovarian cancer.
DEPENDENCE OF LYMPH NODE COUNT BY LAPAROSCOPIC LYMPHADENECTOMY FROM THE EXAMINING PATHOLOGIST

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Objectives: Lymph node number as benchmark in gynaecologic oncologic operations depends on patient's anatomy, surgeon's skills and pathologist's accuracy. The influence of the examining pathologist is barely evaluated.

Material and methods: Retrospective analysis of lymph node number was done after 700 standardised laparoscopic pelvic and/or paraaortic transperitoneal lymphadenectomies (LAE) in correlation to the examining pathologists between 10/2004 and 2/2010. Three surgeons performed or supervised all the operations in two Campus of Charité University Medicine Berlin with 2 separately working pathologic institutions. The appropriation of the removed lymph node specimen to any of 62 involved pathologists was randomly chosen.

Results: All 3 surgeons had an equal mean number of lymph nodes. Lymph node specimens were analyzed in pathological institutes I and II in 416 and 284 cases, respectively. The mean number of lymph nodes was 36 in Campus II and 30 in Campus I (p< 0.0001) after complete pelvic and paraaortic lymphadenectomy. There was also a significant difference in pelvic (19.9 vs. 17.7; p< 0.0001) and paraaortic lymph node counts (16.2 vs. 14.1; p< 0.01) between both pathologic institutes. In campus II 22.6% of pathologists failed to meet oncologic standards for pelvic and 16.7% for paraaortic lymph nodes. Moreover, in campus I 35.5% and 20.8% of pathologists undercut oncologic limit of pelvic and paraaortic lymph nodes, respectively.

Conclusions: The number of removed lymph nodes is not an absolute parameter for surgical radicality. Interdisciplinary cooperation with pathologists is mandatory to meet oncologic standards for most of gynaecologic oncology patients.
IS PET-CT A SUPERIOR INVESTIGATION FOR DETECTING DISTANT METASTASIS IN CERVICAL CANCER?

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Background: FIGO staging of cervical cancer remains clinical. CT and MRI are the commonest imaging modalities used to detect lymph node spread and parametrial invasion. Ovarian and peritoneal metastases from squamous cell carcinoma (SCC) cervix is rare (< 1%). This case demonstrates increased sensitivity of PET in detecting extra-pelvic spread in SCC cervix unsuspected on CT/MRI.

Clinical scenario: Examination of 63yr old lady with post-menopausal bleeding was suspicious of a cervical malignancy and pelvic mass. Examination under anaesthesia and cervical biopsy confirmed stage2B SCC of cervix. CT and MRI suggested a bulky cervical tumour with no obvious parametrial involvement, 23 cms, unilocular, simple left ovarian cyst and bilateral iliac lymphadenopathy without ascites or omental disease. Following MDT discussion chemo/radiotherapy was planned. PET-CT was recommended due to growing patient discomfort from rapidly enlarging cyst which demonstrated increased uptake of FDG in the ovarian cyst wall. Laparotomy and removal of both ovaries along with staging biopsies confirmed SCC confined to left ovary and iliac nodes with no disease in the para-aortic nodes and omentum and negative washings.

Discussion: In contrast to CT or MRI, both of which provide morphologic information regarding tumours, FDG PET noninvasively assesses metabolic activity in tumour. Indications for routine use of PET CT are being explored to enhance detection of disease spread.

This case demonstrates the superiority of PET-CT compared to conventional imaging in extra pelvic staging by increasing anatomical resolution of distant metastases. It helped detect ovarian metastases confirmed on histology thereby restaging the disease(4B).
ULTRASONOGRAPHIC COMPARISON BETWEEN TYPES I AND II ENDOMETRIAL ADENOCARCINOMAS


Pio XII Foundation - Barretos Cancer Hospital, Barretos, Brazil

Background: Endometrial carcinoma is classified into type I and type II according to its biological behavior. Ultrasonography has relative high sensitivity and specificity to indicate endometrial biopsy for patients with vaginal bleeding, mainly in postmenopausal women.

Aims: To evaluate the ultrasonography features in types I and II endometrial adenocarcinoma.

Methods: This was a retrospective study on 134 women from a Brazilian cancer center between 2007 and 2009 (117 women with type I and 17 with type II). Seven ultrasonographic parameters were analyzed: uterine size, endometrium thickness, myometrium echogenicity, endometrium echogenicity, presence of polyp, endometrial surface and endometrial cavity echogenicity. Numerical variables and categorical variables were compared respectively by means of Mann Whitney test and Fisher’s exact test.

Results: There was no significant statistic difference between the two groups (types I and II) according to: uterine size (median: 91 cm$^3$ vs. 116 cm$^3$; p=0.510), endometrium thickness (median: 18 mm vs. 21 mm; p=0.356), endometrium echogenicity (heterogeneous: 65% vs. 80%; p=0.651), endometrial surface (irregular: 32% vs. 50%; p=1.000), endometrial cavity echogenicity (filled: 52% vs. 43%; p=0.701) and presence of polyp (yes: 95% vs. 100.0%; p=1.000). There was a significant difference in myometrial echogenicity between the two groups: heterogeneous myometrium was more common in type II than in type I (80.0% vs. 20%; p=0.039).

Conclusion: The echogenicity of the myometrium seems to be useful for differentiating types I and II endometrial adenocarcinoma preoperatively. However, further studies including larger samples are needed to validate this result.
IS ULTRASOUND A GOOD EXAM TO EVALUATE PATIENTS WITH OVARIAN MASSES BEFORE SURGERY?

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Department of Gynaecologic Oncology, University of Turin Mauriziano Umberto I Hospital, Turin, Italy

The aim of our study was to assess the necessity to use an ultrasound score to evaluate patients with ovarian masses before surgery. At the Department of Gynaecologic Oncology of the University of Turin we enrolled over two years (from May 2007 to May 2009) 149 consecutive patients with ovarian mass considered for laparoscopic surgery. Patients demographics, clinical features, Ca125 values and surgical procedures were recorded. We collected ultrasound data: presence of uniloculate or multiloculate cysts, diameter, presence of papillary structures, liquid or solid content, regular or irregular wall, presence of papillary flow. Following the ultrasound exam all patients obtained a preoperative risk of malignancy and were scheduled in low and high risk class (benign vs malignant). Finally we obtained a pathological result for all ovarian masses. The mean age was 46.34 (range 17-79 years). The 73.82 percent (110/149) of patients presented a low risk mass and 26.17 percent a high risk mass. After surgery we obtained the following results: 104 benign masses with a negative ultrasound exam (true negative), 32 benign masses with positive exam (false positive), 7 malignant masses with positive exam (true positive), 6 malignant masses with negative ultrasound exam (false negative). The sensibility of the exam was 53% and the specificity was 76%. There is the necessity to create an ultrasound score to study all ovarian masses. We have already designed a prospective study to compare the result of an ultrasound score with the subjective ultrasound evaluation and to create an appropriate surgical approach.
PREOPERATIVE ASSESSMENT OF ENDOMETRIAL CARCINOMA BY 3D POWER DOPPLER ULTRASOUND: MATURE RESULTS OF A PROSPECTIVE STUDY

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¹Obstetrics and Gynecology, Tampere University Hospital, ²University of Tampere, Tampere, Finland

Background and objectives: Preoperative evaluation of the depth of myometrial invasion in endometrial carcinoma is challenging. The objective of this study is to evaluate the usefulness of three-dimensional power Doppler angiography (3D-PDA) in this setting.

Patients and methods: Sonographic and histologic data on 97 women diagnosed with endometrial carcinoma were analyzed. The myometrial vascularity indexes VI, FI and VFI (vascularization index, flow index, and vascularization flow index) were calculated by 3D-PDA. The indexes were measured from 10 mm shell surrounding the endometrium. The results were correlated with complete surgical staging.

Results: The mean age of the patients was 66.7 years (range 33-87 years). 52 patients had FIGO (2009) Stage IA carcinoma and 45 patients had Stage ≥IB disease. 14 patients had metastases, and 11 of them had a deep invasion in the myometrium. The mean myometrial power Doppler indexes VI and VFI were higher in the group with deep invasion in the myometrium than in the group with no deep invasion (2.120±2.472 vs 1.060±1.629, p=0.006, and 0.778±0.981 vs 0.383±0.620, p=0.008, respectively). There was no difference in the mean FI between the two groups.

Conclusion: Our study suggests that vascularity indexes VI and VFI correlate with the depth of invasion in endometrial carcinoma.
PET/CT IN MANAGEMENT OF RECURRENT GYNECOLOGICAL CANCER
Obstetrics and Gynecology, Tsinghua University, Yuquan Hospital, Beijing, China

To explore the role of PET/CT in management of malignant gynecological cancer, especially in determine recurrence.

Methods: The patients suspicious of recurrence (localize to the pelvis or remote metastasis) clinically or by CT/MRI received PET/CT in order to make the final diagnosis and determine further management.

Results: 33 patients, including 18 of cervical cancer, 6 of ovarian cancer, 5 of endometrial cancer and 4 of vaginal cancer. After PET/CT examination, 28 patients confirmed of recurrence (84.8%). Five excluded (15.2%) patients were followed up for 1-3 years without recurrence. Among 10 patients with localized recurrence prepared for pelvic exenteration, only 5 performed because of remote metastasis in the other 5 cases by PET/CT diagnosis.

Conclusion: PET/CT examination had great value in the diagnosis of recurrence in gynecological cancer, especially in determine remote metastasis before pelvic exenteration.
BORDERLINE OVARIAN TUMORS - STILL A CHALLENGE FOR AN ACCURATE PREOPERATIVE DIAGNOSIS

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Obstetrics and Gynecology, The Lady Davis Carmel Medical Center, Haifa, Israel

Objectives: We sought to compare the accuracy of preoperative diagnosis of borderline ovarian tumors (BOTs) using "expert opinion" to a stricter model suggested lately by the International Ovarian Tumor Analysis (IOTA) study group.

Methods: Files of women diagnosed with epithelial BOTs were reviewed retrospectively for demographic, clinical and ultrasonographic parameters. The operative procedures were reviewed for elements of formal staging steps. The sonographic parameters were than tested according to the IOTA model for the ultrasonographic diagnosis of ovarian cancer.

Results: 23 consecutive cases of epithelial BOT were identified in our institution during a 5 year-period. Using our clinical parameters, including ultrasonography, patient age and preoperative CA 125 levels, 11/23 (47%) of the women were referred for oncology-related procedure, and formal staging was electively performed. When the IOTA model was tested, 12/23 (52%) cases were not classifiable. In 6 cases, the diagnosis was of a malignant tumor, and that was in agreement with the original decision in 83.3% of the cases (5/6). In 5 other cases the new model diagnosed a benign tumor, with 80% agreement with the original decision. Both models were accurate in only 50% of the cases.

Conclusion: The IOTA model for prediction of malignancy in ovarian tumors was accurate in only 50% of BOTs cases identified in our institution. The prediction of malignancy did not improve significantly. Therefore, the challenge of accurate preoperative diagnosis of BOTs remains unresolved.
LARGE METASTASIS PELVIC LYMPH NODE IN LAPAROSCOPIC UTERINE CANCER STAGING SURGERY

C.-L. Lee, H. Su, K.-G. Huang, C.-F. Yen

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou and Chang Gung University, Tao-Yuan, Taiwan R.O.C.

Objective: To safely reduce the conversion rate of laparoscopic endometrial cancer staging surgery. Video demonstration: Laparoscopic staging surgery in early stage endometrial cancer is well known that could be an alternative safety procedure. The conversion to laparotomy may happened due to severe adhesive disease, uncontrollable hemorrhage, anesthetic complications, extraterine disease, and unexpected ovarian neoplasm. But the conversion rate will be differed according to the facility of the hospital and surgical technique of the surgeon. We present a video demonstration to safely remove large solid pelvic metastasis lymph node on the external iliac vessels laparoscopically and discussing of the key point techniques of the complicated laparoscopic staging surgery. key point techniques including two hand maneuver, suture technique for vesicular repair, bowel repair and ureteral repair.

Conclusion: If surgeon could have the key point techniques for complicated laparoscopic endometrial cancer staging surgery. We could reduce the conversion rate safely.
UTERINE ARTERY DOPPLER IN PERIMENOPAUSAL UTERINE BLEEDING

F. Tanase, A. Comanescu, L. Dijmarescu, C. Marinas, F. Cornitescu, N. Cernea

Obstetrics & Gynecology, Universitaty of Medicine and Pharmacy, Craiova, Romania

Uterine artery Doppler can be considered as part of the ultrasound investigation in gynecological patients with perimenopausal uterine bleeding. The paper presents the results obtained in comparing Doppler scores (RI&PI of the uterine arteries) with the histopathological results of the D&C products. The study encompasses 86 cases of perimenopausal uterine bleeding in which both RI&PI of the uterine arteries and D&C were performed. The causes ranged from leiomyoma (17%), endometrial polyps (15%), endometrial hyperplasia and endometrial cancer (68%).

When malignant changes were detected in the endometrium, uterine artery resistance index was always below 0.82. The mean uterine artery resistance index was significantly higher in the group of women with non pathologic changes (RI = 0.84 +/- 0.09) compared to the group with pathologic changes of the endometrium (RI = 0.76 +/- 0.04).

Doppler ultrasound can be an useful adjunct in deciding the need for a D&C in perimenopausal uterine bleeding, especially with patients that are not compliant with the procedure per primam.
ADEQUACY, ACCURACY AND SAFETY OF ULTRASOUND GUIDED TRU-CUT BIOPSY IN THE MANAGEMENT OF ABDOMINAL AND PELVIC TUMORS

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Objective: We analyzed adequacy, accuracy and safety of ultrasound guided tru-cut biopsy in a group of 190 patients managed between 2005-2008.

Methods: Main indications for tru-cut biopsy were: a) signs of primary suboptimal operability on ultrasound or CT in 104, b) suspicious recurrence in 27, c) suspicious duplicity (known non-genital tumor and current pelvic tumor) in 31, and d) atypical morphology in 28 patients. Biopsy was performed using Fast-gun biopsy system with 18G/25cm needle. No anesthesia was needed for vaginal biopsy, local anesthesia was used for transabdominal biopsy.

Results: 195 biopsies were performed (5 re-biopsies in 5 patients). Adequate sample for histological evaluation was obtained in 178 of 190 (93,7%) cases, corresponding to 183 (93,9%) biopsies. Only six patients with inadequate tru-cut biopsy underwent laparotomy or laparoscopy for the assessment of histological diagnosis. In 85 patients with adequate samples from tru-cut biopsy, an interval debulking surgery or primary surgery was performed in further management, and final histology report was not in agreement with the result from tru-cut biopsy in only two cases (2,35%). There were two complications (1,05%) in the whole group requiring laparotomy and laparoscopy; one hemoperitoneum in a patient with moderate thrombocytopenia and one bleeding from the biopsy site visible on ultrasound during the procedure.

Conclusions: Our experience indicates that the ultrasound guided tru-cut biopsy is an efficient, minimally invasive, accurate and extremely safe diagnostic method in the management of either advanced, recurrent or atypical abdomino-pelvic tumors, where unnecessary laparotomy or laparoscopy can be avoided.
LEARNING CURVE OF THE LAPAROSCOPIC STAGING PROCEDURE FOR EARLY STAGE OVARIAN CANCER

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Aims: We assessed the effect of increasing experience of the surgeon (learning curve) in the laparoscopic staging of women with early ovarian cancer on the surgical outcome of these patients.

Methods: Between June 2001 and October 2009, 25 women with apparent early stage ovarian cancer underwent a laparoscopic full staging procedure by the same surgeon. Three time periods, based on date of surgery, were compared with respect to surgical outcome using one-way analysis of variance.

Results: There was no significant difference in operation time, estimated blood loss and hospital stay between the three groups. There was a significant increase in the number of pelvic and para-aortal lymph nodes harvested (group 1 = 6.9, group 2 = 9.1 and group 3 = 20.0, p< 0.005). For the groups together mean operation time was 224 minutes and mean estimates blood loss was 193 ml. The mean length of hospital stay was 3.8 days. Two intraoperative and two postoperative complications occurred. The upstaging rate was 32.0%. The mean delay between initial surgery and laparoscopic staging was 51.2 days. Mean duration of follow up is 43 months, range (1-116). Five patients had recurrences and 2 (8%) patients died of the disease.

Conclusion: There is a significant learning curve for the laparoscopic full staging procedure in ovarian cancer. In our study this is mainly reflected in the amount of lymph nodes harvested and not by the total operating time.
PRE-TREATMENT STAGING AND PROGNOSTIC VALUE OF 18-FDG PET/CT AND MRI IN CERVICAL CANCER IB1-IIA

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Background: Cervical cancer staging follows FIGO criteria and is utilizing radiologic scans e.g. positron tomography, magnetic resonance imaging (MRI) or sonography. Lately, possibilities of positron emission tomography/computed tomography (PET/CT) are studied.

Aims: To analyze the diagnostic benefit of preoperative [(18)F]fluoro-2-deoxyglucose activity of positron emission and computed tomography (F-18 FDG PET/CT) in preoperative management of women with cervical cancer, and to compare it with MRI and palpation in detection of parametria involvement and lymph node metastases.

Methods: The study reviewed patients with cervical cancer stage IB1-IIA who had undergone both MRI and F-18 FDG PET/CT before radical hysterectomy, including lymphadenectomy.

Results: 14 patients were identified of whom 21.4% had pelvic lymph node metastasis and 14.3% infiltration of parametria. The sensitivity, specificity, and positive predictive value for detecting paracervical infiltration were 100%, 66.7%, and 33.3% (area under receiver operating curve AUC=0.833; p=0.07) for PET/CT, and 50%, 81.8%, and 33.3% for MRI (AUC=0.659; p=NS), respectively. The similar values for detecting metastatic lymph nodes were same for PET/CT and MRI 33.3%, 90.9%, and 50.0% (AUC=0.621; AUC=0.708; p=NS), respectively.

Conclusion: The MRI and PET/CT has the same diagnostic value for detecting metastatic lymph nodes in patients with cervical cancer, however MRI was more specific than PET/CT for detecting the extent of parametrial invasion. The value of PET/CT in the detection of paracervical tumour spread was same as for the palpation.

*This work was supported in part by grant of MZSR 2005/14-MFN-06 and by the Center of Excellence for Perinatology Research co-financed from EC sources.
ARE PRE-OPERATIVE COMPUTED TOMOGRAPHY (CT) SCANS A RELIABLE INDICATOR OF OPTIMAL SURGICAL CYTOREDUCTION? FOR STAGE 3-4OVARIAN CANCER

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Introduction: EOC remains the most lethal of the gynaecological cancers with some 7,000 new cases reported annually in the UK. Surgery is offered either upfront prior to any chemotherapy or following 3–4 cycles as interval debulking surgery (IDS) provided there has been response to chemotherapy.

Studies of EOC have demonstrated that the maximal diameter of residual tumour prior to initiation of chemotherapy is an important determinant of prognosis. Optimal surgery is associated with both a more favourable response to chemotherapy and prolonged survival.

Aim: The aim of this study is to assess reliability of CT scans in predicting optimal surgical cytoreduction pre-operatively in 115 cases.

Materials and methods: Retrospective identification of patients from gynaecology database. Pre-operative patient demographics, surgical findings and outcome collected from medical records. CT scans of same patients retrospectively scored by 2 radiologists blinded to the surgical outcome and to each others findings on visual analogue scale (VAS) for each criteria.

Results: 15 cases analysed till date. Scoring of each case compared with case notes for assessment of involvement of disease and inter-observer variability.

In 4/15 cases involvement of rectosigmoid by disease necessitating bowel surgery not identified by both radiologists on VAS. In 11/15 involvement of chest disease accurately reported. Diaphragmatic and pelvic disease only reported in 6/15 cases. Only in 9/15 cases was potential to optimally debulk disease mentioned.

Conclusion: Study is currently ongoing and we hope to present more data as this will help improve CT reporting as well as managing patient expectations from surgery.
THE EVALUATION OF OVARIAN TUMORS - THE ROLE OF 3D ULTRASOUND

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Obstetrics & Gynecology, University of Medicine and Pharmacy, Craiova, Romania

The objective was to explore role of 3D ultrasound and 3D Power-Doppler (3DPD) as a third step to discriminate between benign and malignant complex adnexal masses.

Twentyseven women (mean age 63 years) diagnosed as having complex vascularised adnexal mass with B mode ultrasound and 2D - Power Doppler sonography were evaluated by 3D. Additional techniques used were TUI and VCI. 3D-PD was then used to assess the vasculature in the papillary projections and solid areas. With the help of the VOCAL program, 3D-PD vascular indexes (VI, FI, and VFI) were calculated automatically. Definitive histological diagnosis was obtained in each case.

3D ultrasound has allowed the structural analysis of ovarian masses, the percentage of solid structures and the volume faction. When assessing the value of the parameters we recorded 3DPD malignant corresponding cut-off sites similar to other authors (VI (cut-off: 3.77), IF (cutoff: 21.35) VFI (cut-off: 21.03)).

3D ultrasound allows to analyze the complex structure of ovarian formations can replace CT scan, in some situations. 3D-PD vascular parameter values seem to be a promising tool for prediction of ovarian cancer in complex vascularised adnexal masses.
CLINICAL MANAGEMENT OF ADNEXIAL MASSES: A RETROSPECTIVE COHORT


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Introduction: Adnexial masses are a common finding in many women. Current methods of identifying those masses at high risk of malignancy remain insufficient. Our objective is to evaluate the predictive value of different diagnostic tools to establish a suspicion of malignancy.

Materials and methods: 197 patients treated of adnexial mass from Jan-08 to Dec-09 in Gynecology Department of Hospital del Mar and Santiago Dexeus Gynecological Center were included. We performed a retrospective approach taking into account ultrasound diagnosis, Doppler captation, CA 125 and CT-scan compared to pathologic diagnosis.

Results: 195 patients were diagnosed by ultrasound, with suspicion of malignancy in 14 cases (7.2%). Pathological findings were: benignancy (57.9%), carcinoma (17.8%), border-line (12.7%), other neoplasms (4.1%) and normal (7.6%). The analysis showed a positive predictive value for malignancy of: 90% (ultrasound + CA 125), 80% (ultrasound + Doppler), 78.6% (ultrasound), 80% (ultrasound + Doppler + CA125), and 79.5% (CT-scan). The negative predictive value was of 100% for all diagnosis tests and their associations, apart from CT scan, with a 91% NPV. The sensitivity was 34% (ultrasound), 30.8% (ultrasound + Doppler), 37% (ultrasound + CA125), 36.4% (ultrasound + Doppler + CA125), and 83% (CT-scan). Specificity was 49% (ultrasound), 44.8% (ultrasound + Doppler), 55.9% (ultrasound + CA 125), 51.4% (ultrasound + Doppler + CA125) and 37% (CT-scan).

Conclusions: According to our results, ultrasound has a low sensitivity and specificity for adnexial masses diagnosis, which is slightly improved with the addition of CA 125. Our results don’t support the benefit of adding Doppler captation. Although CT scan has the highest sensitivity, its cost and lack of specificity don’t justify its use for triage adnexal masses. In conclusion, we consider that after an adnexial mass is diagnosed by ultrasound, adding CA 125 could be the more efficient choice to differentiate between benign and malignant conditions.
ROLE OF SENTINEL NODE DETECTION IN HIGH RISK ENDOMETRIAL CANCER

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Aim: To evaluate the role of sentinel node (SN) detection in patients with high risk endometrial cancer.

Material and methods: The study included 70 patients (mean age 66 y) with high risk endometrial cancer who underwent laparoscopic surgery (hysterectomy, bilateral salpingo-oophorectomy, and regional nodal dissection). The day before surgery, 99mTc-Nanocolloid was injected with a volume between 2-4 ml in first 17 cases (Group A), and 8 ml in the remaining patients (Group B). Injection was performed in anterior and posterior uterine walls, by transcervical way and ultrasonography guidance. Planar lymphoscintigraphy and SPECT/CT images were acquired 2-4 h after injection.

Results: Lymphoscintigraphy showed at least one SN in 50/70 patients (71.4%), 35% vs 83% in group A and B, with significant differences (X² 10.5, p< 0.006). Unilateral drainage was seen in 37/70 (74%). Sentinel node was involved in 5 patients, all of them from group B: 2/5 were ITC and in 1/5 micrometastases were found. Lymphadenectomy was positive in 7 patients. In 4/7 cases, SN was not seen on lymphoscintigraphy (1 patient with peritoneal diffusion and 3 cases with no drainage). In 1 case, SN could not be removed. The remaining patient represents a false negative SN.

Conclusions: Transcervical injection guided by ultrasonography provides a great number of cases with SN detection and reduces the morbidity of this technique. Increasing the volume of tracer improves the drainage. SN detection could be of interest in the staging of high risk endometrial cancer. Nevertheless, more studies are required for its application.
PREOPERATIVE ASSESSMENT OF MYOMETRIAL AND CERVICAL INVASION BY ENDOMETRIAL CARCINOMA WITH TRANSVAGINAL SONOGRAPHY AND MR IMAGING

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Objective: The aim of the study was to assess the accuracy of ultrasonography and magnetic resonance imaging in determining the depth of myometrial and cervical invasion in preoperative evaluation in patients with endometrial carcinoma.

Material and method: A group of 60 patients with histologically proven endometrial carcinoma was investigated from 2004 to 2008 in the Institute of Oncology Vojvodina. Ultrasound examinations were performed using Sienna, Siemens, endovaginal probe 7 MHz, MR examinations were performed on a 1.5 T Avanto Siemens. The parameters of the tests were compared to postoperative histological findings and the diagnostic accuracy was assessed.

Results: In ultrasound findings, detecting myometrial invasion has overall sensitivity 0.71, specificity 0.83, PPV 0.93, NPV 0.47, accuracy 0.63; detecting superficial invasion 0.82, 0.84, 0.76, 0.88, 0.85; deep invasion 0.75, 0.87, 0.84, 0.93, 0.81; and invasion of cervical stroma 0.71, 0.94, 0.62, 0.96, 0.91, respectively.

In MRI findings, detecting myometrial invasion has overall sensitivity 0.82, specificity 0.81, PPV 0.88, NPV 0.71, accuracy 0.81; detecting superficial invasion 0.86, 0.91, 0.80, 0.91, 0.86; deep invasion 0.82, 0.90, 0.88, 0.84, 0.86; and invasion of cervical stroma 0.85, 0.92, 0.60, 0.81, 0.90.

Conclusion: Magnetic resonance imaging is superior to ultrasound in detecting the myometrial and cervical invasion. The difference is not significant. Ultrasound can be used in cases when MRI is not available and the patient have low risk disease. All patients with a endometrial carcinoma where there is a strong clinical suspicion of high risk disease should undergo MR pelvic imaging.
QUANTITATIVE, MULTI-PARAMETRIC IMAGING AT 3 TESLA TO MONITOR TREATMENT RESPONSE IN OVARIAN CANCER

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Objective: To assess early response to chemotherapy in ovarian cancer using quantitative, multi-parametric MRI/MRS.

Materials and methods: Patients with recurrent ovarian cancer were evaluated with T1- and T2-weighted, diffusion-weighted (DWI), and dynamic contrast-enhanced (DCE) magnetic resonance imaging, and localized MRS at 3 Tesla. Scans were performed within 4 days before and 7 days after a new chemotherapy regimen. Localization scans, conventional T2-weighted, and T1-weighted fat suppressed images were obtained. Data was collected regarding quantitative T2 maps centered on the lesion of interest, ADC values after shimming the B₀ field over the region of interest, and IAUC60 at the region of interest. Skeletal muscle was used as a reference for T2, ADC, and DCE metrics. Single-voxel spectroscopy was obtained using point resolved spectroscopy (PRESS) localization technique and quantified using water as an internal reference.

Results: T2 and ADC values were analyzed at baseline and post-chemotherapy in 4 women. T2 values decreased in all patients post-chemotherapy compared to baseline, with a mean difference of 42.2 ms (SE 1.4). ADC values increased in all patients post-chemotherapy, with a mean difference of -0.31 (SE 0.02). Two women did not receive contrast injection secondary to impaired renal function, therefore DCE data was not available for interpretation. In 3 of the 4 patients, spectra quality was insufficient for analysis.

Conclusions: Quantitative analysis of T2 and ADC values may provide an early indication of chemotherapy response in women with recurrent ovarian cancer. Quantitative, multi-parametric data may predict early response to chemotherapy in these patients.
CURRENT LEVEL OF AWARENESS AGAINST CANCER IN TURKISH CITIZENS

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**Objective:** To evaluate the level of awareness against cancer in Turkish population.

**Method:** A total of 3096 people were randomly selected from different 24 cities to represent the whole population and a questionnaire was applied, involving 46 questions about different aspects of cancer and epidemiologic characteristics. The sample homogeneously represented Turkey with 24 cities attendees.

**Results:** Median age was 37. 93% was accepting cancer as a lethal disease. A great majority was informed about cancer on TV programmes and only 17% was admitted to a medical professionalist for further information. 84% claimed smoking as the major cause of cancer. However, only 44% did show a reaction to cessate smoking to prevent cancer. Surprisingly, a great majority (50%) thougt blood tests to be used for cancer diagnosis and was not aware of screening tests. And a majority (>80%) answered the questions regarding to cancer protective nutritions correctly.

**Conclusion:** Current level of awareness seems to be in mid levels in Turkish citizens. Media has a high impact on their informations and therefore nutritional habits came out as a high priority subject. To inform the patients correctly and to increase the percentage of screened people, media awareness campaigns seems to be the best tool to work on in next years.
PREVENTION OF VAGINAL STENOSIS; A COLLABORATIVE APPROACH TO MAKE CHANGES IN PRACTICE THAT ARE BOTH EVIDENCE BASED AND SUSTAINABLE

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Introduction: Radiotherapy to the pelvis is an effective treatment used for many women's cancers including gynaecologic, anal and colorectal. This treatment can result in vaginal stenosis caused by the formation of adhesions, along with circumferential fibrosis of the vagina (Brand 2006). Vaginal stenosis can lead to dyspareunia, effecting psychosocial health and intimate relationships. It can also result in painful vaginal examinations and even preclude a full clinical examination which is often an essential component for follow up care. Using best practice guidelines and management techniques vaginal stenosis can be prevented in most women. (Denton 2007 & Lancaster 2005)

Methods: In Western Australia a nurse led, collaborative approach was taken between two treating hospitals. This included identification of gaps in current care, literature search and establishment of a nurse led pelvic fitness clinic.

Results: Best practice guidelines have been introduced and a documented clinical pathway for prevention of vaginal stenosis has been established. In addition, ethics approval has been given to undertake a retrospective audit to ascertain if these changes have resulted in an improved understanding of vaginal stenosis by women, as well as an increase in the use of vaginal dilators.

Conclusion: There is little consensus in current literature regarding definition, risk factors and prevention of vaginal stenosis, further research is required. Patients often move across services in order to receive specialist cancer treatment. It essential that service providers collaborate in order to establish best practice for cancer patients.

Results of the retrospective audit will give direction for further research.
INTENT OF REGULAR PAP TEST AND ITS RELATING FACTORS IN KOREAN WOMEN

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Background: To present, regular Pap test is still the best way to detect early cervix cancer. Recently HPV awareness is increasing in relation to cervix cancer development, but general understanding of HPV is low among Korean.

Aim: This study was done to identify the intent of regular Pap test and its relating factors including HPV knowledge, sociodemographic and obstetric characteristics.

Methods: Design was a cross-sectional survey. Participants were 324 women visiting OBGY outpatient clinic in Korea. Data were collected using the questionnaires including intent of regular Pap test, HPV knowledge, HPV hearing, age, education, income, condom use, status of smoking & alcohol drinking, level of previous Pap test, cervix cancer family history, STD, Abortion, parity and marital status. Data analysis were including descriptive, Pearson correlation coefficients and binary logistic regression using SPSS package.

Results: Of the 324 women, women having intent of regular Pap test was 66%. In correlations, HPV knowledge and HPV hearing were significantly related to intent of regular Pap test. In Logistic regression, relating factors were smoking (wald 13.75), previous Pap (wald 13.14), HPV hearing (wald 11.16), Abortion (wald 4.32), parity (wald 6.62) and marital status (wald 7.19).

Conclusions: Enhancing HPV understanding would facilitate to increase intent of regular Pap test. Health behaviors and other obstetric history also should be assessed and intervened if possible for cervix cancer prevention.

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SUPRA REGIONAL CENTRES IN GYNAECOLOGICAL ONCOLOGY

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**Background:** Cancer referral guidelines in the UK follow the 'spoke and wheel' pattern with each cancer centre acting as a hub for the management of certain gynaecological cancers. However, few cancer centres have the infrastructure and expertise in dealing with complex surgical challenges especially in recurrent gynaecological cancers. Referral patterns were studied to identify if there was a need for supra regional centres.

**Methods:** Patients referred for second opinions from other cancer centres who subsequently underwent surgery at our institution from 1 April 2007-31 March 2010 were included in the study. Patients referred from our own cancer network were excluded.

**Results:** A total of 101 patients underwent surgical procedures at the Royal Marsden Hospital following referral from other cancer centres. Of these, 38 patients (37.6%) were referred for fertility sparing surgery in early stage cervical cancer and had a radical vaginal trachelectomy.

Sixty three patients (62.4%) were referred for a second opinion of which 56% had subsequent primary or completion surgery while 44% were treated for recurrent disease. The commonest referrals were for ovarian cancer (47.6%) followed by recurrent cervical cancer (20.6%). Most of the referrals were from hospitals (71.4%) while 20.6% were from the patient’s general practitioner requesting a second opinion.

**Conclusions:** About 21.6% of our operative work during the study period was from referrals outside our cancer network. This may demonstrate a need for the establishment of supra regional centres where early referral for complex and recurrent disease can be facilitated.
CAN AN EDUCATIONAL INTERVENTION IMPROVE VAGINAL DILATOR USE? A PROSPECTIVE STUDY

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Aims: From 2005 to 2009, patients undergoing radiotherapy treatment (XRT) for a gynaecological malignancy were educated about the use of vaginal dilators and entered into a prospective 12 month follow-up study to evaluate their use. We hypothesized that compliance would improve, and the incidence of stenosis be reduced.

Methods: All eligible gynaecological oncology patients were approached and 60 agreed to participate. Patients had a structured educational intervention regarding dilator use. Data collected included patient demographics, treatment, incidence of stenosis, and frequency of dilator use.

Results: The median age of patients was 60 years. Primary disease site was cervix (40%) and uterus (57%). At 12 months, no patients had complete stenosis but 22% had partial stenosis (from filmy adhesions only up to stenosis to mid-vagina). The only significant independent factor that predicted development of stenosis was treatment group (surgery and XRT vs. XRT alone, HR 0.201). Excluding those who had recurrent disease (14.8%) and those who did not return questionnaires (24.6%), 75% of the remaining 36 patients were still using the dilators at 12 months. Of these, 57% were using the dilators at least 2-3 times per week. There was an inverse relationship between frequency of dilator use and frequency of sex (p=0.035). Frequency of dilator use was greater in those >50 years of age (after adjusting for sexual activity) (p=0.005), and in those experiencing pain on vaginal examination (p< 0.001).

Conclusions: An educational intervention facilitates compliance with vaginal dilators and potentially reduces stenosis in women undergoing radiotherapy for gynaecological malignancy.
STRESS IN WOMEN WITH ABNORMAL PAPANICOLAOU SMEAR

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Background: In developing countries, overall rate of cervical cancer deaths have declined since the introduction of the Papanicolaou smear test. Pap smear test is useless if the women are not further diagnose and treated after the abnormal screening result. This study aim to explore the stress situation in women with abnormal Pap smears. The Lazarus and Folkman stress, appraisal and coping theory was used for guiding this study.

Methods: The researcher screened for the women who reported abnormal Pap smear as a stressful situation by asking a question, “Did you feel stress, distress, or anxious when you had informed about the abnormal Pap smear?” If the women feel stress, the women would be recruited in this study. Seventy women with abnormal Pap smears were recruited at the time they visited to Colposcope clinic Ramathibodi hospital, Thailand. Data were collected in the 6 month. The women were given a demographic questionnaire, a semi-structured interview.

Results: The result showed that women's stress emerged from the interview data: Three themes of stress situation were stress situation related to: 1) fear of having Cervical cancer, 2) anxiety about treatments 3) impact on family's life.

Conclusion: This study provides information for nurses as key persons to give information before an examination. It also allows the assessment stress situations of women with abnormal Papanicolaou smear and helps them to find appropriate ways of coping; i.e. by providing them with knowledge, information, and emotional support.
CHANGES OF SYMPTOM CLUSTER OCCURRENCE IN THAI WOMEN WITH CERVICAL CANCER FROM PRE TO POST TREATMENT

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Background and aims: Pattern of symptom occurrence has been changed from pre to post treatment. Evidenced supported that set of symptoms usually occurred at the same time. To know a cluster of symptom occurrences at each time of treatment is necessary for heath care providers to care for women with cervical cancer from pre to post treatment. Aim of this study was to describe change of symptom cluster occurrence in Thai women with cervical cancer receiving treatment.

Methods: This is a secondary analysis of the prospective study in 190 women recruited from four hospitals: 1 hospital affiliated university, 2 military hospitals, and 1 hospital under the National Cancer Institute. The Memorial Symptom Assessment Scale and the Demographic, Disease, and Treatment Questionnaires were used at pre, during, and one month post treatment. Data were analyzed by factor analysis.

Results: Results reported that symptom cluster occurrences are different at each treatment. There were 12 clusters of symptom occurrence at pre and during treatment while there were 14 clusters of symptom occurrence at post treatment.

Conclusions: These findings indicate that there was change in symptom cluster occurrences from pre to post treatment in Thai women with cervical cancer. This finding can be provided as evidenced base for appropriate care in Thai women with cervical cancer from pre to post treatment. Intervention program should be provided for women with cervical cancer appropriate with symptom cluster occurrence at each time of treatment is recommended for further study.
KNOWLEDGE, BEHAVIORS, AND BELIEFS RELATED TO CERVICAL CANCER AND THE PAP SMEAR TEST AMONG TURKISH WOMEN

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Aim: To describe the knowledge, behaviors and beliefs of cervical cancer and the Pap smear test of Turkish women.

Methods: The study was designed as a descriptive methodologies. This investigation was performed between September 2009 and April 2010 in northern Turkey. Sample included 387 women and the study datum was collected by the questionnaires about social demographic specialities, information level of the cervical cancer and the Pap smear, and the Champion's Health Belief Model Scale of Cervical Cancer Screening.

Results: The average age of study subjects was 34.9±10.2. Most of women have poor knowledge. 84.0 % of women don't know the signs of cervical cancer. 66.1 % of the women could not correctly explain what they pay attention a true Pap smear for, and few (17.1) were aware the usefulness of the human papillomavirus (HPV) vaccine.

In our study, women have a lower perceived benefit (32.2±6.2), seriousness (24.7±5.3), susceptibility (7.5±2.3) and health motivation (9.6±2.6) for cervical cancer screening. However, women have the more negative Pap smear barriers (36.7±9.0).

Conclusions: In view of these results, the knowledge, cultural beliefs and structural barriers influence cervical cancer screening and Health Belief Model of Cervical Cancer may help to develop strategies to enhance compliance with cervical cancer screening and pap smear follow-up.

Keywords: Cervical cancer, prevention, early detection, health belief model
REHABILITATION TREATMENT OF REPRODUCTIVE-AGED PATIENTS WITH STAGES IB-IIB CERVICAL AND UTERINE CANCER

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Materials and methods: 83 reproductive-aged patients with stage Ib-Iib cervical and uterine cancer were recruited into the study. Rehabilitation procedures were administered to 43 patients of group I 3-6 months after ending of the anti-tumor treatment. No rehabilitation procedures were administered to another 40 patients of group II. The complex of rehabilitation procedures included preformative physical factors, reflexotherapy, balneotherapy, phytotherapy and exercise training in conditions of Rehabilitation Center. The level of anxiety and depression was evaluated in all the patients using HADS, the level of menopausal disorders by means of Kupperman's scale, the quality of life using EORTC questionnaire.

Results: The median level of neurovegetative disturbances in patients of group I after rehabilitation measures was significantly lower than in patients of group II (14.6 and 18.7, respectively). Similar situation is observed on analysis of anxiety indices (6.7 and 9.5, respectively). On analysis of the quality of life in patients of group I before and after rehabilitative therapy a significant increase of the emotional level (48.7 and 56.5 scores, respectively) and social functioning (57.9 and 65.1, respectively) was noted whereas there was no dynamics of these indices in patients of group II. On evaluating distant results of therapy in the group I and II, there is no significant differences in the level of the 2-years overall survival rate (100% and 100%, respectively) was recorded. Similar results were obtained concerning the 2-years disease-free survival rate (92% and 93.3%, respectively).
SEXUAL FUNCTION IN PATIENTS WITH GYNECOLOGIC CANCER AFTER TREATMENT

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Background and aims: Sexual problems are widespread among patients with gynecologic cancer after treatment. Dysfunction may result from surgery, chemotherapy, radiation therapy. Sexual function as a health topic of gynecologic cancer patients after treatment was not routinely evaluated. The goal of this study was to analyze and assess the status of sexual function of patients with gynecologic cancer after treatment in Seoul, Korea.

Methods: A total of 20 cancer survivors with gynecologic cancer between April and May 2010 were asked to fill in the questionnaire. Each subject was assessed for sexual function by Female Sexual Function Index (FSFI), and semistructured interview. FSFI composed of 6 items in 19 questionnaires - Desire, Arousal, Lubrication, Orgasm, Satisfaction, Pain.

Results: The patient population has mean age 50.85(±6.66) years and 95% lived with their husbands. Subjects were diagnosed with ovarian cancer (85%), endometrial cancer (15%). Sexual function (the total score) for patients with gynecologic cancer was 52.60(±11.88, range, 2-95). Desire score is 5.6(±1.67, range, 2-10). Arousal score is 10.40(±4.23, range, 0-20). Lubrication score is 9.25(±2.44, range, 0-20). Orgasm score is 8.65(±1.87, range, 0-15). Satisfaction score is 11.30(±1.38, range, 0-15). Pain score is 7.40(±3.33, range, 0-15). Patient's age were significantly associated with arousal(p=0.037), lubrication(p=0.023) and total score(p=0.033). Younger patients were more likely to recover sexual activity than older.

Conclusions: Management of sexual dysfunction in patients with gynecologic cancer after treatment is an important issue. Sexual counseling or education for women with gynecologic cancer should be considered by medical professionals in order to improve their quality of life.
THE EFFECT OF HEALTH EDUCATION ABOUT SERVICIAL CANCER AND THE PAP SMEAR TEST

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Introduction: Knowledge, beliefs, attitudes among Turkish women are negatively effecting the success rate of cancer screening programs in Turkey.

Purpose: This study was carried out to identify the effect of health education on Turkish women's knowledge, beliefs, behaviors to cervical cancer and the Pap smear test.

Methods: This study was performed between January and February 2010 among 173 women from eastern part of Turkey. The data were collected by a questionnaire about social demographic specialties, information levels and beliefs about cervical cancer and the Pap smear. The beliefs are analyzed by using the Champion's Health Belief Model Scale of Cervical Cancer.

Results: There were no statistically significant difference between the social demographic specialties of control and study groups (p>0.05). A statistically significant difference was found between knowledge scores of two groups (t=11.245; p< 0.001). The Champion's Health Belief Model Scale of Cervical Cancer Screening has five different subscales. There were a statistically significant difference between benefits of Pap smear test (t=4.225; p< 0.001) and barriers to Pap smear testing (t=3.757; p< 0.001) subscales of the two groups. But there were no statistically significant difference between the scores of susceptibility to cervical cancer, perceived seriousness of cervical cancer and health motivation subscales of the two groups. The 20% (n=15) of the women taken education had a pap smear test during the two mounts period after education.

Conclusions: Understanding the beliefs of women in respect of cervical cancer and the Pap smear test will help nurses to develop more effective education programs.
SURGICAL MANAGEMENT OF GYNAECOLOGICAL MALIGNANCIES IN WOMEN OLDER THAN 70 YEARS: THE ROYAL MARSDEN HOSPITAL

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Purpose: With increasing life expectancy there is an increased incidence of gynaecological malignancies e.g. endometrial, ovarian and vulval, affecting the older age group. It is presumed in such a patient population there is increased morbidity and mortality after cancer treatment due in particular to co-morbidities. Such concern is especially for radical surgery. We present our experience in the management of patients older than 70 years with gynaecological malignancies.

Methods: A retrospective review of 41 consecutive patients who underwent surgery during 2009.

Results: Median age at time of diagnosis was 76.5 years (range, 70-94). 20/49 (49%) had co-existent morbidity. Primary tumour site was: uterine cancer, 10/41 (24%); ovarian, 11/41 (27%); vulval, 9/41 (22%). Histological FIGO staging at initial diagnosis was: I, 9/41 (22%); II, 5/41 (12%); III, 12/41 (29%); and IV, 1/41 (2%). 13 had histological adverse prognostic factors. Types of procedures: TAH + BSO + omentectomy, 17/41 (42%) including 9 pelvic lymph node sampling and 1 hemicolecotomy; radical local excision of vulva, 4/41 (4%), 2 of whom had unilateral groin node dissection; 2/41 (4%) posterior exenteration; and 1/41 (2%), anterior exenteration. 2/41 (4%) underwent laparoscopic TAH + BSO. Median hospital stay was 11.5 days (range, 3-42 days). Operative morbidity rate was 7% (3/41). There were no postoperative deaths. 14 patients received adjuvant therapy: 8 radiotherapy; 6 platinum-based chemotherapy. 2 patients have progressive disease and 1 patient has died of their disease.

Conclusion: This series demonstrates low rates of morbidity and no post-operative mortality in a group of older patients with primary gynaecological malignancies. This supports offering older patients the same surgical options as younger patients. A multidisciplinary approach with the availability of anaesthetic and intensive care support is crucial. Physiological status is more important than chronological age.
INCIDENCE OF HEPATITIS B INFECTION IN A NYC PUBLIC HOSPITAL WITH GYNECOLOGIC MALIGNANCIES

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Immunosuppressants can precipitate an increase in HBV replication, followed by a flare of hepatitis B that can be severe and even fatal. The Center for Disease Control has recommended screening for HBV prior to starting chemotherapy and initiating lamivudine prophylaxis for HBsAg carriers. We performed a quality assurance review of HBV infection and flares in gynecologic oncology patients in a public hospital.

Methods: Women with gynecologic cancers who received chemotherapy from 2003 to 2008, in a NYC public hospital were identified. We evaluated the number of patients who had baseline HBsAg performed and identified those who tested positive and subsequently treated with prophylactic lamivudine. The endpoint of this study was to assess for HBV reactivation.

Results: 300 women with gynecologic malignancies received chemotherapy - 33 (12.2%) white, 125 (46.3%) Hispanic, 28 (10.4%) black, 80 (29.6%) Asian and 4 (1.5%) other. 212/300 (71%) of these women did not have HBsAg performed prior to commencing chemotherapy. Of the 88 (29%) that were tested, 5 (6%) white, 46 (54.8%) Hispanic, 7 (8.3%) black, 25 (29.8%) Asian, and 1 (1.2%) other. 4/88 (4.5%) tested positive (all Asian) and all were started on lamivudine prior to chemotherapy. HBV reactivation was not observed in the patients who were positive for HBV.

Conclusion: A more conscious effort should be made in our public hospital to test patients for hepatitis B infection especially with a predominantly immigrant population. Not surprisingly, all the patients who tested positive in this study were of Asian descent given a high proportion of HBV in this population.
KNOWLEDGE OF HUMAN PAPILLOMA VIRUS INFECTION IN CORRELATION WITH CERVICAL CANCER AMONG MEDICAL STUDENTS AND MIDWIFERY STUDENTS

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Objective: General practitioners and midwives are considered as the first health service providers in Indonesia, a country with a huge number of populations and high geographical challenge. New doctors and midwives are obliged to do their compulsory duties in the rural area after finishing their education. They should be equipped themselves with Human Papilloma Virus (HPV knowledge) in order to become agents of change in their coverage area in the future.

Method: As many as 500 medical students and midwifery students in Jogjakarta were enrolled in the study and filled out a questioner with objective questions which assessed the knowledge of HPV infection and cervical cancer and one open question on the cervical cancer screening method.

Results: The majority of midwives and medical students have already known the connection between HPV infection and cervical cancer (80% versus 87% respectively, \( p > 0.05 \)). They were also aware that the causal connection was greater between HPV infections to cervical cancer compared to other co-factors (midwives 78% vs medical students 85%, \( p > 0.05 \)). Although, they were not sure whether the HPV infection could be prevented (midwives 43% vs medical students 33%, \( p > 0.05 \)). They could not mention one of methods of cervical cancer screening (only 30% of midwives and 37% of medical students who answered an open question of cervical cancer screening method).

Conclusion: Emphasizing on the knowledge of screening and prevention should be integrated in the education system in order to gain high awareness of cervical cancer.
THE IMPACT OF GYNAECOLOGICAL CANCER AND THE ASSOCIATED TREATMENT ON NUTRITIONAL STATUS AND QUALITY OF LIFE OVER TIME

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Malnutrition is recognised as a significant dilemma in women diagnosed with gynaecological cancer (GC). Nutritional status can be impacted in a number of ways. Prolonged symptoms or pressure from a growing cancer leading to loss of appetite, bloating and other stomach and bowel related complaints all reduce bother the amount and quality of nutritional intake. While surgery may improve the symptoms associated with cancer, poor nutritional status can lead to a delayed recovery from surgery; an extended hospital stay, or a delay in receiving other anti-cancer therapies. Nutritional status can also be further undermined by the surgery and subsequent treatment. Despite this knowledge, malnutrition screening and assessment are not routinely undertaken in most GC centres in Australia.

The aim of this study is to describe the impact of multimodal cancer treatment on nutritional status and quality of life (QOL) through prospective assessment across three time periods.

Data were collected prospectively from 40 women at 3 time points; diagnosis, 3 and 6 months. The patient generated subjective global assessment (PG-SGA) tool was used to assess nutritional status. QOL was measured using the SF-36 and the symptom distress scale.

33\% of women were found to be at risk of malnutrition at the time of diagnosis of GC. Symptom distress has a significant impact on QOL and nutritional status. The results of this study have led to a proactive approach to managing nutritional status in women with GC.
AUDIT OF URGENT REFERRALS OF SUSPECTED GYNAECOLOGICAL CANCERS UNDER A TWO WEEK WAIT SYSTEM


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Background: In the United Kingdom, there is a timeline of care for suspected cancers. Women should be seen within 2 weeks of referral. The referral to diagnosis, referral to decision to treat, decision to treat to the treatment date must each be within 31 days. The time between referral and the treatment date must be within 62 days.

Aims: To determine whether waiting times complied to the national standards and to review the outcomes of these cases.

Methods: Women referred between January and December 2008 were identified from the cancer services database. Individual medical records were retrospectively reviewed for data collection.

Results: There were 322 index cases. The mean age was 57.4 (range 23-92). The mean referral to consultation time was 7.8 days (SD 5.9). The mean referral to diagnosis time was 13.5 days (SD 10.7). Seventy seven (23.9%) were diagnosed with cancer, of which 21 (27%) were advanced. Most women 51.9% had endometrial cancer, 35.1% ovarian, 6.5% cervical, 3.9% vulval and 1.3% vaginal cancer. The mean time between referral to the decision to treat was 13.5 days (SD 10.7). Four cases (5.1%) breached. The mean time between the decision to treat and the treatment date was 18.2 days (SD 8.7). Two (2.5%) cases breached. The mean time between referral to the treatment date was 33.7 days (SD 13.3). One case (1.2%) breached. None of those that breached were advanced cancers.

Conclusion: This audit showed that a majority of cases adhered to the recommended cancer waiting time targets.
COMPARISON OF REFERRALS FROM AN URGENT TWO WEEK WAIT SYSTEM TO ALTERNATIVE ROUTES IN A GYNAECOLOGY CANCER CENTRE


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Background: In the United Kingdom women with suspected cancers are referred from the general practitioner through an urgent (two week wait) system or from an alternative route such as the general gynaecology department, urology or other specialty.

Aim: To compare referrals from the two week wait system to those from alternative routes.

Methods: This was a retrospective review of referrals between January to December 2008. Index cases were identified from the cancer services database. The data was collected from individual medical records.

Results: There were 85 cases of confirmed cancer. 77/85 (90.5%) were referred through the two week wait system and 8/85 (9.5%) by an alternative route. The mean ages of both groups were similar (61.1 and 58.6 years). The mean referral to decision time was less in the urgent group (18 v/s 35 days). The mean time between decision to treat and treatment dates were similar in both groups. The mean referral to treatment time was significantly longer in the alternative route than the urgent group (60 v/s 36 days).

Breaches to waiting times were greater in the alternative route group for referral to diagnosis times (25% v/s 5.1%), referral to decision times (37.5% v/s 5.1%), decision to treatment times (12.5% v/s 2.5%) and referral to treatment times (37.5% v/s 1.2%).

Advanced cancer was greater in the alternative route group (50% v/s 27%).

Conclusion: Women referred through an alternative route were more likely to breach the waiting time targets. They were more likely to have an advanced stage of cancer.
GYNECOLOGIC CANCER IMPACT ON COUPLE RELATION AND SEXUALITY. A FRENCH PSYCHO-ANTHROPOLOGICAL STUDY

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Introduction: In common representations, cancer is associated to death and sexuality to life though they meet each other for woman in gynecologic cancer situation. FECAPSE tries to analyze sexuality in this case by studying the evolution of the couple, from the diagnosis to the end of cancer treatments, using both psychological and anthropological investigations.

Methods: 30 women with a gynecologic cancer (cervix, uterus or ovaries) were followed by a psychologist (15) or an anthropologist (15) : T1 (diagnosis), T2 (T1 + 3 months) and T3 (three months after the last treatment).

At each encounter, patients had a research interview, in the psychological approach a questionnaire (SAQ) and a projective test (TAT) were added.

Results: At T1-T2-T3, the gynecologic cancer’s differences reside in the impossibility for women to keep the same relationship to the spouse and adequate representation of the invisible parts of their internal body (gynecologic organs). The no-representation of internal body makes sexual intercourse difficult or impossible for patients.

The revival of sexuality is very linked to these representations, the spouse reactions, and medical information.

Conclusions: At this time of analysis, it appears that :

- T1 : Vital risk seems stronger that sexual concerns because sickness becomes concrete with treatments. It is the happening of breakdown.

- T2 : Sexuality becomes a matter of concern, even a stake in the treatment..

- T3 : Sexuality theme is coming back in an attempt of normalization for the woman aiming at finding something she lost with cancer.
MANAGEMENT OF FAMILIES AT HIGHER RISK FOR BREAST AND OVARIAN CANCER: THE EXPERIENCE OF THE EUROPEAN INSTITUTE OF ONCOLOGY

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The management of subjects at high risk for familial/hereditary predisposition is typically based on a multidisciplinary approach which should be maintained during time with a tailored follow up.

Currently in Italy the role of the nurse involved in the genetic counseling process is not yet established. However, there is a rising need for a professional figure to be included in this new area of clinical oncology.

We use a multidisciplinary approach where all team members have a specific role in the patient's pre and post counseling care. This team includes a nurse, a geneticist, an oncologist (expert in cancer treatment and prevention), a patient manager and a secretary.

The role of the nurse includes the submission and evaluation of a dedicated questionnaire. She starts the pedigree drawing and the risk assessment, then she discusses with the other members of the team the patient's eligibility for either genetic or cancer prevention counseling. The nurse has an active role during counselling sessions, including educational issues, psychological items, informed consent discussion, counselling on lifestyle changes (diet and physical activity) and various clinical aspects along follow-up and prevention treatments.

From Jan 2000 to April 2010, we evaluated 2,900 questionnaires, offered 1,451 genetic counselling sessions (1,167 performed) and 1,449 cancer prevention visits, and performed 930 DNA testings (178 BRCA1 and 168 BRCA2 mutations).

In conclusion we have taken our work model from the established US and UK models, and we are developing our own, tailored for the Italian population.
CANCER BREACH ANALYSIS IN A DISTRICT GENERAL HOSPITAL

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Aim: To analyse 89 cancer breaches to identify re-occurring issues contributing to the patients not being treated within the required National waiting time standard.

Design: Retrospective cohort analysis.

Setting: District General Hospital

Method: During 2009/2010, 89 patients who were not treated within the required National waiting time standard breached and were identified and analysed for the reasons for breaching. The data was further examined to determine the cancer specialities which were breaching in each category.

Results: The largest breach category was identified as being complex which accounts for 40.4% of all breaches in 2009/10. Second largest set of breaches were unavoidable at 33.7%, followed by avoidable, 25.8%. Analysis of the patients timeline even though they had been categorised as having a Complex pathway identified issues which were avoidable, and contributed to the breach. The contributing factors to the category Unavoidable breaches are the same across all specialisms, and include:

- Patient holidays
- Patients decision to delay whilst making decision regarding treatment
- Presentation of other illnesses during pathway
- Hospital wards closing due to the Noro-virus infection.
- Patient failing to attend for appointments
- Patient cancelling their appointments

Conclusion: Pro-actively manage the patient pathways through the introduction of cancer pathways; develop a robust system for tracking cancer patients; effective management of staff to ensure patient pathways are not compromised by a lack of staff; review the administration services, with the intention of identifying staffing levels; implementation of an information leaflet for the GP to give to patients.
IS GYNAECOLOGICAL CANCER A REASON FOR EXTENDING THE LENGTH OF HOSPITAL STAY?

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Background: The gynaecological oncology department at the Norfolk and Norwich University Hospital developed a programme of enhanced post operative recovery. High risk patients are assessed preoperatively where their general condition is optimised, blood results checked and consent obtained. Patients are admitted on the same day of surgery with earlier post-operative ambulation and feeding. In this study we compared the length of stay for cancer and non-cancer patients.

Materials and methods: A prospective case control study assessing 463 patients who had surgery at the Obstetrics and Gynaecology department at the Norfolk and Norwich University Hospital. 235 patients had major surgery for benign pathology and 228 for gynaecological cancer. Patients’ age, weight, co-morbidities, types of abdominal incision and type of anaesthesia were identified.

Results: For patients with cancer, the mean age was 61 years (range 16 - 89), mean weight 75kg (range 46 - 128) and the median hospital stay was 3.0 days. For patients with benign pathology, mean age was 56 years (range 19-88), mean weight 74 kg (range 44 - 130) and the median hospital stay was 3.0 days. The following factors were found to increase LOS: age more than 70 years, presence of hypertension, immobility before surgery and the use of epidural analgesia for post operative pain relief. Factors that did not affect length of stay: diagnosis of cancer, type of incision, patients´ weight more than 100 kg, presence of diabetes, pulmonary or coronary heart disease.

Conclusions: In this study cancer surgery did not increase the LOS compared to surgery for benign conditions.
KNOWLEDGE AND SEXUAL BEHAVIOR REGARDING HPV INFECTION IN YOUNG POLISH WOMEN

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Introduction: Adolescents and young adults are at highest risk of STDs which includes HPV infection - the factor triggering carcinogenesis for cervical cancer. The aim of the study was to describe the potential risk factors of HPV infection in adolescents and young women in Poland.

Material and methods: A sample of 1478 female students (university and secondary school students), aged 18 - 29 were withdrawn to the study. The material was gather by the use of an anonymous questionnaire.

Results: Of the women investigated 85.2% were aware of the Human Papilloma Virus and from these 93.9% correctly associated it with cervical cancer. 2.5% of the students had been vaccinated for HPV, while 64.3% were willing to take the vaccine.

Of the women studied sexual activity had been initiated by 67.2%, at the mean age of 18.7 years (±1.97). The first intercourse was experienced under the age of 16 years by 12.4% of the young women and under the age of 18 years by 48.8%. A total of 41.8% of the women admitted to multiple instances of unprotected sexual intercourse, while 48.4% to sexual intercourse repeatedly without contraceptive protection. In the group of 313 women with potentially high risk behavior (coincidence of both factors) over half declared that their behavior did not carry any risk, similarly in statistical terms (p>0.05) to those whose behavior placed them only at a low risk.

Conclusions: Good knowledge about the HPV did not correlate with adequate protective sexual practices and critical assessment of own behavior.
COMPREHENSION LEVEL AND TIME REQUIRED TO COMPLETE EORTC-CX24 AND FACT-CX QUESTIONNAIRES

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Background: EORTC-CX24 and FACT-CX questionnaires were designed in order to evaluate the quality of life (QOL) of women with cervical cancer.

Aims: To evaluate EORTC-CX24 and FACT-CX questionnaires regarding comprehension level and time required to complete them.

Methods: One hundred Brazilian women from Barretos Cancer Hospital were invited to fill out EORTC-CX24 and FACT-CX between May and August, 2009. The comprehension level of each questionnaire was classified by the women by employing a visual numerical scale ranging from 1 (worse) thru 5 (better). If the woman had difficulty to understand any question, this was classified into four categories: difficult to understand, confusing, with difficult words and uncomfortable. Time required to fill out the questionnaires was measured using a chronometer.

Results: The comprehension level was similar between the questionnaires. Both visual numerical scale ranged from 3 thru 5 (EORTC-CX24:median=4.86; FACT-CX:median=4.85; Wilcoxon´s test:P=0.739). In EORTC-CX24, 5 questions were considered difficult to understand (by 5 women), 8 were considered confusing (by 25 women) and 5 had difficult words (by 6 women). No question was considered uncomfortable in EORTC-CX24. In FACT-CX, 3 questions were considered difficult to understand (by 4 women) and 19 were considered confusing (by 38 women). No question was considered to have difficult words or to be uncomfortable in FACT-CX. The mean time to fill out the questionnaires was 12.1 min and 8.2 min, respectively for EORTC-CX24 and FACT-CX (Wilcoxon´s test:P< 0.001).

Conclusions: The time required to complete EORTC questionnaire was significantly higher. However, FACT-CX seems to have more confusing questions.
EORTC-CX24 AND FACT-CX QUALITY OF LIFE QUESTIONNAIRES: A BRAZILIAN STUDY FOR VALIDITY AND RELIABILITY

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Background: Treatment can compromise the quality of life (QOL) of women with cervical cancer. The QOL of those women can be measured by means of specific questionnaires, such as EORTC-CX24 and FACT-CX.

Aims: To evaluate the validity and reliability of EORTC-CX24 and FACT-CX in Brazil.

Methods: One hundred Brazilian women from Barretos Cancer Hospital were invited to fill out EORTC-CX24, FACT-CX and SF-36 questionnaires between May and August, 2009. All these women filled out the questionnaires twice. The first moment was at the hospital and the second moment, around 15 days after, at their homes. We analyzed the following items: internal consistency, reliability, convergent and discriminant validities. SF-36 was the standard questionnaire for convergent validity. Cancer staging and type of treatment were used for discriminant validity analyses.

Results: EORTC-CX24 had a good internal consistency (Cronbach’s alpha: 0.753-0.773) and good reliability (intraclass correlation coefficient: 0.517-0.801; all P values < 0.001). Convergent validity was poor in menopausal symptoms, sexual activities and sexual enjoyment (P>0.05). EORTC-CX24 was able to discriminate staging and type of treatment in the following scales (P< 0.05): body image, sexual/vaginal function and menopausal symptoms. FACT-CX had a good internal consistency (Cronbach’s alpha: 0.466-0.796), but a poor reliability (intraclass correlation coefficient: 0.283; P=0.057). Convergent validity was good in four out of eight scales (P< 0.05). FACT-CX was not able to discriminate cancer staging (P=0.137), but discriminated the type of treatment (P=0.021).

Conclusions: Both questionnaires had good internal consistency and convergent validity. FACT-CX had poor performance regarding reliability and discriminant validity.
NURSE-LED EDUCATION IN PRIVATE PRACTICE FOR WOMEN AT RISK OF DEVELOPING LOWER LIMB LYMPHOEDEMA FOLLOWING TREATMENT OF GYNAECOLOGICAL CANCER

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Background: Women who develop lower limb lymphoedema (LLL) following treatment for gynaecological cancer can be left with significant physical and psychosocial concerns and a serious impact on their quality of life. Over 1400 women are diagnosed with a gynaecological malignancy in NSW each year (Cancer Institute NSW 2007). Results have shown that 28-47\% of these women will develop lymphoedema following treatment (Lymphoedema Framework).

Aims and methods: We propose the initiation of a nurse-managed, three-phase strategy that will positively impact on our patients' ability to recognise and manage the potential onset of lymphoedema. Phase 1 - Discussion and provision of written information at pre-operative consultation. Phase 2 - In-depth lymphoedema education after post-operative check. This includes detailed discussion regarding skincare and trauma avoidance, exercise which includes specific exercises to promote lymphatic flow, advice regarding long-distance travel and support resources. Phase 3 - AIDE - MEMOIRES outlining content of pre and post-operative discussions plus a user-friendly resource tool in the form of a magnetised fridge chart.

Results: Women at risk of developing LLL following treatment will receive continuity of care in the form of information and support from the Clinical Nurse Specialist working in the private practice they attend. They will be offered time for discussion and education, avenues of support, an easy-access resource tool, and regular follow-up.

Conclusion: With improved survival rates from gynaecological malignancies comes the challenge of survivorship issues - paramount of which is LLL and its impact on quality of life.
WOMEN WITH GYNAECOLOGICAL CANCERS: 30 YEARS OLD AND UNDER

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Objectives: To determine the incidence and review the outcomes of gynaecological cancers in the 30 years and under age group in a cancer centre.

Methods: This was a retrospective review and index cases were identified from the cancer services database between 2002 and 2009. Individual notes were reviewed for data collection.

Results: Eighteen women were diagnosed with cancer (cervical n=14 (77.7%), ovarian n=3 (16.7%), vaginal n=1 (5.6%). Twelve women (66.6%) had stage 1a or b cancer. The incidence increased from zero in 2002 to seven in 2009. Two women were nulliparous. Three women were between 22-24 years. Surgical treatment consisted of nine radical hysterectomies (of which 2 were combined with caesareans), four total abdominal hysterectomies, and five excisional biopsies. Postoperative complications were wound infection (n=1), vault haematoma (n=1) and anaemia (n=2). Eight women did not require adjuvant therapy.

Conclusion: A significant number of women were affected by cancer. Cervical cancer was the most common, with three women below the age of 25. This prompts the question 'should the age of cervical screening be lowered?' Counselling is an essential part of the management because these women are faced with a life threatening disease at a young age and surgical treatment most often represents the end of their reproductive lives.
THE ENHANCED RECOVERY PROGRAMME IN GYNAECOLOGY- THE CONCEPT AND THE EXPERIENCE

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The enhanced recovery programme looks at improving the patient's experience through her inpatient stay; will improve the team's input and reduce hospital stay. Using techniques learnt from colorectal surgery, the Department of Health is supporting pilot sites in developing local solutions to deliver this approach.

Managing the patient's and carer's expectation is key. The process from the initial visit to the patient's safe discharge home will be described. Laparoscopic surgery will be employed where possible with a day-of-surgery admission policy and the use of carbohydrate fluid loading pre-operatively. Attention to pain relief protocols, early mobilisation and discharge planning will improve the patient stay, reduce the length of stay and detect complications early.

In the first three months of the programme, we saw 0.5 day reduction in length of stay (LOS) to 4.6 day for open hysterectomies and a LOS fall of 0.3 days for laparoscopic hysterectomies to a man of 1.4 days. Day of surgery admission was already running in excess of 80% for all cases and is now over 90%. There have been no increase in complication or re-admission rates.

The benefit to the patient in the form of a better outcome, the staff in the form of better satisfaction and the institution in terms of saving are obvious. Access to support and clinical advice (best practice, information sheets, protocols and pathways) will be disseminated and gynaecologists should be encouraged to engage.
THE DEVELOPMENT OF A NURSE-LED PSYCHOSOCIAL INTERVENTION WITH PEER SUPPORT FOR WOMEN BEING TREATED WITH RADIOTHERAPY FOR GYNAECOLOGICAL CANCER (GC)


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Aims: Radiotherapy for GC has numerous potentially distressing side-effects which impact on psychosocial functioning and intimate relationships. Distress can be ameliorated by comprehensive preparation for treatment and addressing informational, physical and psychosocial needs during treatment. The proposed intervention combines tailored specialist nursing consultations with peer support (GC survivor). The objective is to develop, refine and pre-test an intervention package to ensure its relevance and acceptability to patients and clinicians.

Methods: Drawing on literature reviews and consumer input, the following 3-stage process based on UK Medical Research Council Framework was used:

i) problem definition;

ii) refining the intervention by iterative clinician and consumer review; and

iii) pre-testing the intervention.

Results: The list of unmet needs was combined with best available evidence for self-care to draft two intervention manuals. The nurse manual specified the content of 3 nurse-led consultations at the pre-, mid- and end of treatment to provide tailored information, self-care coaching and MDT care-coordination. The peer manual specified the content of 5 phone calls (pre-, mid-, end of treatment and twice post-treatment) to provide psychosocial support and encourage adherence to the self-care plan.

Conclusions: The intervention package was well-received by consumers and multidisciplinary clinicians. The consumer feedback indicates that access to accurate and timely medical and self-care information from nurses is critically important, and the unique perspective of a peer lends authenticity to support that facilitates coping. The effectiveness of the intervention to reduce psychological distress and needs, psychosexual difficulties and symptoms will be assessed via RCT.
UNMET SUPPORTIVE CARE NEEDS OF YOUNG GYNAECOLOGICAL CANCER PATIENTS AND SURVIVORS; THE FIRST STEP

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Background and aims: Unmet needs predict poor psychological adjustment. Needs assessment research suggests that younger/female cancer patients are more likely to report higher levels of unmet needs compared to older/male patients respectively. Consequently, younger gynaecological cancer patients may be at an increased risk of psychological distress. There are currently no gynaecological cancer-specific needs measures and little qualitative information is available regarding the type and timing of interventions these women would find helpful. Therefore, this pilot study aimed to qualitatively explore and identify the supportive care needs of young gynaecological cancer patients and survivors.

Methods: A cross section of twenty women aged 18-54, with a gynaecological cancer, participated in individual semi-structured interviews to discuss their experiences during diagnosis, treatment and survivorship. Sampling continued until theoretical saturation was achieved. The interview content was coded and interpreted using thematic analysis.

Results: Preliminary analyses have identified the following themes relevant to this population: i) isolation (e.g. lack of support networks of aged-related peers with similar diagnoses; perceptions of stigma), ii) support and information needs (e.g. assistance with understanding the female anatomy; support during treatment-related decision process); iii) fertility options, and iv) self-concept. Women emphasised the importance of appropriately timed support; especially regarding re-initiating sexual relationships.

Conclusions: Several areas of needs were identified which are not adequately addressed by current needs assessment measures. These results informed the development and psychometric evaluation of a self-report gynaecological cancer specific needs assessment questionnaire (currently underway), and will be valuable for future age-specific interventions.
PERIPHERAL NEUROTOXICITY ASSOCIATED WITH A CHEMOTHERAPY IN GYNECOLOGIC CANCER PATIENTS

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Background and aim: Chemotherapy induced peripheral neuropathy (CIPN) is a common and often dose limiting side effect of chemotherapy. The purpose of this study was to analyze the status of CIPN of gynecologic cancer patients who underwent chemotherapy at Asan Medical Center in Seoul, Korea.

Methods: A total of 20 patients treated for gynecologic cancer between January and February 2010 were asked to fill in the questionnaire. Each subject was assessed for CIPN by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) subscale questionnaire. The FACT/GOG-Ntx subscale is designed to evaluate the severity and impact of neuropathy. The lower score indicate better status.

Results: The subjects of this study were patients who had undergone six cycles of paclitaxel (175mg/m2), carboplatin (AUC 5). The mean age was 49.35±8.19, performance status (ECOG) 0 was found in 4 patients(20%), and grade 1 was found in 16 patients(80%). Most had cancers of papillary serous carcinoma(13, 65%), and grade 3(18, 90%). The FACT/GOG-Ntx subscale score was 7.95±6.32(0~16). Ovarian cancer patients(n=16) had 8.44±6.29, endometrial cancer patients(n=4) had 6.00±6.98(p=.437). Stage I patients(n=3) had 9.00 ±6.56, stage II(n=2) had 3.50±2.12, stage III(13) had 7.46±6.72, stage IV patients(n=2) had 14.00±2.83(p=.459). After three month later of last chemotherapy, the score was 5.33±9.24, two month later was 9.00±5.53, one month later was 7.95±6.32.

Conclusion: Chemotherapy induced peripheral neuropathy of patients with gynecologic cancer is adversely affected patients' quality of life and activities of daily living. Therefore, to improve patients' quality of life, it is important that accurate assessment and appropriate management CIPN in gynecologic cancer patients.
THE EFFICACY OF VAGINAL DOUCHING WITH DILATOR VERSUS DILATOR ALONE IN PREVENTING RADIATION THERAPY-INDUCED VAGINAL ADHESION AFTER PELVIC RADIATION

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Introduction: Radiation therapy (RT) for gynaecological malignancies may result in radiation-induced toxicities such as vaginal adhesion and stenosis. Various preventive methods such as vaginal dilator and douching are available to minimize these side effects, however, studies on the effectiveness of using vaginal dilator and douching in preventing vaginal adhesion and stenosis were limited. The purpose of this study was to evaluate the efficacy of using a dilator with vaginal douching vs. dilator alone in preventing radiation-induced vaginal adhesion after pelvic radiation.

Methods: This was a randomized controlled trial of patients with newly diagnosed Stage I-III cervical or uterine cancer recruited from a single institution. 47 patients was recruited and followed-up during the study period of 36 months. Patients were assigned to either dilator group or dilator with douching group. They were taught to perform the procedure three times a week for a period of three months post-radiation and once a week subsequently. Assessment was then perform at regular interval.

Results: A total of 47 patients were recruited, 24 were recruited in the dilator group and 23 in the dilator with douching group. Patient in the douching and dilator group had a higher risk of developing vagina adhesion and stenosis compare to the dilator group (RR 1.19 and 3.16 respectively). There is also a 10% decrease in sexual activity in this group of patient.

Conclusion: With better compliant rate, the finding of this study supports the use of a dilator as a proactive measurement in the prevention of radiation-induced vaginal adhesion.
EFFECT OF PHYSIOTHERAPEUTIC PROCEDURES ON POST-MAMECTOMY CONDITIONS - OWN EXPERIENCES

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Physiotherapy is a concept inseparably related to medical rehabilitation. It is a complex of treatment methods using the effect of organism reactivity to stimuli. Its purpose is preventing the disease from progressing to recurrences, eliminating various ailments and restoring physical fitness.

Objectives: The purpose of the present work is evaluating the effectiveness of physiotherapeutic procedure by women after mastectomy.

Material and methods: The material consisted of 100 subjects (women) aged from 35 to 75 years treated in our Surgical Ward in the period from 1999 to 2000 for breast cancer. The patients were treated by individual gymnastics. They attended the procedure in one series.

Results: All patients treated by means of physical methods were found to have their pathological symptoms as improvement of hand motion and subsided (20%) or alleviated (80%).

Conclusions: Physiotherapeutic procedures result in subsiding or alleviating ailments from post-mastectomy lesions.
CONTINENT CUTANEOUS ILEOCECAL RESERVOIR USING THE SUBMUCOSALLY EMBEDDED APPENDIX AFTER ANTERIOR EXENTERATION FOR GYNAECOLOGICAL MALIGNACIES: TECHNIQUE AND COMPLICATIONS

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Introduction: Patients with advanced gynecological malignancies or recurrences of gynecological malignancies (vaginal carcinoma, endometrial carcinoma and cervical carcinoma), who had to be treated by anterior exenteration and did not have an appendectomy, were reconstructed by continent cutaneous ileocecal reservoir using the submucosally embedded appendix. Data of 7 patients from the years 2008 and 2009 were analysed for intraoperative and early postoperative complication rate.

Material and methods: The appendix-pouch technique starts with the transsection of the terminal ileum about 12 cm away from the ileocecal valve and of the colon ascendens about 15 cm away from the hepatic flexure. In order to reduce the tension of the wall of the pouch a teniamyotomy of the colon is performed. The efferent segment of the pouch is built by the appendix and is passed out at the umbilicus.

Results: The mean operation time for the complete anterior exenteration was 280 (range 230 - 320) minutes, for the reconstruction by the appendix pouch 75 (range 60 - 90) minutes. The main complications were: problems with wound healing and retention of secretion in the small pelvis. Insuffiences of the sutures were not observed.

Conclusion: Our experience shows, that the appendix-pouch-technique is a good alternative for continent reconstruction of the bladder after anterior exenteration. This technique is combined with a quite low complication rate.
PRELIMINARY PROSPECTIVE RESULTS OF TREATMENT APPROACH OF CERVICAL INTRAEPITHELIAL NEOPLASIA III (CINIII) WITH THE USE OF ULTRASOUND KNIFE

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Background: The treatment approach of cervical intraepithelial neoplasia III consists on both ablative and excisional methods. Cold knife conization, laser conization and loop electrosurgical excision procedure (LEEP) are the most common used excisional methods. We present a new procedure which uses an ultrasound knife.

Aims: To present the early results of a prospective study of the use of ultrasound knife for the treatment of HGSIL/CIN3.

Methods: From 2003 to 2008, 185 women with histological diagnosis (through colposcopy and biopsy) of HGSIL/CINIII have undergone conization with ultrasound knife. Follow up consist on clinical-gynecological examination, liquid based cytology, colposcopy and HPV-DNA test, every 4 months during the first postoperative year, every 6 months during next 2 years and then after one year.

Results: The middle operative time of the method is 13.5 minutes, the middle bleeding's volume is 23.1cc and the middle cone's volume is 1.3cc. 10.7% of the patients presented postoperative complications, mainly bleeding (2.7%), cervicitis (3.3%) and stenosis of the cervical canal (4.7%). One woman presented recurrent CINI disease at postoperative 32 month and one woman presented CINII disease at postoperative 57 month.

Conclusions: The use of ultrasound knife for the treatment of CINIII offers a histological specimen with minimal thermal lesions and of ideal shape. The operative time is short, bleeding is limited, colposcopy is satisfactory during follow up and stenosis of the cervical canal is rare. Long term follow up of these patients and the use of the method in other centers will probably confirm the preliminary results.
Complete Cytoreduction of Advanced Ovarian Malignancy Using Neutral Argon Plasma

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Background: “Optimal cytoreduction” (< /=1cm) is associated with increased survival and disease free interval for EOC with best results following complete resection. PlasmaJet™(PJ), a new device producing a jet of argon plasma by heating argon gas may be used to vaporise small tumour nodules.

Aim: Evaluate the feasibility and outcome of conversion from optimal cytoreduction (< /=1cm) to microscopic disease only in open and laparoscopic surgery.

Materials and methods: Prospective study in tertiary oncology centre. PJ used in 8 laparotomies and 3 laparoscopic debulking.

Patient demographics, intra and post-operative data collected. Size/location of pre-surgical disease, procedures performed, tissue and anatomical location subjected to PJ, power settings and time taken to ablate tumour deposits recorded.

Results: 8 patients underwent open cytoreduction. All 8 had been diagnosed with Stage IIIC EOC. 5/8 underwent interval surgery with optimal debulking following 3 cycles of chemotherapy and 1/8 suboptimally debulked.

PJ used to treat peritoneal deposits of EOC metastases on serosal surface of small and large bowel in all 8 cases and treat deposits on serosal surface of the liver, diaphragm and peritoneal undersurface of the pericardium with no adverse affects. 2/3 presented with recurrent disease >19 months following treatment. Laparoscopic ablation of diaphragmatic deposits carried out using PJ in 3 cases. Disease on liver surface and diaphragmatic nodules resected with no visible disease.

Conclusions: Preliminary data on feasibility and safety are reported suggesting that PJ is an innovative surgical device with several features well suited for the destruction of EOC implants and tumour plaques.

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ENDOMETRIAL CANCER AND SENTINEL NODE PROCEDURE
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Background: Lymphadenectomy is associated with increased peri-operative risk and longterm side effects. Therefore a sentinel node (SN) procedure for endometrial cancer patients could be of advantage.

Aims: To evaluate the feasibility and sensitivity of a SN procedure in endometrial cancer patients.

Methods: A hysteroscopy was performed with a 4.5 mm hysteroscope, and 100-150 MBq $^{99m}$Tc-nanocoll® was subendometrially injected in four sites around the tumor followed by a dynamic scintigram. At the operation, the SN(s), identified with a gamma probe, was resected, and frozen sections was performed, follow by radical pelvic and paraaortic lymphadenectomy.

Results: Included were 32 patients. Five patients had macrometastasis. Among the remaining 27 patients, the SNs were detected by gamma probe in 23 (85.2%) and in most patients (n=17, 74.0%) one (n=12) or two (n=5) SN was found. The consistency between the scintigram and the per-operative findings was higher (71.5%) when 150 MBq $^{99}$Tc-Nannocol was used compared to lower doses (54.5%), mostly because the detection failure rate was lower (4.8% vs.18.2%). By frozen section all macro metastases were confirmed, but only one micro-metastasis was diagnosed. All subsequent lymph node metastases found in the final histology, were in the sentinel nodes, i.e. no false negative sentinel nodes were found. The operative procedure was well tolerated, and few severe long term complications were seen after an average follow-up of 25 month.

Conclusions: The SN procedure is safe and easy to perform. No metastases were found outside the SNs, but frozen sections are not suitable for diagnosis of micro metastases.
LAPAROSCOPIC OOPHERECTOMY OF HUGE OVARIAN CYSTS

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Objectives: Extremely large ovarian cyst poses a challenge to the gynecologic laparoscopic surgeon due to technical difficulties related to removal of the cyst like cyst rupture, space constrains and risk of malignancy. Therefore huge ovarian cysts are conventionally managed by laparotomy. We present 5 cases of patients with huge ovarian cysts managed by Laparoscopy without complications.

Materials and methods: Case series of five patients, describing patient’s presentation, surgeries performed and the final pathology.

Results: All patients presented with abdominal discomfort, the maximum diameter of all cysts ranged between 18-42 cm as measured by ultrasound. The ultrasound showed unilocular cysts, there were fine or no septations and no solid component in all patients and the tumor makers were normal. Patient’s age ranged between 19-69 years.

All patients had open laparoscopy, after evaluation of the cyst capsule, the cysts were drained under laparoscopic guidance, 1-12 liters were drained from the cysts (mean=5L), then the patients had laparoscopic oopherectomy using the conventional technique. One patient had LAVH and BSO as she was 69 years of age. The procedures were done using three ports only except for the LAVH, where four ports were introduced.

The final pathology confirmed benign serous cystadenoma in four patients and one patient had a benign mucinous cystadenoma.

There was minimal blood loss and no complications for all patients.

Conclusion: With advancing techniques, proper patients selection and availability of experts in gynecologic endoscopy, it is possible to remove giant cysts by laparoscopy.
SINGLE PORT ROBOTIC ASSISTED LAPAROSCOPIC POSTERIOR PELVIC EXENTERATION IN PATIENTS WITH STAGES IIIC AND IV EPITHELIAL OVARIAN CANCER: FARGHALY’S TECHNIQUE

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Robotic assisted laparoscopic surgery in gynecological cancer has been shown to be efficient, safe and feasible. It provides three-dimensional image, through its camera which give the system a life-like view of the surgical field. Patients with stage IIIC and IV epithelial ovarian cancer undergoing posterior exenteration for involvement of the sigmoid colon, and cul de sac area are selected for the procedure. All patients undergo preoperative lab work, imaging studies, and bowel preparation prior to surgery. IV tricarbidin/ clavulanate 3.1 gm is given prior to surgery, and all patients receive prophylactic doses of low molecular weight heparin from post operative day 1 until discharge. Single port laparoscopic access is used as it enhances the cosmetic benefits, and minimizes the potential morbidity associated with multiple incisions. The da Vinci surgical system is used to perform total hysterectomy, bilateral salpingo-oophrectomy, bilateral pelvic adenectomy (including obturator, hypogastric, external iliac, and common iliac lymph nodes in primary cytoreduction surgery. Debulking to less than 1 cm is performed in secondary cytoreduction surgery. Low anterior rectosigmoid resection with the reproductive organs and pelvic peritoneum performed in an bloc retroperitoneal approach. Primary colonic anastomosis is performed. Operative time can be maintained in 4 hours, mean blood loss 200ml, and hospital stay for 5 days. To conclude, Farghaly’s technique of single port robotic assisted laparoscopic pelvic exenteration in patients with advanced primary and recurrent epithelial ovarian cancer is safe, feasible, cost effective with acceptable operative and clinical outcome. It retains the advantage of minimally invasive surgery.
DOES LAPAROSCOPY PROVIDE ADEQUATE STAGING IN ENDOMETRIAL CARCINOMA COMPARED WITH LAPAROTOMY

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Aim: To assess the feasibility of laparoscopic surgery in the treatment of patients with endometrial carcinoma and to compare their outcomes with those of patients treated with laparotomy.

Methods: The records of 151 patients with endometrial cancer treated by laparoscopic-assisted vaginal hysterectomy (LAVH) or laparotomy between January 2003 and January 2007 were retrospectively reviewed.

Results: Thirty-eight (25%) were treated by laparoscopic assisted vaginal hysterectomy (LAVH) and 113 (75%) by laparotomy. All patients underwent pelvic lymphadenectomy. Lymphadenectomy has been extended to paraaortic space in 53% of LAVH group and 70% of laparotomy group. The majority of patients (75%) had stage I-II disease. The median number of removed pelvic lymph nodes was 19 for the LAVH group and 18 for the laparotomy group (p =0.213). The median number of removed paraaortic node was 7.5 for the LAVH and 10 for laparotomy group (p=0.199). Body mass index was 26 for the LAVH group and 32 for the laparotomy group (p=0.001). Operative time, age, tumor histology, paraaortic lymphadenectomy, complication rates were similar in two groups. Four (10.5%) patients in LAVH group and 12 (10.6%) in laparotomy group had recurrence of disease (p=1.0). There was no statistical difference for overall survival between two groups.

Conclusion: These findings showed that in endometrial carcinoma cases laparoscopy has provided adequate staging and survival rates like laparotomy.
EVALUATION OF ARGON BEAM COAGULATION FOR THE TREATMENT OF VULVAR INTRAEPITHELIAL NEOPLASIA III

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Background: Argon beam coagulation (ABC) has unique properties which make it suitable for the local treatment of superficial epithelial disorders such as VIN III.

Objective: To evaluate argon beam coagulation in treating VIN III.

Method: Argon beam coagulation was used in twenty-nine patients. ABC was set at 80W, 7L/min. All patients were given 1% Silvadene cream to apply to vulva. Patients had follow-up appointments two weeks and six weeks postoperatively. Patients were followed every three to six months for the subsequent year.

Results: 2 of 29 (6.8%) experienced moderate pain within the first two weeks postoperatively requiring prescriptions for percocet. 2 of 29 (6.8%) had yeast infection requiring diflucan. Mean follow-up time was 34.9 months (11.7-37.4). 15 of 29 (51.7%) had no recurrence within the follow-up period. 14 of 29 (48.3%) recurred within the follow-up period. The mean time to recurrence is 23.2 months.

Conclusion: This small retrospective review is the first to evaluate argon beam coagulation in treating VIN III. This review indicates that ABC is comparable to other vulva organ conserving therapies. ABC retains cosmesis, form, and function of the vulva. This is a major advantage over surgery. Repeat treatments are also possible, which is important in a condition such as VIN, which tends to be multifocal and recurrent.
MONOPARESIS OF LEG AFTER RADICAL HYSTERECTOMY TYPE II

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Introduction: occurrence of postoperative pelvic lymphoceles variate between 8% and 54%, but clinically significant lymphoceles accounts only in 2.3% - 3.4% resulting in abdominal or pelvic pain, venous or ureteric compression, unilateral leg edema and leg pain, hydronephrosis with deterioration in renal function, and deep vein thrombosis.

Case report: 40 years old women presenting with cervical cancer stage IB1, Grade III being operated with radical hysterectomy type II without salpingoophorectomy. During operation significant bleeding from bifurcation of internal and external iliac veins, from another place below bifurcation on internal iliac vein and from obturator vein occurred and they were additionally sutured. In postoperative period progressive weakness of right lower extremity was observed. On 10th postoperative day during ultrasonographic examination hypoechoic area of 5.3 x 9.7 cm was observed and it was drained immediately through the vaginal cuff by cutting 2 separate stitches.

Despite the leakage of considerable amount of serous fluid from the vagina, on 14th postoperative day on CT pathologic collection of fluid 9.3 x 7.3 x 2.3 cm and edema of pre-sacral region still was observed. After neurological examination damage of lumbosacral plexus with prevail of sciatic nerve harm was stated. After 5 months there is gradual recovery of leg functions and sensitivity of the skin.

Discussion: Damage of lumbosacral plexus is more likely caused by postoperative lymphocele than direct injury of the plexus during stopping of the bleeding.
EXPERIENCE WITH AN ENHANCED SURGICAL RECOVERY PROGRAM

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Objective: Fast Track (FT) or Enhanced Surgical Recovery (ESR) programs have been developed in a number of specialties. They combine a variety of techniques to optimise patient outcomes and as a consequence minimise length of stay (LOS).

Design: This audit reports the experience of 2 full years of patients referred to a single gynaecological oncologist undergoing a FT or ESR program.

Aim: The aim of the audit was to answer the following questions (i) How many patients can successfully complete a FT or ESR program? (ii) What is the peri operative morbidity? (iii) What is the LOS?

Results: During the 2-year audit period 172 patients underwent a laparotomy. Average age was 54 years, with an average BMI of 26. Ninety-eight (57%) patients were confirmed as invasive malignancies. Vertical midline incisions were performed in 148 (86%). Average duration of surgery was 2.4 hours with 148 (86%) surgeries lasting between 1 to 3 hours. Median length of stay, for all patients was 3.0 days. On univariate analysis the following were found to be significant for reduced LOS: benign pathology, age < 50 years, private medical insurance status, operating time, early oral feeding, use of COX II inhibitor and a “0” performance status. On stepwise regression analysis only shorter OR time, early oral feeding and performance status were significant. Only 7 (4%) patients throughout the study period were readmitted to hospital.

Conclusions: Based upon the compelling data presented here and elsewhere, we strongly recommend all gynaecologic surgeons initiate FT or ESR programs.
RADICAL SURGICAL TREATMENT WITH NERVE-SPARING TECHNIQUE IN EARLY CERVICAL CANCER- STAGE 1A-2A. OUR AND FOREIGN EXPERIENCE

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Introduction: We tried to make clear the role of sparing of the autonomous pelvic nerves during radical hysterectomy in cervical cancer stage 1A-2A. We compared the radicality, the possibility to introduce this type of operation, the level of local recurrence, the safety and the survival rate of these patients.

Methods: We summarized 50 scientific publications in this field. We analyzed the level of local recurrence, survival rate and safety of this surgical technique.

Results: The groups with or without nerve-sparing had comparable parameters and results. The sparing of the autonomous pelvic nerves from unilateral or bilateral part of the pelvis was possible in 70-85% of the patients.

We found local recurrences in 5% without nerve-sparing operations and in 9,1% in radical hysterectomies with nerve sparing technique.

Local recurrences in the group without sparing the nerve inervation appeared after 24 months, and in the group with nerve-sparing technique after 21 months. The duration of the operation and the blood loss were less in the group with nerve-sparing technique. The death and survival rate in both groups were equal.

Conclusions: As a result of our literature review and our own experience we consider that the sparing of the autonomous pelvic nerves in radical hysterectomies in early cervical cancer can be applied without problems and safely.

Keywords: Cervical cancer stage IA-IIA, nerve sparing radical hysterectomies, survival rate, safety.
A COMPARISON OF ROBOT-ASSISTED AND TRADITIONAL RADICAL HYSTERECTOMY (RH) FOR EARLY-STAGE CERVICAL AND ENDOMETRIAL CANCER

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Background and aims: To compare perioperative outcome of robot-assisted radical hysterectomy with abdominal radical hysterectomy for early-stage cervical cancer and endometrial cancer and to evaluate the feasibility of robot-assisted radical hysterectomy.

Methods: We reviewed medical records of 37 patients who had radical hysterectomy at Hallym university for cervical cancer stage Ia1 to IIa and endometrial cancer stage Ia to Ib. Abdominal radical hysterectomy was carried out in 27(Abdominal group) patients and robot-assisted radical hysterectomy was carried out in 10 patients(Robotic group). We compared patient's characteristics between two groups(age, parity, previous medical disease history, abdominal surgery history, body mass, index(BMI)). Perioperative characteristics compared included cancer stage, operative time, number of nodes, estimated blood loss, length of hospital stay, and complications.

Results: There were no differences in age, parity, history of medical disease, BMI between two groups(p>0.05). Robotic operative times were significantly longer than for abdominal(480.0±117.8 vs 286.9±65.6min, p< 0.0001). Blood loss(660.0±245.9 vs 1,137.0±608.4mL, P< 0.0001) and length of hospital stay(7.2 versus 17.1 days, P< 0.0001) were significantly lower for the robotic group. Lymph node yield in the robotic group was equivalent to that for the abdominal group(30.1±8.7 vs 35.4±16.9, p=0.356). No major operative complications occurred with both groups. Robot-assisted radical hysterectomy was associated with a significant reduction in blood loss and hospital stay. Less pain was observed with the robotic group.

Conclusion: Robot-assisted radical hysterectomy appears safe and feasible in early-stage cervical and endometrial cancer and further investigation is warranted in a prospective fashion.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

PERIOPERATIVE MORBIDITY AND MORTALITY OF GYNAECOLOGICAL ONCOLOGIC SURGERY

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Objective: To examine intra-operative and postoperative morbidity associated with surgery for ovarian, endometrial and cervical cancer.

Study design: Gynecologic cancer patients who underwent surgical treatment in Obstetrics and Gynaecology Dept., Faculty Hospital Nitra, from January 1995 to December 2009. The study cohort consisted of 1028 women undergoing laparotomy due to uterine, ovarian or cervical cancer. Clinical data included patients' age, comorbidities, chronic use of medications, body mass index (kg/m²), past and current surgical procedures, surgical FIGO stage, histologic type and number of dissected lymph nodes, optimal versus nonoptimal debulking, occurrence of perioperative complications, and postoperative hospital stay (days). Participants were divided to 450 (43.8%) patients with uterine cancer, 320 (31.1%) patients with ovarian cancer, and 258 (25.1%) patients with cervical cancer. Perioperative and postoperative complications observed were fever, wound complications, transfusion, cardiovascular morbidity, thromboembolic morbidity, urinary tract morbidity, paralytic ileus, respiratory morbidity and mortality. The mortality rate 0.5%. Causes of death were as follows: Venous thromboembolism and pulmonary embolus 3x, uncontrolled haemorrhage 1x, myocardial infarction 1x. Incidence of intraoperative adverse events were as follows: bowel injury 22 (2.15%), bladder injury 12 (1.2%), vascular injury 6 (0.6%), nerve injury 2 (0.2%), intraoperative blood transfusion 48 (4.7%), ureteric injury 2 (0.2%). Postoperative adverse events were: wound infection 168 (16.3%), wound dehiscence 54 (5.3%), wound hematoma 38 (3.7%), urinary tract infection 25 (2.4%), ileus 14 (1.4%), cardiac 18 (1.8%), pelvic abscess 8 (0.8%), septicaemia 5 (0.5%), deep venous thrombosis 42 (4.1%). Advanced gynecological surgery may be associated with significant perioperative morbidity.
EFFICACY OF PROPHYLACTIC APPLICATION OF FIBRIN GLUE (TISSEEL®) IN REDUCING POSTOPERATIVE DELAYED BLEEDING AFTER LOOP ELECTROSURGICAL EXCISION PROCEDURE

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Objectives: The objective of this study was to determine whether the prophylactic application of fibrin glue (PAFG) at excision wound of loop electrosurgical excision procedure (LEEP) reduce the postoperative delayed bleeding (PDB).

Methods: From 1104 women who received LEEP at our institute between 2001 and 2009, 212 women with follow-up < 2 month and 59 women who received LEEP from operators with LEEP cases < 50 during study period were excluded. For remaining 833 women, the association of electrocautery for PDB within two months after LEEP with clinicopathologic variables (age of patients, histological diagnosis of cervical lesion, PAFG) was evaluated using the chi-square and logistic regression analysis.

Results: Of 833 women, 86 women (10%) received an electrocautery for PDB within two months after LEEP. In univariate analysis, age ≥ 60 (p = 0.015) and PAFG (p = 0.024) were associated with electrocautery for PDB. In multivariate analysis, only PAFG (p = 0.029, OR = 0.387, 95% CI 0.165 - 0.908) was associated with reduced chance of electrocautery for PDB after LEEP.

Conclusions: The PAFG at excision wound of LEEP might reduce the chance of PDB after LEEP.
TREATMENT OF HIGH GRADE LESION AND MICROINVASIVE CANCER OF THE VAGINA WITH LASER SKINNING COLPECTOMY

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Background: To assess the efficacy of laser-skinning colpectomy in the treatment of vaginal intraepithelial neoplasia (VAIN). VAIN is a rare asymptomatic preneoplastic lesion with a high rate of occult carcinoma.

Methods: Retrospective review on eleven patients with VAIN3 treated with laser-skinning colpectomy (LSC) using a carbon dioxide (CO2) laser between 2005 and 2010. Colpectomy in all cases was done under colposcopic control. 40-100% of vaginal epithelium including all VAIN lesions was excised in one piece with a depth of 2-3 mm. After excision a tamponade with Estriol was invaginated to avoid initial adhesions of the vaginal walls.

Results: The mean age of the patients was 62 years (38 to 85 years). Ten patients were hysterectomied and one had a history of re-conisation. All patients were transferred because of abnormal smears or biopsy proven VAIN.

In all cases LSC was done without complications and little bleeding. VAIN 3 was found in all cases, in three cases additionally a microinvasive squamous cell carcinoma was found. A complete resection was achieved in all cases.

Conclusion: LSC is a save and less invasive alternative procedure to total colpectomy in cases of VAIN 3. Morbidity is comparable to extended laser-vaporisation but in contrast to ablative methods LSC allows for diagnosis and staging of underlying early invasive disease.
INTERIM RESULTS FROM RCT TO EVALUATE PLASMAJET FOR PREVENTION OF LYMPHOCYST FORMATION FOLLOWING BILATERAL GROIN NODE DISSECTION (BGND) FOR VULVAL CANCER

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Background: Vulval cancer is the 4th common gynaecological malignancy. Surgical excision in the form of wide local excision achieves excellent local control. BGND is performed along with radical vulvectomy for all central tumours with depth of invasion (DOI) > 1mm. Loco-regional recurrence is reduced, but significant post-operative morbidity is common. Immediate post-operative complications include wound-breakdown and lymphocyst formation in > 50% cases.


Materials and methods: Prospective crossover double blind pilot RCT in a tertiary oncology centre. Following approval from local ethics committee, 10 patients recruited into the study and PJ use randomised to one groin prior to surgery. PJ used at power setting of 40% between 5-7 minutes following node dissection.

Patient demographics, intra and post-operative data, daily drain outputs and groin wound healing recorded.

Results: Mean Patient age was 71.9(37-92) years. LN node yield on both sides was comparable (Range 5-12). Daily drain output from PJ side was 20-100mls and 100-430mls on contralateral side. 3/10 patients developed lymphocysts on PJ side requiring subsequent drainage and 1/3 required VAC dressing for wound breakdown. 7/10 on the non-PJ side developed lymphocyst. 3/7 required re-admission and intravenous antibiotics for wound infection. Length of stay unaffected as each patient acted as their own control

Conclusion: RCT still ongoing but early results suggest that use of PJ appears to reduce daily lymph drain outputs and lymphocyst formation. Ischaemia rates and wound infection were lesser on the PJ side.
CASE CONTROLLED STUDY OF OPEN, LAPAROSCOPIC AND ROBOTIC ASSISTED HYSTERECTOMY, BILATERAL SALPINGO-OOPHORECTOMY AND PELVIC LYMPHADENECTOMY IN PATIENTS WITH ENDOMETRIAL CANCER

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Aim: To compare the safety, length of stay and costs to the NHS of three surgical techniques in the treatment of patients with endometrial cancer.

Patients and methods: This study compares three surgical techniques used in the treatment for these patients. Sixty women with histologically proven endometrial cancers treated in a period of 24 months (February 2008 to February 2010) with open (laparotomy), laparoscopically assisted and robotic assisted ( 20 patients in each group) THBSO BPLND were assessed for perioperative, postoperative complications, length of stay, analgesia and cost of each surgical method in the NHS.

Results: In this case controlled study Robotic assisted THBSO BPLD had less blood loss when compared to laparotomy and laparoscopic approaches(mean 70 mls vs 200 mls vs 300 mls) ; less analgesic requirement (oral analgesia only vs Epidural vs epidural+PCA );shorter length of stay (mean 1.5 vs 3 vs 5 days) ; with cost to NHS ( £2000vs £2000vs £2500) respectively without compromising the results of the surgery eg. lymph node harvest( mean number of nodes:26 vs 18 vs 22 ) and surgical complications ( 1 pelvic abcess vs 2 wound infections vs 2 wound infections).

Conclusions: The results of this case controlled study indicate that Robotic assisted THBSO BPLND is a safe surgical technique with advantages to both patients and th Health Service. We recommend a randomised study to establish this finding.

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INITIAL EXPERIENCE WITH ROBOTIC ASSISTED LAPAROSCOPY IN THE STAGING OF ENDOMETRIAL CANCER - COMPARISON WITH LAPAROSCOPY

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Objective: To describe our initial experience with robotically assisted laparoscopic staging of endometrial cancer patients as compared with previous cases staged by standard laparoscopy.

Methods: The first university robotic center in the Czech Republic was opened in August 2009 in Faculty Hospital Olomouc. The first fifteen patients with early stage endometrial cancer underwent hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy using four-armed da Vinci S HD surgical system (TRH) and were compared with previous 30 cases of laparoscopic staging procedures (TLH). All cases were performed by two surgeons (P.R., D.P.), at a single institution. Body mass index, clinical stage of disease, length of operation, nodal yield, estimated blood loss, hospital stay and complications were documented and compared.

Results: Patients in TRH group were older (63 vs. 56 years) and more obese (BMI 30 vs. 27) than those staged by standard laparoscopy. Operative time was longer for TRH (286 vs. 168 min.), blood loss was higher for TLH (214 vs. 150 ml) group. There was one conversion to laparotomy in TRH group. Node yield (20 nodes) was identical in both groups. Within the „learning curve“ gradually shortening operation time, recovery time and lowering blood loss were observed with number of performed operations.

Conclusion: Robotic hysterectomy and staging had longer operative times and lower blood loss than standard laparoscopy during „learning curve“ period. Perfectly well coordinated team presents an essential condition in robotic surgery beside motivated surgeon.
PROSPECTIVE STUDY OF ANALGESIA REQUIREMENT AFTER ROBOTIC HYSTERECTOMY: PRELIMINARY RESULTS

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Introduction: There is no UK study (anaesthetic) evaluating pain control for robotic hysterectomy due to limited services. Robotic surgery is gaining wider acceptance as evidence accumulate for better outcomes1.

Aim: To look prospectively into postoperative analgesic requirements for robotic hysterectomy.

Methods: Intraop, recovery, post op pain scores and analgesia, recovery time, nausea, discharge time were recorded. Data was analysed using Microsoft Excel 2007.

Results: 9 patients (3 radical hysterectomy, 6 TAH/BSO) received 75 mg diclofenac, 1 g paracetamol and 20/20 ml 0.25% bupivacaine in the drain and wound. All received IV morphine 30 min before the end of surgery.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intraop mean; range</th>
<th>Recovery mean; range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>16 mg; 10-20</td>
<td>6.7 mg; 4-15</td>
</tr>
<tr>
<td>Duration of surgery</td>
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<td></td>
</tr>
<tr>
<td>Time recovery</td>
<td></td>
<td>86 min; 30-210</td>
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<tr>
<td>Pain score in recovery</td>
<td></td>
<td>1; 0-2</td>
</tr>
</tbody>
</table>

Post operatively 3/9 had pain scores >5/10 while the rest were < 3/10. 7/9 needed regular NSAIDs, paracetamol and DF118. Only 1 needed more than one dose of oromorph. None needed IV/IM morphine. None had severe nausea till discharge. 7/9 were discharged on post operative day one.

Conclusions: Preliminary results show that majority have low pain scores requiring only simple analgesia. Nausea scores are very low as well, majority are discharged on day 1 post op, for the rest total hospital stay was 3 days.

SENTRY NODE DETECTION IN ENDOMETRIAL CANCER: DIAGNOSTIC ACCURACY EVALUATION

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Background and aims: Intraoperative lymphatic mapping and detection of sentinel node have generated much interest to reduce the invasiveness of lymphatic nodal dissection in the diagnosis and treatment of several neoplasms. To evaluate the sensitivity, the specificity, the positive and negative predicting value of hysteroscopic injection technetium 99m (Tc) in the detection of sentinel node in endometrial cancer patients by lymphoscintigraphy and radio-guided surgery a perspective study was conducted.

Methods: From 2004 to 2010, 77 patients with endometrial cancer were submitted to hysteroscopic injection of 111 MBq of Tc. Ten patients were excluded from the study. After hysterectomy and frozen section assessment of surgical specimen, in 67 patients by laparoscopy or by laparotomy a detector probe was used to locate and remove the sentinel lymph nodes. Systematic pelvic and paraortic lymphadenectomy was further carried out. Histological evaluation was assessed by hematossilin-eosin and immunohistochemistry in case of histological negativity

Results: In all but three cases at least one sentinel node was detected using radio-guided surgery. In all the cases more than one site was positive to Tc. In four patient sentinel nodes and non sentinel nodes where histologically positive for cancer, in 6 cases sentinel nodes where histologically positive and non sentinel nodes where negative. In 45 cases no cancer cells where found in removed lymph nodes.

Conclusions: The hysteroscopic injection of Tc⁹⁹ labeled human albumin colloid particles in the detection of sentinel node(s) in endometriai cancer is a feasible technique. This study confirm the good sensitivity and specificity of this technique.
EFFECT OF POSITION CHANGES ON VENTILATION DURING ROBOTIC HYSTERECTOMY

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Background: Radical hysterectomy for early endometrial and cervical cancer is increasingly being performed with a minimally invasive approach, with robotic assisted technique offering significant intraoperative advantages. We identified 5 phases during the procedure which may impact ventilatory parameters. The aim of this study is to assess the impact of these intraoperative phases on ventilation during robotic hysterectomy.

Methods: Pressure control ventilation was used on 10 ASA I-II patients undergoing robotic hysterectomy with or without bilateral salpingo-oophorectomy or lymph node clearance. Ventilatory settings were recorded and adjusted to achieve tidal volumes (Vt) of 6-8 ml/kg. The 5 phases we identified were lithotomy position, 40° Trendelenberg tilt (TT), pneumoperitoneum in TT, robot ports inserted and an hour after docking of the robot. The changes of ventilatory parameters during these phases was recorded.

Results: Vt significantly reduced in TT by an average of 25% (124.4mL), with pneumoperitoneum by 40% (185.70 mL) and with robot port insertion by 17% (84 mL).

Conclusion: The most significant impact of Vt was seen upon initiation of pneumoperitoneum. Vt was also significantly reduced on commencement of TT and robot docking. PS requirements matched this trend, most significantly increasing with pneumoperitoneum, followed by Trendelenburg position and robot docking. To our knowledge, this is the first categorisation of the 5 phases of this operation on ventilation.
PELVIC PERITONIZATION AFTER ABDOMINAL RADICAL TRACHELECTOMY

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**Aims:** The main goal in abdominal radical trachelectomy is the oncologic radicality. But also, as a fertility sparing technique, the procedure must ensure the best anatomical relations for achieving a pregnancy and to prevent postoperative complications.

**Method:** The surgical technique of radical abdominal trachelectomy, with or without preservation of the uterine arteries, is more or less standardized, till the utero-vaginal suturing. We describe our technique of peritonization and pelvic drainage to prevent internal hernias, lymphocele formation and adhesions.

**Technique** - After a thorough hemostasis control, the rectal peritoneum is sutured to the posterior part of the uterine isthmus. The big space below the ovarian vessels and lateral to the uterus is closed bilaterally by suturing the posterior leaf of the broad ligament to the sigmoid peritoneum, without tension to the ovarian vessels. Then, the round ligaments initially cut are re-sutured and the bladder peritoneum is sutured to the anterior uterine isthmus. Finally, the dissected retroperitoneum is drained by the space left between the round ligaments and the ovarian vessels by two drains placed in fossa obturatoria bilaterally. All this procedure takes less then 10 minutes.

**Results:** The postoperative febrile morbidity and lymphocele formation are less frequent after introduction of this technique. It is early to appreciate if there is an increase in the rate of spontaneous pregnancies obtained after abdominal radical trachelectomy.

**Conclusions:** A more careful peritonization after abdominal radical trachelectomy could improve the fertility outcome, but further studies are needed.
LAPAROSCOPIC NERVE-SPARING RADICAL HYSTERECTOMY; DESCRIPTION OF THE TECHNIQUE AND PATIENTS’ OUTCOME

A. Kavallaris
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Introduction: The radical hysterectomy type III can be accompanied by postoperative morbidity, such as dysfunction of the lower urinary tract with loss of bladder or rectum sensation. We describe the technique of laparoscopic nerve-sparing radical hysterectomy and patient's outcome.

Patients and methods: 32 patients underwent laparoscopic nerve-sparing radical hysterectomy with pelvic lymphadenectomy. Both the hypogastric and the splanchnic nerves were searched and identified bilaterally during pelvic lymphadenectomy.

Results: The median age of the patients was 52 years and the average operating time was 221 min. There were no intra- or postoperative complications considering the nerve-sparing radical hysterectomy. Postoperatively, in all patients spontaneous voiding was possible on the third postoperative day with a median residual urine volume of < 50 ml.

Discussion: Laparoscopic identification (neurolysis) of the inferior hypogastric nerve and inferior hypogastric plexus is a feasible procedure for trained laparoscopic surgeons who have a good knowledge not only of the retroperitoneal anatomy but also of the pelvic neuro-anatomy as this qualification could prohibit long-term bladder and voiding dysfunction during nerve-sparing radical hysterectomy.
MORBIDITY AND MORTALITY STUDY REPORT IN GYNAECOLOGY ONCOLOGY (MAY - OCT 2009)

M. Kodampur, N. Sumar, A. Bonsu, S. Raju
Guy’s and St Thomas’ NHS Foundation Trust, London, UK

Aim: To analyse the morbidity and mortality associated with Gynaecological Oncology surgeries.

Materials and methods: 140 women underwent major Gynaecological Oncology surgeries over a period of six months between May to October 2009. All relevant data were collected on a computerised database. Case notes and electronic records were used as source of information for data collection.

Results: Majority of cases involved laparotomy for Gynaecological cancers. 3 cases underwent exenteration procedure and 4 cases involved plastics reconstructive surgery.

Intraoperative complication: Bowel injury = 4, Bladder injury = 0, Ureteric injury = 1, Acute allergy (atricurium) = 1, Blood loss (1.6L - 5L)= 5.

Post operative complication: Wound infection = 2, Pulmonary embolism = 3, Urinary tract infection = 5, Blood transfusion = 9, Pneumonia = 3, Intraabdominal collection = 2, Atrial fibrillation = 1, Bradycardic arrest requiring pacemaker = 1, Sepsis unknown source = 2, Re-exploration laparotomy = 3, Small bowel fistula = 1.

Mortality = 1 (due to medical complications and reexploratory laparotomy).

Delayed discharge was noted in 23 cases of more than 5 days and in 8 cases of more than 10 days.

Post discharge complication: Wound infection = 4, Haematoma = 3, Lymphoedema = 1, Pelvic collection = 1, Retained swab = 1.

Conclusion: In our study group a significant number (31/140) were noted to have delayed discharge. It was multifactorial due to convalescence care, adult vulnerable team review and slow recovery resulting from wound infection, diarrhoea, UTI, pulmonary embolism and pelvic collection.
TOTAL LAPAROSCOPIC HYSTERECTOMY WITHOUT UTERINE MANIPULATOR (TLHWM): DESCRIPTION OF A NEW TECHNIQUE AND ITS OUTCOME

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Introduction: Hysterectomy remains the most common major gynecological operation. This is the first study that describes a new technique of TLH without using any kind of uterine manipulator or vaginal tube (TLHwM) and analyzes the intra- and postoperative surgical outcome of the first 67 cases.

Patients and methods: Between Oktober 2008 and December 2009, 67 patients underwent TLH without uterine manipulator or vaginal tube. We analyzed the differences in the outcome by using three different kind of surgical instruments: In 21 cases the TLHwM was performed using conventional 5 mm bipolar and scissors, in 22 cases using Sonosurgical and in 24 cases using PKS Cutting Forceps.

Results: There was no intra- or postoperative complications. The overall mean operating time was by TLHwM with salpingo-oophorectomy 98 minutes and without salpingo-oophorectomy was 80 minutes. The mean operating time using cutting forceps was significant lower. The mean uterine weight was 263g.

Discussion: TLHwM seems to be a safe and practical surgical method especially in patients with vaginal stenosis and possible to perform in cases of enlarged uterus. With its short operation time and no complication rate, we believe that this method is an enrichment of the laparoscopic hysterectomy techniques.
PATIENTS ON THE MOVE: A PROSPECTIVE STUDY OF FAST TRACK SURGERY IN GYNAECOLOGICAL ONCOLOGY PATIENTS

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¹Department of Gynaecological Oncology, Westmead Hospital, Westmead, ²University of Sydney, Camperdown, NSW, Australia

Aims: Fast track surgery is a multidisciplinary approach to perioperative care that expedites recovery and decreases length of stay (LOS). The aim of this study was:

1. To determine the post-operative LOS and complication rate in a group of patients to whom a “fast track” protocol was applied

2. To determine what factors might predict increased LOS.

Methods: Fast track protocol was applied to 104 consecutive patients, with known or suspected malignancy, admitted for laparotomy to a gynaecological oncology unit over a 6 month period. Data collected included patient demographics, medical co-morbidities, surgical details, LOS and complications.

Results: Median age was 55.5 yrs. Thirty-nine percent were obese (BMI>30 m/kg²) and 79% had at least one medical co-morbidity. Ninety-five percent had a midline incision. The median duration of surgery was 100 minutes. Final pathology was malignant disease in 60% of patients. Median LOS was 4 days (range 2-18), with 26% staying 3 days or less. Patients were followed until 6 weeks postoperatively, with only 3 lost to follow-up. Complications occurred in 20 patients; of which 4 were major (all were venous-thrombolic events, 3 DVT’s and 1 PE). Three of the seven readmissions were possibly related to early discharge (pulmonary embolus, poor pain control, constipation). A multivariate analysis revealed that increasing duration of surgery and increasing age were independent statistically significant predictors of longer LOS.

Conclusion: Fast track surgery can be applied non-selectively to gynaecological oncology patients, to shorten the LOS, with low complications, and without excessive readmissions.
REVIEW OF LYMPHOABSCESS FOLLOWING RETROPERITONEAL LYMPHADENECTOMY IN THE GYNECOLOGICAL CANCER

S. Suga

Gynecology, Juntendo University, Bunkyo, Japan

Lymphocysts are fluid-filled spaces that develop after extensive retroperitoneal lymph node resection. In the gynecological field, pelvic lymphocysts have been occurred mainly following pelvic lymphadenectomy for cervical cancer. Pelvic and para-aortic lymphadenectomy is a part of the FIGO(International Federation of Gynecology and Obstetrics) staging system for endometrial cancer and ovarian cancer. Several non-randomized controlled trials(RCTs) data suggested pelvic and para-aortic lymphadenectomy improved the survival of women with endometrial and ovarian cancer. The incidence of lymphocysts after operations in these patients appears to have been increasing, although recent publications have shown that leaving the peritoneum open reduces the incidence of lymphocyst formation following retroperitoneal lymphadenectomy.

We analyzed 373 patients with endometrial cancer, ovarian cancer, cervical cancer who underwent retroperitoneal lymph node resection from Jan 2004 to Dec 2009 at Department of Obstetrics and Gynecology, Juntendo University. There were 23 cases of lymphoabscess. 4 cases of lymphoabscess appeared within 1 month after operation, 9 case within 1 month after chemotherapy. The incidence in the retroperitoneal no-closure group of lymphoabscess was lower than closure group. Surgical treatment (open surgical drainage) was performed of cases, including drainage. We concluded some experiences, especially lymphoabscess is one of the complications following systemic chemotherapy.
ROBOTIC RADICAL HYSTERECTOMY VERSUS TOTAL LAPAROSCOPIC RADICAL HYSTERECTOMY: USING NERVE SPARING TECHNIQUE PERFORMED BY A SINGLE SURGEON

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Department of Obstetrics and Gynecology, Kyungpook National University Hospital, Daegu, Republic of Korea

Background: To compare surgical outcome of robotic radical hysterectomy (RRH) with total laparoscopic radical hysterectomy (TLRH) in the treatment of cervical cancer.

Methods: We retrospectively reviewed the charts of initial 10 patients who underwent TLRH, and initial 10 patients who underwent RRH.

Results: Both group were similar with respect to age (48.9 years vs 47.6 years; P=0.684), body mass index (24.7 kg/m² vs 24.1 kg/m²; P=0.436), length of hospital stay (7.4 days vs 9.5 days; P=0.143), time to normal residual urine (8.7 days vs 10.0 days P=0.684)), and acquired number of pelvic lymph nodes (25.5 vs 19.8; P=0.089). The mean operating time of TLRH group was significantly shorter than that of RRH group (198.1 min vs 242.0 min; P=0.003). However, the mean blood loss was significantly lower in the RRH group than in the TLRH group (285.0 mL vs 22.5 mL; P=0.000). There were no significant intra- and postoperative complications in the 2 groups.

Conclusions: Although our limited experience, the mean blood loss of RRH group was significantly less than that of TLRH group. Robotic system has several advantages such as, more comfortable in dissection, especially deep in the cardinal ligament and vesicouterine ligament, and more stable in laparoscopic view the deep in pelvis, especially the inferior hypogastric plexus.
TWO CASES OF ABDOMINAL TRACHELECTOMY : DETECTION OF TUMOR MARGINS BY TRANSRECTAL ULTRASONOGRAPHY
F. Demirkiran, C. Onculoglu, E. Meseci
Obst&Gynecology, Acibadem Kozyatagi Hospital, Istanbul, Turkey

Introduction: Abdominal radical trachelectomy (ART) can be performed easily by all surgeons trained in gynecologic oncology. In our two cases, the uterus was mobilized without transsection of the round ligaments and the safe margin of trachelectomy is determined by transrectal ultrasonographic guide.

Cases and technique: Cases were 27 and 28 years old with FIGO stages Ia2 and Ib1 accordingly. Squamous cell carcinoma was the histologic type. The retroperitoneal spaces were entered without transection of round ligaments. Pararectal and paravesical spaces were prepared as in radical hysterectomy. The lymph nodes on both pelvic and paraaortic areas were collected . All of the lymph nodes were evaluated by frozen section procedure. After confirmation of no malignancy in lymph nodes , the uterin arteries were ligated at their origins from hypogastric arteries and the ureters were dissected till the bladder as in radical hysterectomy. When the level of upper third of vagina anteriorly and rectum posteriorly was reached, transrectal sonography was used to determine the extend of the resection of cervix. A sonographically visible guide was inserted at the level of isthmus and the cervix was excised with a safety margin about 10 mm. Frozen sections were done from the lower end of the uterin korpus to exclude microscopic metastases. After the resection of the cervix was completed, uterine corpus was resutured to the vaginal cuff with interrupted sutures . There was no intraoperative complication.

Conclusion: Transrectal ultrasonographic guided resection of cervix is feasible procedure in ART.
HAND-ASSISTED LAPAROSCOPY FOR THE REMOVAL OF PELVIC MASSES

R.W. Naumann, M. Elliot, N.D. DiMaria, R. Akers

Obstetrics and Gynecology, Carolinas Medical Center, Charlotte, NC, USA

Background: Pelvic masses present a laparoscopic challenge due to the risk of malignancy and the consequences of rupture. Hand-assisted laparoscopy can overcome the limitations of laparoscopy and allow the removal of very large masses without intraperitoneal spillage. The purpose of this study was to review our experience and determine the feasibility of this procedure.

Methods: Patients who presented with a pelvic mass without evidence of advanced ovarian cancer all underwent laparoscopy. If the surgery could not be performed with the laparoscope, a hand-assisted laparoscopy was attempted. During surgery, all masses were isolated from the peritoneum using a bag and removed in a way as not to contaminate the peritoneum.

Results: Twenty-four patients were identified that required hand assisted laparoscopy. The mean size of the pelvic mass was 16 cm (4 - 40 cm). Length of surgery averaged 215 minutes with a median hospital stay of 2.0 days. Mean EBL was 317 ml. Of these patients, 9 had ovarian cancer and required staging or debulking including 2 with small bowel and 3 with colon resection. Three patients (12.5%) were converted to open surgery and the mass was ruptured in 4 laparoscopic cases (20%) and one case that was converted to laparotomy (33%).

Conclusions: Overall, hand assisted laparoscopic surgery is feasible for the majority of patients with a pelvic mass. Very large masses can be removed laparoscopically with a relatively low risk of spill.
ROBOTIC SURGERY IN GYNECOLOGIC ONCOLOGY: TAIWAN EXPERIENCE
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Dept of Obs&Gyn, Chang Gung Memorial Hospital at Linkou, Taiwan, Taoyuan County, Taiwan R.O.C.

Introduction: The use of robotic technology to facilitate laparoscopic procedures has increased over the past years. In numerous studies, it has been shown to be a safe and effective alternative to conventional laparoscopic surgery in a variety of surgical disciplines.

Materials and methods: The surgeries were performed with the da Vinci system (Intuitive Surgical, Inc.). We collect data retrospectively including docking times, operative times, estimated blood loss, length of hospital stay, lymph node yields, and complications.

Results: Six patients with early-stage cervical cancer and underwent robotic-assisted staging laparoscopy from July 2007 to December 2008. The median lymph node count was 25.5 (range, 20 to 28). Mean operating time was 264 minutes (range, 215 to 309). The average estimated blood loss was 200 mL. Another six patients with early-stage endometrial cancer underwent robotic-assisted staging laparoscopy from July 2007 to August 2008. The median lymph node count was 24.8 (range, 9 to 30). Mean operating time was 200 minutes (range, 143 to 261). The average estimated blood loss was 178 mL.

No conversion was required, no intraoperative or postoperative complications occurred. All patients in this group were alive and free of disease at the time of last follow-up. To date, we are the first institute to perform robotically-assisted laparoscopy in treatment of gynecologic oncology in Taiwan.

Conclusions: The brilliance of this technology is simple: by restoring dexterity, 3D vision, and autonomy to the abdominal surgeon while leveraging the patient outcome advantages that come from minimally invasive techniques, better surgical outcomes will be achieved.
LAPAROSCOPIC RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY FOR EARLY CERVICAL CANCER - THE FIRST EXPERIENCE IN MACEDONIA

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Background: To describe our experience and technique of total laparoscopic radical hysterectomy with pelvic lymphadenectomy, which is the first institutional experience in Macedonia.

Methods: Six patients with early invasive cervix carcinoma were included in study. Laparoscopic radical hysterectomy with pelvic lymphadenectomy was done. Simple repetitive steps were used to perform this surgery and develop an easily replicable technique. Harmonic Shears (Ethicon Endo-Surgery) and Liga Sure (Valleylab, Tyco Healthcare) were used for lymphadenectomy and dissection of ligamentary and vascular tissue in the pelvis.

Results: Histopathologically, four were 3 (75%) cases of squamous carcinoma, two (25%) was adenocarcinoma. The operation was performed entirely by laparoscopy in all patients and by the same surgical team. The patients median age was 49 years (range 39-63), the median operative time was 260 min. (range 210-350 min.), the median blood loss was 170 ml (range 90-210 ml), the median number of resected pelvic nodes was 25 (range 17-33), the median parametrial ressection was left 2.0 cm, right 2.4 cm, the median vaginal tissue ressected was 1 cm (range 0.7-1.5 cm). None patient converted to the open technique. The median bladder drainage was 2 days, the median length of hospital stay was 5 days.

Conclusions: Our technique of laparoscopic radical hysterectomy is performed safety, oncologically comparable to open surgery in terms of margins, lymph node clearance and parametric resection. It’s technically feasible and economically visible, there is less postoperative pain and earlier ambulation and return to work. The patients are also able to start adjuvant therapy earlier.
NERVE SPARING RADICAL HYSTERECTOMY. EARLY POSTOPERATIVE URODYNAMIC STUDY

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Gynecology & Obstetrics, S.Maria Goretti Hospital, Latina, Italy

To demonstrate the bladder function following nerve sparing radical hysterectomy C1, 15 pts (age median 48 yrs, range 34-67; BMI median 24, range 21-30) with cervical cancer stage IB1-IIB [squamous 14 (93%), adeno 1 (7%)] were evaluated with urodynamic test before and within 6 month from surgery. 9 (60%) pts were treated with platinum based NACT. Bilateral nerve sparing was feasible in 12 (75%) patients. Median duration of surgery was 280 minutes (range 250-320), and of postoperative stay 9 days (range 6-28). 5 (33%) patients received blood transfusion. Median number of pelvic nodes removed was 35 (range 19-45). Catheter was removed in postoperative day 4, and patients educated to clean intermittent self catheterization until residual urine was < 50 ml, its median duration was 4 days (range 2-24). At postoperative day 10 only 3 (20%) pts continued self catheterization. Before surgery 2 (12.5%) patients showed urodynamic symptoms of incontinence, and 3 (20%) overactive detrusor. Postoperative urodynamic (median 4 months, range 2-6) showed reduced detrusor activity in 8 (53%), overactive detrusor in 4 (27%), and normal profil in 3 (20%) pts. Reduced bladder sensation was observed in 2 (12.5%) pts, and residual urine > 30% of bladder capacity in 2 (12.5%). No patients showed de novo incontinence. Bladder compliance was unchanged (mean + DS: pre 37.5+30.3; post 44.2+45.2 NS). These data suggest moderate bladder functional impairment in the early postoperative period of nerve sparing radical hysterectomy.
ULTRASONIC ENERGY IN OPEN SURGERY IN GYNAEONCOLOGY

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Introduction: Open surgery for gynaecological malignancy is complex and time consuming. Multiple procedures are often performed to stage disease and to excise metastatic tumours from different sites within the abdomen and pelvis. Increased radicality of such surgery in the presence of malignancy also increases risk of significant blood loss. Many surgeons, however, continue to use traditional surgical techniques of clip, cut and tie when performing open surgery in gynaecological oncology.

The HARMONIC WAVE™ (W) is an ultrasonic scalpel that is a simplified form of HARMONIC ACE™ developed for open general surgery.

Materials and methods: Prospective, observational study in a tertiary gynaecological- oncology centre with 2 surgeons.

Primary outcome of the study was effectiveness and ease of use of the (W) assessed in terms of time taken to complete omentectomy and blood loss during this procedure.

Results: 35 cases and controls were performed as either primary surgery or interval debulking for advanced ovarian cancer involving supracolic or infracolic omentectomy.

Time taken to perform procedure was significantly lesser with W (6-33) minutes vs (6-133) minutes. Blood loss also consistently lesser. Omentum weight was similar and no other adverse intra-operative findings were recorded on using the W. Appendectomy (9 cases), hysterectomy (5 cases), peritoneal stripping (3 cases) and hemicolectomy (2 cases) also performed as familiarity with device grew.

Conclusion: W appears safe for use in open surgery in gynaecological oncology. The present cost of the device does not make it amenable for omentectomy use only but with simultaneous procedures performed, reduced blood loss and operating time makes it cost-effective.

<table>
<thead>
<tr>
<th></th>
<th>Primary surgery Supracolic</th>
<th>Primary surgery Infracolic</th>
<th>IDS Supracolic</th>
<th>IDS Infracolic</th>
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<tbody>
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<td>264.2(70-437)</td>
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<td>[cases and controls]</td>
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CLASS III NERVE-SPARING RADICAL HYSTERECTOMY VERSUS STANDARD CLASS III RADICAL HYSTERECTOMY: A CASE-CONTROL STUDY

A. Ditto¹, F. Martinelli¹, F. Hanozet¹, F. Matana², C. Reato³, E. Solima¹, F. Zanaboni¹, B. Grijuela¹, M. Carcangiu⁴, F. Raspagliesi¹

¹Gynecologic Oncology, ²Statistics, National Cancer Institute of Milan, Milan, ³Obstetric and Gynecology, Traviglio/Caravaggio Hospital, Bergamo. ⁴Pathology, National Cancer Institute of Milan, Milan, Italy

Background and aims: To analyze morbidities and oncologic outcome of class III nerve-sparing radical hysterectomy (NSRH) when compared with standard class III radical hysterectomy (RH).

Patients and methods: One hundred and eighty-five Patients with CC FIGO stage IB-IIB who underwent NSRH between 04/01/2001 and 29/09/2009 and 311 patients who underwent standard RH between 20/03/1980 and 28/12/1995 have been enrolled in this case/control study. The median follow-up was 93 months; 42 and 159 months for NSRH and RH group, respectively.

Results: Intraoperative complications was 1.6% and 3.5%; overall G3-4 complication rate was 9.7% and 9.6 for NSRH and RH, respectively.

The pathological analysis showed: positive pelvic nodes in 21.6% and 19.6 of patients Vagina involvement was present in 25% and 89.9%; parametrial involvement was present in 33 (17.8%) and 21 (6.7%) for NSRH and RH, respectively.

The number of relapses was 30 and 60 for NSRH and RH, respectively, this difference was not statistically significant. Multivariate analysis showed that vagina involvement, residual disease after NACT and lymph node metastases were associated with a worst DFS and OS in both groups. The 5 year OS was comparable between NSRH and RH.

Conclusions: The oncologic results of NSRH was comparable between the two surgical techniques. The early and late complications rate related to autonomic injury was significantly lower in NSRH group. The nerve-sparing technique should be considered in all cervical cancer patients addressed to surgery.
IS TOTAL LAPAROSCOPIC HYSTERECTONY FOR ENDOMETRIAL CANCER A REALISTIC GOAL WITH CURRENT SKILL LEVELS IN UK PRACTICE?

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Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Edinburgh, UK

**Background:** Endometrial cancer is the fourth most common cause of cancer in women in the UK and total abdominal hysterectomy (TAH) has been widely accepted as the treatment of choice. TAH is however invasive surgery with associated morbidity. Total laparoscopic hysterectomy (TLH) is a minimally invasive technique and studies have shown it to be safe and effective, with less morbidity, shorter hospital admissions and less pain.

**Aim:** To evaluate the feasibility of TLH as an alternative to TAH for the treatment of endometrial cancer in a tertiary centre with limited laparoscopic experience.

**Methods:** A retrospective case note review was performed for all patients undergoing TLH or TAH for endometrial cancer or complex atypical hyperplasia during a 10-month period.

**Results:** The treatment groups were comparable with no statistically significant differences in patient demographics. The majority of procedures were performed by Specialist Registrars or Consultants, all with no previous experience of TLH, under the supervision of an experienced Gynaecology-Oncology surgeon.

There was no significant difference in theatre time for each treatment group but there were statistically significant reductions in the admission time and operative blood loss. TLH patients used less potent analgesia, less polypharmacy and had fewer complications than TAH patients.

**Conclusions:** TLH is a safe and effective operation for the management of endometrial cancer and should replace TAH as the gold standard of treatment in all patients. Additionally, this project demonstrates that TLH can be easily introduced into current practice led by the current workforce, under appropriate supervision.

**Table I: Patient demographics**

<table>
<thead>
<tr>
<th></th>
<th>TLH, n = 48</th>
<th>TAH, n = 38</th>
<th>Chi2, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Median (Range)</td>
<td>65 (47 - 94)</td>
<td>66 (50 - 87)</td>
<td>0.93</td>
</tr>
<tr>
<td>BMI (kg/m2), Median Range</td>
<td>33 (21 - 56)</td>
<td>29 (19 - 60)</td>
<td>0.612</td>
</tr>
<tr>
<td>Parity, Median (Range)</td>
<td>2 (0 - 5)</td>
<td>2 (0 - 4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Previous laparotomy</td>
<td>4%</td>
<td>17%#</td>
<td>0.005*</td>
</tr>
<tr>
<td>Significant PMH</td>
<td>57%</td>
<td>49%</td>
<td>0.471</td>
</tr>
</tbody>
</table>

*statistically significant, #50% of laparotomies were pfannensteil scars for caesarean sections.

**Table II: TLH vs TAH**

<table>
<thead>
<tr>
<th></th>
<th>TLH, n = 48</th>
<th>TAH, n = 38</th>
<th>Chi2, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theatre time (minutes) Median Range</td>
<td>100 (64 - 192)</td>
<td>95 (40 - 258)</td>
<td>0.720</td>
</tr>
<tr>
<td>Hospital Stay (hours) Median Range</td>
<td>46 (18 - 506)</td>
<td>121 (49 - 480)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Blood loss (ml) Median Range</td>
<td>50 (50 - 600)</td>
<td>300 (50 - 650)</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

*statistically significant
BOWEL SURGERY IN GYNAECOLOGICAL ONCOLOGY TRAINING PROGRAMME

M. Abu Freij¹, N. Burbos¹, S. Kapur², T. Duncan¹, S. Crocker¹, J. Nieto¹

¹Norfolk and Norwich University Hospital, ²Colorectal Surgery, Norfolk and Norwich University Hospital, Norwich, UK

Background: Training in gynaecological oncology has undergone major changes since the introduction of a subspecialty programme. According to the Royal College of Obstetricians and Gynaecologists (RCOG) curriculum for subspecialty in gynaecological oncology, a trainee should be independent to: oversew bowel serosa, repair small bowel injury, resect and reanastomose small bowel. However, independent practice is not essential in other procedures such as performing ileostomy, resecting large bowel, performing colostomy, primary anastomosis of large bowel, abdominal perineal resection. In our center a trainee has a weekly session with colorectal surgeons as part of the rota, enabling better understanding of bowel surgery and improving surgical skills necessary to achieve maximum cytoreduction in ovarian cancer surgery.

Methods: Retrospective analysis of major surgical procedures undertaken at Norfolk and Norwich University Hospital cancer centre between October 2007 till March 2010.

Results: 86 patients had bowel surgery out of 705 cases treated at the study period (12%). Some patients had more than one procedure. 131 procedures were done during the study period including rectosigmoid colectomy, right hemicolecctomy, small bowel resection and reanastomosis, anterior resection, exenteration, splenectomy, abdominoperineal resection, colostomy, appendectomy. Subspecialty trainee performed 74 (64 %), Consultant gynaecological oncologist 38 (29%), colorectal team 9 (7%).

Conclusions: The majority bowel procedures are done by the subspecialty fellow. Competencies in bowel procedures including upper abdominal disease are essential to achieve complete debulking. We strongly recommend including regular colorectal rotation in the training programme to improve the exposure and consequently independent practice in this field.
ROBOTIC RADICAL HYSTERECTOMY IN CERVICAL CARCINOMA: THE BELGIAN EXPERIENCE IN 49 CASES

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Objective: To analyse the operative results of robotic radical hysterectomies (RRH) in cervical cancer in Belgium.

Methods: Forty-nine RRH were performed in Belgium in patients with cervical carcinoma between April 1st 2007 and May 20th 2010, and analysed in one data base.

Results: RRH was performed using the Da Vinci Surgical System in cervical carcinoma FIGO (2009) stage Ia1 (n=2), Ia2 (n=4), Ib1 (n=37), Ib2 (n=3), IIA1 (n=2) and IIb (n=1). Median age was 48 years (range, 31-80), median BMI 23.9 kg/m² (range, 18.6-40.9), median number of pelvic lymph nodes 21 (range, 5-59), median operative blood loss 150 mL (range 25-1000), median hospital stay 6 days (range, 2-19), and median operative time 300 minutes (range, 205-450). Peroperative complications included 2 bladder lesions (sutured robotically) and 1 compartment syndrome of the lower leg. Postoperatively 6 patients complained of bladder retention for more than 28 days and 1 patient developed a vesicovaginal fistel. Six patients were postoperatively treated with external beam pelvic radiochemotherapy because of unfavourable prognostic variables. At the time of analysis (median follow-up of 13 months) 5 recurrences were observed and all patients were still alive.

Conclusion: This series reports on the early experience of RRH in six Belgian centres, and shows that RRH is feasible with an acceptable morbidity. Radical hysterectomy is one of the best indications to use the robot in the field of gynaecological oncology.
FACTORs AND COSTS ASSOCIATED WITH ROBOTIC VS. LAPAROSCOPIC VS. OPEN SURGERY FOR ENDOMETRIAL CANCER - ANALYSIS OF 540 PATIENTS

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Objectives: To determine the trends and factors associated with the use of robotic surgery in endometrial cancer.

Methods: An analysis of 2008-09 statewide inpatient hospital discharge database was performed. Using the newly established ICD procedure code (ICD-9: 17.42) for robotic surgery in October 2008, all patients who underwent laparoscopic robotic assisted hysterectomy for endometrial cancer was extracted and those who had laparoscopic and exploratory surgery were used for comparison. Chi squared analyses were used for statistical analysis.

Results: From October to December of 2008, 540 patients who underwent surgery for endometrial cancer; of which, 108, 339, and 93 patients had robotic (group A), laparoscopic (group B) and open surgery (group C), respectively. The proportion of whites vs. others in groups A, B, and C are 83%, 73%, and 62% (p=0.003). Those who underwent a robotic, laparoscopic, and open surgery had a mean length of stay of 1.9 (±1.9), 4.4 (±4.3), and 7 (±9.4) days (p< 0.001). The median hospital charge associated with procedures performed in group A, B, and C was $57,411, $37,987 and $27,447 adjusted for length of stay. The incremental charge of robotic surgery over other surgeries was due to the cost of operating room time.

Conclusions: In this large series of endometrial cancer patients who underwent robotic surgery, whites were more likely to undergo a robotic procedure compared to non-whites. There was a significant increase in the cost with shorter length of hospitalization. Trends and factors associated with robotic surgery require further investigation.
NERVE SPARING SURGICAL TECHNIQUE (NS) IN CERVICAL CANCER. ITS ROLE ON BLADDER FUNCTION, PRELIMINARY RESULTS OF A RANDOMIZED STUDY

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¹Oncology Unit, Obstetrics and Gynecology Department, ²Urology Department, ³Obstetrics and Gynecology Department, Buenos Aires University Hospital, Buenos Aires, Argentina

Objective: To analyze the role of NS on bladder function in patients with cervical cancer

Materials: 13 patients were included. The mean age was 39 (range 33-72). FIGO stage was: Ia1 in 2 cases, Ia2 in 1, Ib1 in 6, Ib2 in 3 and Iia in 1. Patients were submitted to an urodynamics evaluation prior to treatment and randomized in two arms to perform NS or not during Radical Hysterectomy.

Two patients stage Ib2 received neoadjuvant chemotherapy, the third one was an adenocarcinoma.

Results: 7 patients were included in the NS arm and 6 in the other one. Among the 13 patients, only 11 presented detrusor muscle contraction (DMC) in the preoperative study. The 2 patients with no contraction were in the no NS arm but both presented DMC in the postoperative evaluation.

Among the 7 patients in the NS arm, 6 presented DMC in the postoperative study. Among the 6 patients in the no NS arm, all them presented DMC in the second study.

Conclusion: We found no role of NS on DMC in these preliminary results. We are enrolling more patients in order to follow with this analysis.
TOTAL LAPAROSCOPIC HYSTERECTOMY FOR EARLY-STAGE ENDOMETRIAL CANCER USING AN INTRA-UTERINE MANIPULATOR: IS IT A BIAS FOR FROZEN SECTION ANALYSIS? A CASE-CONTROL STUDY

M.L. Gagliardi¹, A. Fagotti¹, G.F. Zannoni², G. Vizzielli¹, B. Costantini¹, V. Gallotta¹, G. Scambia¹, F. Fanfani¹

¹Dept. Obstetrics and Gynecology, ²Dept. of Anatomic Pathology and Histology, Catholic University of the Sacred Heart, Roma, Italy

Background: To evaluate the accuracy of frozen section diagnosis comparing the results by a laparoscopic or laparotomic approach, in order to analyze if the use of an intrauterine manipulator can alter the specimen.

Methods: Women with early stage endometrial cancer divided into a study group (114 patients), and a control group (204 patients). All patients underwent to a total hysterectomy, bilateral salpingo-oophorectomy, ± pelvic lymphadenectomy, ± aortic lymphadenectomy (according to our internal protocol) and peritoneal washing. Accuracy, over and under diagnosis of frozen section in the two groups.

Results and conclusion: In the study group, all patients underwent to a total hysterectomy and bilateral salpingo-oophorectomy. Systematic bilateral pelvic lymphadenectomy was performed in 50 patients (43.8%) and 1 patients (0.8%) underwent to a para-aortic lymphadenectomy because had positive pelvic nodes at FS examination. In all cases (100%) the FS diagnosis has been obtained. For the myometrial invasion, histological type and grading, the accuracy rate was of 91.2%, 98.2% and 93%, respectively. In the control group, all patients underwent to the same surgical treatment respect to the study group. Pelvic lymphadenectomy was performed in 114 patients (55.8%) and the median number of pelvic lymph nodes removed was 22 (range 9-58). Seven (3.4%) patients underwent to a para-aortic lymphadenectomy because had positive pelvic nodes at FS examination. For the myometrial invasion, histological type and grading, the accuracy rate was of 85.2%, 98.5% and 95.1%, respectively. Total laparoscopic hysterectomy is feasible and safe, and the intrauterine manipulator seems not to alter the frozen section.
ADMINISTRATION OF AMINO ACIDS AGENTS FOLLOWED BY INTRAPERITONEAL IRRIGATION WITH SODIUM BICARBONATE IS EFFECTIVE THERAPY IN PATIENTS OF PSEUDOMYXOMA PERITONEI

S. Kusunoki, K. Kato, S. Suga, M. Kimura, Y. Terao, S. Takeda

Juntendo University, Tokyo, Japan

Pseudomyxoma peritonei (PMP) is a rare disease, which presents with large amounts of mucinous ascites. The primary tumor is often a mucinous cystadenoma or cystadenocarcinoma of the appendix. The main treatment is surgical resection of the tumor and the removal of mucus, but it is impossible to remove mucus completely. Intraperitoneal irrigation with 7% sodium bicarbonate was effective as mucolytic agents. However, it has been reported that alkalosis occurred in patients who underwent its therapy. We recently experienced two cases with PMP who underwent intraperitoneal irrigation with 7% sodium bicarbonate. In one case, alkalosis occurred after irrigation with 7% sodium bicarbonate and gradually improved. Blood gas analysis became normal after operation. She was performed right salpingo-oophorectomy, omentectomy and appendectomy. Review of the histology confirmed a mucinous tumor of low malignant potential of the right ovary. In the other case, we administered amino acids agents intravenously followed by intraperitoneal irrigation with 7% sodium bicarbonate. After 5 minutes of irrigation, alkalosis occurred, but improved very quickly. She was performed total abdominal hysterectomy, bilateral salpingo-oophorectomy and appendectomy. Review of the histology confirmed an appendiceal mucinous cystadenocarcinoma with metastases in the bilateral ovaries. Mucus in peritoneal cavity was almost removed in these cases. Both patients are doing well with no recurrence. Administration of amino acids agents followed by intraperitoneal irrigation with 7% sodium bicarbonate is effective therapy in patients of PMP.
ROBOTIC RADICAL HYSTERECTOMY: COMPARISON OF OUTCOMES AND COST

W. Gotlieb¹, D. Haliday², S. Lau¹

¹McGill University, Montreal, QC, Canada, ²University of the West Indies, Nassau, Bahamas

Objectives: Comparison of outcomes and cost of radical hysterectomy for cervical cancer with negative sentinel nodes completed via robotics versus laparotomy.

Methods: Forty patients underwent radical hysterectomy with/o bilateral salpingo-oophorectomy, for early stage cervical cancer (16 robotic, 24 laparotomy). The data for the robotic group was collected prospectively and compared to the historic cohort, who underwent laparotomy. Evaluation of real direct hospital cost was performed comparing both modalities.

Results: Patients undergoing robotic radical hysterectomy experienced longer operative time than the laparotomy cohort (351 min vs. 283 min p =0.0001). Estimated blood loss was significantly reduced for the robotic cohort (106 ml vs. 546 ml p < 0.0001). The complication rate was lower in the robotic cohort relative to the laparotomy (18.8% vs. 70.8% p = 0.003). Average hospital stay for the robotic patients was significantly shorter than those undergoing laparotomy (1.9 days versus 7.2 days, p < 0.0001). Lymph node retrieval did not differ between the two groups (robotic 15 nodes, laparotomy 13 nodes). The total average peri-operative costs for radical hysterectomy with lymphadenectomy completed via laparotomy was CAN $11764±6790, and for robotic assistance 8183±1089 (p=0.002). When amortization of the robot was included, there remained a trend in favor of the robotic approach, but it did not reach statistical significance.

Conclusions: While robotics takes longer to perform than traditional laparotomy, it provides the patient with a shorter hospital stay, less need for pain medications and reduced peri-operative morbidity. In addition real average hospital costs tend to be lower.
OUTCOME AND QUALITY OF LIFE IN ELDERLY PATIENTS UNDERGOING ROBOTIC SURGERY FOR ENDOMETRIAL CANCER

W. Gotlieb¹, Z. Vaknin¹, T. Perri², C. Deland¹, N. Drummond¹, Z. Rosberger¹, S. Lau¹, I. Gourdji¹

¹McGill University, Montreal, QC, Canada, ²Tel Aviv University, Tel Aviv, Israel

Objective: Evaluation of surgical outcomes, including quality of life, in patients with endometrial cancer in the early phase of implementation of a robotic surgery program, comparing elderly patients to younger patients.

Methods: Prospective evaluation of peri-operative data and quality-of-life survey following robotic surgery for endometrial cancer performed. Women were divided in two groups based on age, allowing comparison of outcome between the elderly-group (≥ 70 years), and the younger-group (< 70 years).

Results: Out of the first one-hundred patients, 41 were elderly (mean age 78 years). The elderly-group had significantly higher number of co-morbidities and more advanced disease when compared to the younger-women. Despite this, elderly- women had similar mean operative times (252 min vs 243 min), mean console times (171 min vs 175 min), and mean blood-loss (83 vs 81 ml) as compared to the younger-group. Conversion rate to mini-laparotomy was 6%, all of which were performed at the end of surgery for the removal of enlarged uteri that could not be delivered vaginally. The overall perioperative complication rates were not statistically different between the age groups. Median hospital stay tended to be longer for the elderly women (2 days vs 1), but was not statistically significant. The post-operative quality-of-life assessment revealed that patients, young, and old alike were highly satisfied with the procedure.

Conclusions: Prospective evaluation indicates that even in the early phases of implementation of a robotic surgical program for endometrial cancer, the procedure appears safe and confers an excellent quality-of-life for elderly patients.
IMPACT OF OBESITY ON ROBOTIC SURGERY FOR ENDOMETRIAL CANCER

W. Gotlieb, K. Buzaglo, Z. Vaknin, S. Brin, R. Kaufer, S. Aubin, S. Lau

McGill University, Montreal, QC, Canada

Objective: Prospective evaluation of outcome of robotics, comparing patients with different body mass indexes (BMI).

Methods: Prospective cohort study of all women undergoing surgery for endometrial cancer at our institution since the initiation of a robotic program in December 2007. Surgical and personal outcome, including quality of life and recovery, was compared between normal weight (n=52), obese (n=33) and morbidly obese (n = 23) patients undergoing robotic surgery for endometrial cancer.

Results: Women were divided into three groups based on BMI. The average BMI in each group was 25 (18.7-29.4), 34 (30.1-38.4), and 46 (40.0-58.8) respectively. Women with higher BMI were younger, (67.7 vs. 67.1 vs. 55.2, p< 0.0001), had a higher ASA level (1.7 vs. 2.0 vs. 2.3, p< 0.01) and were more likely to suffer from diabetes (4% vs. 27% vs. 25%, p< 0.32) and hypertension (37% vs. 73% vs. 75%, p< 0.19). Despite these, console time (168 min. vs. 174 min. vs. 188 min., p< 0.36), evaluated blood loss (67mL vs. 113mL vs. 98mL, p< 0.23), and length of stay in days (1.7 vs. 3.2 vs. 2.0, p< 0.30) were not statistically different between the three groups. In addition there was no increased conversion rate to laparotomy in the obese patients. Patients in all three groups reported quick recovery, low pain and high satisfaction with the procedure.

Conclusion: Obese and morbidly obese patients with endometrial cancer are good candidates for robotic surgery. These women benefit considerably from MIS, reducing peri-operative complications.
ROBOT ASSISTED LAPAROSCOPIC TRANSPERITONEAL PARA - AORTIC LYMPHADENECTOMY IN THE MANAGEMENT OF GYNAECOLOGICAL CANCERS

M. Fastrez, J. Vandromme, S. Rozenberg, M. Degueldre

CHU Saint Pierre, Brussels, Belgium

Objectives: Optimal cancer staging is essential. Imaging techniques sometimes underestimate tumours' extension. Para-aortic lymph node metastases in locally advanced cervical cancer (LACC) identifies patients with poor prognosis. Occult para-aortic node metastases are found in 10% of stage 1 ovarian cancer. Laparoscopic para-aortic lymphadenectomy is one of the diagnostic tools. We evaluated the feasibility and safety of robot assisted laparoscopic para-aortic lymphadenectomy.

Study design: We prospectively followed up 15 patients who underwent robot assisted transperitoneal laparoscopic para-aortic lymphadenectomy, among which 13 had LACC, 1 a stage I epithelial ovarian cancer, 1 an advanced endometrial carcinoma.

Results: We isolated from 1 to 38 nodes per patient: 2 out of 13 patients with LACC had para-aortic node metastases and were treated with adapted radiotherapy fields. The patient with endometrial carcinoma had bulky para-aortic node metastases. The patient with ovarian cancer had negative nodes. One patient died at day 14 post operation from a necrotizing fasciitis. We encountered 1 intraoperative arterial injury which was managed by laparotomy. One out of the 15 patients had chylous ascites that was spontaneously resolved and 2 patients had subcoetaneous lymphoedema which both spontaneously disappeared.

Conclusions: In this small prospective series, we observed that robot assisted laparoscopic para-aortic lymphadenectomy is feasible and provides the surgeon with great precision. Post operative mortality was probably independent of the use of robot surgery. Larger prospective trials are needed to validate the use of this technique.
VAGINA RECONSTRUCTIVE SURGERY IN PRIMARY VAGINAL MELANOMA AFTER EXTENSIVE SURGERY


Obstetrics and Gynecology, Tsinghua University, Yuquan Hospital, Beijing, China

Surgery is one of the major methods to treat primary vaginal melanoma. However, the choice of different approaches in terms of extensive surgery or local excision is controversial. We reported two cases of primary vaginal melanoma underwent radical hysterectomy, radical vaginectomy and vagina reconstruction with the anterior and posterior tunica of serosa uterus. So far, they had survived for 35 and 54 months, respectively with a normal sexual function as well. We suggested that the extensive surgical extirpation should be performed as a primary treatment to achieve ideal clinical effectiveness and vagina reconstruction with tunica serosa uteri should be performed to improve quality of life.
ROBOTIC ENDOMETRIAL CANCER STAGING IN THE MORBIDLY OBSE

A. Burnett¹, P. Stone¹, A. Stevens², J. Roman¹

¹Gynecologic Oncology, ²Obstetrics and Gynecology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Morbid obesity (BMI ≥ 40 kg/m²) is a risk factor for endometrial cancer. It is also a significant risk factor for complications from endometrial staging via laparotomy.

We report on 15 morbidly obese women who underwent endometrial cancer staging using the da Vinci S robotic system.

The median age was 65.5 years (32-79). Median BMI was 43.9 (40-66). 8 patients were grade 1; 2 grade 2; 3 grade 3; and one each MMMT and clear cell. The median pelvic lymph nodes removed was 10 (2-20); para-aortic lymph nodes was 6 (2-11). Median length of staging was 188 minutes (130-255) - the first three cases averaged 220 minutes; the last three averaged 141 minutes. Median EBL was 125 cc (minimal-800cc) with no perioperative transfusions. The average length of stay was 1.25 days (1-2 days). There were two complications: one patient was hospitalized for vaginal bleeding 30 days post-operatively; one patient developed a vesico-vaginal fistula. No wound complications occurred.

Three patients had positive para-aortic nodes, 2 of whom also had positive pelvic nodes. The stage of the patients was Ia in 6; Ib in 4; Iib in 2; and IIic2 in 3. With median follow-up of 6 months (2-21 months), 3 patients are currently on adjuvant chemo and/or radiation, 1 recurred at six months and is currently NED, 1 patient is alive with disease, and 10 are NED.

Robotic staging for endometrial cancer is feasible in morbidly obese women and results in decreased length of stay and may decrease morbidity.
LAPAROSCOPIC RETROPERITONEAL LYMPHADENECTOMY IN GYNAECOLOGICAL CANCER

M. Cusido, S. Baulies, F. Fargas, I. Rodriguez, J. Browne, R. Fabregas

Institut Universitari Dexeus, Barcelona, Spain

Introduction: To evaluate the feasibility and effectiveness of laparoscopic retroperitoneal lymphadenectomy in gynaecological cancer.

Study desing: 18 retroperitoneal lymphadenectomies were performed in Institut Universitari Dexeus from 2007 to 2010. The following data were reviewed: pathological data and postoperative follow-up.

Results: The mean age was 55.6 years. 50% of tumors were endometrioid type endometrial carcinoma, 16.66% papillary serous endometrial carcinoma, 16.66% cervical carcinoma, 5.55% carcinosarcoma, 2.22% ovarian cancer. In 2 cases ovarian cancer was observed concomitant to endometrial carcinoma. 50% of cases were classified as stage II. The number of aortic lymph nodes analyzed varied from 4 to 29 (mean 13.11) and 11.11% showed node involvement. A single retroperitoneal aortic lymphadenectomy was performed in 22.22% and an hysterectomy with both pelvic and aortic lymphadenectomy in 77.78%. Operating time was 161.25. minutes (range 90-255) in a single retroperitoneal aortic lymphadenectomy and 277.85 minutes (180-330) when hysterectomy and pelvic/aortic lymphadenectomy were performed. The mean drop in haemoglobin in single aortic lymphadenectomy was 1.22 compared to 1.69 in the hysterectomy group. The mean length of hospital stay was 3.83 days (range 2-8). Blood transfusion was not required. There were no intra-operative complications but 3 cases presented minor postoperative complications: deep vein thrombosis in lower extremity (5.55%), lymphocele (11.11%) and wound infection (11.11%).

Conclusions:

- Lower rate of intestinal adhesions and complications.
- Reduced hospital stay and shorter recovery time.
- Do not delay the onset of adjuvant radiotherapy or chemotherapy.
- It requires a learning curve for the surgeon and the standardization of the technique.
ROBOTIC ASSISTED RADICAL HYSTERECTOMY FOR CERVICAL CANCER

S.K. Raju¹, G. Mehra¹,², M.A. Kodampur¹, I. Ahmed³, O. Devaja²

¹Gynaecological Oncology, Guy's and St Thomas' NHS Foundation Trust; Cancer Centre for South East London Cancer Centre, London, ²Gynaecological Oncology, Maidstone NHS Hospital, Cancer Centre for West Kent Cancer Network, Kent, ³Anaesthesia, Guy's and St Thomas’ NHS Foundation Trust; Cancer Centre for South East London Cancer Centre, London, UK

Background & aims: Robotic surgery is being increasingly used to perform minimal access surgery with its advantages of improved dexterity for the surgeon and higher precision of dissection. Our aim was to assess the feasibility of robotic surgery at our cancer centre in the United Kingdom for cervical cancer patients.

Methods: We recruited 4 women who were undergoing surgical treatment for ≤FIGO stage-Ila cervical cancer. Robotic assisted Radical Hysterectomy (RARH) was performed using Da Vinci-I robot with three robotic arms. The operating time, blood loss, hospital stay and complications were recorded for each patient.

Results: All 4 women successfully completed RARH. The age ranged from 22-51 years with the range of BMI from 28-33 kg/m². All women had Squamous cell carcinoma. Median estimated blood loss was 75 ml (50 - 120) with a median operating time of 210 min (180 - 240 range), Median hospital stay was 1 day (1 - 2 range). The median lymphnode yield was 26 nodes (26 - 32 range). One woman had urinary retention requiring catheterisation and stayed an extra day in the hospital.

Conclusion: RARH is feasible for surgical treatment of early stage cervical cancer. It has it´s advantages in terms of early recovery & short hospital.
CHOOSING THE RIGHT PATIENT: PREDICTING THE CONVERSION OF LAPAROSCOPY TO LAPAROTOMY DURING THE SURGICAL MANAGEMENT OF ENDOMETRIAL CANCER

K. Kieser¹, A. Ball¹, C. O'Connell², J. Bentley¹

¹Obstetrics & Gynecology, Dalhousie University, ²Perinatal Epidemiology Research Unit, IWK Health Centre, Halifax, NS, Canada

Background: Endometrial cancer remains the leading cause of gynecologic cancer in North America. The staging and initial treatment of endometrial cancer involves surgery. Laparoscopic surgery is increasingly being used as an alternative to laparotomy. By examining factors involved in the choice of surgical approach and the ultimate procedure performed, patient selection for laparoscopy may be optimized.

Objective: To identify factors which may be barriers to laparoscopic surgery in endometrial cancer patients undergoing surgery by the gynecologic oncology group at the Capital District Health Authority (CDHA) in Halifax, NS.

Methods: A retrospective review of cases of preoperative histologically confirmed endometrial cancer diagnosed from 2005 to 2007 who received surgery at the CDHA.

Results: 428 patients were diagnosed with endometrial cancer between 2005 and 2007. 289 cases with a preoperative diagnosis received surgery at CDHA. Of these, 66.1% of patients underwent a planned laparotomy while 33.9% had a planned laparoscopy. The proportion of attempted laparoscopies increased from 21.9% to 57.1% (p=0.002) over time, while there was no significant change in the conversion rate 17.3%. Conversion to laparotomy did not result in longer OR times than laparoscopy, 153min vs 151min, (p>0.05) nor in increased operative morbidity. Independent predictors of laparoscopic conversion to laparotomy were age over 70 (p=0.03) and non-endometrioid histology (p=0.002).

Conclusion: Our data identify age and non-endometrioid histology as independent factors for conversion to laparotomy. We are reassured that patients undergoing a conversion to laparotomy do not have a significant increase in OR time or operative morbidity.

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<tr>
<td>• Blood transfusion within 30 days</td>
<td>29 (15.1%)*</td>
<td>0</td>
<td>0</td>
<td>*p&lt;0.001</td>
</tr>
<tr>
<td>• Vascular</td>
<td>5 (2.6%)</td>
<td>0</td>
<td>1 (5.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>• Bowel</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>• Bladder/ ureteric</td>
<td>2 (1.0%)</td>
<td>1 (1.2%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>• DVT/PE</td>
<td>1 (0.5%)</td>
<td>1 (1.2%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>• Fascial dehiscence</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>• Wound complication</td>
<td>32 (16.7%)</td>
<td>6 (7.4%)</td>
<td>1 (5.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>• Ileus</td>
<td>11 (5.8%)</td>
<td>1 (1.2%)</td>
<td>1 (5.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>• Abscess</td>
<td>3 (1.6%)</td>
<td>3 (3.7%)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

[Operative Complications]
LASER ABLATION VERSUS LLETZ FOR THE TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA: SHORT AND LONG TERM OUTCOMES

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Aim: To determine short and long term effects of 2 alternative treatment options for CIN.

Design: Retrospective cohort analysis

Setting: District General Hospital, UK

Methods: Clinical details and study data retrieved from colposcopy database. Pregnancy data obtained from patient files. A previous history of knife conisation or more than 1 previous treatment were excluded from the study.

Main outcome measures: Short term parameters- negative first post treatment smear; need for repeat treatment or smear. Long term parameters- recurrence of abnormal smear; late miscarriages and preterm delivery as a result of cervical incompetence; cervical stenosis and its sequelae.

Results: 46 patents underwent LLETZ; 22 had laser ablation. 37 had LLETZ (80.43%) and had negative smear after treatment; 4 (8.69%) had repeat LLETZ; 3 (6.52%) had repeat colposcopy; 1 had hysterectomy for Stage 1a1 cervical cancer. 5 (10.87%) had further interval abnormal smears and 3 required treatment. 3 (60%) had term pregnancies; 1 (20%) late miscarriage and 1 (20%) preterm delivery. One patient had haematometra due to cervical stenosis.

In laser group, 15 had negative smear after treatment (68.18%); 1 had repeat laser (4.55%); 5 had repeat colposcopy (22.73%). 2 (9.09%) patients had further abnormal interval smears and none required treatment. 4 (80%) patients had term pregnancies. One (20%) delivered at 36 weeks.

Conclusions: Although laser ablation is associated with a higher number of positive post treatment smears, the repeat treatment rate is lower than for LLETZ but the recurrence rate of interval smear abnormalities is similar.
ROBOT-ASSISTED SURGICAL STAGING FOR ENDOMETRIAL CANCER COMPARED TO LAPAROSCOPY AND LAPAROTOMY

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Objective: To compare outcomes of endometrial cancer patients who had surgical staging by 3 different methods.

Design: Retrospective chart review.

Setting: Academic institution.

Patients: Endometrial cancer patients.

Interventions: Robotic (TRH), Laparoscopic (TLH), and Open (TAH) surgical staging (100, 30, and 100 patients, respectively).

Results: The body mass index (BMI) of patients undergoing TRH (median; range, 34; 19-63) was significantly higher than those undergoing TLH (median; range, 31; 20-54) (P= 0.034). There was no difference in BMI between the TRH group and the open group (median; range, 34; 19-56) (P=0.727). The length of hospital stay was similar in the TRH group (median; range, 1; 0-9) and the TLH group (median; range, 1; 1-3) (P=0.68). Length of stay was significantly higher in the TAH group (median; range, 3; 2-13) than the other two groups (P=0.0001). Lymph node count was similar in the TRH (median; range, 21; 0-64), the TLH (median; range, 20; 0-38), and the TAH (median; range, 23; 0-41) groups (P=0.12). Uterine weight was significantly lower in the TLH compared to the TAH group (P=0.034). Estimated blood loss (mL) was significantly lower in the TRH group (median, range;100, 50-400) and the TLH group (median, range;150, 50-500) than in the TAH group (median, range;300, 100-1400) (P< 0.002).

Conclusion: Robot-assisted surgical staging for endometrial cancer can be performed in patients with higher BMI, including super morbid obesity, and larger uteri than laparoscopic staging, and with less blood loss and a shorter hospital stay than laparotomy.
THE USE OF LAPAROSTOMY IN GYNAECOLOGICAL ONCOLOGY PATIENTS

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¹Division of Gynaecological Oncology, St George’s Hospital, ²Division of Gynaecological Oncology, Royal Marsden Hospital, London, UK

Background: Following major abdominal surgery for gynaecological cancer, primary closure of the abdominal wound may be contraindicated because of the excessive tension and raised intra-abdominal pressure that would result in the abdominal compartment syndrome. In these circumstances a temporary closure or covering of the abdominal viscera (laparostomy) is provided and delayed primary closure effected a few days later.

Aims: To review our experience in the use of laparostomy in patients requiring surgery for gynaecological cancer.

Method: Retrospective case review of all abdominal surgery performed in a 7-year period.

Results: In a 7-year period, 7 patients had a laparostomy, representing approximately 0.56% of all abdominal procedures. The mean age of these patients was 63.6 years old. Four patients had ovarian cancer, 3 of whom had recurrent disease and bowel obstruction. One required a laparostomy following an anterior exenteration for recurrent vaginal cancer, and one had a posterior exenteration for recurrent cervical cancer. One patient developed bowel obstruction after a major laparoscopic procedure and had an infarcted bowel segment at a port site. In five of the seven cases the abdominal procedure was an emergency. The most common method to cover abdominal viscera is an open saline bag. Six of seven patients survived, in 6 cases the laparostomy was closed uneventfully within 72 hrs.

Conclusion: Laparostomy is rarely required in gynaecological oncology practice but can be lifesaving to avoid the abdominal compartment syndrome. Patients needing a laparostomy are more likely to have recurrent ovarian cancer and to be undergoing an emergency procedure.
Intravenous leiomyomatosis extending to the right ventricle: successful one-stage operation without cardiotomy and cardiopulmonary bypass through manual extracting method

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\(^1\)Ulsan University Hospital, UUCM, Ulsan, \(^2\)Inje University Haeundae Paik Hospital, Pusan, Republic of Korea

**Aims:** Intravenous leiomyomatosis (IVL) with cardiac extension has been rarely described in gynecological literatures. Most of reports suggested that the best treatment is complete surgical resection of the tumor under cardiopulmonary bypass (CPB) and total circulatory arrest with cardiotomy. Because most of IVL has an absent or minimal attachment to vessel and heart, complete resection of tumor without cardiotomy and CPB is practicable when appropriate imaging and surgical skills on operation.

We describe a unique surgical method of IVL that progressed along the inferior vena cava (IVC) up to the right ventricle through the left gonadal vein, which was removed through abdominal approach without cardiotomy and CPB.

**Case:** A 53-year-old woman was admitted to our institution with 2-month history of chest discomfort when stooping position and intermittent syncope. Preoperative imaging study (echocardiogram, CT) suggested that uterine mass, approximately 23.0 X 17.0 X 15.0, with left gonadal vein thrombus extending to IVC up to right ventricle. Additionally, transesophageal echocardiogram (TEE) revealed that the mass was free-floating without attachment to IVC and heart. Surgical approach was performed through laparotomy without CPB. After hysterectomy and adnexectomy, venotomy was performed in IVC around left renal vein and gonadal vein. Thereafter, 27-cm length of intracardiac and intravenous tumor was removed by manual extraction under TEE.

**Conclusions:** If IVL with cardiac extension is non-adherent to vessel and heart, as in the present case, cardiotomy and CPB may not be required. Also, IVC and cardiac leiomyoma may be successfully extracted through manual extraction using intraoperative TEE.
LAPAROSCOPIC ASSISTED VAGINAL HYSTERECTOMY VERSUS LAPAROSCOPIC TOTAL HYSTERECTOMY

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Objectives: To compare operative time and blood loss in LAVH vs LTH by a single operator.

Materials and methods: Retrospective retrieval of medical records of LAVH and LTH operated by a single operator between the period 2000 to 2007. Statistics was performed using Mann-Whitney test.

Results: Forty LAVH were performed by the first author before mid-2006 and 27 LTH were performed after mid-2006. Majority were uterine/cervical preinvasive or invasive lesions. The median age, body weight and uterine weight of LAVH and LTH were 50.5 and 54 years old ; 58 and 58.5 kg and 122 and 106 gm respectively. All has no statistic difference. The operative time was shorter in LAVH group, P=0.045. The ranges of operative time in LAVH and LTH were 63-210 and 65-230 minutes with a median of 114 and 123 minutes respectively. On the other hand, blood loss was less in LTH group, P=0.001. The ranges of blood loss in LAVH and LTH were 20-1200 and 50-600 ml with a median of 300 and 150 ml respectively.

Conclusions: LTH though may need slightly longer duration of operative time has less blood loss than LAVH. The reason could be due to the early dessication of the uterine vessels at the origin of the internal iliac arteries in LTH before further dessication and division of uterine vessels next to the cervix. The limitation of this study was the difference in time period where the difference could be due to increasing experience of the operator.
UTILITY OF PERITONEAL LAVAGE CYTOLOGY DURING LAPAROSCOPIC SALPINGO-OOPHORECTOMY

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Background: Laparoscopic salpingo-oophorectomy is carried out for various indications when the suspicion of malignancy is low. Peritoneal lavage cytology is usually performed at the same time to aid in detection of occult malignancy. The evidence base for this practice is weak. The aim of our study was to assess the significance of peritoneal washing cytology at the time of laparoscopic salpingo-oophorectomy.

Patients and methods: Four hundred and nine women who had laparoscopic salpingo-oophorectomy under the gynaecology oncology team at Addenbrooke’s hospital between 2004 and December 2009 were included in the retrospective analysis. One hundred and eleven women had risk reducing salpingo-oophorectomy, 103 women had salpingo-oophorectomy as a part of management of breast cancer, 59 had simple and 111 had complex ovarian cysts and 23 had the procedure done for other reasons. Histology and cytology results were revisited and all hospital records checked for subsequent malignancy.

Results: Eleven of the 409 women in our study had unsuspected cancer on histo-pathological examination and 3 of them had positive peritoneal washings. One patient had positive washings from metastatic breast cancer. Thirteen patients developed different malignancies subsequently but none had primary peritoneal/ovarian cancer within a median follow-up interval of 34 months.

Conclusion: Peritoneal lavage cytology did not pick up any additional unsuspected malignancy in the study population. Based on the evidence we present we suggest that peritoneal washing cytology during laparoscopic salpingo-oophorectomy is of limited value and should not be routinely practised.
SIMULTANEOUS COMBINE OPERATIONS ON PATIENTS WITH CARDIOVASCULAR AND FEMALE GENITAL DISEASES

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¹Gynecological Oncological, National Cancer Center of N.N. Alexandrov, ²Labotatory Heat Surgery, Republic Scientific Practical Center 'Cardiology', ³Oncological, Belarussian Medical Academy of Postgraduate Education, Minsk, Belarus

Combination cardiovascular diseases (CVD) and female genital organs diseases (FGOD) represents the problem as for to the oncogynecologists and also cardiovascular surgeons (CVS).

Materials and methods: 13 simultaneous surgical operations (SSO) were performed by CVS from Republic National Scientific Center «Cardiology» and oncogynecologists from National Cancer Center of N.N. Alexandrov in 2003 - 2010. The mean patient’s age was 50.8±10.8. Benign tumors of FGO were found out in 8 cases. Leiomyoma was detected in 4 cases, therefore hysterectomy with bilateral salpingooophorectomy were done. Borderline ovarian tumors were found in 4 cases. In these cases hysterectomy bilateral salpingooophorectomy, omentectomy with surgical staging procedures were performed. Malignant tumors were detected in 5 cases: uterine cancer of I stage was found in 3 cases, ovarian cancer I and II stages was detected in 2 cases. In these cases surgical operations were performed as the first phase antitumor treatment how component of SSO. Chronic rheumatic cardiac disease with forming mitral and aortic defects was revealed in 6 cases; accordingly the prosthetic repair of failed hearts values was performed when necessary with plastic of atrium. Coronary heart disease with aorta atherosclerosis and stenosis of coronary arteries was performed in 7 cases. In this group coronary arterial bypass graft and mammocoronary were done. All these patients had NYHA 2 - 4. Postoperative period was unremarkable in all cases.

Conclusion: Performing simultaneous surgical operations in patients with CVD and FGOD is the actual and important interdisciplinary problem.
BUDDY OPERATING AS A TOOL TO ACCELERATE SKILL ACQUISITION FOR LAPAROSCOPIC RADICAL HysteRCTOMIES

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\textsuperscript{1}Obstetrics and Gynecology, \textsuperscript{2}Statistics, \textsuperscript{3}Gynecologic Oncology, McMaster University, Hamilton, ON, Canada, \textsuperscript{4}Gynecologic Oncology, St Augustinus Hospital, Antwerpen, Belgium

Objective: Total Laparoscopic radical hysterectomy (TLRH) requires advanced skill in laparoscopy. We evaluated various objective measurements of surgical skill representing the learning curve throughout the first two years of implementation of TLRH at our institution. We also describe our technique of ‘buddy operating’.

Study methods: Charts were retrospectively reviewed for 45 patients undergoing TLRH and pelvic lymphadenectomy (PND) at the Hamilton Health Sciences from August 14, 2007 to August 14, 2009. A discriminant function analysis was used to describe the learning curve. Chi square and t-tests were used for discrete variables.

Results: The most predictive learning curve model divided the sample in two, with an accurate group assignment 67.4\% of the time. After the first 23 procedures, operative time was significantly shorter (201.7 vs. 176.6 min, \textit{p}=0.02), estimated blood loss was significantly lower (355.7 vs. 196.3 ml, \textit{p}=0.01), the number of lymph nodes removed was significantly higher (11.5 vs. 15.3, \textit{p}=0.02), and hospital length of stay was significantly shorter (1.56 vs. 0.13 days, \textit{p}=0.002). There were non-significant trends toward decreasing intra-operative complications and post-operative morbidity.

Conclusions: TLRH with PND is an important procedure in gynecologic oncology. After a fellowship training program including laparoscopy, the learning curve improves after 23 cases. This is shorter than previously reported, and may be due to the technique of buddy operating.
LAPAROSCOPIC MANAGEMENT OF LYMPHOCYST AND SEVERE ADHESION POST CONVENTIONAL RADICAL HYSTERECTOMY

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¹Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand, ²Obstetrics and Gynecology, Chang Gung Memorial Hospital, Tao-Yuan, Taiwan R.O.C.

Unpredictable pelvic mass after radical hysterectomy can develop on the troublesome of diagnosis. A 46-year-old woman with chronic renal disease, regular hemodialysis and history of cervical cancer IB2 who underwent conventional radical hysterectomy 10 years ago. Unknown origin of left adnexal cyst and right common iliac soft tissue lesion were demonstrated on the imaging study during regular follow up.

The less invasive operation using laparoscopic surgical technique was chosen. Lymphocyst at left pelvic area and right ovary were discovered. Excision of lymphocyst and right ovary were performed smoothly. In laparoscopic skilled institute, the minimally invasive procedure became the useful method for high risk patients with expected low operative morbidity outcome.
INTRA-OPERATIVE COMPLICATIONS IN GYNAECOLOGICAL ONCOLOGY: THE NEED FOR CLINICAL GOVERNANCE

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Northern Gynaecological Oncology Centre, Gateshead, UK

Objectives: To assess the incidence and outcome of intra-operative surgical complications of major abdominal gynaecological oncology procedures and to determine if clinical governance reduces complications and improves outcomes.

Methods: Prospectively collected data of 825 laparotomies (March 2008-April 2009 and May 2009-Jan 2010) were analysed. We compared the relative risks of intra-operative complications between two calendar period using Poisson regression. We also analysed indicators of post-operative outcomes between two calendar periods.

Results:

<table>
<thead>
<tr>
<th>Laparotomies</th>
<th>Total (n=825)</th>
<th>Total (%)</th>
<th>Period-1 (n=496)</th>
<th>Period-1 (%)</th>
<th>Period-2 (n=329)</th>
<th>Period-2 (%)</th>
<th>Poisson Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intra-op complications</td>
<td>120</td>
<td>14.5%</td>
<td>84</td>
<td>16.9%</td>
<td>36</td>
<td>10.9%</td>
<td>(p^* = 0.006)</td>
</tr>
<tr>
<td>Blood loss (&gt;2L)</td>
<td>87</td>
<td>10.5%</td>
<td>63</td>
<td>12.7%</td>
<td>24</td>
<td>7.3%</td>
<td>(p^* = 0.018)</td>
</tr>
<tr>
<td>Visceral injuries</td>
<td>64</td>
<td>7.7%</td>
<td>47</td>
<td>9.5%</td>
<td>17</td>
<td>5.2%</td>
<td>(p^* = 0.004)</td>
</tr>
</tbody>
</table>

[Intra-operative complications]

<table>
<thead>
<tr>
<th>Intra-op Complications</th>
<th>Total (n=120)</th>
<th>Total (%)</th>
<th>Period-1 (n=84)</th>
<th>Period-1 (%)</th>
<th>Period-2 (n=36)</th>
<th>Period-2 (%)</th>
<th>Fisher's exact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to theatre</td>
<td>11</td>
<td>9.2%</td>
<td>10</td>
<td>11.9%</td>
<td>1</td>
<td>2.8%</td>
<td>(p = 0.203)</td>
</tr>
<tr>
<td>Prolong recovery (&gt;6 weeks)</td>
<td>5</td>
<td>4.2%</td>
<td>5</td>
<td>5.9%</td>
<td>0</td>
<td>0%</td>
<td>(p = 0.937)</td>
</tr>
<tr>
<td>Mortality (30 day)</td>
<td>6</td>
<td>5.0%</td>
<td>5</td>
<td>5.9%</td>
<td>1</td>
<td>2.8%</td>
<td>(p = 0.831)</td>
</tr>
</tbody>
</table>

Mean | SD | Mean | SD | Mean | SD | t-test |
<table>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care stay (days)</td>
<td>2.1</td>
<td>1.4</td>
<td>2.9</td>
<td>5.8</td>
<td>1.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>10.4</td>
<td>10.5</td>
<td>10.8</td>
<td>11.9</td>
<td>9.6</td>
<td>6.3</td>
</tr>
</tbody>
</table>

[Outcome of intra-operative complications]

Conclusions: Major intra-operative blood loss and visceral injury in women undergoing laparotomy occurred in 10.5% and 7.7% respectively. Our analysis provides evidence that the relative risk has reduced between the two calendar periods for overall intra-operative complications, blood loss, visceral injuries and intensive care stay. These results are supportive of user specific improvement in intra-operative complications and their outcomes secondary to clinical governance.
NOVEL ROBOTIC VAGINAL SUTURING TECHNIQUE

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Introduction: The rate of vaginal cuff dehiscence has seem been shown to increase after both robotic and laparoscopic surgery compared to the open approach. The aim of this study is to describe the vaginal cuff dehiscence rate with a novel vaginal suturing technique performed by robotic approach in the treatment of oncological cases.

Methods: Medical records of all robotics procedures from January 1st, 2009 until February 28th, 2010 performed at the European Institute of Oncology of Milan were reviewed. 101 vaginal closures were carried out with a novel technique after extrafascial or radical hysterectomy.

Results: Among the 101 patients treated with the novel technique endometrial pathology was observed in 34 cases (33.7%), ovarian disease in 13 cases (12.9%) and cervical malignancies in 27 (26.7%). Two vaginal cuff dehiscences (1.9%) were observed after a median follow-up time of 300 days.

Conclusions: We suggest our vaginal closure technique may decrease the vaginal cuff dehiscence rate for robotic surgery, although longer follow-up time is needed and larger studies should been carried out, encouraging gynaecologic surgeons to perform it.
PET PROBE ASSISTED SURGICAL DEBULKING IN WOMEN WITH ISOLATED RECURRENT GYNECOLOGICAL TUMORS

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Objective: With current imaging technology recurrences in gynecological malignancies can be detected earlier and smaller. This study seeks to investigate the potential to improve survival by completely excising small isolated tumors with the help of the PET probe.

Study design: 17 patients from 2007-2010 with isolated recurrence had their tumors completely excised with the help of the PET probe. 18F-flourodeoxyglucose was administered 4-6 hours prior to surgery. A high-energy gamma probe was used to locate the tumor intra-operatively. A tumor-to-background-ratio of 1.5 counts-per-second and above was used for confirmation of the target lesion.

Results: Of the 17 patients there were 9 epithelial ovarian cancers, 5 cervical cancers, 2 uterine cancers, and 1 vulvar cancer. The tumors were completely removed in all but one case and were confirmed by pathology. The median overall survival was 14 months (range 3-33). Of the 9 ovarian cancers 7 were platinum resistant. The median overall survival of the ovarian cancer patients was 14.2 months (range 9-33) and the median progression free survival was 13 months (range 9-20). All 9 patients are still alive and 5 of the 9 are without evidence of disease.

Conclusion: This is the largest series to date involving PET probe debulking of gynecological malignancies. These results show that patients with isolated small volume recurrent gynecological tumors can potentially do well if the tumor can be accurately located and completely excised prior to adjuvant chemotherapy.
NEOADJUVANT CHEMORADIATION FOLLOWED BY LAPAROSCOPIC RADICAL HYSSTERECTOMY IN FIGO STAGE IIB - IIIB CERVICAL CANCER

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¹National Cancer Institute of Rome, ²University of Rome Tor Vergata, Rome, ³Catholic University, Campobasso, Italy

Objective: To evaluate the surgical outcome and the oncologic results of total laparoscopic radical hysterectomy (TLRH) after neoadjuvant chemoradiation therapy (NACRT) for locally advanced cervical carcinoma.

Material and methods: Between September 2003 and April 2010 five patients with locally advanced cervical cancer underwent TLRH type C₁, in 4 patients FIGO stage IIB, and type C₂ in 1 patient FIGO stage IIIB after NACRT were reviewed.

Results: Mean age was 51 years (range, 39 - 73 years); mean BMI was 25 kg/m² (range, 21 - 29 kg/m²); mean operative time was 264 minutes (range, 185 - 430 minutes); mean estimated blood loss was 250 ml (range, 100 - 400 ml), with no postoperative blood transfusion; mean number of removed pelvic lymph nodes was 19 (range, 11 - 31). Mean length of hospital stay was 5 days (range, 3 - 8 days). We registered 1 early postoperative complications. Clinical responses were observed in all patients. At pathological examination, 2 patients showed complete response, 2 patients had only a microscopic disease, 1 patient had a partial response. Mean follow-up time was 30 months (range, 2 - 81 months), with no evidence of disease

Conclusions: TLRH can be safely performed in patients with stage IIB-IIIB carcinoma of cervix after NACRT, with advantages of minimal blood loss, less postoperative morbidity and hospital stay.
THE EVALUATION OF ANXIETY LEVEL IN WOMEN TREATED BY LAPAROSCOPY AND LAPAROTOMY IN GYNECOLOGIC ONCOLOGY SETTING

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¹Gynecologic Oncology, ²Department of Physiotherapy, ³Medical Statistic, Maria Skłodowska-Curie Memorial Cancer Centre, Warsaw, Poland

Study objective: To evaluate the anxiety level in women with gynecologic tumors (cervical cancer, endometrial cancer and ovarian tumors) treated by surgery with laparoscopy and laparotomy.

Design: prospective non randomized study (Canadian Task Force classification II-1)

Setting: Oncological research institute.

Patients: The anxiety level was evaluated by State-Trait Anxiety Inventory in 319 women treated in Gynecologic Oncology Department, the Maria Skłodowska-Curie Memorial Cancer Center in Warsaw.

Interventions: Patients were treated by laparoscopy or laparotomy.

Measurements and main results: The regression analysis demonstrated that the level of state anxiety was significantly affected by the type of surgical procedure and the age of patients; the level of trait anxiety was dependent of patients age. The level of state anxiety was higher in patients treated by laparotomy and lower in patients scheduled for laparoscopy. The change in score of the state anxiety brought about by the surgery was lower in laparoscopy group. The diagnosis had no effect on the levels of both state and trait anxiety.

Conclusion: The type of surgical method affects the level of anxiety, laparoscopy produces less anxiety than laparotomy. The anxiety level related to the treatment method is an important factor that influence the quality of life and it should be taken into account in planning the treatment strategy in patients with gynecologic tumors.
RECTOSIGMOID RESECTION WITH VS. WITHOUT PROTECTIVE OSTOMY AS PART OF CYTOREDUCTIVE SURGERY FOR ADVANCED OVARIAN CANCER

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¹Gynecologic Oncology, ²Obstetrics and Gynecology, ³Obstetrics and Gynecology, Gynecologic Oncology, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

Objectives: The aim of this study is to assess the usefulness of protective ostomy after rectosigmoid resection as a part of cytoreductive operations in ovarian cancer.

Methods: A retrospective analysis of 38 advanced stage ovarian cancer patients, who underwent rectosigmoid colon excision and en bloc pelvic resection as a part of primary or secondary cytoreductive surgery in our clinic between 2000 and 2009, was performed. Surgical outcomes were evaluated.

Results: Mean age was 53.2±13.9 (min 21, max 79). All patients had preoperative bowel preparation (both oral and rectal). Three (7%) patients had stage 3b disease, 23 (60%) patients had stage 3c disease and 12 (31%) patients had stage 4. Protective ostomy was performed in 18 of 38 patients (47%). Methylen blue was injected from rectum in all patients and no leakage was observed during surgery in any of the patients. None of the patients had ascites and there was no tumor in anastomosis area. There was no residual tumor in 19 (50%) women; remaining 19 (50%) women had residual tumor of < 1 cm. Disease recurrence developed in 8 patients; 6 in the pelvic side and 2 in the liver. Six days after surgery 1 patient who did not have protective ostomy had leakage (5%). None of the patients with protective ostomy had leakage after surgery.

Conclusion: Cytoreductive surgery, including rectosigmoid colon resection, is indicated in the treatment of patients with advanced ovarian cancer. Protective ostomy has no impact on leakage after rectosigmoid resection.
RETROPERITONEAL DEBULKING IN RECURRENT GYNECOLOGICAL CANCER - THE CHALLENGE OF MULTISPECIALTY COOPERATION

J. Špaček¹, M. Broďák², Z. Bělobrádek³, P. Dvořák⁴, P. Navrátil², E. Křepinská¹, A. Řezáč¹

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Background: This study was aimed at evaluation of results of retroperitoneal debulking in recurrent disease in our oncogynecological centre during last five years.

Methods: Seven women underwent resection of solitary retroperitoneal localized recurrent disease in our centre during last five years. Results of the surgery were assessed as overall and disease-free survival.

Results: The median follow-up was 17 (6-28) months. The mean age was 57.4 (37-73) years. The mean size of tumors was 7.8 (5-13) cm. In one case (leiomyosarcoma of the cervix) we reported heavy hemorrhage (10000 ml).

Conclusions: Complete resection of tumor is the most effective modality of the treatment in solitary recurrent disease. We want to emphasize multispecialty gynecologic-urology and surgery collaboration in these complicated and sometimes heavy pretreated cases.

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MY BODY MYSELF: BODY IMAGE IN WOMEN WITH CANCER

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Purpose & content: Women who have had cancer experience significant changes to their body image as a result of the treatment (surgery, radiation, chemotherapy). These changes are often most acute in the survivorship phase of the cancer journey, when the threat to life has passed and when the woman is expected to go back to normal. But there is no normal for the woman who has survived the diagnosis and treatment of cancer. For women, body image is closely linked to sexual image, and changes to the physical body often result in sexual distancing or lack of pleasure.

Strategies: Using case examples of women with different kinds of cancer - cervical, uterine and vulvar - the presenter will illustrate the kinds of body image issues facing women who have survived cancer and their struggles to achieve an integrated sense of self. The presenter will also make suggestions for therapeutic strategies that have shown to be helpful in her clinical practice with this population.

Results: At the conclusion of this presentation, audience members will have a deeper understanding of the many challenges facing women who have been treated for cancer, and will be able to identify the most important issues for these women as they attempt to achieve a new normal in their lives.
DISTRIBUTION AND SUFFICIENCY OF PAIN CENTERS ACROSS TURKEY

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Objective: Palliative care units are a must for a comprehensive control of cancer treatments. There are only few number of palliative care in Turkey. Pain centers can never be a substitute for such centers, however, these centers may be a good step to initialize the palliative care concept across the country. This study aimed at analyzes the current status of Turkey with respect to pain centers.

Method: Each data is prospectively recorded by the questionnaires applied to Health governors of Turkish provinces. The number of pain centers and the medical staff working in these centers are prospectively collected. Annual number of patients diagnosed with cancer was accepted as 25 million according to Ministerial data.

Results: There were around 72 pain centers across the country in 33 provinces. Of these centers, 35 were within the governmental hospitals, 31 were in university hospitals and the remaining 6 were involved in private hospitals. Total number of medical staff working in these centers was 334 of which 254 (76%) were medical doctors. 28 (38.9%) centers were located in Istanbul and Ankara. The majority of these centers were in West and Middle Anatolia (56/72, 77.7%) compared to East, South and North regions.

Conclusion: The number of pain centers may be sufficient for Turkey however these centers are not evenly distributed, concentrated in only big cities.
EVALUATION OF PROPHYLAXIS EFFECTS OF GLYCIRRHIZA GLABRA AND ACHILLEA MILLEFOLIUM ON RADIOThERAPY SKIN-INDUCED REACTION IN BREAST CANCER CASES

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Background: The objective of this study was to compare the effect of Achillea millefolium and Glycyrrhizin glabra and comparison with placebo on radiotherapy skin-induced reaction in breast cancer cases.

Materials and methods: This double-blind randomized clinical trial was conducted in 75 patients with breast cancer after mastectomy. Patients were randomly divided in three groups (G1 = Achillea millefolium, G2 = Plasebo, G3 = Glycyrrhizin glabra). The rate and grade of desquamation were recorded in dose of 0, 30 and 50 Gy.

Results: No statistical significance was discovered for total characteristics of patients. The total complications were similar in three groups (G1 = 37.6%, G2 = 46.2%, G3 = 15.4%, p = 0.53) in dose of 30 Gy. However the severity of complication was lower in group 3 (Grade 2 =15.4%) and it was not reported in treatment groups grade 3 and 4 of desquamation. In most of the patients especially in treatment groups, grade 1 complication was occurred but in placebo group grade 2 was higher than the other groups and grade 3 was similar in group 3 with placebo. At the end, the rate of severe complications (grade 2 and 3) was higher in placebo group, but it was not statistically significant.

Conclusion: Our result was not manifested the significant differences between three groups of Glycirrhiza glabra and Achillea millefolium and placebo. However the severity of skin reactions was lower in two herbal groups.

Keywords: Breast cancer, Glycirrhiza glabra, Chilla millefolium, Desquamation
FACTORS ASSOCIATED WITH HOSPICE USE IN OVARIAN CANCER

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Objective: To determine the factors and trends in hospice use in ovarian cancer patients in the Medicare population.

Methods: All women age 65 or older who were diagnosed and died of ovarian cancer between 1991 and 2002 were identified from the Medicare-SEER database. Chi squared analyses were used to examine hospice use and length of stay in hospice.

Results: Of 8,740 patients, the overall rate of hospice use was 30.5% (n= 2,667). Of these patients, 29.8% were White and 41.3% were Black. The proportion of patients age 65-70, 71-75, 76-80, and >80 years was 30.4%, 32.3%, 30%, and 29.7%, respectively. The median length of stay was constant (approximately 30 days) across all the age groups. Hospice use by married women was 28% vs. 33% in widowed and/or single women. There was an association between higher income (< $30,000 to $30,000-$75,000 to >$75,000) and decreased hospice use (35.4% to 21.6% to 19%). Over the time periods (1991-1994 vs. 1995-1998 vs. 1999-2002), hospice use varied from 35.17% to 36.7% to 22.7%, while the average length of stay remained constant (32.2 days vs. 32.09 days vs. 31.9 days) over the three time periods.

Conclusions: In this patients cohort, race and income level are factors associated with hospice use. Factors associated with hospice use can help guide the development of palliative care programs to improve the quality of care given to ovarian cancer patients.
PAIN MANAGEMENT IN INDIAN WOMEN SUFFERING FROM CANCER CERVIX

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Introduction: This study was planned to assess the need of pain management in women suffering from cancer cervix in Indian population and to evaluate the response of simplified WHO guided pain management protocol.

Methodology: In patients of cancer cervix pain assessment was done using Visual Analogue Scale (VAS). For pain management WHO guided step ladder pattern protocol was used. Step 1 - tab diclofenac 50 mg BD to TDS, step 2 - tab tramadol - 50 mg TDS to QID, step 3 - tab morphine 10 mg BD to 30 mg BD. Evaluation for pain relief was done after 48 hours by VAS.

Results: At initial assessment, of 140 cases of cancer cervix 77 (55%) had pain, distributed as mild, moderate and severe in 10 (7%), 40(29%) and 27(19%) respectively. Out of 77 cases, 50 had mild to moderate pain and were given step 1 medication. 44 responded while 6 of them had to be given step 2 along with 27 more of severe pain group. Out of these 14 required step 3 drug i.e. oral morphine out of which 12 responded and 2 still did not get satisfactory relief. Pain could be managed by step 1, step 2 and step 3 drug in 57%, 24% and 16% respectively.

Conclusion: 55% of women suffering from cancer cervix had pain. Pain relief could be achieved in 97% of the patients using simplified WHO step ladder analgesic protocol. Oral morphine was found to be safe and effective for pain management in cancer patients.
A SURVEY OF PREVALENCE, INCIDENCE OF ANEMIA IN PATIENTS WITH GYNECOLOGICAL CANCER

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Background and aims: Anemia is a common condition in cancer patients. Gynecological malignancies are among the tumors characterized by a higher prevalence and incidence of anemia during the survey. This prospective, 6-month observational study aims to evaluate the prevalence, incidence, frequency and treatment of anemia in patients with gynecologic malignancy.

Methods: 186 consecutive patients with gynecologic malignancy were recruited between June and December 2009. Hemoglobin level data were collected for up to six data points or 6 months of scheduled visits. Tumor type, disease status, cancer treatment and anemia treatment as well as trigger hemoglobin level for starting treatment were evaluated.

Results: The mean age of patients was 51 years. Prevalence of anemia at enrollment was 66.1% (123/186), with 29.3% having moderate to severe anemia. The highest prevalence was found among patients with endometrial and ovarian cancer (72%), newly-diagnosed/receiving treatment (70.9%) and those receiving radiotherapy (100%). Incidence of anemia was 85.7% (54/63) and ovarian cancer had the highest incidence of anemia (87%). For disease status and cancer treatment, the incidence was highest in patients with persistent/recurrent disease (95.2%) and those who received radiotherapy (100%). 177 of 186 patients (95.2%) were ever anemic during the survey. The mean hemoglobin trigger level for initiating transfusion as treatment of anemia was 8.6 g/dL.

Conclusion: The prevalence and incidence of anemia are high among patients with gynecologic malignancy. Concerning anemia has the adverse impact on both quality of life and treatment outcome, physicians taking care of these patients should take this into consideration.
CLINICAL AND NUTRITIONAL ASPECTS OF ORAL SUPPLEMENTATION WITH AGARICUS SYLVATICUS FUNGI IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY

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Aims: Evaluate the clinical and nutritional aspects of a oral supplementation with Agaricus sylvaticus fungi in breast cancer patients undergoing chemotherapy.

Methods: A randomized, placebo-controlled, double-blind clinical trial. Sample of 46 women with breast cancer at stages II (61.5%) and III (38.5%) during chemotherapy, average age 52.41±5.94 years, divided in two groups: placebo (n = 23) and experimental (n = 23). The placebo group received starch only, orally, for six months. The experimental group was received Agaricus sylvaticus fungus (2.1g/day), orally, 3 times daily for six months. The trial consisted of: evolution of the disease, gastrointestinal symptoms, response to chemotherapy, prognosis, tumor size (observed by mammography) and body weight.

Results: After six months of supplementation with Agaricus sylvaticus, it was observed a substantial improvement in clinical and nutritional status as well as reduction of vomiting (30%), nausea (20%), diarrhea (10%) and constipation (10%) in the group supplemented with mushroom when compared with the placebo group.

Conclusions: The patients with breast cancer can experience significant improvement in their nutritional status if supplemented with Agaricus sylvaticus fungi.

Keywords: Nutritional aspects, breast cancer, Agaricus sylvaticus.
EVALUATION OF THE NEED FOR RED BLOOD CELL TRANSFUSIONS IN ANEMIC PATIENTS WITH GYNECOLOGIC CANCER RECEIVING CHEMOTHERAPY - A JGOG STUDY


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Aims: Anemia is a frequent complication in cancer patients treated with chemotherapy. Red blood cell (RBC) transfusions may be required if cancer patients develop severe or symptomatic anemia. The purpose of this study was to evaluate the need for RBC transfusions in anemic patients with cancer receiving chemotherapy in JGOG (Japanese Gynecologic Oncology Group).

Methods: We sent a questionnaire to 245 institutions of which 218 replied. The data covered the period January to December, 2008 and we analyzed 75,542 cancer patients. There were 26,468 endometrial cancers, 23,733 cervical cancers, 21,917 ovarian cancers and 3,424 other cancers. The need of RBC transfusions was evaluated according to hemoglobin levels and symptoms for individual patients.

Results: The RBC transfusion rate was 3,689 (4.9%) of the 75,542 patients. The baseline hemoglobin levels for RBC transfusions were < 7.0 g/dl in 129 (59.2%), < 8.0 g/dl in 46 (21.1%), and other in 43 (19.7%) institutions. The baseline anemic symptoms for RBC transfusions were mainly palpitation/dyspnea, fatigue and collapse. The number of institutions with patients/ doctors showing resistance to RBC transfusions was 164 (75.2%)/137 (62.8%), and the proportion of institutions with/without requirement of substitutive therapy for RBC transfusions was 196 (89.9%)/21 (9.6%).

Conclusions: Although the need of substitutive therapy for RBC transfusions was recognized as one of the therapeutic options in anemic patients with cancer receiving chemotherapy, it is a fact that substitutive therapy is not always required due to less effective prognosis in cancer patients receiving erythropoiesis-stimulating agent (ESA). Further investigations are required for patient population receiving ESA.
PSYCHOLOGICAL CHARACTERISTICS OF JAPANESE GYNECOLOGIC CANCER PATIENTS AFTER LEARNING THE DIAGNOSIS ACCORDING TO THE HOSPITAL ANXIETY AND DEPRESSION SCALE


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Objectives: Although mental problems are often overlooked in cancer patients, it is important to control psychological distress, improve the quality of life, encourage patients to express requests about cancer therapy appropriately, and reduce the burden on family members.

Methods: The subjects were 214 patients who were admitted to the Department of Obstetrics and Gynecology of St. Marianna University Hospital for treatment of cancer between January 2007 and December 2008. At 2 weeks after learning the diagnosis of cancer, these patients completed a Hospital Anxiety and Depression Scale (HADS) questionnaire, and their psychological characteristics were investigated in relation to age, tumor type, and time after learning the diagnosis. The cut-off value for intervention to manage maladjustment and major depression was set at a HADS score 11. Of the 10 patients with more than 11 HADS score were treated with Fluvoxamine for eight weeks, and then the psycho-oncological assessment was performed by the SF-36 Health Survey.

Results: The HADS score was 11 in 118 of the 214 patients (55.1%). The HADS score for anxiety was higher in younger patients, while the HADS score for depression was higher in older patients. SSRI treatment showed statistically significant improvements in the quality of life SF-36 scores in Vitality, Role emotional and Mental health.

Conclusion: Assessment based on the HADS score revealed a high prevalence of psychological problems after announcement of the diagnosis of gynecologic cancer. SSRI was effective and well tolerated in improving depressive symptoms and quality of life in women with gynecologic cancer.
EFFICIENCY AND SATISFACTION OF PAIN MANAGEMENT IN WOMEN WITH GYNECOLOGIC ONCOLOGY RECEIVING SURGERY IN RAMATHIBODI HOSPITAL THAILAND

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Background and aims: Pain is the main cause of suffering in post operative gynecologic oncology women. To know what types of management is effective to relief pain in these women is necessary for health care providers to care for them. Aims of this research were to examine types, efficiency and satisfaction after pain management in women with gynecologic oncology receiving surgery.

Methods: This research was descriptive study. Fifty women with gynecologic oncology who admitted in Ramathibodi hospital for surgery were recruited in the study. The pain assessment, pain management, and satisfaction after pain management were used to collect data after operation.

Results: Results found that mean age of samples was 53.74 (SD = 10.87), with range 28-78. Majority of women were diagnosed with CA corpus and ovary (56%), 58 % of women were removed total abdominal hysterectomy with bilateral salpingo- oophorectomy. Multi mode of opioid (76 %) was commonly used. The medication use was the most effectiveness for relieving pain. The most complication of opioid was nausea and vomiting (28 %). The most common type of non pharmacological pain management was relaxation (82 %). Satisfaction of pain management after operation was range from 3-5, with mean was 4.60 (SD = .53). There was no correlation between effectiveness and satisfaction of pain management at .05.

Conclusions: Findings recommended types, efficiency, and satisfaction after pain management in gynecologic oncology patients. These results provide health care providers to improve effective pain management in women with gynecologic oncology receiving operation.
FACTORS THAT INFLUENCE TREATMENT DECISIONS IN TERMINALLY-ILL CANCER PATIENTS - A SURVEY OF PRE-CLINICAL MEDICAL STUDENTS

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Objective: To determine demographic and clinical factors that influence treatment decisions in terminally-ill female patients with metastatic cancer.

Methods: A survey containing five clinical scenarios involving women with metastatic cancer was completed by preclinical medical students. Demographic factors of students were collected. Students decided between aggressive vs. conservative treatment options. Chi-squared tests and logistic regression analyses were employed for statistical analyses.

Results: Of 105 medical students, median age 23 (range 21-39 years), 67.6% identified with a religious affiliation of which 53.5%, 15.5%, and 12.7% identified as Christian, Jewish, and Hindu, respectively. The majority (57.1%) chose radical surgery with significant risks for complications to improve survival even if only by three weeks. The majority (53.3%) also chose aggressive surgery to palliate symptoms over no intervention. Those who have had a family member undergo hospice chose less aggressive treatment options (69.8% vs. 54.9% p=0.12). Moreover, 43.1% of those with a religious background selected more conservative approaches compared to 22.2% of non-religious students (p=0.022). However, other factors including age, sex, race, or family history of cancer, are not associated with decision-making. On multivariate analysis, having a religious belief was an independent factor for selecting more conservative treatment (OR: 0.33; 95%CI: 0.13-0.79; p=0.013).

Conclusions: In a survey of preclinical medical students regarding terminally ill female cancer patients, responders are more likely to choose aggressive therapy to palliate symptoms and prolong survival. Furthermore, having a family member with cancer and identifying with a religious belief appear to influence medical decisions towards more conservative approaches.
A REVIEW OF ANXIETY AND DEPRESSIVE SYMPTOMS IN GYNAECOLOGICAL CANCER PATIENTS

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Aims: Women with gynaecological malignancies are at risk of adverse psychological outcomes. The aim of this study was to explore the psychiatric symptomatology experienced by patients in a tertiary hospital in a disease-specific manner, and to identify demographic variables that influence each patient's psychological outcome.

Methods: Under the Women's Emotional Health Programme, a collaborative scheme between the Department of Psychological Medicine and Department of Obstetrics and Gynaecology at the National University Hospital Singapore, patients were screened for psychiatric distress via the HADS (Hospital Anxiety and Depression Scale), and definitively diagnosed through clinical interviews.

Results: Of 121 patients assessed from September 2008 to March 2010, 21 had cervical, 57 had ovarian, 40 had endometrial, and 3 had other gynaecologic cancers. Of these 121 patients, 74 were in early stage (1 and 2), 46 were in advanced stage (3 and 4), and 1 was unstaged. Other demographic and tumour data were obtained separately. More than half (52%) of these patients had a diagnosable psychiatric disorder. The majority (44%) suffered from adjustment disorder with depressed/anxious mood, whereas a minority (8%) experienced diverse psychiatric symptomatology that ranged from major depressive, anxiety and panic disorders to obsessive-compulsive behaviour and acute situational reaction. Contrary to expectations, no significant difference in the prevalence of psychiatric illness was demonstrated in early (50%) versus advanced stage (54%) cancer.

Conclusion: The spectrum of psychiatric disorders in gynaecological cancer patients is significant regardless of tumour stage and cannot be overlooked. Risk stratification and targeted psychosocial interventions must be in place to address both medical and psychological realms of care.

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QUALITY OF LIFE AND DISTRESS IN WOMEN WITH GYNECOLOGIC CANCER

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Background: This study investigates the changes in the quality of life (QOL) and the NCCN Distress Thermometer (DT).

Methods: QOL and DT was administered to 103 women undergoing operation, radiation or chemotherapy for gynecologic cancer over a one-year period. Prior to that first treatment, three, six, nine and twelve months after initial treatment the patients were asked to complete the same assessment at the National Oncologic Hospital, Clinic of Gynecological Oncology and at the Medical Center Gineka, Sofia, Bulgaria. The patients were examined on three occasions using the EORTC QLQ-C30. The DT is a self-administered scale for patients to rate their level of distress from 0 to 10, where 0 represents no distress and 10 represents extreme distress. Further, patients are asked to choose from among 34 items that constitute sources of distress.

Results: Although the global QOL decreased before discharge, the emotional function was lowest before surgery. Over half (57%) of women reported a score of 4 or greater on the DT and were then assessed by the psychologist. Women who were younger than age 60 and single were more likely to be distressed. There were no associations between the type of cancer, stage of cancer, method of the treatment.

Conclusions: A significant percentage (57%) of these women experienced distress at levels that indicate further evaluation is indicated. This study suggests that early screening and evaluation are essential in this group of cancer patients.
INCIDENCE AND MANAGEMENT OF SYMPTOMATIC PELVIC LYMPHOCYST AFTER RADICAL PELvic OR PELVIC AND PARAAORTIC LYMPHADENECTOMY FOR CERVICAL AND ENDOMETRIAL CANCER

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Introduction: Pelvic and paraaortic lymph node dissection as part of the staging surgery for cervical and endometrial carcinoma, interrupts the afferent lymphatics. The high acceptance by the community of gyn-oncologists, was after finding that laparoscopic lymphadenectomy can be performed in the majority of patients and is associated with low complication rate. Incidence of lymphocele formation and incidence of severe complications associated with lymphocele, such as infection, deep venous thrombosis or urinary tract occlusion, were retrospectively evaluated in the last year's (01.2001-01.2007) after surgery.

Patients and methods: From January 2001 to January 2007, 226 women underwent surgery including pelvic or/and paraaortic lymphadenectomy for primary gynecological pelvic malignancies, of which 68 (30%) patients with cervical cancer and 158 (60%) patients with endometrial cancer, all of them were retrospectively analysed.

Results: 23 out of 226 (10.2%) patients were diagnosed to have symptomatic pelvic lymphocyst. Additionally, 2 of the 23 patients had lymphedema, other 2 of 23 patients had lymphocyst infection, 1 of 23 patients had deep venous thrombosis, and 1 of 23 patients had ureteral stenosis.

A partial-(ventral)-resection of the lymphocyst was performed. Median duration of the hospital stay was 12.5 days and median duration of the drainage was 10 days.

Laparoscopic lymphocyst resection and drainage was in 22 patients successful. In 1 patient a relaparoscopy was necessary because of a recurrent lymphocyst formation 6 months after the operation.

Conclusions: The Laparoscopic lymphocyst resection is a safe and effective procedure and was applied in all 23 patients successfully.
UTILIZATION OF A CANCER CENTER SYMPTOM MANAGEMENT PROGRAM BY GYNECOLOGIC ONCOLOGY PATIENTS

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Objectives: Women undergoing treatment for gynecologic cancers deserve a concurrent management of symptoms. Our institution has developed an outpatient Symptom Management Service (SMS) to address management of symptoms in physical, emotional, and existential domains. We sought to characterize patients receiving SMS to identify how we can best benefit these women in need.

Methods: Patients seen in the Gynecologic Oncology Practice were asked to fill out a Likert scale survey rating symptoms from 0-10 and asking if they would like a referral to the SMS. We identified 42 women with gynecologic cancer seen by SMS during 2007-09 and compared them to 42 gynecologic oncology patients in our practice who declined referral to SMS. We abstracted disease and treatment information from the medical record.

Results: Women who seek out SMS are similar in age, cancer diagnosis, and stage to the general gynecologic oncology population. They are more likely to be on treatment (42% vs. 19%, p=0.03) and facing recurrent/persistent disease (60% vs. 26%, p=0.002). Mean symptom scores are higher for pain (4.21 vs. 2.22, p=0.003), fatigue (5.85 vs. 3.63, p=0.002), anxiety (4.35 vs. 3.03, p=0.042), depression (2.95 vs. 2.05, p< 0.001), and lower for well-being (3.25 vs. 3.48, p=0.029), and sense of peace (2.88 vs. 3.34, p=0.016). There was a trend towards more utilization of SMS among women with a history of chronic pain preceding their cancer diagnoses.

Conclusion: Patients being seen by a Symptom Management service are more likely to have somatic and emotional symptoms. SMS complements routine gynecologic care.
THE CHALLENGES OF PALLIATIVE CARE AFTER THE 2010 HAITIAN EARTHQUAKE

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In the aftermath of the January 12, 2010, earthquake in Haiti, rescue workers and emergency medical teams were confronted with both severe earthquake related injuries and people with chronic illness who had lost their healthcare system. The environment within Port Au Prince was apocalyptic. There was no onsite potable water, electricity, food, or shelter. The physical environment was difficult both for earthquake survivors and for relief workers due to extreme heat, an inability to wash, malaria carrying mosquitoes, the lack of a functioning sewage system, fires, continuous aftershocks, and dead bodies.

Acute earthquake related injuries included complex fractures, crush injuries, and wounds. Delayed earthquake related effects which were seen within two days to two weeks included respiratory failure, metabolic derangements, and infections. Severely ill patients with preexisting medical conditions such as advanced tuberculosis, cancer, heart failure, kidney and liver disease, and psychiatric illness were in desperate need of care after the earthquake.

United States Health and Human Services Disaster Teams arrived in Port Au Prince forty eight hours after the earthquake. This report focuses on the experience of palliative care for severely ill survivors at the Gheskio Tent Hospital in Port au Prince. The challenges of medical and nursing decision making and triage of limited resources for diagnosis and care led to both creative solutions and tragic outcomes. The psychological impact of triage of severely ill and dying patients on the healthcare workers was significant.
QUALITY OF VENOUS THROMBOEMBOLISM PROPHYLAXIS IN PATIENTS UNDERGOING GYNECOLOGIC CANCER SURGERY

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Objectives: Venous thromboembolism (VTE) is a significant cause of mortality in women undergoing oncologic surgery. We analyzed the use of VTE prophylaxis in patients undergoing gynecologic cancer surgery and examined the influence of surgeon and hospital volume on use of prophylaxis.

Methods: Patients undergoing major gynecologic cancer surgery from 2003-2007 and recorded in the Perspectives database were reviewed. Receipt of any (pharmacologic or mechanical) prophylaxis as well as receipt of appropriate (pharmacologic) prophylaxis based on the American College of Chest Physicians guidelines were examined. We analyzed the influence of surgeon and hospital volume on utilization of prophylaxis while controlling for other clinical variables using generalized estimating equations. Surgeon and hospital volume was classified into tertiles for analysis.

Results: A total of 40,613 patients were identified. Prophylaxis was more commonly utilized by high-volume than low-volume surgeons (85% vs. 75%) (p< 0.0001) and more frequently given to patients treated at high-volume rather than low-volume hospitals (82% vs. 77%) (p< 0.0001). Likewise, patients treated by high-volume surgeons were more likely to receive appropriate, pharmacologic prophylaxis (61% vs. 40%) (p< 0.0001) as were patients operated on at high-volume hospitals (56% vs. 43%) (p< 0.0001). After adjusting for clinical variables as well as physician and surgeon volume, patients treated by high-volume surgeons were over 90% (OR=1.99; 95% CI, 1.30-3.06) more likely to receive appropriate, pharmacologic prophylaxis.

Conclusions: VTE prophylaxis is underutilized in patients undergoing gynecologic cancer surgery. Patients treated at high-volume hospitals by high-volume gynecologic oncology surgeons are more likely to receive evidence-based prophylaxis.
THE VALUE OF TRANSVAGINAL SONOGRAPHY AND SONOHYSTEROGRAPHY IN THE DETERMINATION OF THE CAUSE OF ABNORMAL UTERINE BLEEDING

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Objective: To assess the diagnostic value and usefulness of transvaginal sonography (TVS) and sonohysterography (SHG) in the detection of uterine intracavitary lesion in abnormal uterine bleeding.

Methods: 105 patients with abnormal uterine bleeding were evaluated with TVS and SHG. The pathologic results were obtained by means of dilatation and curettage, hysteroscopy and hysterectomy. Diagnoses of TVS and SHG were compared with pathologic reports.

Results: The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of TVS and SHG were 85.5%, 68.9%, 87.8%, 64.5%, and 80.9% vs. 94.7%, 82.8%, 93.5%, 85.7%, and 91.4%, respectively. SHG showed better results than TVS in the diagnoses of endometrial polyp and submucosal myoma. However, no statistical differences between TVS and SHG were found regarding the diagnosis of endometrial hyperplasia.

Conclusion: For diagnosis of uterine intracavitary lesions, SHG is superior to TVS. The proper use of SHG and reduce unnecessary surgical procedures and help the selection of the best surgery.
COMPRESSION STOCKINGS PLUS LOW MOLECULAR WEIGHT HEPARIN VERSUS COMPRESSION STOCKINGS ALONE AFTER GYNECOLOGIC ONCOLOGY SURGERY

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Objective: To compare the efficacy and safety of compression stockings plus low molecular weight heparin with compression stockings alone in the prevention of venous thromboembolism (VTE) after gynecologic oncology surgery.

Methods: 145 pts undergoing a major gynecologic oncology operation were randomized to receive either compression stockings plus low molecular weight heparin (n=75) or compression stockings alone (n=70) for the prophylaxis of VTE. Compression stockings were applied from the morning of operation to the day of discharge. Low molecular weight heparin (Fraxiparine, 3075AXaIU daily) was given within 24 hours after operation for at least 8 days. All the patients underwent Doppler ultrasound of the lower extremities on days 4-7 post-operatively to detect occult deep vein thrombosis. The incidence of VTE and side effects were evaluated.

Results: Altogether 4 patients were diagnosed with VTE in compression stockings alone group and no patients developed VTE in compression stockings plus low molecular weight heparin group (P=0.052). The volume of post-operative bloody drainage and the incidence of wound separation were similar between the two groups. No thrombocytopenia and injection-site hematoma occurred in both groups.

Conclusions: Compression stockings plus low molecular weight heparin may be more effective than compression stockings alone in the prevention of VTE after gynecologic oncology surgery. The addition of low molecular weight heparin is safe and does not increase bleeding complications.
STEREOTACTIC RADIOSURGERY IN THE MANAGEMENT OF RECURRENT GYNECOLOGIC MALIGNANCIES

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Recurrent gynecological malignancies often present difficult treatment dilemmas, particularly when a patient is unable to receive additional conventional radiation therapy, or wishes to avoid a return to the systemic toxicity of chemotherapy. Stereotactic Radiosurgery (SRS) for localized recurrence offers a novel and effective treatment alternative. From May 2006 through February 2010 there were 12 patients treated with 17 tumor sites with Stereotactic Radiosurgery (SRS). Primary sites included uterine adenocarcinoma-3, uterine leiomyosarcoma-2, ovary-3, cervix-2 and vagina-2. Treatment sites included the pelvis-9, vaginal apex-2, lung-1, retroperitoneum-1, kidney-1, spleen-1, abdominal wall-1 and para-aortic lymph node-1. The frameless SRS body technique for these patients used a combination of multi-field non-coplanar approaches with forward planned weight and aperture optimization to achieve an optimal dosimetric distribution maximizing the dose to the intended treatment volume and minimizing the dose to surrounding organs at risk. Prior pelvic radiation was given in 8/12 patients and all patients had undergone systemic therapy. 7/12 patients were symptomatic at presentation and palliation was noted in 6/7 (86%). Post treatment imaging with PET or CT was performed in all patients and a complete response was noted in 8/17 tumor sites (47%) and a partial response was noted in 8/17 sites for an overall response rate of 94%. Complications were noted in 2 patients with one small bowel obstruction and one recto-vaginal fistula. SRS can be delivered in previously irradiated sites with excellent palliation and radiological response and should be considered in patients with isolated or oligometastatic recurrent disease.
CHYLOUS ASCITE FORMATION FOLLOWING RETROPERITONEAL LYMPH NODE DISSECTION FOR ENDOMETRIAL CARCINOMA

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Background: Postoperative chylous ascite is a rare condition after surgery for gynecologic malignancies and observed as a result of surgical trauma to the retroperitoneal lymphatic system.

Case: A 57-year-old woman underwent surgical staging for endometrial carcinoma. As a part of surgical staging, pelvic and paraaortic lymph node dissections until below the renal vein were performed. In the postoperative period drainage of chylous ascite was observed from drain (approximately 1000-1500 ml). On the third day of postoperative period, low fat diet was started. Drainage was observed with the same amount until the 7th day and subsequently decreased dramatically. On the 12th day postoperatively drain was removed. Ultrasonographic control on 20th day was revealed no intraabdominal ascites.

Conclusion: In management of chylous ascites low fat diet, medium-chain triglycerides diet, and octreotid are used. Although in some cases re-operation was reported to control the chylous ascite, conservative management may be an adequate approach such as this case. To prevent chylous ascites, surgeons should avoid from lymphatic system injury.
FACTORS RELATIONSHIP AND PREDICT PAIN INTENSITY AMONG POST OPERATIVE PATIENTS

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Background and aims: Acute pain after surgery is the main problem in post operative patients. To understand pain intensity, factors related and factors predicting pain intensity which is necessary for health care providers to care for these patients. Aims of this research were to examine (1) relationships between pain intensity, activity, sleep, mood and satisfaction and (2) factors predicting pain intensity in patients receiving surgery using the Symptom Management Model.

Methods: This research was correlative predictive study. 365 patients admitted for surgery in Ramathibodi hospital were recruited in the study. The pain assessment and management questionnaires were used to collect data after operation 24 hours.

Results: Results found that there were positively correlations between pain intensity and activity (r = .50), sleep (r = .38), and mood (r = .42) at .05 whereas there was negatively correlation between pain intensity and satisfaction (r = -.12) at .05. Pain intensity was predicted by activity and mood at .001 as the equation pain intensity is equal to 1.228 + .318 (activity) + .172 (mood).

Conclusions: Findings recommended relationships and factor predicting pain intensity in patients receiving surgery. These results can provide health care providers to improve effective pain management by providing appropriate activity and psychosocial care in patients after operation.
MANIFESTATION OF SOMATIC DISTURBANCES IN EARLY POST MENOPAUSE IN WOMEN AFTER PHYSIOLOGICAL AND SURGICAL MENOPAUSE

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Objectives: Major purpose of the study was to provide information about the most common symptoms of early menopause after surgical removing of the ovaria.

Design and methods: Study is designed as a prospective study and enclosed 120 women age 41-55, divided into two groups: physiological and induced menopause. Every subject checked special evidence list consisted of disease history questions, physical and gynecology examination and data about phisiological variables and labarotory examination.

Results: The most frequently symptoms in both group were vasomotor symptoms. Headache is more intensive sign in group after induced menopause. Extrasistolic heart excursion represents common symptom in both group. Arterial tension, no matter of type of menopause, was in physiological frame. Frequent organic signs of menopause, more intensive in group after induced menopause, were genitourinary and skin atrophy. Analysis of Body Mass Index marks subjects in both group as fatigue. Lipids analysis confirmed predomination of hyperlipoproteinemia type IIa in group with phisiological menopause and type IIb after induced menopause.

Conclusion: Dominant signs of menopausal syndrome are bone-joint symptoms, more frequent in group after induced menopause. There are no statistic significant differences between groups according to the signs of aging. Menopausal hormonal changes, no matter the way of menopause developing, increase the risk for hyperlipoproteinemia. Frequency of somatic signs in early post menopause is typically higher after induced menopause.
ARE WE REMEMBERING TO MONITOR VITAMIN B12 LEVELS AFTER PELVIC RADIOTHERAPY OR TERMINAL ILEAL RESECTION IN PATIENTS WITH GYNAECOLOGICAL MALIGNANCIES?

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Background: Low levels of vitamin B12 frequently cause tiredness. Severe deficit causes anaemia and irreversible neurological damage. 20% of women undergoing pelvic radiotherapy will develop vitamin B12 deficiency by direct damage to the ileal uptake mechanisms. Small bowel resection may cause vitamin B12 deficiency directly proportional to the length of terminal ileum removed. Vitamin B12 deficiency may also indicate development of bile acid malabsorption or small bowel bacterial overgrowth, both common sequelae of pelvic radiotherapy and terminal ileal resection.

Aims: To review the current practice of vitamin B12 monitoring post radiotherapy or post small bowel resection in patients with gynaecological malignancies at a single institution.

Method: Retrospective case note review of gynaec-oncological patients treated with radiotherapy, bowel surgery or a combination of both from 1 December 2008 to 31 December 2009.

Results: 207 patients were identified, age median 60.5 (range 19 - 96 years). 11 had surgery alone, 2 had surgery and RT, and 194 had RT alone. Vitamin B12 monitoring occurred in only 11% (n=23) patients. Of these, 17 had normal serum levels and 6 were abnormal. Vitamin B12 median was 437pg/ml (range 151 - 1516 pg/ml). Of those monitored 26% had low serum vitamin B12 levels. If this data was extrapolated to the whole group 54 patients would have a low serum vitamin B12.

Conclusion: Vitamin B12 levels should be undertaken routinely in this subset of at-risk patients. Despite excellent evidence that this is useful, it occurs infrequently.
PALLIATIVE RADIOTHERAPY FOR CERVICAL CANCER: A SYSTEMATIC REVIEW

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Background and aim: Worldwide 493,100 new cases of cervical cancer occurred in 2002. Many of these women live in resource poor countries with limited access to treatment. They often present with advanced stage disease and are only amenable for palliative treatment. There is a need for fractionation schemes that makes optimal use of the available resources. This study aims to identify the optimal radiation dose and fractionation scheme in terms of symptom control and quality of life.

Methods: The literature on the use of palliative radiotherapy for cervical cancer is systematically reviewed.

Results: Eight observational studies were included describing the use and effect of four different palliative fractionation schemes. Interpretation of the results is hampered by the observational study designs with considerable sources of bias and confounding. Hypofractionation with monthly single doses of 10 Gy repeated up to 30 Gy is most frequently described. All authors report reduction of symptoms such as bloodloss, pain and discharge with mostly reasonable short and long term side effects. However different treatment schemes have not been compared. No study reported the effect on quality of life. Attrition rates are often high.

Conclusion: Studies report favourable effect on bleeding, pain and discharge but data are limited and no comparative data are available to guide palliative treatment of advanced cervical cancer. Because of poor access to care in large parts of the world and because of resource constraints there is a need to establish effective fractionation schemes that provide optimal symptom reduction and require minimal resource use.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

CHANGES IN SHORT-TERM HEALTH-RELATED QUALITY OF LIFE IN WOMEN UNDERGOING GYNECOLOGIC ONCOLOGIC LAPAROTOMY: AN ASSOCIATED FACTOR ANALYSIS

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Objectives: The primary purpose is to evaluate quality of life (QOL) of gynecologic cancer patients undergoing laparotomy. The secondary purpose is to compare QOL of women with ovarian cancer to women with other gynecologic malignancies.

Methods: As part of randomized controlled trial, women who underwent laparotomy by gynecologic cancer completed the C30 and OV28 questionnaires pre-surgery and at 1-month postsurgery.

Results: Of the 181 women studied between January 2007 and March 2008, 116 women (64.1%) had ovarian cancer, 27 (14.9%) had cervical cancer, and 29 (16.0%) had endometrial cancer. By 1-month post-surgery, there was a significant decrease in QOL on the global, abdominal/GI score, body image, chemotherapy side effects, and other single items of OV28 questionnaire, as well as on physical functioning, role functioning, social functioning, fatigue, nausea and vomiting, pain, insomnia, constipation, appetite loss, and financial difficulties items on C30 questionnaires. Emotional functioning on C30 questionnaires was significantly improved 1-month after surgery. The majority of these items remained affected only in patients with ovarian cancer. Women with other gynecologic malignancies showed a statistically significant difference between baseline and postsurgical QOL scores on the abdominal/GI score on OV28 questionnaires as well as on role and physical functioning on C30 questionnaires, not on the other items.

Conclusion: The results suggest that interventions focused on symptom control need to be tested to ameliorate QOL among gynecologic cancer patients undergoing laparotomy, particularly among those with ovarian cancer.
INCIDENCE OF PULMONARY EMBOLISM AFTER LAPAROSCOPIC SURGERY IN GYNECOLOGIC ONCOLOGY

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Objectives: The incidence of pulmonary embolism (PE) in patients undergoing laparoscopic surgery for gynecologic malignancies is unknown. The aims of this study were to determine the true incidence of PE after laparoscopic treatment of gynecologic cancer patients by using perfusion lung scan. The results were compared with those obtained in patients treated with open surgery.

Methods: In a prospective cohort study, 45 patients with gynecologic malignancies were laparoscopically treated (laparoscopy group: LS). Graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) were used in all patients for the perioperative thromboprophylaxis. In the latter half of the study period, low dose unfractionated heparin (LDUH) was added the combination of ES+IPC. Within 10 days after surgery, routine perfusion lung scan was performed for the detection of PE irrespective of clinical symptoms. The results were compared with those obtained from 46 control patients treated with traditional open surgery (laparotomy group: LT).

Results: Pulmonary embolism developed in 6 cases (17.6%) in LS and in 5 cases (15.6%) in LT. The addition of LDUH resulted in smaller number of PE detected in both LS (from 4/14, 28.6% to 2/31, 6.5%) and LT (from 2/10, 20% to 5/36, 13.9%), but the differences were not statistically significant.

Conclusion: The incidence of PE after laparoscopic and open surgery for gynecologic cancer was not different. Appropriate preventive measures against PE should be taken even in laparoscopic surgery of gynecologic malignancies. Combination of GCS, IPC and LDUH may be a promising protocol.
SIGNIFICANT DECREASES IN BONE MINERAL DENSITY ASSOCIATED WITH PELVIC RADIOTHERAPY: A PROSPECTIVE LONGITUDINAL STUDY OF WOMEN WITH GYNECOLOGIC MALIGNANCIES

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Objective: To prospectively examine longitudinal changes in bone mineral density (BMD) and biomarkers of bone turnover in women undergoing pelvic radiotherapy.

Methods: A prospective cohort study of women treated with definitive pelvic radiotherapy for gynecologic malignancies is currently being performed. BMD scans are obtained prior to treatment, and repeated 3 months, 1y and 2y following treatment. Biomarkers of bone turnover including bone-specific alkaline phosphatase (BAP) and telopeptide of type I collagen (ICTP) are measured at the same time points. Imaging studies from similar intervals are evaluated for fractures.

Results: To date, 92 patients with cervical (n=55), endometrial (n=32) and vaginal (n=5) cancer have been enrolled. Median age at diagnosis was 51y (range 31-83) and 68.1\% of patients were postmenopausal. Significant decreases were noted in median BMD measurements from baseline (n=85) to 3 months (n=42) for the lumbar spine (95\%CI, -0.033 to -0.014, p< 0.001), left hip (95\%CI, -0.059 to -0.021, p< 0.001), and right hip (95\%CI -0.059 to -0.029, p< 0.001). Similar BMD decreases were noted from baseline to 1y (n=12). There were no significant changes in BAP or ICTP levels from baseline to 3 months or 1y. With a median follow-up of 4 months, one pelvic fracture has been diagnosed 12 months after completing treatment.

Conclusion: Significant and rapid decrease in BMD is noted in women undergoing radiotherapy for gynecologic cancers. Continued follow-up is currently underway to determine the incidence of pelvic fractures. Our preliminary findings may have implications for BMD screening and pharmacological intervention in this population.
PERMANENT PERITONEAL CATHETER INTRODUCED UNDER ULTRASOUND GUIDANCE AS A PALLIATIVE TREATMENT OF RESISTANT ASCITES

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We present our experience with permanent peritoneal catheter as a palliative support in patients with only symptomatic treatment and resistant ascites requiring frequent paracentheses.

We used pediatric catheter for peritoneal dialysis with two dacron cuffs tunnelized in subcutaneous tissue. The catheter was inserted in 8 patients under ultrasound guidance using combined local anesthesia and intravenous analgosedation, no general anesthesia was needed. The median of operational time was 21 minutes, procedure required half-day hospitalization.

Patients started to emit the ascites (200-500ml) second postoperational day and continued every 2-3 days. Peroral protein supplementation was given. Ionts, renal and hepatic functions, albumin and total protein were monitored every 2 weeks. The average duration of catheter usage was 4 months. There were no infectious complications and no patient needed hospitalization due to hypoproteinemia or hypohydration.

In conclusion, we can recommend this procedure as well-tolerated and comprehensive support for incurable patients with resistant ascites.
CANCER PAIN MANAGEMENT IN ABUTEACHING HOSPITAL ZARIA: THE HEALTH CARE PROVIDERS PERSPECTIVE

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Introduction: Pain is one of the most frequent and disturbing symptoms of cancer. Experts estimate that 25% of all cancer patients die without adequate pain relief, despite the fact that the tools for adequate pain control are available.

Objective: A survey to determine the attitude and practice of cancer pain Management among physicians practicing in ABU Teaching Hospital Zaria, Nigeria.

Methods and materials: This was a collaborative, cross-sectional study on provider perspectives on pain management among cancer patients. A structured self-administered questionnaire was completed by 109 medical practitioners of various specialties and ranks.

Results: Seventy five (68.3%) were males. The Registrars constitutes majority of the respondents accounting for 51(46.8%). In the study, Majority 61(59.4%) of the respondent were within the age group 31-40. The survey cuts across wide range of specialty. Majority of the respondents 50.1(46%) believe that pain is the commonest symptom in cancer patients. Most 85 (78%) of the doctors assess pain using subjective methods. Ninety two 84.5% of the respondents qualified pain as severe. Only 29% of the respondents are conversant with other treatment options for pain. Seventy (64.3%) use analgesia and their choices are guided mainly by the response of the patients. 61.5% of those who admit to the use of analgesia were actually limited by the side effects of these drugs. More than half (57.6%) believed that pain management in our settings is suboptimal.

Conclusion: Medical education and its curriculum needs to focus on the proper assessment of pain, as well as the management of its side effects.
RECOVERING AFTER PELVIC RADIATION THERAPY: A PILOT STUDY OF AN INFORMATION BOOKLET TO HELP WOMEN WITH GYNAECOLOGICAL CANCER

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Aims: Women who undergo pelvic radiation therapy for gynaecological cancer (GC) often experience physical and psychosexual side effects that can be prevented or reduced with the appropriate care. However, research and clinical data suggest that information provision about recovery and rehabilitation options is currently suboptimal. To address this gap we have developed a booklet to improve women's knowledge of:

i) the importance of using dilators to minimise vaginal stenosis and enable adequate pelvic examinations,

ii) radiation-induced side-effects that may affect sexual functioning,

iii) self-care strategies to minimize post-treatment vaginal changes.

This pilot study aimed to:

i) obtain feedback about the booklet's content, format and utility, and

ii) evaluate the assessment process to be used in the next (RCT) phase.

Methods: 20 women who were treated with pelvic radiation therapy for cervical or endometrial cancer within the last 5 years, and were provided with vaginal dilators, provided feedback on the content and format of the booklet via a semi-structured phone interview and a set of standardised and purpose-designed questionnaires.

Results: Women had good understanding of the booklet content (90% provided correct answers). The booklet was perceived as very helpful, easy to read and understand, was not distressing, and provided additional information to that discussed with clinicians. The assessment process seemed appropriate.

Conclusions: This study addresses an important component of post-radiation care by introducing a novel, simple and much needed resource. The impact of the revised booklet on psychosexual and clinical outcomes will be evaluated in a multi-centre RCT.
“METRONOMIC” CYCLOPHOSPHAMIDE CHEMOTHERAPY FOR THE PALLIATIVE TREATMENT OF PATIENTS WITH GYNAECOLOGICAL CANCER

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Objective: To evaluate the antitumour activity and safety of metronomic Cyclophosphamide in recurrent or advanced gynaecological cancer patients having exhausted all effective therapies under standard care.

Material and methods: Patients with measurable disease and prior treatment with a platinum-containing regimen were eligible. Up to two different regimens for recurrent disease were allowed. Treatment consisted of oral Cyclophosphamide 50 mg/d. The primary end point was median time to progression.

Results: Between December 2007 and March 2010, 21 patients were enrolled (12 ovarian cancer; 5 endometrial cancer and 4 cervical cancer). Partial response was achieved in 8 patients (38.1%) while 13 patients had progression of disease. At time of analysis, 3 out of 8 responding had progression of disease. In the overall series median time to progression (TTP) was 4.5 months (range, 2 - 21 months). In particular cervical cancer patients had median TTP of 3.2 months while endometrial and ovarian cancer patients had median TTP of 5.1 months. These data suggests that this treatment is active above all in endometrial and ovarian cancer. At present, with a median follow-up of 4.7 months (range, 2 - 9 months), 5 patients are still free of progression and 3 out of 21 patients are alive with disease and with good quality of life. No toxicities were observed.

Conclusions: Metronomic Cyclophosphamide is well tolerated and provides stable disease in such vulnerable and poor-prognosis cancer patients. This regimen warrants further evaluations.
SHOULD WE CONSIDER CANCER/TESTIS ANTIGENS NY-ESO-1, MAGE-A4 AND MAGE-A1 AS POTENTIAL TARGETS FOR IMMUNOTHERAPY IN VULVAR SQUAMOUS CELL CARCINOMA?

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Cancer/testis (CT) antigens are protein antigens with normal expression restricted to adult germ cells and yet they are aberrantly expressed in a variety of malignant tumours, particularly those with a squamous histology. They have been identified as a group of highly attractive targets for immunotherapy, the most important cancer vaccine candidates being MAGE-A1, MAGE-A4 and NY-ESO-1. The aim of the study was to evaluate the potential targets for immunotherapy in vulvar squamous cell carcinoma (SCC). We examined the expression of MAGE-A1, MAGE-A4 and NY-ESO-1 in primary tumours, lymph node metastases and local and groin recurrences and evaluated their prognostic significance. Vulvar SCC did not express NY-ESO-1. MAGE antigens were expressed as both nuclear and cytoplasmic proteins that were heterogeneously distributed. MAGE-A1- and MAGE-A4-specific positivities were detected in 13% and 65% of 76 primary tumours and in 19% and 69% of 32 lymph node metastases respectively.

The expression of both antigens was a constant qualitative and repeatable feature that was uncorrelated with commonly recognized prognostic factors. Significant correlation was observed between the expression of MAGE-A4 and the differentiation grade of the tumour (GOG). We found that prognosis in early-stage cases that expressed MAGE-A4 was significantly better than in cases without expression.

The protective role of the expression of MAGE-A4 in the early stages of the disease suggests that it may represent a tumour suppressor protein and that it therefore requires further molecular investigation.
**HPV-NEGATIVE, UNIFOCAL AND SUBCLITORAL CARCINOMA OF THE VULVA IN YOUNG WOMEN**

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**Objective:** To determine the pathogenesis of subclitoral, HPV-negative and unifocal vulvar lesions in young women.

**Study design:** We conducted a retrospective review of the medical records of 18 patients with a mean age of 50.8 years. All of the patients had an unifocal, subclitoral vulvar lesion. The DNA was extracted from the tumor tissue and subjected to the polymerase chain reaction (PCR) using highly conserved L1-primer (GP5+/GP6+) and specific primers for the upr-region of the HPV16-genome. Furthermore we immunohistochemically determined the expression of the tumorsuppressor gene p16\(^{INK4A}\).

**Results:** Seventeen of the 18 patients had a squamous cell carcinoma (SCC) of the vulva; one patient suffered from a vulvar intraepithelial neoplasia (VIN) III. The histopathological classification was as follows: pT1 pN0: 13 patients pT1 pN1: 2 patients pT2 pN1: 2 patients pTis: 1 patient. Seventeen out of the 18 patients were HPV-negative. All HPV-negative patients showed no or a low immunohistochemical expression of p16\(^{INK4A}\), while the HPV-positive patient had a strong expression of p16\(^{INK4A}\). The patient with a VIN III lesion showed a low expression of p16INKA.

**Conclusion:** The unifical, subclitoral, HPV-negative vulvar cancer seems to have a specific pathogenesis which might be different of the pathogenesis of multifocal vulvar lesions. The immunohistochemically determined expression of p16\(^{INK4A}\) could be a biomarker for HPV 16-related vulvar cancer.
**V-Y FASCIOCUTANEOUS ADVANCEMENT FLAPS FOR VULVAR RECONSTRUCTION**

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**Purpose:** Vulvar reconstruction is an integral part of restoring the individuality and sexual identity of the afflicted patient after radical vulvectomy for carcinoma. Many techniques of vulvar reconstruction have been described in the past. Although prior methods focus mostly on basic wound coverage, the evolution of reconstruction has aimed more at also maintaining morphofunctional capabilities and an aesthetic appearance. The goal of this review is to outline the V-Y fasciocutaneous advancement flaps for their utility, reliability for vulvoperineal reconstruction, and patient acceptance.

**Methods:** A retrospective chart review was performed on the last fifteen consecutive vulvar reconstructions performed by one senior author (S.S.) using the V-Y fasciocutaneous advancement flaps from May 2005 to October 2009. All reconstructions were done in an immediate fashion following radical vulvectomies performed by one gynecological oncologist. The technique entails fascial release of large unilateral or bilateral triangular flaps from the inner thigh or mons pubis regions with V-Y advancement of fasciocutaneous islands for coverage of radical vulvectomy defects.
PATHOLOGY SLIDE REVIEW IN VULVAR CANCER DOES NOT CHANGE PATIENT OUTCOME

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Objective: To analyze the value of pathology slide review in vulvar cancer.

Methods: A retrospective chart review of all cases of vulvar cancer treated in a tertiary oncology centre between January 1st 2000 and April 1st 2006 was performed. Histopathology reports from the referring clinic and tertiary centre were compared and discrepancies were analyzed. Discrepancies were considered “minor” when the differences had no clinical consequence and “major” when they altered the clinical intervention. In addition, completeness of the histopathology assessment was scored. Reports were regarded as “complete” when tumor type, depth of invasion, presence or absence of vascular space invasion, and - in excisional biopsies only - resection margin were depicted, “partially complete” when tumor type and infiltration depth were described, and “incomplete” when fewer than these criteria were noted.

Results: A total of 121 squamous cell tumors of the vulva from 112 patients were reviewed. One minor discrepancy was found, but no major discrepancies. None of the reports of the referring clinics could be considered complete. 55 reports were categorized incomplete and 66 reports were partially complete. For the reviewer's reports these numbers were 40, 61 and 20 respectively.

Conclusion: There were no major discrepancies between the referring and the tertiary centre that influenced patient management, but many reports lacked information on invasion depth. To reduce cost and effort we suggest that vulvar cancer biopsies should be reviewed only in selected cases.
VAGINAL BENIGN LESIONS: A CLINICOPATHOLOGICAL STUDY OF 105 CASES
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Aim: The aim of this study is to present the clinicopathological characteristics of 105 benign lesions of the vagina.

Material and methods: This is a retrospective study of benign vaginal lesions performed the period 2000-2009 in our Department. Demographic data, diagnosis and pathologic examination are presented.

Results: The lesions were classified according to the pathologic findings in the following categories:

- Developmental lesions: 3 cases of vaginal adenosis (age of patients 14-20, mean age 16.6) and 5 cases of vaginal septum (age of patients: 13-28, mean age: 18.2). Postoperative/postradiation lesions: 18 cases with granulomas of the vaginal cuff (age 40-70, mean age 52.7), 1 cystovaginal fistula (age 72) and postradiation lesions (age 53-73, mean age 63).

- Vaginal cysts: 15 cases of Gartner cysts (age 20-60, mean age 36.7), 4 mullerian cysts (age 34-55, mean age 40.5), 12 cysts of the Bartholin ducts (age 23-54, mean age 39.9) and 11 epidermal cysts of inclusion bodies (35-75, mean age 48.6).

- Benign neoplasms: 5 cases of papilloma tumors (age 28-44, mean age 31.6), papilloma accuminatum (age 25-55, mean age 39.3), 14 cases of polyps (age 38-75, mean age 56.8), 4 leiomyomas (age 28-44, mean age 38.8), 1 case of endometriosis (age 26) and 1 case with decidual conversion (age 30).

We also present the clinical characteristics of the lesions: size, symptoms and localisation and the differential diagnosis of them.

Conclusion: Benign lesions of the vagina show a variety of symptoms from asymptomatic cysts up to large lesions which cause obstruction phenomena.
INVASIVE AND PREINVASIVE VULVAR LESIONS: A CLINICOPATHOLOGICAL STUDY OF 63 CASES

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Aim: The increased incidence of VIN, Ca in situ the last years led to an increase in the medical investigation regarding their epidemiology, prevention and treatment. In this study, we present the clinicopathological findings in 63 cases with invasive and/or preinvasive lesions, their treatment and their differential diagnosis.

Material and methods: This is a retrospective study of all cases with vulvar invasive or preinvasive lesions diagnosed in our Department during the period 2005-2009. The clinical findings were correlated with the histopathologic results. Immunohistochemistry was used in cases with problems in the differential diagnosis.

Results: 41 out of 63 cases were invasive carcinomas (65.07% mean age 68.33 years), 32 out of 41 were squamous carcinoma, 2 out of 41 basaloma, 1 out of 41 verrucose carcinoma, 1 out of 41 case with Paget disease, 2 out of 41 were adenocarcinomas. 1 out of 41 were sarcoma and 1 out of 41 melanoma. On the other hand, 22 out of 63 cases were preinvasive lesions (34.92% mean age 48.56 years). 11 out of 22 were VIN I, 5 out of 22 VIN II, 6 out of 22 VIN III, respectively. The most common symptom was pruritus in all the patients. Immunohistochemical methods helped us in the diagnosis of invasive carcinomas of squamous origin with low grade differentiation, sarcomas, Paget disease and melanoma.

Conclusion: The differential diagnosis of preinvasive or invasive lesions of the vulva is rather difficult especially in tumors with low differentiation where immunohistochemistry is essential for the diagnosis.
BENIGN LESIONS OF THE VULVA: A CLINICOPATHOLOGICAL STUDY OF 93 CASES

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Aim: The study of vulvar lesions is the aim of different medical subspecialties such as pathology, gynecology, dermatology and urology. This fact leads to the partial study of vulvar lesions. In this study, we present the clinical and pathological characteristics of 93 benign vulvar lesions and we emphasize in their differential diagnosis.

Material and methods: During 2005-2009 a retrospective study was conducted in our Department. The clinical and pathological characteristics of benign vulvar lesions were studied. Age and clinical signs have been compared with the findings of the histological examination.

Results: 54 out of 93 lesions were chronic dystrophic corruptions. 25 out of those 54 cases were cases of sclerotic or atrophic lichen (26,88% with mean age 59,86 years) and 29 out of 54 were squamous hyperplasia (31.18% with mean age 44.29 years). The cystic lesions included 14 cysts of the bartholin ducts (15,05% mean age 36,33 years) and 3 inclusion epidermal cysts (3,23% mean age 41,67 years). Furthermore, 6 cases of intraepithelial polyps (6,45% mean age 36,67 years), 2 papillary hidradenomas (2,15% mean age 49,50 years), 10 angiokeratomas (1,08% mean age 52 years) and one trichoidic hemangioma (1,08% mean age 52 years) were found. Finally, 2 pigmentosum maculas, one intrachoriotic (1,08% mean age 20 years) and one mixed (1,08% mean age 21 years), 2 cases of granular tissue (2,15% mean age 65 years) and one case of vasculitis (1,08% mean age 31 years).

Conclusion: Strict criteria for the differential diagnosis from intraepithelial or malignant lesions are proposed.
DIFFERENTIATED VIN IS OFTEN FOUND IN LESIONS, PREVIOUSLY DIAGNOSED AS LICHEN SCLEROSUS, THAT HAVE PROGRESSED TO VULVAR SQUAMOUS CELL CARCINOMA

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Background and aims: 2-5% of all Lichen Sclerosus (LS) lesions progress to vulvar squamous cell carcinoma (vSCC). Differentiated vulvar intraepithelial neoplasia (dVIN) has been proposed to be the direct precursor lesion, but is only recently recognized as a separate entity. The aim of this study was to test the hypothesis that of all lesions that have been diagnosed as LS in the past, a part might currently be diagnosed as dVIN and to identify histopathological differences between LS lesions with and without progression to vSCC.

Methods: All LS slides were revised by two expert gynecopathologists. The presence of hyper-, para-, and dyskeratosis, hyperplasia, basal cellular atypia, mitoses, edema, hyalinization and subepithelial inflammation were documented. The presentation of rete ridges and basal cell layer were examined and the epithelial thickness counted.

Results: After revision of LS biopsies without progression (n=61), 58 were reclassified as LS. Revision of LS biopsies with progression yielded concordant diagnoses in 18/60 cases (30%). 25/60 (41.7%) lesions were reclassified as dVIN. Median time from dVIN to vSCC was shorter (27.5 months) than from LS to vSCC (83.8 months) (p< 0.001). LS that did progress to SCC more often showed parakeratosis (p=0.004), dyskeratosis (p< 0.001), hyperplasia (p=0.048) and basal cellular atypia (p=0.009) compared to LS without progression.

Conclusion: dVIN has been frequently missed and is associated with rapid progression to SCC. Patients with LS with dys- and parakeratosis, hyperplasia and/or basal cellular atypia should be kept under close surveillance as these lesions also tend to progress to SCC.
LOCALLY ADVANCED VULVAR CANCER IN ELDERLY WOMEN: IS CHEMORADIATION BENEFICIAL?

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Background and aims: There is a high incidence of invasive vulvar cancer in the elderly population. With multiple medical comorbidities, radiation with sensitizing chemotherapy is complicated. The goal of our study was to investigate whether elderly patients are more likely to die of intercurrent disease (ICD) or of treatment-related complications.

Methods: A meta-analysis of published data was performed to compare in elderly and non-elderly patients with vulvar cancer treated with chemoradiation: remission rates, death from ICD or treatment complications, and rates of surgery. Eligibility criteria included prospective studies of women with advanced (FIGO III or IVa) primary squamous cell carcinoma of the vulva receiving preoperative or primary chemoradiation with curative intent. Data collected included: age (elderly defined as ≥ 65), stage, treatment (chemotherapy, radiation, and surgery), follow-up times, and mortality (disease-related, treatment-related, or intercurrent).

Results: Seventy subjects were identified from seven studies that met eligibility criteria. Seventy-eight percent (25/32) of patients < 65 years old were without evidence of disease after treatment versus 66% (25/38) of patients ≥ 65 years of age. Three percent (1/32) of patients < 65 years of age died of ICD or treatment complications versus 11% (4/38) of patients ≥ 65 years old.

Conclusions: Death from ICD or treatment complications was nearly four-fold higher for elderly patients. Despite the heterogeneity of studies and a small sample size, the data is compelling. Future research should focus on treatment with chemoradiation in the elderly population with regard to: survival benefit, toxicity, and death from ICD or treatment complications.
V-Y FASCIOCUTANEOUS FLAP IN THE TREATMENT OF INVASIVE VULVAR CANCER

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Introduction: Different surgical procedures in vulvar cancer are available and the choice depends on 3 main factors: size of primary tumor, depth of penetration into stroma, and spread into regional lymph nodes. A special problem exists with treatment of tumor which covers large areas, urethra, bladder, perineum or anus.

Objective: Demonstration of surgical technique in creation of V-Y sliding fasciocutaneous flap for covering the defect following the surgical excision of vulvar cancer and evaluation of obtained results.

Method: Seven patients aged 59-75 years (x = 65.5) were operated in the period from 2005 to 2008. After inguinal lymphadenectomy, wide local excision 4 (57.1%) and radical vulvectomy 3 (42.9%) were performed, followed by covering of the defect by V-Y fasciocutaneous flaps. Histopathological examination confirmed squamocellular type of carcinoma in all cases. Staging of the disease was determined postoperatively according to current FIGO classification. The period of monitoring and follow up was 29 months on average (24-36).

Results: We applied 11 V-Y fasciocutaneous flaps (3 unilateral and 4 bilateral). The average duration of operation was 155 minutes, and average blood loss was 250 ml. Regarding postoperative complications, we had 2 cases (18.2%) of partial superficial dehiscence at the junction of bilaterally created flaps. Local recurrence was recorded at one patient in the area of perianal region 36 months after the operation.

Conclusion: Based on the donor-site scar, thickness and degree of flap advancement, the fasciocutaneous V-Y flap is a good method for reconstruction of vulvoperineal defect after radical tumor excision.
PAGET DISEASE OF THE VULVA IN A 44-YEAR-OLD WOMAN: CASE REPORT, SURGICAL APPROACH AND EIGHT-MONTHS FOLLOW UP

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**Background:** Paget disease occurs mainly in breast. Extra-mammary and especially vulvar localization is quite rare in postmenopausal women and even rarer in premenopausal women. In this study, we present a case of primary vulvar Paget disease in a 44-year-old woman, the used treatment method and the follow up.

**Aims:** The aim of this study is to present a rare case of vulvar Paget disease in a premenopausal woman and to describe the surgical approach and the results of the used treatment in an 8-months period. Moreover, authors try to find if there are differences, depending on age, in treatment, care and follow-up.

**Methods:** A 44-year-old virgin woman, with histological diagnosis of vulvar Paget disease made by biopsy, has undergone simple vulvectomy. The patient is being followed up regularly.

**Results:** The histopathologic examination revealed vulvar Paget disease without invasion of the underlying stroma. Surgical margins were free of tumor. The patient was discharged home on postoperative day 15 without complications. She received no further treatment and remains well eight months after the operation. Wound healing is completed and no indication of recurrent disease is presented.

**Conclusion:** Although vulvar Paget disease is a rare condition, especially in premenopausal women, a biopsy must be taken from every suspicious area. Surgical approach, with simple vulvectomy downward to free surgical margins, seems to be an indicated treatment method, independently of the age. Follow up is essential to detect early recurrent disease.
EPIDEMOLOGICAL CHARACTERISTICS OF VULVAR CANCER IN VOJVODINA FROM 1988 TO 2007

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Vulvar cancer is a rare malignancy and it participated with four percents in total new genital cancer cases in Vojvodina (region in Serbia) in 2007. During the studied period the average incidence rate was 2,82/100 000.

We analyzed with descriptive epidemiological method the vulvar cancer in Vojvodina. The data were from Cancer Registry of Vojvodina for the period from 1988 to 2007.

Total number of diseased was 586 and annual average number was 29. The standardized incidence rates were between 0,8/100 000 in 2002 and 2,06/100 000 in 1997. The trend of incidence rates had an increasing tendency (Y=0,07X + 2,07, R=0,59). Annual percent change was 2,87 percents. The highest rate was between 80-84 years of age (20/100 000). About 3 percents women were until 40 years old. We regestered 6 cases of melanoma and 9 cases of sarcomas in this period. The annual average number of death was 18 and average mortality rate was 1,76/100 000. An increasing tendency for mortality was regestered (Y=0,07X + 1,06, R²=0,43).

From our data we can conclude that vulvar cancer is rare cancer but it shows an increasing trend from incidence and from mortality too. Regular gynecological visits (specialy for olderl women) are important for prevention this disease.

Keywords: Vulvar cancer, epidemiology, incidence
DETECTION OF SENTINEL NODE IN SQUAMOUS CELL CANCER OF THE VULVA. SAFETY AND CLINICAL APPLICATIONS


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Background and aims: The aim of this study was to identify inguinofemoral sentinel nodes in patients with squamous cell vulvar carcinoma and to evaluate the safety of the procedure.

Methods: With Tc99m-nanocolloid (preoperative lymphoscintigram and intraoperative γ-probe) and methylene blue we tried to identify sentinel nodes. Completion inguinofemoral lymphadenectomy was performed in all patients. Sentinel and inguinofemoral nodes were sent separately for pathologic examination. Only sentinel nodes found to be negative with the HE-staining were examined with ultrastaging.

Results: 64 inguinofemoral node dissections were performed in 34 patients. At least one sentinel node was identified in all 34 patients and in 52 of 64 dissections (detection rate 81.2%). In 7 patients only methylene blue was used and 69 sentinel nodes were identified. All were hot and 65 of 69 were blue. Surgical staging revealed 18 stage I-II patients, and 16 stage III-IV. Detection rate was not significantly higher in the combined vs blue dye only technique (84% vs 71% respectively, p=0.438). Lymph nodes in 19 dissections had metastatic disease and in 11 of them the sentinel node was the only positive. Four false-negative sentinel nodes were observed in three patients with tumors of >4cm. No false-negative sentinel node was found in well-differentiated tumors < 4cm in patients < 70 years.

Conclusion: The concept of sentinel node seems to be safe for well-differentiated tumors < 4cm in patients < 70 years.
SOME NEW TENDENCIES IN DIAGNOSIS AND COMPLEX TREATMENT OF VULVAR CANCER-
OUR AND FOREIGN EXPERIENCE

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Introduction: The aim of this research work was to summarize our and foreign experience in the field of diagnosis, complex treatment and prognostic factors connected with vulvar cancer.

Material and methods: We evaluated our and foreign experience for 10 years period (2000-2010) and evaluated 625 patients diagnosed and treated for vulvar cancer. We assessed the complex treatment, prognostic factors and some new tendencies towards more conservative surgical treatment of vulvar cancer.

Results: The all 5 years survival rate was 70%; 10 years survival rate was 50%. The level of recurrence was 30% (187p.), local recurrences were 50% (93p.), the groin recurrences were 7% (13p.). The biggest recurrence rate was in local recurrences of the vulva. Older age and metastases in lymph nodes were independent bad prognostic factors. The stages of the lymph nodes, LVSI and the stage were connected with survival and disease free survival. The different kinds of treatment were analyzed—surgery, chemo and radiotherapy. We analyzed the tendencies towards more conservative surgical treatment connected with vulvar cancer.

Conclusions: We tried to summarize our and foreign experience in the complex treatment of vulvar cancer for 10 years period. Our main idea was to show some new tendencies in the latest 10 years towards relatively more conservative treatment of this neoplasia.

Keywords: Vulvar cancer, conservative surgical treatment, prognostic factors, survival rate.
PRIMARY MALIGNANT MELANOMA VAGINA: A LARGE, SINGLE INSTITUTION EXPERIENCE

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Objective: To evaluate the clinical and pathologic features of vaginal melanoma to determine predictors of outcomes.

Methods: Thirty-seven women with vaginal melanoma clinically and radiographically limited to the vagina (clinical stage I) were identified and included in this retrospective study.

Results: Median age was 60.6 years. Eighty-four percent were Caucasian and vaginal bleeding was the most common presenting symptom. Sixty-five percent of patients had lesions in the distal third of the vagina, while 26% had tumor in the proximal third, 6% had their disease found in the middle third of the vagina and 3% had multifocal disease. Initial management included wide local/radical excision (76%), pelvic exenteration (14%) and radiation and/or chemotherapy (10%). At a median follow-up of 17.4 months, 32 women had recurred. The two surgical groups had significantly longer survivals than those treated non-surgically (p=0.01). Median progression free survival was 11.4 months and median overall survival was 19 months. The 5-year progression free and overall survivals were 9.5%, and 20.0%, respectively. Recurrence was local in 7 (22%) patients, distant in 20 (63%), and both in 5 (15%) patients. The most common sites of distant recurrence were lungs and liver. Radiation therapy after wide excision reduced local recurrence and increased survival from 16.1 months to 29.4 months (p=0.46).

Conclusion: Even when localized at diagnosis, malignant melanoma has a very poor prognosis. Patients who underwent pelvic exenteration or wide excision had longer survival than those who had non-surgical treatment. Radiation therapy after wide excision reduces local but not distant recurrences.
THE GREAT MIMIC MIGHT BE A HARBINGER OF A MORE PROFOUND DISEASE. PAGET'S DISEASE OF THE VULVA: A CASE REPORT

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Paget's Disease of the vulva is rare, accounting for one percent of vulvar malignancies. It is characterized by a superficial white skin lesion which on microscopy shows large vacuolated cells with granular cytoplasm within the epidermis. It follows an insidious course and is often mistaken for more common conditions, causing delay in diagnosis and definitive treatment. More importantly, it may be associated with adenocarcinoma in other sites.

Reporting a 58 year old nulligravid who complained of an eczematoid lesion of the left labia majora associated with pruritus for nine years. Antihistamines, topical antifungals and steroids gave no relief prompting biopsy of the lesion.

[gross examination of the vulva]

The cervix and vagina were normal on examination and on visual inspection with acetic acid, Pap smear and colposcopy. CA125, CEA, transvaginal ultrasound, digital mammogram and abdominal CT scan were normal. She underwent wide local excision of lesion. Frozen section revealed Paget's Disease of the vulva without invasion and clear margins of resection were obtained.

[scanner and high power view of Paget's Cells]

Primary closure of the incision was done. She was closely monitored and showed no clinical evidence of disease.
FATAL CUTANEOUS METASTASIS FROM VULVAR CANCER

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Cutaneous metastasis of Vulvar Squamous cell carcinoma (SCC) is a rare event. To our knowledge up to now seven cases have been reported in the literature.

We report a 45-year-old woman with Vulvar SCC stage II. She underwent radical Vulvectomy and bilateral inguinal and femoral Lymphadenectomy. She received 6000 cGY radiation due to positive margin.

Seven months later, she referred with local lymph node recurrence and metastatic SCC that confirmed with biopsy, and received chemoradiation after surgery of metastasis.

Five months later, she came back with skin lesion in mons pubis after excision she received chemo radiation.

Few months later, she referred with multipel skin metastasis in lower abdomen and lower limbs. Pathologic examination revealed metastatic SCC. She gave three cycles’ chemotherapies and then oral etuposide. Three months later she was expired.

Keywords: Cutaneous metastasis, Vulvar Squamous cell carcinoma, Vulvectomy, chemo radiation
RADIOCHEMOTHERAPY IN ADVANCED VULVAR CANCER

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In cases of advanced vulvar cancer with non-resectable lesions, permanent cure is extremely rare. At present, chemosensitivity of vulvar cancer is relatively well documented. Implementation of synchronous chemotherapy with a 15-20% reduction of total dose radiotherapy provides a favorable therapeutic index.

**Aim:** The evaluation of tumor response to radiochemotherapy in patients with advanced vulvar cancer, based on own-experience to-date.

**Material and methods:** Between January 2005 and December 2008 at Maria Sklodowska-Curie Memorial Cancer Centre in Warsaw, 17 squamous cell vulvar cancer patients, staged T3-T4, N0-N2M0, aged 56-81 years, were treated. The patients were irradiated with photons X(6-15 MeV), over vulvar area, inguinal lymph nodes and pelvis. Total doses, delivered to vulvar area ranged between 50 and 65 Gy, to pelvic and inguinal lymph nodes, 45-65 Gy. Chemotherapy consisted of 5-FU at the dose of 750-1000 mg/m², administered in a 96-hours' infusion on days 1st- 4th and cisplatin at a dose of 50 mg/m² on day 1st, administered on the 1st and 5th week of radiotherapy.

**Results:** Complete regression of the tumor was achieved in 7(41%) patients, partial response in 9(53%) patients, progression of the disease in spite of the therapy was observed in 1(6%) patient. In 3(33%) patients, who obtained partial response, only radiation-induced damage with no viable tumour remnants was observed intraoperatively.

**Conclusions:** Radiochemotherapy should be considered as the treatment of choice in far-advanced vulvar cancer. Surgery should be reserved for patients with recurrent disease or those with incomplete regression after radiotherapy.
“I NEVER UNDERSTOOD WHAT IT WAS…” EXPERIENCES OF WOMEN WITH VULVAR INTRAEPITHELIAL NEOPLASIA

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Background: Although vulvar intraepithelial neoplasia (VIN) is a relatively rare condition, the incidence of VIN is on the rise, particularly in younger women. Consequently, women with VIN are surviving longer and undergoing repeated, disfiguring treatments to prevent the development of vulvar cancer. However, psychosocial research to date has primarily focused on vulvar cancer patients or used mixed samples, with only few studies investigating the psychosocial impact of VIN.

Aim: The aim of this qualitative study was to explore women’s experiences with VIN, including the impact of diagnosis and treatment on personal relationships, sexuality, body image and, overall quality of life, and to identify areas of unmet needs.

Method: Semi-structured telephone interviews were conducted with 25 women treated for VIN within the past 5 years. Purposive sampling was used to recruit women of different ages, with varying stages of disease and recovery.

Results: The main themes that emerged from qualitative analysis based on Grounded Theory centered around issues of initial misdiagnosis and misunderstanding the nature of VIN, its causal factors, the extent of disease severity, or the importance of continued surveillance. Participants also reported a mixed impact of VIN on sexuality, relationships and support. All participants reported the need for improved information delivery about diagnosis, treatment and post-operative care.

Conclusion: Very few women with VIN understand their diagnosis, or how to best care for themselves post-operatively. Recommendations for various information interventions targeting the nature and etiology of VIN, post-operative care, and the importance of continued surveillance, will be discussed.
PATIENT OUTCOMES FOLLOWING RADICAL VULVAL EXCISIONS AND PLASTIC FLAP RECONSTRUCTION

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Background and aims: Extensive tumour resections and operations performed on disease recurrence are examples of frequent indications for local or regional tissue flap reconstruction. The aim of this study was to assess tissue flap use and outcomes.

Methods: Retrospective cohort study design of all patients undergoing vulval or perineal tissue flap construction at BCH between 1st Jan 2004 and 31st Dec 2009 were included. Data was collected via proforma and subsequently analysed.

Results: 22 patients underwent 24 flaps. Range of patient age was 41 years to 90 years (mode 61-70 years) with parity range 0-6 (mean 2.05). 12 patients had previous radical vulval excision. Indication for surgery was recurrence of cancer in 11 patients (50%). 12 patients had wide local excision, 5 had radical vulvectomy and 5 modified radical vulvectomy. 4 cases of return to theatre were required (1 re-suturing, 2 debridement, 1 drainage of lymphocyst). Hospital stay ranged from less than 1 week to greater than 6 weeks. Approximately half of patients experienced some degree of wound breakdown and / or infection whilst necrosis (4 cases) and lymphocyst (2 cases) were less common. 50% of patients experienced some form of medical complication. 13 patients (59%) had no long term complications. There were 3 cases of further recurrence, 3 vaginal stenosis and 1 each of chronic cellulitis, urethral stricture and abscess.

Conclusions: Flap reconstruction utilisation and outcomes have been described. Medical complications are a common post-operative occurrence. Promising long-term results have been demonstrated.
VULVAR LEIOMYOSARCOMA, WHICH MIMICKS BARTHOLIN GLAND ABSCESS CLINICALLY


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A 52-year-old case with vulvar leiomyosarcoma admitted to our out-patients clinic with a painful and hyperemic mass at Bartholin’s gland region. An incisional biopsy was performed for the diagnosis and the patient underwent radical vulvectomy and bilateral inguinal lymphadenectomy. A follow up for 5 years postoperatively did not reveal any metastases or recurrences. The clinical course of these tumors may be aggressive with early systemic metastases or may lead local recurrences and late fatal systemic metastases with a relatively longer survival. Radical vulvectomy must be the choice of therapy, however a lymphadenectomy seems to be an overtreatment if there is no enlarged lymph nodes. Radiation and chemotherapy may regress the metastasis but do not change the outcome of the disease. With the current data, it is not possible to make a comment on the correlation between the histopathological criteria and the risk of the recurrence.

Keywords: Vulva, Leiomyosarcoma, Bartholin gland
MANAGEMENT OF PRIMARY VAGINAL ADENOCARCINOMA OF INTESTINAL TYPE


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Background: Primary cancer of the vagina comprises 0.3% of all malignant neoplasm of the female genital tract. Vaginal adenocarcinoma of intestinal type, in the absence of diethylstilboestrol exposure (DES), is an extremely rare neoplasm and few cases had been reported in the literature.

Case: 35 years old women with postcoital bleeding and vaginal mass was admitted to our institution. A physical examination revealed a 1.5x1.5x0.5 cm polypoid lesion derived from 1/3 lower part of the right vaginal sidewall. Excisional biopsy revealed an adenocarcinoma of the intestinal type. She received external pelvic radiotherapy with brachytherapy and she doing well since 22 months.

Conclusion: While the optimal treatment of vaginal adenocarcinoma of intestinal type is not yet defined we considered to manage with simple excision and radiotherapy; because of the high morbidity rate of radical vaginectomy and its long term sequels. Due to rarity of this type of malignancy, the optimal management is not yet known. We chose radiotherapy for the treatment because of her young age. Radical surgery as an alternative treatment modality may be to cause high morbidity and deleterious effect on sexual function.

Keywords: Primary Vaginal adenocarcinoma, Intestinal type.
EXPLORING THE PROTEOME CHARACTERISTICS OF HPV-POSITIVE VS HPV-NEGATIVE VULVAR CARCINOMA USING MASS SPECTROMETRY

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Background: Vulvar squamous cell carcinoma (VSCC) is 4% of all gynecological malignancies. It can be divided into two subtypes, one related to high risk human papilloma virus (HPV) infection, and one that is not. Studies indicate that patients with HPV-positive VSCC have a better survival and prognosis compared to HPV-negative VSCC.

Aim: The primary objective of the present study was to compare the protein expression between HPV+ and HPV- VSCC.

Material and methods: Proteins extracted from fresh frozen tumour samples, 7 HPV-positive, and 7 HPV-negative were labelled with 8-plex iTRAQ and quantified by IEF-LC-MS/MS (LTQ Orbitrap Velos). The proteins identified with a maximum false discovery rate of 5% were selected using the software MAYU. Multivariate statistics and modelling was performed with SIMCA (Umetrics). The web based software Ingenuity Pathway Analysis has been used for network generation and comparison with canonical pathways.

Results: After data curation, 449 quantitatively accurate proteins were found in all the samples and 88 of those proteins were able to separate HPV+ from HPV- by an O-PLS model (p< 0.05), see figure..

Conclusion: The results indicating that the selected proteins are unique to the model, different proteins are expressed in HPV+ and HPV- tumors which may contribute to understand the differences in tumourbiology and prognosis.
[Protein expression in HPV+ and HPV- vulvar cancer]
GRANULAR CELL TUMOR OF VULVA - A RARE TUMOR OF FEMALE GENITAL TRACT: CASE REPORT AND REVIEW OF THE LITERATURE

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Background: GCT is a rare benign tumor of neurogenic origin resembling Schwann cells. Only 1-2% are malignant. The granular cell tumor (GCT) of vulva is a rare female genital tract tumor.

Case report: A 59 years old Chinese female attended vulva clinic at Gynaecology cancer centre at KKWCH. She had a small vulva lump in the left labium majus for 9 to 10 years that was less than 3 cm in size with out causing any symptoms. She noted recent increase in the size of the lump. Her medical history revealed hypertension and hyperlipidemia. Her Gynecological history and examination was unremarkable. On examination the lump was firm, nodular and painless. No inguinal lymphadenopathy was noted. The lump was excised with diathermy under general anesthesia. She recovered uneventfully. No recurrence noted in the further follow ups.

Conclusion: Although benign and slow growing, it has a tendency for recurrence and can cause morbidity and mortality when presenting with multiple organ involvement. Therefore, clinicians should be aware the diagnosis.
NUCLEAR DNA CONTENT, PROLIFERATIVE ACTIVITY AND LAMININ-5-γ2CHAIN EXPRESSION AS PREDICTORS OF PROGNOSIS IN VULVAR CANCER (VSCC) AND CORRELATION TO HPV

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Background: Studies indicate that patients with HPV+ VSCC have better survival and prognosis compared to HPV- VSCC. Their rarity and diversity have contributed to the lack of consensus on risk factors to distinguish between the low- and high-risk patients.

Aim: The purpose of this study was to evaluate the prognostic impact of DNA ploidy S-phase fraction (SPF), Ki67(MIB-1), Laminin-5-γ-2 (Ln-5) chain and HPV in patients with vulvar cancer stages I-IV.

Material and methods: In tumorspecimens from 85 patients the expression of Ln-5 (n=74), Ki 67 (n=70) by IMH, DNA ploidy and SPF (n=67) using flow cytometry and PCR for HPV were studied.

Results: In univariate analyses Ln 5 was a significant predictor of survival (p=0.009) and recurrence free survival (p=0.016). No significant differences were seen for DNA ploidy, SPF and Ki67. There was an overexpression of Ki67 in HPV positive tumors (p=0.002) and a significant correlation between the grade of the tumor and Ki67, Ln-5 and SPF (p=0.008, 0.031 and 0.015 respectively).

Conclusion: Ki67 was significantly overexpressed in HPV+ tumors. In this study Ln-5 overexpression had a strong prognostic impact in VSCC.
A CASE REPORT: AUTOLOGUS SKIN GRAFT IN DEHISCENCE OF RADICAL VULVECTOMY

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Introduction: Vulvar cancer is an uncommon cancer representing approximately 4% of female genital tract cancers. Vulvar squamous cell carcinoma (SCC) is predominantly a disease of post menopausal women and is rarely observed during pregnancy and lactation. Vulvar carcinoma in younger patients is related to Hpv infection, smoking and immune suppression.

Case: A 29 years old women referred to the educational center with an ulcerative lesion in right and left labia while measured about 5×3 cm in right side and 2×2 cm in left labia. She had no previous disease and delivered 6 months ago by cesarean section. Vulvar biopsy showed SCC of vulvae and colposcopy of vagina was negative. The procedure of radical vulvectomy and bilateral lymhadenectomy was successfully done. In the 5th days of operation wound dehiscence occurred and daily dressing and washing and debridement was done to remove necrotic tissues. Extensive dehiscence occurred and autologus skin graft planned to restore the anatomy and coverage of the vulva and the perineum.23 days after first operation a second plastic surgery was scheduled to graft denuded area. The resulting cosmetic effect was acceptable.

Discussion: wound dehiscence of patients with Vulvar cancer is a known complication and related to lesion size and extent of excision. This case with autologus skin grafting was an interesting one due to her young age and beginning of the disease in lactation period and its complicated course.

Keywords: Vulvar cancer, wound dehiscence, autologus skin graft
VAGINAL CANCER: CLINICAL EXPERIENCE OF A 10-YEARS PERIOD

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Objective: This retrospective study, presents the cases of vaginal cancer, the therapeutical methods and their results, of patients which referred to our outpatient department or were diagnosed in our clinic at the time of period 2000-2009.

Material and methods: The material emanates from the oncology clinic of our department. Women suffering from vaginal cancer were categorized depending on the histological type of disease, the clinical aspect of cancer, the methodology of confrontation of illness and the results of therapeutic effort. The median age of patients was 65 years (range: 45 - 80).

Results: Diagnosis was based on symptomatology, clinical examination, biopsies and was confirmed with the histological examination of chirurgical material. From the point of view of histological type, 6 were primary vaginal squamous carcinomas, 4 were metastatic vaginal adenocarcinoma, and 6 were endometrioid carcinoma of vaginal vault. The therapeutic confrontation was Radical Hysterectomy, Radical Vaginectomy and pelvic lymphadenectomy (in the majority of the cases). In most of the cases additional radiation therapy was necessary. The 5-year survival rate was 70%.

Conclusion: Primary vaginal cancer is a relatively uncommon tumour, representing only 1% to 3% of malignant neoplasms of the female genital tract. The incidence of invasive vaginal cancer is 0.42 per 100,000 women and has remained relatively unchanged since the 1980s. Primary vaginal cancer should be differentiated from cancers metastatic to the vagina. Metastatic cancers constitute the majority of vaginal cancers (80% to 90%). The diagnosis in advanced stages is accompanied by a short-term survival.
HPV IN VULVAR CANCER - DOES ITS PRESENCE DEMAND AN EXTENDED ADJUVANT TREATMENT?

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Objectives: Human Papilloma Virus (HPV)-dependent vulvar cancer often occurs in younger patients. The proof of HPV-DNA in lymph nodes in cervical cancer showed an increased risk for a fatal course of disease.

Aims: of the study were to investigate whether HPV-DNA could be detected in non-metastatic lymph nodes and its influence on tumor stage, disease-free- and overall-survival.

Methods: Surgical tissue of patients with squamous-cell-carcinoma of the vulva was collected. HPV-DNA was isolated via sensitive real time PCR. Follow-up data were obtained from patients`records.

Results: were combined and compared with respect to initial extend of the disease and to HPV status. Results Histological samples were obtained of 40 patients. Patients with HPV positive (HPV+) tumors had significant more advanced tumor stages following the TNM classification ($p = 0.0046$). None of the non-metastatic lymph nodes was HPV+. Average age of patients of with HPV+tumors was lower than of the HPV negative (HPV-)tested patients (62.5 yrs versus 71.3 yrs, $p=0.0569$). There were no statistically significant differences in nodal metastatic spread and FIGO classification. More patients with HPV+tumors suffered from recurrence or fatal course than in the HPV- group.

Conclusions: We found significant differences in tumor stages in HPV+ vs. HPV- tumors in vulvar squamous cell carcinoma. The group is too small to find more statistically significant results, nevertheless, a tendency towards more fatal courses in the HPV+group was found. As this form often occurs in younger women, a controlled trial should be conducted, implementing a more aggressive adjuvant treatment to prevent early recurrence.
WOMEN'S EXPERIENCES FOLLOWING TREATMENT FOR EARLY STAGE VULVAR CANCER: A QUALITATIVE INSIGHT

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Background: Despite the potential for significant adverse psychosexual consequences, there is limited information available on perceptions of sexuality and body image following treatment for early stage vulvar cancer. A review of the literature shows paucity of qualitative insights for this topic. This study was undertaken to address this deficiency, and to add to the existing body of knowledge describing the psychosexual outcomes for these women.

Aim: To describe women's experience of sexuality and body image following treatment for early stage vulvar cancer.

Methods: A qualitative approach based on interpretive phenomenology was used to interview a purposive sample of 10 women who had previously been treated for an early stage vulvar cancer. Data were generated from verbatim transcription of the semi structured in-depth interviews and thematic analysis was used to develop key themes.

Results: The mean age of women interviewed was 58 years. Interviews took place one year or more after surgery. Four essential themes were identified that described the participants' experiences. These themes comprised: information limitations, sexuality, body image and a private cancer.

Conclusions: The majority of women experienced little to no long term disruption to sexuality and body image. Intimacy and relationship status were more important to women than physical arousal. Factors contributing to women experiencing disruption to body image were more radical vulvar excision, multiple vulvar procedures and/or the development of lymphoedema. An overwhelming majority of the participants indicated the need for more information and better timing for the provision of existing information.
RAPID SPONTANEOUS REGRESSION OF ACUTE ONSET VIN 3/VULVAR CARCINOMA IN SITU IN YOUNG WOMEN: A CASE SERIES

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Objective: VIN 3/vulvar carcinoma in situ is currently treated by surgical excision, laser ablation or with topical immunomodulators. The peak incidence of invasive carcinoma of the vulva occurs in the sixth decade which may indicate that HPV related pre-invasive disease in the younger population has a lower progression rate. However, risk of invasive disease cannot be disregarded.


Results: Complete spontaneous regression of acute VIN 3/vulvar carcinoma in situ in five young women from ages 20-36. New sexual partners were reported in two of the five cases preceding the onset of vulvar lesions within 6 months. All patients were non-smokers, immunocompetent and noted the acute onset of multifocal vulvar lesions. VIN 3/vulvar carcinoma in situ was diagnosed on biopsy and confirmed upon independent review. Time to spontaneous regression was between 6 and 20 weeks after initial biopsy. Recurrence has not been noted in any of cases with in the follow up period of 3 to 36 months.

Conclusion: Short term follow-up with conservative management of acute onset VIN3/vulvar carcinoma in situ in this young patient population correlates with similar treatment strategies for HPV related CIN of the cervix and may prevent disfigurement, pain, and complications associated with the current recommended therapeutic modalities. The timing of intervention for VIN3/vulvar carcinoma in situ in the young population needs clarification. Future studies are in order.
VULVAR INTRAEPITHELIAL NEOPLASIA: CLINICAL EXPERIENCE OF A 10-YEARS PERIOD


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**Objective:** This retrospective study, presents how we diagnose, treat and follow up women having vulvar intraepithelial neoplasia(VIN).

**Materials and methods:** Among approximately 13,200 women, aged 18 - 80 (mean 39) examined in the oncology clinic of our department 85 were found having VIN. They were categorized depending on the histological type of disease, the methodology of confrontation of illness, and the results of therapeutic effort.

**Results:** Diagnosis was based on symptomatology(itching, irritation), clinical examination (colposcopy - vulvoscopy), multiple biopsies, and was confirmed with the histological features. 30 found having VIN I, 25 found having VIN II and 30 found having VIN III. Those with VIN I followed up with vulvoscopy and biopsies. Half of them progress to VIN II and VIN III. We treat women having VIN II and VIN III with surgical excision of the lesions.

**Conclusion:** Only 5 patients having VIN I developed vulval cancer in a five year period. Most women with VIN aged 25 - 45, probably because of high incidence of risk factors such as HPV infection and smoking (other risk factors are multicentric disease, immunosuppression). After surgical excision most patients expressed high levels of satisfaction in comparison with those treated firstly with conservative therapy (imiquimod, 5 - FU).
GASTROINTESTINAL STROMAL TUMOR IN THE RECTOVAGINAL SEPTUM: A MOLECULAR ANALYSIS OF A RARE DIAGNOSIS

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Background: Gastrointestinal stromal tumors (GIST) are mesenchymal neoplasms that commonly arise in gastrointestinal tract, but they are uncommon in rectovaginal space.

Aims: The present study reports a case of a rare rectovaginal GIST and the current knowledge of this entity is reviewed.

Methods: A 60-year-old female underwent nodule resection in the rectovaginal septum at another hospital fifteen days before her admission at Barretos Cancer Hospital with an initial pathological report of a low-grade fusiform cell neoplasm. Fifteen months later, a nodule was detected on gynecological examination. This lesion was located on the right side of the rectovaginal septum and an excisional surgical procedure was performed. The pathological analysis attributed an unequivocal diagnosis of GIST. Both initial and recurrent lesions were assessed for immunohistochemistry and KIT mutation analyses.

Results: The immunohistochemistry analysis of a panel of 16 antibodies showed that all reactions were negative except for CD117, CD34 and Bcl2 (focal). The mutational analysis of KIT exons 9, 11, 13 and 17 in the primary and in the recurrent tumor showed the presence of a somatic deletion mutation (p.Trp557_Lys558del) at exon 11.

Conclusions: An extensive review of the literature found thirteen cases similar to the current case, emphasising the need to consider a GIST diagnosis when a tumor composed of fascicle of fusiform cells is found in rectovaginal space or vagina. Based on the review of available data, it is warranted to discuss the extra gastrointestinal nature of these lesions.
QUALITY OF LIFE AND URINARY FUNCTION AFTER RADICAL VULVECTOMY WITH OR WITHOUT FLAP REPAIR


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Objective: The aim of this study was to evaluate quality of life and urinary function in patients submitted to vulvectomy with or without flap repair plastic reconstruction.

Methods: One hundred thirty four patients diagnosed with vulvar carcinoma referred to our departments of Gynecology and Obstetrics between January 1997 and January 2009. Patients were divided in two groups: Group one consisted of 80 patients treated with radical vulvectomy or hemivulvectomy in combination with inguinal lymphadenectomy. Group two included 54 women treated with radical vulvectomy and inguinal bilateral lymphadenectomy associated with vulvar reconstruction with V-Y amplified sliding flap or island flap raised from gluteal folds.

All patients were submitted to Vulvar Cancer Specific Sub Scale VWB questionnaire constituted of 15 items regarding quality of life, sexual function, body image and urinary function scored by 0 to 4; moreover urinary flow quality was evaluated.

Results: Patient’s quality of life and aesthetic deficit was better in patients submitted to radical vulvectomy with plastic reconstruction. In particular we had detected better clinical conditions in Group two regarding self body image. Moreover, the depth and width of the vagina can be preserved by reconstructing the three dimensional structure of the vaginal wall which facilitates the follow up of these patients.

Conclusions: Disfiguration of the external genitalia which are an important part of a woman’s identity has a strong negative effect on the patient’s body appearance, therefore surgical reconstruction of the vulva improve morbidity and quality of life after treatment.
CYTOLOGY OF THE VULVA: FEASIBILITY OF A NEW BRUSH

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Objective: A pilot study to evaluate the use of a new brush in the cytological diagnosis of (pre)malignant vulvar lesions.

Introduction: In women with vulvar premalignancies such as usual vulvar intraepithelial neoplasia (VIN) and lichen sclerosis long-term follow-up is indicated. Biopsy is considered standard when patients develop a suspicious lesion, although malignant potential is low. The use of vulvar cytology might spare unnecessary vulvar biopsies and reduce morbidity. Until now, the results of a cervex-brush® for vulvar smears were disappointing.

Methods: A newly developed brush was used to take smears from normal and abnormal vulvar skin in 107 cases; 42 to study the optimal brushing method in normal vulva, 65 to compare with histology.

Results: In comparison with the cervex-brush®, cellularity turned out to be higher in 70% of smears by using the new brush. Moistening the vulva with saline gave better results than taking dry smears. It was possible to reach cells of the basal layer. Thirty-two of the 65 women had biopsy-proven (pre)malignancies. Preliminary results show promising correlations between cytology and histology.

Conclusion: By using the new brush higher cellularity can be seen when compared to the cervex-brush®. Promising correlations were found between cytology and histology. We hypothesize that this new brush will be useful in clinical management.
TUMOUR GRADE AND PROGNOSTIC FEATURES IN VULVAL CANCER - THE GLASGOW EXPERIENCE

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Background: There are a number of pathological factors which are of prognostic significance in vulval squamous cell carcinoma including nodal involvement, tumour size and depth of invasion. Tumour grade is categorised as well, moderate and poor. The effect of grade on prognosis is of unclear significance.

Aims: To assess the relationship of tumour grade to other prognostic features.

Methods: All cases of vulval cancer were reviewed between September 2003 and August 2008. Prognostic factors including tumour size, depth of invasion (DOI), nodal status, pattern of invasion and lymphovascular invasion (LVI) were compared between low and high grade squamous cell carcinomas. A chi-squared test was performed for statistical analysis with a P value of < 0.001 considered significant.

Results: 90% of the cases reviewed during the study period were squamous cell carcinomas. There were 45 low grade and 131 high grade tumours. There was a statistically significant difference between grade of tumour and tumour size, DOI and presence of LVI. There was only 1 positive node in the low grade group (12.5%) compared with 20 positive nodes in the high grade group (40.8%), however, statistical analysis is inconclusive.

Conclusion: This study highlights the relationship between grade of tumour and prognostic factors in vulval cancer. Further research is needed to assess grade of tumour as an independent prognostic factor. Classification into low (well differentiated) and high (moderate or poorly differentiated) grade tumours may be more helpful.
RECURRENT VULVAR SARCOMA

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Objectives: Sarcoma of the vulva is extremely rare. Early diagnosis is usually difficult due to the benign appearance of the lesion. Treatment maybe delayed and sometimes repeated relapsing lesions appear and require extent surgery. The aim was to discuss the management of recurrent vulvar cancer, and the management of a patient of our clinic.

Methods: We report a rare case of vulvar sarcoma of an undifferentiated type, which arises from a lichen sclerosing lesion, with a high grade differentiation and a great potential of relapse. A 66 yo woman was admitted to our department due to the recurrence of a lesion of the vulva (1.3x1cm) located in the right upper limit of the labium major and superiorly to the urethral orifice. A wide excision with disease free surgical margins was performed and the histology confirmed the presence of a sarcoma of uncertain origin. The patient had a recurrence within 3 months and a radical vulvectomy with bilateral inguinal lymphadenectomy was performed, followed by radiation therapy.

Conclusions: We discuss the optimal management of vulvar sarcoma with the different histological types and different treatment approaches. Factors such as tumor size, grade and surgical margins have no established prognostic significance for vulvar sarcoma due to its rare incidence.
PRIMARY INTESTINAL CANCER OF NEOVAGINA WITH UTERINE INVOLVEMENT: A CASE REPORT

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Primitive carcinoma of the vagina is rare, but carcinoma of neovagina is even more unusual. Only 30 reports of malignancies arising in a neovagina have been described in literature. A 61-year-old Caucasian female with negative personal or family history of neoplasm was observed in our Department for abnormal genital bleeding. Her medical history included congenital recto-vaginal fistula, interesting the superior third of the vagina, associated with bicorn uterus. The recto-vaginal fistula was corrected 13 years after the birth utilizing the wall of the rectum for the reconstruction of the posterior vaginal wall. At the clinical examination an important external genitalia atrophy and vaginal stenosis were observed and this condition prevents the examination and trans-vaginal ultrasonography. Vaginoscopy and hysteroscopy were performed under general anaesthesia. Vaginoscopy revealed an irregular vegetant neoformation with superficial necrosis at the superior third of posterior vaginal wall. Hysteroscopy revealed an atrophic endometrium. The vaginal neoformation was biopsed. One day after the hysteroscopy an abdominal peritonitis imposed an urgent Computer Tomography (CT) and median explorative laparotomy. The CT was not significant. During surgical intervention a pelvic abscess with uterine, parametrial and posterior vaginal wall involvement was observed. Multiple peritoneal biopsies, total radical hysterectomy with salpingo-ovariectomy and asportation of third superior of vagina was performed. At the histological examination we found an intestinal adenocarcinoma extended to the cervix and the one of two uterine corns with necrosis and lymphocytes infiltration, parametria were negative for malignancy. HPV test was negative. The post surgery stadiation was negative. At six months follow-up was not evidence of recurrence.
THE POSTERIOR EXENTERATION WITH RADICAL VULVECTOMY AFTER NEOADIUVANT CHEMORADIATION IN STAGE IVA PATIENTS WITH VULVAR CANCER. A PRELIMINARY REPORT

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Background: Unfortunately locally advanced big malignant tumor of the vulva usually cannot be radically treated only by the primary cytoreductive surgery. Chemoradiation is offered then instead especially if a patient is old and suffering from many other diseases. In selected cases the radicality of the surgery can be achieved after neoadiuvant chemoradiation. This radicality means not only radical vulvectomy with lymphadenectomy but also the resection of the vagina, TAH/BSO, and the resection of the rectum or the bladder as dependent on the cancer spread. Such extreme aggressive therapy is very hard for the patients but on the other hand may be the only chance to survive and sometimes it should be considered.

Case report: We would like to present 2 cases of patients with stage IVA of vulvar cancer infiltrating the rectum. Both women were in the fifties and in good general condition so we offered them radical surgery after achieving tumor size reduction due to neoadiuvant chemoradiation. In both patients we performed radical vulvectomy with inguinofemoral lymphadenectomy, TAH/BSO and pelvic lymphadenectomy and abdominal and perineal resection of the rectum with colostomy. The recovery time was prolonged and difficult in both women and demanded reoperation of vulvar scar dehiscence in one of the patients. The follow-up is short - 14 months - but so far these patients are progression free.

Conclusions: In selected patients with advanced vulvar cancer radical surgery is possible after initial response to neoadiuvant chemoradiation though the impact on the overall survival is not clear.
SIGNIFICANCE OF POSITIVE MARGINS IN VIN III

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VIN III is a presumably precancerous lesion of the vulva that merits surgical treatment. Skinning vulvectomy, total vulvectomy, laser ablation, and partial wide local excision are all techniques that are accepted. Because of cosmetic reasons and the proximity of many such lesions to the clitoris and anus, we have used wide local, partial excision as our treatment of choice.

We reviewed the charts of 29 patients coded for VIN III, and two patients were excluded because of extensive co-morbidities and multiple procedures over decades. (Renal transplant, HIV + alcoholism) and a third because she only had laser ablation without a surgical specimen.

Of the twenty six patients, an astounding, 72%, were current or former heavy smokers. Average age was 52.6 (range 38-87). Nineteen were found to have positive margins for VIN III, with three cases having “suspected” microinvasion. Recurrence rate was 40% (10/26), but two of those patients had negative margins.

In analyzing this group of patients, we found a wide discrepancy in the extent of disease at the time of original surgery, and difficult to interpret pathology reports and operative notes.

It appears that positive margins are more common than we appreciated, but the significance, with no patients progressing to invasive disease, is unknown. At this time, close follow up is indicated for all patients with VIN III.
MANAGEMENT OF VAGINAL CANCER


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Primary cancer of the vagina comprises approximately 0.3 percent of all malignant neoplasms of the female genital tract. Here, we reported the clinical pathological characteristics and management in 7 cases of vaginal cancer with different histological types in our hospital from 2005 to 2010. The average ages of patients were 40.8 (27-50). Histology showed 2 of melanoma, 2 of leiomyosarcoma, 1 of squamous cell carcinoma, 1 of clear cell carcinoma and 1 of myofibroblastoma. The clinical stages showed 4 of stage 1, 1 of stage 2 and 2 of stage 3. Three patients had recurrent tumor after previous treatment in other hospital (2 localized surgery and 1 after radical radiation therapy). Three cases of stage 2-3 received neoadjuvant aterial chemotherapy and super-selective embolisation. All patients underwent radical hysterectomy (type II-III)+pelvic lymphadenectomy+total(partial) vaginectomy+vaginal reconstruction. 3-6 courses of adjuvant chemotherapy were given in 6 patients after surgery. All the patients were followed up and the average period was 9.7m (1-54) without recurrence except 1 of the melanoma patients who had a localized recurrence in the vulva after 6 months. Second localized surgery was performed and the patient had DFS for totally 48m. We may conclude that radical surgery is one of the important methods in management of vaginal cancer for the negative margin, even if in the recurrent tumor. Chemotherapy is the important adjuvant step in control of vaginal cancer with high risk factors. Vaginal reconstruction should be considered after exenterative procedure in order to solve the psychosexual issues.
THERAPEUTIC EFFECT OF TOPICAL 5-FLUOROURACIL FOR VAGINAL INTRAEPITHELIAL NEOPLASIA DIAGNOSED AFTER CERVICAL CANCER TREATMENT: A SERIES OF 12 CASES

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Background: Vaginal intraepithelial neoplasia (VaIN) is a premalignant condition that represents 1% of all intraepithelial neoplasias of the lower genital tract. A major risk factor associated with VaIN is HPV infection in women who received pelvic radiotherapy. These lesions can be easily removed by means of surgery. However, the treatment can be challenging when the vagina is fibrotic due to radiation therapy.

Aims: To determine the compliance and the effectiveness of topical 5-fluorouracil in the treatment of VaIN diagnosed during the follow up of patients who had undergone pelvic / vaginal radiotherapy.

Methods: Twelve patients from Barretos Cancer Hospital (Brazil) were enrolled between September 2009 and February 2010. 5-FU was applied topically (1 g/dose), once a week for ten weeks. Assessment by gynecologic examination was performed weekly during the treatment. A new Pap smear and colposcopy were performed two months after the last application.

Results: All patients completed the treatment. The therapy was delayed only in one patient on the last application because she had a moderate colpitis, but without ulcer. In 11 of 12 patients (91.7%) VaIN went into complete remission.

Conclusions: These results suggest that 5-FU is useful for treating VaIN after pelvic / vaginal radiotherapy. Both, compliance and remission rates, seems to be good.
ASSESSMENT OF REVISED FIGO STAGING FOR CARCINOMA OF THE VULVA


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Objectives: The aim of this study was to assess the revised FIGO staging for carcinoma of the vulva and to evaluate whether it allows better prognostic discrimination between stages.

Patients and methods: Retrospective analysis of clinico-pathologic data from 58 patients treated for vulvar cancer at Seoul National University Hospital between 1982 and 2009 was performed. Revised FIGO staging system was applied to this study population. For survival analysis, Kaplan-Meier estimates, log-rank tests and Cox regression models were used.

Results: The 5-year progression-free survival (PFS) was 74.9% for stage I, 100% for stage II, 45.0% for stage III, and 0% for stage IV disease (P<.001) defined by the revised system, which gave a better spread of prognostic groupings than 1988 FIGO staging (83.1%, 68.9%, 67.3%, and 33.3% for stages I, II, III, and IV, respectively; P=.109). However, stage II showed better prognosis than stage I. Combining stage I and II disease, margin status was the only risk factor for recurrence with marginal significance (P=.077), which needs further verification in a larger cohort. In stage III, the PFS was 56.3% for stage IIIA (n=9) and 0% for stage IIIB (n=3), demonstrating good prognostic discrimination (P=.010).

Conclusion: The revised FIGO staging system seems generally acceptable in its present form, although further validation in a larger population, especially on stage II disease, is warranted.
RISK FACTORS FOR VAGINAL INTRAEPITHELIAL NEOPLASIA IN CHINA

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Background and aims: Vaginal intraepithelial neoplasia (VAIN) is a rare disease, and its epidemiology is still unclear. The aim of this study was to ascertain the risk factors for VAIN in a Chinese population.

Material and methods: A case-control study was carried out between Jan 2005 and Jan 2010 and consisted of 63 patients with VAIN and 64 healthy controls with frequency matching by age. All the subjects were given a Pap smear and HPV test. A questionnaire survey was distributed, covering information on socio-demographic characteristics, smoking, past history, reproductive and sexual histories. The cases were diagnosed by colposcopy-directed biopsy for histopathological examination. Meanwhile, their clinicopathological data were collected from medical records including symptoms, Pap smear, grade of lesions, and HPV status.

Results: Menopausal women were at a 2.09 times higher risk for VAIN than pre-menopausal women (\(P=0.024\)). The patients with previous hysterectomy for cervical lesions showed an increased risk of VAIN (OR=4.67; \(P=0.003\)). And patients with a history of cervical cancer or its precancer were predisposed to VAIN (OR=78.75; \(P=0.000\)). Rate of HPV infection in VAIN was significantly higher than in controls. And an elevated risk of VAIN was observed with higher viral load (OR=126.00; \(P=0.000\)). However, no correlations were found for other factors such as reproductive and sexual histories, or the grade of lesions.

Conclusion: These data suggested that menopause, previous hysterectomy, HPV infection and viral load, history of CIN or cervical cancer are the risk factors for the development of VAIN.
FREQUENCY ASSESSMENT OF HPV-INDUCED PRECANCEROUS LESIONS IN PATIENTS WITH BORDERLINE CYTOLOGY IN THE EMILIA-ROMAGNA REGION: THE PATER STUDY

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Background: The management of atypical cytology such as ASCUS and low-grade CIN lesions could lead to substantial unnecessary costs. The PATER study was conducted to assess the frequency of high-risk and low-risk HPV in precancerous lesions diagnosed in ASCUS patients.

Methods: A retrospective, observational, cohort study was designed to evaluate patients who referred to the Department of Gynecology and Obstetrics at the S. Orsola-Malpighi University Hospital (Bologna), in the period January 2000-December 2007 due to ASCUS detected through the implementation of a local cervical cancer screening programme.

Results: In the 1,047 patients enrolled (age range 23-65 years), 34.8% (n=364) were HPV DNA positive. The mean age of patients with a HPV infection was significantly lower compared with the negative group (36.8 ± 9.4 versus 39.3 ± 9.6 years; p< 0.001). An age less than 40 years determined a risk of being HPV positive 1.68 fold greater than older patients (CI95%: 1.28-2.19; p=0.0001). Overall, 357 (34.1%) women were positive for cervical lesions: 279 with CIN1, 18 with CIN2 and 60 with CIN3+. HR-HPV genotype was detected in 83.3%, and 91.5% of patients with CIN2 and CIN3+ lesions respectively. Among 124 CIN1 HPV-positive women, 80.6% harboured HR-HPV genotypes and 19.4% LR-HPV (6 and 11).

Conclusion: Findings of our study suggest:

a) in ASCUS patients over 40 there is a lower risk of positivity for HPV infection;
b) the recorded frequency of LR-HPV (also combined with HR) in ASCUS is not negligible;
c) management costs of ASCUS can be largely avoided with tetravalent vaccination.
SPINDLE CELL CARCINOMA IS PREDICTIVE FOR CLINICAL OUTCOME IN VULVAR SQUAMOUS CELL CARCINOMA

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Background: Vulvar carcinoma is a relatively rare gynecological malignancy with an incidence of 2 per 100,000 women each year. Approximately 90% of all vulvar carcinomas are squamous cell carcinomas (VSCC). Sporadic cases of VSCC with a spindle cell component are known to exist.

Aims: We tested the hypothesis that VSCCs that contain spindle-shaped tumor cells are less differentiated and form an aggressive subgroup. Presence of spindle shaped tumor cells was related to prognosis in patients with VSCC.

Materials and Methods: In a retrospective study, all paraffin embedded tissue blocks of primary VCSS patients stored in the Leiden University Medical Centers’ archives between 2000 and 2009 (N=130) were examined for spindle-shaped tumor cells.

Mean follow up was 37 months (range 2-123). Age at diagnosis was comparable for both groups. Kaplan-Meier and Cox-regression with correction for clinical FIGO-stage analysis were performed.

Results: Twenty-nine tumors (22.3%) contained spindle cells infiltrating stromal tissue, 83 tumors (63.8%) were free of spindle-shaped tumor cells. Eighteen tumors had an unclear spindle cell component of which 9 had spindle-shaped cells close to the invasive border and 9 were indistinguishable because of lymphocytic infiltrates.

Mean survival between patient groups with and without VSCC differed significantly (p 0.000), with a mean survival of 35 months for spindle cell positive and 78 months for spindle cell negative patients.

Conclusion: Spindle cell vulvar squamous cell carcinoma is an aggressive tumor type that may occur more frequently than is often reported and has a worse prognosis compared with ‘classic’ vulvar squamous cell carcinoma.
IMPACT OF THE PATHOLOGICAL RESECTION MARGIN DISTANCE FOR DISEASE RECURRENCE IN VULVAR CANCER

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Background: A tumor-free resection margin of at least 8mm is considered state of the art in vulvar cancer. This standard is based on small and heterogeneous patient cohorts and its implementation can result in mutilation. We therefore reanalysed the impact of the pathological margin distance for disease recurrence in vulvar cancer.

Methods: One-hundred consecutive patients with primary squamous-cell vulvar cancer treated at our institution were prospectively analyzed. All patients received surgery via triple incision resulting in complete tumour resection. Median follow-up was 30.5 months. Minimal margin distances were pathologically determined in all dimensions.

Results: Median age of the patients was 62 years; 44.9% had FIGO stage I, 19.4% stage II, 26.6% stage III and 9.1% stage IV disease. The median minimal resection margin was 5mm (range 0.5-24mm). Sixteen patients (16.3%) developed disease recurrence (75% at the vulva). The margin distance had no significant impact on disease-free survival when analysed as a continuous variable (p=0.910). Cases were then divided into 3 subgroups of ≤3mm (40.8%), >3-< 8mm (31.6%) and ≥8mm (27.6%) resection margin. Neither univariate nor multivariate analysis revealed a difference in disease-free survival between these subgroups. These results were also consistent when only vulvar recurrences were analysed. There was no significant difference between any of the subgroups regarding tumour stages and adjuvant radiotherapy of the vulva.

Conclusion: Tumor-free resection margins are essential for loco-regional control in vulvar cancer. However, in this large single-center analysis of homogenously treated patients we could not demonstrate any prognostic impact of the margin distance.
PRIMARY YOLK SAC TUMOR OF THE VULVA: CASE REPORT AND REVIEW OF THE LITERATURE

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Background: Primary yolk sac tumor (YST) of the vulva is an extremely rare but highly malignant germ cell tumor. Eleven cases of such cases have been reported in the English literature. Here we presented the twelfth such case.

Case: A 64-year-old woman presented with a 1.5×1×1cm right labial mass. Initial excisional biopsy diagnosis was a malignant tumor but without further specification. Modified radical vulvectomy was then performed and the diagnosis of YST of the vulva was made. She was treated with combined chemotherapy (BVP regimen, bleomycin, etoposide, cisplatin). The serum α-fetoprotein (AFP) was not elevated at the time of initial diagnosis. The patient has been free of disease 5 months after the surgery.
VULVAR AND VAGINAL CANCER IN THE “DR. SALVATORVUIA” CLINICAL OBSTETRICS AND
GYNECOLOGY HOSPITAL ARAD DURING THE 2000-2009 PERIOD

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This paper intends to present the frequency of vulvar cancer in our hospital during the 2000-2009 interval, the data being collected from the Histopathology Exams (HPE) registers. During the 2000-2009 period, 83,006 patients were admitted in our hospital and 16,063 HPE were performed (19,35% of all patients). Vulvar cancer was discovered in 31 cases, representing 3,13% of all genital cancers, and vaginal cancer in eight cases, representing 0,64% of all genital cancers (1246 cases).

The fragments sent to the histopathology departments were obtained by biopsies in 25 cases (64,10%) and from surgical specimens in 14 cases (35,90%).

Most cases (38 or 97,44%) were represented by carcinomas, while one patient had a carcinoma combined with sarcoma (2,56%).

The mean age of the group was 65,97±9,77 years; the mean ages for vulvar and vaginal cancer were 65,90±9,65 and 66,25±10,90 years, respectively.

Vulvar and vaginal cancer, although less frequent, is diagnosed late in many cases, thus making treatment less effective.
A CASE OF MICROINVASIVE PAGET’S DISEASE OF THE VULVA: TREATMENT OF POSITIVE RESECTION MARGIN WITH TOPICAL 5-FU CREAM APPLICATION

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Extramammary Paget’s disease of the vulva is a rare lesion that accounts for 1-2% of vulvar neoplasms. Paget’s disease often has a microscopic extension beyond the gross lesion and shows a multifocal distribution. Positive resection margin is common. We applied 5-FU cream on the lesion who had a positive resection margin. There was no residual lesion on multiple punch biopsies after 5-FU cream treatment three months later. And there has been no evidence of disease recurrence in the 12-month follow-up period. We experienced a case of effective treatment with 5-FU cream in microinvasive Paget’s disease of the vulva with positive resection margin. We present it with a brief review of literatures.
PROXIMAL TYPE EPITHELIOID SARCOMA OF THE VULVA - CASE REPORT AND REVIEW OF THE LITERATURE

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Background: Epithelioid sarcoma of vulva is an extremely rare and aggressive tumor. In most patients it is asymptomatic, and the lesions are usually mistaken for benign processes, leading to diagnosis at later stages.

Case report: We report a case of a 38 year old women diagnosed as having a proximal-type epithelioid sarcoma (PES) of the vulva. Wide local excision of the lesion at the right labium majus was performed. There was no evidence of local or distant metastasis at the time of diagnosis. Following adjuvant chemoradiotherapy, the patient developed bilateral inguinal lymph node metastasis 3 months after surgery and lung metastasis 6 months after surgery. 10 months after diagnosis patient died as a result of disseminated disease.

Conclusion: Up to now only 21 cases of primary epithelioid sarcoma of the vulva have been reported in the English literature. Epithelioid sarcoma is best treated by early diagnosis and initial eradication. The role of adjuvant treatment remains to be determined.

Keywords: Proximal-type, epithelioid sarcoma; vulva; chemotherapy
PLASTIC SURGERY IN THE THERAPY OF THE VULVAR DEFECT AFTER ONCOGYNECOLOGICAL TREATMENT

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Case report: A 49 year-old woman with vulvar cancer. She underwent radical vulvectomy with bilateral inguinalfemoral lymphadenectomy in February 2008. Spinocelullar cancer of the labium major with lymphonodus metastasis was histopathologically verified - pT1b pN1(1/26) pM0. She received adjuvant radiotherapy (55 Gy). The patient had post-radiotherapy vulvar defect with necrosis. At first we performed necrectomy of vulvar defect and plastic surgery with two transposition local skin flaps in January 2009. The flaps completely necrotized under tension. The second plastic surgery was provided by using myocutaneous flap of gracilis muscle at the end of January 2009. The vitality of the muscle was preserved, but cutaneus area got unvital because of insufficient blood supply. The third plastic surgery was provided with antero-lateral thigh flap in February 2009. We used microsurgery technique. The free flap of the descending branch of the lateral circumflex femoral artery was fixed on the vascular branch of gracilis muscle. The flap was successfully fixed. Today the patient is in good condition, without any problems. Restaging negative.
LIPOMATOUS VARIANT OF ANGIOMYOFIBROBLASTOMA ON THE VULVA

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Angiomyofibroblastoma (AMFB) is a rare, benign tumor of the vulva and shows a distinctive, well-circumscribed myofibroblastic feature. The tumor was firstly reported by Fletcher et al. in 1992. The lesion is mainly composed of conspicuous blood vessels and stromal cells. Interestingly, intralesional adipose tissue in AMFB was reported in only six cases (i.e. lipomatous variant). Most of cases are usually premenopausal and present with a slowly growing mass without pain.

A 46-year-old woman presented with a swelling of the left labium major. The lesion was thought to be a Batholin’s gland cyst or a lipoma preoperatively and a local excision was performed. The tumor was well demarcated and rubbery. On microscopic examination, the alternating hypercellular and edematous hypocellular component with abundant vessels was noted. A large amount of adipose tissue was scattered in the lesion. Stromal cells were positive for vimentin, estrogen receptor, and progesterone receptor and negative for desmin antibody immunostaining. The local excision was enough for complete treatment. No recurrence was noted for 7 months after surgery.
QUALITY OF LIFE AT THE PATIENTS TREATED FOR MALIGNANT DISEASE OF VULVA AND UTERUS

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Background: Aim of the study was to establish is there any statistical significance of the correlation between emotional condition coefficient (ECC) as the component of the quality of life (QOL) at the patients with malignant disease of vulva and uterus before and after the surgical treatment.

Methods: In our prospective study (375 patients) the measurement of emotional condition has been taken by EORTC QLQ-C30 questionnaire before and three and six months after the surgical treatment.

Results: Patients treated for malignant disease of uterus: before the surgical treatment ECC was 72.4, SD=18.6, after the surgical treatment ECC was 86.09, SD=12.81, three and six months after the surgical treatment the ECC was 77.2, SD=20.9 and 65.57, SD=21.26 at the patients who did not have radiation treatment. ECC was 75.42, SD=10.09 six months after the surgical treatment at the patients who were radiation treated. Patients treated for malignant disease of vulva: before the surgical treatment ECC was 64.8, after the surgical treatment the ECC was 73.5, three and six months after the surgical treatment the ECC was 67.3 and 65.8. Obtained results have shown that analyzing the $X^2$ test, correlation among ECC of the patients who were cured for malignant illness of uterus and vulva is not statistically significant.

Conclusion: The aim of each modern society is to reach the maximum of QOL at the patients treated for malignant illness. We can attain it, by prevention, adequate surgical and other methods of treatment.
**SENTINEL LYMPH NODE DETECTION IN VULVAR CANCER - OUR EXPERIENCE**

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Vulvar cancer represents approximately 4% of all gynaecological malignancies. The mean age of patients with vulvar cancer is 70 years. Lymph node metastases are the most important prognostic factor. The morbidity associated with radical vulvectomy is serious.

**Background and aims:** The purpose of our study is to evaluate the feasibility and accuracy of the sentinel lymph node (SLN) procedure in vulvar cancer.

**Methods:** From January 2002 to May 2010 at our Dpt. of Gynaecological Oncology the SLN identification has been used in 32 patients with vulvar cancer. In the day of surgery 99mTc-labelled nanocolloid was administered intradermally at four locations around the tumor. Lymphoscintigraphy was performed in all patients within 60 minutes. After induction of anesthesia the blue dye was injected around tumor. SLN was located by use of gamma-detecting probe intraoperatively. The SLNs were submitted for histological examination by hematoxylin-eosin and cytokeratin immunohistochemistry.

**Results:** SLNs were identified in 100% cases. Four sentinel nodes were involved including isolated tumor cells in one SLN. In one patient with negative sentinel lymph node one non-sentinel node was involved. Clinically the lymph node involvement was detected preoperatively by ultrasound in this case. The sensitivity of the method was 80%.

**Conclusions:** Sentinel lymph node detection in vulvar cancer appears to be a promising method with potential for decreasing unnecessary surgery radicality and for staging clarification. Our results correlate with data from large trials and suggest the sentinel lymph node biopsy is feasible in patients with early stage vulvar cancer.
AN AUDIT OF THE SURGICAL TREATMENT MODALITIES AND OUTCOME IN 17 CASES OF EXTRAMAMMARY PAGET’S DISEASE OF THE VULVA

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Extramammary Paget’s Disease (EMPD) of the vulva represents 1-5% of all vulval malignancies and surgery remains the mainstay of treatment.

Our aim is to compare the likelihood of local recurrence in cases treated by local and more extensive surgical procedures, the significance of margin status and the value of preoperative mapping biopsies.

From 1st January 1988 to 31st December 2008, 19 cases of surgically treated EMPD of the vulva were identified and the medical records were reviewed. The treatment modalities, the margin status and recurrence rate were recorded and analysed. Two cases with insufficient data were excluded.

Nine patients underwent local excision alone (2 had preoperative mapping biopsies). Eight patients had wide local excision and a plastic reconstruction procedure (7 had preoperative mapping biopsies).

We found that the patients treated with wide local excision and reconstruction procedures (with preoperative mapping biopsies) for intraepithelial EMPD of the vulva had lowest recurrence rate (37.5%) whilst local excision alone is associated with high local recurrence rate (77.8%)

Four patients with clear surgical margin status remained disease-free. Three of the thirteen patients who had positive margin involvement achieved complete disease clearance despite margin involvement. The ten remaining patients developed local recurrence.

We proposed that wide local excision with pre-operative mapping biopsies and further reconstruction is an appropriate treatment of non-invasive EMPD of the vulva.

The value of joint Gynaecology-Dermatology clinics is also validated.
HUMAN EPIDIDIMIS PROTEIN 4 (HE4): IT COULD BE USEFUL IN VULVAR CANCER?

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Aim: The human epididymis protein 4 (HE4) is frequently over-expressed in ovarian and endometrial cancer, whereas its expression in other gynecological malignancies, including vulvar cancer, has not been previously investigated. The aim of this preliminary study was to assess the concentration of both HE4 and CA125 in patients affected by vulvar cancer.

Methods: The study population included 15 patients with vulvar cancer (median age: 72.0 ys, min-max: 50.0-82.0 ys) and 15 postmenopausal healthy subjects (median age: 68.0 ys, min-max: 60.0-91.0; p=0.72). In all patients, serum samples were collected on the day before scheduled surgery. Serum levels of CA125 were determined using a chemiluminescent enzyme immunoassay on the Liaison (DiaSorin, Saluggia, Italy). Serum levels of HE4 were determined using ELISA kit developed by Fujirebio Diagnostic, Inc. (Malven, PA, USA). Tumor marker levels between groups were compared using the Mann-Whitney test.

Results: The median HE4, but not CA125 serum levels were significantly higher among vulvar cancer patients as compared with healthy subjects (median value 76.8 vs. 40.3 pmol/L, p=0.004).

The Receiver Operating Characteristics (ROC) curve analysis on healthy controls and patients with vulvar cancers revealed that HE4 had a significantly higher Area Under the Curve (AUC) when compared with CA125 (0.81 versus 0.66). The sensitivity and the specificity of HE4 using a cut-off level of 49 pmol/L were 80% and 73%, respectively (AUC=0.81, p=0.004).

Conclusions: HE4 seems a promising vulvar cancer marker, and its measurement could improve the diagnostic approach to patients affected by this tumor.
LOWER LIMB LYMPHEDEMA IMPACTS QUALITY OF LIFE IN WOMEN WITH VULVAR CANCER SUBMITTED TO SURGICAL TREATMENT

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Objective: To investigate the occurrence and impact of lower limb lymphedema (LLL) on quality of life in patients with vulvar cancer submitted to surgical treatment.

Methods: Twenty-eight vulvar cancer patients submitted to vulvectomy and inguino-femoral lymphadenectomy and 28 healthy age-matched women (control group) were prospectively evaluated. The LLL occurrence and severity were determined by Miller Clinical Evaluation. Quality of life was assessed by the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30). The differences between groups and correlations were assessed by Chi-square, Student’s t and Spearman tests.

Results: The occurrence and severity of LLL were higher in women with vulvar cancer compared to the control group (p< 0.05 and p=0.003, respectively). There was no association between stage, adjuvant treatment, laterality and complications with the lymphedema severity. Patients with advanced age and higher body mass index were associated to more severe LLL (p=0.04). The physical, cognitive, emotional, social, fatigue, pain, sleep, and financial issue domains of quality of life were associated with the LLL severity (p< 0.05).

Conclusion: Patients submitted to vulvectomy and inguino-femoral lymphadenectomy for vulvar cancer present higher risk of developing LLL, which negatively impacts the quality of life.

Keywords: Vulvar cancer; Lymphadenectomy; Vulvectomy; Lymphedema; Quality of life
REPERCUSSIONS FROM VULVECTOMY AND INGUINAL LYMPHADENECTOMY ON URINARY FUNCTION AND QUALITY OF LIFE IN WOMEN WITH VULVA CANCER

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Objective: To investigate the occurrence of sexual and urinary dysfunction in women with cancer of the vulva before vulvectomy and lymphadenectomy.

Methods: Observational, prospective, transverse study of 28 women undergoing surgical treatment for cancer of the vulva and 28 healthy women (control group), matched for age. Their urinary function and sexual performance were assessed using the International Consultation on Incontinence Questionnaire - Short Form (SF-ICIQ) and Female Sexual Function Index (FSFI) questionnaire. The following statistical tests were used: chi-squared, Student’s ‘t’, and Mann Whitney-U tests. Differences or correlations with p< 0.05 were considered significant.

Results: Correlation was seen between sexual quality of life and age (p=0.01) and stable partnership (p=0.02). The following variables did not influence urinary function: BMI, menopause, and cancer of the vulva. There was correlation between age and urinary function (p=0.01) and deliveries (p=0.01).

Conclusion: Women undergoing surgical treatment for cancer of the vulva have no worsening in quality of sexual life or urinary function.

Keywords: Cancer of the vulva, lymph node, vulvectomy, urinary function, sexual function
COLLOID CARCINOMA OF THE VULVA

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Introduction: Vulvar cancer accounts for approximately 3-5% of gynecological malignancies.

About 90% of vulvar cancers are squamous carcinomas, with the other 10% being tumours ranging from melanomas to adenocarcinomas, sarcomas and undifferentiated carcinomas. There is continuous debate whether lichen sclerosus is a premalignant condition. It is estimated that 3-5% of vulvar cancers develop from lichen sclerosus. Colloid carcinomas of the vulva are very rare tumours, and are postulated to arise from breast-like tissue of the ano-genital region.

Clinical case: Mrs UM is a 64-year-old patient referred to our unit with vulvar cancer. She presented to a district hospital with a year’s history of vulva pruritis, and progressive swelling over six months. On clinical examination, she had a 10 x 8 cm smooth left labial mass with a central area of necrosis. The patient also had bilateral hypo-pigmentation of the perineal skin, suggestive of lichen sclerosus. A biopsy showed an invasive colloid carcinoma of the vulva. A radical vulvectomy and bilateral inguinal node dissection was done.

Histology: The final histology report confirmed an invasive colloid adenocarcinoma with metastatic tumour in 2 out of 13 inguinal nodes. Immunocytochemical stains for oestrogen receptor (ER) showed strong nuclear positivity, but negative for progesterone receptor.

Conclusion: The patient was treated as for squamous cell carcinoma. The strong ER positivity may point towards a possible role for hormone treatment in this patient.
SQUAMOUS CELL CARCINOMA OF THE VULVA IN A MOTHER AND DAUGHTER: A CASE REPORT INDICATING POSSIBLY NON-CLASSICAL TUMORIGENIC PATHWAYS

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Squamous cell carcinoma (SCC) of the vulva is believed to occur through two different pathways: tumors occurring in younger women usually have warty or basaloid morphology, are related to high-risk HPV infection and usual VIN (u-VIN) and are immunohistochemically p16-positive and p53-negative; tumors occurring in older women usually are well differentiated keratinizing tumors, not related to HPV infection that can be associated with lichen sclerosus (LS), differentiated VIN (d-VIN), squamous cell hyperplasia and p53 mutations and are immunohistochemically p16-negative and p53-positive. Here, we report a rare case of a mother and daughter with SCC of the vulva. Mother: 84-year-old female with a history of LS, presented with a 7-cm vulvar tumor in the left labium majus, clinical staging II (T2 N0 Mx). Daughter: 54-year-old female with a history of u-VIN, and a tumor with the same size and location of her mother’s, but clinical staging III (T2 N1 Mx). The patients underwent modified radical vulvectomy. The daughter surgery was followed by adjuvant concomitant radiotherapy and platin-based chemotherapy and the mother had no further treatment. The tumor of the mother was a well differentiated keratinizing SCC with focal cells resembling koilocytic atypia, associated with LS with focal atypia and differentiated VIN (d-VIN), immunopositive for p53 but also focally weakly positive for p16. The tumor of the daughter was a poorly differentiated SCC with acantholytic foci creating pseudoangiosarcomatous areas, negative for p16 and focally immunopositive for p53. These morphological and immunohistochemical findings may indicate different and non-classical tumorigenic pathways for these tumors.
SKINNING VULVECTOMY FOR TREATMENT OF VIN II-III

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Background: Vulvar intraepithelial neoplasia (VIN) is the precursor lesion of vulvar carcinoma. There are different kinds of treatment modalities available used in VIN such as wide local excision, skinning vulvectomy, and laser ablation.

Objective: To analyse the results of fifteen patients with VIN usual type which were treated with skinning vulvectomy.

Material & methods: This study includes all women with histologically diagnosed VIN between 2007 and 2009. Diagnosis was made according to the histologic criteria of the International Society for the Study of Vulvo-vaginal Disease (ISSVD).

Results: The mean age at diagnosis was 51.5 years. The most common presenting symptom was found as non-spesific vulvar lesion(%53). One of their cervico-vaginal smears were reported to be as LGSIL and the other two were reported to be as HGSIL.

Three patients' with vulvar lesion had biopsy results as VIN III before the operation but their postoperative pathology specimen evaluations revealed no histologic abnormality(%20). Two patients with VIN III had the pathology result as carcinoma in situ. Seven patients beginning pathology report were VIN III and final pathology report were the same. One patient with VIN II had the result as VIN III on the final pathology. Specimens revealed multifocality on three patient. Four patients with VIN III had positive surgical margins after the operation and two of these were came with recurrent disease.

Conclusion: Skinning vulvectomy is a valid treatment option for high grade VINs.
TRANSURETHRAL BLADDER PROLAPSE, A RARE CONDITION: CHALLENGES IN DIAGNOSIS AND MANAGEMENT

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Complete bladder prolapse is rare condition and only reported in women. Our case involved a 73 year old patient who was presented with abdominal mass, procidentia and a mass over urethral orifice. Patient was diagnosed with large ovarian cyst, bilateral hydronephrosis and complete transurethral bladder prolapse. She was managed with ultrasound drainage of ovarian cyst, bilateral nephrostomies, followed by reduction of bladder prolapse, bladder neck closure, insertion of suprapubic catheter and colpocleisis.

Due to rarity of the cases, there is no recommended standard treatment. The exact mechanism of bladder eversion is unclear. Several explanations have been described through the case reports. Widening of urogenital hiatus in uterovaginal prolapse can result in pulling of bladder base subsequently opening the proximal urethra and allowing the bladder to evert. Post menopausal women are more susceptible.

Acute or chronic damage to urethra, secondary to indwelling catheter or chronic infection has been observed in some of the cases. Denervation of the external sphincter of urethra may also explain the occurrence of bladder prolapse in patient following hemipelvectomy. Prolonged, severely elevated intra-abdominal pressure is the most likely explanation for cases reported following labour.

External transurethral reduction is sometimes successful. Aim of management is to reduction and prevention of further bladder prolapse, maintenance of continence as well correction of any concurrent uterovaginal prolapse. Half of the reported cases had hydronephrosis. Assessment of upper urinary tract is therefore an essential part of management.
LOTUS PETAL FLAP REPAIR FOR PERINEAL RECONSTRUCTION AFTER RADICAL VULVECTOMY FOR VULVAL CANCER

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We present a series of 16 cases of vulval cancer which were operated by radical vulvectomy and bilateral inguinal lymphadenectomy using a Lotus petal flap repair approach.

The complete surgical procedure including the Lotus flap repair was performed by same gynaecological oncology surgeon. All the cases were operated in Calderdale Royal Hospital in UK. Majority of the cases were followed for more than 5 years and the rest are under follow up. The data was statistically analysed. The rate of complications and hospital stay of lotus petal flap repair was compared with the other techniques from the published literature.

**Results:** The Inguinal and groin wound dehiscence 12.5\% and 6\% respectively. The wound infection was seen in 12.5\% cases. Lymphedema was seen in 62.5\% cases and the rate of local recurrence in 25\% .

The duration of hospital stay was less than 2 weeks in 68\% of cases. The groin drain was removed after a minimum of 10 days and in cases of complications left longer.

**Conclusions:** The study clearly shows that the use of Lotus petal flap repair approach for perineal reconstruction significantly reduces local complication rates and the length of hospital stay when compared with other surgical approaches.
PROLIFERATING TRICHILEMMAL TUMOURS AND EPIDERMOID CARCINOMA OF THE VULVA

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The proferating trichilemmal tumour (PTT) is a common benign cutaneous tumour in women with a preferential distribution in the head and trunk. The location of this tumour in the vulva is exceptional.

We present the case of a 78-year-old patient with a PTT of the vulva, and four years later developed an epidermoid carcinoma in the same location. The initial lesion consisted of a cutaneous structure with a multi-cystic formation without any connection of the epidermis.

Four years later atypical squamous cells from a malignant tumoral proliferation were observed in a vulvar core biopsy, which showed changes of a koilocytic type in some areas. A tumour measuring 4.7 cm and a thickness of 0.7 cm was observed in the vullectomy specimen, which microscopically corresponded to an infiltrating epidermoid carcinoma. The neoplastic epidermoid cells, but not the PTT cells of the initial lesion, were positive for the HPV 18 using PCR technique.

The location of the PTT in the vulva is an extremely uncommon finding and we only know of three previous cases, which are reported in elderly women. The microscopic study provides arguments in favour of a possible histogenesis of the tumour related with the isthmic portion of the external radicular sheath of the hair.

The possible viral relationship of these lesions, with HPV is a controversial subject. We detect, the presence of HPV genome in cells of the epidermoid carcinoma which developed later in the vulva, but we could not identify viral signs in the PTT.
MICROINVASIVE CARCINOMA OF THE VAGINA

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Microinvasive carcinoma (MC) of the vagina is an ill-defined, rare, diagnostically-difficult and therapeutically-challenging disease. Vaginal MC is arbitrarily defined as a primary vaginal carcinoma where the depth of stromal invasion is < 3mm.

A series of 19 patients managed over a 32-year period will be presented. Histotypes included SCC (18) and adenocarcinoma (1). Fourteen patients had undergone a prior hysterectomy. Past history included cervical SCC (8), CIN3 (5), ACIS (1). Six patients had VAIN3 treated prior to the diagnosis of MC and were treatment/surveillance failures.

The vaginal MC involved the upper vagina/vault (13), lower 1/3 (3) and was diffuse (3). One patient presenting with bilateral inguinal lymphadenopathy was found to have a 1.6mm invasive MC located in the lower 1/3 of the posterior vaginal wall.

In each case initial treatment was by excision. Surgical margins were positive in 14 patients, 8 of whom were managed by repeat surgery and 6 by postoperative RT. Despite the use of RT two patients had progressive disease which required exenterative surgery. The MC involved the upper vagina (1 patient) and the lower 1/3 (1). The latter patient with died of a CVA postoperatively and was the only death in the series.

Follow-up is from 1-32 years and there have been no other tumour recurrences or deaths.

The presentation will address the problem of the definition of vaginal MC and some of the management difficulties especially when the cancer is diffuse and/or involves the lower 1/3 of the vagina.
THE EFFICACY OF 4 WEEK NEOADJUVANT PHENOXODIOL MONOTHERAPY IN PRIMARY OR RECURRENT SQUAMOUS CELL CARCINOMA OF THE CERVIX AND VULVA

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Objective: To assess the efficacy of phenoxodiol when administered as monotherapy in patients with primary or recurrent squamous cell or adenocarcinoma of the cervix, or squamous cell carcinoma of the vulva.

Methods: Phenoxodiol was administered orally, three times daily, for 4 weeks, prior to initiation of conventional treatment, in three different dosages: 50 mg, 200 mg, and 400 mg. The tumors were measured by MRI at initiation and completion of phenoxodiol treatment.

Results: The 50 mg group consisted of 6 patients: 3 with vulvar cancer (2 recurrent, 1 primary) and 3 with cervical cancer. Within 4 weeks, all vulvar cancers regressed (-3% to -60%). Two cervical cancer patients had stable disease and 1 progressed.

The 200 mg group incorporated 2 patients with vulvar cancer and 7 patients with cervical cancer. One recurrent stage III vulvar tumor regressed (-34%). One recurrent stage IV vulvar cancer progressed. Only 1/7 patients with cervical cancer the tumor showed a 35% reduction in tumor size after 4 weeks and had stable disease after 9 months of phenoxodiol monotherapy.

In the 400 mg group, 2 patients with primary vulvar carcinoma progressed during treatment. One/7 cervical cancer patients had complete resolution of a 2.3 cm tumor with no residual carcinoma in the surgical specimen; 1 had stable disease and 5 had tumor progression.

Conclusions: Phenoxodiol was well tolerated and surgery or chemoradiation were not delayed after its administration. In spite of the short treatment, patients with vulvar carcinoma seem to benefit from neoadjuvant therapy with oral phenoxodiol.
PREDICTING GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN): IS URINE HCG (UHCG) THE ANSWER?

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\textbf{Background:} Previous studies on significance of hCG to predict GTN have been too small for robust conclusions to be reached. We conducted the first and largest study to date using the database at Sheffield trophoblastic disease centre to analyse the significance of UhCG in predicting GTN.

\textbf{Methods:} Details of 5648 patients were available. Information regarding age, dates of diagnosis and registration, UhCG levels, antecedent pregnancy and chemotherapy were prospectively collected and used for analyses. Patients were stratified into different groups according to UhCG level; < 50IU/L, 50-99IU/L, 100-249IU/L, 250-499IU/L and ≥500IU/L. Multivariate analyses were used to identify the prognostic indicators of GTN.

\textbf{Results:} UhCG and antecedent pregnancy were the most powerful indicators for developing GTN (P < 0.01). None of the patients with partial mole and UhCG < 50IU/L (Normal level = 40IU/L) developed GTN. The risk of GTN was >35% in all patients with UhCG ≥500IU/L. GTN developed in 70% of patients with complete mole and UhCG ≥10000IU/L. Reduced time interval between diagnosis and registration increased risk of receiving chemotherapy in patients with UhCG < 500IU/L (P=0.015), however this impact wasn’t observed in patients whose UhCG was ≥ 500IU/L (P= 0.56).

\textbf{Conclusions:} UhCG is sensitive test for GTN. UhCG level is a powerful prognostic indicator for the GTN. Patients with partial mole could be safely discharged from the surveillance programme once their hCG have normalised. Patients with complete mole and UhCG≥ 10000IU/L may benefit from empiric chemotherapy.
OVARIAN CANCER IN HEREDITARY NONPOLYPOSIS COLORECTAL CANCER; CLINICAL CHARACTERISTICS, MORPHOLOGY AND MISMATCH-REPAIR MUTATIONS

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Ovarian cancer represents the third most common cancer type in females with hereditary nonpolyposis colorectal cancer. We characterized ovarian cancer in the Swedish and Danish HNPCC cohorts with respect to morphology, mismatch repair (MMR) protein expression, and contribution from the different MMR genes. In total, 65 epithelial ovarian cancers were identified in 65 mutation carriers. These tumors developed at mean 48 (range 32-75) years of age. Endometrioid and clear cell tumors were overrepresented and constituted 35% and 25%, respectively, whereas serous tumors represented 29% and mucinous 10% mucinous. The MMR gene mutations affected MSH2 in 53%, MSH6 in 30% and MLH1 in 17%. Our pooled analysis of HNPCC-associated ovarian cancer thus confirms differences between hereditary ovarian cancer caused by HNPCC and BRCA mutations with a lower age at onset and predominance of endometrioid-clear cell tumors in the former groups.
TOPOTECAN/CARBOPlatin VS. PACLITAXEL/CARBOPlatin OR GEMCITABIN/CARBOPlatin OR CARBOPlatin/PEGylATED DOXORUBICIN: A PLANNED 200 PTS INTERIM SAFETY ANALYSIS OF THE HECTOR-STUDY (NOGGO/AGO-OVAR/GEICO/AGO-AUSTRIA)


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Background: We present the preliminary safety results from the phase III study of topotecan/carboplatin (TC) vs standard therapy with paclitaxel/carboplatin (PC) or gemcitabine/carboplatin (GC) or carboplatin/pegylated doxorubicin (PLDC). While the primary endpoint of the study is PFS, the specific toxicity observed from these regimens is critically relevant. Therefore this planned safety analysis of the experimental arm (TC) and the standard therapy (control arm = CA) was conducted.

Methods: From 02/07 to 12/09, 590 pts were screened and 550 pts were randomized to either T (0.75mg/m²/d1-3/q21d) + C (AUC 5/d1/q21d) or to PC or GC or PLDC based on patient preference.

Results: The data from the first 200 pts were analyzed. Median number of cycles was 6 in the two arms. Most patients preferred the standard therapy with GC (78%) due low alopecia rate since the PLDC arm was opened after the publication of CALYPSO data. Haematological toxicity contributed to 41% of cycle delays in the CA and 36% in the TC arm. Neutropenia & infection rates were similar in both arms. G-CSF was administered more frequently to pts in CA arm (26%) than in TC arm (21%). Grade (G) > 2 non-haematological toxicity was not more frequent in the C-P arm. There were more severe adverse events (SAE) in the CA (66 %) than in the TC arm (55%).

Conclusions: This planned interim safety analysis on the first 200 patients confirmed the safety of the experimental arm and allowed to continue the study enrolment. Study recruitment was completed in 12/2009.
HE-4 A NOVEL TUMOR MARKER FOR OVARIAN CANCER: COMPARISON WITH CA 125 IN PATIENTS WITH GYNECOLOGICAL DISEASES

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We studied the specificity and sensitivity of HE-4 a novel tumor marker for ovarian cancer and CA 125 in 111 healthy subjects, 299 patients with benign gynecological diseases (65 endometriosis, 56 myomas, 81 cysts and 97 patients with abdominal masses), and 197 patients with gynecological cancer (121 ovarian, 27 squamous cervical cancer and 49 with endometrial Adenocarcinomas). Abnormal serum tumor marker levels were found in:

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<th>HE-4 (&gt; 150 pg/ml)</th>
<th>CA 125 (35 U/ml)</th>
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<tr>
<td>Benign Ovarian Cancer</td>
<td>1.3%</td>
<td>32.4%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>74%</td>
<td>84%</td>
</tr>
<tr>
<td>Squamous cancer</td>
<td>30%</td>
<td>31.8%</td>
</tr>
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<td>Squamous cancer</td>
<td>0%</td>
<td>17.6%</td>
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ROC curve showed a higher area under the curve for HE-4 (0.939) than for CA 125 (0.849). Both tumor markers were related to tumor stage and histological type, with significantly higher concentrations in serous malignancies (p< 0.001). It is interesting to indicate that HE-4 showed a higher sensitivity in early stages (I-II) and CA 125 in advanced stages (III-IV). One or another tumor marker was abnormal in 93.6% of patients with ovarian cancer. The inclusion of ROMA algorithm to suggest malignancy, increase the specificity obtained with CA 125 and the sensitivity of HE-4. In summary HE-4 is an useful tumor marker for ovarian cancer, with highest sensitivity and efficiency than CA 125. The combined use of both tumor markers increase the sensitivity obtained individually, with abnormal levels in 93.6% of patients with ovarian cancer (80% in stage I-II).
FERTILITY-SPARING SURGERY IN YOUNG WOMEN WITH BILATERAL GERM CELL TUMOR

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Introduction: Malignant germ cell tumors are frequently diagnosed in young, premenopausal women, and therefore preservation of the ovarian function and fertility is an important issue. In this study we analyzed the effect of fertility sparing surgery (FSS) on the oncological outcome and fertility of women with bilateral ovarian involvement, which is a relatively uncommon condition.

Material and methods: Between 1982 and 2009, 320 women with germ cell ovarian tumors were referred to San Gerardo Hospital. Twentyfour (7%) had bilateral involvement: 16 dysgerminoma, 4 immature teratoma, 2 mixed-germ cell, 2 endodermal sinus tumour. Six cases had a microscopic involvement of one ovary. Median age was 22 years (range 9-69).

Eleven women underwent radical surgery, while 13 were treated with FSS.

Two patient treated with FSS was premenarchal and nine of them received postoperative chemotherapy.

Results: With a median follow-up of 17.8 years all 13 women treated conservatively and 9/11 treated radically are alive without disease.

Among patients treated with FSS, two underwent resection of the preserved ovary at the second look surgery: one was a premenarchal woman who had primary amenorrhea and required hormonal replacement therapy and the second was performed for a suspected, unconfirmed recurrence.

The remaining 11 patients conservatively treated maintained their menses (8 after chemotherapy) and 4 of them gave birth to 6 healthy babies.

Conclusion: Treatment with fertility-sparing surgery is safe in treating women with ovarian germ cell tumor with bilateral involvement of and should be offered to patients who wish to preserve their childbearing potential.
PATIENTS’ PREFERENCES FOR INTRAPERITONEAL CHEMOTHERAPY FOR ADVANCED OVARIAN AND RELATED CANCERS: WHAT MAKES IT WORTHWHILE?

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Background: Intraperitoneal (IP) chemotherapy for advanced ovarian cancer improves overall survival, but is toxic and inconvenient. We sought patients’ judgements about the survival benefits needed to make IP chemotherapy worthwhile.

Methods: Patients with optimally debulked stage III ovarian cancer participating in a single-arm, phase II trial of IP cisplatin and paclitaxel completed validated questionnaires before chemotherapy. Preferences were elicited for baseline survival times of 5 years and 3 years, and baseline survival rates of 50% at 5 years and at 3 years. Aspects of health-related quality of life (HRQOL) were assessed by the Patient DATA Form (0 'no trouble at all' to 10 'worst I could imagine').

Results: Preferences questionnaires were completed by 20 women: median (range) age 53 years (24-75), ECOG performance status of 0 (0-1). 50% of patients judged an extra 6 months beyond 3 years and 5 years, and 5% beyond survival rate of 50% at 3 years and 5 years, sufficient to make IP chemotherapy worthwhile. The benefits judged sufficient ranged from an extra: 1 day to 15 years, and from 0.1% to 50%. The most troublesome aspects of HRQOL at baseline (mean) were: thought of actually having treatment (3.6), anxiety (3.1), lack of energy (2.9), pain (2.9), and fatigue (2.7), but these were not correlated with preferences. Age was correlated with preferences (rho 0.455, p=0.044).

Conclusions: The survival benefits judged sufficient to make IP chemotherapy worthwhile were moderate and varied widely. Individual patients’ preferences for IP chemotherapy should be incorporated into clinical decision-making.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

PHASE II STUDY OF PELVIC INTENSITY MODULATED RADIOTHERAPY +/- CHEMOTHERAPY FOR POST-OPERATIVE PATIENTS WITH ENDOMETRIAL OR CERVICAL CARCINOMA (RTOG 0418)

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Purpose/objectives: The primary endpoint of RTOG 0418 was to determine the transportability of pelvic IMRT to a multi institutional setting for endometrial and cervical carcinoma patients. The secondary endpoint was to test for a reduction in grade 2 or more short-term (within 90 days) bowel injury compared to standard treatments and to evaluate chemotherapy compliance for the cervical cancer patients.

Materials/methods: Pelvic IMRT to a dose of 50.4 Gy in 28 fractions, was delivered to endometrial and cervical cancer patients requiring adjuvant pelvic radiation. Cervical cancer patients also received weekly cisplatin 40 mg/m². Adverse events (AEs) were assessed using the CTCAE v. 3.0.

Results: From March 2006 to October 2008, 106 patients were enrolled (58 endometrial and 48 cervical cancer), and 83 were eligible for analysis. There were 0 and 1 cases with deviation unacceptable scores for protocol compliance with the delineation of planning target volume for the vagina and pelvic lymph nodes, respectively. Only 21 patients (25%), developed grade 2 or higher short term bowel AEs. No patients developed grade 4 bowel AEs. In the cohort of cervical cancer patients, bone marrow toxicity was minimal thus allowing for chemotherapy completion as planned in 80% of patients.

Conclusion: This prospective multi institutional study confirms that pelvic IMRT is transportable and associated with a lower risk of bowel toxicity when compared to historical data from standard pelvic radiation. This may translate to an improved quality of life for women who need to receive pelvic radiation.
CERVICAL CANCER IN A TERTIARY HOSPITAL OF BANGLADESH

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Cervical cancer is the most common female cancer in Bangladesh and an important cause of early loss of life. The aim of the study was to observe the pattern of clinical stage and management for cervical cancer at one of the gynae-oncology units of Bangabandhu Sheikh Mujib Medical University (BSMMU). During the period of April 2007 to March 2010, a total of 296 women were admitted with cervical cancer in Gynae Oncology of BSMMU. Among them, data were collected from 146 (49.32%) women. The mean age at presentation was 43.3 years (SD±9.2) with a range of 22 to 75 years. Sixty one (41.8%) and 54 (37.0%) of the women of cervical cancer were in the age group of 31-40 and 41-50 years respectively. Seventeen (11.6%) women presented with stage I, 40 (27.4%) with stage IIa, 68 (46.6%) with stage IIb, 19 (13.0%) with stage III and 2 (1.4%) presented with stage IV disease. About eight percent (8.2%) women were managed by Wertheim’s hysterectomy only, 21.9% had Wertheim’s hysterectomy and Radiotherapy, 5.5% had Wertheim’s hysterectomy and chemo-radiation. Moreover, 6.8% women received chemo-radiation and 57.5% women were referred for radiotherapy. Majority of the women had invasive squamous cell carcinoma (95.2%). In culmination, 39.0% of the women presented with early stage disease and 35.6% could avail operative treatment. Recently, more women of cervical cancer presented with early stage disease, which may be a reflection of developing Visual Inspection of Cervix with Acetic Acid (VIA) programme in Bangladesh.
THE IMPACT OF INDUCTION CHEMOTHERAPY FOLLOWED BY INTERVAL DEBULKING SURGERY IN ADVANCED OVARIAN CANCER - CHANGING TREND...

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Objective: To determine the role of Induction chemotherapy, to assess chemotherapeutic response, to analyse optimization at Interval debulking surgery, to study survival benefits & quality of life issue

Methods: Between January 1983 & June 2008, 1034 patients with advanced epithelial ovarian cancer were subjected to neoadjuvant chemotherapy (NACT)& 748 (72%) were evaluable to treatment. Patient referred with suboptimal surgery, with poor performance status, gross ascites with pelvo-abdominal mass, medically unfit for primary cytoreductive surgery were subjected to 2-3 cycles Taxol + platinum / Platinum based chemotherapy followed by Interval debulking surgery (IDS) at 2-3 week interval depend on the clinical response.

Results: The age of the patient ranged between 32-85 years (median age 49.8 years) Of the 1034 patients 748 (72%) were evaluable. Overall response was found in 477 patients (63.77%) and 368 (77%) patient underwent IDS. The indication for NACT were massive ascites + fixed pelvo-abdominal mass (77%), fixed pelvic mass (19%) & distant metastases (4%). Diagnosis was established either by histopathological or by cytology. Of the 477 clinical responders 368 underwent IDS, 261 had optimal surgery (70.92%-R0).

Conclusion: This study confirms that those patient received NACT for advanced epithelial ovarian cancer increase the chance of resectability by downstaging the disease with less postoperative morbidity & improved quality of life in selected subgroup of patient in low resource settings.

Key Words: NACT, CT response, Interval Debulking Surgery
THE STUDY OF GESTATIONAL TROPHOBLASTIC DISEASE IN KERMANSHAH, IRAN

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This study was a review of 79 GTD (Gestational Trophoblastic disease) during 8 years in Imam reza and Moatazedi hospital in Kermanshah city. The incidence of GTN (Gestational Trophoblastic Neoplasia) was 0.3%. GTN showed approximately 64.3% following a hydatidiform mole, 28.5% following an term pregnancy and 7.15% developed after an abortion. The diagnosis of gestational trophoblastic neoplasia was made primarily by persistently evaluated serum hCG level. In most cases, there was no tissue to submit for pathological study however 14 cases were shown choriocarcoma and 3 cases had an invasive mole in pathology. 4 cases of choriocarcinoma following by term pregnancy. 36 out of 79 patient of GTD had been relieved although the rest of them were in stages 1, 2, 3 and 4, (34, 2, 4 and 3 respectively). 23 out of 34 patients got the single cheemothrapy and 22 patients got the combination cheemothrapy. 14 patients with GTN had metastasis. The most common sides of metastasis were lung 78.5%, the vagina 28.5% in about 28% brain and 21.4% liver metastasis. 5 in 23 patients who got the single cheemothrapy unlikely persisted in combination cheemothrapy.

Acknowledgement: I respect of Gynecology and Oncology ward in Imam Reza and Moatazedi hospital to help me for data collection.
SALVAGE COMBINATION CHEMOTHERAPY WITH FLOXURIDINE, DACTINOMYCIN, ETOPOSIDE, VINCRIStINE (FAEV) FOR PATIENTS WITH RELAPSED/CHemo-RESISTANT GESTATIONAL TROPHOBLASTIC NEOPLASIA

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Background: Although most patients with gestational trophoblastic neoplasia (GTN) are cured by conventional chemotherapy, some develop drug resistance or relapse. The use of new combination drugs has been studied to treat those with resistant or relapsed disease. We evaluated the results of floxuridine, dactinomycin, etoposide, and vincristine (FAEV) chemotherapy in patients with relapsed/chemo-resistant GTN.

Patients and methods: Clinical data and outcome of the patients with relapsed/chemo-resistant GTN from 1 January 2005 to 30 June 2008 were retrospectively reviewed. Eligible patients had received at least one cycle of FAEV chemotherapy. The primary endpoints were response rate and toxicity of FAEV regimen, the secondary endpoint was assessment of clinical predictors of response.

Results: In total, 91 patients were included. Fifty-five of these patients (60.4%) achieved serologic complete remission (SCR), 29 patients had no response (NR), 7 patients experienced recurrent grade ≥3 or intolerable toxicity. SCR of FAEV chemotherapy was significantly associated with number of previous chemotherapy regimens (≤2) in multivariate analysis (p=0.005). The most serious adverse events were grade 3 neutropenia (26.4%), febrile neutropenia (6.6%), grade 3 thrombocytopenia (3.3%).

Conclusion: FAEV is an effective, well-tolerated regimen for patients with relapsed/chemo-resistant GTN. Further studies of this regimen are warranted.
EARLY PREDICTION OF POSTMOLAR GESTATIONAL TROPHOBLASTIC NEOPLASM BY USING REGRESSION RATE OF HCG FROM WEEKLY MEASUREMENT

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Objective: For early prediction of progression to postmolar GTN (gestational trophoblastic neoplasm) after evacuation of hydatidiform mole through a comparison of hCG (human chorionic gonadotrophin) regression rate

Patients and methods: 127 patients diagnosed H-mole (hydatidiform mole) were analyzed weekly hCG follow-up retrospectively from January 1 of 1996 to June 30 of 2009. hCG regression rate was compared between spontaneous regression group and postmolar GTN group. The sensitivity and specificity for prediction of postmolar GTN were assessed by using receiver operating characteristic curves. Results: Mean regression rate of hCG between two groups were compared and showed significant difference from 2nd weeks. hCG regression rate were 0.50% in spontaneous regression group and 1.43% in postmolar GTN group (P=0.012) at 2nd week. At 2nd week, the prediction of postmolar GTN with hCG regression rate revealed the sensitivity of 70 % and specificity of 63% with cut-off value of 0.389% and AUC of 0.729 (p=0.038). At 3rd and 4th weeks, the sensitivities of prediction for postmolar GTN were 77 and 88% and specificities were 84 and 91 % with cut-off value of 0.178 and 0.119% while AUC displayed 0.872 and 0.946 respectively (p< 0.001 and p< 0.001).

Conclusion: The hCG regression rate after molar evacuation was obtained in uneventful mole patients. The occurrence of postmolar GTN was predicted on 2nd week

<table>
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<tr>
<th>weeks after evacuation</th>
<th>spontaneous regression</th>
<th>spontaneous regression</th>
<th>postmolar GTN*</th>
<th>postmolar GTN*</th>
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<tr>
<td>Initial</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>1 day hCG/initial hCG</td>
<td>25.7</td>
<td>23.4-28.1</td>
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<td>1 week hCG/initial hCG</td>
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<td>2 week hCG/initial hCG</td>
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<td>3 week hCG/initial hCG</td>
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<td>4 week hCG/initial hCG</td>
<td>0.054</td>
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<td>5 week hCG/initial hCG</td>
<td>0.030</td>
<td>0.016-0.045</td>
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<th>AUC</th>
<th>cut-off value of hCG/initial hCG (%)*</th>
<th>sensitivity</th>
<th>specificity</th>
<th>P-value</th>
<th>No of postmolar GTN</th>
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<tr>
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<td>0.513</td>
<td>18.9</td>
<td>92</td>
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<td>1 week</td>
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<td>92</td>
<td>40</td>
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<td>2 week</td>
<td>0.729</td>
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<td>70</td>
<td>63</td>
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<td>3 week</td>
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<td>77</td>
<td>84</td>
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<tr>
<td>4 week</td>
<td>0.946</td>
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<td>86</td>
<td>91</td>
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<td>5 week</td>
<td>0.947</td>
<td>0.077</td>
<td>92</td>
<td>95</td>
<td>&lt;0.001</td>
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</table>

[the comparison of the mean regression rate of hCG] [cut-off value of hCG regression to predict GTN]
COMPARISON OF βHCG REGRESSION CURVE IN MOLAR PREGNANCY AND GESTATIONAL TROPHOBLASTIC NEOPLASIA

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Objectives: All cases of gestational trophoblastic neoplasia are curable in first stage of the disease if exact diagnosis and early suitable treatment be performed. The serum β-Human chorionic gonadotropin (βHCG) titer is a sensitive marker of clinical disease. The aim of this study is comparison of βHCG regression curve in molar pregnancy and gestational trophoblastic neoplasia.

Method: 40 cases with uneventful hydatiform mole and 40 cases with gestational trophoblastic neoplasia that had referred to Gynecology-Oncology clinic of Ghaem hospital were studied. A log-value regression curve was developed from the mean and 95% confidence limit of serial weekly serum βHCG of the patients.

Results: Mean age in mole group was 26.3 yrs and 26.7 yrs in gestational trophoblastic neoplasia group. There was history of previous abortion in 25% of patients in both groups. 67.5% of patients were in stage 1 of the disease and they were 100% curable. The βHCG regression curve exceeded normal range in gestational trophoblastic neoplasia groups (P = 0.001).

Conclusion: Nowadays, gestational trophoblastic neoplasia is diagnosed 8-10 weeks after evacuation. This study showed that gestational trophoblastic neoplasia can be diagnosed earlier (a few weeks after evacuation) with the use of βHCG regression curve; therefore treatment will be started sooner.

Keywords: Hydatiform mole, βHCG regression curve, Gestational Trophoblastic Neoplasia
OUTCOME OF GTD CASES OVER A PERIOD OF 5 YEARS IN A TERTIARY CARE TEACHING HOSPITAL OF INDIA

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Aim: To study the outcome of GTD cases with respect to changing concepts of diagnosis, treatment and follow up over 5 years.

Methods: The retrospective study included 21 GTD patients admitted between Jan 2005 & Dec 2007 while prospective cohort study was conducted on 20 cases admitted between Jan 2008 & June 2009. Data was recorded about age, parity, type of GTD, stage, treatment, follow up and final outcome of disease and analyzed in terms of adequacy of treatment; follow up feasibility and outcome as per newer protocols. Statistical analysis was done on SPSS 11 of windows 2003.

Results: The annual incidence of GTD admissions in 2008 was 0.36%. The GTN cases were 1.5% of all gynecological malignancies admitted. 22 (53.7%) cases were H. MOLE and only 2 were partial moles.

GTN was seen in 19(46.3 %) cases of GTD; 17 were GCC and 2 were suspected PSTT. 16 were treated with chemotherapy and 3 had hysterectomy. Chemotherapies used were Methotrexate (8), MAC (3) and EMACO (5). Complete follow up was available in 11 cases and they were all cured. bHCG follow up of 8 cases was not available.

Conclusions: Almost 50% of GTD cases are malignant. Treatment with the latest protocols gives 100% success but recommended follow up is deficient due to travel & cost factors. We recommend central record keeping in OPD and national registry systems for complete clinical profile and outcome of the disease.
INTER- AND INTRA-OBSERVER VARIABILITY IN THE DIAGNOSIS OF HYDATIDIFORM MOLE AND HISTOLOGICAL DIAGNOSTIC CRITERIA

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Not uncommonly, the pathologist has to differentiate complete hydatidiform mole (CHM) from partial hydatidiform mole (PHM) or hydropic abortion (HA), when encountering hydropic villi in product of conception specimens. It is important to distinguish CHM from PHM, as the former has greater malignant potential and, consequently, requires stricter patient management and follow-up. The histological diagnostic criteria are subjective and demonstrate considerable inter-observer variability.

This study assessed diagnostic inter- and intra-observer variability of hydatidiform mole in two pathologists.

We retrospectively studied 90 specimens of abortus conception. One hematoxylin and eosin-stained slide from each case was given independently to the pathologists asked to make the diagnosis of CHM, PHM or HA. In order to evaluate the intra-observer agreement rate, each pathologist blindly reviewed the same slides 6 months later. Kappa value was calculated for the inter- and intra-observer agreement in the first and second rounds.

κ statistics showed that although CHM could be reliably distinguished from non-molar pregnancy, neither non-molar pregnancy nor CHM could be easily differentiated from PHM. Of the total 36.7% disagreement between two pathologists, 24.4% and 12.2%, respectively, related to differentiating PHM from CHM and PHM from HA. The intra-observer agreement regarding the distinction of CHM from non-molar pregnancy was almost perfect for both pathologists (kappa=1 and 0.960).

These results mean that the reported histological criteria are not being consistently applied and the difference in diagnostic agreement rates in existing studies may imply that each center needs to evaluate its own inter-observer agreement rate and attempt to improve it.
LUNG LOBECTOMY IN THE TREATMENT OF CHEMO-RESISTANT GESTATIONAL TROPHOBLASTIC NEOPLASIA WITH LUNG METASTASIS WITHIN NORMAL RANGE SERUM HCG

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Objective: To investigate the value of lung lobectomy in the treatment of chemo-resistant gestational trophoblastic neoplasia (GTN) with lung metastasis within normal range of serum hCG level. The data of patients with normal preoperative hCG level were compared with abnormal preoperative hCG level.

Methods: The clinico-pathological features and outcome of 46 patients with chemo-resistant GTN who underwent lung lobectomy at Peking Union Medical College Hospital between Jan 1995 and Dec 2008 were retrospectively reviewed.

Results: Of the 46 cases, 21(45.7%) manifest normalized preoperative hCG level while the other 25 were abnormal; There was no statistically significance in age, antecedent pregnancy, courses of preoperative chemotherapy between these two groups. At the completion of treatment, 40 patients achieved serum complete remission (SCR) (88.9%), 2 died of postoperative brain hemorrhage and the other 4 had no response. The SCR in normal hCG group and abnormal hCG were 95% and 88%, respectively (p=0.614). 22 of 46 patients (47.8%) had positive pathology, with 6 of 21 patients (28.6%) and 16 of 25 patients (64%) in the normal hCG group and abnormal hCG group, respective (p=0.021). The positive rate of pathology remained to be 27.3% in 11 patients who had received at least 2 courses of consolidation chemotherapy before lobectomy.

Conclusions: Lung lobectomy combined with chemotherapy is effective in the treatment of chemo-resistance GTN with lung metastasis. But almost 1/3 patients who had normal serum hCG level after salvage chemotherapy have positive pathology. For these patients, lung lobectomy at appropriate time could improve the SCR.
HYPOXIA MODULATES CLUSTERIN OVEREXPRESSION IN THE HUMAN CHORIOCARCINOMA CELL LINE JEG-3

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Background: Clusterin (CLU) is expressed in a wide variety of human tissues and fluids. Overexpression of clusterin (CLU) has been implicated in cancer development and progression.

Aims: The aim of the present study is to evaluate the association of CLU overexpression with in vitro hypoxia model in the human choriocarcinoma cell line JEG-3.

Material and methods: To make an in vitro hypoxia model, we cultured JEG-3 cells with 0.1, 0.2, 0.5, 1, 2 and 5 mMole of CoCl₂. To identify hypoxic levels, we examined the expression of HIF-1α (biochemical marker of cellular hypoxia) in 1, 3, 6, 12 and 24 hr. We also examined the expression of CLU in 3, 6, 12 and 24 hr after treated CoCl₂ by Western blotting, respectively.

Result: The CLU was overexpressed in the hypoxia. The treated time of CoCl₂ and concentration of maximal expression was a 3, 6hr and 1mMole, respectively.

Conclusion: This study show that hypoxic level has dose-dependent effect in expression of CLU in JEG-3.

Keywords: Clusterin, Hypoxia, JEG-3
SUCCESSFUL TREATMENT OF PLACENTAL SITE TROPHOBLASTIC TUMOR --3 CASES REPORT AND REVIEW OF LITERATURE

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Objective: To report the clinical features, diagnosis method, treatment, and outcome of 3 cases placental site trophoblastic tumor (PSTT) and to review pertinent literature.

Method: 3 cases of PSTT were reviewed. Data obtained included age at diagnosis, antecedent pregnancy (AP), interval from AP until diagnosis, presenting features, image features, presenting serum human chorionic gonadotrophin hormone (hCG) level, any metastases, treatment received, outcome and follow-up.

Result: The average age of the three patients was 35(23-46) years old. Two patients presented with amenorrhea and one with irregular per vaginal bleeding. AP was full-term pregnancy in two patients and abortion in another. Interval from the AP was 18, 26 months and 18 years, respectively. Hypervascular echogenic masses were showed in ultrasonography. The range of serum βHCG before treatment was from 22.1 to 1976 IU/L. All the patients presented the disease confined to the uterus. Hysterectomy was performed, in two patients: subtotal hysterectomy in one patient and modify radical hysterectomy in another. Both of them received postoperation adjuvant chemotherapy(3 cycles of EMA-CO). The other patient was 23 years old. She received D&C and EMA/CO chemotherapy alternately for several times. So far, all of the patients are alive and without evidence of disease.

Conclusion: PSTT is rare and its course is unpredictable. Primary hysterectomy is the main therapy. Repeated dilatation and curettage combined with chemotherapy could be a choice of conservative treatment for the disease confined to the uterus. Serum β-hCG level is a valuable marker to follow the disease and treatment course of PSTT.
GESTATIONAL TROPHOBLASTIC DISEASE: ASPECTS OF CLINICAL PRESENTATION, MANAGEMENT AND OUTCOME IN UNIVERSITY OF BENIN TEACHING HOSPITAL, NIGERIA

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Objective: To describe some aspects of clinical presentation, management and outcome of patients with gestational trophoblastic disease (GTD).

Methods: A descriptive analysis of data obtained retrospectively of patients with GTD who were hospitalised and managed over a period of 6 years in a tertiary care centre. Clinical records of these patients were reviewed with regards to presentation, investigation, management and outcome.

Results: Of 92 patients studied, 60.9% had molar pregnancy and 39.1% had choriocarcinoma with a resultant incidence of 0.56 per 1000 and 0.36 per 1000 deliveries for molar pregnancy and choriocarcinoma respectively. The mean age of the study population was 32.5 ± 8.2 years. Over two-thirds of patients were found to be less than 35 years of age. The most common presenting complaint was vaginal bleeding (97.8%). The antecedent pregnancy was abortion in 50.7%, 8.7% had previous normal term pregnancy and 32.6% had previous molar pregnancy. Suction curettage was the main treatment modality for patients with molar gestation while choriocarcinoma was treated primarily with chemotherapy. Complete cure was achieved in 67.4% of patients. Presence of theca-lutein cyst and uterine size > 24 weeks was found to be prognostic for the occurrence of persistent disease.

Conclusion: GTD is potentially curable. Early referral to specialist centres following a high index of suspicion for the institution of appropriate therapy will improve the overall cure rate. Regular follow up is important to detect persistent disease.
TWO NEW FAMILIES WITH RECURRENT COMPLETE HYDATIDIFORM MOLE: ONE HAS BIPARENTAL GENOTYPE WITH A NEW MUTATION, OTHER HAS ANDROGENETIC GENOTYPE

S. Buyukkurt\(^1\), R.A. Fisher\(^2\), M.A. Vardar\(^1\), C. Evruke\(^1\)

\(^1\)Obstetrics & Gynecology, Cukurova University School of Medicine, Adana, Turkey, \(^2\)Institute of Reproductive and Developmental Biology, Imperial College, London, UK

Familial or biparental complete hydatidiform mole (HM) is a rare condition, transmitted in an autosomal recessive fashion, in which the genome is derived from both partners. However, in sporadic complete HM there is no maternal contribution to the nuclear genome and two sets of paternal genomic material are present.

Two new Turkish families with repetitive complete HM are presented. Their family members have a normal reproductive history and consanguinity is not present. Case 1 had five complete HM without any normal pregnancy. Genotyping demonstrated a biparental contribution to the nuclear genome. Additionally, sequence analysis of the exonic regions showed a novel mutation of the \(NLRP7\) gene. The patient was homozygous for an insertion in exon 8 which may be anticipated to cause a truncated protein. Case 2 had four complete HM pregnancies and we were able to examine the last three. Surprisingly, all had a typical androgenetic genotype. Microsatellite polymorphisms showed that the conceptus developed following duplication of a monospermic fertilization.

This report presents two different examples of recurrent complete HM. The first case is a classical presentation of biparental complete HM demonstrating a new mutation. The second is unusual with all three complete HM examined being androgenetic complete HM. While the clinical history is similar in these patients, the genetic analysis is different. Currently the genetic pathways that give rise to recurrent complete HM are not clearly defined. However, genetic examination and counseling should not be omitted in women with repetitive HM.
RISK FACTORS FOR COMPLETE MOLAR PREGNANCY, A STUDY IN IRAN

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¹Obstetrics & Gynecology, ²Epidemiology, Iran University of Medical Sciences, Tehran, Iran

Introduction: Complete molar pregnancy is the most common gestational trophoblastic disease. Where its incidence is different in various societies, the evaluation of its risk factors may make the reason for these differences clear.

Objective: The purpose of the present study is to evaluate some of the risk factors of complete molar pregnancy.

Method: A case-control study was performed on 91 cases of complete molar pregnancy (case group), and 295 cases of normal term pregnancy with a live neonate (control group). Then the maternal age, parity and gravidity, blood group and Rh, history of molar pregnancy, consanguinity, history of spontaneous abortion, contraception method, and race (Afghan or Iranian), were compared in the two groups.

Results: History of molar pregnancy OR, CI 95%=5.7 (1.2-25.6), spontaneous abortion OR, CI 95%=2.1(1.7-2.6), maternal age higher than 35 year old OR, CI 95%=2.3 (1.3-3.9) and lower than 20 year old OR, CI 95%=1.6 (1.4-1.9), consanguinity OR, CI 95%=1.3 (1.1-1.5), and Iranian OR, CI 95%= 1.9(1.5-2.4), were found to be risk factors for molar pregnancy.

Conclusion: History of molar pregnancy and spontaneous abortion, maternal age more than 35 and less than 20, consanguinity and race may be the risk factors for molar pregnancy.
UTERUS CHORIOCARCINOMA WITH CERVIX INVASION, A CASE REPORT

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Objective: To present a case of chorionicarcoma with cervix invasion.

Materials and methods: A multiparous 27 years old, referred to our department mentioning secondary amenorrhea for 10 weeks. β-hCG was 5690 mlU/ml at 5 weeks and 37220 mlU/ml at 10 weeks. The rest of the laboratory examinations were normal except for a positive finding of HbsAg. Uterus was found to be larger in size and soft in texture. The uterus U/S examination revealed a snowstorm-like image(multicystic echogenic pattern) within the uterus cavity. The chest x-ray was normal. Because of the non compatible findings with a 10 week pregnancy, dilatation and curettage was decided.

Results: After curettage a major degree of bleeding occurred and total hysterectomy without the adnexa, was decided and performed. Resicutation was excellent and post operative course normal. The histological examination revealed chorionicarcoma with invasion of the uterus wall and the cervix. Patient followed a treatment of methotrexate 50 mg i.v. on the 1st, 3rd, 5th, 7th day in turn with calcium folinate on the 2nd, 4th, 6th, 8th day. Chemotherapy treatment was performed in three cycles with a two week interval between them, while the patient was monitored by laboratory examinations and clinically. After the end of the treatment the patient is clinically healed, her β-hCG testing is negative and blood count, CT scan of the chest and abdomen and transvaginal U/S are normal.

Conclusion: Treatment of chorionicarcoma during pregnancy is a combination of syrgical and medical treatment and has excellent results.
PREGNANCY OUTCOMES AFTER GESTATIONAL TROPHOBLASTIC DISEASE: A 30-YEAR REVIEW

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**Background and aims:** Gestational trophoblastic disease (GTD) is a condition that mainly occurs among women of reproductive age. This study aims to determine pregnancy outcomes after remission of GTD and to compare pregnancy outcomes between hydatidiform mole (HM) and gestational trophoblastic neoplasia (GTN).

**Methods:** The data from GTD registry of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, were retrospectively reviewed from 1977-2006. Clinical data regarding types of GTD (HM, low-risk GTN, high-risk GTN), treatment modalities (single-agent or multi-agent chemotherapy), pregnancy outcomes (term, preterm, abortion) and complications of pregnancy were collected for analysis.

**Results:** During the 30-year period, there were 571 GTD patients with 170 subsequent pregnancies, of these 150 pregnancies had complete data for analysis. Among 81 pregnancies after HM, 65 (80.25%) resulted in term delivery, 5 (6.17%) were preterm and 6 (7.41%) were spontaneously aborted. Among 69 pregnancies after GTN (65 low-risk GTN and 4 high-risk GTN), there were 52 (75.36%) term deliveries, 3 (4.35%) preterm deliveries and 12 (17.39%) spontaneous abortions. There were no statistically significant differences of preterm and spontaneous abortions between pregnancies after HM and GTN (p=0.45 and 0.06, respectively). After HM, there were 4 pregnancy induced hypertension (PIH), one perinatal death and one postpartum hemorrhage (PPH). After GTN, there were one PIH, 3 PPH and 2 cases had manual removal of placenta.

**Conclusions:** Pregnancy outcomes after treatment of GTD were generally satisfactory, with comparable rates of term and preterm deliveries. Spontaneous abortion rate was higher after treatment of GTN, however without statistical significance.
DOES PRIMARY HYSTERECTOMY IN ELDERLY HYDATIDIFORM MOLE DECREASE THE INCIDENCE OF POSTMOLAR GTN?

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Background and aims: Hydatidiform mole in elderly patients seems to increase risk of postmolar gestational trophoblastic neoplasia (GTN). This study aims to evaluate the role of primary hysterectomy to prevent the incidence of postmolar GTN.

Methods: Patients who were diagnosed as hydatidiform mole with age 40 or older were recruited from two university hospitals in Bangkok, Thailand during 2000-2009. Clinical characteristics, pathological data and clinical outcomes were collected. Patients who received hysterectomy as primary treatment were compared with patients who received suction curettage as primary treatment.

Results: There were 26 cases of elderly hydatidiform mole in 10 years period. Ten patients were treated by primary hysterectomy and 16 patients were treated by suction curettage. Age, gestational age and initial hCG level in both group were comparable. During follow up, 10/26 (38.5%) patients developed postmolar GTN according to FIGO criteria; 8/16 patients (50%) in suction curettage group and 2/10 patients (20%) in hysterectomy group, which was not significantly different (p=0.2). All patients who developed postmolar GTN were treated successfully by single agent chemotherapy with or without adjuvant hysterectomy. The mean interval from primary treatment to hCG remission between hysterectomy and suction groups was not significantly different (11.9 vs 12.7 weeks, p=0.73). Hysterectomy specimens revealed invasive mole in 6 of 14 (42.9%) cases (10 primary and 4 adjuvant hysterectomies).

Conclusion: The incidence of postmolar GTN in elderly patients was high. Primary hysterectomy in elderly hydatidiform mole tends to decrease the incidence of postmolar GTN but had no statistical difference in this study.
A CASE OF MOLAR ECTOPIC PREGNANCY

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The incidence of ectopic pregnancy is 20 per 1000 pregnancies. Hydatidiform moles occur in 1 per 1000 pregnancies. Thus the incidence of the two occurring together is very rare. Only 40 cases have been reported in the medical literature, and in many of these accurate diagnosis is uncertain. Hydropic changes can occur that, although not molar in nature indicate an abnormal pregnancy. Without the use of strict clinical criteria, overdiagnosis of molar pregnancies and inappropriate follow-up care can occur, which might result in delayed attempts at conception, inappropriate exposure to chemotherapeutic agents, and increased medical expense.

Objective: To evaluate the occurrence of molar pregnancies in tubal ectopic pregnancy.

Design: Case report.

Setting: Outpatient clinic.

Patient: 23-years old woman

Intervention: Right Salpingectomy.

Main outcome measure(s): Molar ectopic pregnancy.

Results: Ectopic partial molar pregnancy.

Conclusion(s): Molar pregnancy can occur in ectopic pregnancy. Molar pregnancy clinically mimics normal tubal ectopic pregnancy.

Keywords: Tubal ectopic pregnancy, molar pregnancy.
GESTATIONAL TROPHOBLASTIC DISEASE AS SEEN IN A UNIVERSITY TEACHING HOSPITAL: A 5-YEAR REVIEW

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Background: Gestational trophoblastic diseases (GTD) including hydatiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumor, is highly treatable and has excellent prognosis.

Aim: To determine the incidence, clinical presentations and histological types of GTD.

Methods: This was a retrospective study of patients managed for GTD at the Emam Hossein Hospital, during Jan2004-Dec2009. Their sociodemographic characteristics, clinical presentations and histology reports assessed. Data analyzed by SPSS17.

Results: During 5years, 66 women managed for GTD, confirmed by histology recorded. The incidence of GTD was 13.3 /1000 deliveries. Histological findings showed complete mole in 63.6% (42), partial mole in 28.8% (19), invasive mole 4.5% (3), choriocarcinoma 3%(2). The mean age was 28.6 years in complete mole, 28.1 in partial mole, 42 in choriocarcinoma and 35.7 in invasive mole. The major symptom was abnormal vaginal bleeding (89.4%). The mean gestational age was 10.6&9.9 week for complete and partial mole respectively (PValue=0.47). Ultrasonography suggested complete mole in 79.5% and partial in 40% (PValue=0.005). Overall, the most common Blood group (BG), were O&A (each 37.9%); A(19;43.2%) in complete mole, O(11;64.7%) in partial. The mean rate of HCG was 123x10³UI/l. Chemotherapy and hysterectomy were performed exclusively for women with invasive mole (7.6%)and choriocarcinoma(3%)respectively. All patients cured completely with no death.

Conclusion: The prevalence of GTD in this study was higher than reports proposed in the literature. Although it needs more investigations in larger population, we suggest all women with vaginal bleeding in early pregnancy, be assessed for GTD, by sonography, serum BHCG and histopathology of abortion products.
WHO SCORE, THE ONLY PREDICTOR OF TREATMENT OUTCOME FOR LOW RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA IN WEEKLY INTRAMUSCULAR METHOTREXATE REGIMEN

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1Kashan University of Medical Sciences, Kashan, 2Tehran University of Medical Sciences, Tehran, 3Islamic Azad University of Iran, Kashan Branch, Kashan, Iran

Background: Gestational trophoblastic neoplasia (GTN) includes a spectrum of disease ranging from hydatidiform mole to choriocarcinoma. Low risk GTN is defined as persistent molar pregnancy with a score lower than seven. The optimal chemotherapeutic regimen still remains controversial.

Aim: The objectives of this study was to determine efficacy and safety of weekly intramuscular methotrexate in the treatment of low risk gestational throphoblastic neoplasia (LRGTN) and also identify prognostic factors associated with treatment failure, necessitating second line chemotherapy.

Methods: Sixty-one women with (LRGTN) from 1996 to 2006 in the gynecology oncology clinic of Tehran University of Medical Sciences were treated with weekly intramuscular methotrexate at 40mg/m2 as first line therapy. Monitoring of treatment was done with weekly checking of hCG level. Three consecutive negative hCG showed complete response. After first negative hCG, one additional dose was administered for consolidation.

Results: Complete remission with first line therapy happened in 43 from 61 patients (70.3%).

Change of treatment to second line dactinomycin happened in eleven cases because of resistance to first line and in six patients because of liver enzyme elevation. Sixteen of these 17 responded to dactinomycin as second line and one needed hysterectomy for complete response. One patient received multiagent chemotherapy for complete remission. WHO score prior to starting chemotherapy was the only predictive marker of requiring second line chemotherapy according to our data.

Conclusion: We recommend this effective and safe method of chemotherapy especially for women with LRGTN and WHO scores of two and less.
REMARKABLE INCREASE OF GESTATIONAL TROPHOBLASTIC DISEASE IN THE NETHERLANDS

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Objective: To determine incidence rates and time trends of gestational trophoblastic disease (GTD) in the Netherlands with the use of population-based data.

Methods: Data on patients with a pathologically confirmed diagnosis of GTD from 1995 to 2008 were obtained from PALGA, a national archive containing all histopathology reports in the Netherlands. Data on the number of deliveries were obtained from the Database of Statistics Netherlands.

Results: During the study period, 4249 patients with GTD were registered. The overall incidence rate of hydatidiform mole (HM) was 1.34 per 1000 deliveries. Incidence rates increased from 1.02 per 1000 deliveries in 1995 to 1.56 per 1000 deliveries in 2001 (95% CI 0.081;0.101), after 2001 the incidence rate remained constant (95% CI -0.045;0.024). Incidence rates of partial HM were higher than those of complete HM. Highest incidences were observed in women under 20 years of age, and in women older than 40 years. The number of women delivering after the age of 40 increased with 85 percent. The portion of live births being of Asian descent increased from 2.6% to 3.7%. The incidence rate of choriocarcinoma and PSTT was 3.1 and 1.0 per 100.000 deliveries, respectively.

Conclusion: The incidence of GTD in the Netherlands increased. This can partially be explained by increasing maternal age and an increasing portion of live births being of Asian descent. However, most of the documented increase is probably the result of improved diagnostic techniques.
REPRODUCTIVE OUTCOME, MALIGNANT SEQUELAE AND MOLECULAR GENETICS IN RECURRENT MOLAR PREGNANCIES

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Objective: To study the obstetric and family history, malignant sequelae and molecular genetics in 13 women (including three sisters) with recurrent molar pregnancies.

Methods: Over 6 years (2004-2009), 13 women with at least two molar pregnancies who attended the PGIMER, Chandigarh, India, were enrolled. Obstetric, treatment and family history of reproductive outcomes was recorded. Blood samples from them and available family members were collected for DNA extraction. The number of pregnancies ranged from 3-5. Seven required chemotherapy for persistent trophoblastic disease (low-risk, non-metastatic), one underwent hysterectomy for invasive mole due to toxicity to chemotherapy. Till date, all are alive and disease-free; only two have had a normal reproductive outcome (2/49 pregnancies). DNA for molecular analysis was available in 12 women, including 2/3 sisters. Mutation analysis revealed the presence of three NLRP7 mutations in 11/12. Six were homozygous for p.Arg693Pro (including the sisters), one homozygous for p.Asp913Ser, one homozygous for p.Leu398Arg, and three were compound heterozygous for p.Arg693Pro and p.Asp913Ser. Haplotype analysis revealed inheritance of the same mutation on identical haplotypes demonstrating the presence of a strong founder effect for these mutations in this population.

Conclusion: Women with recurrent molar pregnancies have a poor reproductive outcome, higher chance of malignant sequelae and have NLRP7 mutations. These mutations affect sites for restriction enzymes that can be used in molecular diagnosis to detect these mutations. The presence of a founder effect for this condition that prevents the reproduction of homozygous females is intriguing, and might reveal in the future male or heterozygous female advantage.
WEEKLY VINCristine PLUS HIGH ESCALATED DOSES OF METHOTREXATE FOR THE TREATMENT OF CNS METASTASES OF CHORIOCARCINOMA (A CASE REPORT)

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Purpose: In most reports, patients with brain metastasis of choriocarcinoma have a poor outcome & are treated with combination chemotherapy regimens with radiotherapy “WBRT”. Dose of Methotrexate (MTX) don’t exceed 1g/m² in all schemes.

Case report: We report the case of a patient 31 y old with high risk choriocarcinoma (score 11 according to WHO scoring system for GTD). Initial level of B-hCG was 717 500 UI. Pretreatment staging found metastasis in lung, spleen, supra-renal gland and multiple symptomatic brain localizations. She received weekly: Vincristine 1mg/m² + MTX 3g/m² for 4 cycles then escalation of dosage to 5g/m², 8g/m² then 12g/m² also with Folinic acid 25 mg /4h for 3 days started 24 h after MTX. Serum B-hCG was evaluated weekly with a complete biologic monitoring. A radiologic evaluation (CT scan of brain, lung, abdomen & pelvis) programmed every 4 cycles since obtained a CR.

After 4 cures, a complete regression of brain metastasis & a partial response on other localizations (60%) was noted. Serum B-hCG level decreased: 187 UI after 5 cures. Chemotherapy was well tolerated and hepatic function still normal. An update of outcome will be given in our presentation.

Conclusion: Schemes with MTX high dosage may avoid radiotherapy in CNS metastasis & improve prognostic of this category of pts with a good quality of life making them curable like germinal tumors.
METHOTREXATE ASSOCIATED PNEUMONITIS: SUCCESSFUL TREATMENT WITH SECOND LINE SINGLE AGENT ACTINOMYCIN D FOR LOW-RISK GESTATIONAL TROPHOBLASTIC DISEASE

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Low-risk gestational trophoblastic disease is highly sensitive to chemotherapy. First line treatment with methotrexate (MTX) is well accepted and results in high cure rates. The Dutch guidelines advise actinomycin D as second line therapy in medium risk patients.

MTX can cause interstitial pneumonitis, a severe inflammatory reaction in pulmonary tissue impeding further treatment with MTX.

We report 2 consecutive cases of low-risk gestational trophoblastic disease with MTX associated pneumonitis. The first patient is a 26 year old woman, who developed persistent trophoblastic disease after termination of a pregnancy with a hydatiform mole and co-existing twin after 16 weeks of gestation. She was treated with 9 courses of MTX chemotherapy, after which she developed MTX associated pneumonitis. The second patient is a 27 year old woman, who developed persistent trophoblastic disease after termination of a pregnancy with a hydatiform mole (weeks of gestation not known). She developed MTX associated pneumonitis after 4 courses of MTX chemotherapy. For both patients, HCG levels had not normalized when MTX associated pneumonitis was diagnosed.

Both patients were promptly treated with second line actinomycin D, without waiting for the pneumonitis to resolve. Clinical symptoms of interstitial pneumonitis subsided under treatment with actinomycin D. HCG levels normalized for both patients.

Conclusions: MTX associated pneumonitis does not preclude continuation of chemotherapy in low-risk gestational trophoblastic disease. Instant switching of chemotherapy to actinomycin D did not potentiate pulmonary toxicity and resulted in normalization of HCG levels.
SINGLE AGENT CHEMOTHERAPY IN THE TREATMENT OF LOW RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)

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Background: The selection of first line chemotherapeutic agent for treatment of low risk GTN is still not fully decided.

Design: Randomized clinical trial to compare pulsed Methotrexate, Methotrexate alternating with Folinic acid 8-day regimen and Actinomycin D.

Setting: Gynecological Oncology unit of the Ain Shams University in Cairo, Egypt.

Material and methods: Forty six women with low risk GTN (FIGO score ≤ 6) were included in the study and randomly assigned to one of 3 treatment groups: Actinomycin D (Group 1), pulsed Methotrexate (Group 2) and Methotrexate alternating with Folinic acid - 8 day regimen (Group 3). Measured outcomes were success of first line treatment, shift to a second line chemotherapy and primary toxicity.

Results: The 3 groups were similar regarding age, parity past history of molar pregnancy, FIGO score and pretreatment hCG. Median number of weeks till cure were 10 weeks, 10 weeks 1nd 9 weeks for the three groups respectively. There was no significant difference between three groups regarding primary line success or toxicity although there was a trend favoring Methotrexate-Folinic 8-day regimen. A pretreatment hCG level of 3250 mIU/ml and FIGO score ≥2 was predictive of failure of first line treatment. The cost of treatment was significantly lower for pulsed Methotrexate regimen than Methotrexate-folinic acid and Actinomycin D.

Conclusion: Methotrexate-Folinic acid 8-day regimen is associated with a higher (though non significant) success rate than pulsed Methotrexate or Actinomycin D in the treatment of low risk GTN.
MATERNAL AGE AND GESTATIONAL TROPHOBLASTIC TUMORS

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Aims: Maternal age at diagnosis is known to be one of the most important risk factor for hydatidiform mole and it is considered as prognostic factor in gestational trophoblastic tumors (GTT) score. In this study we evaluated the effect of maternal age in clinical presentation of hydatidiform mole and as prognostic factor for GTT development.

Methods: We included in this study all patients that received a histological diagnosis of hydatidiform mole at our hospital. We excluded all patients referred to us after diagnosis to start chemotherapy.

Results: Between 1998 and 2008 we observed 278 patients with histological diagnosis of hydatidiform mole at our hospital. Mean maternal age at diagnosis was 33.1259 (range 15-51, median value 33). We analyzed data regarding clinical presentation at diagnosis and incidence of PTT at follow-up. At presentation vaginal bleeding were present in 63.9% patients older than 40 and in 44.6% patients younger (p=0.03), theca-lutein cysts incidence was respectively 11.1% and 10.7% (not significant) while large than gestational age uterus incidence was respectively 61.1% and 33.1% (p=0.001). The incidence was significantly higher in patients older than 40 years old (36.1% instead of 6.2%, p< 0.0001 at Fisher Exact Test), with a Risk Ratio of 5.82.

Conclusion: In women older than 40 years old clinical presentation is significantly different: the incidence of large for gestational age uterus and vaginal bleeding are significantly higher, while asymptomatics patients are rare. Age older than 40 is also a risk factor for development of GTT and needing of chemotherapy treatment.
THE EVOLUTION OF TREATMENT FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN): THE FIRST FIVE DECADES AT THE JOHN I BREWER TROPHOBLASTIC DISEASE CENTER

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Background and rationale: The Brewer Trophoblastic Disease Center of Northwestern University was established in 1962 and has treated over 850 women with GTN during the last five decades. The goal of this retrospective study is to chronicle the evolution of chemotherapy for low-risk and high-risk GTN, as well as placental site trophoblastic tumor. During this time, the chemotherapy and bone marrow support options have evolved significantly. The outcomes for high-risk disease and PSTT are correlated with this evolution of chemotherapy options.

Methods: This is a retrospective review of previously published results from the Brewer Trophoblastic Disease Center between 1962 and 2008. These results are qualitatively aligned with the introduction of new chemotherapy regimens to document the evolution of primary and salvage therapy for GTN.

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The overall complete response rate to the initial chemotherapy regimen given at the Brewer Center was 77%: 92% for sequential single-agent chemotherapy for nonmetastatic and low-risk metastatic disease (78% for primary methotrexate and 73% for secondary actinomycin D) and 82% for sequential multiagent chemotherapy for high-risk metastatic disease (67% for primary MAC or EMA-CO and 44% for secondary platinum-based regimens). The overall survival rate was 94%: 87% from 1962-1978 and 98% from 1979-2008. All patients treated for low-risk disease since 1962 were cured, however, the cure rate for patients with high-risk disease increased from 78% during 1962-1978 to 92% during 1979-2008.
EXPRESSION PATTERN OF THE CLASS I HOMEobox (HOX) GENES IN OVARIAN CARCINOMA

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Objective: Although some sporadic reports revealing the link between the homeobox genes and ovarian carcinoma, there is no comprehensive analysis of the expression pattern of the class I homeobox (HOX) genes in ovarian carcinoma to determine the candidate genes involved in ovarian carcinogenesis.

Methods: The different patterns of expression of 36 HOX genes were analyzed, including 4 ovarian cancer cell lines and 4 normal ovarian tissues. Using a reverse transcription-polymerase chain reaction (RT-PCR) and quantification analysis, the specific gene that showed a significantly higher expression in ovarian cancer cell lines than in normal ovaries was selected, and western blot analysis was performed adding 7 ovarian cancer tissue specimens. Finally, immunohistochemical and immunocytochemical analyses were performed to compare the pattern of expression of the specific HOX gene between ovarian cancer and normal ovaries.

Results: Among 36 genes, 11 genes had a different level of mRNA expression between the cancer cell lines and the normal ovarian tissues. Of the 11 genes, only HOXB4 had a significantly higher level of expression in ovarian cancer cell lines than in normal ovaries (p=0.029). Based on western blot, immunohistochemical, and immunocytochemical analyses, HOXB4 was expressed exclusively in the ovarian cancer cell lines or cancer tissue specimens, but not in the normal ovaries.

Conclusion: We suggest HOXB4 can be a novel candidate gene involved in ovarian carcinogenesis.
VALUES OF SERUM MICRORNAS IN DIAGNOSIS OF EPITHELIAL OVARIAN CANCER

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Background and aims: Ovarian cancer is the most lethal disease of the gynecologic malignancies worldwide. New approaches that can complement and improve on current strategies for cancer detection are urgently needed. Our study is aimed to detect the expression of serum miRNAs of the patients with epithelial ovarian cancer and to determine whether miRNA can be used as a new biomarker for the pre-operative diagnosis of ovarian cancer. And estimate the clinical value of combinational detection of miRNA and CA125.

Methods: TaqMan quantitative RT-PCR (qRT-PCR) was used to detect the quantity of miR-200a and miR-125b-1 in the serum of 30 patients of epithelial ovarian cancer and 30 healthy women as controls. The CA125 in the serum of these samples was detected by ELISA.

Results: We quantified the level of miR-200a and miR-125b1 in the serum of the cases and controls. MiR-200a was significantly over expressed in the serum samples of ovarian cancer patients compared to controls, while miR-125b1 was up-regulated in the patients of stage I, compared with stage II and stage III. The combinational detection of CA125 and miR-200a showed the sensitivity of 100% and the specificity of 80%, which had an advantage in the early diagnosis of ovarian cancer.

Conclusions: MiRNAs may be regarded as new circulating biomarkers for epithelial ovarian cancer. The combinational detection of miRNA and CA125 will help to improve the sensitivity of diagnosis of ovarian cancer.
GROWING TERATOMA SYNDROME

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Growing teratoma syndrome (GTS) is a rare phenomenon characterized by conversion of a malignant germ cell tumor into a benign germ cell despite chemotherapy, with only 37 cases presented in world literature. Presented is the first documented case of GTS in the Philippines. A 22 year old nulligravid, diagnosed with immature cystic teratoma of the ovary, stage IA, underwent 4 cycles of bleomycin-etoposide-cisplatin. In spite of normal tumor markers, there was growth of a new pelvic mass after the 4th cycle. On debulking surgery, what was initially thought of as tumor progression showed mature teratomatous implants, suggestive of conversion from immature to mature implants on histopathologic examination. The case fulfilled the 3 criteria of GTS, namely:

1. enlargement of the primary tumor or development of a new one during or after chemotherapy,

2. normal tumor markers, and

3. metastases consisting of pure mature teratoma.

This condition was hypothesized to be the result of either the induction of differentiation of the malignant cells into mature cells, or the selective destruction of the malignant tissues with concomitant resistance, persistence and further growth of the mature components. The presence of benign elements with neuroepithelial tissues are identified predictive factors for its development. Surgery is the mainstay in the diagnosis and management of the condition. Proper management of this condition is necessary to prevent known complications such as mechanical obstructive effects and malignant transformation of the resulting mature teratoma. After debulking surgery, the patient, until present, has no evidence of disease.
RECTO-SIGMOID RESECTION AT THE TIME OF PRIMARY CYTOREDUCTION FOR ADVANCED OVARIAN CANCER. A MULTI-CENTER ANALYSIS OF SURGICAL AND ONCOLOGICAL OUTCOMES

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Background and aims: The aim of this study was to determine the impact on morbidity and survival of bowel resection at the time of primary cytoreductive surgery for ovarian cancer.

Methods: We performed a retrospective medical chart review of all patients who had undergone recto-sigmoid resection for ovarian, tubal and peritoneal cancer between 1998 and 2008 at the IEO in Milan and JHMI in Baltimore.

Results: A total of 238 patients were identified with a median age of 59.7 years; 180 (75%) were stage IIC-IIIC and 58 (25 %) were stage IV. Optimal cytoreduction was achieved in 86% of the cases. Stapled coloproctostomy was performed in 98% while hand sewn in only 2%; a protective ileostomy was constructed in 2 (0.8 %) cases, and colostomy in 5 (2%) cases. The median EBL was 1000 cc with 64% of patients requiring intra-operative blood transfusion; the median operative time was 300 minutes. The complications associated to recto-sigmoid resection were anastomotic leakage in 7 (3%) patients and pelvic abscess in 9 (3.7%). The median HS was 10 days. Post-operative platinum-based chemotherapy was administered in 96.3% of patients. After a mean of follow up of 34 months, 46% of the patients died for progression of their disease.

Conclusions: Rectosigmoid colectomy can significantly contribute to the cytoreductive surgical efforts for advanced stage ovarian, tubal and peritoneal cancer. The morbidity rate observed with recto-sigmoid colectomy was considerably low, with an anastomotic leak rate of only 3%. Protective colostomy or ileostomy was necessary only in selected cases.
TREATMENT OF PSEUDOMYXOMA PERITONEI BY INTRAOPERATIVE AND INTRAPERITONEAL CHEMOTHERAPY

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Introduction: Pseudomyxoma peritonei occurs mostly in conjunction with the type of intestinal mucinous borderline tumour and is characterized by building up a lot of mucus pour of cells. The most common tumor is the pseudomyxoma peritonei with mucinous borderline tumours of the ovaries or with mucinous tumours of the appendix, normally without showing a rupture of the ovarian tumour pre- or intraoperatively. The diagnosis of pseudomyxoma peritonei is mainly difficult and guidelines for the treatment are unknown.

Material and methods: In the period from 1991 to 2009, 52 patients with pseudomyxoma peritonei were treated by tumour debulking and intraoperative and intraperitoneal chemotherapy with Novantron (40 mg in 300 ml of NaCl over 72 hours). During the tumour debulking a CUSA system was used.

Results: The median follow-up was 8.9 years. There were the following histologies: mucinous cystadenoma of the ovary n= 26, mucinous cystadenoma of the appendix n= 10, mucinous cystadenocarcinoma n= 16. Recurrences were seen in five patients. These patients were treated for recurrences by the same way as mention above. All these patients were now without any recurrences. The other 47 patients are still alive without recurrences.

Discussion: The instillation of novantron intraperitoneally and intraoperatively is an effective and safe therapy without major side effects after maximal tumour debulking of pseudomyxoma peritonei.
THE SAFETY AND EFFICACY OF LAPAROSCOPIC SURGICAL STAGING, DEBULKING OF APPARENT ADVANCED STAGE OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS

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Objective: Studies on the role of laparoscopy in cytoreductive procedures for advanced stage ovarian cancer are limited. The objective of this study is to describe our preliminary experience with laparoscopic total primary or interval cytoreduction in patients with advanced ovarian, fallopian, and primary peritoneal cancers.

Methods: This is a prospective case series. Women with presumed advanced cancers deemed appropriate candidates for laparoscopic debulking were recruited. The patients underwent exploratory laparoscopy and subsequent biopsy, primary, or interval cytoreduction by laparoscopy or laparotomy from January 2005 to June 2009. Outcome variables analyzed included stage, site of disease, extent of debulking, operative time, blood loss, length of hospital stay, complications, and survival time. Statistical analysis was performed using Systat 12.0.

Results: Thirty-two patients were recruited. Seventeen underwent total laparoscopic primary/interval cytoreduction, with 88.2% optimally cytoreduced. Eleven underwent diagnostic laparoscopy and conversion to laparotomy for cytoreduction, with 72.7% optimally cytoreduced. Four patients had limited cytoreduction. In the laparoscopy group, 9 patients have no evidence of disease (NED), 6 are alive with disease (AWD), and 2 have died of disease (DOD), with mean follow-up of 19.7 months. In the laparotomy group, 3 patients are NED, 5 are AWD, and 3 have DOD, mean follow-up of 25.8 months. Complication rates were not different. Median time to recurrence was 31.7 and 21.5 months for the laparoscopy and laparotomy groups.

Conclusions: Laparoscopy can be used for diagnosis, triage and debulking of patients with advanced ovarian, fallopian, or primary peritoneal cancers and is technically feasible in a well-selected population.
THE SAFETY AND EFFICACY OF LAPAROSCOPIC CYTOREDUCTION OF RECURRENT OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS


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Objective: Studies on the role of laparoscopy in secondary or tertiary cytoreductive procedures for recurrent ovarian cancer are limited. The objective of this study is to describe our preliminary experience with laparoscopic secondary, tertiary, and quaternary cytoreduction in patients with recurrent ovarian, fallopian, and primary peritoneal cancers.

Methods: This is a prospective case series. Women with recurrent ovarian cancers deemed appropriate candidates for secondary, tertiary, or quaternary laparoscopic cytoreduction were recruited. The patients underwent exploratory laparoscopy, subsequent biopsy, and either secondary, tertiary, or quaternary cytoreduction by laparoscopy from June 1999 to October 2009. Outcome variables analyzed included stage, site of disease, extent of cytoreduction, operative time, blood loss, length of stay, complications, and survival time. Statistical analysis was performed using Systat 12.0.

Results: Thirty-three patients were recruited. Twenty-five patients (76%) were stage IIIC at the time of their initial diagnosis. Twenty-six patients underwent secondary, six underwent tertiary, and one underwent quaternary cytoreduction. Twenty-nine of the patients (85%) underwent optimal laparoscopic cytoreduction. Overall, 14 patients have no evidence of disease (NED), 8 are alive with disease (AWD), and 11 have died of disease (DOD), mean follow-up of 26.7 months. Mean operative time was 198 minutes. Mean blood loss was 108 ml. Mean hospital stay was 2.82 days. There were no intra-operative complications. There was one post-operative complication (ileus). Median time to recurrence was 16 months.

Conclusions: Laparoscopy can be safely utilized to optimally cytoreduce patients with recurrent ovarian, fallopian, or primary peritoneal cancers, and is technically feasible in a well-selected population.
LAPAROSCOPIC PRIMARY CYTOREDUCTION OF ADVANCED OVARIAN CANCER

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¹Gynecologic Oncology, St Luke's-Roosevelt, ²Minimally Invasive Surgery & Gynecologic Robotics - OBGYN, St Luke's-Roosevelt Hospital Center, ³General Surgery, Winthrop University Hospital, New York, NY, USA

The following presentation is a video illustration of a 61 y/o who underwent optimal laparoscopic primary cytoreduction of advanced ovarian cancer in the form of radical hysterectomy, bilateral salpingo-oophorectomy, pelvic mass resection, anterior and posterior culdectomy, omentectomy, posterior exenteration, with end to end rectosigmoid anastomosis. Final pathology revealed stage IIIC poorly differentiated papillary serous carcinoma of the ovary based upon omental involvement, and stage IB well differentiated endometrial adenocarcinoma, FIGO Grade I. The patient is being followed every 3 months. She received a total of 6 cycles of Carboplatinum and Taxol. She is currently alive and well and without any evidence of disease.
NEW RISK -OF -MALIGNANCY INDEX IN PREOPERATIVE EVALUATION OF ADNEXAL MASSES IN IRANIAN WOMEN

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1Reproductive Research Health Center, Obstetrics and Gynecology Department, Shahid Beheshti Medical University, 2Shahid Beheshti Medical University, 3Pathology, Taleghani Hospital, Shahid Beheshti Medical University, Tehran, Iran

Objective: To assess the risk-of-malignancy index (RMI) in preoperative diagnosis for Iranian Women with adnexal masses.

Materials: In this case-control, cross-sectional study, 36 women with adnexal masses, admitted to the gynecology ward for surgical exploration from Sep 2007 to Sep 2009, was selected. The RMI was calculated by multiplying serum CA125 levels, ultrasound score (US) and menopausal status (M) preoperatively. Ultrasound findings were classified according to the shape, size, and multiplicity, presence of wall involvement or ascites. M was considered 1 for premenopausal, 3 for postmenopausal women. CA125 were considered in absolute values. The majority of variables were included in a logistic multiple regression model, fitted using the US, the M and the serum CA 125 level. The model was used for assessing the value of each predictor in assessing the malignancy of these tumors individually as well as determining the value of RMI in Iranian Women.

Result: Among all predictors the best individual act was found in CA125 levels (sensitivity 60%, specificity 99%), followed by US(64% and 77%, respectively). The performance for the RMI at the cut-off point of 95 had a sensitivity and specificity of 79% and 77% respectively which was the best in this study. The area under the ROC curve for the RMI was 0.78, which was greater than the area for CA125 levels (0.73) or ultrasound score (0.71).

Conclusion: The RMI might be of value in the preoperative assessment of ovarian masses in Iranian women. The new cutoff of 95 needs to be more analyzed in the larger population.
THE ASSESSMENT OF LYMPH NODE METASTASES DISTRIBUTION IN OVARIAN CANCER PATIENTS

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Among gynecological malignancies, ovarian cancer is the one, which disseminates along lymphatic way most frequently. The regional lymph nodes assessment is the integral part of ovarian cancer diagnostics. Is the important part of classification procedure, which is the way to the proper therapeutic method determination.

Aim: The assessment of lymph nodes distribution in ovarian cancer patients.

Material and methods: The retrospective analysis of 211 consecutive ovarian cancer patients, treated at Maria Sklodowska-Curie Memorial Cancer Centre in Warsaw between 1998 and 2006, was performed. According to the protocol, all patients were treated with total abdominal hysterectomy and pelvic and periaortal lymphadenectomy. After the surgical treatment, the adjuvant chemotherapy was administered. The analysis of lymph nodes metastases localization, and its dependence on the most important clinocopathological factors, as: clinical stage of the tumor, grade and the histology of the tumor, was performed.

Results: In early ovarian cancer patients (FIGO I, II), the percentage of pelvic and periaortal lymph nodes metastases is similar. In advanced ovarian cancer (FIGO III, IV), the percentage of periaortal lymph nodes metastases is higher, than pelvic.

Conclusions: The percentage of lymph nodes metastases in ovarian cancer patients is high. Their frequency depends on the clinical stage, grade and the histology of the tumor.
ANALYSIS OF 3057 CASES OF OVARIAN TUMOR IN NORTHWEST OF CHINA

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Aim: To investigate the character of ovarian tumor and etiology regulation for 10 years in northwest of China.

Methods: To statistic 3057 cases of ovarian tumor in Xijing Hospital from 1999-2009.

Results: The incident rate of surface epithelial-stromal tumor is the highest (47.89%), and the second one is sex germ cell tumor (43.17%), and the third one is sex cord-stromal tumor (8.79%) respectively. In surface epithelial-stromal tumors, the highest incident rate is between 41-53 years old, in germ cell tumor the highest incident rate is among age 31, in sex cord-stromal tumor is about 60 years old, and secondary tumor is between 31-40 age, miscellaneous tumor is between 45-50 age, in lymphoid and haematopoetic tumor is between 51-60 age.

Conclusion: The incident rates of various ovarian tumor are increasing which should be pay much more attention. Each type of ovarian tumor shows close relationship with age of patients and it is valuable in their diagnosis.

Keywords: Ovarian tumor, etiology, age
CLINICAL AND OPERATIVE OUTCOME OF TERTIARY SURGICAL CYTOREDUCTION IN EPITHELIAL OVARIAN CANCER RELAPSE

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Background and aims: The impact of tertiary cytoreductive surgery (TCS) on the overall survival (OS) of patients with relapsed epithelial ovarian-cancer (ROC) remains controversial considering the associated morbidity of the heavily pre-treated patients. Aim of the present study was to evaluate the operative and clinical outcome after TCS.

Methods: We systematically evaluated all consecutive patients undergoing TCS. Tumor-dissemination-pattern, operative-morbidity, tumor-residuals and survival are described based on a validated intraoperative documentation-tool. Predictors of survival and complete tumor-resection are analyzed with Cox-regression or logistic-regression-models.

Results: Between 10/2000 and 12/2008, 135 patients (median-age:51years; range:22-80) of mainly initial FIGO-stage≥III (106 patients;78.5%) were evaluated. In 53(39.3%) patients a complete tumor resection was obtained. One-month-operative-mortality was 6%(8 patients). During a median follow-up-period of 9.6 months (range:0.1-75) 78(57.8%) patients died, while 52(38.5%) patients experienced a further relapse. Median-OS was 19.1 months for the total collective (95%CI: 14.84-23.35), 37.8months (95%CI:12.7-62.7) for patients without tumor-residuals, 19.0mo(95%CI:9.8-28.2) for tumor-residuals≤1cm and 6.9mo(95%CI:3.05-10.7) for tumor-residuals>1cm (p< 0.001). The presence of peritoneal carcinomatosis did not seem to significantly affect OS. Complete tumor-resection was identified as the strongest predictor of OS. Other independent predictors of survival were interval to primary diagnosis ≥3years (HR:0.28;95%CI:0.14-0.59) and serous-papillary-histology (HR:0.23;95%CI:0.09-0.56). Forty-two patients(31.1%) presented at least one major complication. Multivariate analysis identified tumor involvement of the middle abdomen and peritoneal carcinomatosis as independent predictors of complete tumor-resection.

Conclusions: Postoperative tumor-residual-disease remains the strongest predictor of survival even in TCS-setting. To identify the optimal candidates for TCS, the predictive value of ascites and peritoneal carcinomatosis should be confirmed by future prospective trials.
SYSTEMATIC REVIEW OF PACLITAXEL INTENSIVE THERAPY FOR OVARIAN EPITHELIAL CANCER

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The current standard treatment of epithelial ovarian cancer is paclitaxel plus carboplatin. There are two ways of medication, paclitaxel given weekly (we call it: intensive therapy) and paclitaxel used every 3-4 weeks (we call it conventional therapy). In order to find the differences between these two therapies, we do meta-analysis to evaluate the efficacy and the adverse reactions of intensive therapy compared with conventional therapy. We search the Cochrane Library, Cochrane Central Register of Controlled Trials, Medline, Embase, Chinese Biomedical Literature Database, China National Knowledge Infrastructure to get all the random control trials (RCTs) till December 2008 about paclitaxel intensive and conventional therapies for ovarian cancer. Use Revman 5 to perform meta-analysis. 6 RCTs involving 572 patients are included. Meta-analysis shows the efficacy of intensive therapy and conventional therapy is similar. There are no significant differences in response rate (RR 1.06, 95% CI 0.94–1.20), median survival time, survival rate, median progression free survival and median time to progression. When taking the safety into consideration, intensive therapy can significantly reduce the occurrence of Grade III and IV neutropenia (RR 0.49, 95% CI 0.35-0.69, \( P < 0.0001 \)) and Grade III and IV neuropathy (RR 0.43, 95% CI 0.24-0.78, \( P = 0.006 \)), but there are no significant differences between intensive therapy and conventional therapy in flush, Grade III and IV vomiting, anemia, leucopenia, Grade III and IV thrombocytopenia and alopecia. In conclusion, paclitaxel intensive therapy is a good substitution for conventional therapy.
A SELECTIVE IMPACT ON GROWTH AND METASTASIS OF OVARIAN CANCER BASED ON N-TRIMETHYL CHITOSAN CHLORIDE-ENCAPSULATED CAMPTOTHECIN

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Background and aims: Camptothecin (CPT) derivatives exhibit excellent activity against a broad spectrum of cancers. However, the extreme water insolubility restricted its application. It is necessary to establish an efficient and safe protocol to increase its water-solubility and antitumor effect. N-trimethyl chitosan (TMC) has recently attracted increasing attention as a potential drug carrier which could increase the drug solubility, stability and minimize side effects.

Methods: In the previous study, we established a lymphatic metastatic mouse model of ovarian cancer by transfecting high expression VEGF-D into SKOV3 cells (SKOV3/VEGF-D). Here, we encapsulated camptothecin with TMC (CPT-TMC), and evaluated its potent antitumor and ant метастatic activities in nude mice subcutaneously inoculated with SKOV3/VEGF-D cells at the left hindlimb feet pad.

Results: CPT-TMC resulted in significant inhibition in primary tumor volume and obvious reduction in lymphatic metastasis compared with NS and TMC groups following a 3-week course of intravenous therapy performed twice per week; complete tumor regression happened in one of the five mice treated by CPT-TMC. Statistical differences between CPT-TMC and CPT happened in primary tumor volume yet not in lymphatic metastasis. These effects were associated with markedly decreased blood and lymphatic sprouts, increased apoptosis index, down-regulated VEGF-D expression.

Conclusions: Our data emphasize that TMC can effectively increase water-solubility of camptothecin. CPT-TMC displays outstanding activities in vitro and in vivo, it may become a potentially safe therapeutic strategy against human advanced ovarian cancer.

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CT SCAN DOES NOT PREDICT OPTIMAL DEBULKING IN ADVANCED OVARIAN CANCER: A MULTICENTRE VALIDATION STUDY

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Background and aims: Ovarian cancer is often advanced at presentation. Optimal cytoreduction improves survival. Suboptimal cytoreduction increases morbidity without conferring a survival advantage. A tool to predict suboptimal cytoreduction has been sought. It is important to crossvalidate such tools before their use can be supported.

Methods: Consecutive patients who underwent primary debulking surgery for stage III-IV ovarian cancer at 4 London hospitals between November 1995-October 2003, whose preoperative CT scan and medical records were available, were selected. CT scans were reviewed for 15 prognostic factors by radiologists blinded to surgical outcome. Univariate and multivariate logistic regressions ascertained radiological features predictive of suboptimal cytoreduction. A second dataset of patients operated on between June 2005-March 2007, at hospitals within Greater Manchester and Cheshire Cancer Network was subject to the same tests.

Results: The initial dataset comprised 91 patients (rate of optimal cytoreduction 35.2%). Multivariate analysis identified liver surface disease (p< 0.0005, 95% CI 3.56-32.3) and infrarenal paraaortic lymph node involvement (p=0.007, 95% CI 1.78-35.2) as predictive of suboptimal cytoreduction with an accuracy of 80%. When this equation was applied to the second dataset of 35 patients (rate of optimal cytoreduction 51.6%) accuracy dropped to 60%. Logistic regression analysis of the second dataset suggested only supracolic omental disease was predictive of suboptimal cytoreduction (p=0.044).

Conclusions: CT prediction of suboptimal cytoreduction may be unreliable. Accuracy is not reproducible between patient groups. In the absence of favourable data from larger, prospective trials it should not be used as the basis for treatment decisions.
GROWING TERATOMA SYNDROME AFTER SURGICAL TREATMENT AND CHEMOTHERAPY FOR OVARIAN IMMATURE TERATOMA

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Objectives: To describe the essential points for the correct diagnosis and best treatment for “Growing Teratoma Syndrome GTS” developed after surgery and chemotherapy for ovarian immature teratoma.

Methods: Retrospective review of the clinicopathological characteristics and long term follow up results of 22 cases of ovarian growing teratoma syndrome providing the knowledge about the natural history and prognosis of the tumor.

Results: All cases of GTS but two who were associated with concurrent somatic cell malignancy run benign clinical course with good health in the long follow up periods (3.5-23 years). Only a minority of patients showed some clinical progressive latency:

1) Tumors growing up to huge size.

2) Late recurrence of the tumor but still with benign histology.

3) May be associated with somatic cell malignancy.

Two patients with association of concurrent somatic cell malignancy failed treatment and died within short periods.

Conclusion: GTS is a benign tumor developed after surgery and chemotherapy for malignant ovarian immature teratoma. The natural history of this disease including its occurrence, progression and final result has been acknowledged only recently. To study its clinicopathological characteristics and its long clinical course more in detail would enable us to give the patients correct diagnosis and best treatment. The time interval between the development of GTS and the previous initial surgery usually exceeds one year. Such time interval can be used as an important reference for its diagnosis. GTS is a tumor with good prognosis; only a few cases occurred in association with somatic cell malignancy.
ADULT GRANULOSA CELL TUMORS OF THE OVARY: TUMOR DISSEMINATION PATTERN AT PRIMARY AND RECURRENT SITUATION, SURGICAL OUTCOME AND IMMUNOHISTOCHEMICAL CHARACTERISTICS

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Objective: Granulosa-cell-tumors of the ovary (GCT) constitute a rare group of neoplasms with malignant potential. By the rarity of the disease intraoperative tumor-dissemination-patterns are not well defined. Aim of the present study was to describe surgical and clinical outcome and dissemination pathways in the primary and recurrent situation of the disease.

Methods: All primary and relapsed GCT-patients, operated between 01/2001 and 02/2010 in our institution were evaluated using a systematic intraoperative documentation-tool. Surgical outcome, intraoperative tumor-dissemination-pattern, pathological and immunohistochemical findings were separately analyzed for the primary and recurrent situation.

Results: Eighteen patients with primary and 27 patients with recurrent GCT were evaluated. Tumor-dissemination-patterns differed significantly between primary and recurrent patients, by the latter having significantly higher rates of diffuse peritoneal carcinosis (15.8% vs. 52%; p=0.027) and of extraovarian tumor involvement of the middle (15.8% vs. 48.1%; p=0.05) and upper abdomen (0 vs. 33.3%; p=0.006). While all primary patients could be operated tumorfree, this was the case for 85.2% of the relapsed patients. A multivisceral operative approach with extensive peritoneectomy, intestinal or diaphragmatic resection, splenectomy and partial hepatectomy/pancreatectomy had to be performed only in recurrent-GCT (55.6%). Immunohistochemical examination identified significantly higher rates of positive estrogen- receptor-status in the patients with relapse (91% vs. 43%, p=0.0002).

Conclusions: Tumor-dissemination-pathways followed in primary and recurrent GCT differ significantly by higher rates of multivisceral tumor involvement in the recurrent situation of the disease. While at primary presentation extrapelvic involvement with peritoneal carcinosis appears only rare, surgical cytoreduction during relapse is more challenging involving a multivisceral approach.
PEGYLATED-NANOPARTICLES OF CDP BOUND TO MULTITARGETED SIRNA AGAINST BMI1 AND SURVIVIN CONJUGATED WITH MIR-373 (SEVIN-A) ERADICATES METASTATIC OVARIAN CARCINOMA

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Introduction: Vinorelbine in metastatic ovarian carcinoma and other solid tumors induces potent chemoresistance caused by activation of downstream signaling pathways of antiapoptotic survivin, aurora etc, induction of endopolyploidy, and efflux proteins including MDR1/Pgp, ABCG2 and MRP2.

Materials and methods: After vinorelbine treatment in metastatic ovarian carcinoma, we observed potent chemoresistance caused by generation of cancer stem cells which were characterized by overexpression of miR-520c, CD44, BIRC5/survivin (IAP), aurora serine/threonine kinases leading to endopolyploidy, Ras/c-Myc, Nanog, MAP4, MDR1/Pgp, ABCG2, MRP2 (cMOAT), Hedgehog signaling pathway components including PTCH1, Gli1, Gli2, and downregulation of BRCA1, p53, PTEN and p21. The Vinorelbine-induced Chemoresistant (VIC) cancer stem cells (CSCs) termed as VIC-CSCs were targeted with pegylated nanoparticles of cyclodextrin containing polycation (CDP) bound to multitargeted siRNA molecules against BMI1, and survivin conjugated with miR-373 targeting CD44. The formulation was termed as SEVIN-A.

Results: Post-treatment, we observed induction of D2 apoptotic stage of PCD type1 in VIC-CSCs leading to a bystander killing effect after downregulation of the chemoresistant antiapoptotic factors and their downstream signaling pathways, and upregulation of apoptotic tumor suppressor genes and downstream target genes.

Treatment with SEVIN-A even induced apoptosis in chemoresistant endopolyploid VIC-CSCs by downregulating Aurora-B.

Conclusion: Treatment with SEVIN-A eradicated vinorelbine induced chemoresistant cancer stem cells (VIC-CSCs) of metastatic ovarian carcinoma.
IMMUNOCHEMOGENIC TREATMENT WITH STEALTH NANOPARTICLE FORMULATION CONSISTING OF CLAMP PNA AGAINST MRNA-FOXC2, ANTI-CD44 CHIMERIC-MAB, AND TAXOTERE ERADICATED ADVANCED OVARIAN EPITHELIAL CA

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Introduction: We aim to eradicate ovarian epithelial Ca, and inhibit metastasis by blocking tumor cells from undergoing epithelial mesenchymal transition (EMT).

Methodology: We obtained surgically tumor cells from patients with stage-IV chemoresistant ovarian epithelial Ca characterised by upregulation of FOXC2, CD44, and bcl-2. We synthesized antisense clamp peptide nucleic acid oligomers (DNA-analogs), which hybridized to the 3'-end of AUG start codon region on mRNA of FOXC2. We incorporated clampPNA anti-FOXC2 in polar phase, and we entrapped taxotere molecules in lipid phase which was surrounded by hydrophilic layer with linked chimeric MAb against CD44 of the nanoparticle formulation, with which we treated xenograft animal models developed from ovarian epithelial Ca cells obtained from the stage-IV patients.

Results: Post-treatment, we observed downregulation of CD44 and Fra-2. ADCC was induced. The clamp PNA inhibited translation of FOXC2 activating Jak2/Stat5a, which led to suppression of epithelial mesenchymal transition of Ca cells. Undifferentiated epithelial cells undergoing epithelial to mesenchymal transition (EMT) exhibited overexpression of FOXC2, and this expression was lost when these cells returned back to their initial differentiated epithelial state blocking invasion, and metastasis. Taxotere blocked tumor cells at G2/M cell cycle, and phosphorylated bcl-2. This circumvented resistance to anoikis inducing apoptosis in tumor cells. Except the induction of caspase dependent apoptosis or PCD type I in tumor cells, bcl-2 downregulation caused release of beclin-1, and upregulation of BIM inducing type II PCD or autophagy. DNA synthesis, and metabolic activity of tumor cells was inhibited according to BrdU, and MTT tests, respectively.

Conclusion: The immunochemogene Tx induced epithelial differentiation by reversing the mesenchymal phenotype, promoted homotypic adhesion, inhibited metastatic cell motility/invasiveness, and eradicated tumor cells by induction of PCD.
COMPARISON OF DIAGNOSTIC VALUE OF SCORING SYSTEMS THAT ARE USED AT BENIGN-MALIGN DISTINGUISHING OF ADNEXAL MASSES

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The aim of our work was to test and compare the accuracy of six different scoring systems to identify malignant ovarian masses in a prospective study. Four of six systems are morphological and had previously been reported by Sassone, Lerner, DePriest and Ferrazzi. One of six is a vascular system and had reported by Caruso. And the last is RMI (Malignancy Risk Index) which was reported by Jacobs.

A total of 102 ovarian neoplasms were collected in Obstetrics And Gynecology Department of Gulhane Military Medical Academy. Of these 82 (%80) masses were benign, 16 (%16) were malign and 4 (%4) were borderline. If the cut-off values were 5, 234, 5, 4, 9 and 9 for respectively Caruso, RMI, DePriest, Lerner, Sassone and Ferrazzi, we obtained the sensitivity and the diagnostic accuracy of these tests were %90/%90, %80/%88, %80/%88, %70/%73, %75/%67 and %75/%68. We found that the Caruso and the RMI had the highest diagnostic accuracy rate.

As a result, we tested that the Caruso and the RMI scores were better than the other four traditional scoring systems at distinguishing malignant from benign lesions.
PROGNOSIS AND PROGNOSTIC FACTORS OF A LARGE RETROSPECTIVE SERIES OF MUCINOUS BORDERLINE TUMORS OF THE OVARY (EXCLUDING PERITONEAL PSEUDOMYXOMA)


_Institut Gustave Roussy, Villejuif, France_

**Background:** To determine the prognosis and prognostic factors in a large series of mucinous borderline tumors of the ovary (MBOT).

**Methods:** A retrospective review of patients with MBOT treated or referred to our institution. Three inclusion criteria were defined: 1. centralized histological review by our expert pathologist; 2. exclusion of peritoneal pseudomyxoma and any synchronous malignant tumor in the abdominal cavity; 3. available data on the management and outcomes of patients.

**Results:** From 1997 to 2004, 97 patients fulfilled inclusion criteria (95 stage I and 2 stage II disease). Eight patients had stromal microinvasion and 24, intraepithelial carcinoma. Conservative surgeries were performed in 69 patients. After a median follow-up of 48 months, 13 patients had developed 14 recurrences: 7 were borderline and 7 were invasive lesions. The probability of recurrence in the form of carcinoma, 5 and 10 years after the diagnosis was respectively 9% and 13%. The only prognostic factor for recurrence attaining statistical significance was the use of a cystectomy (compared to other surgeries RR = 5.6; \( p = 0.003 \); compared to salpingo-oophorectomy RR = 5.5; \( p = 0.012 \)).

**Conclusions:** In the present series of 97 MBOT, mainly early-stage disease and excluding peritoneal pseudomyxoma, the cumulative risk of recurrence in the form of invasive carcinoma at 10 years was 13%. MBOT do not appear to be such a safe disease. The only prognostic factor for recurrence was the use of a cystectomy suggesting that a salpingo-oophorectomy should be preferred in case of conservative treatment.
HOW TO FOLLOW-UP ADVANCED-STAGE SEROUS BORDERLINE TUMORS OF THE OVARY: ANALYSIS OF THE MODE OF DIAGNOSIS OF RECURRENCE

Institut Gustave Roussy, Villejuif, France

Background: The aim of this study was to describe how recurrences has been diagnosed in the largest series of patients treated for advanced-stage serous borderline ovarian tumors.

Methods: From 1969 to 2006, 45 patients with a serous borderline and peritoneal implants recurred out of the 162 patients with a follow up > 1 year. Datas about recurrences and its mode of diagnosis were reviewed.

Results: The median duration of follow-up was 98 months (range, 19-286). The mode of diagnosis was imaging (n = 19), clinical symptoms (n = 8), rising CA125 level (n = 7), a secondary surgery (n = 5) and unknown (n = 6). The median time-to-recurrence was 31 months (range, 4-242). Type of recurrence was invasive disease for 14 patients. Five patients died of their recurrence. Among the 39 patients with identified mode of diagnosis, the most frequent diagnostic tool of invasive recurrence was raised CA125 blood (6/13) and majority of non invasive recurrences was diagnosed by imaging (16/23).

Conclusions: This study demonstrates that ultrasounds is the most relevant procedure for the follow-up in this context. Nevertheless, the CA125 blood test has an interest, particularly to point out invasive recurrent diseases, which are the most crucial event to detect.
PROGNOSTIC FACTORS OF A LARGE SERIES OF PATIENTS WITH SEROUS BORDERLINE TUMORS OF THE OVARY AND PERITONEAL IMPLANTS


Institut Gustave Roussy, Villejuif, France

Background: To determine prognostic factors in a large series of patients with stage II or III serous low malignant potential ovarian tumor (LMPOT) and peritoneal implants.

Methods: A retrospective review of patients with a serous LMPOT and peritoneal implants treated or referred to our institution. The slides of ovarian tumors and peritoneal implants were reviewed by the same pathologist.

Results: From 1969 to 2006, 168 patients were reviewed, 21 of whom had invasive implants. Tumors exhibited a micropapillary pattern in 56 patients. Adjuvant treatment had been administered to 61 patients. The median duration of follow-up was 57 (range, 1-437) months. Forty-four patients had relapsed and 10 patients had died. Five year overall survival of patients was 98%. Among patients with noninvasive and invasive implants, 8% and 10% respectively relapsed at 5 years in the form of invasive disease (p=0.08). In the multivariate analysis the use of conservative treatment was the only prognostic factors.

Conclusions: The prognosis of serous LMPOT with peritoneal implants remains good. The strongest prognostic factor in patients with an advanced-stage borderline tumor is the use of conservative surgery. In this series, a micropapillary pattern and implant subtypes (invasive vs noninvasive) were not prognostic factors.
PROGNOSIS AND PROGNOSTIC FACTORS OF THE MICROPAPILLARY PATTERN IN PATIENTS TREATED FOR ADVANCED STAGE SEROUS BORDERLINE TUMORS OF THE OVARY


Institut Gustave Roussy, Villejuif, France

Background: To determine the prognosis of a micropapillary (MP) pattern in patients with advanced-stage serous borderline tumor of the ovary (SBOT).

Patients and methods: Retrospective review of patients with advanced-stage SBOT treated or referred to our institution with characterization of MP pattern and its clinical impact.

Results: From 1969 to 2006, 168 patients were reviewed. Fifty-six patients had SBOT-MP. The rate of conservative surgery was lower in the SBOT-MP group compared to the typical SBOT group but the rate of patients with > 3 peritoneal sites with implants was higher in the SBOT-MP group. The rate of invasive implants was not statistically different between the two groups. Eighteen recurrences were observed (6 of them under the form of invasive disease) in the SBOT-MP group. Only one death was observed. Overall survival and recurrence-free interval were similar in both groups. The only prognostic factor for recurrence in the SBOT-MP group was the use of conservative surgery.

Conclusions: In the present series, MP pattern doesn't appear to signify a poor prognosis. The only prognostic factor for recurrence in SBOT-MP was the use of conservative surgery. Further studies on MP pattern are needed to evaluate prognosis and results of conservative surgery.
LNA MODIFIED OLIGONUCLEOTIDES TARGETING MRNA-DICER IN PEGYLATED COLLOIDAL NANOPARTICLES WITH LINKED ABS AGAINST CD44 ERADICATE OVARIAN CANCER STEM CELLS (OCSCS)

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Introduction: Metastatic Ovarian Ca is incurable due to chemoresistance caused by cancer stem cells due to overexpression of oncomirs which upregulate oncogenes and hypermethylation in CpG islands which inactivates tumour suppressor genes.

Methods: We obtained metastatic ovarian Ca and CSCs from patients and we injected them in xenograft animal models which were treated with LNA oligonucleotides targeting DICER where the 2'-Oxygen is bridged to the 4' position via a methylene linker leading to formation of a rigid bicycle locked into a C3 endo (RNA) sugar conformation encapsulated in PEG colloidal nanoparticles with linked Abs targeting CD44. Microarray, RT-PCR, IHC, flow cytometry, MTT, BrdU, TUNEL, and TEM were used.

Results: There was inhibition of Dicer RNAIII endonuclease which blocked exportin5 cleavage blocking formation of mature oncogenic miRNA segments. This inhibition of oncomirs led to silencing of oncogenes such as transcription factors, apoptotic inhibitors, chromatin modifiers, growth factors (tyrosine kinases-integral membrane proteins), signal transducers (cytoplasmic regulators, membrane associated G-proteins, GTPase exchange factors, and serine/threonine kinases). Dicer silencing led to inhibition of angiogenesis, invasion, metastasis, ovarian Ca and CSC proliferation by inhibiting stem cell pathways Bmi-1, Notch, SHH and Wnt. There was inhibition of hypermethylation of CpG islands reactivating apoptotic tumour suppressor genes inducing irreversible D2 stage of type I PCD/apoptosis which led to a bystander killing effect. BrdU and MTT exhibited inhibition of DNA synthesis and metabolic activity of ovarian Ca and CSCs.

Conclusion: Silencing of DICER exerted a synergistic apoptotic effect by activation of tumor suppressor genes after demethylation, and inhibition of oncomirs and linked oncogenes leading to eradication of chemoresistant CSCs and metastatic ovarian Ca.
ADMINISTRATION OF GENE-MODIFIED-CELLULAR-VACCINE COMPOSED OF AUTOLOGOUS-ADIPOSE-DERIVED MESENCHYMAL-STEM-Cells TRANSFECTED WITH LIPID-CATION-HSP70 ACTIVATES INNATE AND ADAPTIVE IMMUNITY ERADICATING METASTATIC OVARIAN CARCINOMA

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Introduction: Metastatic ovarian Ca leads to fatalities due to resistance in conventional anticancer therapies.

Methods: Animal models characterized by metastatic ovarian Ca refractory to conventional treatment were developed and treated with IV administration of the Gene-Modified Cellular Vaccine (GMCV) termed as SV/AS2 (under patent), which is composed of Autologous Adipose-derived Mesenchymal Stem Cells (AADMSCs), which were transfected with lipid-cation immunodominant molecule Hsp70.

Results: Post-treatment, we observed molecular remission in all tumor/metastatic sites, and activation of CD4+ T-cells by antigen presenting cells (APC), enhancement of MHC class I expression, generation of tumor-specific cytotoxicity with CTLs induced by the antigenic fingerprint/repertoire, activation of natural-killer (NK) cells, generation of peptide-specific tumor immunity induced by CD91 and C19 overexpression on dendritic cells (DCs), CD40 on macrophages, and LOX-1, CD14 and TLR2-4 on monocytes. Furthermore, hsp70 induced Th1-type immune response inducing secondary necrosis, which is the most potent immunogenic mode of cell death, and phagocytosis of tumor cells by activated macrophages leading to a lethal bystander effect. Finally, we observed repair of damaged tissue, and organs by renewal of injured cells.

Conclusions: The Gene Modified Cellular Vaccine (GMCV) consisting of autologous adipose mesenchymal stem cells expressing Hsp70 activated the innate and adaptive immunity leading to eradication of metastatic ovarian Ca cells, and there was stem cell renewal of injured cells.
RELAPSE OF DYSGERMINOMA DURING PREGNANCY

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Case report: We present what we believe to be the first report of relapse of a previously diagnosed and treated dysgerminoma during pregnancy. Our patient was diagnosed with stage 1A dysgerminoma in 2005 and underwent fertility-sparing surgery. She became pregnant in early 2008. Massive intra-abdominal relapse of her tumour was detected at gestational week 29 (figure). Spontaneous delivery of a healthy baby occurred the following week. Despite significant complications including renal failure and hypotensive shock, she underwent successful salvage chemotherapy with cisplatin, etoposide and bleomycin, and both mother and child remain alive and well.

Discussion: With the increasing adoption of fertility-preserving surgery followed by surveillance for early stage dysgerminoma, it is likely that relapse during pregnancy will become more common in the future. Issues regarding optimal surveillance of a gravid patient, including the limitations of tumour marker assessment during pregnancy are discussed. Whereas AFP and bHCG are essentially uninformative during pregnancy, a rise in LDH should alert the clinician to the possibility of relapsing tumour. Treatment options and, in particular, the literature regarding chemotherapy administration for ovarian germ-cell tumours during pregnancy are reviewed.

[Figure]
COLLOIDAL-CDNA ENCODING RECOMBINANT PROTEINS-RMDVA COMPRISING DISINTEGRIN/CYSTEINE-RICH-DISULFIDE BOND 2RGD, AND C-TERMINAL DOMAIN, METALLOPROTEASE-DOMAIN, AND DIMERIC DISINTEGRIN/MLD-VGD DOMAIN (VADD) INDUCED APOPTOSIS IN OVARIAN CA

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Introduction: We investigate if venom proteome of vipera ammodytes can induce apoptosis in ovarian Ca.

Materials and methods: We developed a large scale expression system with ovarian cell line (OCL), which we modified genetically by cloning. We expressed cDNA encoding multimodular disintegrin (rMDVA) comprising 3 domains from the venom of vipera ammodytes. The cDNA of rMDVA was cloned into the plasmid vector pcDNA III, which was transferred into OCL. The multimodular peptide rMDVA was encapsulated in the hydrophilic phase of liposomes termed as LIP-rMDVA. The in-vivo studies with human metastatic ovarian Ca were performed in an orthotopic xenograft model.

Results: The venom proteome contained 140 proteins. We isolated the multimodular disintegrin displaying cysteine rich disulfide bond 2RGD, and C-terminal motif (ammodystatin), the dimeric MLD/VGD motif (VADD) and metalloprotease-domain (ammodylsin). Ammodystatin with the 2 (ARG-GLY-ASP) RGD motifs interacts with integrins avb5, a5b1 inhibiting invasion, angiogenesis/vasculogenesis and blocked the bFGF-induced avb3 integrin, and avb5 downregulating VEGF. It also disrupts the actin cytoskeleton inducing G1 DNA replicative phase arrest, and blocks endothelial cell (EC) secretion of MMP-2, MMP-9, and urokinase type plasminogen activator with its receptor inhibiting proteolysis, and dissolution of ECM blocking invasion. Ammodystatin and ammodylsin lead to type I PCD/apoptosis of tumor cells in masses up to 2 mm, and EC. Beyond that size, ammodystatin inhibits the development of the required vascular network according to HUVEC, MVD, and IHC. VADD causes burring and blocked adhesion of a4b1 integrin to VCAM1. LDH, BrdU and MTT exhibited inhibition of tumor and EC proliferation. TEM exhibited apoptotic signs of irreversible D2 stage in tumor and ECs.

Conclusion: Novel liposomal formulation LIP-rMDVA is an effective angiostatic, and cytostatic agent against metastatic ovarian Ca minimizing systemic toxicity.
TREATED OVARIAN CANCER PATIENTS WITH GENERIC PACLITAXEL, IS IT EFFECTIVE?


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Background and aims: As in the developing countries, generic paclitaxel in Thailand is commonly administered to treat ovarian cancer combined with carboplatin in carboplatin & paclitaxel (PT) regimen as adjuvant setting. With the question that if this worked as the original one or not, we conducted the retrospective study to analyze the outcome of ovarian cancer patients treated with generic paclitaxel in our center.

Methods: Between January 2004 and December 2008, the medical records of ovarian cancer patients treated with generic paclitaxel and carboplatin were reviewed. The clinical characteristics, the outcome of treatment and the survival were analyzed.

Result: A total of 168 patients were identified. The patients were in stage I,II,III,IV as 63(37.5%),23(13.7%),65(38.7%) and 17(10.1%) , respectively. Only 33% of the studied patients were underwent complete surgical staging procedure. The patients received neoadjuvant in 17%. The most common histology was clear cell CA (35.1%) followed by serous cystadenocarcinoma (33.3%) and endometrioid CA (16.7%). The response rate was 85.1% (complete response = 60.7%, partial response =24.4%). Fifty-nine patients (35%) were recurrence. The 5-year progression free survival and overall survival rate were 35.4 % and 51.0%, respectively. In advanced stage, the median overall survival rate was 32 months. This outcome was corresponding to the outcome in the previous reports that using the original paclitaxel.

Conclusion: The outcome of patients who received generic paclitaxel in PT regimen seems to be response and gives the survival rate rather well.
EXPRESSION OF COX-2 ENZYME IN PLATIN SENSITIVE AND RESISTANT OVARIAN CANCER PATIENTS

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Background and aims: To investigate the effects of cyclooxygenase-2 (COX-2) expression on platin sensitivity or resistance and prognosis in ovarian cancer.

Materials and methods: Seventy four epithelial ovarian cancer patients were enrolled in the study. After primary surgery, ≤1 cm residual tumor was accepted as optimal and >1 cm residual tumor was accepted as suboptimal. Patients received 6 cycles of platin based chemotherapy. Patients who recurred within the first 12 months after chemotherapy were accepted as resistant to platin therapy. Immunohistochemical methods were used for detection of COX-2 expression.

Results: COX-2 was positive in 18 (47%) of 38 chemosensitive and 22 (61%) of 36 chemoresistant patients. In chemoresistant group, COX-2 tended to be more expressed however this remained insignificant (p=0.254). Logistic regression analysis revealed that stage was the only parameter which affected chemotherapy response. Overall survival did not differ significantly between COX-2 positive and negative patients in both univariate (p=0.166) and multivariate analyses (p=0.34). On the other hand, there was no significant survival difference between COX-2 positive and negative patients in optimal surgery group (p=0.305); although COX-2 positive patients were found to live significantly shorter compared to COX-2 negative patients in suboptimal surgery group (p=0.043).

Conclusion: Expression of COX-2 does not determine the response to platin based chemotherapy in ovarian cancer patients. COX-2 expression has no benefit on prediction of overall survival in optimally cytoreduced patients.
COMPARISON OF SERUM YKL-40 AND CA125 IN THE EARLY DETECTION OF OVARIAN CANCER

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Objective: To compare the value of serum YKL-40 and CA125 in the early detection of ovarian cancer.

Methods: Experimental group consists of 49 patients including 42 epithelial ovarian cancer and seven borderline epithelial ovarian tumor. Control group consists of 36 women including 20 cases of benign disease and 16 healthy women. ELISA was used to measure serum YKL-40 and CA125 levels.

Results: Both the YKL-40 and CA125 levels were significantly increased in experimental group than that in the control group. The sensitivity and specificity of YKL-40 in the detection of epithelial ovarian cancer are 92.9% and 94.4%. CA125 has a sensitivity and specificity of 37.8% and 86.1% respectively. YKL-40 has a sensitivity and specificity of 78.6% and 94.4% in the detection of early ovarian cancer, these number for CA125 are 42.9% and 94.4%.

Conclusions: YKL-40 may act as a better marker than CA125 in the detection of ovarian cancer and its ability in the diagnosis of early ovarian cancer pursues further study.
COMPARISON OF FOUR RISK OF MALIGNANCY INDICES IN EVALUATION OF OVARIAN MASSES IN SINGAPORE

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Objectives: The aim of this study was to determine the value of the risk of malignancy index (RMI) as a triage tool at our hospital by evaluating the four risk of malignancy indices (RMI 1, RMI 2, RMI 3, and RMI 4) and to compare their specificity and sensitivity in discriminating a benign from a malignant ovarian mass.

Materials and methods: This was a 5 year retrospective study of 228 women aged 10 to 65 years of age admitted to the National University Hospital, Department of Obstetrics and Gynecology between November 2004 to October 2009 for laparotomy or laparoscopic surgery for ovarian masses. RMI scores were calculated based on standardized preoperative serum CA125 (cancer antigen 125) levels, ultrasound findings (U), menopausal status (M) and tumor size (S) based on ultrasound. Postoperative histopathologic diagnosis was regarded as the definite outcome. The data was analysed using SPSS Version 17 and the Mann Whitney U test was used to compare the individual RMI between benign and malignant cases.

Results: Our study showed no statistical difference of RMI 1, RMI 2, RMI 3 and RMI 4 between benign and malignant cases. Individual variables were analysed and showed significant difference of median CA125, and tumor size (p = 0.044 and p < 0.0005 respectively) between benign and malignant cases.

Conclusion: Although our study does not show RMI as a valuable method in triaging patients in our local hospital, RMI is still a potentially useful tool and would require further prospective validation.
THE GENE PROTEIN EXPRESSION OF ERCC1 AND SURVIVIN IN EPITHELIAL OVARIAN CARCINOMA

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Objective: To investigate expression of ERCC1 and survivin gene expression in platinum-resistant and platinum-sensitive epithelial ovarian carcinoma (EOC) and to reveal the correlation between the two gene expression and the major clinicopathological characteristics and platinum sensitivity.

Methods: Expression of ERCC1 and survivin gene protein were detected in 64 epithelial ovarian carcinoma tissues by immunohistochemistry. There were 28 platinum-resistant and 36 platinum-sensitive patients among them.

Results: There was an overall ERCC1 gene protein expression of 43.75%(28/64). The positive incidence of platinum-resistant patients' tissues was 67.85%(9/28) while in platinum-sensitive group it was 25.00%(9/36)(P=0.00). The expression of ERCC1 was not significantly correlated with age, FIGO stage, pathological type, histological grade, pelvic lymph node and/or vessel infiltration (P>0.05).

There was an overall survivin gene protein expression of 76.56%(49/64). The positive incidence of survivin gene protein expression in platinum-resistant group was 78.57%(22/28) while in platinum-sensitive group it was 75.00%(29/36)(P=0.74). The expression of ERCC1 was not significantly correlated with age, FIGO stage, pathological type, histological grade, pelvic lymph node and/or vessel infiltration (P>0.05). ERCC1 and survivin gene protein expression were not relevant to each other. (rs=0.12, P=0.36).

Conclusions: ERCC1 and survivin gene protein expression in EOC were independent with each other. Expression of ERCC1 gene protein might act a key role in the process of platinum resistance and survivin gene protein might be irrelevant to platinum resistance of EOC.
EVALUATION OF IL-10 AND TGF-BETA IN THE PLASMA AND PERITONEAL FLUID OF PATIENTS WITH ADVANCED OVARIAN CANCER

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Aim: The study determined interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) concentrations in the plasma and peritoneal fluid (PF) from 54 patients with epithelial ovarian carcinoma (EOC) and 33 women with benign tumor of the ovary.

Methods: IL-10 and TGF-β concentrations were determined by Immunoassay kit (ELISA).

Results: In patients with ovarian carcinoma (median 215.863 pg/ml) and in patients with benign ovarian tumor (median 30.151 pg/ml) the IL-10 level was significantly higher in the PF than in plasma (median 28.952 pg/ml vs 14.487 pg/ml). The PF and plasma IL-10 level was significantly higher in EOC than in benign ovarian tumor patients. Although TGF-β levels were detected in the PF of all ovarian cancer patients, these levels were significantly lower when compared with plasma samples (median 5.67 and 8.68 ng/ml). The PF TGF-β levels in patients with benign ovarian tumors were also significantly lower than those in plasma (median 3.16 and 6.81ng/ml). PF levels of TGF-β were significantly higher (median 5.67 ng/ml) in EOC patients compared with the reference group (median 3.16 ng/ml). Plasma levels of TGF-β did not differ significantly between studied groups.

Conclusion: Ovarian carcinoma cells are able to synthesize and secrete IL-10. The observation that plasma levels of TGF- β are higher than those detected in the PF suggest that cells other than tumor cells are responsible for TGF- β release in the bloodstream of these patients.

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OVARIAN MASSES IN CHILDREN AND ADOLESCENTS IN CHINA: ANALYSIS OF 203 CASES

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Objective: The true incidence of ovarian tumors in children is unknown. Few studies beyond case reports and case series have been published concerning pediatric ovarian tumors. Herein we review a large number of ovarian tumor cases.

Methods: The charts of 203 patients who presented with adnexal masses were reviewed.

Results: The patient's ranged in age from 2 to 18 years (mean = 15.6 years), with 30 being premenarchal (14.8%). The main complaint was abdominal pain or abdominal distension in 117 patients (57.7%). A high AFP level in a pre-pubic girl with an adnexal mass is indicative of a malignant ovarian tumor. The 214 adnexal masses (11 patients had bilateral cysts) consisted of benign tumorous oophoropathy (107 masses, 50.0%), borderline and malignant tumors (29 masses, 13.6%), and nontumorous oophoropathy (78 masses, 36.5%). Of the 136 neoplasia, germ cell tumors accounted for 71.5%. Surgical intervention was performed in 98.5% of cases. There were decreased blood loss, surgery duration and days of hospitalization with the laparoscopic procedure when compared with an open surgery.

Conclusions: The incidence of ovarian tumor increases with age, especially in patients older than 14 years. Abdominal pain is the most common complaint in young patients with adnexal masses. AFP is the most useful diagnostic biomarker of ovarian tumors in young females. Laparoscopic resection of ovarian cysts is a safe operative approach.
DIFFERENTIATION BETWEEN PRIMARY AND SECONDARY MUCINOUS OVARIAN TUMORS
BY AN ALGORITHM USING THE NOVEL MARKER DPEP1

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Distinguishing primary mucinous ovarian cancers (MOC) from ovarian metastases of digestive organ cancers (DO-meta) is often challenging. We tried to make an algorithm for discriminating between them. By the analysis of a gene expression microarray (GSE2109), Dipeptidase 1 (DPEP1) was selected as the candidate novel marker of colorectal cancer (CRC). Next, five immunohistochemical markers (DPEP1, ER, CK7, CK20, and CDX2) were analyzed in combination. Finally, the five immunohistochemical markers were combined with six preoperative factors (patient's age, tumor size, laterality, serum CEA, CA19-9, and CA125) and combinations were analyzed. Immunohistochemical analysis indicated that 13/16 ovarian metastases of CRC, but only 1/58 MOC, were DPEP1 positive (threshold; ≥25% expression, $p<0.0001$). In a hierarchical clustering analysis, the mutually exclusive expression of CK7 and DPEP1 specifically identified the ovarian metastases of CRC ($p<0.0001$). In a decision tree analysis, CK7, CDX2, and DPEP1 classified MOC and DO-meta with 90% accuracy. Of the eleven factors, four (DPEP1, CK7, CDX2, and tumor size) were used to generate a decision tree to classify MOC and DO-meta with 93% accuracy. In conclusion, we identified a novel immunohistochemical marker, DPEP1, to distinguish MOC from ovarian metastasis of CRC. The algorithm using immunohistochemical and clinical factors to distinguish DO-meta from MOC will be useful to establish a protocol for the diagnosis of ovarian metastasis.
THE EFFECT OF ENDOSTATIN MEDIATED BY HUMAN MESENCHYMAL STEM CELLS ON OVARIAN CANCER CELLS IN VITRO

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Introduction: Endostatin is the most potent inhibitor of tumor angiogenesis. However, endostatin protein has a short half-time and virus-mediated endostatin gene therapy has serious toxicity, which limits the application of endostatin in clinical therapy. Mesenchymal stem cells (MSCs) are considered to be able to accumulate at the site of cancers with high specificity and may be used as a new delivery of endostatin.

Materials and methods: The MSCs from the human bone marrow were transfected with recombinant adenovirus encoding endostatin and EGFP (MSC-EN cells). The tropism capacity of MSCs was quantitatively assayed in vitro using the Millicell system. To investigate the impact of secreted endostatin on cancer cells, SKOV3 cells were cocultured with MSC-EN cells in Millicell for 48 h, then apoptosis and cell cycle were analyzed on a flow cytometer.

Results: In contrast with 293 cells and saline, SKOV3 cells significantly stimulated migration of MSCs, the number reached 919.67 ±19.96 (P < 0.05). The endostatin produced by MSC-EN cells made 13.08 ± 0.21% SKOV3 cells undergo early stage apoptosis (control 3.23 ± 0.73%, P < 0.05) and 82.05 ± 2.65% SKOV3 cells accumulate in the G0/G1 phase (control 66.51 ± 2.91%, P < 0.05).

Conclusion: We found that MSCs possessed great migratory capacity in vitro and the human ovarian adenocarcinoma cell line SKOV3 could significantly induce the migration of MSCs. Our results provided evidence that MSCs could be utilized as a powerful delivery system of endostatin. The endostatin produced by MSC-EN cells could inhibit the proliferation of SKOV3 cells.
RISK OF MALIGNANT INDICES TO DETECT MALIGNANT PELVIC MASSES IN THE PREOPERATIVE EVALUATION


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Background: The preoperative determination of malignant pelvic mass has been considered as important prognostic factors. We developed Korean version of RMI in 2005. The aim of this study was to validate the RMIkr and compare it to other RMIs to predict malignancy in an adnexal mass by applying the models to Korean data.

Methods: We recruited 327 patients who were diagnosed and received surgery from 2004 to 2008 at Hanyang university hospital. We analyzed age, menopause, a level of CA125, tumor size and ultrasound findings.

Results: Of 379 patients, 66(20.2%) had malignant and borderline disease and 261(79.8%) had benign pathology. The mean age of the patients with malignant disease was 44.6±2.08 years and 39.2±0.90 years in benign disease. The AUCs of the RMIs ranged from 0.86-0.89. RMI 4 showed highest AUC value (AUC 0.89, 95%CI 0.85-0.94) and the RMIkr showed lowest AUC value (AUC 0.86, 95%CI 0.80-0.92). The RMIkr using Sassone`s ultrasound scoring had higher level of sensitivity and lower level of specificity than other RMIs using Jacobs` scoring system (84.8%, 65.5% vs. 57.6~62.1%, 94.6~96.6%). RMIkr could detect all the epithelial cancer with stage II-IV, non-epithelial cancer and metastatic cancer. However, the detection rate (%) of Epithelial cancer stage I and borderline tumor were 70% and 60% respectively.

Conclusion: RMIkr is simple and useful in patients with pelvic mass. However, it has a tendency to refer more benign masses to specialist than other RMIs. Therefore, evaluation of new Korean version of RMI including various ultrasound scoring systems could be considered.
THE CUT-OFF VALUE INVESTIGATION OF SERUM CA125 FOR EVALUATING THE DISEASE RECURRENCE OF THE EPITHELIAL OVARIAN CARCINOMA

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Background: According to clinical follow-up, when CA125 is ≤35U/ml, some postoperative patients of the epithelial ovarian carcinoma are already recurrent.

Aims: To investigate the cut-off value of CA125 for evaluating the disease status of the postoperative recurrence of the epithelial ovarian carcinoma.

Methods: We retrospectively analyzed 170 postoperative patients of epithelial ovarian carcinoma, including 135 cases of catabatic and 35 cases of recurrent patients, 105 cases of menopause women and 65 cases of the postoperative patients of gynecological malignant tumor except the epithelial ovarian tumor chosen as control group. Use the 5U/ml, 10U/ml, 15U/ml, 20U/ml, 25U/ml, 30U/ml, 35U/ml as the cut-off value to compare their sensitivity, specificity, positive predictive value, negative predictive value.

Results: The median value of CA125 for menopause women and the postoperative patients of gynecological malignant tumor is 8.4U/ml, 6.9U/ml; X±S is 9.1±4.2U/ml, 7.3±2.6U/ml. When use 35U/ml as the cut-off value, although the specificity is 100.0%, the sensitivity is only 40.0%. The cut-off value of 15 U/ml produced the following results: 74.3% sensitivity, 97.0% specificity.
CAN CADET (CANCER RISK EVALUATION & EARLY DETECTION) SOFTWARE IDENTIFY ABNORMAL OVARIAN FINDINGS AS A TOOL FOR OVARIAN CANCER SCREENING?

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Objective: This pilot study aimed to assess the use of a modified ovarian cancer focused CADET score and abnormal ultrasonographic ovarian findings in order to define the usability of the CADET score as a preliminary screening tool for ovarian cancer by general gynecologists.

Methods: This is a prospective study including 181 peri and post-menopausal women who attended their gynecologist for a routine check-up. All women were asked to fill the CADET questioner before seeing their gynecologists who were blinded to the CADET results. 154 women were sent by the treating physician to perform pelvic trans-vaginal ultrasonographic examination as part of the check-up. The results of the scan were compared with the CADET score.

Results: In 38 of the 154 women (24%) ultrasonographic exam revealed an abnormal ovarian finding - 30 simple cysts and 8 complex adnexal findings (group A). 76% of women had no abnormal sonographic findings (group B). Demographic characters were similar in both groups. 34% of women in group A and 45% of women in group B had positive CADET score (P=non significant). Average CADET score in the two groups was also not significantly different (0.8 + 1.7 in group A and 1.7 + 2.5 in group B, P=NS).

Conclusion: CADET score did not correlate with abnormal ultrasonographic ovarian findings. However, the group with positive score may prove to be at a higher risk to develop ovarian cancer despite the lack of ovarian findings at this stage, and need close follow-up.
PROGNOSTIC IMPACT OF CONCOMITANT P53 AND PTEN ON OUTCOME IN EARLY STAGE
(FIGO I-II) EPITHELIAL OVARIAN CANCER (EOC)

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Aims: Patients with early stages of EOC have a 75% 5-year survival. Different biological behavior of the tumor could explain different survival between clinically similar cases. The prognostic impact of the apoptosis regulators p53 and PTEN together in EOC was evaluated.

Methods: In a series of 131 patients the clinical outcome in relation to p53 and PTEN were evaluated after primary surgery and chemotherapy. Tissue-microarray and IHC were used. The monoclonal antibody DO-7 for p53 and PTEN/MMAC1 for PTEN were used.

Results: Positive staining for p53 and PTEN were found in 25% and 22% of cases, respectively. In total series recurrent disease was found in 33/131 (25%) patients after a mean follow-up time of 65 months. DFS was 68.0%. The p53-status was associated with tumor grade and DFS. The PTEN-status alone was not associated to any of the factors analyzed. However, in concomitant analyses for p53 and PTEN in four subgroups, 12/22 (54%) recurrences were found in the second subgroup of patients whose tumors had concomitant p53-positivity and PTEN-negativity compared to 4/11 (36%) recurrences in the first subgroup whose tumors had positivity for both. In survival analysis DFS in the second group (N=22) was worse (p=0.006) compared to others (N=109) (figure 1). In separately Cox multivariate regression analysis both p53 (OR=2.60) and p53PTEN (OR=0.47) were significant and independent prognostic factors for DFS.
Conclusion: PTEN expression status divided 53 positive tumors in two distinct groups after prognosis in this study.
MECHANISMS OF DYSREGULATION OF EFEMP1 AND CDKN1C IN EPITHELIAL OVARIAN CARCINOMA

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Background: EFEMP1 codes for Fibulin3, a secreted glycoprotein that mediates cell-to-cell communication and antagonizes angiogenesis. EFEMP1 is inactivated by promoter hypermethylation in lung cancer. CKDN1C(p57) negatively regulates the cell cycle and is a recognized tumor suppressor gene. We recently identified a decrease in EFEMP1 and CDKN1C gene expression in BRCA1 mutated normal fallopian tube epithelium and in BRCA1 ovarian carcinomas. We assessed a series of hereditary and sporadic ovarian cancers for somatic mutations in these 2 genes, as well as EFEMP1 promoter hypermethylation, RNA and protein expression.

Methods: Forty-seven ovarian carcinoma samples were analyzed for mutations in EFEMP1 and CDKN1C. EFEMP1 promoter hypermethylation was assessed by methylation-specific PCR, RNA expression was measured with RT-PCR, and Fibulin3 protein expression with immunohistochemistry.

Results: For EFEMP1 there was one somatic missense mutation (Val>Leu) and one silent mutation (Ser>Ser) identified in the coding sequence that were not present in paired normal DNA. For CDKN1C, one somatic missense mutation (Pro>Ser) and 2 silent mutations were identified. Twenty-one [21/47(45%)] showed evidence of hypermethylation within EFEMP1 promoter. However, EFEMP1 promoter hypermethylation did not correlate with decreased EFEMP1 RNA expression or Fibulin3 protein expression and was observed in normal tissues.

Conclusions: Deleterious somatic mutations of EFEMP1 and CDKN1C were infrequent in ovarian carcinomas and did not explain the decreased expression observed in BRCA1 carcinomas. EFEMP1 promoter hypermethylation was frequently identified, but does not explain the expression differences given the lack of correlation with RNA/protein expression. We are currently evaluating alternative epigenetic mechanisms of EFEMP1 and CDKN1C expression.
LEPTIN RECEPTORS EXPRESSION IN NEOPLASTIC AND NORMAL OVARIAN AND ENDOMETRIAL TISSUE

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Background and aims: Leptin receptors have been incriminated for cancer growth. The objective of this study was to investigate the expression of leptin receptors in benign and malignant tumours of ovaries and endometrium.

Materials and methods: Histological samples from 37 patients aged 37-72 years were collected between years 2004-2007. The examination of preparations for the expression leptin receptors was made with the method of RT-PCR. The study included 35 samples, which were eventually suitable for evaluation.

Results: The majority of neoplasms were adenocarcinomas and serous neoplasms. Uterine neoplasms were correlated statistically significantly with higher BMI values, compared with ovarian ones. A BMI >30 was correlated with increased expression of leptin receptors. Both Ra and Rb receptors were expressed in normal and neoplastic tissues. A statistically significant difference in leptin receptors expression was detected between normal and neoplastic tissue, with expression being around 5-fold higher in neoplastic tissue. A statistically significant difference was also traced in normal tissue Rb concentrations depending on BMI.

Conclusion: Endometrial neoplasms were associated with an increased BMI and obesity was associated with increased expression of long leptin isoform receptor in normal tissue. In neoplastic tissue a marked increase in ObR-b was observed. These results support an important role of long isoform in endometrial carcinogenesis.
WOMEN WITHOUT OVARIAN CANCER WHO REPORT DISEASE-SPECIFIC SYMPTOMS

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Background: We recently examined symptom patterns reportedly related to the presence of ovarian malignancy and found them to be absent in 80% of ovarian malignancies (Cancer 2009;115:3689-98). The present studies examine women without ovarian cancer who report disease-specific symptoms.

Methods: 13569 women were recruited from 35,000+ women enrolled in the ovarian screening program and completed the symptoms evaluation between April 2008 and May 2009 during their screening appointment. These women remained free of an ovarian cancer diagnosis for at least 12 months of follow-up to May 2010. Symptom results were correlated to ultrasound as well as to clinical/demographic characteristics.

Results: Of the 13189 women considered to be free of malignancy, 380 reported disease-specific symptoms. Disease-specific symptoms decreased with age >60yrs, but increased with weight & BMI and were not significantly different in normal vs abnormal TVS findings (p< .05). However, an abnormal finding associated with an ovarian volume >10cm³ was 27X more likely to be accompanied by reports of disease specific symptoms than when the volume was < 10cm³. Pre-menopausal women reported pelvic pain 2X more than postmenopausal women. 88.9% reporting a disease-specific symptom also reported other symptoms so that coincident disease-specific & disease nonspecific reporting was frequent.

Conclusions: Disease-specific symptoms are reported by women who do not have ovarian cancer at a rate that is 50-60X higher than the estimated prevalence of ovarian cancer. Weight, pre-menopausal status, large ovarian volumes, and coincident nonspecific symptoms reports are most associated with disease-specific reporting in women that do not have ovarian cancer.
HI-CON1, A FACTOR VII-IGGFC CHIMERIC PROTEIN TARGETING TISSUE FACTOR, FOR IMMUNOTHERAPY OF CHEMOTHERAPY RESISTANT OVARIAN CARCINOMA

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Objective: To evaluate the expression of Tissue Factor (TF) in ovarian carcinoma and the potential of hi-con1, an antibody-like-molecule targeted against TF, as a novel form of immunotherapy against chemotherapy resistant ovarian cancer.

Methods: Sixty-three fresh-frozen ovarian tumors including 30 serous (OSPC), 14 clear cells (CC), 12 endometrioid (END) and 7 undifferentiated (UND) carcinomas were tested by real-time-PCR for TF expression. Sensitivity to hi-con1-dependent-cell-mediated-cytotoxicity (IDCC) was evaluated in 5-hrs ⁵¹chromium-release-assays against multiple chemotherapy resistant ovarian cancer lines in vitro. To investigate the effect of interleukin-2 (IL-2) on IDCC, 5-hrs ⁵¹Cr-release-assays were also conducted in the presence of low doses of IL-2 (50 IU/ml).

Results: Ovarian carcinomas with CC histology significantly over-express TF (mean ±SEM = 20.4±6.5, range 0.1-80.5) when compared to OSPC (1.4±0.2, range 0.08-4.1, p< 0.0001), to END (1.7±0.3, range 0.1-3.8, p=0.01) or to UND tumors (2.4±0.8, range 0.3-6.9, p=0.01). All primary ovarian cancer cell lines tested overexpressing TF, regardless of their resistance to chemotherapy or histology, were highly sensitive to IDCC (mean killing ± SD, 50.1% ± 10.5%, range, 33.0%- 60.0%, P< 0.001), while negligible cytotoxicity was seen in the absence of hi-con1 or in the presence of Rituximab-control-antibody. The addition of low doses of interleukin-2 increased the cytotoxic-effect induced by hi-con1 (P< 0.001).

Conclusion: TF is highly expressed in ovarian carcinomas, particularly in tumors with CC histology. HI-con1 induces strong cytotoxicity against primary chemotherapy resistant ovarian cancer cell lines overexpressing TF and may represent a novel therapeutic agent for the treatment of ovarian tumors refractory to standard treatment modalities.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

MICRORNA EXPRESSION PATTERN OF HUMAN AGING WITH HISTOTYPES OVARIAN CANCER

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MicroRNAs (miRNAs) are a new class of small noncoding RNAs that regulate gene expression at post-transcript stage. Although miRNAs have been implicated a causal role in tumorigenesis, little is known about miRNAs that underlies in huamn aging ovarian cancer. Ovarian adenocarcinomas(OAC) occur as four major histologic subtypes, serous, mucinous, endometrioid, and clear cell, with serous being the most common, but clear cell causing the highest mortality. To investigate the molecular genetic effect of aging on OAC histotypes, in particular, the specific miRNAs that underlie OAC mortality, we defined human genome-wide miRNA expression profiling in a large set of human clear cell and serous OAC tissues by using TaqMan Real-Time PCR-miRNA array from ABI, and the data were analyzed by StatMiner software (ABI). The results showed that: in comparison to serous OAC at patients ages between 50 and 75 years, miRNAs are differently expressed in clear cell OAC. The overall miRNA expression could clearly separate subtype of clear cell versus serous. The most significantly up-regulated miRNAs were miR-507, miR-30a*, miR-30c-2*, miR-30e*, and miR-505*, whereas miR-589*, miR-942, miR-548a, and miR-130a* were among the most down-regulated miRNAs. Our data indicate that miRNA profiles may not only aid in discriminating between different ages with histotypes OAC, but may also represent novel therapeutic targets for patients with chemo-resistant disease.

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RISK OF MALIGNANCY INDEX IN EVALUATION OF PELVIC MASSES

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Background and aims: The aim of this study was to evaluate the use of a Risk of Malignancy Index (RMI) based on a serum CA125 level, ultrasound findings and menopausal status in primary evaluation of patients with adnexal masses in daily clinical practice.

Methods: Between October 2008 and November 2009, one hundred and fifty one women with adnexal masses were enrolled. Ultrasound characteristics, menopausal status and serum CA 125 level were registered preoperatively, and combined into the RMI afterwards. The sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of the RMI in prediction of ovarian cancer were calculated. Final diagnosis was based on routine histopathologic examination.

Results: The RMI identified malignant cases more accurately than any individual criterion in diagnosing ovarian cancer. Using a cut-off level of 238 to indicate malignancy, the RMI showed a sensitivity of 89.5%, a specificity of 96.2%, a PPV of 77.3%, a NPV of 98.4% and an accuracy of 95.4%.

Conclusions: RMI is a simple, easily applicable method in the primary evaluation of patients with adnexal masses with high risk of malignancy and forwarding to gynecological oncology centers and centralized primary surgery for suitable surgical operations. At the same time, referral of patients with non-invasive (benign and borderline) lesions would be reduced.

Keywords: Pelvic masses, Preoperative evaluation, Ovarian cancer, Risk of Malignancy Index
EXTRAOVARIAN CONDITIONS MIMICKING OVARIAN CANCER - A SINGLE CENTER EXPERIENCE OF 15 YEARS

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Objective: The present study aims to review cases of extra-ovarian conditions that resembled ovarian malignancy and thus, to evaluate the distribution of primary pathology mimicking ovarian malignancy.

Methods: A retrospective review of women, with final pathology of extra-ovarian diseases mimicking ovarian malignancy, which were managed at Zekai Tahir Burak Women's Health Education and Research Hospital, from January 1995 to April 2010 was undertaken.

Results: Among the 2210 women treated during the study period, extra-ovarian diseases accounted for 5.11% (113/2210) of all cases. Of the 113 extra-ovarian diseases, 42 (37.17%) were peritoneal tuberculosis, 25 (22.13%) were gastrointestinal malignancies, 20 (17.70%) were pelvic abscess, 8 (7.08%) were pelvic echinococcosis, 8 (7.08) were schwannoma and other retroperitoneal tumors, 4 (3.53%) were malignant lymphoma, 2 (1.77%) were chronic ectopic pregnancy, gossypiboma, and mesenteric cyst, respectively.

Conclusion: Medical awareness of infectious diseases such as peritoneal tuberculosis, pelvic abscess and pelvic echinococcosis in the differential diagnosis of ovarian malignancy is still lacking, especially in developing countries. In addition, in case of a pelvic mass, gastrointestinal and retroperitoneal tumors and malignant lymphoma should always be considered to avoid pitfalls in diagnosis and therapy.
MICRORNA-31 MODULATES SENSITIVITY TO PACLITAXEL IN AN OVARIAN CANCER CELL LINE

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MicroRNAs (miRNAs), which is critical and essential for many important processes such as development, differentiation, and carcinogenesis, has been reported to regulate the chemosensitivity of tumor cells. We performed miRNA microarray to screen aberrant expression of miRNAs which might some roles in resistance to paclitaxel (TX) in ovarian cancer cells. Among aberrantly expressed miRNAs, we focused on the expression and function of miRNA-31 (miR-31), which is one of the most down-regulated miRNAs in TX-resistant ovarian cancer cells compared with parental cells in our miRNA microarray. Quantitative RT-PCR verified the down-regulation of miR-31 in TX-resistant cells compared to control cells. Cell viability assay, MTT assay, and FACS analysis revealed that ectopic expression of miR-31 significantly increased apoptotic outcome in response to TX in TX-resistant cells. Two dimensional gel electrophoresis followed by silver staining revealed differential expression of proteomic profile between control and miR-31-overexpressing clone. Mass spectrometry suggested that manganese superoxide dismutase (MnSOD), which has been reported to be related to chemoresistance mechanism in ovarian cancer cells, was down-regulated by miR-31. Western blot analysis confirmed down-regulation of MnSOD expression in miR-31-overexpressing cells compared with control cells. We conclude that miR-31 modulates sensitivity to TX at least in part through the regulation of MnSOD expression in ovarian cancer cells.
SYNCHRONOUS OVARIAN ENDOMETRIOID ADENOCARCINOMA WITH A FUNCTIONING STROMA AND ENDOMETRIAL ENDOMETRIOID ADENOCARCINOMA DEMONSTRATED DIFFERENT MICROSATellite INSTABILITY FINDINGS

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Mucinous epithelial ovarian tumors have been most commonly reported to have estrogenic stroma, although the frequency of endometrioid adenocarcinoma with functioning stroma is very low. Here, a rare case of a 31-year-old woman with endometrioid adenocarcinoma of the ovary with functioning stroma and endometrial endometrioid adenocarcinoma is presented. The symptom was virilization. The preoperative level of serum testosterone was as high as 553 ng/dL and level of estradiol was as high as 177 pg/mL, and serum gonadotropin levels were suppressed. The surgical specimens consisted of a solid ovarian tumor of 120 mm in diameter and an enlarged uterus. Histologically, the ovarian tumor was composed of proliferating, atypical, columnar cancer cells resembling early secretory endometrial cells, and condensation of plumed stromal cells resembling theca lutein cells. After surgery, the serum levels of testosterone and estradiol decreased and of follicle-stimulating hormone increased. To make a differential diagnosis for synchronous primary ovarian and endometrial cancers or metastatic cancer, we performed a microsatellite analysis. Five dinucleotide microsatellite markers were selected, and microsatellite analysis was performed by a high-resolution method using fluorescence-labeled polymerase chain reaction and laser scanning. In this case, both ovarian carcinoma and endometrial carcinoma demonstrated microsatellite instability (MSI). However, MSI findings of the ovarian tumor and endometrial tumor were different. High-resolution MSI analysis may be helpful to differentiate synchronous primary ovarian and endometrial cancers or metastatic cancer.
POSSIBLE PROTECTIVE EFFECT OF STATINS IN GYNECOLOGICAL CANCERS

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Background: Statins have been shown to be associated with risk reduction of a variety of malignancies, including a survival benefit in ovarian cancer.

Methods: The Cancer in the Uterus and Ovary Study (CITUOS) is a case-control study of consecutive gynecological cancer cases treated at Carmel Medical Center and age/clinic/ethnic-group matched population controls. Use of statins was assessed in 302 consecutive gynecological malignancies and their matched controls.

Results: Statins were used, for one year or more prior to diagnosis, by 32.5% of the ovarian cancer cases and by 36.1% of the endometrial cancer cases. One year use of statins was associated with a significantly reduced risk of endometrial cancer (Odds Ratio=0.54, 95% CI: 0.35-0.83) and a reduction of borderline significance in risk of ovarian cancer (Odds Ratio=0.62, 95% CI: 0.36-1.07). The association with endometrial cancer remained significant after adjustment for confounding factors (OR=0.53, 0.30-0.94, p=0.03). The use of statins after the cancer diagnosis and at the end of the follow-up was associated with a significantly better overall survival of endometrial cancer patients (HR=0.17, 0.04-0.74, p=0.02) and with a better survival of borderline significance of ovarian cancer patients (HR=0.46, 0.21-1.04, p=0.06) compared to non-users of statins.

Conclusions: The use of statins for more than one year was associated with a 47% relative reduction in the risk of endometrial cancer and a reduction of borderline significance in risk of ovarian cancer. Statin use after diagnosis was associated with better overall survival.
DO WOMEN WITH SYNCHRONOUS CARCINOMAS OF THE ENDOMETRIUM AND OVARY HAVE A FAVOURABLE PROGNOSIS COMPARED WITH EPITHELIAL OVARIAN CANCER PATIENTS?


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Objectives: Synchronous carcinoma of ovary and endometrium is a relatively uncommon event and patients are assumed to have a better prognosis than epithelial ovarian cancer (EOC) patients. The aim of this population based study was to compare clinicopathological characteristics and survival between double primary carcinoma (DPC) and EOC-only patients.

Methods: From the population-based database of the nationwide Netherlands Cancer Registry (NCR), women with localization of carcinoma in ovary and endometrium were identified. Differences in disease characteristics and overall survival (OS) between the DPC and EOC-only patients were tested using the Pearson's Chi-Square ($\chi^2$) test, the t-test and Kaplan-Meier survival analyses. Multivariable Cox regression was used to identify factors that independently influence survival.

Results: Among the 1105 EOC patients, 29 (2.6%) DPC patients were identified. DPC patients were more often premenopausal ($P<0.00$), in early stage of disease ($P<0.00$) and more often had low grade ($P=0.01$) endometrioid ($P<0.00$) tumours compared to EOC-only patients. OS was better in DPC patients ($P<0.00$). In patients with early or advanced stage of disease separately the OS was similar in both groups ($P=0.88$ and $P=0.19$, respectively). In multivariable analysis patients with DPC did not show a favourable prognosis after adjustment for age, stage of disease, histology, tumour grade and residue after surgery.

Conclusion: DPC patients constitute a prognostically favourable group among EOC patients because they present more frequently with early stage of disease and low grade endometrioid tumours. This may be caused by the early presentation of the endometrial carcinoma.
ANALYSIS OF RNA BINDING PROTEINS IMP1, IMP2, IMP3, LIN 28B EXPRESSION IN OVARIAN CANCER

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Background and aims: Vertebrate RNA-binding protein family, which regulate mRNA transport, translation, turnover and some with microRNAs process is associated with cancer cells behavior i.e. migration, metastasis, apoptosis. In this study, we try to elucidate the relationship of RNA-binding proteins IMP1, IMP2, IMP3, LIN28B and ovarian caner.

Materials and methods: Epithelial ovarian cancer and normal ovarian samples were collected and analyzed. The frozen tumor tissues have been collected from patients immediately after surgical removal. Real-time PCR was carried out using the LightCycler Real-Time detection system with TaqMan probe as fluorescent dye enabling real-time detection of PCR products according to the manufacturer’s protocol. Specific primer were designed for determining the mRNA levels of IMP1, IMP2, IMP3, LIN28B and phosphalipase-2(PLA2), a standard control gene. Clinical informations of patients were collected and analyzed, compared with various gene expression levels.

Results: Samples with tumor cell less 50 \% or necrosis by H and E stain were excluded from study. 47 ovarian cancer cases and 28 normal tissues were analyzed. Data values were showed as target gene /PLA2. In IMP family, IMP2, IMP3 are significantly up-regulated in cancer compared with normal ovaries (\(P < 0.05, t\) test). For LIN28B analysis, patients with stage IV disease were associated with higher expression of LIN28B compared with stage I to III diseases (\(P < 0.05, \text{one-way ANOVA}\)); and higher expression of LIN28B were associated with less chance of optimal debulking operation(\(P < 0.05, t\) test).

Conclusions: IMP2, IMP3 and LIN28B may be biomarkers of prognostic significance in ovarian carcinoma.
SERUM KL-6 FOR DIAGNOSIS OF OVARIAN CANCER ASSOCIATED WITH DERMATOMYOSITIS: TWO CASE REPORTS AND CLINICOPATHOLOGICAL FACTORS


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It is widely recognized some malignant tumors are often seen in patients with dermatomyositis (DM) and significant association between the presence of malignancies and poor prognosis is clear. Ovarian cancer is especially more frequently detected among the women patients with DM than without it. Some patients of ovarian cancer with DM showed relatively higher levels of serum KL-6 (Krebs von den Lungen-6), which is a useful serum marker for interstitial pulmonary disease. We report two cases of ovarian cancer associated with DM and investigate the clinical significance of high serum KL-6 levels in DM. One is that a woman aged 46 years with stage1b ovarian cancer had the histological type of serous papillary adenocarcinoma. She had a 13-year history of DM and serum KL-6 levels had been elevated. The cytoreductive surgery led to help decrease of serum KL-6 levels. On those ovaries, anti-KL-6 staining by immunohistochemistry was positive. The other is that a woman aged 58 years with stage IV ovarian cancer had the histological type of mucinous adenocarcinoma. The patient was treated by chemotherapy agents before the initial surgery. During the treatment, a decreased level of serum KL-6 was measured, and we could also ascertain that primary lesion was much reduced at the time of surgery. We were able to confirm that both cases indicated that high serum KL-6 levels may be correlated with the appearance of ovarian cancer. In conclusion, serum KL-6 may be considered as hopeful detectable marker for ovarian cancer in DM women without interstitial pneumonia.
OVARIAN CANCER: OLDER AGE, ADVANCED STAGE AND TIME PERIOD FREE OF RELAPSE SHOW LINEAR CORRELATION WITH THE DISEASE RECURRENTNESS

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Purpose: In present study we investigated the linear correlation between the occurrence of postoperative epithelial ovarian cancer relapse and patient’s age, performance of extirpatio uteri, period without a relapse and stage of the disease.

Materials and methods: We took the data from 60 patients having epithelial ovarian cancer, who were selected for the investigation of tumoral angiogenesis via the computer-aided evaluation of microvessel patterns. Using several statistical software packages (SPSS 17, TIBCO Spotfire, SigmaStat, StatsDirect, MedCalc) we calculated the Spearman correlation coefficient for the selected pairs of numeric values.

Results: We found statistically significant linear correlation between the pairs of relapse and the following parameters: age (two sided p = 0.012084223, Spearman’s rank correlation coefficient, Rho = 0.322088), period without relapse (p = 0.000172824, Rho = 0.46637), stage (p = 0.002311331, Rho = 0.386112). No strong correlation was estimated for the occurrence of ovarian cancer relapse and the performed extirpatio uteri surgery (p = 0.343861956).

Conclusion: In our study the operation of extirpatio uteri has no significant associative effect on ovarian cancer recurrence. Our data show that the relapse of ovarian cancer is directly associated with the older age of patients, advanced stage of the disease and the time period without the relapse.
GRANULOSA CELL - STROMAL TUMORS : AN IMMUNOHISTOCHEMICAL STUDY INCLUDING A COMPARISON OF CALRETININ AND INHIBIN

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Background: Histopathological evaluation of granulosa cell tumors (GCT) of the ovary may be confused morphologically with a wide variety of the tumors. Immunohistochemical staining for inhibin and calretinin can be a used for better diagnosis. Although it has been suggested that inhibin can be a sensitive marker for GCT, it may be had negative results in some cases. Also caltrinin has been proposed as a marker for GCT.

The aim of this study was to investigate the immunohistochemical methods (IHC) including a comparison of calretinin and inhibin markers in the diagnosis of these tumors.

Materials and methods: A total 23 ovarian GCT specimens were immunostained with commercially available antibodies to find out calretinin and inhibin for diagnosis

Results: For diagnosing GCT, the sensitivity of calretinin was 100% and that of the inhibin was almost 73.9%.

The extent and severity of staining was more extensive for calretinin compared to inhibin P< 0.001

Conclusion: Calretinin is a more sensitive biomarker for GCT than inhibin.

Keywords: Calretinin - inhibin - Granulosa cell tumors- Immunohistochemistry -stromal tumor.
ALTERED PROX1 GENE EXPRESSION IN OVARIAN CANCER

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Prospero-related homeobox 1 (PROX1) is known to play a key role in lymphangiogenesis but also is engaged in abnormal cellular proliferation via down-regulated expression of the cell cycle inhibitors p27kip1 and p57kip2. Prox1 was found to be frequently inactivated by mutation, abnormal DNA methylation or genomic deletion in several cancers. Hence, we examined the PROX1 gene expression and possible genomic aberration causing its abnormal function in epithelial ovarian tumor (EOC). 47 ovarian cancer patients and 13 healthy ovarian tissue were subjected to PROX1 gene and protein expression analysis using respectively Real-Time PCR and western blot. Additionally the cause of abnormal Prox1 gene expression was analyzed by the means of aCGH. Prox1 expression was significantly lower in EOC than in healthy group (p< 0.001). The same tendency was observed in advanced (FIGO III / IV - lower expression, p=0.001) versus less advanced EOC (FIGO I / II). There were 21% of CN gains, 9% of high copy gains and 4% of CN loss in locus coding PROX1 gene (1q32.2-32.3) in studied EOC patients. Low expression of PROX1 in ovarian cancer tissue and in more advanced FIGO stage may be responsible for excessive proliferation and more aggressive character of ovarian cells. It implies the role of PROX1 gene in pathogenesis of ovarian cancer. Considering high percentage (nearly 30%) of copy number gains in locus coding PROX1 gene among EOC patients we assume that there exists different epigenetic mechanisms (e.g. methylation) responsible for low expression PROX1 in ovarian tumor tissue.
THE EFFECT OF PRE- AND THROUGHOUT CHEMOTHERAPY HEMOGLOBIN LEVELS IN PATIENTS WITH PRIMARY EPITHELIAL OVARIAN CARCINOMA TREATED WITH PLATINUM-BASED CHEMOTHERAPY

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Objective: The aim of this study was to evaluate the prognostic impact of hemoglobin (Hb) levels before and throughout the course of platinum-based chemotherapy in patients with primary epithelial ovarian cancer (EOC).

Methods: Medical records of patients who had undergone initial surgery followed by platinum-based chemotherapy for EOC was retrospectively studied. Univariate and Cox-regression model were used to evaluate the prognostic impact of various factors including Hb levels before and throughout chemotherapy in term of overall survival. Additionally, sensitivity/specificity of the Hb levels were calculated using receiver operating curve (ROC) and Kaplan-Meier studies were used to determine the optimal cut-off levels.

Results: The median duration of follow-up was 37.0 months. Degree of anemia before starting chemotherapy was significantly related to overall survival (normal, 96%; mild anemia, 76%; and moderate to severe anemia, 53%; p = 0.001), however, the correlation between Hb level throughout chemotherapy and overall survival showed only borderline significance (p = 0.062). Only residual tumor after surgery and degree of anemia before starting chemotherapy were the independent prognostic factors (p = 0.013 and 0.015, respectively). Sensitivity/specificity and Kaplan-Meier analyses revealed that Hb level before starting chemotherapy of less than 10.5 g/dl was related to shorter overall survival (p = 0.002).

Conclusion: Pre-chemotherapy Hb level has a prognostic impact on overall survival in patients with EOC candidate to first-line platinum-based chemotherapy. However, the prognostic significance of decreased Hb levels throughout chemotherapy needs to be clarified in further prospective studies to determine optimal Hb level for achieving favorable outcome.
A NEW TREATMENT STRATEGY USING AN M-TOR INHIBITOR (EVEROLIMUS) FOR OVARIAN CLEAR CELL CARCINOMA (CCC)

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Purpose: We have performed basic studies on the possible usefulness of everolimus as an mTOR inhibitor for the treatment of ovarian clear cell carcinoma (CCC) by inhibiting the mTOR-HIF pathway. In this study, the effects of the mTOR inhibitor were evaluated using:

(1) a CCC cell strain and

(2) model mice that underwent CCC implantation.

Methods:

(1) Everolimus was added to a human ovarian CCC cultured strain (RMG-1) at various concentrations, and serial changes in the cells were observed. In addition, changes in the expression of proteins of the HIF family (mTOR, phospho-mTOR, phospho-4EBP1, HIF-1a, and VEGF-A) were evaluated using immunohistochemical methods and the immunoblot method, those in VHL expression using real-time RT-PCR, those in Ki-67(MIB-1) expression using the labeling index, and inhibitory effects on cell growth using the MTS assay.

(2) In vivo, cultured cells (5 x 10^6 cells/0.1 ml) were subcutaneously transplanted into nude mice, and a control group and groups treated with everolimus alone or in combination with CDDP were compared.

Results:

(1) Everolimus dose-dependently inhibited the expression of the HIF family, increased VHL expression, and decreased the MIB-1 labeling index.

(2) In nude mice, the tumor size decreased in the group treated with everolimus alone compared with the control group or the group treated with everolimus + CDDP.

Conclusion: Our results suggest the usefulness of mTOR inhibitors as novel drugs for the treatment of CCC via the mTOR-HIF-1 pathway.
THE LYMPHADENECTOMY COMPLICATIONS IN OVARIAN CANCER PATIENTS

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The assessment of regional lymph nodes status is the integral part of diagnostics in ovarian cancer patients. Because of the complications risk, the lymphadenectomy in ovarian cancer patients, as the routine procedure, is still the subject of controversy.

Objectives: The assessment of surgical complications in ovarian cancer patients.

Material and methods: The retrospective analysis of 211 consecutive ovarian cancer patients, treated at Centre of Oncology in Warsaw, between 1998 and 2006, was performed. All patients were treated with surgery, according to the actual protocol, with pelvic and periaortal lymphadenectomy. The control group constituted of 258 ovarian cancer patients, treated with surgery, without lymphadenectomy, at the same time. All patients were treated with complementary chemotherapy. The analysis of intraoperative and postoperative complications was performed.

Results: The most frequent intraoperative complications in both groups were: haemorrhage, urinary system damage, digestive tract damage. The difference was not statistically significant (p=0.683). The most frequent postoperative complications were: haemorrhage, intestinal junction dehiscence, eventrations, wound dehiscence, anaemia, wound healing complications, intestinal fistulas. The haemorrhage, eventrations, and the wound healing complications were the most frequent in the group with lymphadenectomy. The difference was statistically significant (p= 0.002). Because of postoperative complications, reoperation was necessary in two women in the group without lymphadenectomy (0.78%) and in 15 women with lymphadenectomy (7.11%). The difference was statistically significant (p=0.000).

Conclusion: The treatment modality decision in ovarian cancer patients should be balanced individually between the benefits and the risk of complications probability.
ID1 EXPRESSION WITH SERUM EGF/EGF-R CONCENTRATION ASSESSMENT IN MALIGNANT OVARIAN TUMORS

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Background: Inhibitors of DNA binding/differentiation (Id) protein family may play an important role in cancer angiogenesis stimulation through interactions with mitogenic/angiogenic factors such as EGF and EGFR.

Aims: To assess if the expression of Id1 protein with EGF and EGF-R assessment are associated with selected clinical and histological features (tumor type, histological grading and FIGO stage) of malignant ovarian masses.

Methods: The study group included 95 women operated because of ovarian tumors. Id1 protein was assessed by immunohistochemistry and EGF with EGF-R serum concentrations were examined by ELISA.

Results: The mean age (±SD) of the patients was 52,6±15,1 years and 43 (45,2%) of women were premenopausal. Malignant tumors (83 masses) included 38 serous cancers, 23 mucinous cancers and 7 endometrioid cancers. Of 15 other malignant tumors 6 were metastatic to the ovary. Significant differences between malignant and benign tumors were found in concentrations of EGF and EGF-R depending on patient’s menopausal status (p=0,01 and p=0,002, respectively). Malignant tumor histological grade was significantly correlated with EGF concentrations (p=0,01). FIGO stage was not significantly correlated with Id1 expression (p=0,09), but correlated with EGF concentration (p=0,01). Significant correlations were found between Id1 expression and histological grade and tumor FIGO stage (both p=0,005). EGF and EGF-R concentrations were significantly correlated with each other (p=0,008). Moreover, both EGF and EGF-R concentrations were correlated with Id1 expression ((p=0,0005 and p=0,004, respectively).

Conclusion: Id1 protein with EGF and EGF-R concentration assessment may be used as additional prognostic markers in women with various types of malignant ovarian tumors.
ENCOURAGING RESPONSES WITH BEVACIZUMAB IN RECURRENT LOW-GRADE SEROUS OVARIAN CANCER

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Objective: Low-grade serous ovarian carcinomas (LGSOC) represent approximately 10% of serous ovarian cancers, but are notoriously resistant to conventional chemotherapeutic agents. The objective of this study was to examine the clinical efficacy of bevacizumab alone or with concurrent chemotherapy in patients with recurrent LGSOC.

Methods: A retrospective review of patients with recurrent LGSOC treated with bevacizumab between 2005 and 2009 was performed. All cases were reviewed by a gynecologic pathologist to confirm low-grade serous histology. Demographic and clinical variables were abstracted from the medical record. Response was determined using the modified RECIST criteria.

Results: We identified 21 patients with LGSOC treated with bevacizumab. All patients had recurrent disease and were previously treated with cytotoxic chemotherapy and/or hormonal agents with a median of 4 previous regimens (range 1-12). Bevacizumab was given alone (n=2), or in combination with other agents including taxane and platinum (n=3), taxane alone (n=2), carboplatin alone (n=1), gemcitabine (n=4), cyclophosphamide (n=3), topotecan (n=3), capecitabine (n=2), and leuprolide (n=1). Of the 15 patients evaluable for response, 5 (33.3%) had a partial response and 5 (33.3%) had stable disease for a clinical benefit rate of 66.6%. Two patients (11%) developed a bowel perforation and one patient (5%) developed an enterocutaneous fistula while on treatment with bevacizumab. No other serious adverse events were noted.

Conclusion: Our results suggest that bevacizumab may have activity in LGSOC. Further study is warranted to develop anti-VEGF therapy in this group of patients.
A RETROSPECTIVE ANALYSIS OF NEOADJUVANT PLATINUM-BASED CHEMOTHERAPY VERSUS UP-FRONT SURGERY IN ADVANCED EPITHELIAL OVARIAN CANCER

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Objective: To report the results of patients (pts) with advanced epithelial ovarian cancer (AEOC) treated either with neoadjuvant chemotherapy (NAC) followed by cytoreductive surgery or primary cytoreductive surgery (PCS) followed by adjuvant chemotherapy.

Methods: 22 consecutive patients with FIGO IIIC-IV AEOC treated at our Institution were retrospectively analyzed.

Results: Median age of patients at diagnosis was 60 years. The serous cell type was the most common histology in 18 pts (82%). The distribution by stages was: 13 pts (60%) stage IIIC and 9 pts (40%) stage IV. 13 pts received NAC (59%), 6 and 8 pts stage IIIC and IV, respectively. 9 were finally operated (69%); the 9 pts left had PCS and postoperative CT. All pts received Carboplatin and Paclitaxel as treatment. From the 9 patients finally operated in the NAC arm, 8 (89%) had an optimal debulking surgery and in the other case the surgical result from operation was missing. In the arm of PCS, 7 pts (78%) had an optimal debulking surgery and the other 2 had a suboptimal debulking. After a median follow up time of 24.6 months (Range: 1-64), 12 out of 22 pts (54.5%) are still alive, 7 pts (53.8%) in the NAC arm and 5 pts (55.5%) in the PCS arm.

Conclusion: The results of this retrospective analysis confirm that NAC with subsequent interval debulking surgery is a suitable therapeutic approach in primary inoperable patients with advanced epithelial ovarian cancer, in terms of optimal debulking and survival rates.
SIGNIFICANCE OF SECRETED PROTEIN ACIDIC AND RICH IN CYSTEINE (SPARC) EXPRESSION IN EPITHELIAL OVARIAN CANCER

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Objective: Secreted protein acidic and rich in cysteine (SPARC) is an extracellular matrix-associated protein implicated in the modulation of cell adhesion, migration, cell cycle regulation, and angiogenesis. It has been associated with the progression or suppression of various cancers. This study aimed to correlate SPARC protein expression with tumor progression and clinicopathological features in epithelial ovarian cancer.

Methods: Epithelial ovarian cancer (n=69), borderline tumor (n=18), benign tumor (n=10) and normal ovary tissues were obtained after operation. and SPARC protein expression was examined using immunohistochemistry.

Results: Cytoplasmic SPARC immunoreactivity was observed in stromal cells in nearly all cases of normal ovary, benign and borderline tumors (100%, 94.7%, and 100%). In contrast, SPARC was detected in the stroma of 63.8% (44/69) and the score of immunoreactivity was significantly reduced in malignant tumors (p=0.000). SPARC expression in ovarian epithelial cancers was significantly associated with FIGO stage. However, it was not correlation with other clinicopathologic parameters, including histologic type, tumor grade, nuclear grade, mitoses, tumor size, local recurrence, distant metastasis, and survival.

Conclusion: This study showed that reduction of SPARC expression in epithelial ovarian cancer is significantly correlated with tumor invasiveness.
SIGNIFICANCE OF PERIOSTIN EXPRESSION IN EPITHELIAL OVARIAN CANCER

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Obstetrics and Gynecology, Pusan National University Hospital, Busan, Republic of Korea

The aim of this study is to evaluate the expression of periostin, an extracellular matrix protein, in cancer-associated stromal fibroblasts of human epithelial ovarian cancer tissues. In human epithelial ovarian cancer tissues, periostin was mainly expressed in cancer-associated stromal fibroblasts, but not in cancer cells. We showed that cancer-derived lysophosphatidic acid may be involved in the expression of periostin in stromal fibroblasts, suggesting tumor-stroma interaction in the regulation of periostin expression. Periostin expression levels were highly correlated with poor prognosis of ovarian cancer patients and periostin stimulated adhesion, invasion, and migration of ovarian cancer cells. These results suggest that expression levels of periostin highly correlated with poor survival and tumor recurrence of ovarian cancer patients.
COMPUTED TOMOGRAPHY- GUIDED HIGH-DOSE-RATE BRACHYTHERAPY (HDRBT) ABLATION OF LIVER METASTASIS FROM OVARIAN CANCER - INITIAL EXPERIENCE

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Purpose: To evaluate the clinical outcome of Computed Tomography (CT)-guided high-dose-rate-brachytherapy (HDRBT) of liver metastases from ovarian cancer with the goal of local tumor control in selected patients with isolated hepatic metastases.

Materials and methods: Between February 2008 and April 2010 7 patients with 12 isolated ovarian cancer metastases to the liver and overall limited macroscopic disease were treated with HDRBT in 9 sessions. The mean age was 67.1 years (range: 45-79). All patients had undergone repeated surgery and chemotherapy before HDRBT. Treatment was performed by CT-guided applicator placement and HDRBT with an iridium-192 source. Mean radiation dose of target volume was 18 Gy (SD 3.5). CT or MRI follow-up was performed 6 weeks and every 3 months post intervention. The primary endpoint of the study was local tumor control, the secondary endpoint was overall survival (OS).

Results: Patients were available for MRI or CT evaluation at a mean follow-up time of 14.7 months (range: 7-19 months). Mean tumor diameter was 31.9 mm (range: 13-120 mm). Complete ablation was achieved in all lesions and no additional re-ablations were required for a technique effectiveness rate of 100%. No major and minor complications were observed. No local recurrence was observed in any of the included patients. OS was 100% after 12 months. Two patients died after 14 and 25 months respectively.

Conclusion: CT-guided HDR brachytherapy is a promising technique for performing minimally invasive cytoreduction of isolated liver metastases from ovarian cancer. HDRBT warrants an excellent rate of local control.
PATIENT-REPORTED OUTCOMES IN PATIENTS WITH RELAPSED, PLATINUM-SENSITIVE OVARIAN CANCER (ROC): RESULTS FROM A LARGE RANDOMIZED PHASE III TRIAL


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Background: OVA-301 is a large randomized trial that showed superiority of trabectedin plus pegylated liposomal doxorubicin (PLD) over PLD alone in ROC. Patient-reported outcomes (PROs) in the overall population were presented (ASCO 2009). This analysis provides an evaluation of PROs in the platinum-sensitive (PS; platinum-free interval [PFI] ≥6 months) and the partially platinum-sensitive (PPS; PFI 6–12 months) subsets.

Methods: PRO questionnaires EORTC-QLQ-C30 were completed at baseline, on Day 1 of every other treatment cycle starting from Cycle 3, and at the end-of-treatment visit. Global Health Status scale (GHSs) was chosen for these ITT analyses.

Results: Among the 430 pts in PS stratum, 214 were PPS. Compliance with questionnaire completion was 90% at baseline in both subgroups and was well maintained up to 21 treatment cycles (≥82% compliance). Median treatment cycles in the PS/PPS subgroup was 6 (162 days) / 6 (154 days) for trabectedin + PLD, and 5 (149 days) / 4 (134 days) for PLD, respectively. Both the longitudinal mixed-effect model analyses (covariance first-order autoregression), predicting the baseline and follow-up scores as a function of treatment, days after baseline, interaction between treatment and days, and the cross-sectional mean score changes showed no significant differences between treatment arms in the PS/PPS stratum (p=0.96/p=0.62). GHSs improvement was observed with trabectedin+PLD compared to PLD alone in responding patients beyond cycle 5-7.

Conclusions: The addition of trabectedin to PLD resulted in superior efficacy with no added decrement in overall health status as assessed by PROs in pts with platinum-sensitive relapsed ovarian cancer.
COST-EFFECTIVENESS OF COMBINATION VERSUS SEQUENTIAL DOCETAXEL AND CARBOPLATIN FOR THE TREATMENT OF PLATINUM SENSITIVE RECURRENT OVARIAN CANCER

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Background: In a recent randomized controlled trial (RCT), combination weekly docetaxel and carboplatin was associated with higher progression-free survival (PFS), but lower quality of life (QoL), than sequential single agent docetaxel followed by carboplatin for treatment of platinum-sensitive recurrent ovarian cancer. Our aim was to determine the cost-effectiveness of the combination versus sequential regimens.

Methods: An RCT of concurrent docetaxel and carboplatin (combination arm) versus docetaxel followed by carboplatin (sequential arm) was the basis for a Markov decision model, with primary outcome PFS. Costs were derived using US Medicare reimbursements. QoL data using FACT-G questionnaire was converted to utilities. Costs and incremental cost-effectiveness ratios (ICERs) were reported in US dollars ($) per quality-adjusted life year (QALY). Extensive one way sensitivity analyses were performed.

Results: The least expensive strategy was sequential docetaxel followed by carboplatin, with average cost $20,381, compared to combination docetaxel and carboplatin, with average cost $25,122. Combination treatment had an ICER of $25,239/ QALY compared to sequential treatment. If QoL was assumed equivalent between regimens, the ICER of combination treatment became $17,734. Combination regimen remained cost-effective with an ICER below $50,000/QALY over a range of costs (cost of salvage regimens, cost of bone marrow support when administered), and estimates (probability of requiring bone marrow support for each regimen, probability of severe neurologic toxicity).

Conclusion: Combination weekly docetaxel and carboplatin appears to be cost-effective compared to sequential single agents as a treatment strategy for platinum sensitive ovarian cancer, even when accounting for slightly lower QoL during treatment.

<table>
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<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incremental Cost</th>
<th>Incremental Effectiveness</th>
<th>Cost/ Effectiveness</th>
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[Base Case Results]

<table>
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<th>Parameter</th>
<th>Base case estimate</th>
<th>Range for sensitivity analysis</th>
<th>ICER range for combination versus sequential arms ($/QALY)</th>
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<td>$3000-$25,000</td>
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<td>Probability of EPO support in combination arm</td>
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<td>Probability of severe neurologic toxicity in combination arm</td>
<td>0.029</td>
<td>0-0.15</td>
<td>$25,013-$26,180</td>
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[Key Sensitivity Analyses]
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

SUSPECTED OVARIAN CANCER AND THE PATHS TO DIAGNOSIS

L. Hess¹, M. Method², F. Stehman¹, T. Weathers¹, P. Gupta¹, J. Schilder¹

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Background and aims: Health care (HC) in the U.S. is a complex system. It is unclear how patient concerns and health care factors are related to the patient’s experience in reaching a definitive diagnosis. The purpose of this study was to quantify patient and HC system factors related to time to diagnosis among women suspected of having ovarian cancer (OC).

Methods: Women who were referred to gynecologic oncology for a suspected OC were enrolled to this study. Patient interviews were used to identify events from the time of first indication of a problem to diagnosis.

Results: 107 patients were consented; 92 patients completed the study. Of these, 68.5% were found to have cancer at surgery. Of those, 59.6% were diagnosed with advanced OC (AOC). A greater number of pre-diagnosis health encounters were reported among patients with benign disease than early or AOC (p=0.03). Women with benign disease were less likely to report having symptoms than those with cancer (p=0.005). 92.9% of women with AOC and 89.5% with early disease reported symptoms, compared with 65.5% of women with benign findings at surgery. There was an average of 86, 24, and 49 days from the first HC visit to diagnosis for benign, early stage and AOC, respectively (p=0.07).

Conclusions: Patient reported symptoms were more common among patients with OC; however, symptoms were not associated with reduced time or number of HC visits prior to diagnosis. Analysis is ongoing using participant medical record data to identify HC system factors related to diagnosis.
DIFFERENTIAL MICRORNA EXPRESSION IN CISPLATINUM RESISTANT VS. SENSITIVE OVARIAN CANCER CELL LINES

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Objective: To determine the association of differential microRNA expression and cisplatinum resistant vs. sensitive ovarian cancer.

Methods: MTT assays were used to determine drug resistance in cisplatinum resistant (A2780-CP) vs. sensitive (A2780) ovarian cancer cell lines. MicroRNA microarray was performed to identify potential targets for reversing drug resistance and validated by qRT-PCR. To confirm our in vitro findings, we employed The Cancer Genomic Atlas (TCGA) data portal. We evaluated data from 443 patients with corresponding genomic, chemotherapy, recurrence, and outcomes data. Student's t-test, Kaplan-Meier survival estimates and Cox proportional hazards models were employed for statistical analyses. Targetscan and Pictar genomic sequence analyses were utilized.

Results: The A2780-CP ovarian cancer cells had a 3.2 fold higher resistance to cisplatinum (IC₅₀ 5.74 vs. 1.80 µM; p=0.049). MicroRNA microarray analysis identified differentially expressed (>2 fold) microRNAs including mir-181a, mir-10b, mir-27b and mir-126. Specifically, mir-181a had a 3.4 fold over-expression in resistant compared to sensitive cancer cells, confirmed with qRT-PCR. Of 443 tumor specimens from TCGA data, a 1.25 fold higher expression of miR-181a was associated with a median recurrence-free survival of 23 months vs. 59 months in those with lower miR-181a expression (p=0.013). A greater proportion of patients with high miR-181a expression recurred within 24 months (28.7% vs. 18.8%; p=0.062). Furthermore, miRanda algorithms identified target gene BCL2L11 associated with miR-181a, a known facilitator of apoptosis.

Conclusion: Our data suggests that miR-181a may be implicated with platinum-resistant serous ovarian cancer. Targeting microRNA expression may have significant promise in the treatment of drug-resistant ovarian cancer.
IS IT MORE COST EFFECTIVE TO USE BEVACIZUMAB IN THE PRIMARY TREATMENT SETTING OR AT RECURRENCE? - AN ECONOMIC ANALYSIS

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¹University of California, San Francisco, ²University of California, Irvine, ³Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Stanford University School of Medicine, Stanford Cancer Center, Stanford, CA, ⁴Nova Southeastern University, Ft. Lauderdale, FL, USA

Objective: GOG 218 evaluated the addition of bevacizumab to standard chemotherapy in the primary treatment of ovarian cancer. OCEAN trial studied the use of bevacizumab in recurrent disease. We propose to compare the cost effectiveness of bevacizumab in primary versus recurrent setting.

Methods: Using the superior arm of GOG-218 PCB + mB as comparison, a cost effectiveness analysis was performed to compare GCB + mB in the recurrent setting.

Results: Estimated costs of single dose B (15mg/kg) is $6,450 for an average female weighing about 75 kg. Based on Medicare payment for administration of chemotherapy, the actual and estimated costs of treatment (for PCB+mB = [PC ($440) + B ($6450)]/cycle + $6,450/maintenance cycle), plus the cost of potential complications were determined. In those with primary disease, the median PFS is approximately 16 months after combination chemotherapy. In the recurrent setting with platinum sensitive disease, the median PFS is approximately 8 months after combination chemotherapy. Assuming that the addition of B and mB improves PFS by 6 and 3 months in those with primary and recurrent disease, respectively, the estimated treatment cost per patient is $140,285 in the primary setting and $92,940 in the recurrent setting. The ICER of PCB + mB is $270,900 per LYS vs. $361,100 per LYS in the primary vs. recurrent setting.

Conclusions: In this economic model comparing bevacizumab in primary versus recurrent setting, our data suggest that bevacizumab in the primary setting may be more cost effective.
SURVIVAL BENEFIT OF NEOADJUVANT CHEMOTHERAPY IN ADVANCED EPITHELIAL OVARIAN CANCER WITH HIGH CA-125 LEVEL

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¹Division of Gynecologic Oncology Research, National Cancer Center, Korea, Goyang, ²Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: This study aims to determine whether neoadjuvant chemotherapy (NAC) has survival benefit in selected patients with advanced epithelial ovarian cancer (EOC) who have high risk of suboptimal cytoreduction which is represented by high serum CA-125 level.

Patients and methods: We retrospectively reviewed records of 314 patients with EOC including 94 patients who received NAC. After stratification by preoperative CA-125 levels, the progression-free survival (PFS) was compared between the NAC group and the primary debulking surgery (PDS) group.

Results: The NAC group had more FIGO stage IV disease (P < 0.001) and higher CA-125 levels (P < 0.001). Although suboptimal resection rate was higher in the PDS group (50% vs. 18%, P < 0.001), however, NAC was not associated with increased PFS in multivariate Cox analysis (P = 0.334). Nevertheless, after stratification according to CA-125 levels, NAC showed survival benefit in the subgroup with high CA-125 levels (> 2,000 U/ml; HR 0.62, P = 0.037).

Conclusion: NAC may have survival benefit in selected patients with higher risk of suboptimal cytoreduction. The current data emphasize that it is important to evaluate the results of NAC according to the risk factor of suboptimal cytoreduction to estimate the survival benefit of NAC in future trials.
COMBINED GYNAECO-PLASTIC APPROACH TO PROPHYLACTIC SURGERY FOR OVARIAN AND BREAST CANCERS

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Background and aims: The familial ovarian cancer clinic has been established for ten years and it functions in parallel to breast and colorectal familial clinics. The Manchester scoring system is used to quantify the risk of each patient being a carrier or BRCA1 and/or BRCA 2. Patients who tested positive for BRCA1 and/or BRCA2 underwent clinical assessment and counselling prior to the planning of one-stage surgery.

The aim was to assess outcomes of risk-reducing surgery in BCH.

Methods: All patients undergoing one stage risk reducing surgery were identified and data collection and analysis performed.

Results: Over the study period of 2005-2009 19 patients underwent combined surgery (5 were +ve for BRCA1, 7 +ve for BRCA2 and 7 were +ve for both). 16 patients underwent total laparoscopic hysterectomy and 3 patients underwent laparoscopic bilateral salpingo-oophorectomy. 17 patients had bilateral prophylactic mastectomy with the remaining 2 undergoing unilateral skin sparing mastectomy. 11 patients received fixed volume implants whilst 8 received expander implants. 17 of the cases were completed in less than 3.5 hours total and 18 patients were discharged from hospital on or before day 3 post-operatively. 11 patients received HRT post-operatively and 16 patients experienced no complication. 3 minor complications consisting of a seroma, a case of constipation and a local reaction to a dressing were reported. We estimate the cost of one stage surgery to be £5000, compared to £6400 for the same two step procedure.

Conclusions: Combined risk-reducing surgery for breast and ovarian cancer is safe, efficient and economical.
THE IMPACT OF P53 PROTEIN EXPRESSION ON TOPOISOMERASE I, TOPOISOMERASE IIA IMMUNOPOSITIVITY IN OVARIAN CARCINOMAS

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¹Department of Pathomorphology and Clinical Cytology, ²Department of Pathomorphology, ³First Department of Gynaecology, Medical University, Wroclaw, Poland

Background: Associations between topoisomerase I (topo I), topoisomerase IIα (topo IIα) and p53 protein expression were revealed in in vitro studies. So far, the role of p53 in regulation of topo I and topo IIα expression in ovarian carcinoma tissues has not been analyzed.

Aims. The study was to examine and compare expression of topo I, topo IIα and p53 protein between each other in ovarian neoplasms in relation to clinicopathological parameters.

Methods: The expression of topo I, topo IIα and p53 protein was estimated by immunohistochemical staining in tumor sections from 136 malignant and 30 benign ovarian tumors.

Results: The differences between topo I, topo IIα and p53 expression in malignant and benign tumors were statistically significant (P = 0.001, P = 0.02, P = 0.03). Topo IIα and p53 protein expression was associated with advanced stage of ovarian carcinomas (P = 0.01). Positive correlation was found between topo I and topo IIα, topo I and p53, and topo IIα and p53 protein expression in ovarian carcinomas (P = 0.001). Both p53/topo I and p53/topo IIα immunofenotypes were associated with advanced stage of ovarian carcinomas (P = 0.045, P = 0.009). There was borderline significance (P = 0.07) between p53/topo IIα positive cases and tumor grade.

Conclusions: Revealed association between p53 protein and topo I or topo IIα expression in ovarian carcinomas might be useful as a biological feature in selection of patients to target therapy especially with advanced tumor stage.

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CEDIRANIB IN RELAPSED OVARIAN CANCER: STAGE I DATA FROM A RANDOMIZED, DOUBLE-BLIND PHASE III TRIAL (ICON6)

F. Raja¹, C. Griffin², W. Qian², A.M. Swart², M. Parmar², H. Hirte³, J. Ledermann¹, On behalf of ICON6 Collaborators

¹UCL Cancer Trials Centre, University College London, ²MRC Clinical Trials Unit, London, UK, ³Juravinski Cancer Centre, Hamilton Health Sciences, Hamilton, ON, Canada, ⁴University College London Hospital, London, UK

Background: Cediranib is a potent oral VEGF signalling inhibitor with activity against all 3 VEGF receptors. ICON6 was initiated based on evidence of single-agent activity in ovarian cancer with acceptable toxicity.

Methods: ICON6 is a 3-arm, 3-stage, double-blind, placebo-controlled randomized trial in first relapse of platinum-sensitive ovarian cancer. Patients were randomized (2:3:3) to receive 6 cycles of carboplatin (AUC5/6) plus paclitaxel (175 mg/m²) with either placebo (reference), cediranib 20 mg/day followed by placebo (concurrent) or cediranib 20 mg/day followed by cediranib (concurrent plus maintenance). Cediranib or placebo were continued for 18 months or until disease progression. The primary outcome measure for Stage 1 was safety, with the analysis planned after 60 patients had received a minimum of 3 cycles of chemotherapy. Primary outcome measures for stage 2 and 3 are progression-free and overall survival respectively.

Results: Of 60 patients in the Stage 1 analysis, 53 patients had received 3 cycles and 42 received 6 cycles of chemotherapy. Reasons for not completing 6 cycles included: adverse events/intercurrent illness (n=3), death (n=3), other (n=1). 19/60 patients discontinued cediranib or placebo during chemotherapy due to: AE/intercurrent illness (n=9), disease progression (n=1); death (n=3); patient decision (n=1), multiple reasons (n=5). Grade 3 and 4 toxicity was experienced by 30 (50%) and 3 (5%) patients, respectively. No gastrointestinal perforations were observed. Treatments remain blinded.

Conclusion: The addition of cediranib to platinum-based chemotherapy is considered sufficiently well tolerated for expansion of the trial. With Independent Data Monitoring Committee approval, ICON6 is now recruiting to Stage 2.
OVARIAN SERTOLI-LEYDIG CELL TUMORS- A CLINIC-PATHOLOGICAL ANALYSIS OF 40 CASES

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OB/GYN, Peking Union Medical College Hospital, Beijing, China

Background: Ovarian Sertoli-Leydig Cell Tumors (SLCT) are uncommon and few reports can be seen.

Methods: 40 cases of ovarian SLCT treated in PUMC Hospital were reviewed to demonstrate their clinic-pathological features.

Results: The patients' average age was 28. All tumors were limited in one ovary with 12 spontaneous ruptures. 25(62.5%) patients presented symptoms of androgen excess. Their average testosterone level was 16.8 nmol/l. 6 patients presented symptoms suggesting estrogen excess. 9 patients presented no endocrine symptoms. The average tumor size of them were 7.6, 7.5 and 10.1cm respectively. 4 (10%), 14(35%) and 20 (50%) tumors were well differentiated(G1), of intermediate differentiation (G2) and poorly differentiated(G3). 7 of 9(77.8%) patients without endocrine symptoms were poorly differentiated. One cystectomy, 27 unilateral salpingo-oophorectomy and 12 hysterectomy with salpingo-oophorectomy were done. 23 patients (G3 or G2) received chemotherapy after the surgery. One patient died of diabetes mellitus. Two were lost to follow up. The rest were alive from 10 to 133 (average 62) months postoperatively. Two G3 tumors recurred at the 13rd and the 21st month after the operation respectively but both achieved CR after the second surgery and chemotherapy.

Conclusions: 62.5% of Ovarian SLCTs exhibit symptoms of excess androgen. The patients without endocrine manifestations had larger tumors and higher rate of spontaneous rupture and poor differentiation. Most tumors were in the early stage and the overall survival of SLCT is good while some G2 or G3 tumors may recur. Conservative surgery is acceptable and chemotherapy is recommended for those with higher risk factors.
EAG AND HERG POTASSIUM CHANNELS AS NEW THERAPEUTIC TARGETS IN OVARIAN CANCER

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¹Obstetrics and Gynaecology, School of Graduate Entry Medicine and Health, University of Nottingham, ²University of Derby, ³Obstetrics and Gynaecology, Royal Derby Hospital, Derby, UK

Background and aims: Ovarian cancer is known to be associated with poor prognosis. There is a need for treatments based on new therapeutic targets to improve survival of patients with this deadly disease. Eag and HERG potassium channels have shown promising role as potential therapeutic targets in cancers of differing origin. The aim of this study was to determine expression of these channels in ovarian cancer and demonstrate the effect of their blockade on ovarian cancer cell proliferation.

Methods: The presence of Eag and HERG channels was determined on a Tissue Microarray of 336 patients with Immunohistochemistry and staining was correlated with clinico-pathological characteristics. Inhibition of SK-OV-3 ovarian adenocarcinoma cell line proliferation with Eag and HERG blockers was studied using the MTS assay. The mechanism of inhibition of these cells was further analysed by Flow cytometry using Propidium Iodide and Annexin dyes.

Results: We have shown that high Eag staining is associated with poor survival and correlates with higher stage and presence of residual disease. HERG staining failed to demonstrate an effect on survival. Eag blockers affect cell proliferation by inducing cells to undergo early apoptosis while HERG blockers act through effect on cell cycle.

Conclusion: We have demonstrated for the first time that Eag and HERG channels are expressed in ovarian cancer and Eag is associated with poor survival. Both Eag and HERG affect ovarian cancer cell proliferation through different pathways and can be potentially used as novel therapeutic targets for the treatment of ovarian cancer.
EXPRESSION OF THE K2P CHANNELS TREK1 (KCNK2) AND TREK2 (KCNK10) IN EPITHELIAL OVARIAN CANCER

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Background and aims: Potassium channels, including the K2P subtype, are involved in cell cycle progression and cell proliferation. Overexpression of K2P channels has been described in a number of cancers and in some cases e.g. in prostate cancer expression can be correlated with tumour grade and stage. Our aim was to identify expression of TREK 1 and 2 in epithelial ovarian cancer as this has not previously been reported.

Methods: Immunofluorescence was used to investigate expression of TREK 1 and 2 using the SKOV-3 epithelial cancer cell line and cultured cells obtained at biopsy. Immunohistochemistry and Western blotting for TREK 1 and 2 was performed on prospectively collected ovarian cancer samples. Proliferation experiments were conducted on the SKOV 3 cell line using a MTS assay. All experiments were conducted with commercially available antibodies and ethical approval.

Results: TREK 1 and 2 are expressed by both the SKOV 3 cell line and in cultured ovarian cancer tissue (n=2) on immunofluorescence. Both immunohistochemistry (n=24) and western blotting (n=15) have demonstrated that the ovarian cancer biopsies studied express both TREK 1 and 2. The proliferation of SKOV-3 cells was also reduced at 96 hours after incubation with the TREK 1 blockers curcumin and zinc.

Conclusions: We conclude that TREK 1 and 2 are expressed in ovarian cancer and TREK 1 blockade affects cell proliferation. Our future research will aim to determine whether TREK 1 and 2 can be used as prognostic markers and/or therapeutic targets in epithelial ovarian cancer.
GENE EXPRESSION OF OVARIAN CANCER AND THEIR IN VITRO CELL LINES - ADDRESSING THE PROBLEM OF TRANSLATIONAL CELL CULTURE RESEARCH

F. Hilpert¹, A. Sommer², S. Hammer³, K. Bräutigamm⁴, A. Strauss¹, W. Jonat¹, N. Arnold¹

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Introduction: Results of cell culture experiments in ovarian cancer (OC) are only heterogeneously assignable to clinical questions. Gene expression profiling of OC and their corresponding in vitro cultivated cell lines (CCL) can be used to address this issue of translational research.

Methods: Gene expression data of 23 primary OC and 41 corresponding tumor and ascites CCL were analysed using the Affymetrix HGU133Plus2.0 array. CCL were also characterized with regard to proliferation rate, response to cytostatic drugs and Interphase-in-situ-hybridisation (I-FISH).

Results: For 27 CCL, sufficient growth rates enabled the IC50 determination to standard chemotherapeutics. In contrast, no IC50 score was found for 14 CCL due to lack of cell proliferation. A distinct cluster was seen in primary tumor cells, fast proliferating CCL and slow proliferating CCL using principle component analysis (PCA). These clusters were also seen in paired samples of primary OC tissue and corresponding CCL: they did not only differ in proliferation associated genes but also in the expression of stromal, mesenchymal and epithelial markers as well as steroid-modifying enzymes and drug-resistance-genes. Interestingly, an up-regulation of drug resistance genes was observed in fast proliferating CCL in contrast to primary OC tissue. I-FISH analysis indicate genomic instability of the fast proliferating CCL.

Conclusion: Gene expression profiles and I-FISH-analysis are useful methods for a more detailed characterization of the molecular characteristics of OC-derived CCL. The observed genomic change in CCL in contrast to corresponding primary tumor cells underlines the well-known problem for translation of cell culture experiments into clinical practice.
NEOADJUVANT CHEMOTHERAPY PLUS SURGERY VERSUS PRIMARY SURGERY IN ADVANCED EPITHELIAL OVARIAN CARCINOMA

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Objective: The aim of this study was to compare the survival and peri-operative morbidities of patients with advanced epithelial ovarian cancer (EOC, stage IIIC and IV) who were treated with primary debulking surgery (PDS) followed by adjuvant platinum-based chemotherapy, or neoadjuvant chemotherapy followed by cytoreductive surgery (NAC).

Material and methods: The data of patients with Stage IIIC and IV epithelial ovarian cancer who were treated with either a primary surgery or neoadjuvant chemotherapy plus surgery between the years 2006-2009, were assessed retrospectively. Duration of surgery, feasibility of adequate surgery, complications during and after surgery, intraoperative blood transfusion requirements, duration of hospital stay, and average survival time were compared between groups.

Result: Group 1 consists of 30 patients who underwent cytoreductive surgery after neoadjuvant chemotherapy group 2 consists of 28 patients who underwent primary cytoreductive surgery. Optimal cytoreductive rate is 80% in group 1, this rate was found as 67.9% in the second group. Duration of surgery, the blood transfusion rate, and duration of hospital stay were significantly decreased with neoadjuvant chemotherapy. The mean survival was increased after neoadjuvant chemotherapy, but this difference was not statistically significant.

Conclusion: This study demonstrates that neoadjuvant chemotherapy followed by optimal debulking may be a safe and valuable treatment alternative in patients with primarily unresectable advanced-stage bulky ovarian cancer.
PREVENTION AND EARLY DETECTION OF METASTATIC OVARIAN TUMORS. IS IT POSSIBLE?

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Purpose: To investigate the presence of ovarian micrometastasis during surgery for gastric and colorectal carcinoma, and seek to identify risk factors for the development of synchronous ovarian metastasis.

Patients and methods: A cross-sectional study was performed from March 1, 2007 to the end of March, 2009. It included 24 patients with gastric and colorectal carcinoma who underwent surgical treatment. Cases with apparently normal ovaries were subjected to bilateral ovarian biopsies and examined immediately by frozen section technique, while cases with gross ovarian lesions were subjected to bilateral salpingo-oophorectomy or panhysterectomy.

Results: Ovarian metastases are confirmed in our study in 7 cases (29.2%). Two of these cases (8.3%) were associated with normal ovaries while, in the other 5 cases (20.8%), ovarian metastases were associated with unilateral or bilateral gross ovarian pathology. The 7 cases were exposed during the same procedure to bilateral salpingo-oophorectomy (5 cases) or panhysterectomy (2 cases). For patients who underwent ovarian biopsy, there were no reported intraoperative or early postoperative complications.

Conclusion: Bilateral ovarian biopsies can be performed during surgery for gastric and colorectal carcinomas for cases with apparently normal ovaries as a novel technique for the detection of ovarian micrometastasis.
SECONDARY CYTOREDUCTIVE SURGERY FOR RECURRENCE OF MULLÉRIAN CALCINOMA

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Aims: The aim of the study was to evaluate the effects of secondary cytoreductive surgery on survival in patients with recurrent mullérian carcinoma. Methods. Among all patients who underwent primary therapy for epithelial ovarian, tubal, and peritoneal cancer between 1992 and 2006 at our institute, the medical records of patients who were submitted to secondary cytoreductive surgery were retrospectively investigated.

Results: During this period, 223 patients received treatment for recurrence, of whom, 37 patients (15%) including 29 ovarian, 3 tubal, and 2 peritoneal cancer received surgery for recurrence. The distribution of stage was I, 4; II, 6; III, 19; IV, 5; and histological subtype was serous, 26; endometrioid, 4; clear cell, 4. Median age at treatment for recurrence was 57 years (range 47-76). Following primary therapy, recurrence was diagnosed after a median treatment-free interval of 10 months (range 2-137). The median CA125 value at recurrence was 29U/ml (range 8-234). Complete cytoreduction was achieved in 24 patients (75%). In a univariate analysis, early stage (I-II), longer treatment-free interval (>or=12 months), complete cytoreduction, and low CA125 level at recurrence (< 100) were significantly associated with better survival after recurrence. In a multivariate analysis, complete cytoreduction and low CA125 level were the only independent prognostic factors.

Conclusions: The impact of secondary cytoreductive surgery on a significant survival benefit was identified in not only patients who achieved complete cytoreduction but those with low CA125 level at recurrence. When considering treatment for recurrence, CA125 could contribute to therapeutic decisions and improvement of survival after recurrence.
BORDERLINE AND MALIGNANT OVARIAN TUMOURS REVIEW OF 105 PATIENTS

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Background: Ovarian malignancies are the most lethal of the gynaecologic tumours. They represent a great clinical challenge, and the lack of specific symptoms and effective screening may explain this high mortality. Most of the tumours are diagnosed at stages III and IV.

Aims: Determine the differences of our population when compared with classic literature.

Methods: We conduct a retrospective study in a public Hospital setting, with a miscellaneous population of Caucasian, African and Asiatic patients. The clinical files of the patients with ovarian tumours (borderline and malignant) treated in this Institution between June 1996 and February 2009 (n=105 patients) were analyzed. Evaluation was performed regarding cancer incidence by age, histological type, patient symptoms at presentation, levels of serum Ca125, and distribution by FIGO stages.

Results: The most frequent tumours were the epithelial serous malignant type. The great majority of cases were found in the age group 40-60 years, and the principal symptom that led to diagnosis was abdominal distension (41%). Measurement of serum Ca125 levels revealed a global sensitivity of 61% rising to 79% when considered only the serous malignant type. The distribution by stages revealed 44.8% of patients in stage I, 12.4% in stage II, 38% in stage III and 4.8% in stage IV.

Conclusions: Our population when compared with classic literature shows some differences: tumours were diagnosed in younger women (about a decade younger), serum Ca125 shows a decreased sensitivity, and most tumours were diagnosed in stage I.
MIGHT TGFβ HAVE AN INFLUENCE FOR PROGRESSION OF CLEAR CELL ADENOCARCINOMA OF THE OVARY? - A PRELIMINARY STUDY

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Objectives: Patients with stage lc clear cell adenocarcinoma of the ovary are shown to bad prognosis. It is very important to treat for microscopic dissemination into peritoneal cavity to improve their prognosis. In our previous studies, TGFβ inhibited the proliferation of ovarian clear cell adenocarcinoma cells directly. In addition, we demonstrated to show additive effect of TGFβ and several anti-cancer agents for growth inhibition of them. In this study, we examined the evidence of TGFβ for progression of RMG-1, which is a typical cell-line of ovarian clear cell adenocarcinoma.

Methods:

1) We studied the difference of adhesion activity and invasion activity of RMG-1 induced by TGFβ in vitro.

2) We investigated the RMG-1 tumorgenesis treated by TGFβ in peritoneal cavity of SCID mice.

3) We also studied the expression of MMP-2, MMP-7, MMP-9 in RMG-1 induced by TGFβ in vitro.

Results:

1) RMG-1 did not demonstrate the difference of the adhesion activity by the presence of TGFβ. On the other hand, it demonstrated the difference of the invasion activity.

2) The weight of intraperitoneal RMG-1 tumors in SCID mice was inhibited by TGFβ.

3) Although TGFβ was increased the expression of proMMP-7, it inhibited the expression of proMMP-2 and activeMMP-2.

Furthermore, there was no difference for expression of proMMP-9 by TGFβ.

Conclusions: TGFβ might decrease the invasion activity through the inhibition of activation of MMP-2 for ovarian clear cell adenocarcinoma cells. In addition, TGFβ might inhibit the progression of ovarian clear cell adenocarcinoma cells in peritoneal cavity.
CONSERVATIVE TREATMENT OF EARLY STAGE MALIGNANT EPITHELIAL OVARIAN CANCER: ONCOLOGICAL AND FERTILITY OUTCOME IN A SERIES OF 189 PATIENTS

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¹Clinic of Obstetrics and Gynecology, San Gerardo Hospital, University of Milan-Bicocca, Monza, ²Laboratory of Clinical Trials, Department of Oncology, Mario Negri Institute, Milan, Italy

Introduction: Approximately 10% of epithelial ovarian cancer (EOC) is diagnosed in premenopausal women. In these patients the identification of risk factors is crucial for choosing fertility-sparing treatment, and for planning subsequent management and follow-up.

Patients and methods: All patients treated in our centre with fertility-sparing surgery for stage I-II EOC were considered for this analysis. Demographics, anatomopathological, clinical data, recurrence and survival, as well as number of pregnancies obtained after treatment were recorded. Univariate and multivariate analysis were used to test demographic characteristics and clinical features for their association with OS, PFS and fertility.

Results: From 1981 and 2008 38 patients were treated in our centre and 151 patients were referred after first conservative surgery. At a median follow up of 10.3 years 25 patients relapsed (13%) and 12 patients (6%) died for progressive disease. At the univariate analysis age, clear cell histotype, grade 3 and chemotherapy treatment were significantly associated with a worsening of both PFS and OS. However, at the multivariate analysis only grade 3 confirmed to be a negative prognostic factor (OS: p-value=0.0067; PFS:p-value=0.0044). A total of 74 (40%) patients tried to conceive after treatment, 51 (69%) successfully. At the multivariate analysis the only factors affecting fertility were age and chemotherapeutic treatment. Patients who received chemotherapy had a lower probability of becoming pregnant (OR:0.26, p-value:0.0503).

Conclusion: Women with early stage EOC can be safely treated with conservative surgery. Patients with G3 tumors should be intensively monitored. Chemotherapy should be administered with caution, as it could impair fertility.
ID-2 PROTEIN EXPRESSION AND MICROVESSEL DENSITY ASSESSMENT IN VARIOUS TYPES OF MALIGNANT OVARIAN TUMORS

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Background: Selected DNA inhibitor/differentiation (Id) proteins of Helix-Loop-Helix family may be involved in growth and angiogenesis control in various types of malignancies.

Aim: To assess if the expression of Id2 protein is associated with microvessel density (MVD) and selected clinical features of malignant ovarian tumors.

Methods: The study group included 56 women operated because of malignant ovarian tumors. Tumor Id2 protein was assessed semiquantitatively (as 1 to 9 points) by immunohistochemistry and MVD was examined likewise as CD-34 expression. The findings were correlated with the tumor type, histological grading and tumor FIGO stage.

Results: The mean age (± SD) of the patients was 57±12.8 years and 37 (66.1%) of women were postmenopausal. There were 27 serous ovarian cancers (n=27), 12 mucinous cancers, 4 endometrioid cancers and 13 other malignant tumors. Expression of Id2 protein was found in 52 cases. Id2 protein was found in both nuclei and cytoplasm of cancer cells, however, some staining was seen in pericytes adjacent to tumor microcapillary lumen. Menopausal status had no influence on the intensity of protein staining. Low FIGO stage (I and II) tumors had medium or high Id2 expression. Microvessel density, but not Id2 expression was significantly correlated with tumor histological type (p=0.008). A significant correlation between Id2 expression and MVD was found (R=0.38; p=0.003). Median MVD was lower in patients with low when compared to high Id2 protein expression.

Conclusion: Id2 protein and MVD assessment may be used as additional factors characterizing angiogenesis in various types of ovarian malignancies.
RETROSPECTIVE ANALYSIS OF PATIENTS WITH ADVANCED EPITHELIAL OVARIAN CANCER WHOSE OVERALL SURVIVAL TIME IS BEYOND FIVE YEARS

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Objective: To evaluate the clinicopathological features of advanced epithelial ovarian cancer in recent 10 years and to analyze the factors associated with prognosis improvement.

Methods: One hundred and forty-one patients with advanced epithelial ovarian cancer treated in our hospital from January 1994 to December 2004 were analyzed retrospectively. They were divided into two groups based on their overall survival time. Forty-six patients whose overall survival time was beyond five years were included in the first group and the other ninety-five patients in the second group. The clinicopathological features were compared and factors associated with survival were identified.

Results: The residual tumor size was remarkably different. Those with residual tumor sizes≤2cm was 80.4% in the first group, which was 45.3% in the second group respectively. There is a difference in chemotherapy cycle between two groups, 89.1% patients in the first group were given 6 or more cycles of chemotherapy, the number was 77.9% in the second group. Univariate analysis revealed that patients with stage IIIa and IIIb, residual tumor sizes≤2cm, 6 or more cycles of chemotherapy were associated with better prognosis. Cox regression analysis identified only residual tumor size and chemotherapeutic courses were independent prognostic factors.

Conclusions: The optimal cytoreductive surgery and 6 or more cycles TP chemotherapy are necessary to improve the survival of patients with advanced epithelial ovarian cancer.
MALIGNANT EPITHELIAL OVARIAN CANCERS UNDER THE AGE OF 30 YEARS KK HOSPITAL EXPERIENCE

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Objective: To understand the incidence, tumor pathology, and management and subsequent fertility of young women with malignant epithelial ovarian cancers who are under 30 years of age.

Materials and methods: Between Jan 1993 to Jan 2008, A retrospective study conducted by analyzing the patient records and pathology reports in KK women’s and Children's hospital Singapore.

Results: A total of 187 cases of ovarian tumors were identified in young women under the age of 30 years. 26 patients were identified to have malignant epithelial ovarian tumors (14%). Mucinous adenocarcinoma was the commonest histological type identified. N=16 (62%). 15 patients (58%) were identified in Stage IA. 6 patients (23%) were identified in Stage IC. 3 patients were in advanced stage 3c and one patient was unstaged. Two patients were pregnant at the time of diagnosis. The median follow up time was 18 months (0 to 163months) there were 5 deaths in 26 patients. The mean survival time was 117 months (95%CI, 83months to 153months). 3 years survival is 75.8% and 5 years survival was 66.4%.

Conclusion: Epithelial ovarian malignancies are not uncommon in young women who wish to retain their fertility. Conservative surgery is feasible in stage 1a ovarian carcinoma.
A STUDY OF SYMPTOMS FOLLOWING TREATMENT FOR OVARIAN CANCER

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Background: Despite a 46% 5-year overall survival rate for ovarian cancer, little is known about the medium and long term consequences of anti-cancer therapy.

Aim: The aim of this study was to assess the effect of treatment on ovarian cancer patients attending oncology follow-up clinic.

Methods: We conducted a prospective study of women attending follow-up at Hammersmith Hospital from February-June 2010. Eligible patients had an original diagnosis of epithelial ovarian cancer, had completed first-line treatment (or treatment for relapse) and had no current clinical evidence of active disease. The questionnaire comprised a distress thermometer and 44 validated EORTC questions covering general, psychological, neurological, gastro-intestinal, respiratory, dermatological and hormonal symptoms.

Results: We received and analysed 100 completed questionnaires from patients, mean age 63 years (range: 31-88), mean time following treatment 560 days (range: 20-2181 days). Over 95% of patients experienced persistent psychological, neurological or general symptoms. Psychological: 96% had negative attitude to disease/treatment, 82% emotional disorders, 61% depression (19% severe) and 64% dissatisfaction with body image. Neurological: CNS symptoms in 79%, 77% had general neurological problems (weakness and frequent urination) and 63 % peripheral neuropathy (28% moderate/severe). General symptoms: 90% had performance difficulties, 81% pain (35% moderate/severe) and 75% social difficulties. Gastrointestinal: 89% mild symptoms. Thermometer scores close correlated with total questionnaire scores.

Conclusions: We concluded that ovarian cancer patients have a predominantly high incidence of psychological, neurological and general problems following treatment for ovarian cancer. The distress thermometer is a valid method of quickly assessing wellbeing.
INTRAPERITONEAL ALPHA-PARTICLE RADIOIMMUNOTHERAPY OF OVARIAN CANCER PATIENTS: PHARMACOKINETICS AND DOSIMETRY OF AT-211-MX35 F(AB’)2 - A PHASE I STUDY

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1Dept. of Oncology, 2Dept. of Radiation Physics, Sahlgrenska Akademy, University of Gothenburg, Gothenburg, Sweden, 3Memorial Sloan Kettering Cancer Center, New York, NY, USA, 4Dept. of Nuclear Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden, 5The Cyclotron and PET Unit, Rigshospitalet, Copenhagen, Denmark, 6IAEA Headquarter, Vienna, Austria

The alpha-emitter At-211 labeled to an antibody has proven safe and effective in treating microscopic ovarian cancer in the abdominal cavity of mice. Women in complete remission after second-line chemotherapy for recurrent ovarian carcinoma were enrolled in a phase I study. The aim was to determine the pharmacokinetics for assessing absorbed dose to normal tissues and investigating toxicity. Nine patients underwent laparoscopy before the therapy; a peritoneal catheter was inserted, and the abdominal cavity was inspected to exclude the presence of macroscopic tumor growth or major adhesions. At-211 was labeled to MX35 F(ab’)2. Patients were infused with At-211-MX35 F(ab’)2 in dialysis solution via the peritoneal catheter. Gamma-camera and SPECT scans were acquired after infusion. Samples of blood, urine, and peritoneal fluid were collected at 1-48 h. Hematology and renal and thyroid function were followed for a median of 23 mo. Pharmacokinetics and dosimetric results were related to the initial activity concentration (IC) of the infused solution. The activity concentration decreased with time in the peritoneal fluid to 50% IC at 24 h, increased in serum to 6% IC at 45 h, and increased in the thyroid to 127% +/- 63% IC at 20 h without blocking and less than 20% IC with blocking. The cumulative urinary excretion was 40 kBq/(MBq/L) at 24 h. No adverse effects were observed either subjectively or in laboratory parameters. Conclusion: This study indicates that by intraperitoneal administration of At-211-MX35 F(ab’)2, it is possible to achieve therapeutic absorbed doses in microscopic tumors without significant toxicity.
HEPATIC SAFETY PROFILE OF TRABECTEDIN IN PHASE II AND III CLINICAL TRIALS IN RELAPSED OVARIAN CANCER (ROC)


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Background: Trabectedin received European approval for platinum-sensitive ROC (in combination with pegylated liposomal doxorubicin [PLD]). Although transaminase elevations are common, no evidence of permanent drug-induced liver injury has been found in liver biopsies (Ann Oncol., 2008).

Methods: Clinical trial data in 628 ROC-patients were reviewed by presence/absence of liver-metastases (LM).

Results: c/u>Base-line characteristics: Median-age: 58(25-87), ECOG-PS≤2. All received prior platinum-based chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Trabectedin</th>
<th>Trabectedin+PLD</th>
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<tbody>
<tr>
<td>Total Patients (pts)</td>
<td>295</td>
<td>333</td>
</tr>
<tr>
<td>Pts with/without LM</td>
<td>83/212</td>
<td>101/232</td>
</tr>
<tr>
<td>Median number of cycles(range)</td>
<td>4(1-29)</td>
<td>6(1-21)</td>
</tr>
<tr>
<td>ALT/AST elevations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts</td>
<td>&lt;u&gt;G3+4-ALT&lt;/u&gt; - &lt;u&gt;G3+4-AST&lt;/u&gt;</td>
<td>&lt;u&gt;G3+4-ALT&lt;/u&gt; - &lt;u&gt;G3+4-AST&lt;/u&gt;</td>
</tr>
<tr>
<td>Pts with LM</td>
<td>111 (38%) - 53 (18%)</td>
<td>167 (50%) - 46 (14%)</td>
</tr>
<tr>
<td>G3+4 AST-onset:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts/with LM(*)</td>
<td>7(4-8)/8(7-8)</td>
<td>8(6-8)/7.5(6.5-8)</td>
</tr>
<tr>
<td>Days to recovery AST or retreatment:</td>
<td></td>
<td></td>
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<tr>
<td>All pts/with LM(*)</td>
<td>7(6-8)/7(7-7)</td>
<td>7(6-8)/7(7.7-5)</td>
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<tr>
<td>G3+4 ALT-onset:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts/with LM(*)</td>
<td>8(5-8)/8(8-8)</td>
<td>8(7-8)/8(7-8)</td>
</tr>
<tr>
<td>Days to recovery ALT or retreatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts/with LM(*)</td>
<td>11(7-14)/8(7-14)</td>
<td>7(7-12)/7(7-8)</td>
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</table>

(*)=Interquartile-range (days)

Results

Trabectedin-treated pts (295): 5 presented G3/4 hepatobiliary disorders(1 with LM); 12 (4.1%) discontinued treatment due to hepatobiliary-events; 6 (2%) went off-study (ALT/AST elevations). Trabectedin+PLD (333 pts): 7 (4 with LM) presented G3-4 hepatobiliary-disorders. No discontinuations observed due to increased transaminases. G3/4 ALT-elevations followed a pattern of decreasing severity with continuous treatment (monotherapy: p=0.0065; trabectedin+PLD: p< 0.0001).

Conclusions: Trabectedin causes transient, non-cumulative, reversible transaminase elevations with a low-rate of clinical hepatobiliary-disorders, even in patients with liver-metastases. These laboratory changes appear early and decrease in incidence and intensity, allowing prolonged treatment.
CORRELATION OF CA-125 AND RECIST IN THE MANAGEMENT OF PLATINUM-SENSITIVE RELAPSED OVARIAN CANCER (ROC): RESULTS FROM OVA-301 PHASE-III RANDOMIZED STUDY

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¹GROW-School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands, ²Oncological Institute Maria Skłodowska-Curie Memory, Krakow, Poland, ³Tom Baker Cancer Center, Calgary, ⁴Cross Cancer Institute, Edmonton, AB, Canada, ⁵Centre Hospitalier Lyon Sud, Lyon, France, ⁶Weston Park Hospital, Sheffield, UK, ⁷AZ Sint-Augustinus, Antwerpen, Belgium, ⁸Klinikum der Stadt Villingen-Schwenningen, Villingen-Schwenningen, Germany, ⁹Institut Català Oncologia Germans Trias i Pujol, Badalona, Spain, ¹⁰Sahlgrenska University Hospital, Gothenburg, Sweden, ¹¹PharmaMar, Madrid, Spain, ¹²Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ, USA, ¹³Gynecologic Oncology Unit, Catholic University, Rome, Italy

Background and aims: Study OVA-301 showed superiority of trabectedin-pegylated liposomal doxorubicin (PLD) over PLD in ROC patients. This analysis aims to examine the impact of early CA-125 (i.e. assessed at the 1st and 2nd evaluation post baseline) changes over the subsequent best response (BR) by RECIST and the concordance between BR determined by CA-125 and RECIST; and then observe the value of CA-125 to predict radiological response in the platinum-sensitive (PS) (platinum-free interval [PFI] ≥6 months) and partially PS (PPS) patients with PFI 6-12 months.

Methods: Tumor assessments/CA-125 were performed at baseline and every 8 weeks. PFS and responses were assessed by investigators (IA) and independent radiology (IR).

<table>
<thead>
<tr>
<th>Response by RECIST (IR)</th>
<th>Trabectedin+PLD</th>
<th>PLD</th>
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<tbody>
<tr>
<td>PS</td>
<td>35 %</td>
<td>23 %</td>
</tr>
<tr>
<td>PPS</td>
<td>33 %</td>
<td>15 %</td>
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<tr>
<th>CA-125 response</th>
<th>Trabectedin+PLD</th>
<th>PLD</th>
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<tbody>
<tr>
<td>PS</td>
<td>59 %</td>
<td>41 %</td>
</tr>
<tr>
<td>PPS</td>
<td>52 %</td>
<td>34 %</td>
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<tr>
<th>% of RECIST responders with ≥25% CA-125 decrease</th>
<th>Trabectedin+PLD</th>
<th>PLD</th>
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<tbody>
<tr>
<td>PS (1st evaluation)</td>
<td>88%</td>
<td>83%</td>
</tr>
<tr>
<td>PPS (1st evaluation)</td>
<td>87%</td>
<td>77%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% of RECIST-responders with ≥25% CA-125 decrease</th>
<th>Trabectedin+PLD</th>
<th>PLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS (2nd evaluation)</td>
<td>98%</td>
<td>90%</td>
</tr>
<tr>
<td>PPS (2nd evaluation)</td>
<td>97%</td>
<td>82%</td>
</tr>
</tbody>
</table>

By IA

<table>
<thead>
<tr>
<th></th>
<th>Concordance</th>
<th>PPV (positive predictive value)</th>
<th>NPV (negative predictive value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>77%</td>
<td>67%</td>
<td>87%</td>
</tr>
<tr>
<td>PPS</td>
<td>82%</td>
<td>72%</td>
<td>90%</td>
</tr>
</tbody>
</table>

By IR

<table>
<thead>
<tr>
<th></th>
<th>Concordance</th>
<th>PPV (positive predictive value)</th>
<th>NPV (negative predictive value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>70%</td>
<td>49%</td>
<td>91%</td>
</tr>
<tr>
<td>PPS</td>
<td>74%</td>
<td>50%</td>
<td>93%</td>
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</tbody>
</table>

[Table 2. CA-125 Response and Response by RECIST]
PREOPERATIVE PLATELET LYMPHOCYTE RATIO AS AN INDEPENDENT PROGNOSTIC MARKER IN OVARIAN CANCER

V. Asher¹, J. Lee², A. Innamma¹, A. Bali²

¹Obstetrics and Gynaecology, School of Graduate Entry Medicine and Health, University of Nottingham, ²Obstetrics and Gynaecology, Royal Derby Hospital, Derby, UK

Background and aims: Ovarian cancer is known to be associated with high mortality. Established prognostic markers like stage and presence of residual disease are only amenable to assessment postoperatively. Various preoperative markers including CA 125 have not shown to be associated with survival. Therefore there is a need for new prognostic markers to individualise treatment in patients with ovarian cancer. The aim of our study was to evaluate the prognostic significance of the preoperative haematological markers; Platelet Lymphocyte ratio (PLR) and Neutrophil Lymphocyte ratio (NLR) in patients with ovarian cancer.

Methods: Retrospective data on preoperative full blood count, Age, stage, tumour grade, extent of cytoreduction, histological subtype, details of adjuvant treatment, and disease specific survival on 235 patients undergoing surgery for ovarian cancer at Royal Derby Hospital from 1998 to 1998 was identified and recorded on a database. The prognostic significance of PLR and NLR was then determined using uni and multivariate analysis.

Results: High preoperative PLR (P< 0.001) and NLR (P=0.001) were significantly associated with poor survival using univariate Cox survival analysis. The median overall survival in patients with a PLR of < 300 was 37.4 months (95%CI 26.1-48.7) and 14.5 months (95%CI 11.7-17.2) in those with a PLR of >300. PLR (P=0.03) but not NLR (P=0.575) retained its significance as a prognostic marker on multivariate Cox's regression analysis, along with stage (P< 0.001) and residual disease (P=0.015).

Conclusion: We have shown for the first time that PLR is a novel Independent prognostic marker in patients with ovarian cancer.
STRATIFY, ADJUST OR INTERACT IN TIME-TO-EVENT ANALYSIS IN OVARIAN CANCER PATIENTS? LESSON TO BE LEARNED

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¹Medical Oncology, ²Pathology, ³Surgery, Cancer Institute 'Ion Chiricuta', ⁴Surgical Oncology, University of Medicine 'Iuliu Hateganu', Cluj-Napoca, Romania

**Background:** Ovarian cancer is the most common cause of cancer death from gynaecologic tumours in the US. The age impact on survival according to different statistical approaches was less explored.

**Methods:** The endpoint was to evaluate how the type of analysis affects the impact of age as a continuous variable on survival (calculated between diagnosis and death or last follow-up for censored patients): stratified, adjusted or using interaction-term. Hazard ratio (HR) were estimated with 95% confidence interval (CI) using Cox regression analyses.

**Results:** One thousand ovarian cancer patients diagnosed between 1991-2009 were included. Median age was 54 years (11-91); 24% deaths were observed. Median and 5-years survival with 95% CI: 6 years (4.2-7.7), 54% (49-59%), respectively. Age was associated with the outcome (p< 0.0001). FIGO stage as stratification or confounded variable has little impact on results.

**Conclusions:** This powered analysis demonstrates that age has a real impact on survival and should be included in all future analyses, itself and as an interaction-term.

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>% of patients</th>
<th>Median survival, years (95% CI)</th>
<th>5-year survival,% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>~</td>
<td>88 (80-97)</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>~</td>
<td>64 (42-86)</td>
</tr>
<tr>
<td>III</td>
<td>60</td>
<td>4.2 (2.3-6.1)</td>
<td>48 (41-54)</td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
<td>3.1 (1.8-4.5)</td>
<td>37 (24-50)</td>
</tr>
</tbody>
</table>

[Survival according FIGO stage]

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Unstratified</th>
<th>Stratified</th>
<th>Adjusted</th>
<th>Interaction-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables</td>
<td>~</td>
<td>FIGO stage</td>
<td>age * FIGO stage</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.026 (1.014-1.038)</td>
<td>1.022 (1.010-1.034)</td>
<td>1.021 (1.009-1.033)</td>
<td>1.086 (1.030-1.145)</td>
</tr>
</tbody>
</table>

[Survival according type of analysis]
THE EFFECTS OF HOPE AND SPIRITUALITY ON QUALITY OF LIFE (QOL) IN NEWLY DIAGNOSED OVARIAN CANCER PATIENTS

L. Ramondetta1, D. Zhukovsky2, D. Urbauer3, A. Brown4, K. Basen-Enquist5, C. Levenback1, M. Bevers1, P. Thacker6, S. Rodriguez1, C. Sun1

1Gynecologic Oncology, 2Palliative Care and Rehabilitation Medicine, 3Biostatistics, UT MD Anderson Cancer Center, Houston, TX, 4Johns Hopkins Medical Institutions, Baltimore, MD, 5Behavioral Science, UT MD Anderson Cancer Center, Houston, TX, 6Washington University in St. Louis, St. Louis, MO, USA

Background: The objective of this ongoing longitudinal IRB approved study is to unravel the relationship between hope, spirituality and QOL over time in newly diagnosed ovarian cancer patients.

Methods: Baseline surveys were collected prior to chemo cycle #2. Surveys included FACT-O (QOL), FACT-Sp Faith (religiosity) and Meaning/Peace (M/P) (spirituality) subscales, Hoge Intrinsic Religiosity, Herth Hope (HHS), Death Anxiety (DA), Edmonton Symptom Assessment (ESAS) and Hospital Anxiety and Depression (HADS). Regression analyses includes FACT-Sp, HOGE, HHS, hospital setting, race, and chemotherapy anaphylaxis as independent variables and FACT-O, HADS, DA and ESAS as dependent variables.

Results: Baseline data (83 pts) presented. Mean age 55.4 yrs; 65% White; 17% Hispanic; 13% AA. Hope was statistically associated with better QOL, fewer symptoms and lower anxiety (HADS and DA). Higher M/P was associated with lower depression/anxiety and better EWB, FWB, and SWB. M/P was not associated with PWB or FACT-O, symptom burden, or DA. Regression coefficients (b) and p values are below. Neither intrinsic religiosity nor Faith Fact-Sp was related to QOL, HADS or ESAS. Hispanics had poorer SWB (b = -2.74; 95%CI [-4.71, -0.76]); AAs had more anxiety (b=2.53; 95%CI [0.43, 4.64]).

<table>
<thead>
<tr>
<th></th>
<th>PWB</th>
<th>EWB</th>
<th>FWB</th>
<th>SWB</th>
<th>OVCA-WB</th>
<th>Symptom Burden (ESAS)</th>
<th>Anxiety (HADS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hope</td>
<td>0.53; p&lt;.001</td>
<td>0.37; p=.002</td>
<td>0.46; p=.009</td>
<td>0.40; p&lt;.001</td>
<td>0.65; p&lt;.001</td>
<td>-1.62; p&lt;.001</td>
<td>-.29; p=.007</td>
</tr>
<tr>
<td>Meaning/Peace</td>
<td>NS</td>
<td>0.39; p&lt;.001</td>
<td>0.50; p=.002</td>
<td>0.22 p=.014</td>
<td>NS</td>
<td>NS</td>
<td>-.29; p=.003</td>
</tr>
</tbody>
</table>

Conclusions: Although directionality is unclear, our data suggest increased hope, and to a lesser extent spirituality (M/P) are associated with better QOL and decreased symptom burden. Religiosity was not related to QOL.
THE USE OF FLUOROURACIL (5FU) WITH LEUCOVORIN IN WOMEN WITH HEAVILY PRETREATED ADVANCED OVARIAN CARCINOMA

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Gynecologic Oncology Division, Department of Obstetrics and Gynecology, Rabin Medical Center, Tel Aviv University - Sackler School of Medicine, Petah Tikva, Israel

Background: Women suffering recurrent platinum resistant ovarian carcinoma go through several lines of chemotherapy but eventually fail all conventional chemotherapy options. After exhausting other regimens, we incorporate Fluorouracil (5-FU) in a weekly regimen with leucovorin. For those women who failed to react to multiple lines of treatment, fluorouracil has been shown to be a reasonable option with reported response rates of 10 to 33%. We aim to report our experience with 5FU+Leucovorin in this patient population.

Methods: This is a retrospective chart review of women treated for recurrent ovarian carcinoma between January 2003 and December 2009. Women with recurrent ovarian carcinoma having been treated with at least 3 previous chemotherapy regimens whom received 5FU were eligible for the study. 5FU and leuocovorin are given at 600mg/m2 weekly for 6 weeks of an 8 week cycle. Patient charts were reviewed for demographics and disease history relevant to the administration of 5FU. Response was assessed clinically and by CA125 levels.

Results: Fifty-five patients matching inclusion criteria received 5FU during the study period. Twenty-eight percent of patients achieved a partial response and 7% stable disease for an overall response rate of 35%. We were able to administer only a median of 4 weekly doses (range 1-26). Patients died a median of 7 weeks after the last dose of 5FU administered.

Conclusions: In this population of heavily pre-treated patients, a significant response to 5FU can be achieved. Unfortunately the response is short lived and mostly partial. 5FU prolongs life in selected patients only.
THE DIAGNOSTIC VALUE OF PREOPERATIVE SERUM M-CSF LEVELS ALONE AND IN COMBINATION WITH CONVENTIONAL TUMOR MARKERS IN OVARIAN CANCER

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Dr. Zekai Tahir Burak Women Health Hospital, Ankara, Turkey

Introduction: Ovarian cancer has the highest fatality-to-case ratio of all the gynecologic malignancies. Up to 90% of patients can be cured when it is diagnosed in stage-I. M-CSF is a hematopoietical-cytokine thought to have an important role in tumoral immunopathogenesis.

Materials and methods: Preoperative M-CSF levels were retrospectively measured in 36 patients with ovarian cancer and in 35 patients with benign ovarian disease. M-CSF was evaluated for its ability to discriminate malign from benign pelvic masses. Serum CA125, CA19-9, CA15-3, CEA and AFP levels were also determined, and all the markers are combined with stepwise logistic regression analysis to form a diagnostic multiple-marker model.

Results: The mean value of M-CSF among cancer patients was approximately 3.2-fold higher than the control group's. M-CSF's sensitivity and specificity were 97.2% and 80% at the cut-off value of 990.55pg/ml. M-CSF and CA125 combination could detect all the early-stage ovarian cancer cases. In addition to CA125/M-CSF combination, CEA was determined to exist in the logistic regression model. The overall predictivity of the model was 90.1%.

Discussion: Both the sensitivity of M-CSF(97.2%) when its cut-off was chosen to be 990.55pg/ml, and the overall predictivity(90.1%) of the diagnostic model formed with logistic regression, were higher values than those in the previous reports. Correct diagnosis of all the early-stage cases with the CA125/M-CSF combination is a remarkable observation. Using multiple markers and combining these with a systematic statistical approach shows the promise of early detection of ovarian cancer. M-CSF seems to have a significant place in the future of oncology.
MALIGNANT TRANSFORMATION ARISING FROM MATURE CYSTIC TERATOMA OF THE OVARY: A RETROSPECTIVE STUDY OF 20 CASES

H. Tokunaga¹, M. Sakuma¹, A. Otsuki¹, N. Shiga¹, T. Otsuki¹, K. Yoshinaga¹, H. Utsunomiya¹, S. Nagase¹, T. Takano¹, H. Niikura¹, K. Ito¹, K. Otomo², T. Tase², Y. Watanabe³, N. Yaegashi¹

¹OB/GYN, Tohoku University Hospital, Sendai, ²Gynecology, Miyagi Cancer Center, Natori, ³OB/GYN, Kinki University School of Medicine, Sayama, Japan

Objectives: Mature cystic teratoma (MCT) of the ovary rarely undergoes malignant transformation. Malignant transformation (MT) carries a poor prognosis, regardless of whether postoperative chemotherapy or radiotherapy is applied. The rarity of this tumor has posed a significant challenge to developing standardized postoperative management protocols. The aim of this study was to review our experience with MT and to describe our current treatment practices.

Methods: A retrospective chart review of these patients was performed which identified 20 women treated for MT of MCT at our centers between 1988 and 2008.

Results: The median age was 52.5 (29-77). Fifteen patients had squamous cell carcinoma (SCC), and 5 patients had other histological subtypes. The FIGO stage distribution was as follows: 11 were stage I, 4 were stage II, 4 were stage III, and 1 was stage IV. All patients underwent an initial laparotomy. Eleven patients were received adjuvant treatment: eight were treated with chemotherapy, two with concurrent chemoradiation therapy and one with radiation therapy. Platinum-based chemotherapy was the first line regimen. The overall one-year survival rate was 70%. One patient in stage III patient had a disease free interval of two years. Two cases of SCC treated with combination platinum/taxane chemotherapy temporarily responded. In the other two cases of SCC, concurrent chemoradiation therapy with nedaplatin was also resulted in tumor regression.

Conclusions: The prognosis of MT is highly dependent on age, stage, and optimal cytoreduction. Adjuvant treatment has not been standardized though our experience supports the use of combination platinum/taxane chemotherapy.
COLON AND RECTAL RESECTIONS DURING PERITONECTOMY PLUS HIPEC IN PATIENTS WITH DIFFUSE OVARIAN PERITONEAL CARCINOMATOSIS

S. Sibio, P. Sammartino, M. Cardi, F. Accarpio, D. Blacchi, A. Baccheschi, T. Cornali, A. di Giorgio

Department of Surgery ‘Pietro Valdoni’, University of Rome ‘La Sapienza’, Roma, Italy

Introduction: Rectum and colon are very frequently involved in ovarian carcinomatosis. Due to need for multiple colorectal resections during peritonectomies, surgical strategy for colorectal resections needs to be carefully stated.

Methods: We attempted to find standardized criteria for colorectal resections during peritonectomy, reviewing our series of 70 patients treated for ovarian carcinomatosis in nine years.

Results: Out of 70 patients treated, 52 underwent colorectal resections: 47 rectal resections, 23 rectal resections with left hemicolectomy, 4 right hemicolectomies, 1 left hemicolectomy with rectal preservation, and 6 rectal, left and right colectomy with transverse colon preservation.

Conclusion: Extent of colorectal resections during peritonectomy is a debated issue. Our experience suggest that final extent of resections should not exceed half of total length, to avoid functional disorders. We prefer rectal resection to simple Douglas peritoneum stripping, because of high probability of recurrence in this site. Usually, we avoid bowel continuity restoration, performing a temporary colostomy, in order to minimize the anastomosis leakage risk related to HIPEC. We perform bowel restoration after adequate follow up during second look. We prefer to perform right, left and rectal resection preserving transverse colon in order to perform a colostomy rather than ileostomy, with less patient's discomfort. In rectal and left colon resection, we perform inferior mesenteric artery section at its aortic origin, which let to remove all the meso with its lymph nodes, often metastatic. Statistical analysis identified deepness of involvement of colorectal layers, from serosal to mucosal one (“reverse” TNM) and CC-score as independent prognostic factors.
IDENTIFICATION OF PROTEOMIC BIOMARKERS IN OVARIAN CANCER

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\textsuperscript{1}CLIPP - Centre Hospitalier Universitaire Dijon,\textsuperscript{2}Pathology and Tumour Biology,\textsuperscript{3}Medical Oncology, Centre George-François Leclerc, Dijon, France

The prognosis of advanced ovarian cancers remains very poor, due to tumour extent at the time of diagnosis and to the limited efficacy of treatment for advanced stages. It would be extremely valuable to identify early indicators of the response to chemotherapy in order to optimize therapeutic management. Today, biomedical research is making use of new technologies to improve understanding of disease characteristics and drug resistance. In recent years, the use of mass spectrometry in particular has been increasing in this field.

In this retrospective study, this technology was applied to the identification of early prognosis markers. Plasma from 30 patients treated in the Georges-François Leclerc Center in Dijon were collected before and just after primary surgery, as well as after the first four chemotherapy courses. The follow-up of the patients studied ranged from 5.6 to 12.1 years (median = 8.6 years), and 83% of them died from their cancer. The plasma samples were treated and the resulting proteomic fractions were then analyzed through a MALDI-TOF mass spectrometer, which allows the separation and large-scale detection of proteins present in plasma. Survival Cox models adapted to the high dimensional setting were performed on the resulting data to identify relevant biomarkers at each stage of the treatment. This led to the selection of potential biomarkers predictive of overall and relapse-free survival.

This study identified potential markers of overall and relapse-free survival. A further study is planned on a bigger cohort to confirm these first findings.
AN ECONOMIC ANALYSIS OF BEVACIZUMAB IN RECURRENT TREATMENT OF OVARIAN CANCER

J. Chan¹, B. Monk², K. Fuh¹, R. Urban¹, L. Hu¹, A. Caughey¹, X. Yu³

¹University of California, San Francisco, ²University of California, Irvine, CA, ³Nova Southeastern University, Ft. Lauderdale, FL, USA

Objective: To determine whether the addition of bevacizumab (B) to chemotherapy for the recurrent treatment of advanced ovarian cancer is cost effective.

Methods: An economic analysis compared the two arms of the OCEANS trial (Gemcitabine, Carboplatin=GC vs. Gemcitabine, Carboplatin with concurrent and maintenance Bevacizumab (GCB+B).

Results: Of 240 patients entered into each arm of OCEANS trial, the baseline estimates of progression-free survival (8.6 month for GC group, and 11 month for GCB+B group, assuming 21% improvement of new treatment) and bowel perforation, the cost of GC was $4.0 million, compared with $36.5 million for GCB + B. These costs resulted to an ICER of $677,250 per LYS for GCB+B compared with GC. If one were to assume a PFS of 15 months (6 additional months of benefit) associated with GCB + B, then this results in an ICER of $253,968.

Using a maximum ICER threshold of $100,000 per LYS to deem an intervention as cost-effective, the cost of B would have to be decreased by 76%, or extend the progression-free survival to 25 months for GCB+B. If no additional risk of intestinal perforation is attributed to the addition of B (2% all arms and 25% of them are fatal perforation), the ICER in GCB+B continued to exceed $665,229 per LYS.

Conclusions: In this exploratory analysis of the OCEANS trial, the addition of bevacizumab to combination chemotherapy to the treatment of recurrent ovarian cancer is associated with significant costs with potential benefits. Further investigations are warranted.
MICRORNA EXPRESSION PROFILES THAT PREDICT FOR DISTANT METASTASIS IN SEROUS OVARIAN CANCER

A. Sherman¹, A. Sultan¹, D. Kapp², J. Chan¹

¹University of California, San Francisco, ²Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Stanford University School of Medicine, Stanford Cancer Center, Stanford, CA, USA

Objective: To compare the differential microRNA expression in patients with loco-regional vs. metastatic serous ovarian cancer.

Methods: Demographic, clinico-pathologic, recurrence, survival, and genomic data were extracted from The Cancer Genomic Atlas (TCGA) data portal. 443 specimens with matched normal tissue controls and analyzed all specimens using Agilent microRNA array platform. Chi squared and logistic regression models were employed for statistical analyses. Targetscan and Pictar genomic sequence analyses were utilized to identify gene targets of specific microRNAs.

Results: Of 443 tumor specimens, all were of serous histology. Those with loco-regional disease had a five-year overall survival of 35.4% vs. 27.9% in those with metastatic disease (p=0.12). Fifteen microRNAs were found to have differential expression in stage IV tumors vs. others. A significant proportion of stage IV tumors had high expression of miR-139-5p (21.3% vs. 6.3%; p=0.001) and miR-224 (21.3% vs. 8.6%; p=0.034). Other microRNAs such as miR-25 and miR-542-3p had lower expression in stage IV disease. On multivariate analysis, elevated miR-139-5p (HR: 2.01; 95%CI: 1.24-3.24; p=0.004) and miR-224 (HR: 1.74; 95%CI: 1.12-2.71; p=0.015) remained as independent predictors for metastatic disease after adjusting for age and residual disease. MiRanda algorithms for complementarity identified HS2ST, TBX, and GPR56G as gene targets associated with miR-139-5p. GPR56G has been implicated as an inhibitor of tumor progression, and has been found to be down-regulated in metastatic cancers.

Conclusions: Our data suggests that miR-139-5p and miR-224 are associated with metastatic serous ovarian cancer. Targeting microRNA expression may have significant promise in the treatment of ovarian cancer.
TUBULOGLANDULAR-VARIANT OF HIGH-GRADE OVARIAN SEROUS CARCINOMA: CLINICOPATHOLOGIC FEATURES OF AN UNCOMMON AGGRESSIVE TUMOR EASILY MISDIAGNOSED AS LOW GRADE ENDOMETRIOID ADENOCARCINOMA

A. Aysal, I. Medhi, J. Grenert, J. Rabban

Pathology, University of California, San Francisco, CA, USA

Aims: Pathologic distinction of ovarian serous carcinoma (OvSC) from ovarian endometrioid adenocarcinoma (OvEA) is essential for proper management. Generally this distinction is straightforward on microscopic examination; however, high grade OvSC may rarely exhibit pure tubuloglandular architecture that mimics low grade OvEA, potentially leading to misdiagnosis and under-treatment. This study defines the incidence, clinicopathologic features, and behavior of tubuloglandular high-grade OvSC that were reclassified from a cohort originally diagnosed as pure OvEA.

Methods: Pathology slides of 96 pure OvEA from women treated at a single institution between 1985 and 2009 were reviewed by gynecologic pathologists. The tubuloglandular variant of high-grade OvSC was defined as a carcinoma with discordant architecture and cytology: the architecture mimicked low grade OvEA but high grade nuclear atypia resembled high grade OvSC. Diagnoses were confirmed by immunohistochemical expression of WT-1, p16 and p53.

Results: Among 96 primary ovarian carcinomas originally diagnosed as pure OvEA, 8 (8.3%) were reclassified as tubuloglandular variant OvSC. Average age was 56 versus 51 for OvEA. Among OvSC, WT-1 was positive in 87%; p16: 100%; p53: 62%. Among confirmed OvEA, WT-1 was positive in 4 %; p16: 18 %; p53: 2 %. Among OvSC, 75% were stage III versus 25% among OvEA. Within available followup time, twice as many OvSC died versus OvEA (37.5% versus 17%).

Conclusion: The uncommon tubuloglandular variant of high-grade OvSC is easily misdiagnosed as OvEA but has worse behavior. Attention to discrepant architecture versus cytology and confirmatory immunostaining may minimize pathological misclassification and allow for appropriate management.
COMBINATION OF INTRA-PERITONEAL HYPERTHERMIA AND ALPHA-GALACTOSYLCERAMIDE IN TREATING OVARIAN CANCER

C.-L. Chang¹,², Y.-H. Huang¹, K.-L. Wang¹, Y.-C. Yang¹

¹Department of Obstetrics and Gynecology, Mackay Memorial Hospital, ²Department of Medicine, Mackay Medical College, Taipei, Taiwan R.O.C.

Background: Recent studies confirmed the clinical benefit of combining intra-operative hyperthermia with chemotherapy. However, vaporization of chemotherapeutic agents remained the main concern of this treatment modality. Alpha-galactosylceramide(α-GalCer), a NK cell activator, has also been applied clinically in treating cancers. The aim of our study was to evaluate the efficacy of combing hyperthermia with non-vaporized glycolipid in treating ovarian cancer.

Methods: We utilized two mouse ovarian cancer cell lines, HM-1 and ID8 to develop study models of mice with disseminated intra-peritoneal metastasis and ascites. The hyperthermia facility composed of a heating probe and a temperature detector to achieve intra-peritoneal hyperthermia at 43°C. Response to treatment and immunoassays including NK(T) cell analysis and cytotoxicity assay, phagocytosis and maturation of DC cells, systemic IFN-γ and tumor-specific CD4+, CD8+ T cell analysis were analyzed in different groups with individual treatment.

Results: Intra-peritoneal hyperthermia exhibited marked apoptosis and cell death. Serum IFN-γ concentration reached the peak at 20 hours after treatment. NK cells were induced instead of NKT cells 3 hours after intra-peritoneal α-GalCer infusion. Significant elevation of activated antigen-specific CD8+ cells, phagocytosis of splenic DC and cytotoxicity were observed in combination of hyperthermia and α-GalCer group, compared to by α-GalCer alone or hyperthermia alone group.

Conclusion: Treatment in combination of intra-peritoneal hyperthermia and α-GalCer possessed great anti-tumor effect and improvement on survival in mice with advanced ovarian cancer. The in-vitro result is encouraging and warranted further evaluation for maximizing therapeutic benefit and potential on clinical application.
NOVEL ROLE OF METFORMIN IN THE TREATMENT OF OVARIAN CANCER

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Objective: To evaluate the potential anti-neoplastic effects of metformin, a widely used first line anti-diabetes drug and reported recently to lower cancer risk and the rate of cancer deaths in ovarian cancer in vitro and in vivo.

Materials and methods: The human ovarian cancer cell lines, TOV112D and SKOV3 were used. Cell proliferation was assessed after exposure to sequential doses of metformin. Cell cycle progression and apoptosis were also evaluated by flow cytometry. Western immunoblotting was performed to determine the expression of the downstream targets of metformin. The anti-tumor effect of metformin against ovarian cancer cells in vivo was assessed in murine ovarian cancer OVHM-bearing mice.

Results: Metformin inhibited growth in a dose-dependent manner in both cell lines. Treatment with metformin resulted in G1 arrest in TOV112D cells and apoptosis in SKOV3 cells. Western immunoblot analysis demonstrated that metformin induced phosphorylation of AMPK within 24 hours of exposure. Furthermore, metformin inhibited tumor growth significantly in OVHM-bearing mice. Interestingly, metformin treatment up-regulated the expression of estrogen receptor (ER) and the inhibition of cell growth is ER-dependent.

Conclusion: Metformin was demonstrated to be effective as a cytotoxic agent against ovarian cancers in vivo and in vitro. The mechanism of tumor inhibition is relevant to estrogenic network. Combining the documented effect of immune-modulation, metformin appeared to be a potential therapeutic agent against ovarian cancer.
PREOPERATIVE ANGIOPOIETIN-2 SERUM LEVELS - A MARKER OF MALIGNANT POTENTIAL IN OVARIAN NEOPLASMS AND POOR PROGNOSIS IN EPITHELIAL OVARIAN CANCER

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Background and aims: We aimed to explore the levels of angiopoietin-1 and angiopoietin-2 in patients with benign, borderline or malignant epithelial ovarian tumours and to compare them to those of healthy controls. In addition, we aimed to study how Ang-1 and Ang-2 levels predict the clinical course and survival of patients with epithelial ovarian cancer.

Methods: We enrolled 150 patients with ovarian neoplasms and 34 women with healthy ovaries in this study. Further, we measured the levels of Ang-1 and Ang-2 in patients having an ovarian metastasis of another cancer (n = 29). Serum samples were collected preoperatively at the time of diagnosis and Ang-1 and Ang-2 levels were measured with ELISA.

Results: Ang-1 and Ang-2 levels were significantly elevated in serum samples of ovarian carcinoma patients compared to normal controls (P= 0.0005 and P< 0.0005, respectively). In addition, Ang-2 levels were significantly higher in patients with ovarian carcinoma compared to patients with benign (P< 0.0005) or borderline ovarian tumours (P=0.011). High serum levels of Ang-1 and Ang-2 were associated with primary residual tumour >1cm after debulking surgery and high Ang-2 levels correlated positively with an advanced tumour stage (P= 0.042). Elevated Ang-2 level (> 2.7 ng/mL) was a significant predictor of poor overall and recurrence free survival (P= 0.043 and P= 0.033, respectively) when assessing Kaplan-Meier curves by a log rank test.

Conclusions: These results suggest that Ang-2 may have potential as a diagnostic tool for screening ovarian tumours and may serve as an angiogenic marker of decreased patient survival.
THE RISK OF LAPAROSCOPY COMPLICATION IN OVARIAN TUMOR EXTRACTION

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Objective: Ovarian tumours can occur in all stages of a woman’s life. During reproductive age, functional cysts, endometriotic cysts, dermoids and benign epithelial tumours predominate. Most commonly malignant ovarian tumors can be detected in perimenopausal women. The aim of our study is to evaluate the risk of complication such as spillage or detorsion of an ovarian tumor during laparoscopy.

Material and methods: Conservative laparoscopic surgery was performed from June 2007 to December 2009 in 42 patients with middle and low risk ovarian cysts of 8,8 cm mean diameter (±4,2 cm). All women were in premenopausal status from 35 to 44 years of age. Suggested preoperative assessment for ovarian tumor as transvaginal ultrasonography for morphologic evaluation, color Doppler transvaginal ultrasonography to assess vascular resistance index and pulsatility index and serum levels of CA125 with cutoff value of 35 U/mL were performed in all our patients. Laparoscopic surgery was successful in 40 (95.2%) patients.

Results: The tumors, mostly low risk ovarian cysts (n=37), were extracted using endobags in women submitted to successful laparoscopic surgery without spillage in thirty-one cases (77.5%). Ovary spillage occurred in nine cases (22.5%). There were no operative or post-operative complications.

Conclusion: Most of ovarian masses can be operated laparoscopically. Meticulous preoperative assessment can reduce the risk of laparoscopy surgery on ovarian masses. It is a good practice to use an endobag before rupturing and or extracting any ovarian cyst. Non malignant ovarian pathology remains the most common indication for laparoscopy surgery and it results a safe procedure for women.
CISPLATIN AND HYPERTHERMIA IN OVARIAN CANCER CELL LINE COC1, COC1/DDP
APOPTOSIS AND DRUG RESISTANCE

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Purpose: We discuss the proliferation, apoptosis and drug resistance of hyperthermia, chemotherapy and their combination on ovarian cancer cell line coc1, coc1/DDP and try to explore their possible mechanism.

Methods: We adopt MTT method to test the growth inhibition of different concentrations of cisplatin and hyperthermia (42 °C, 60min) and their combination on cell coc1, coc1/DDP. RT-PCR used to detect the two groups of cells between the expression of Survivin and ERCC1.

Results: Hyperthermia on cell killing effect is a certain, especially in 42 °C, 60min role in the best. Compared hyperthermia combined with cisplatin and cisplatin alone (2.5ug/ml) or hyperthermia alone (42 °C, 60min), the apoptosis rate was significantly increased (p < 0.05). And the heating of the cells have enhanced sensitivity to chemotherapy.

Conclusion: Hyperthermia combined with chemotherapy can significantly inhibit the cell line coc1, coc1/DDP proliferation and induce apoptosis, and increases the cells sensitivity to cisplatin. The mechanism may be related to reduced survivin, ERCC1 gene expression. The experiment of combination of hyperthermia and chemotherapy in the human body heat to provide a basis for in vitro experiments.
RECURRENT EPITHELIAL OVARIAN CANCER - WHICH CHEMOTHERAPY LINE SHOULD BE THE LAST ONE?


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Introduction: Recurrent epithelial ovarian cancer (EOC) is considered a chronic disease, with need for multiple chemotherapy treatments of considerable toxicity. Treatment efficacy beyond the second line of chemotherapy is not well studied. We aimed to find out which chemotherapy line should be the last one.

Methods: Retrospective consecutive chart review of 215 women with EOC stage I-IV, diagnosed between 1994-2001 and treated at our medical center was carried out. Data collected included demographic and clinical characteristics. Cox proportional Hazard model was performed to determine the optimal number of chemotherapy lines adjusted for conventional risk factors.

Results: Mean age at diagnosis was 65.7±12.6 (range 23-94y). Median survival was 42.3 months (Range 1 month-6 years). Optimal debulking was achieved in 143 patients (74%). 177 (82%) of patients were platinum sensitive. Fifty percent of patients received three or more treatment lines (25.1% ≥5 treatment lines). Better survival was in correlation with lower CA125 and better Karnofsky score at diagnosis, optimal debulking, and platinum sensitivity.

Response rates from the 4th treatment line and up were low (0-13%).

In patients with recurrent EOC, the hazard ratio for survival, adjusted for optimal debulking, platinum sensitivity, stage and age for patients who received>2 treatments was 1.64 (95% CI 1.03-2.6). The hazard ratio for survival for patients who received>3 treatment lines was 1.3 (95% CI 0.85-1.9).

Conclusions: According to our retrospective data, in patients with recurrent EOC, the added value of the fourth treatment line and up is questionable.
DOES INTRAPERITONEAL CHEMOTHERAPY BENEFIT OPTIMALLY DEBULKED EPITHELIAL OVARIAN CANCER PATIENTS AFTER NEOADJUVANT CHEMOTHERAPY?

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Objective: To compare the outcome of optimally debulked ovarian cancer treated with neoadjuvant chemotherapy followed by intraperitoneal (IP) versus intravenous (IV) chemotherapy.

Methods: Ovarian cancer patients treated with neoadjuvant chemotherapy who received at least 3 cycles of IP chemotherapy after interval surgery were identified from the ovarian cancer database. A matched cohort of patients treated with standard dose IV platinum/taxane chemotherapy were chosen as control patients. The IP regimen administered was similar to the GOG 172 protocol. Cox regression and Kaplan Meier analysis was used to model progression free and overall survival respectively.

Results: 54 IV and 17 IP treated patients were identified. 51/71 (72%) patients had grade 3 tumour. There was no significant difference between the 2 groups with respect to age and the percentage of patients with microscopic residual. Clinical complete response was observed in 67% and 88% of IV and IP treated patients respectively. The median follow up time was 29 months. Estimated median progression free survival (PFS) was 18 months and 14.1 months in IV and IP treated patients respectively (p=0.42). The post surgical chemotherapy treatment regimen was not significant in the Cox model for PFS when adjusted for age and microscopic residual status (p=0.56). Macroscopic residual disease was significantly predictive of PFS (HR=2.2 ,p= 0.01). There was no statistically significant difference in overall survival between the 2 groups.

Conclusion: Survival benefit from IP chemotherapy may not be significantly increased over IV chemotherapy in neoadjuvant setting. This observation needs to be confirmed in larger prospective randomized studies.
THE CLINICAL BENEFIT OF CIS-PLATIN-ADRIAMYCIN COMBINATION IN HEAVILY PRETREATED OVARIAN CANCER PATIENTS

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Cis Platin-Adriamycin combination (50 mg/m² / 3 weeks) was used to treat ovarian cancer patients after failure of various chemotherapy lines. Eighteen patients were treated. Their median age was 67 years (41-79). They all had post operative first line carboplatin combination therapy and 88% achieved NED status at end of therapy. They progressed within 1-74 months from end of carboplatin therapy (median 9, mean 14). 13/25 (52%) of patients were platinum resistant. Cis platin - Adriamycin combination was used as 2nd to 6th line of therapy (median 4th). 12/25 patients (48%) had severe symptoms of disease, 6/25 (24%) mild to moderate symptoms and 6/25 (24%) were asymptomatic. 2-10 cycles of therapy were administered (median 6) using 60-100% of planned dose (median 80). Grade III toxicity was noted in 9/25 patients (36%) - (myelotoxicity in 5, neuropathy in 2 and asthenia in 2 patients). 7/25 patients (28%) reported quality of life improvement, 13/25 (52%) stable quality of life and 5/25 (20%) reported quality of life deterioration during therapy. 17/25 patients (68%) benefited from therapy. 5/25 (20%) achieved complete response, 5/25 (20%) partial response and 7/25 (28%) disease stabilization. 8/13 (61%) platinum resistant patients responded: 3 achieved complete response, 2 partial response and 3 minimal response. Mean time to progression was 8 months (median 8, 3-16). We concluded that Cis-Platin - Adriamycin combination used as 4th line (median) chemotherapy regimen is still effective in heavily pretreated ovarian cancer patients. Clinical benefit can be achieved with reasonable toxicity.
A RAPID DECREASE FOLLOWED BY A PLATEAU CONCENTRATION OF CA125 IN OVARIAN CANCER DURING ADJUVANT CHEMOTHERAPY COULD PREDICT PATHOLOGICAL RESPONSE

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The prognostic value of the decreasing patterns of serum CA125 (measured as percentage decrease at each cycle of chemotherapy) was tested in 71 patients affected by advanced epithelial ovarian cancer treated at our institute with primary debulking surgery followed by 6 cycles of platinum based chemotherapy in clinical complete response who underwent a second look operation.

These observations were retrospectively matched with the recorded outcomes at second look operation. Mid-set plateau decrement pattern patients showed a pathological complete response (pCR) in 60% of cases, while late-set decrement pattern patients showed pathological complete response only in 25% of cases.

To increase the performance of the analysis we applied a LOOCV test (Leave-one-out Cross-Validation), using a single observation from the original group (either pCR vs non-pCR group) as the validation data, and the remaining observations as the training data.

Among the ROC curves built on the statistical models that have been tested, the best predictive value was relevant to the late percentage decrease between the samples obtained after 2nd, 3rd, and 6th cycle of chemotherapy.

This model \[ \log(\text{Odds}(Y = \text{pCR} \mid \text{CA125})) = 2.1 + 4.3t^2 - 6.4t^3 \] carries specificity of 73% and sensitivity 61% in identifying in advance patients with surgically proved complete remission after a full course of chemotherapy.

In conclusion, this statistical tool could help the clinicians in treatment planning.
CYTOREDUCTIVE SURGERY AND SEQUENTIAL MAINTENANCE CHEMOTHERAPY WITH TAXANE AND ORAL ETOPOSIDE FOR ADVANCED OVARIAN CANCER AND PERITONEAL CANCER

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Background: Majority of patients with advanced ovarian cancer will recur and have poor prognoses even if they once achieve clinical remission with initial treatment. In this study we demonstrate our preliminary results of sequential maintenance chemotherapy with taxane and oral etoposide for these advanced cases.

Methods: Sixteen cases with Stage III ovarian cancer or peritoneal cancer were treated between August, 2007 and December, 2009. As initial treatment for these cases, we performed cytoreductive surgery including diaphragm stripping, peritoneal stripping, bowel resection, or systematic pelvic and aortic node dissection, and thereafter administered standard tri-weekly chemotherapy with taxane and carboplatin for 6 to 8 courses. Two cases underwent interval cytoreductive surgery after neoadjuvant chemotherapy. Cases with multiple dissemination at the surgery achieved clinical remission were eligible for maintenance chemotherapy with taxane at the same dosage as initial therapy given monthly for 10 to 12 cycles, then oral etoposide (50 mg/ day x 21 days) given monthly for three or four cycles.

Results: Fifteen out of 16 cases (93.7 %) achieved optimal resection, and 11 cases among them achieved macroscopically complete resection. Eight cases were provided the maintenance chemotherapy and 6 cases of them have completed or are continuing as scheduled without any severe adverse effects. Progression free survival is 76.9% with 350 days of median follow up period (105 days to 851 days).

Conclusion: Sequential maintenance chemotherapy with taxane and oral etoposide is feasible and may improve the prognoses of the patients with advanced ovarian or peritoneal cancer.
CONCURRENT SEROUS BORDERLINE TUMORS PREDICT BETTER OUTCOME IN LOW GRADE SEROUS OVARIAN CARCINOMAS

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Objective: To compare low-grade serous ovarian cancers (LG) and their potential precursors, serous borderline tumors (SBT), to determine any predictors of progressive disease or worse outcome.

Methods: A single institution review was conducted to identify patients with SBT and LG diagnosed between 1/95-12/08. Mann-Whitney, Fisher's exact test, Kaplan-Meier, and Cox regression were performed.

Results: During this time period, 118 SBT and 69 LG were diagnosed with 79.7% of LG Stage III-IV and 73.7% of SBT Stage I-II. Intraoperative frozen section incorrectly identified LG specimens as SBT in 26.1% of cases. LG patients were more likely to be of advanced stage (OR=4.6, p< 0.001) and demonstrate higher preoperative CA-125 levels (200.0 vs. 91.9, p=0.02) but no differences were seen in age (48.6 vs 45.9, p=0.28), race (p=0.13), maximum tumor size (10.5 vs 9.9 cm, p=0.54), or implant site (p=0.73). Advanced stage LG patients presented nearly 9 years later (mean age 48.3 vs. 39.1, p=0.006), and of these, 4 had a history of prior SBT. LG patients with concurrent SBT (n=30) had an improved overall survival (94.8 vs. 61.6 months, p=0.04), and only the presence of concurrent SBT and residual disease status independently predicted overall survival.

Conclusion: Patients with SBT that intraoperatively appear to be of advanced stage need to undergo optimal surgical cytoreduction when feasible given the risk of actual LG at diagnosis. While few preoperative clinical characteristics exist to predict more aggressive disease, concurrent SBT in LG specimens suggests a transitional disease process that may have a better prognosis.
THE UP-REGULATION OF MITOCHONDRIAL ANTI-OXIDATION SIGNAL IN OVARIAN CANCER CELLS WITH AGGRESSIVE BIOLOGIC BEHAVIORS

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Objective: Recently, high frequency of mutation of mtDNA has been detected in ovarian cancer. To explore the alterations of mitochondrial proteins in ovarian cancer, a pair of human ovarian carcinoma cell lines (SKOV3/SKOV3.ip1) with different metastatic potential were examined.

Method: Cancer cells SKOV3.ip1 was originated from ascitic tumor cells of nude mice bearing tumor of ovarian cancer cells SKOV3. SKOV3.ip1 exhibited a higher degree of migration potential than its paired cell line SKOV3. The mitochondrial proteins of these two cells were isolated and separated by 2-D Gel Electrophoresis respectively. The different expressed proteins were extracted and identified by using MALDI-TOF/TOF, and finally, a selected protein candidate was further investigated by immuno-histochemistry method using nude mice bearing tumor tissues of these two cells.

Results: A total of 35 spots with different expression were identified between the two cells by using 2D-PAGE approach. Among them, 17 spots were detected only in either SKOV3 or SKOV3.ip1 cells. 18 spots expressed with different levels that over 3 folds between two cells. 20 spots were analyzed using MALDI-TOF/TOF. 11 of them were identified successfully; 4 were known located in mitochondria, include superoxide dismutase 2 (SOD2), fumarate hydratase (FH), MRPL38 and MRTO4. The increased staining of SOD2 was observed in SKOV3.ip1 than that of SKOV3 in IHC analysis by using tumor tissues came from nude mice load tumors.

Conclusion: Our results indicated that the enhanced anti-oxidation and metabolic potentials of ovarian cancer cells might contribute to their aggressive and metastatic behavior. The underlining mechanism is warrant further study.
BODY MASS INDEX (BMI) DOES NOT AFFECT THE SURVIVAL IN PATIENTS WITH OVARIAN CANCER


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Background and aims: Obesity has consistently shown a positive association with ovarian cancer risk. However, study results about the effect of obesity on the treatment and survival of ovarian cancer are controversial. We attempted to determine the impact of obesity on surgical outcomes, clinicopathologic factors, and survival in ovarian cancer.

Methods: We reviewed the medical records of patients undergoing surgery for ovarian cancer between January 2000 and February 2010. Patient demographics, surgical outcomes, clinicopathologic factors and survival were evaluated and compared based on BMI. We used Asian criteria of BMI for Korean people.

Results: Of a total of 556 identified patients, 45 (8.1%), 253 (45.6%), 202 (36.4%), and 55 (9.9%) were underweight (BMI< 18.5), ideal (18.5≤BMI< 23), overweight (23≤BMI< 27.5), and obese (27.5≤BMI), respectively. There were no differences in progression free survival (PFS) (p>0.05) and overall survival (OS) (p>0.05) across BMI strata. Even in subcohort of stage III and IV, we could not find any difference in PFS (p>0.05) and OS (p>0.05) among BMI strata. The surgical outcomes such as optimal debulking rates, operation time, estimated blood loss, or postoperative complications and platinum resistance rates (recurrence < 6months from completion of chemotherapy) also failed to show a significant difference across BMI strata. However, the higher BMI, the more comorbidities patients had significantly (p=0.002), which included cardiovascular diseases, diabetes mellitus, thyroid disease, chronic obstructive pulmonary disease, and end stage renal disease.

Conclusions: Obesity itself does not affect surgical, clinicopathologic outcomes and even survival in ovarian cancer patients in Korea.
RESTAGING IN BORDERLINE OVARIAN TUMORS: SINGLE INSTITUTION EXPERIENCE AND REVIEW OF THE LITERATURE

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Introduction: Borderline ovarian tumors are a category of epithelial ovarian tumors and 70% of them are stage I at the time of diagnosis. Since initial stage is the most important prognostic factor, restaging procedure could be justified. This study aims to evaluate the role of restaging surgery in the management of patients with borderline ovarian tumors referred to our centre after an under-staged previous surgery in other hospitals.

Material and methods: We retrospectively reviewed the charts of patients with borderline ovarian tumors who were referred to our centre to undergo restaging procedure. From December 1995 to May 2008, 186 patients were treated of BOT and 67 patients met the inclusion criteria. Data collected included patients' age, primary surgery features, re-staging surgery features, FIGO stage after first and second procedures, pathological findings and follow-up details.

Results: FIGO stage after primary surgery was IA in 46 patients (68.6%), IB in 7 patients (10.4%), IC in 12 patients (17.9 %, 6 due to cyst rupture), IIA in 1 patient (1.4%), IIB in 1 patient (1.4%). We found 12.3% (8 patients) of upstaging rate within initial stage I which represents 97% of all patients. The mean follow-up time was 60.4 months from restaging surgery (SD 30.6 months). We found 8 recurrences of the disease and 3 second recurrences.

Conclusions: There are no differences concerning overall survival between upstaged patients and non-upstaged patients, although initially conservative procedures were upstaged more often than non-conservative with a mild increase of recurrences after conservative surgery.
SECOND LINE CHEMOTHERAPY WITH GEMCITABINE AND CARBOPLATINUM REGIMEN IN PATIENTS WITH PERSISTENT OVARIAN CANCER

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Background: Patients with epithelial ovarian cancer who relapse more than six months following completion is platinum-based primary chemotherapy are considered platinum sensitive and can be effectively retreated with cisplatin or carboplatin. Gemcitabine is among the candidates as combination partner is second line chemotherapy.

Patients and methods: We performed a study with escalating doses of gemcitabine combined with carboplatin in 42 patient’s. All patients who were treated in vali-e-Asr hospital Between “2006-2010” evaluated. Gemcitabine was given on days 1, 8, and 15 followed by one week rest period for a 28 day cycle. CA125 levels were evaluated for response after completion of each course of chemotherapy and clinical examination or CT scan evaluated for response after completion of three course of chemotherapy.

Results: Median age was 51 years (23-77). Median follow up was 8 months total cycle of chemotherapy was 182.

Median cycle was 4 (range 2-6). Thrombocytopenia (Grade 1) and leucopenia (Grade 1) was seen 6% and 9% All Patients.

Overall the rate of response was 49.2% in all of patients. Median progression free interval in patients was 3 months. Mean survival rate in our patients was 39 months.

Conclusion: The combination of carboplatinum and gemcitabine is a well tolerated in patients with relapsed platinum-sensitive.

Keywords: Ovarian carcinoma- Gemcitabine
ABERRANT METHYLATION OF BRCA1 IN CHEMOSENSITIVE HUMAN OVARIAN CANCER CELLS DOES NOT INVOLVE THE PHOSPHATIDYLSINOSITOL 3'-KINASE-AKT PATHWAY

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Methylation is an important silencing mechanism of breast and ovarian cancer susceptibility gene 1 (BRCA1) expression in sporadic ovarian cancer. However, the role of BRCA1 methylation in chemotherapy in sporadic ovarian cancer and the related pathways have not been understood completely. This study has determined the roles of BRCA1 hypermethylation in chemotherapy of sporadic ovarian cancer and its related signaling pathways.

We used bisulfite sequencing, real-time polymerase chain reaction, and western blotting to check the methylation state and expression levels of BRCA1 of the following cell lines: platinum-sensitive human ovarian cancer cell line COC1, platinum-resistant cell line COC1/DDP, SKOV-3, and 5-Aza-dC treated COC1. The cisplatin sensitivity of ovarian cancer cells was examined by MTS (methyl-thiazol tetrazolium) assay.

Tumorigenicity in vivo and DDP-based chemosensitivity were compared among the above cells. Phosphatidylinositol 3'-kinase (PI3K)-Akt pathway activation in ovarian cancer cells was studied by western blotting. The frequency of BRCA1 methylation in the COC1 cell line was higher than in COC1/DDP and SKOV-3 cell lines, whereas the mRNA and protein expression of BRCA1 were lower than in the COC1/DDP and SKOV-3 cell lines. DNA demethylation decreased the chemosensitivity of COC1 cells and partially increased the expression levels of BRCA1. The activation of the PI3K-Akt pathway was low in ovarian cancer cells.

Our results indicate that hypermethylation of BRCA1 might play an important role in the chemosensitivity of ovarian cancer, and that the PI3K-Akt pathway is not involved in this response.
GENETIC DIAGNOSIS FOR CHEMOSENSITIVITY WITH PACLITAXEL-SENSITIVE GENES IN EPITHELIAL OVARIAN CANCER

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Paclitaxel which is well known by a common mechanism of blocking cell mitosis is often used in clinic to treat cancers. Nevertheless, some carcinomas such as breast cancer, ovarian cancer, and non-small cell lung cancer demonstrate resistance to paclitaxel treatment. We screened a lentiviral siRNA library against the entire human genomes to assess the ability of clones to influence the sensitivity of paclitaxel. We identified three paclitaxel-resistant clones, which were determined as targeting for septin 10 (SEPT10), ubiquitin-specific protease 15 (USP15) and budding uninhibited by benzimidazoles 3 (BUB3), respectively. USP15 is the deubiquitinating enzyme and we found the USP15 as an important regulator of the microtubule stability. Interestingly, either SEPT10 or USP15 plays an essential role during paclitaxel-induced cell apoptosis through controlling some cleaved caspases, for instance, caspase-3, -9, -7. We conducted the present study to investigate whether and how chemosensitivity can be determined by means of genetic diagnosis using these genes in patients with epithelial ovarian cancer. A total of 61 samples were obtained with informed consent from patients who had epithelial ovarian cancer and received first-line chemotherapy, consisting of paclitaxel and carboplatin (TC). The mRNA expression of SEPT10 and USP15 was measured by real-time reverse transcription-polymerase chain reaction. These expressions were significantly higher in patients who did not respond to TC therapy. The present study suggests that genetic diagnosis by these genes may be useful to determine chemosensitivity in patients with epithelial ovarian cancer. Furthermore, these genes may candidate a novel cancer therapeutic method for paclitaxel-resistant cancers.
NUCLEAR KARYOPHERIN A2 IS A POTENTIAL PROGNOSTIC MARKER FOR HUMAN EPITHELIAL OVARIAN CANCER


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Background and aims: To investigate the relationship between karyopherin α2 (KPNA2) and clinicopathologic features of patients with epithelial ovarian cancer (EOC).

Methods: KPNA2 expression patterns in EOC specimens were detected using gene microarray, quantitative real-time reverse transcription-PCR (qRT-PCR), and immunohistochemistry assays, and these data were compared with clinicopathologic features of EOC patients. The effect of KPNA2-targeted siRNA on cell proliferation, cell cycle distribution, and apoptosis of OVCAR-3 cells was also determined using MTT assays, flow cytometry, and gene microarray studies.

Results: Expression of KPNA2 in EOC specimens was found to be 5.3-fold and 2.6-fold higher than in normal human ovarian surface epithelial (HOSEs) specimens as detected by microarray and qRT-PCR assays, respectively, while positive staining for KPNA2 was detected in 49.0% (50/102) of EOC specimens and 6.7% (1/15) of HOSEs. A significant association between KPNA2 expression and the FIGO stage and histologic grade of EOC specimens was also observed (P < 0.001). Furthermore, univariable and multivariable analyses showed that KPNA2 expression is an independent prognostic factor associated with relapse-free survival of EOC patients. In vitro, inhibition of KPNA2 expression in OVCAR-3 cells significantly decreased the percentage of cells in the G2 phase, increased the percentage of cells in the G1 phase, and increased the rate of apoptosis. The list of genes affected by KPNA2-targeted siRNA included those related to cell proliferation, cell cycle distribution, and cell death as determined from gene microarray experiments.

Conclusions: This study provides evidence that KPNA2 represents a valuable indicator of poor prognosis for EOC patients.
ANTIANGIOGENIC GENE THERAPY WITH SOLUBLE VEGF RECEPTOR-1, -2 AND -3 PROLONGS SURVIVAL OF MICE WITH HUMAN OVARIAN CARCINOMA

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Background and aims: We compared effects of antiangiogenic gene therapy with a combination of soluble VEGFR-1, sVEGFR-2 and sVEGFR-3 to chemotherapy with carboplatin and paclitaxel, and to antiangiogenic monoclonal anti-VEGF-antibody bevacizumab in an intraperitoneal ovarian cancer xenograft model in mice (n=80). Gene therapy was also combined with chemotherapy.

Methods: Therapy was initiated when sizable tumors were confirmed in magnetic resonance imaging. Adenovirus-mediated gene transfer was performed intravenously (2.1 x E9 pfu); while chemotherapy and monoclonal anti-VEGF-antibody were dosed intraperitoneally. The study groups were: AdLacZ control (n=21); combination of AdsVEGFR-1, -2 and -3 (n=21); combination of AdsVEGFR-1, -2, -3 and paclitaxel (n=9); bevacizumab (n=14); paclitaxel (n=9); carboplatin (n=5). Antitumor effectiveness was assessed by sequential MRI, immunohistochemistry, microvessel density, overall tumor growth and survival time.

Results: In the gene therapy group survival was significantly prolonged compared to the antiangiogenic monoclonal anti-VEGF-antibody (p=0.009), and the control group (p=0.022). Gene therapy combined with paclitaxel prolonged the survival significantly compared with the single treatment of paclitaxel and carboplatin. Survival of the bevacizumab group did not significantly differ from the survival of the control group. In the combination gene therapy group the sizes of the tumors were significantly smaller than in the control group (p=0.002). Mean vascular density and total vascular area were also significantly smaller in the tumors of the gene therapy group (p=0.005).

Conclusions: These results show potential for the antiangiogenic gene therapy to improve survival and support testing this approach in a phase I clinical trial for the treatment of ovarian cancer.
TUMOR MARKER CA 125 AS A RESPONSE INDICATOR IN ADVANCED OVARIAN CANCER AND PREDICTOR OF OVERALL SURVIVAL, TIME TO PROGRESSION

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Background: The tumor marker CA 125, although not specific for ovarian cancer, is widely used for the evaluation and monitoring of the treated advanced ovarian cancer.

Aim: Our study examines relationship between ovarian tumor response to primary chemotherapy and corresponding serum CA 125 response. A secondary objective was assessment of relationship of CA 125 dynamics and TTP, RD and OS.

Methods: We studied retrospectively 69 patients who received primary for advanced epithelial ovarian cancer. Blood serum CA 125 was determined on the days of CT scans and ultrasound using a one-step immunoenzymatic assay.

Results: There was statistically significant difference (p < 0.001) in ovarian cancer objective tumor response according to CA 125 response, but those patients whose CA 125 levels decreased to below the upper limit of normal (CR) not show to have significantly longer TTP, RD, OS than those whose CA 125 levels has been decreased, but remained elevated (PR). There was statistically significant difference (p=0) in RD, TTP and OS according to CA 125 response among patients with advanced ovarian cancer in our study, but not between CR and PR CA 125 marker.

Conclusion: Significant reduction in the values of CA 125 marker level at the end of primary treatment should be a potential predictor of OS, TTP and response. Those patients with a CR marker CA 125 not show to have significantly longer TTP, RD, OS than those with PR marker CA 125.
THE ROLE OF REGULAR SURVEILLANCE IN THE DETECTION OF OVARIAN CANCER RECURRENT

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Background and aims: To evaluate the role of regular surveillance in the detection of recurrence after initial therapy for epithelial ovarian cancer.

Methods: From December 1995 to September 2005, 286 patients underwent surgery for invasive epithelial ovarian cancer at Vali Asr Hospital, Tehran, Iran. Among these patients, 69 were available for the retrospective analysis. They routinely followed-up with a combination of history, examination and serum Ca125 assay, and in recurrence suspicion, sonography and CT scan. Data from the patients' files and pathologic reports were analyzed. Recurrence was diagnosed when at least one of the following criteria was abnormal: symptoms, physical examination or elevated serum CA125 levels.

Results: forty-one cases were identified who had tumor recurrence after a median disease-free interval 11months. The median follow-up period was 23months. At the time of diagnosis the recurrence about 80% of patients had no symptoms. Of all recurrence, 3(7.3%) only picked up by physical examination. Twenty-two patients (53.7%) first presented with raised Ca 125 level. Eight first presented with symptoms and only 3 first presented with physical findings. The recurrences were finally diagnosed by raised Ca 125 and positive imaging in 29 patients, by histology or cytology in 9 patients, by imaging alone in three patients.

Conclusions: According to this study, physical examination would have limited value as part of the follow up strategy. Imaging may have an important role in early detection of recurrent ovarian cancer.

Keywords: Epithelial ovarian cancer, recurrence, detection.
PLATINUM-RESISTANCE IN OVARIAN CANCER IS MEDIATED BY THE IL-6-CIAP-2 AXIS

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Ovarian cancer (OC) patients are initially responsive to platinum-based therapy, but eventually become refractory to treatment and succumb to the disease. High concentrations of IL-6 are present in the sera and ascites of OC patients and predict poor clinical outcome. Our goal, within the realm of translational medicine, is to analyze the role of IL-6 and its down-stream target, the apoptosis inhibitor cIAP-2, in platinum-resistance.

We studied OC cell lines and cells drawn from OC patients. Microarray analysis was performed on OC cells upon treatment with cisplatin, and validated by ELISA and WB. OC cells were treated with IL-6 and cIAP-2 inhibitors following cisplatin treatment: anti-IL-6 antibody and siRNA for IL-6, or siRNA for cIAP-2. Cytotoxicity was evaluated by XTT.

Microarray analysis of cisplatin-treated OC cells revealed a highly significant increase in mRNA of IL-6 (10 fold) and of cIAP-2 (12 fold), these results were confirmed at the protein level. WB analysis of cisplatin-treated OC cells exhibited decreased cIAP-2 expression level following anti-IL-6 antibody addition. Furthermore, adding IL-6 by itself, to OC cells, significantly increased cIAP-2 levels. Cytotoxicity assays exhibited the sensitization of cisplatin-resistant OC cells to cisplatin following the addition of anti-IL-6 antibody (from 5% to 30% at 10mM cisplatin), siRNA for IL-6 (from 4% to 38% at 5mM cisplatin), and siRNA for cIAP-2 (from 7% to 30% at 20mM cisplatin).

We propose that combining IL-6/cIAP-2 inhibitors with cisplatin should improve the current treatment, and provide new hope for OC patients.
CYTOKINE GENE EXPRESSION SIGNATURE IN OVARIAN CANCER

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Objectives: Alterations of cytokine expression and an imbalance in Th1/Th2 cytokine response have been previously shown in ovarian cancer. In this study, we sought to clarify whether the cytokine gene expression profile could have clinical association with ovarian cancer development and/or progression.

Methods: We analyzed the expression profiles of 16 cytokine genes (IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p35, IL-12p40, IL-15, IFN-γ, TNF-α, IL-6, HLA-DRA, HLA-DPA1, and CSF1) in 50 ovarian cancers with informed consent. Unsupervised hierarchical clustering analysis was performed with the use of Cluster View and Tree View programs. The results were used to analyze the association with several clinical characteristics including prognosis.

Results: The clustering analysis from 12 cytokine gene expression in 50 ovarian cancers revealed two main clusters. The relationship between the two clusters and clinical parameters showed statistically significant differences with histological type and clinical stage, but not with survival. In particular, clear cell adenocarcinoma (CCA) showed relatively Th-2 dominant expression pattern when compared to the other type of tumor. In 20 ovarian serous adenocarcinoma, a 12-cytokine gene expression profile was associated with patients' prognosis.

Conclusion: A cytokine gene expression signature of ovarian cancer could distinguish the histological subtypes and prognosis. A unique expression pattern found in CCA might be involved in the pathogenesis of the ovarian cancer subtype.
PREOPERATIVE LEVELS OF PLASMA FIBRINOGEN AS A PREDICTOR FOR STAGE, OPTIMAL DEBULKING, AND PLATINUM-RESISTANCE IN EPITHELIAL OVARIAN CARCINOMA

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Objectives: This study was conducted to evaluate whether preoperative levels of fibrinogen, CA-125 and neutrophil to lymphocyte ratio (NLR) are predictive for FIGO stage, optimal debulking surgery and platinum resistance in epithelial ovarian cancer (EOC) patients.

Methods: Preoperative plasma levels of fibrinogen, CA-125 and neutrophil to lymphocyte ratio were retrospectively analyzed in patients with EOC who underwent primary cytoreductive surgery between January 2000 to December 2009. Clinico-pathologic characteristics including operative finding, FIGO stage, progression free interval after primary adjuvant chemotherapy and overall survival were evaluated. Response was evaluated with image using the RECIST criteria and serum CA-125 levels.

Results: Mean values of fibrinogen, CA-125 levels and NLR were significantly higher in patients with advanced FIGO stage and suboptimal debulking surgery. In advanced stage, suboptimal debulking surgery and high plasma fibrinogen levels correlated with platinum-resistance while CA-125 and NLR were statistically insignificant.

Receiver operating characteristic curve showed the best cutoff values of fibrinogen levels for the prediction for platinum resistance (504.52 mg/dl, sensitivity: 64.4%, specificity: 69.6%, positive predictive value=0.71, negative predictive value=0.64).

In a log rank test, the high plasma fibrinogen levels and suboptimal debulking surgery associated with poor prognosis in progression free interval and overall survival.

Conclusions: The preoperative fibrinogen levels are more useful to predict optimal debulking surgery and platinum resistance than CA-125 and NLR. The preoperative fibrinogen levels may be helpful to predict further prognosis.
OUTCOMES OF RESTAGING PATIENTS INITIALLY PRESUMED AS STAGE I EPITHELIAL OVARIAN MALIGNANCY REFERRED FROM PRIMARY CLinic

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Aim: The aim of this study was to review in restaging of initially presumed as stage I epithelial ovarian malignancy referred from primary clinic, including risk factor for upstaging and survival outcome.

Methods: Outcomes of patients presumed stage I ovarian cancer who underwent complete surgical restaging after having been unstaged in primary clinic, were retrospectively evaluated.

Results: 93 patients were referred and underwent complete staging for presumed as stage I epithelial ovarian malignancy between January 1989 to January 2009. After complete staging, forty-eight patients initially staged as I were upstaged (51.6%). The risk of upstaging was significantly higher among women with initial uni-or bilateral cystectomy (p=0.004), cytology positive (p=0.011) and significantly lower with bilateral salpingo-oophorectomy (p=0.028). In stage I, median follow-up time was 36 months, there was similar overall 5-year survival rate (93% vs 94%, P=.97) between patients who were assigned to restage I and initially staged I in AMC (Asan medical center, Korea). The disease-free survival rate was 89% and overall 10-year survival rate was 72% in upstaged patients. When compared to matched ovarian cancer patients in AMC, restaging patients had worse disease-free survival (P=.004) and overall survival (P=.018)

Conclusion: Although there are many limitation to detect early ovarian cancer in primary clinic, but it is still very important role of gynecologist in primary clinic. When the patients referred to gynecologic oncologist, careful operation is needed to surgeon because incomplete removal of ovary may affects the survival outcome and must consider when counseling patients and considering adjuvant therapy.
UPREGULATION OF TGFβ PATHWAY IN OVARIAN CANCER METASTASIS AND THERAPEUTIC EFFECTS OF ITS INHIBITION

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**Objective:** The biphasic roles of TGFβ pathway in cancer cells are revealed in various types of cancers. Our purpose was to investigate its roles in peritoneal dissemination of ovarian cancer.

**Methods:** By microarray analysis of the publicly accessible dataset (GSE2109), we identified pathways different in metastatic sites and ovarian tumor. We also compared the expressions of TGFβ pathway core proteins between metastatic sites and ovarian tumor with immunohistochemical study. The \textit{in vitro} and \textit{in vivo} effects of an inhibitor of TGFβ receptor kinase A-83-01 were analyzed in HM-1 cell, mouse ovarian cancer cell line.

**Results:** TGFβ pathway was upregulated in omental metastasis (p< 0.01) with microarray analysis. The expressions of TGFBR2 and pSMAD2 were also increased (p< 0.05 each) in omental metastasis. A-83-01 suppressed adhesive, motile and invasive abilities of HM-1 cells (p< 0.05 each), and improved survival of peritoneal dissemination model mouse with HM-1 cells (p< 0.05).

**Conclusion:** In ovarian cancer, TGFβ pathway has tumor-progressive roles and can be a therapeutic target.
VEGFR-3 INHIBITION WITH MONOCLONAL ANTIBODY IN METASTATIC OVARIAN CANCER

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Objectives: To examine the impact of monoclonal antibody monotherapy targeting host VEGFR-3 on ovarian tumor growth and spread.

Methods: Ovarian cancer cell lines were analyzed for presence of VEGF-A, VEGF-C, VEGF-D, VEGF-R3 expression via RT-PCR, Western blotting and ELISA. Utilizing a newly established ovarian cancer mouse model, we evaluated the extent to which blocking endothelial VEGFR-3 effects ovarian cancer growth, spread and ascites formation. Mice treated with mF4-31C1 Mab were compared to matched mice that had been treated with a control antibody following intraperitoneal inoculation with SKOV3ip1/GFP/Luc cells, and tumor growth was monitored. Tissue was analyzed for blood and lymphatic vasculature density; ascitic fluid volume and its biochemical content was analyzed as well. Human ovarian cancer samples were evaluated for VEGFR-3 expression.

Results: A mouse model of ovarian cancer was established that allows for non-invasive continuous monitoring of tumor growth and spread during therapeutic intervention. Ovarian cancer cell lines express VEGF-C and VEGF-D and do not express VEGF-3. In our ovarian cancer model, treatment with a monoclonal antibody that is specific for mouse VEGFR-3 did not affect either tumor growth or animal survival. A significant decrease in blood and lymphatic vessel density, as well as increase in volume of ascites, was observed in the treatment group.

Conclusion: Therapy with VEGFR-3-specific monoclonal antibody alone does not appear to have significant impact on ovarian cancer cell growth. Its utilization in combination with antiangiogenic/cytotoxic therapeutic approaches needs to be studied further with careful attention to the potential side effects associated with such therapy.
A FEASIBILITY STUDY OF INTRAVENOUS PACLITAXEL, INTRAPERITONEAL CARBOPLATIN AND INTRAPERITONEAL PACLITAXEL IN PATIENTS WITH EPITHELIAL OVARIAN CARCINOMA

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Background: The objective of this study was to determine the feasibility of intravenous (IV) paclitaxel, intraperitoneal (IP) carboplatin and IP paclitaxel (TCipTip therapy) in patients with epithelial ovarian carcinoma (EOC).

Methods: The patients with histologically confirmed, stage IC-IV EOC, fallopian tube carcinoma or peritoneal carcinoma were treated by TCipTip therapy. IV Paclitaxel was administered at 135 mg/m² followed by IP carboplatin administration based on the AUC=6 on day 1, and IP paclitaxel was administered at 60 mg/m² on day 8. The toxicity grade was determined by CTCAE version 3. This study has been approved by the institutional review committee.

Results: Twenty patients were entered in this study. These patients included 18 EOC (stage Ic, 8; stage IIc, 2; stage IIIc, 7; stage IV, 1), 1 stage IIc fallopian tube carcinoma and 1 stage IV primary peritoneal carcinoma. Incidences of grade 3/4 hematological toxicities were 70% for neutrocytopenia, 8% for thrombocytopenia, and 21% for anemia. Observed grade 3/4 non-hematological toxicities were 4 for allergy, 1 for ileus. Two patient encountered grade 2 abdominal pain. Ten of 17 patients (59%) except 3 patients who encountered allergy to paclitaxel at the first cycle completed more than 6 cycles of chemotherapy. The reasons of interruption were 3 for anaphylaxis to paclitaxel, 2 for abdominal pain, 1 for anaphylaxis to carboplatin, 1 for disease progression, 1 for pleural embolism, 1 for ileus, 1 for patient refusal.

Conclusions: The toxicities by TCipTip therapy were acceptable, and this therapy is feasible for patients with EOC.
IN Volvement of Mismatch Repair (MMR) Abnormality in the Malignant Transformation of Ovarian Endometriosis

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A subset of ovarian carcinomas is known to arise from endometriotic epithelia of the ovary; however, the mechanisms underlying the malignant transformation have not yet been elucidated. Mismatch repair (MMR) abnormality is reportedly important in the tumorigenesis of uterine endometrial cancer, but the involvement of MMR abnormality in the carcinogenesis of endometriotic epithelia has not been examined. Therefore, the microsatellite instability (MSI) status and the expression of MMR proteins in endometriosis with/without ovarian cancer were investigated.

Immunohistochemical expression of hMLH1 and hMSH2 proteins was examined in 30 cases of ovarian endometriosis, 25 cases of ovarian carcinoma accompanied by endometriosis and 26 cases of ovarian carcinoma. DNA was obtained from 46 cases of tumor by microdissection, and MSI was analyzed in relation with the clinicopathological factors. The effect of inflammatory cytokines, such as IL-6 and TNF-α, on the expression of MMR protein in cultured normal endometrial epithelial cells was examined.

Nuclear expression of hMLH1 and hMSH2 proteins was significantly lower in carcinomas compared with endometriosis. The MSI-positive rate was significantly higher in ovarian carcinomas than in endometriosis and correlated positively with C-reactive protein. In 2 cases of clear cell adenocarcinoma accompanied by endometriosis, decreased expression of MMR proteins with positive MSI was observed both in endometriosis and carcinoma lesions. The expression of MMR proteins was decreased by the addition of IL-6 and TNF-α in cultured normal endometrial epithelial cells.

Our findings suggest that MMR abnormality was involved in the malignant transformation of ovarian endometriosis.
EVALUATION OF HUMAN EPIDIDYMAL SECRETORY PROTEIN E4 (HE4) FOR MONITORING FOR OVARIAN CANCER RECURRENCE

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Introduction: Serum HE4, a new biomarker for ovarian cancer, was shown to have a better sensitivity for detecting ovarian cancer compared to Ca 125, especially in early disease. In this study, we measured the HE4 levels in patients who had relapsed ovarian cancer in an attempt to elucidate its role in disease monitoring and recurrence detection.

Methods: HE4 levels were measured at pre-treatment, immediately post treatment (remission), just prior to diagnosis of recurrence and at recurrence using a commercial available ELISA kit in women with ovarian cancer recurrence. The results were compared with Ca 125 levels. Levels of more than 70 pmol/L and 35 u/ml were considered raised for HE4 and Ca 125 respectively. Chi square test was used to detect difference between groups.

Results: 67 patients with saved sera available at recurrence were included in the study. At pretreatment 59 (88%) have raised Ca 125 compared to 63.6% with raised HE4. The sensitivity for recurrence detection was 92.5% (62/67) and 61.2% (41/67) for HE4 (p=0.004) respectively. Specificity of HE4 and Ca125, based on the levels when there was no evidence of disease were 82.1% for HE4 versus 98% for Ca 125. 12 (24.4%) patients had raised HE4 before the rise of Ca 125, whereas 6 (14.3%) had raised Ca 125 first.

Conclusion: HE4 reflected in the disease process in women with ovarian recurrence but has a lower sensitivity than Ca 125 in recurrence detection.
THE PATTERN OF PERITONEAL SEEDING AND LYMPH NODE METASTASIS IN PATIENTS WITH ADVANCED AND RECURRENT OVARIAN CANCER

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Objective: To evaluate the pattern of peritoneal seeding and lymph node metastasis in patients with advanced and recurrent ovarian cancer.

Methods: We developed peritoneal carcinomatosis index (PCI) for the objective description of tumor burden in which the peritoneal cavity was divided into 20 regions (10 region-specific peritoneal areas and 10 organ involvements) and retroperitoneal lymph nodes were divided into four regions. One hundred fifty six advanced and recurrent ovarian cancer from December 2006 to April 2010 were prospectively included in this study. All patients were treated with cytoreductive operation at the National Cancer Center Korea. The patients were divided into primary vs. secondary cytoreductive surgery group, neoadjuvant vs. non-neoadjuvant chemotherapy group.

Results: One hundred five patients were primary cancer and 51 patients were recurrent cancer. Neoadjuvant chemotherapy was performed in 39 primary cancer patients (37.14 %). Right diaphragm (52.56 %) is the most common peritoneal seeding site, followed by omentum (50.00 %) and sigmoid colon (44.87 %). The peritoneal seeding or metastasis at both diaphragm, omentum, sigmoid colon, descending colon, right para-aortic lymph node and right pelvic node was significantly predominant in primary cancer compared to recurrent cancer. There were no significant differences in the pattern of peritoneal seeding and lymph node metastasis according to the presence of neoadjuvant chemotherapy.

Conclusion: Our findings suggest that newly developed PCI is helpful to find tumor location in advanced and recurrent ovarian cancer.

Keywords: Ovarian cancer, peritoneal carcinomatosis index, peritoneal seeding, lymph node metastasis
WHOLED BLOOD RNA EXPRESSION PROFILES IN OVARIAN CANCER PATIENTS WITH OR WITHOUT RESIDUAL TUMOR AFTER THE PRIMARY CYTHEREDUCTIVE SURGERY

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Significant improvements in the treatment results of ovarian cancer have been achieved during the last decades, but further improvements might depend on finding additional methods allowing early discovery of signs of the disease and its biological behavior, preferably by a simple blood test. We hypothesized that peripheral blood leukocytes might express genes that carry such clinical information. Therefore, we studied the relative gene expressions of cancer- and metastasis-specific genes in blood samples from ovarian cancer patients with different prognosis.

Total blood RNA was extracted from whole blood and the relative gene expressions for 168 genes were analyzed with real-time PCR assays. Two groups of patients were analyzed: one group with residual tumor mass after primary surgery, and one group where the tumor could be macroscopic radically resected, resulting in no visible tumor mass left behind.

The group with remaining tumor mass after surgery showed significantly different gene expressions compared to the group with no remaining tumor mass. Differences were noted for the following genes: MTA2, TNF, CTNNA1, IL1B, KISS1, and MMP10. They were all down regulated with a fold change between 1.15 to 1.57; there were no Upregulated genes.

A set of genes involved in metastasis, invasion and inflammation was found to be significantly down regulated in native unstimulated blood leukocytes from ovarian cancer patients with a poor prognosis. It may thus be possible to develop a blood test to help post surgical follow-up by identifying who are at risk of relapse of the tumor.
BRCA1 MUTATIONS, ALLELIC LOSS AND PROTEIN EXPRESSION IN OVARIAN CANCERS: ASSOCIATIONS WITH CLINICOPATHOLOGICAL AND MOLECULAR DATA

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Somatic changes in BRCA1 and their role in ovarian cancers is not well documented. We aimed to evaluate the BRCA1 status and to confront it with other molecular changes and clinicopathological characteristics of unselected ovarian carcinomas.

BRCA1 mutation analysis was performed on carcinomas from 259 unselected patients with the use of PCR-SSCP, heteroduplex analysis and sequencing. All tumors were tested for the presence of recurrent germline mutations in the Polish population: 185delAG, 300T>G, 3819del5, 3875del4, 4153delA and 5382insC. Loss of heterozygosity (LOH) was determined with use of three intragenic BRCA1 microsatellite markers. BRCA1 protein expression was evaluated immunohistochemically.

BRCA1 defects, consisting of germline mutations (15.8%), allelic loss (75.3%) and reduced nuclear protein level (32%), were found in 82% of ovarian carcinomas. Patients with germline mutations were younger than non-carriers (P< 0.0001). The mutations and LOH were more frequent in undifferentiated, serous and endometrioid than in other tumors (P=0.036, p=0.005, for mutations and LOH, respectively). They were also associated with high FIGO stage (p=0.009, p< 0.0001), high tumor grade (P=0.005, P< 0.0001) and TP53 mutations (P=0.003, P< 0.0001, for mutations and LOH, respectively). LOH alone was associated with serous type (P=0.01), PIK3CA amplification (P=0.003) and wild-type K-RAS and PTEN (P=0.002). Reduced nuclear BRCA1 expression was more frequent in high-grade than low-grade tumors (P=0.034)

Our results suggest that the BRCA1 gene may be inactivated in ovarian carcinomas by different mechanisms. Tumors with various BRCA1 defects have a similar phenotype of high-stage, high-grade carcinomas with frequent TP53 mutations.
MERCURY AND ARSENIC LEVELS IN URINE OF PATIENTS WITH ENDOMETRIOSIS AND ENDOMETRIOID OVARIAN CANCER

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We investigated urine levels of Hg and As in endometriosis and endometrioid ovarian carcinoma and correlated their levels with stage of the disease. Urine samples from 25 patients with endometriosis (4-I, 16-II, 6-III and 1-IV stage) and from 25 patients with endometrioid ovarian cancer (9-I, 1-II, 15-III and 0-IV stage) were extracted before treatment, measured by atomic absorption spectrophotometer and compared with those from healthy control group (n=25).

Difference between urine Hg and As concentrations was statistically significant in these groups of patients. Urine Hg concentrations were lower in endometrioid ovarian cancer compared with the control group (p=0.001) and with endometriosis (p=0.07 - borderline significance). Urine As concentrations were lower in endometriosis compared to endometrioid ovarian cancer (p=0.016).

In the comparison of stages I+II and III+IV (FIGO stages for ovarian cancer and rAFS stages for endometriosis), all parameters were found to be statistically not significant (p>0.05).

In our opinion, significant alterations in trace elements levels in endometriosis and endometrioid ovarian cancer may not be a reason for but is, in fact, a consequence of the disease itself. A positive correlation between urine concentrations of mercury and arsenic of women with endometrioid ovarian cancer indicates possible common role of these elements in the pathogenesis of ovarian cancer.

The exact mechanism responsible for the alterations in these 2 trace elements levels in patients with endometriosis and endometrioid ovarian cancer is largely unclear and requires further evaluation.

This study was financed from sources for science in 2006-2009 as a scientific project number 2P05E06930.
A SUCCESSFUL THERAPEUTIC REGIMEN FOR RECURRENT EPITHELIAL OVARIAN CARCINOMA: CHEMOTHERAPY COMBINED WITH SURGERY AND RADIOThERAPY


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Objectives: This intent-to-treat study was to explore a new kind of treatment, chemotherapy based salvage therapy with a combination of surgery and radiotherapy in patients with recurrent epithelial ovarian carcinoma. We also discussed prognostic factors related to recurrent epithelial ovarian carcinoma.

Methods: Twenty-nine patients with recurrent epithelial ovarian carcinoma were enrolled in this study. They underwent chemotherapy combined with surgery and radiotherapy. Platinum-sensitive patients were retreated with paclitaxel + cisplatin (TP) or carboplatin + cyclophosphamide (CP) regimen. Platinumresistant patients were given paclitaxel + mitomycin (TM) or etoposide+ mitomycin (VM). Local radiotherapy was given for residual tumor following second cytoreductive surgery.

Results: The four-year survival rate after recurrence, four-year progress-free survival (PFS) rate after recurrence and four-year overall survival rate were 54.60%, 48.28% and 58.62 %, respectively. Multivariate analysis indicated the size of residual lesion after secondary cytoreductive surgery (P< 0.05) and the maximal diameter of tumor before radiotherapy (P< 0.01) were two independent prognostic factors to both the survival after recurrence and overall survival. The diameter of tumor before radiotherapy (P< 0.01) was an independent prognostic factor to PFS after recurrence. The major side effects include myelosuppression, diarrhea and impaired liver function, which were all endurable.

Conclusions: Effective chemotherapy combined with optimal secondary cytoreductive surgery and postoperative radiotherapy on residual tumor may improve the survival of recurrent epithelial ovarian carcinoma.
TISSUE FACTOR-FACTOR VIIA COMPLEX INDUCES EPITHELIAL OVARIAN CANCER CELL INVASION AND METASTASIS THROUGH A MONOCYTES-DEPENDENT MECHANISM

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Tumor-associated macrophage (TAM) infiltration and upregulation of tissue factor-factor VII (TF-FVIIa) complex have been observed in the peritoneum and stroma of epithelial ovarian cancer (EOC). However, it is not clear how TAM and TF-FVIIa complex promotes EOC invasion. In the present study, we aimed to determine the mechanism by which interaction of TF-FVIIa and monocyte (MO) promote EOC metastasis. We found that TF-FVIIa complex caused dynamic changes in MOs cytokine and chemokine expression. CD14 and CD163 were also upregulated on MOs by TF-FVIIa. EOC cells were co-cultured with TF-FVIIa-stimulated MOs demonstrated increased invasion potential. IL-8 was proposed as the major chemoattractant mediating EOC invasion based on MOs mRNA and protein expression profile. Anti IL-8 monoclonal neutralizing antibody attenuated EOC cell invasion in a concentration-dependent manner, and TNFα from TF-FVIIa-stimulated MOs was observed amplify IL-8 production. The following transcription factors in MOs were activated by TF-FVIIa and inhibited by tissue factor pathway inhibitor: oncogenes HIF-1α, HIF-1β, Oct I, Oct II, Egr-1; inflammatory mediators c-Fos and c-Rel; STAT family members STAT5A and STAT5B. Our study suggested that interaction between TF-FVIIa complex might play a role in mediating EOC invasion and metastasis depend on MOs mechanism.
CLINICAL AND PROGNOSTIC ROLE OF E-CADHERIN EXPRESSION IN OVARIAN PERITONEAL CARCINOMATOSIS TREATED BY PERITONECTOMY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

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Introduction: Very few studies investigated the prognostic role of bio-molecular markers in peritoneal carcinomatosis from ovarian cancer treated with peritonectomy and hyperthermic intraperitoneal chemotherapy. We analyzed the role of E-cadherin in influencing clinical and pathological parameters and survival in this group of patients.

Methods: Out of 70 patients treated with peritonectomy and HIPEC in nine years, we selected 38 patients in which the expression of e-cadherin was studied by means of tissue micro array and was statistically matched with PCI, CC-score, histology, primary or secondary cytoreduction, stage, nuclear grading (G), overall 5-years (OS) and disease free (DFS) survival.

Results: Overexpression of E-cadherin was observed more in serous carcinoma rather than other histologies. Univariate and multivariate analysis showed E-cadherin overexpression statistically correlated with histology (p< 0.0001), better OS (p< 0.009) and DFS (p< 0.003), but not with PCI, CC-score, G, Stage and primary or secondary cytoreduction.

Conclusions: E-cadherin overexpression in ovarian peritoneal carcinomatosis could be a positive prognostic factor and could be used as target for “tailored” therapies.
ENDOMETRIOSIS AND ASSOCIATED OVARIAN MALIGNANCY ARISING IN THE POSTMENOPAUSAL PATIENTS: A RETROSPECTIVE ANALYSIS OF PRESENTATION, TREATMENT, AND OUTCOME

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Background and aims: To investigate the relationship of age and tumors associated with endometriosis and to compare the behavior of tumors associated with endometriosis in menopausal patients.

Methods: Cases of ovarian cancers with clear cell (CC), endometrioid (E), or mixed (M) histologies were identified. Tumors were classified as either “arising in” endometriosis, “associated with” endometriosis, or “controls” if there was no documented endometriosis on any pathology specimen. Chart review was performed.

Results: Of the 140 patients identified, 42 had CC, 92 were E, and 6 were M. 28.6% of tumors were associated with endometriosis, 37.1% were arising in endometriosis, and 34.3% were controls. 51 patients were premenopausal and 89 patients were postmenopausal. Tumors in premenopausal women were more commonly associated with endometriosis (p=.005). Premenopausal patients presented with early stage disease (p=.04) and had a better overall survival (p< 0.008). Stage (p< 0.001), grade (p< 0.001), endometrioid histology (p< 0.005), and the presence of endometriosis (p< 0.04) were associated with improved survival. Tumors arising in endometriosis did not show a survival advantage when compared with controls (p=0.27). Among endometrioid tumors, the presence of endometriosis was associated with improved survival (p< 0.04), although the same relationship did not hold true amongst clear cell tumors (p=0.22).

Conclusions: While endometrioid and clear cell ovarian malignancies are more likely to arise in older women, their association with endometriosis occurs more commonly in premenopausal women. The association with endometriosis in endometrioid tumors provides a survival benefit, however, menopausal status, stage, and grade are more powerful predictors.
HEATED INTRAPERITONEAL CHEMOPERFUSION IN THE MANAGEMENT OF PATIENTS WITH CARCINOMA OF THE OVARY

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In an attempt to improve progression-free and overall survival in patients with newly-diagnosed and recurrent carcinoma of the ovary, heated intraperitoneal chemoperfusion (HIPEC) was employed at the conclusion of the surgical procedure. This technique has been used for many years in cancers of the colon and pancreas but has been adopted only recently in selected centers for ovarian carcinoma. From April 2008 to May 2010, 67 patients have been treated with HIPEC. Cisplatin was used in all patients and the technical parameters are listed in Table I.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>100mg/m²</td>
</tr>
<tr>
<td>Average Infusion Time</td>
<td>90 minutes</td>
</tr>
<tr>
<td>Average In-Flow Temperature</td>
<td>42°C</td>
</tr>
<tr>
<td>Average Out-Flow Temperature</td>
<td>41°C</td>
</tr>
<tr>
<td>Average Exchange Rate</td>
<td>2370cc/min</td>
</tr>
</tbody>
</table>

[Table I, TECHNICAL PARAMETERS]

With the exception of one patient with stage II tumor, all newly-diagnosed patients were stage III or IV. Sixteen patients were treated for recurrent tumor. The complications were similar to those associated with the surgical procedure itself except for an increase in prolonged ileus as well as an increase in surgery for small bowel obstruction.

Eleven patients have experienced a recurrence and of those 7 were confined to the abdomen. Distant metastases were seen in 5 patients, 4 to the lung and one to the brain. There have been two deaths, one from growing tumor in the immediate postoperative phase and one from an aspiration at the time of a cystoscopy six months following the HIPEC procedure.

There has not been enough time to evaluate progression free and overall survival. However the HIPEC procedure can be done safely and remains a possible adjunct to the management of patients with ovarian carcinoma.

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A RETROSPECTIVE STUDY OF 43 BORDERLINE TUMORS OF THE OVARY A REVIEW OF CLINICOPATHOLOGIC FEATURES AND TREATMENT MODALITIES

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Introduction: Ovarian tumors of borderline malignancy constitute approximately 10-15% of ovarian carcinomas. They share some of the histologic features of malignant epithelial ovarian tumors but are characterized by the absence of destructive stromal invasion. In view of their biologically less aggressive behavior or low malignant potential fertility-sparing conservative treatments have been attempted.

Methods: 43 patients with borderline tumors diagnosed at University Hospital of Obstetric - Gynecology "Koco Gliozheni" and treated at the Oncologic Hospital "Mother Teresa" in Tirana, between 1981 and 2000, were analyzed retrospectively for clinicopathologic features, treatment, and survival characteristics.

Results: The tumors occurred in patients of younger age than that generally described for invasive epithelial ovarian carcinoma. 16 patients had mucinous tumors, 26 had serous tumors, and 1 patient had endometrioid tumor. There were 38 patients with Stage I, 3 with Stage II, and 2 with Stage III tumors by the classification of the FIGO. Most of the patients were treated in conformity with the protocols for invasive carcinoma at the current time. Total abdominal hysterectomy, bilateral adnexectomy and omentectomy were performed in 5 patients and less extensive surgery was performed in 38 patients. The survival free of disease rate for all patients was 93.02%. Adjunctive postoperative therapy may not influence survival.

Conclusions: Stage, histologic type and age had prognostic significance. Fertility saving surgery can be offered to patients with Stage IA disease with serous or mucinous tumors.
SURGERY TREATMENT PATTERNS AND OUTCOMES OF OVARIAN CANCER PATIENTS WITH NON-EPITHELIAL TUMORS: RESULTS FROM A CDC STUDY, UNITED STATES

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Background: Ovarian cancer is the fifth leading cause of cancer death among women in the United States. Most ovarian cancers are epithelial histology, often diagnosed at later stages with poor prognosis. However, the rarer germ cell (GC) and sex-cord stromal (SCS) histologies have been associated with better survival. We characterized demographic/clinical characteristics and outcomes associated with these non-epithelial tumors.

Methods: Patient, tumor, and treatment information was abstracted from medical records of >3000 patients diagnosed with ovarian cancer in Northern California and New York from 1998-2000. Patients were followed-up through 2006.

Results: The median age of diagnosis was 25 years for GC (n=71) and 52 years for SCS (n=52). Patients with both tumor types were more often non-Hispanic white women (GC:38.6%;SCS:51.9%), though GC tumors were more evenly distributed among other races/ethnicity. Most GC and SCS were FIGO stage 1 (GC:65.0%;SCS:67.4%) and were unilateral at diagnosis (GC:92.9%;SCS:93.9%). Almost all patients with GC and SCS received cancer-directed surgery. Women with GC more often received unilateral salpingo-oophorectomy without hysterectomy (26.8%) than any other surgery, while SCS patients received unilateral or bilateral(salpingo-)oophorectomy with omentectomy and hysterectomy (28.8%). Six-year survival was higher for GC patients (93.0%) compared to those diagnosed with SCS (78.8%) (p=0.0234).

Conclusions: GC and SCS differ demographically and clinically from epithelial tumors. About a quarter of women with GC likely received fertility-sparing treatment, while SCS patients received more aggressive surgery. Survival was high for both histologies. Differences observed in these rare types should be considered in the study and treatment of ovarian cancer.
LEAD-TIME OF RISING CA-125 LEVELS IN NORMAL RANGE (< 35 U/ml) TO RADIOLOGIC RECURRENCE IN PATIENTS WITH EPITHELIAL OVARIAN CANCER

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Background: Many patients with epithelial ovarian cancer (EOC) in remission will relapse and rising CA-125 levels above normal predict recurrent disease. However, serially rising CA-125 levels within normal range (< 35U/mL) are also prognostic for relapse and lead times to radiologic recurrence with modern imaging techniques are not well defined.

Methods: Inclusion criteria for this IRB approved study were an elevated CA-125 at diagnosis (>35 U/ml), EOC, fallopian, and primary peritoneal cancer of any stage, complete response to primary therapy as defined by normalization of CA-125, and no evidence of disease. A rise in CA-125 after a complete response was defined as a successive increase of at least two CA-125 values above the coefficient of variation for the assay (3 U/mL) or doubling in CA-125 level drawn a week apart. Primary modality of radiologic imaging was spiral CT scans with oral and intravenous contrast.

Results: For 52 patients that met inclusion criteria, a rise in CA-125 predated the positive radiology scan by 120 days (range 0-580 days). For those patients who had platinum resistant disease, the lead-time decreased to 73 days versus 149 days for platinum sensitive disease. Ninety-six percent of observations with a lead-time greater than the median (120 days) were noted to be sensitive to platinum therapy whereas 53% of observations with a lead-time less than 120 days were platinum resistant (p=0.001).

Conclusions: A rising CA-125 level in the normal range is ominous and radiologic recurrence is seen at a median of 120 days.

Keywords: CA-125
LEAD-TIME OF RISING CA-125 LEVELS >35 U/ML TO RADIOLOGIC CONFIRMATION OF RECURRENT DISEASE IN PATIENTS WITH EPITHELIAL OVARIAN CANCER (EOC)

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Background: Significant number of patients with advanced EOC in remission will relapse. Per outdated literature, serially rising CA-125 level above normal (> 35 U/mL) will predate radiological and clinical recurrence by 3 months. Advent of better imaging technology and patient awareness of the role of CA-125 demands reappraisal of older data.

Methods: Inclusion criteria for this IRB approved study were elevated CA-125 at diagnosis (>35 U/ml), EOC, fallopian, and primary peritoneal cancer of any stage, complete response to initial therapy as defined by normalization of CA-125, and no evidence of disease. A rise in CA-125 after a complete response was defined as a successive increase of at least two CA-125 values (more than a week apart) above the coefficient of variation for the assay (3 U/mL) or a successive doubling in CA-125 level. The primary modality of radiologic imaging was spiral CT scans with oral and intravenous contrast.

Results: 55 patients met inclusion criteria, and rise in CA-125 predated the positive radiology scan by 47 days (range 0-808 days). Patients with platinum resistant disease had lead-time decreased to 20 days versus 62.5 days for platinum sensitive disease, p=0.01. Patients who had interval debulking had a lead-time of 71 days versus 43 days for those who underwent debulking at presentation, p =0.05

Conclusions: The lead-time of rising CA-125 levels above normal to radiologic recurrence of 47 days is far shorter than previously published older data and may help clinicians design early intervention trials.
REDUCTION IN ONE LOGARITHM BETWEEN PREOPERATIVE AND POSTOPERATIVE CA-125 LEVEL IS AN INDEPENDENT FACTOR FOR SURVIVAL IN ADVANCED OVARIAN CANCER

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**Background:** Ninety percent of patients with advanced ovarian cancer (AOC) present an elevation of CA-125. The antigen can predict the course of the disease, when used during chemotherapy. Conversely, the clinical significance of changes in CA-125 during the perioperative period is uncertain.

**Aim:** The purpose of this investigation is to correlate the level of CA-125 reduction and survival in patients with AOC.

**Method:** This retrospective study includes 79 patients with AOC (FIGO stage III-IV) who had elevated CA-125 (> 35 U/mL) at diagnosis, undergoing primary surgery at our institution between January 1, 2000 and November 30, 2009.

Four to six weeks after surgery a second CA-125 was obtained from all patients, prior to chemotherapy.

Age, FIGO stage, histology, residual disease after surgery, use of paclitaxel as part of first line chemotherapy, and different reduction rates of CA-125 were examined using Kaplan-Meier. Those variables found to be independent in the univariate analysis were tested using Cox's proportional hazard model.

**Results:** In the univariate analysis, age, residual disease of less than 5 mm after primary surgery, use of paclitaxel, and a reduction of 10 times the postoperative CA-125 with respect to preoperative values, proved to be independent variables. In the multivariate analysis only residual disease less than 5mm after surgery and a reduction of 10 times postoperative CA-125 levels with respect to the preoperative ones, remained as independent variables.

**Conclusions:** Patients whose CA-125 levels drop 10 times after surgery could represent a subgroup among those who achieve optimal citoreduction.
GYNECOLOGIC ONCOLGY GROUP (GOG)’S OVARIAN CANCER TRIALS, RESEARCH INTEGRITY, WORLDWIDE ECONOMIC AND MEDICO-LEGAL IMPLICATIONS

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Objectives: To register concern and raise awareness of the alarming cosiness of the (GOG) with Pharmaceutical companies at the expense of “Research Integrity”, “Patients safety” and “Economy”.

Methods: In 1983, we embarked on a combination/multi-modality treatment regimen in epithelial ovarian cancer. After surgery patients were given 4-10 weekly courses of IV cisplatin (1mg/Kg). Adriamycin 30mg/m2 was added to DDP on odd or even, LCV/5FU was added to DDP on even or odd weeks. After induction, patients received alternating courses of MTX/LCV -5FU and Adria + DDP + LCV -5 FU. Later we used guidance of a drug resistance assay. After 6 months patients were advised to have a second look procedure. Those with negative second look were given oral Cytoxan. Patients with microscopic residual disease were given IPP32 and along with those with gross residual disease, received further chemotherapy.

Our results, submitted in 2003 were impressive and encouraging: of 183 patients treated (68% stage 3, 15% stage 4, 17% stages 1c & 2c); 57% had serous, 6% each endometroid, mucinous or clear cell carcinoma, 25%; others. At 2nd look, 51% had negative/microscopic, 47% gross disease. 2% had no 2nd look. At last contact, 51% were alive NED, 7% Al with D, 37% DOD. The GOG operatives claim their GOG 111 protocol had established that in 1989 and 1990’s Carboplatin/Cytoxan or Carboplatin/Taxol were the only Standard Therapy.

Argument: The GOG 111 was flawed in design/analysis; claims of “Standard setting” is reckless. Protocols 111, 114, 132, 182, Maintenance, and our regimen deserve further “Scrutiny”.

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MTOR IS A PROMISING THERAPEUTIC TARGET BOTH IN CISPLATIN-SENSITIVE AND CISPLATIN-RESISTANT CLEAR CELL CARCINOMA OF THE OVARY

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Purpose: mTOR (mammalian target of rapamycin) plays a central role in cell proliferation and is regarded as a promising target in cancer therapy including for ovarian cancer. This study aims to examine the role of mTOR as a therapeutic target in clear cell carcinoma (CCC) of the ovary which is regarded as aggressive, chemo-resistant histological subtype.

Experimental design: Using tissue microarrays of 98 primary ovarian cancers (52 clear cell carcinomas and 46 serous adenocarcinomas), the expression of phospho-mTOR was assessed by immunohistochemistry. Then, the growth-inhibitory effect of mTOR inhibition by RAD001 (everolimus) was examined using 2 pairs of cisplatin-sensitive parental (RMG1 and KOC7C) and cisplatin-resistant human CCC cell lines (RMG1-CR and KOC7C-CR) both in vitro and in vivo.

Results: Immunohistochemical analysis demonstrated mTOR was more frequently activated in CCCs than in serous adenocarcinomas (86.6% vs 50%). Treatment with RAD001 markedly inhibited the growth of both RMG1 and KOC7C cells both in vitro and in vivo. Increased expression of phospho-mTOR was observed in cisplatin-resistant RMG1-CR and KOC7C-CR cells, compared to the respective parental cells. This increased expression of phospho-mTOR in cisplatin-resistant cells was associated with increased activation of AKT. RMG1-CR and KOC7C-CR cells showed greater sensitivity to RAD001 than parental RMG1 and KOC7C cells, respectively, in vitro and in vivo.

Conclusion: mTOR is frequently activated in CCC and can be a promising therapeutic target in the management of CCC. Moreover, mTOR inhibition by RAD001 may be efficacious as a second-line treatment of recurrent disease in patients previously treated with cisplatin.
THE VALUE OF GRIM-19 PROTEIN EXPRESSION IN THE ETIOLOGY OF EPITHELIAL OVARIAN CARCINOMA

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**Background:** The etiology of epithelial ovarian carcinoma (EOC) was unclear, altered mitochondrial functions may be crucial to cancer mechanisms, GRIM-19 protein is one of the mitochondrial complex I subunits.

**Aim:** To investigate the possible value of GRIM-19 protein expression in the etiology of EOC.

**Methods:** A total of 77 samples were enrolled in the study, including 13 samples of normal ovarian epithelial tissues, 26 samples of benign epithelial ovarian tumor tissues, 38 samples of EOC tissues. Immunohistochemistry method was adopted to detected the GRIM-19 protein expression, protein expression was calculated by H-Score method.

**Results:** The GRIM-19 protein expression was located in the cytoplasm. The expression of GRIM-19 protein were significantly lower in benign epithelial ovarian tumor tissues than in normal ovarian epithelial tissues (1.891±0.373 vs 2.690±0.615, t=3.277, p=0.004). The protein expression were significantly lower in EOC tissues than in normal ovarian epithelial tissues (1.451±0.209 vs 2.690±0.615, t=6.852, p=0.001). The expression of GRIM-19 protein were significantly lower in EOC tissues than in benign epithelial ovarian tumor tissues (1.451±0.209 vs 1.891±0.373, t=3.483, p=0.002).

**Conclusions:** The abnormal expression of GRIM-19 protein may be associated with the etiology of EOC.
ANALYSIS OF CA-125 AS A PROGNOSTIC FACTOR IN OVARIAN CANCER PATIENTS

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Objective: We have analyzed CA-125 levels in ovarian cancer patients who received care at the Korea University Anam Hospital. Through an analysis, we will determine whether or not the CA-125 level is useful for management as a prognostic factor in ovarian cancer patients.

Methods: Two hundred fifty-seven patients diagnosed with ovarian cancer had data stored in the database at Korea University Anam Hospital between August 1991 and August 2009. A retrospective study was conducted on 50 of the 257 patients who underwent cytoreductive surgery and received chemotherapy. All of the patients underwent 2nd look surgery and serial CA-125 levels were measured.

Results: Initial CA-125 level is not related to OS. (P=0.436) The more optimal surgery increased OS. (P=0.024) Initial CA-125 level is associated with the op optimality. (P=0.002) When 2nd look op positivity was negative, it increased OS.(P= 0.006) CA-125 level after the first line chemotherapy was associated with OS and PFS. (P=0.017 and P < 0.001) CA-125 nadir level(≤10U/ml) after first line chemotherapy was associated with the OS and PFS. (P=0.048 and P=0.049) Pre 2nd look op CA-125 level and CA-125 nadir level(≤10U/ml) are associated with the 2nd look op positivity. (P=0.015 and P=0.001).

Conclusions: The results will be useful for management of patients. During chemotherapy, to be normal CA-125 level was important factor, moreover to maintain below CA-125 nadir 10U/ml will be good the prognosis for patients.
COMPARISON OF FOUR RISK OF MALIGNANCY INDICES IN DETECTION OF MALIGNANT OVARIAN MASSES

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The aim of this study was to evaluate the ability of four malignancy risk indices (RMI1, RMI2, RMI3, and RMI4), to discriminate a benign from a malignant pelvic mass.

This is a prospective of 102 women admitted to the Department of Obstetrics and Gynecology of Gulhane Military Medicine Academy for surgical exploration of pelvic masses. To diagnose ovarian cancer, the sensitivity, specificity, and positive predictive values of RMI1, RMI2, RMI3, and RMI4 are obtained.

This study confirms that, the accuracy of the RM11 and RMI3 were better than RMI2 and RMI4 (P < 0.001). The RM11 at a cutoff level of 200 yielded a sensitivity of 75%, a specificity of 90%, a positive predictive value of 65.2%, a negative predictive value of 93.5%, and an accuracy of 87%.

We concluded that, in the discrimination between benign and malignant pelvic disease, the RMI1 and 3 methods were more reliable than RMI2 and RMI4. These methods are simple techniques those can be used even in less-specialized gynecology clinics to facilitate the selection of cases for referral to an oncological unit.

Keywords: Pelvic mass, ovarian cancer, risk of malignancy index
TRIAGE WITH RMI RESULTS IN BETTER TREATMENT OF EARLY AND ADVANCED OVARIAN CANCER: A PROSPECTIVE POPULATION STUDY

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Introduction and aims: The Risk of Malignancy Index (RMI) was used in a prospective study to decide if a patient had to be referred to a cancer centre or if a gynaecologic oncologist had to be involved in the surgical treatment. The objective is to increase optimal staging of clinical early disease, stage I (CED) and to increase the optimal debulking rate (residual tumour < 1 cm) and overall survival in advanced ovarian cancer, stage III/IV (AOC).

Patients and methods: From 2004 till 2007 533 consecutive women with an ovarian mass were triaged. Ovarian cancer was diagnosed in 218 patients (of which 39 with CED and 122 with AOC). Two cohorts of consecutive patients with CED and AOC from 1998 (n=164) and 2003 (n=156) were used as historical controls.

Results: Of 218 patients with ovarian cancer 51 (23%) were treated by a gynaecologist while 75 (34%) and 92 (43%) were treated either with or only by a consultant gynaecologic oncologist, respectively. Optimal staging in CED was performed in 9/54 (17%), 12/35 (34%) and 22/39 (56%) patients in 1998, 2003 and in the triage study respectively. Optimal debulking rate for AOC increased from 31/66 (47%) in 1998 and 55/87 (63%) in 2003 to 84/122 (69%) in the triage study. Overall median survival for AOC increased from 21 months and 28 to 29 months respectively.

Conclusion: Introduction of a triage policy in patients with ovarian cancer in the population, using the RMI, further increased the rate of optimal debulking, optimal staging and overall survival.
ACTIVATION OF THE MEK/ERK PATHWAY MAY OVERCOMES THE CISPLATIN-RESISTANCE IN OVARIAN CARCINOMA CELLS


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The present study aimed to elucidate the roles of the mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3'-kinase (PI3K)/Akt signaling pathways in regulating cisplatin (CDDP)-induced cytotoxicity in ovarian carcinoma cells.

We treated seven ovarian carcinoma cell lines (KF, KFr, KOC-2S, SK-OV-3, SHIN-3, TU-OS-3, and TU-OS-4) with CDDP combined with PI3K inhibitor (LY294002 [LY]), MEK inhibitor (PD98059 [PD]), or MEK/ERK activator (phorbol 12-myristate 13-acetate [PMA]), then assessed cell viability, expressions of MEK, phosphorylated (p)MEK, ERK, pERK, Akt, pAkt, and cleaved caspase-9 protein, cell cycle distribution, and apoptotic cells. We also examined the effect of combined treatment on survival in a xenograft model of nude mice.

Proteins pMEK, pERK, and pAkt were expressed in all cell lines. The range of IC_{50} to CDDP was 2.4 to 26.9 µM for those cell lines. CDDP combined with LY had an additive effect on inhibiting cell growth, whereas combined with PD had an antagonism for all cell lines. Interestingly, growth of cells was dramatically suppressed when CDDP was combined with PMA in the CDDP-resistant cells (KFr, SK-OV-3, SHIN-3, TU-OS-3, TU-OS-4). Treatment with PMA up-regulated protein expression levels of pERK and cleaved caspase-9 only in the CDDP-resistant cells. CDDP combined with PMA increased the S-phase fraction and apoptotic cells in the CDDP-resistant cells. Treating nude mice with CDDP and PMA prolonged survival in an ovarian cancer xenograft model (P< 0.01).

These results indicate that MEK/ERK activated by PMA may overcome resistance to CDDP in ovarian carcinoma cells.
DIFFERENTIATION BETWEEN BENIGN AND MALIGNANT OVARIAN TUMORS DURING PREGNANCY

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The routine use of transvaginal ultrasound in early pregnancy has resulted in an increased detection rate of ovarian masses. Although the 2008 guidelines describe their management in Japan, actual management is often difficult. We evaluated 60 pregnancies complicated by ovarian tumor operated on in the past 10 years. The number of patients increased from 8 in the first 5 years to 52 in the second 5. We reviewed 33 patients operated on during their early pregnancy. Mean age was 30.4±4.4 years. Twenty-four patients were nulliparous and 9 parous. Mean gestation week at operation was 14W0D. Twenty-seven patients were asymptomatic, 2 had dull pain, and 2 had severe pain (torsion and rupture, respectively). Mean tumor diameter was 8.6±2.8 cm. Mean CA125 was 108±149 U/mL. MRI was performed in 19 patients. Histopathology showed mature cystic teratoma in 13 patients, paraovarian cyst in 5, endometrial cyst in 4, serous cystadenoma in 2, mucinous cystadenoma in 2, mucinous tumor of borderline malignancy in 1, mucinous cystadenocarcinoma in 1, lutein cyst in 2, thecoma in 1, dysgerminoma in 1, and pseudocyst in 1. Postoperatively, one patient miscarried, 2 had premature birth, and the rest had full term birth. One patient with mucinous cystadenocarcinoma underwent TC chemotherapy and gave birth by cesarean section at 36 weeks' gestation. MRI was useful for malignant/benign differentiation, but tumor size and marker were not. Some ovarian tumors were difficult to differentiate from adult teratoma by transvaginal ultrasound alone.
IMPACTS OF N-FACTOR ON PROGNOSIS OF T3C OVARIAN CANCER AFTER OPTIMAL SURGERY


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Aims: We analyzed the impacts of N factor on prognosis of T3c ovarian cancer patients who underwent optimal surgery (OpS).

Methods: Subjects were 68 patients with T3c serous adenocarcinoma. The overall survival (OS) (5-year survival rate) and the median survival time (MST) were analyzed by the diameter of residual tumor and lymph node metastasis using the Kaplan-Meier method and Log-rank test. The patients in the OpS group were further divided into a complete group with no residual tumor and a group with residual tumor of less than 1 cm, and analyzed. The patients received retroperitoneal lymph node dissection in the pelvic cavity up to $\#326b1$.

Results: OSs in OpS group and Sub-OpS group were 77.5% and 11.1%. According to the analyses made by different levels of lymph node metastasis in all patients, OSs in patients with N0 and N1 were 77.1% and 47.5%, respectively; prognosis was significantly poorer in N1 group. According to the analyses of N factor in OpS group, prognosis was significantly poorer in N1 group even with OpS compared to that in N0 group (53.7% and 86.6%, respectively). Furthermore, in N1 group with OpS, prognosis was significantly better in the complete group than in the other group with residual tumor of less than 1 cm (77.8% and 16.7%, respectively).

Conclusions: The prognosis of T3cN1 ovarian cancer with OpS was as poor as with Sub-OpS. However, the results suggested that prognosis could be improved if the tumor was completely resected in OpS.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

PREVALENCE OF SOMATIC MUTATION HOT SPOTS IN GRADE 2 AND 3 ADVANCED STAGE SEROUS PAPILLARY OVARIAN CANCER

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Background: Despite advances in chemotherapy and radical surgery, grade 2-3 advanced stage serous papillary ovarian cancer is associated with the highest mortality among gynecologic malignancies. Since the molecular determinants modulating outcome in these patients are poorly characterized, we aimed to evaluate somatic mutations in signaling pathways that are key regulators of normal cell growth and malignant transformation.

Methods: DNA was extracted from Formalin-Fixed Paraffin-Embedded or fresh frozen tissues of 143 patients diagnosed with grade 2 or 3, stage III - IV serous papillary epithelial ovarian cancer. Using the Sequenom MALDI TOF MassArray system, we genotyped the most frequent hot spot mutations in KRAS, BRAF, NRAS and PIK3CA and in 14 additional genes, where we covered only a fraction of somatic mutations reported in COSMIC (TP53, CTNNB1, MET, AKT1, AKT2, EGFR, ERBB2, FBXW7, FGFR2, MAP2K4, MAP2K7, PDGFRA, PTEN, SMAD4).

Results: Overall, only 18 samples were mutated (12.6%), of which 8 for TP53 (5.6%), most commonly in codon 273 (37.5%). PIK3CA mutations were observed in 2.1%. Mutations were also observed in MET (2.1%) and KRAS (1.4%), respectively in codon 988 and 12. Other known oncogenes such as AKT2 and PDGFRA were mutated only once.

Conclusion: In contrast to endometrial and colorectal cancer, grade 2 and 3 advanced stage serous papillary ovarian cancers show a low frequency of somatic mutation hot spots. This finding underscores that the genetic causes of this cancer type are heterogeneous. Future studies may have to shift the focus from mutation analysis to the complexity of genomic instability.
SECOND LINE CHEMOTHERAPY FOLLOWED BY CYTOREDUCTIVE SURGERY IN THE MANAGEMENT OF RECURRENT EPITHELIAL OVARIAN CANCER

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Introduction: The role of secondary cytoreductive surgery (SCS) in recurrent epithelial ovarian cancer is still controversial. However, emerging evidences from the literature suggest that survival is improved in patients in which a complete tumor resection is obtained. Chemotherapeutic treatment before secondary surgery could allow reaching the goal of complete debulking in a greater proportion of patients.

Patients and methods: All patients who underwent SCS in our centre were retrospectively analyzed. Demographics, anatomopathological and clinical data, in particular the administration of a preoperative chemotherapy, along with survival were recorded.

Results: Between 1981 and 2006, 141 patients underwent SCS for EOC. Median disease-free interval was 27 months. 135 patients (96%) had ACOG performance status 0, 82 (58%) were stage III at the diagnosis, 81 (58%) had no residual tumor after first surgery, ascites was absent in 135 patients (96%). 117 patients (83%) received chemotherapy before SCS. Complete tumor resection was obtained in a significantly greater proportion of patients in the group of women who received chemotherapy before SCS (68% versus 48%, p: 0.03). No patients experienced operative or postoperative complications. Overall survival from secondary surgery was 41 months. Median survival for patients who had absent residual tumor was 60 months compared with 22 months for patients who had any size of residual tumor (HR 0.49, 95% IC 0.25-0.66).

Conclusion: Our results confirm that SCS is a safe procedure and patients who achieve optimal cytoreduction have a significantly improved survival. Chemotherapy administration before SCS may improve the rate of complete tumor resection.
PHASE II TRIAL OF BIWEEKLY DOCETAXEL AND MONTHLY CARBOPLATIN IN THE TREATMENT OF PLATINUM SENSITIVE RECURRENT OVARIAN OR TUBAL CANCER


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Background: Docetaxel and carboplatin (DC) showed similar activity to paclitaxel and carboplatin with less neurotoxicity for platinum sensitive recurrent ovarian cancer. Nevertheless, DC showed severe hematologic toxicity. A multicenter phase II study was conducted to clarify the efficacy of biweekly docetaxel and bolus carboplatin treatment (biweekly DC).

Method: Eligible patients had responded to Taxan / Platinum chemotherapy in the primary chemotherapy and they had recurrent measurable disease with more than 6 months treatment free interval. Patients were treated with docetaxel 35mg/m2 (day1 and 15) and carboplatin AUC 5 (day1) every 28days. Objective response was assessed by RECIST criteria. Primary endpoint was response rate (RR) and secondary endpoint was toxicity and progression free survival (PFS) and overall survival (OS).

Results: 30 patients were enrolled from January 2005 to September 2009. Adverse effect was evaluated in 26 patients and response was evaluated in 24 patients. Median age was 57.5 yrs (41-75). Median treatment cycle was 4.5 (1-9). RR (CR+PR) rates was 70.8% (8CR, 9PR). Grade 3/4 hematologic toxicities included leukopenia (grade3 38%), neutropenia (grade3 69%, grade4 27%), and non-hematologic toxicities were nausea, constipation, and sensory neuropathy (grade3 all 3.8%). Grade 2 toxicities included alopecia (69%), arthralgia(7.7%), neuropathy (sensory 11.5%, motor 3.8%). No grade3 thrombocytopenia, anemia, or febrile neutropenia were observed. Median PFS was 280 days and OS was 650 days.

Conclusions: Biweekly DC is a new promising regimen for platinum sensitive recurrent ovarian or tubal cancer, which showed higher RR and less hematologic toxicity than the standard tri-weekly scheduled DC treatment.
THE DIFFERENT CLINICAL FEATURES OF EARLY STAGE MUCINOUS OVARIAN CANCER ACCORDING TO THE PATHOLOGIC EXTENT OF STROMAL INVASION

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Objective: To study differences of clinical outcomes in the patients with early stage mucinous ovarian cancer (MOC) according to the pathologic extent of stromal invasion

Methods: We retrospectively reviewed medical records of 117 patients with FIGO stage I - II MOC who were treated at Asan Medical Center, Seoul, Korea from January 1994 to July 2009. From pathologic review, the patients were divided into groups: intraglandular carcinoma (IGC), intraepithelial carcinoma with microinvasion (IECMI), and mucinous adenocarcinoma with extensive invasion (MACEI) according to the extent of stromal invasion. The presences of mucin granuloma which was only composed of cells with non-malignant features were excluded from the definition of IECMI.

Results: The number of patients was 57 (43.2%) in IGC, 15 (12.1%) in IECMI, and 46 (44.7%) in MACEI. There were no differences between groups in terms of age, menopause, CA-125 level, tumor size, surgical procedures, stage, capsular and lymphovascular involvements, adjuvant treatment, and follow-up period. However, the patients with MACEI had recurrences more frequently at the extra pelvic and distant sites (P=0.028). Five year disease-free-survival rate was 97.8% in IGC group, 77.3% in IECMI, 78.2% in MACEI (IGC vs IECMI, P=0.003; IGC vs MACEI, P=0.004; IECMI vs MACEI, P=0.491).

Conclusion: In the patients with early stage MOC, pathologic IGC had better prognosis than IECMI and MACEI. The prognosis of IECMI was similar with that of MACEI.
COST-EFFECTIVENESS ANALYSIS OF PER-OPERATIVE INTRA-PERITONEAL CHEMOTHERAPY (POIPCT) IN ADVANCED EPITHELIAL OVARIAN CANCER (EOC) MANAGEMENT

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Background: In the context of rational decision-making in health care, a major challenge in pharmacoeconomic evaluation is to provide cost-effectiveness data that are relevant to usual practices. Thus, the aim of this study was to estimate the incremental cost-effectiveness of the input of POIPCT in advanced EOC management, from the start of first-line chemotherapy to the death of patients.

Methods: A decision-making analysis Markov model was developed. The cycle length was set at three months to facilitate the patient's follow-up and use of published progression-free survival and overall survival. For each state of health, transition probabilities and direct costs associated with managing advanced EOC are calculated or estimated. This retrospective study was performed from the hospital-payer perspective. Economic parameters were discounted by a 3% annual rate. The uncertainty of the actual cost-effectiveness gained by analysing the "POIPCT" was addressed with a probabilistic analysis involving second-order Monte-Carlo simulations.

Results: The "POIPCT" strategy costs €60,478 euros, as opposed to €43,137 for the "no POIPCT" strategy. With lives extended by 54 months and 41 months, incremental cost-effectiveness was estimated at 16,450 euros per life-year saved (LYS). A Monte-Carlo simulation confirmed the robustness of our results. While the "POIPCT" strategy for patients with platinum-sensitive disease is cost-effective (€12,546 per LYS), the "no POIPCT" strategy for patients with platinum-resistant disease cannot be deemed to be cost effective (€547,949 per LYS).

Conclusions: Our study suggests that "POIPCT" in advanced EOC management, optimally debulked, may be considered as a cost-effective strategy, particularly for patients with platinum-sensitive disease.
EFFECTS OF PHOTODYNAMIC THERAPY IN COMBINATION WITH 2-METHOXYESTRADIOL ON APOPTOSIS IN HUMAN OVARIAN CLEAR CARCINOMA CELL LINE (OVBH-1)

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Background and aims: Recent developments in photomedicine and not promising prognosis of advanced ovarian cancer have lead scientists to focus on PDT application in this type of cancer. The aim of our study was to examine the effect of PDT modified by 2-Methoxysteradiol (2-Me) (superoxide dismutase inhibitor) on apoptosis in human ovarian cells carcinoma (OvBH-1) with p53 overexpression.

Materials and methods: OvBH-1 cell line was used. The cells were treated with 20 µg/ml Photofrin II in complete media for 18 h in the dark. Then, they were irradiated with light intensity of 10 mW/cm² and dose 6 J/cm² and incubated again for 0, 3, 6 h after irradiation. The expression of main pro- and anti-apoptotic proteins (p53, Bax and Bcl-2) were evaluated by immunochistochemical methods. Additionally, we assessed the 2-Me-PDT mediated apoptosis by neutral comet assay and TUNEL.

Results: We observed increased expression of pro-apoptotic proteins and p53 phosphorylation. The highest number of apoptotic cells (ca. 100% ) was observed after 2-Me-PDT in case of both apoptosis tests.

Conclusions: We suggest that the application of SOD inhibitor has potentiated cytotoxic effect of photodynamic therapy and can be applied successfully in the treatment of ovarian carcinoma. There is also implied that the modification of p53 protein by phosphorylation plays an important role in the regulation of its biological function in apoptosis.
OVARIAN MALIGNANT GERM CELL TUMORS COEXISTING WITH OR FOLLOWING COMMON OVARIAN BENIGN TUMORS


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Introduction: The risk factors for ovarian malignant germ cell tumors (OMGCTs) are unknown. The association between OMGCTs and common ovarian benign tumors is not clear.

Methods: Pathology files between January, 1993 and May, 2010 were reviewed in our institute. The association between OMGCTs and common ovarian benign tumors (including endometrioma, mature cystic teratoma, mucinous cystadenoma and serous cystadenoma) was retrospectively investigated. Malignant transformations in mature cystic teratoma was excluded.

Results: A total of 61 patients with OMGCTs (24 immature teratoma, 16 yolk sac tumor, 10 dysgerminoma, 1 choriocarcinoma, 1 embryonal carcinoma, 9 mixed OMGCTs) were diagnosed in our institute. Among the 2225 patients with ovarian mature cystic teratoma, 11 (0.5%) patients had coexisting or subsequent OMGCTs. Interestingly, all of the coexisting (3 patients) or subsequent (2 patients) immature teratoma occurred in the contralateral ovary, while coexisting (4 patients) or subsequent (2 patients) yolk sac tumor in the ipsilateral ovary. In contrast, OMGCTs occurred much less frequently with other ovarian benign tumors. Coexisting or subsequent OMGCTs occurred in 1 (0.03%; coexisting immature teratoma in the contralateral ovary) of the 3652 patients with ovarian endometrioma, 1 (0.08%; coexisting yolk sac tumor and dysgerminoma in the ipsilateral ovary) of the 1294 patients with ovarian mucinous cystadenoma, and 0 of the 466 patients with ovarian serous cystadenoma, respectively (p< 0.001).

Conclusions: OMGCTs occurred much more frequently with or following ovarian mature cystic teratoma than other common ovarian benign tumors. Ovarian mature cystic teratoma might be regarded as a risk factor for OMGCTs.
TREATMENT OUTCOME OF CARCINOSARCOMA OF OVARY: COMPARISON WITH SEROUS EPITHELIAL OVARIAN CARCINOMA

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Objectives: The aim of this study was to compare the response to platinum-based adjuvant chemotherapy after cytoreductive surgery and survival outcomes between ovarian carcinosarcoma (OCS) and ovarian serous epithelial cancer (OSEC).

Methods: Each case of OCS was matched with 2 cases of OSEC with priority given to the International Federation of Obstetrics and Gynecology (FIGO) stage, then residual disease after cytoreductive surgery, followed by age of patient. All patients underwent comprehensive surgical staging and maximal cytoreductive surgery according to FIGO guidelines, and received platinum-based adjuvant chemotherapy after surgery from 1991 to 2009 at Asan Medical Center (AMC, Seoul, Korea).

Results: Thirty-four patients with OCS were matched to 68 patients with OSEC. The response rates to platinum-based adjuvant chemotherapy after cytoreductive surgery were 79% and 82% for patients with OSEC and OCS (P=0.792). The median follow-up time was 72 months (range, 3-235 months). Five-year disease free survival rates were 51% and 41% for patients with OSEC and OCS, respectively (P=3340), and 5-year overall survival rate were 77% and 52% for patients with OSEC and OCS, respectively (P=0.0106).

Conclusion: Current strategy which consisted of platinum-based adjuvant chemotherapy after maximal cytoreduction may be acceptable for management for patients with OCS. However, further study to develop more effective treatment modality for recurrent OCS is required.
ONCOLOGIC AND REPRODUCTIVE OUTCOMES OF PATIENTS WITH OVARIAN YOLK SAC TUMOR AFTER BLEOMYCIN, ETOPOSIDE, CISPLATIN (BEP) CHEMOTHERAPY FOLLOWING SURGERY

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Objective: The aim of this study was to evaluate the oncologic and reproductive outcomes of patients with ovarian yolk sac tumor after bleomycin, etoposide, cisplatin (BEP) chemotherapy following surgery.

Methods: Of 145 patients with histologically confirmed malignant ovarian germ cell tumor, 43 had yolk sac tumor and 38 of them received BEP chemotherapy after surgery. A retrospective analysis of these patients was performed.

Results: The mean age of 38 patients was 23 years (range, 8-43 years). Thirty four patients were nulliparous. Of 179 BEP chemotherapy cycles, grade 3 hematologic and non-hematologic adverse events occurred in 18 cycles in 8 patients, and grade 4 adverse events occurred in 1 patient. Thirty seven patients showed complete remission, 1 patient showed partial remission, and 1 patient had progressive disease during BEP chemotherapy. After median follow-up time of 57 months (range, 3-153 months), 5 patients had recurrent disease and two of them died of disease. The 5-year recurrence free survival rate and overall survival rate were 86 and 94 %, respectively. After chemotherapy, all but two premenarchal patients had normal menstruation. Of them 5 patients tried to conceive and 3 of them succeeded in pregnancy.

Conclusions: BEP chemotherapy was very safe and effective in patients with ovarian yolk sac tumor. Survival outcomes are excellent and reproductive outcomes are promising after BEP chemotherapy.
CA125-SPECIFIC CYTOTOXIC T LYMPHOCYTES FOR THE TREATMENT OF ADVANCED OVARIAN CANCER


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Objective: We evaluated efficacy of immunotherapy using cytotoxic T lymphocytes stimulated by immunogenic peptides derived from CA125 antigen for the treatment of chemotherapy-resistant advanced ovarian cancer.

Study design: We established amino acid analog peptides (OVCA10 and 11) which are derived from amino acid sequence of CA125 core protein and bind to human cytotoxic T lymphocytes. Peripheral blood T cells collected from nine patients with advanced ovarian cancer were stimulated by OVCA10 or 11, and mixed-cultured with CA125 producing ovarian carcinoma cells (HTOA). One patient had the autologous stimulated T lymphocytes injected into cystic mass formed by cancer metastasis or peritoneal cavity.

Results: OVCA11-stimulated T lymphocytes showed significantly high cytotoxic activity against HTOA cells. CA125 values of all the patients were decreased and no obvious side effect was caused by this treatment protocol.

Conclusions: We assume CA125 analog peptide (OVCA11) is an immunogenic epitope and may represent an attractive target for immunotherapy of advanced ovarian cancer with minimal side effect.
EVALUATION OF THE IMMUNE ACTIVATION STATUS OF T-CELLS INFILTRATING OVARIAN CANCER

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Objective: The aim of our study was to compare the activation status of tumor infiltrating T-cells in the tumor tissue and peripheral blood of ovarian cancer patients.

Patients and methods: Five-colour flow cytometry was used to measure the expression of surface activation markers (CD69, CD25 and HLA-DR) on T-cells (CD3, CD4 and CD8) obtained from cancer tissue (n=20) and peripheral blood (n=34) ovarian cancer patients.

Results: The percentage of CD3+, CD4+ and CD8+ T lymphocytes showing CD69 expression was significantly higher on a tumor infiltrating T-cells compared with T-cells derived from peripheral blood (76.40%, 74.84% and 82.36% respectively) vs (3.03%, 3.17% and 6.52% respectively). The HLA-DR late activation marker expression on CD3, CD4 and CD8 cells was also higher on a tumor infiltrating T lymphocytes (69.27%, 69.86%, 60.39%) than on T-cells in blood (16.25%, 8.91% and 16.90%). The percentage of CD3+CD25+ positive T-cells was significantly lower on tumor infiltrating cells (7.74%) in comparison to peripheral blood (16.12%). There was no significant difference between CD25 expression on CD4+ and CD8+ tumor infiltrating and peripheral blood T-cells.

Conclusion: We demonstrated that T lymphocytes isolated from tumor cancer tissue expressed higher amounts of activation molecules: CD69 and HLA-DR in comparison with peripheral blood. These results suggest that CD3+, CD4+, CD8+ T-cells from ovarian cancer tissue are activated cells. On the other hand, reduced expression of CD25 on T infiltrating cells may suggest that these cells have a lower capacity for clonal proliferation. This may be caused by immunosupresive factors secreted by cancer cells.
SURVIVAL IN OVARIAN CANCER PATIENTS WITH RECURRENCES: DOES DETECTION MODE MATTER?

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Background: Ovarian cancer patients treated with curative intent are seen at a regular follow-up schedule. Prior observational studies showed inconsistent impact of routine follow-up on survival. We aimed to determine the recurrence detection pattern and corresponding survival in Dutch ovarian cancer patients.

Methods: Ovarian cancer patients diagnosed between 1996 and 2006 in 4 hospitals in East-Netherlands were included. All 127 patients with a recurrence after complete clinical remission due to primary treatment were selected. The presence of symptoms and the type of visit at which the recurrence was detected, as well as the date of death were assessed. Survival was calculated by the Kaplan-Meier method based on the time since the last primary treatment to death or date last known to be alive.

Results: Eighty-seven (69%) patients had a recurrence detected at a routine visit, of whom 52 (60%) asymptptomatically. Patients with an asymptptomatically detected recurrence had a median survival time of 44 months (95%-CI 38-64). Median survival time of patients with a symptomatic recurrence detected at a routine visit was 29 months (95%-CI 21-38) and 33 months (95%-CI 19-61) if detected symptomatically at an interval visit.

Conclusions: Patients with asymptomatic recurrences detected at a routine follow-up visit had a better survival, though not statistically different, compared to patients with symptomatic recurrences detected at routine or interval visits. Whether this survival benefit trend is a result of the routine follow-up visits is not clear. Selection bias, including length biased sampling may play an important role.
EXPRESSION OF NEUROPILIN-1 IN OVARIAN CANCER

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Background: Neuropilin-1 (NRP-1), a transmembrane glycoprotein, is a key co-receptor for VEGFR-3 and can bind VEGF-C. In several cancer types significant correlations of the expression of NRP with tumor progression and overall survival prognosis were found. Its possible role in epithelial ovarian cancer (EOC) has not been defined yet.

Aims: The aim of this work was to study the correlation of NRP-1 immunohistochemical expression with histological type and grade, FIGO stage and menopausal status.

Material and methods: The study included 61 women (aged 24 to 82, median 59). 24 of the patients were postmenopausal (39,3%). Specific anti-NRP-1 antibody was used in immunohistochemical staining of representative tumor tissue samples of patients with EOC. Percentage of stained cells and intensity of staining were assessed under 200x magnification. The menopausal status, histological type and grade, FIGO stage, were correlated with the results of immunohistochemical staining.

Results: During histological examination 30 cases of serous cancer were found (49,2%), 20 cases of mucinous cancer (32,8%), and 11 endometrioid cancers (18%). No NRP-1 staining was found in 26 cases (42,6%) of EOC, weak (+) staining was found in 15 tumors (24,6%) and strong staining in 20 (32,8%) tumors. Between neuropilin-1 expression and menopausal status no significant differences were found. There were no differences between histological type of EOC and immunohistochemical expression of NRP-1 too. Stage II was correlated with the lack of expression of neuropilin-1.

Conclusions: Expression of neuropilin-1 is probably not related to selected clinical and histological features of malignant ovarian tumors.
INTRACELLULAR EXPRESSION OF INTERLEUKIN-17 (IL-17) IN THE PERIPHERAL BLOOD LYMPHOCYTES OF PATIENTS WITH OVARIAN CANCER

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Objective: To compare the percentage of peripheral blood (PB) CD3+, CD4+, CD8+ T cells producing interleukin-17 (IL-17) in ovarian cancer patients or benign ovarian tumors.

Methods: Thirty-six patients with ovarian cancer (OVC) and thirty-two benign control subjects were recruited. PB mononuclear cells from cancer patients or control subjects were stimulated for 4 hours ex vivo with phorbol myristate acetate (PMA) and ionomycin. The percentage of CD3+, CD4+ and CD8+ T cells producing IL-17 (Th17 cells) was measured using flow cytometry.

Results: The percentage of CD3+ T cells producing IL-17 was lower in patients with OVC 0.56% (0.04-1.84%) in comparison with benign tumor patients 0.70% (0.17-1.29%), but this difference did not reach statistical significance. The percentage of IL-17+CD4+ T cells was lower in ovarian cancer patients 0.74% (0.09-4.17%) compared with control subjects 0.95% (0.21-2.04%), however the difference was not significant. The percentage of IL-17+CD8+ T cells in patients with OVC was lower 0.10% (0.03-0.55%) compared to benign tumor patients 0.12% (0.03-1.10%) but not significantly. There was no difference in the percentage of IL-17+CD3+, IL-17+CD4+, IL-17+CD8+ T cells between patients with grade II and III of OVC and among patients with serous, mucinous, endometroid and undifferentiated carcinoma.

Conclusions: We demonstrated the presence of IL-17+ cells in both CD4+ and CD8+ T cells in patients with ovarian cancer or benign tumor. There was no difference in the percentage of Th17 cells in both study groups, which prove that this cells are probably not useful in differentiating malignant and nonmalignant tumors.
BRCA1 PROTEIN EXPRESSION IN PATIENTS WITH OVARIAN AND BREAST CANCER

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Introduction: Clustering of ovarian cancer (OvCa) and breast cancer (BrCa) in families, and identification of germline mutation in BRCA1 and BRCA2 genes in these families support the notion that there is genotypic association between these two malignancies. The objective of this study is to explore the role of BRCA1 protein expression in patients with OvCa and BrCa and to evaluate the correlation of BRCA protein expression to BRCA1-2 carrier status and p53 expression.

Methods: The study group included 31 patients with double primary malignancies (OvCa and BrCa). Sixty two patients with solitary OvCa and 62 patients with solitary BrCa were comprised the control group. BRCA1 and p53 immunohistochemistry and genotyping for BRCA1-2 mutations were performed.

Results: BRCA1-2 mutations were identified in 48% of the study group. No significant difference in BRCA1 cytoplasmatic staining was identified in the different groups, 41% and 39% of the OvCa and BrCa tumors in the study group compared with 41% and 44% in the solitary OvCa and BrCa controls. Positive BRCA1 immunohistochemistry had a 61% and 66% sensitivity and 43% and 44% specificity for identifying patients with BRCA1-2 mutations in OvCa and BrCa tumors, respectively. There was no statistically correlation between BRCA protein expression and the age at diagnosis. Moreover, BRCA protein expression in the OvCa and BrCa tumors was not correlated to p53 protein expression.

Conclusions: BRCA1 protein expression has a moderate sensitivity and specificity for identifying BRCA1-2 mutation carriers. BRCA1 protein expression was not correlated to age of diagnosis and p53 protein expression.
INFLUENCE OF SIRNA MEDIATED MESOTHELIN-SCIENCE ON GROWTH OF HUMAN OVARIAN SKOV3 CELL XENOGRRAFT IN NUDE MICE

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Objective: To study the influence of mesothelin-science on the proliferation of ovarian cancer cell line SKOV3, and the influence of mesothelin-science on the growth of human ovarian xenograft in nude mice.

Methods: Mesothelin-scilenced cells (SKOV3-MSLN-shRNA) and control cells (SKOV3-MSLN-neg) were built by RNA interferece lentivirus and empty vector lentivirus, and SKOV3 cells were used as black control. Cell proliferation was assayed by clone-forming test and cell counting assay. Nude mice models are established used the 3 kinds of cell lines mentioned above. After 2 weeks, the mice were killed, and the tumor formation rate of each group, the numbers of tumor, average tumor weight and numbers of tumor position of each mouse were investigated.

Results: The ability of proliferation of SKOV3-MSLN-shRNA cells were obviously decreased compared with other two groups. In vivo, the tumor formation rate in the group injected with SKOV3-MSLN-shRNA cells was 60%, while was 100% in other two groups (P>0.05). The average tumor weight, tumor numbers, and numbers of tumor position were all suppressed in this group (P< 0.05).

Conclusion: Cell proliferation of SKOV3 can be decreased by mesothelin-science siRNA lentivirus. Growth of the xenografts can be suppressed by mesothelin small interferece RNA.

Keywords: Ovarian neoplasm; mesothelin; RNA interferece; xenograft
TREATMENT EFFECT OF MESOTHELIN TARGETED SIRNA GENE THERAPY ON OVARIAN EXNOGRAFTS IN NUDE MICE

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Objective: To study the treatment effect of chronic lentivirus mediated mesothelin small interference on ovarian cancer nude mice model.

Methods: Animal model of nude mice is established used the ovarian cancer cell line SKOV3. Mesothelin small interference chronic lentivirus LV-MSLN-shRNA, control vector LV-MSLN-neg and black control PBS were respectively injected into the abdominal cavity of the nude mice every two days, and the effect of them were observed after 14 days of SKOV3 injection. Mesothelin protein expression in transplanted tumor of nude mice was measured using western blotting.

Results: The transplanted tumor growth was obviously suppressed when treated with LV-MSLN-shRNA, compared with other two groups treated with LV-MSLN-neg and PBS. The protein expression of mesothelin in transplanted tumor tissue was decreased after treated with LV-MSLN-shRNA (P<0.05).

Conclusion: Growth of the ovarian transplanted tumor in nude mice can be decreased by mesothelin small interference RNA chronic lentivirus. Mesothelin-targeted gene therapy inhibited growth of the neoplasms obviously.

Keywords: Ovarian neoplasms; mesothelin; RNA interference; chronic lentivirus; gene therapy
VALUE OF SERUM MESOTHELIN IN DIAGNOSIS AND CONDITION MONITORING OF EPITHELIAL OVARIAN CANCER

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Objective: To determine whether serum soluble mesothelin related peptide (SMRP) can be a tumor marker for ovarian cancer, and to evaluate the diagnostic effect of it.

Methods: A MESOMARK ELISA kit was used to quantitate the serum SMRP levels. Sera from 56 ovarian cancer patients, 38 patients with benign ovarian tumors, 34 healthy volunteers, and 23 ovarian cancer patients who accepted operation were analyzed. The levels of serum SMRP were compared in the three groups mentioned above, then calculated the best statistical cutoff, sensitivity, and specificity of SMRP for ovarian cancer diagnosis.

Results: The SMRP concentration was significantly higher in patients with ovarian cancer compared with patients with benign ovarian (P<0.05) and healthy volunteers (P<0.05). As the diagnosis marker of ovarian cancer, the best statistical cutoff of SMRP was found to be ≥1.6432 nM resulting in a sensitivity of 0.821 and a specificity of 1.00.

Conclusions: Serum SMRP levels were significantly elevated in patients with ovarian cancer. Serum SMRP was an ideal and novel marker for ovarian cancer screening and diagnosis.

Keywords: Mesothelin; ovarian neoplasm; diagnosis; condition monitoring; tumor marker
EVALUATION OF OBATOCLAX FOR THE TREATMENT OF OVARIAN CANCER

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The major obstacle to effective long-term treatment of ovarian cancer is the development of resistance to chemotherapy. We have previously shown that the Bcl-2 family antagonist ABT-737 increases the sensitivity of a subset of ovarian cancer cells to carboplatin. However, synergy was not observed in some cell lines and this may reflect the expression of Bcl-2 family members to which ABT-737 does not bind. Obatoclax is a Bcl-2 family antagonist which binds to all known Bcl-2 family members and which is currently being evaluated in clinical trials.

Obatoclax potently inhibited the growth of all 8 ovarian cancer cell lines (IC₅₀ =25-200 nM) and independently of the sensitivity of the cells to carboplatin or paclitaxel. In 2 cell lines, obatoclax dose-dependently induced cleavage of PARP and the appearance of a prominent subG₁ peak when the cells were analysed by flow cytometry after staining with propidium iodide. In the remaining cell lines, significant PARP cleavage was not observed and flow cytometry indicated a substantial decrease in the proportion of cells in G₂/M. In all of the cells lines, obatoclax induced a robust accumulation of LC3, a marker of autophagy. When obatoclax was tested in drug combination studies with either carboplatin or paclitaxel, significant antagonism was observed (C.I. >2).

These results suggest that in addition to inducing apoptosis, obatoclax possesses additional activity which may antagonise the effect of chemotherapy. Clinical trials of obatoclax in ovarian cancer preferably should evaluate the drug’s activity as a single agent rather than in combination with chemotherapy.
PROGNOSTIC SIGNIFICANCE OF THE RELATIVE DOSE INTENSITY OF CHEMOTHERAPY IN PRIMARY TREATMENT OF EPITHELIAL OVARIAN CANCER

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Objective: Utilization of taxane/platinum-based chemotherapy results in clinical remission in 75% of patients with epithelial ovarian cancer (EOC). Studies in breast cancer have demonstrated that full dose chemotherapy improves survival. Relative dose intensity (RDI) is the ratio of delivered dose intensity to standard dose intensity. We sought to determine the prognostic significance of the RDI in patients with EOC.

Methods: A retrospective analysis of chemotherapy naïve patients treated between 2001-2008 with docetaxel or paclitaxel in combination with carboplatin was performed. RDI was calculated as the delivered dose intensity divided by standard dose intensity calculated for each regimen. Standard dose intensity was docetaxel (75 mg/m²) or paclitaxel (175 mg/m²) plus carboplatin (AUC 6) every 21 days for 6 cycles. The RDI for each patient was compared to the progression-free survival (PFS). Multivariate recursive partitioning survival analysis was utilized.

Results: 138 EOC patients were included. 72% of patients were stage III/IV and 71% were optimally debulked. The average age was 63. Reasons for dose delays/reductions included thrombocytopenia (38%) and neutropenia (31%). Forty-eight patients (34%) patients received docetaxel/carboplatin, 88 (64%) received paclitaxel/carboplatin and 2 (2%) received single-agent carboplatin. The average RDI was 90% (range, 24-126%). The mean PFS was 31 months (range, 3-117). Patients that achieved an RDI of 70-110% had a mean PFS of 32 months compared to 20 months in patients with an RDI of < 70% or >110% (p=0.046).

Conclusions: RDI is a significant predictor of survival in patients with EOC. Efforts should be made to achieve an RDI of ≥ 70% in patients undergoing chemotherapy for EOC.
SYNCHRONOUS PRIMARY CANCERS OF THE ENDOMETRIUM AND OVARY: A RETROSPECTIVE CLINICOPATHOLOGICAL STUDY

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Objective: Synchronous tumors of the endometrium and ovary represent 0.7% of gynecological cancers. The aim of the present retrospective study was to assess clinical characteristics, histological patterns and survival rates of patients affected by synchronous endometrial and ovarian cancers.

Methods: Between 2001 and 2009, 20 patients with synchronous primary carcinomas were identified in the Gynecologic Oncology Department of Mauriziano Hospital, Turin and IRCC, Candiolo, Italy.

Results: In our series these tumors coexist in 7.5% of patients with ovarian carcinoma and 5.9% of those with endometrial carcinoma. Median age at diagnosis was 52 years, median BMI was 25 and 30% of the women were nulliparous. Most common symptoms at diagnosis were abnormal vaginal bleeding (41%), abdominal pain (22%) and increase of abdominal volume (18%). Eighty percent of patients had FIGO stage I endometrial carcinoma and 70% had FIGO stage I ovarian cancer. Endometrioid histology and grade 1–2 disease were prevalent in both sites. Endometrial hyperplasia and endometriosis coexisted in 10% and 35% of endometrial and ovarian cancers, respectively. Ten-year overall survival rate was 88%.

Conclusions: Synchronous carcinomas show very favorable pathological features and consequently have an excellent outcome. Distinct characteristics from women with independent endometrial or ovarian carcinoma suggest that hormonal influence has a pathogenetic role. The retrospective design of our study and the limited size of study population do not permit definitive conclusions on this rare disease. A multicentric study is planned to improve the number of cases, to verify histo-pathological reports and to define surgery and adjuvant treatment protocols.
EXTERNAL VALIDATION OF THE ADAPTED RISK OF MALIGNANCY INDEX INCORPORATING TUMOR SIZE IN THE PREOPERATIVE EVALUATION OF ADNEXAL MASSES

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Background and aims: The Risk of Malignancy Index (RMI) is a simple scoring system to standardize and improve the preoperative evaluation of adnexal masses. Since 1990, three versions of the RMI have been validated in different clinical studies. Recently, a fourth version of the RMI (RMI4) was introduced that includes tumor size as an additional parameter. The aim of this study was to validate the ability of RMI4 to discriminate between non-invasive lesions and invasive malignant adnexal masses, and to compare its performance with RMI3.

Methods: Women scheduled for surgery for an adnexal mass between 2005 and 2009 in 11 hospitals were included. Ultrasonographic characteristics, menopausal status and serum CA 125 level were registered preoperatively, and combined into the RMI. The performances of RMI3 and RMI4 were assessed and statistically tested for differences.

Results: A total of 643 patients were included: 469 benign, 73 borderline and 101 malignant tumors. The RMI3 had a sensitivity of 76%, specificity of 82%, positive and negative predictive values (PPV and NPV) of 45% and 95%, and an accuracy of 81%. The RMI4 had a sensitivity of 74%, specificity of 79%, PPV of 40%, NPV of 94%, and an accuracy of 78%. The accuracy of RMI3 was significantly higher than the accuracy of RMI4 (p=.001).

Conclusions: Both RMI3 and RMI4 were able to accurately discriminate between non-invasive lesions and invasive malignant adnexal masses. RMI3 was significantly better in predicting invasive malignancy than RMI4. Including tumor size in the RMI does not improve its performance.
CHARACTERIZATION OF SYNCHRONOUS GYNECOLOGIC CANCERS: A SINGLE INSTITUTION REVIEW OF 44 CASES


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Objective: Gynecologic cancer is categorized into three major cancers: ovary, endometrium and cervical cancers. Invasion of these organs from primary organ represent different stages of cancer. So characterization of coexisting primary gynecologic cancers is possibly important to know characteristics of invasion and prognosis. The purpose of this study was to investigate patients diagnosed with synchronous primary gynecologic cancers.

Methods: After reviewing the medical records of gynecologic cancer patients diagnosed and treated in Samsung Medical Center from 1998 till 2009, 44 patients (36 ovary and endometrium, 4 ovary and cervix, 4 endometrium and cervix) were available for clinical and pathologic information.

Results: Most frequent two symptoms were vaginal bleeding (38%: 17/44) and abdominal pain (34%: 15/44). Mean age was 49 (26~77). Of 44 patients twenty-seven percent (12/44) has a family history of various cancer type. Only twenty two percent (10/44) of women were menopausal. Forty one percent (18/44) were nulliparous. Most common histology were endometrioid adenocarcinoma of ovary (19/40), endometrioid adenocarcinoma of endometrium (30/40) and squamous cell carcinoma of cervix (3/8). p53 mutation was found in 13 cases. Both estrogen receptor (ER) and progesterone receptor (PR) positive cases were 12. Almost patients received adjuvant treatments (36/44) including paclitaxel. Mean follow up period was 39 months (1~116) and recurrence case was 11. Most of them were early stage cancers (31/44) and had a favorable prognosis.

Conclusion: In our case patients are nulliparous and premenopausal and has a high family history risk. This study can give further information of diverse pathologic characteristics and treatment guideline of synchronous gynecologic cancers.
A RETROSPECTIVE REVIEW OF COMBINATION LOW DOSE ORAL CYCLOPHOSPHAMIDE, TAMOXIFEN AND PROPHYLACTIC WARFARIN IN HEAVILY PRETREATED OVARIAN CANCER

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Derby hospital reported a 25% response rate in end-stage patients with ovarian cancer treated with a combination of cyclophosphamide, tamoxifen and prophylactic warfarin (CTW) (personal communication). We have performed a retrospective review of our use of this regimen. 28 patients diagnosed with ovarian cancer between 1994 and 2001 were treated with 6 week 'cycles' of oral cyclophosphamide in a 'metronomic' dose of 50-100mg daily (planning to keep the total white blood count between 1.5 - 2.5 x 10^6/l) together with tamoxifen, 20mg daily and a prophylactic dose of warfarin (keeping INR ~ 2). Women aged between 41 and 85 years at diagnosis (53% 5^th - 6^th decade) had received between 1 and 7 courses (mean of 3) of different chemotherapy lines prior to CTW. 64% had relapsed < 2 months since their previous course of chemotherapy.

**Results:** 10 patients (35%) continued CTW for up to 12 months. Toxicities were very mild and included 1 patient with G1 mucositis although one other patient stopped CTW because of G2 nausea and fatigue. A CA125 response was observed in 2 patients and in a further 4 patients the CA125 stabilised. In this group of very poor prognosis patients it became evident that CTW had modest activity and was very well tolerated. Published data since this work has confirmed a response rate of ~20% using tamoxifen in relapsed ovarian cancer. Preliminary data on the activity of single agent oral cyclophosphamide in a similar but subsequent group of patients will also be presented.
PHASE II STUDY OF IFOSFAMIDE AND CISPLATIN IN RECURRENT OVARY CANCER


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Objective: Standard treatment of advanced ovary cancer is cytoreductive surgery and adjuvant chemotherapy. Paclitaxel and platinum compound has been steady first-line chemotherapy so far but several other agents were competing in recurrent disease. There has been few data regarding ifosfamide combination therapy. So we investigated response rate and toxicity of ifosfamide and cisplatin combination chemotherapy.

Methods: Thirty six patients received ifosfamide and cisplatin combination treatments in Department of Obstetrics and Gynecology, Samsung Medical Center. Ifosfamide was given intravenously at a dose of 5g/m² with mesna 6g/m² during ifosfamide infusion and the following 12 hours. And cisplatin was given 50mg/m² on day 1. Reevaluation followed after 2 to 4 cycles of chemotherapy according to RECIST guideline

Results: Twenty five percents (9/36) completed 6 cycles without severe hematologic/non-hematologic complication. Among them, there was one complete response case and four partial responses. So response rate was 14 percents (5/36). 27 patients didn't complete 6 cycles (mean 2.1). About three different recurrent chemotherapy modality was used before ifosfamide. (1 ~5 regimens). 19 patients received other chemotherapy after ifosfamide because of inadequate response. And 8 patients get supportive care only without any treatment.

Conclusion: Combination agent of Ifosfamide and cisplatin for recurrent ovary cancer has modest response rate. So Ifosfamide and cisplatin combination can be a reasonable second-line treatment choice with recurrent ovary cancer.

Keywords: Ifosfamide, Cisplatin, Ovary neoplasm
FACTORS INFLUENCING THE USE OF FROZEN SECTION ANALYSIS IN THE DIAGNOSIS OF ADNEXAL MASSES: WHICH FACTORS ARE LEGITIMATE?

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Background and aims: Frozen section analysis (FSA) is widely used in the intraoperative evaluation of adnexal masses to determine the extent of surgery. The objective of this study was to determine which factors influence the use and legitimacy of FSA of ovarian tumors.

Methods: Women scheduled for surgery for an adnexal mass between 2005 and 2009 in 11 hospitals were included. Parameters potentially influencing the use of FSA and the presence of malignancy were examined, including menopausal status, CA 125 level, ultrasound characteristics, presence of adhesions and tumor size. Predictive factors for using FSA and for the presence of malignancy were identified by univariate and multivariate analysis.

Results: A total of 670 patients were included. FSA was requested in 323 patients (48%): 531 benign, 70 borderline and 69 malignant tumors. CA 125 level, locularity of the tumor and presence of solid areas were associated with both the use of FSA and presence of malignancy. Adhesivity was associated with malignancy but not with use of FSA. Menopausal status and tumor size were associated with use of FSA and not with malignancy.

Conclusions: In the present study, menopausal status and tumor size were unjustly associated with a higher use of FSA. According to the results of this study, FSA is useful in case of a CA 125 level >35 U/ml, a multilocular tumor, presence of solid areas on ultrasonography, and an adhesive tumor during surgery.
ASSOCIATION OF LYMPHADENECTOMY AND SURVIVAL IN STAGE I OVARIAN CANCER PATIENTS

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Retrospective review of medical records of 148 patients with stage I invasive ovarian cancer from January 2003 to May 2007 was performed. Mean age was 42.4 \pm 12.9 years. In 70\% of patients, surgery was performed by a gynecologic oncologist. Surgery was done in a tertiary institution (88.5\%) and a non-tertiary hospital (11.5\%). Chemotherapy was given in 34.5\% of patients. Most of the patients had bilateral lymph node dissection (66.9\%) while para-aortic lymph node sampling was done in only half of the subjects (52.7\%). Majority of the subjects were in stage IA ovarian carcinoma. Mucinous type of tumor was seen in 43\% of subjects. Forty-three percent of the patients had grade I tumor but the grading was not specified in 45\% of subjects.

Stage, type of surgery, histopathology, grade, chemotherapy and lymphadenectomy were not significant factors in recurrence. There was high 5 year non-recurrence rate in the patients in both patients where bilateral lymph node dissection was done or not, with a total of 14 patients having recurrence. There was no statistically significant difference (p=0.47) between the 2 groups. There was a high proportion of patients surviving (97.3\%) with only 4 mortalities out of the 148 patients included in the study.

Lymphadenectomy in early stage ovarian cancer was not shown to have survival benefit because of the high proportion of patients surviving whether lymphadenectomy was done or not. Stage, type of surgery, histopathology, chemotherapy and lymphadenectomy were not shown be significant factors in recurrence.
TEN YEARS RESULTS OF OVARIAN CANCER TREATMENT IN A SINGLE CENTER

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Background: First line chemotherapy for advanced ovarian cancer with a combination of a taxane and platinum was introduced in the late nineties. We report on the results of treatment in patients who received this treatment in a university hospital outside a clinical study.

Methods: A retrospective cohort study for the period of 1997 to 2007, in patients with newly diagnosed advanced epithelial ovarian cancer was performed. Beside patients characteristics, type of chemotherapy, Ca-125 response, dose-intensity, progression free and overall survival were recorded.

Results: A total of 109 consecutive women (FIGO stage IIb/c n= 7, III n=71 and IV n=31) received first-line chemotherapy and were followed for a median period of 31 months. Forty seven women (43 %) had a complete or optimal result after primary or secondary surgery. The majority (n=98) was treated with combination of a taxane and platinum. Response rate (RR) in this group (n=98) was 80% (56 % complete remission and 24 % partial remission). Median progression-free survival was 13,1 month and median overall survival 24,1 months. Fifty nine patients received 2nd line chemotherapy for recurrent disease with a RR in the platinum-based treatment group of 70% and a median OS of 37,9 months.

Conclusion: The response rates of chemotherapeutical treatment in the University Medical Center of Utrecht are comparable to those reported. The OS is higher in the group that received treatment for recurrent disease or progression.
IS MICROINVASION A RISK FACTOR FOR RELAPSES OF BORDERLINE OVARIAN TUMORS?

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Objective: The aim of this study was to evaluate if the presence of microinvasion in borderline ovarian tumors (BOTs) submitted to surgery represents a major risk factor for relapses.

Methods: One hundred and eighty seven patients with a clinical diagnosis of BOTs were referred to our department of Gynecology and Obstetrics between 1986 and 2009. Patients were retrospectively divided in two groups: group one consisted of 29 women with microinvasive BOTs; group two consisted of 158 with BOTs without microinvasion. All patients were submitted to surgical treatment: in group one 9 patients underwent to cystectomy, 7 patients to monolateral salpingo-oophorectomy, 13 patients to radical surgery; in group two 40 patients underwent to cystectomy, 49 patients to monolateral salpingo-oophorectomy, 79 patients to radical surgery. Specific prognostic factors such as age, stage, histology, micropapillary subtype, exophitic tumor growth, intraoperative spillage, endosalpingiosis, staging procedures, route of surgery were analyzed.

Results: After a mean follow-up of 60 months relapses were present in group one in 17.0% of cases (5/29) and in group two in 18.3% of cases (29/158). All specific prognostic factors analyzed showed no significant differences. Relapses after cystectomy, salpingo-oophorectomy and radical surgery were observed in 13.7%, 3.4% and none in group one, and in 22.8%, 18.0% and 6.0% in group two, respectively.

Conclusions: Our data suggest that natural history of BOTs with microinvasion does not differ from BOTs without microinvasion; therefore a radical treatment or a stricter follow-up are unnecessary.
ROMA ALGORITHM IN THE TRIAGE OF PELVIC MASSES

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Background: Although CA125 is the most widely used marker of epithelial ovarian cancer (EOC), its clinical usefulness is limited by its lack of expression in the early stages of disease, and by its low specificity in premenopausal women. The aim of this study was to validate a predictive model to assess the risk for EOC in women with pelvic mass, based on the combined measurement of CA 125 and human epididymis protein 4 (HE4), frequently over-expressed in this malignancy.

Patients and methods: Serum determination of CA125 and HE4 were run on Architect (Abbott Diagnostics). All subjects had pelvic ultrasound (US). To estimate the risk of finding ovarian cancer the performance of an algorithm combing CA125, HE4 and menopausal status was evaluated (ROMA, Risk of Ovarian Malignancy Algorithm).

Results: Data are now available for 84 patients out of the 180 planned (median age 51 years, range 19-86; 42 patients in premenopausal and 42 in postmenopausal status). The sensitivity of ROMA and CA125 is 92% and 97% respectively, while the specificity is 74% and 56%, respectively. Taking into account the histology report, ROMA correctly classified 82% of the patients, compared to 75% of CA125.

Conclusions: The results of this preliminary analysis show that the ROMA algorithm correctly classified a higher percentage of women with a pelvic mass compared with CA125, and shows slightly lower sensitivity with higher specificity.
INTERNATIONAL COOPERATION FOR CANCER CARE: PROTOCOL DEVELOPMENT FOR OVARIAN CANCER TREATMENT IN KENYA

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Objective: To develop and introduce a protocol for the treatment of advanced stage ovarian carcinoma in resource constrained conditions through international cooperation between physicians in Kenya and Toronto.

Methods: In Moi Hospital in Kenya, the need for a protocol to treat women with advance stage ovarian carcinoma was identified. The standard chemotherapy, Paclitaxel and Carboplatin, is unavailable due to resource constraints. A systematic literature review was performed to identify papers describing experience with chemotherapy in low and middle income countries. Secondly randomized controlled trials comparing the different chemotherapy regimes that are attainable within the budget were identified. Results were summarized by medical students and gynecologists from Kenya and Toronto using e-mail and Skype for communication and data sharing.

Results: Literature originating from low and middle income countries was insufficient to develop a protocol applicable to the Kenyan situation. The guideline was subsequently based on the results from older RCT’s before the introduction of Paclitaxel. Discussion with all parties established tradeoff between effectiveness, toxicity, cost and acceptability. Financial sustainability was ensured by incorporating cost in the 5 year budget. The guideline was introduced by discussion of the content with staff and management involved in treating women with ovarian cancer. Barriers that might hamper clinical application of this guideline will be explored during introduction. Potential barriers include: acceptability to patients and support staff and logistical and organizational factors. Specific interventions will need to target such barriers.

Conclusions: International cooperation for protocol development is feasible in a timely matter with current communication methods.
UNSPECIFIC CANCER-RELATED INFLAMMATION SUBVERTS THE ADAPTIVE ANTI-TUMOR IMMUNE RESPONSE MOUNTED AT THE OVARIAN CANCER SITE

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In the scope of unspecific “cancer-related inflammation”, elevated serum levels of C-reactive protein (CRP) and high urinary excretion of neopterin are characteristic and found to be of prognostic relevance. As release of neopterin from monocytes/macrophages is mainly induced by interferon-γ originating from T-cells, elevated systemic neopterin levels observed in patients with ovarian cancer, were considered to be a surrogate of activated cellular immunity. The objective of this investigation was to elucidate whether urinary neopterin and the serum CRP is related to the adaptive anti-tumor response at the tumor site. In 92 ovarian cancer patients both variables were compared with intratumoral levels of transcripts from factors involved in the cellular immune defense such as CD3, IFN-γ, IRF-1, IRF-2, SOCS1, and iNOS. This study did not reveal an association between urinary neopterin or serum CRP with one of the investigated transcripts. On the other hand urinary neopterin levels were significantly associated with serum CRP concentrations ($r^2=0.356; p=0.001$) indicating that both parameters belong to surrogates of the innate immune activity. IRF-1 expression was the only “on site transcript” that independently predicted favorable disease-free survival ($p=0.038$). High urinary neopterin levels revealed to be an independent prognosticator of adverse overall survival ($p=0.037$). The survival benefit of patients with high IRF-1 expressing cancers was completely abrogated when neopterin concentrations were concomitantly high. These findings show that in ovarian cancer the unspecific “cancer-related inflammation” orchestrated by the innate immunity contributes to a significant subversion of the adaptive anti-tumor immune defense mounted at the tumor site.
(PRE)MALIGNANCIES IN THE FALLOPIAN TUBE OF BRCA-MUTATION CARRIERS: A SITE OF ORIGIN FOR SEROUS PELVIC CARCINOMA OR A PHYSIOLOGICAL FINDING?

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Objective: The pathogenesis of ovarian cancer is still subject of debate. Recently the fallopian tube has been proposed as a possible tissue of origin for serous ovarian and pelvic cancers. In this largest study in literature, we investigated the incidence of premalignancies and/or occult carcinoma in the fallopian tubes of BRCA1/2 mutation carriers compared to an aged-matched control group.

Method: A retrospective evaluation was performed of medical and pathological records of 229 confirmed BRCA1- and BRCA2-carriers that underwent prophylactic salpingo-oophorectomy (pBSO) from 1995-2009 within the Radboud University Nijmegen Medical Centre. As a control group, fallopian tubes were revisited of 103 age-matched patients who underwent BSO exclusively for benign reasons and without malignancy in their personal history. All pathologic specimen were revised by two specialized gyneco-pathologists.

Results: In our BRCA-mutation carrier population, 2 occult carcinoma's were identified, whereas in 11 cases a premalignant lesions or carcinoma in situ (CIS) was diagnosed. The incidence of occult carcinoma in our population would therefore be 0,9% and for CIS 4,8%. In contrast, no occult carcinoma or CIS lesions were found in the control group.

Conclusion: The incidence of occult carcinoma in our pBSO population is lower than in recently published studies. As no (pre)malignancies were identified in the control group, our findings of (pre)malignancies in BRCA-mutation carriers (~6%) are not likely to be physiological. However, it remains unclear in what portion (pre)malignancies of the fallopian tube can be regarded as site of origin for ovarian cancer.
VIDEO-ASSISTED THORACIC SURGERY (VATS) EVALUATION OF INTRATHORACIC DISEASE IN PATIENTS WITH FIGO III AND IV EPITHELIAL OVARIAN CANCER

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Aims: The primary goal of epithelial ovarian cancer (EOC) surgery is an optimal cytoreduction. Up to now, thoracic staging is not a diagnostic standard. It is unknown, whether patients profit from an effort of complete abdominal surgical cytoreduction without an intrathoracic optimal tumor debulking. Furthermore it is unclear, whether the current practice of preoperative thoracic computed tomography (CT) scan is the method of choice for the evaluation of intrathoracic disease.

Methods: EOC patients with suspected supra-diaphragmatic involvement (pleural effusions, pleural carcinomatosis, lung metastasis, or enlarged supra-diaphragmatic lymph nodes) at thoracic CT scan underwent VATS combined with laparoscopy to decide for cytoreduction or neoadjuvant chemotherapy. Binary classification tests to evaluate the validity of the thoracic CT scans compared to VATS were performed.

Results: 12 Patients met the eligibility criteria with a mean age of 63 years and a median CA 12-5 of 1570 U/ml. After VATS, in 3 patients a primary cytoreduction was attempted, all other patients underwent neoadjuvant chemotherapy because of the results of the surgical staging. Thoracic CT scan had a negative predictive value (NPV) of 1 for the involvement of the diaphragm, lung metastasis and enlarged supra-diaphragmatic lymph nodes. However, the positive predictive value and other validity criteria for thoracic CT scan were rather poor.

Conclusion: VATS and laparoscopy altered the surgical management in 9 of 12 EOC patients. Since the surgical related morbidity of the procedure is rather small, minimal invasive surgical staging should be considered in FIGO III/IV EOC patients.
FEASIBILITY AND MORBIDITY OF INTERVAL DEBULKING SURGERY AFTER SIX CYCLES OF NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH OVARIAN CANCER


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Objective: The aim of the study was to evaluate postoperative outcome and morbidity in patients with advanced ovarian cancer treated with six cycles of neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS).

Methods: A prospective evaluation of one hundred thirty one patients with suspected ovarian cancer referred to our Gynaecology Department between January 2005 and January 2010. All patients were submitted to diagnostic laparoscopy to predict optimal cytoreduction (residual tumor zero) or suboptimal cytoreduction. After laparoscopy patients were divided into two groups: group one consisted of 75 patients whose tumor could not be optimally cytoreduced. These patients were treated with six cycles of chemotherapy with carboplatin-paclitaxel and subsequent surgery. Group two consisted of 56 patients whose tumor could be optimally cytoreduced with radical upfront surgery: 29 patients stage I-II, 27 patients stage III-IV. We analyzed intraoperative and postoperative complications, such as blood transfusions, paralytic ileus, wound complications, fever, hospital stay, resurgery and others. Moreover, postchemotherapy fibrosis in the tissues were analyzed at histology and a scoring system based on a grading scale (0-3) was applied.

Results: No significant differences were noted in all items between interval debulking surgery and stage I-II upfront surgery. Moreover, there were no differences in the feasibility of the surgical procedure and incidence of complications in patients with scanty or diffuse fibrosis.

Conclusions: Six cycles of NAC do not increase post-operative morbidity; surgical feasibility is not hampered by fibrosis.
COMPARISON OF PRIMARY DEBULKING SURGERY WITH NEOADJUVANT CHEMOTHERAPY FOLLOWED BY INTERVAL DEBULKING SURGERY IN ADVANCED STAGES OF OVARIAN CANCER

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Aim: To compare primary debulking surgery (PDS) followed by adjuvant chemotherapy and neoadjuvant chemotherapy (NACT) followed by interval debulking in advanced stage ovarian cancer.

Methods: A total of 221 patients with stage III or IV epithelial ovarian carcinomas were evaluated. 74% of the patients (165/221) underwent PDS and the remaining were selected for NACT (56/221)(26%).

Results: Median age, stage IV disease frequency and ascites volume were higher in NACT group (p<0.01). Overall survival (OS) and disease-free survival (DFS) were significantly better in patients treated with PDS group compared with the NACT group (p=0.00001 and p=0.0086, respectively). OS and DFS of patients having optimal PDS (n:116) (residual tumor < 1 cm) were significantly longer than those having suboptimal PDS (n:49) (residual tumor >1 cm) ( P=0.0006 and P=0.0017, respectively). OS and DFS of patients treated with optimal PDS were significantly longer than those treated with NACT (p=0.00001 and p=0.0006, respectively). No significant difference in survival rates was observed in patients having suboptimal PDS (n:49) compared with NACT group ( P value for OS=0.1187 and for DFS = 0.9536). When comparing the OS of which having a residual tumor < 1cm, a significant difference was observed in the favor of PDS.

Conclusion: These results have suggested that PDS provides advantage on survival rates in advanced stage ovarian cancer. However the rates of stage IV, advanced age and larger amount of ascites were higher in NACT, so we believe that NACT may be a feasible option in selected cases to achieve optimal cytoreduction.
THE UNIQUE TUMOUR MICROENVIRONMENT OF OVARIAN CLEAR CELL CARCINOMA

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Background: Clear Cell Carcinoma (CCC) is an uncommon subtype of epithelial ovarian carcinoma (EOC) with significant variability in the reported poor prognosis. Such variability may reflect the diagnostic uncertainty due to the shared morphological features with HGSC.

Certain chemokines and adhesion molecules, notably the cadherin-catenin system, have been reported to significantly correlate with survival in various malignant tumours including ovarian carcinoma.

Aim: The aim of this study was to determine the expression of angiogenic chemokines (CXCR4/CXCL12, and VEGF) and adhesion molecules (E, P and N-Cadherins) in CCC and compare results to HGSC. To our knowledge previous reports on these markers were either on cell lines or on small series of EOC in general.

Methods: A tissue microarray of 212 cases of EOC (177 HGSC and 35 CCCs) were immunohistochemically stained with VEGF, CXCR4, CXCL12, E, N and P cadherin.

Results: Patients with CCC presented at an early stage of the disease (53% stage 1) and showed significantly better overall survival and progression free survival p=0.033 and 0.003 respectively. 37% cases of CCC and 58% cases of HGSC had died at 36 months follow up. Cases of CCC showed a lower expression of P-cadherin (p=0.020), N-cadherin (0.003), CXCL12 (p=0.000), CXCR4 (0.014) and VEGF (P=0.000) in CCC in comparison to HGSC.

Conclusion: Our study reports for the first time the difference in expression of prognostic markers between CCC and HGSC, offering an explanation to the early stage presentation of CCC and possibly aiding future prognostic stratification and the apparent chemotherapy resistance.
ADNEXAL MASSES: RISK FACTORS EVALUATION

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Aim: Adnexal mass can represent a number of different benign and malignant conditions. The aim of the study was to evaluate predictive value for malignancy of routine preoperative analysis.

Methods: This study involved 80 patients treated for adnexal masses during the period of six months. Patients were divided in premenopausal, and postmenopausal group. Preoperative anamnestic factors, body mass index (BMI), ultrasound and laboratory findings were compared with histological finding after surgery.

Results: Out of 80 patients presented with adnexal mass, 51 were in the reproductive period (mean age 36.1, 137 years) and 29 were postmenopausal (mean age 58.2, 207 years). The malignant pathology was statistically significantly higher in postmenopausal group (p=0.034; p< 0.05). The BMI value was statistically significantly higher in patients with malignant histological finding in both groups (t=3.421; p=0.001; p< 0.05). Significantly more patients presented with no symptoms (X^2=11,517; X^2=45,762) and with laboratory findings in normal range (X^2=31,327; X^2=19,862 / X^2=2,842; X^2=0,034) in both groups. In premenopausal group, significantly more patients had tumor diameter between 5.1 and 10 cm than more than 10 cm, but there was no statistically significant difference in tumor size in postmenopausal group (X^2=2,965). No significant difference in histological findings was found (p>0.05) concerning these values.

Conclusion: Significant differences were found between the groups with benign and malignant pathology for age, menopausal status and BMI; therefore, these factors should be included in the preoperative assessment of adnexal mass.
SERUM PROTEOMIC BIOMARKERS FOR OVARIAN CANCER

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Annually only one in 2,500 women aged >50 yrs old will develop ovarian cancer. Therefore from a screening standpoint we need a blood test with high sensitivity and specificity. The best available test at present is CA125 but pending the results of the UKCTOCS trial it remains uncertain whether this will prove of benefit in altering mortality from the disease.

In this study we have used proteomic mass spectrometry methods for the detection of alternative ovarian cancer biomarkers.

Sample collection: The discovery and validation set of samples were obtained from ovarian cancer patients versus age matched hospital patients known to be free of cancer or benign ovarian neoplasms and benign ovarian neoplasm cases versus a second cohort of age matched hospital control patients collected under strict standard operating procedures.

Biomarker discovery: Serum samples were C\textsubscript{18} fractionated, tryptically digested and peptides analysed using MALDI-TOF/TOF mass spectrometry according to established protocols. ANN analysis resulted in a panel of 4 ions for biomarker discovery with greater than 80\% sensitivity and specificity which separated cancer from age matched controls and a panel of 7 ions that distinguished benign cases from a control group. Protein identities of the ion panels were attained using LC-MALDI-MS/MS. Following identification of the key predictive peptides validation was carried out in an independent sample set.

Results: Significantly lower expression of transferrin found in the cancer cases has been confirmed by ELISA. Immunohistochemistry staining of the markers was conducted on tissue sections to validate the expression and localisation in cancerous tissue.
VALUE OF RISK OF MALIGNANCY INDEX AS A PREDICTOR OF ADNEXAL MASSES NATURE

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Aim: Some data indicate that use a risk of malignancy index (RMI) is appropriate for selection of patients with adnexal tumors into those at low, moderate or high risk of malignancy. The aim of this study was to evaluate the reliability of RMI in malignancy prediction in premenopausal and postmenopausal women with adnexal masses.

Methods: The study involved 80 patients with adnexal masses throughout a period of 6 months, who were divided in premenopausal (51) and postmenopausal group (29). According to the RCOG recommendations RMI was calculated as low, moderate or high using UxMxCa125 (U - ultrasound score, M - menopausal status, Ca125 - measurement in u/ml). The link between RMI and histological findings of obtained specimens was evaluated.

Results: Strong positive correlation between RMI and histological finding was found in both groups (Roxy=0.473; df=27; p=0.010; p< 0.01; Roxy=0.312; df=49; p=0.026; p< 0.05).

In premenopausal women benign pathology was significantly higher finding (X^2=15.372). Furthermore, the same group showed significantly lower mean RMI value (X^2=13.059). In postmenopausal group proportion of benign and malignant histological findings was similar (X^2=1.241). Also, all patients in postmenopausal high - RMI group had histologically confirmed malignancy, which was statistically significant difference in comparison to those in moderate and low RMI (P=0.011, P=0.005).

Conclusion: RMI values show strong correlation with histological findings in both investigated groups, especially in postmenopausal women with high RMI. Therefore, we could suggest RMI as a reliable malignancy predictor.
PARTIAL RESPONSE TO IMATININ MESYLATE IN RELAPSING GRANULOSE CELL TUMORS (GCTS) OF THE OVARY


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Background and aims: GCTs of the ovary represent less than 5% of malignant ovarian tumors. GCTs arise from the sex-cord stromal-cell of the ovary. The pathogenesis of these tumors is still unknown. Primary treatment of GCTs is surgery. GCTs present indolent growth and high recurrence-rate. Radiotherapy, chemotherapy and hormonal therapy are of little benefit. We report a case with recurrent GCT heavily pretreated who underwent imatinib with a partial dimensional response.

Case report: A 60-year old woman presented with pleural effusion, bilateral ovarian masses and ascites. Debulking surgery was performed. Pathological findings revealed GCT (pT3b Nx, FIGO stage IIIB). 5 courses of chemotherapy with BEP were performed. 8 months after the patient underwent a second surgery due to an abdominal relapse. Three additional courses of IEP were performed with PD. A third surgical procedure revealed GCT relapse. A second line chemotherapy was started with 18 courses of weekly Taxol with CR at instrumental evaluation. Nineteen months after a new relapse surgically treated was revealed, then she started hormonal therapy (anastrozole). On CT scan evaluation a peritoneal progressive disease was noted. An experimental therapy was started with imatinib (400 mg/ die months 1st and 2nd - 800 mg/ die after). Monthly PET-CT scan evaluation were performed revealing a marked reduction of disease after 6 months.

Conclusion: To our knowledge this is the first case of highly recurrent and unresponsive GCT of the ovary responding to imatinib. Further studies evaluating this drug in recurrent GCT are warrant.
FINAL RESULTS OF A GERMAN SURVEY IN 676 PATIENTS: WHAT DO OVARIAN CANCER PATIENTS EXPECT FROM THEIR DOCTOR?

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Background: The following study was conducted to explore the information needs and preferences of OC patients in Germany with special focus on doctor-patient communication.

Methods: After validation in a monocentric pilot study, the developed questionnaire was administered to OC patients via internet (online) or as a print version.

Results: Between 01 and 11/2009, a total of 676 patients were interviewed (201 online, 475 print version). 64% of all patients had their own internet access. The median age of the online group was 49 years (range 19-73), for the print group 62 years (26-92). 39% of the patients had relapsed OC. The most effective and “patient-relevant” source of information and explanation of treatment options was the consultation with their physician (paper: 79%; online: 85%). All patients judged the therapeutic consultation by their physician on a Likert scale (1: very bad, 10: very well): Completeness: 9; understanding: 8; response to questions: 9; competence of physician: 10; shared decision: 8. When asked to suggest areas for improvement, the most frequent answers were: doctors should have more time for explanations (19%); no alopecia under treatment (16%); There must be more done to counter exhaustion (14%). The most stated answers in the recurrence group to “How do you measure the success of a therapy?” were: response of the tumor marker CA 125 (34%); based on my current well-being (29%); based on the feedback that I receive from my doctor (20%).

Conclusions: This largest analyzes underlines the high need of ovarian cancer patients to discuss all details about treatment options and clinical management.
CARSINOSARCOMA OF THE OVARY: AN UPDATED SERIES

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Introduction: The aim of this study was to review our experience with ovarian carcinosarcomas.

Methods: Eighty seven patients with histologically proven carcinosarcoma of the ovary treated between 1995 and 2005 were identified. The clinical records were reviewed for demographics, treatment, and outcome parameters. Survival estimates were plotted utilizing the Kaplan-Meier method. The log-rank test was utilized to quantify statistically these survival differences on univariate analysis.

Results: The mean age at time of diagnosis was 64 years. Ten patients had stage I, eight had stage II, 61 patients had stage III, five had stage IV, and in two patients the stage was unknown. The median survival for all patients was 24 months. The 3-year overall survival (OS) was 88%, 85%, 37%, and 21% for stages I-IV, respectively. Sixty-six patients with stages IIIC and IV disease were separately analyzed. In this group, optimal cytoreduction (defined as residual disease ≤1 cm in maximal diameter) was achieved in 63% of these patients. Optimal cytoreduction was associated with a median survival of 40 months, compared with 14 months for patients left with suboptimal residual disease (p < 0.001). Patients receiving the combination of platinum and paclitaxel had a median survival rate of 43 months versus 19 months for patients who received other chemotherapy (p = 0.01).

Conclusion: An effort at cytoreduction to no visible residual disease should be made in advanced ovarian carcinosarcoma when feasible. The combination of platinum and paclitaxel is a viable first-line treatment option for patients with ovarian carcinosarcoma.
CLINICAL OUTCOMES IN BRCA1 AND BRCA2 MUTATION CARRIERS WITH EARLY STAGE OVARIAN OR FALLOPIAN TUBE CANCER

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Objective: To evaluate overall clinical outcomes in BRCA1 and BRCA2 mutation carriers with early stage fallopian tube and ovarian cancers.

Methods: Cases of early stage ovarian and fallopian tube cancers were identified in patients with BRCA1 or BRCA2 mutations seen at M. D. Anderson Cancer Center. Early stage cases were defined as stage I-IIIA.

Results: Eighteen cases of early stage ovarian or fallopian tube cancers were identified in women with germline BRCA1 or BRCA2 mutations. Eleven early stage cases were diagnosed in BRCA1 mutation carriers (5 stage I, 3 stage II, and 3 stage IIIA). Six early stage cases were diagnosed in BRCA2 mutation carriers (1 stage I, 4 stage II, and 1 stage IIIA). One patient with both BRCA1 and BRCA2 mutations was diagnosed with stage IIB ovarian cancer. With clinical follow-up ranging from 16 months - 301 months, all 18 patients are currently alive. However, the log-rank test indicates that BRCA2 mutation carriers with early stage ovarian or fallopian tube cancers recur at a faster rate than women with BRCA1 mutations ($p = 0.02$).

Conclusions: These cases illustrate that overall clinical outcome is encouraging for early stage ovarian and fallopian tube cancers diagnosed in women with BRCA1 or BRCA2 mutations. However, in this small set of early stage cases, recurrence is increased in BRCA2 mutation carriers compared to BRCA1 mutation carriers. This finding suggests the importance of studying these two groups of patients separately. Future studies using a larger sample size are necessary to confirm these results.
PATTERN OF FAILURES OF PATIENTS WITH RECURRENT EPITHELIAL OVARIAN CANCER

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Background: Epithelial ovarian cancer typically implant from the pelvis throughout the peritoneal cavity but also distant metastases can arise during the evolution of disease. The aim of this investigation was to assess the pattern of failures of patients with recurrent ovarian carcinoma. Site of first relapse was evaluated in patients with different treatment modalities: optimal cytoreduction and platinum-paclitaxel chemotherapy vs suboptimal and platinum chemotherapy.

Methods: We reviewed the charts of patients with epithelial ovarian cancer treated and followed up at Fondazione S. Matteo Hospital of Pavia from 1992 to 2005. Data were collected regarding age, stage, histology, grade, type of surgery, residual disease, first line chemotherapy, time to recurrence, sites of first relapse.

Results: 82 patients were identified from our database. Stage was Ia in 16.75% patients, Ib in 0.5%, Ic in 3.25%, IIA in 2.25%, IIB in 1.25%, IIC in 2.25%, IIIA in 2%, IIIB in 2.5%, IIIC in 62.75% and IV in 6.5%.

The incidence of pelvic relapse was 12% in patients with optimal cytoreductive surgery and platinum paclitaxel therapy vs 34% in patients with suboptimal cytoreductive surgery and platinum therapy. Abdominal relapse was similar in both groups (28% vs 25%) such as pelvic-abdominal relapse (24% vs 25%). Distant metastases was 20% in patients of first group versus 9% in patients in the second one. Pelvic relapse associated with distant metastases was 10% vs 6%.

Conclusion: Our data suggest an increased of extrapelvic recurrence and distant metastasis in the absence of pelvic and abdominal disease.
OVA1 HAS HIGH SENSITIVITY IN IDENTIFYING EARLY STAGE OVARIAN CANCERS

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Background: OVA1 is an in vitro diagnostic multivariate index assay (IVDMIA) that combines five immunoassays into a single numerical result, including CA125-II, transthyretin (prealbumin), apolipoprotein A1, beta 2microglobulin, and transferrin. Our objective was to evaluate the sensitivity of OVA1 compared to CA125-II in predicting ovarian malignancy in premenopausal women and all women with early stage (I/II) disease.

Methods: Serum OVA1 and CA125-II levels were evaluated in women scheduled for surgery with a known ovarian tumor in a prospective, multi-institutional trial involving 27 primary care and specialty sites throughout the United States. Preoperative results were correlated with the surgical pathology, menopausal status, and stage of malignancy. CA125-II was considered positive if >35 U/mL in premenopausal and >200 U/mL in postmenopausal women.

Results: The study enrolled 590 women and 524 were evaluable. There were 161 malignancies, including: 96 epithelial ovarian cancers (EOC), nine non-epithelial ovarian malignancies (non-EOC), 28 borderline tumors, 18 malignancies metastatic to the ovary, and ten pelvic malignancies with no ovarian involvement. Forty-nine patients had early stage malignancies, including 41 EOC (24 stage I) and 8 non-EOC (7 stage I). For EOC and non-EOC combined, the sensitivities were as follows: early stage- OVA1= 94%, CA125-II= 61%; premenopausal women with early stage - OVA1= 82%, CA-125-II= 29%. For EOC only, the sensitivities were: early stage- OVA1= 98%, CA125-II= 66%; premenopausal women with early stage - OVA1= 93%, CA125-II= 36%.

Conclusions: OVA1 is significantly more sensitive than CA125-II at identifying early stage ovarian malignancies, and particularly early stage cancers in premenopausal women.
MORPHOLOGIC, IMMUNOHISTOCHEMICAL AND MOLECULAR CORRELATIONS OF OVARIAN AND TUBAL DYSPLASIA IN PROPHYLACTIC OOPHORECTOMIES FOR GENETIC RISK

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Background: Histopathological examination of material from prophylactic salpingo-oophorectomies (pBSO) performed in patients at genetic risk has revealed frequent abnormalities interpreted as possible pre-cancerous “ovarian dysplasia” lesions. We sought to study their morphologic, immunohistochemical and molecular features.

Materials and methods: Morphologic features and immunohistochemical expression patterns of Ki-67, p53, Bcl2 and ALDH1 (an enzyme significantly associated with early-stage ovarian cancer) were blindly evaluated in 90 pBSO and 100 normal salpingo-oophorectomies (nBSO). Tubal and ovarian epitheliums from normal and dysplastic tissues were laser microdissected and studied by comparative genomic hybridization.

Results: Mean ovarian and tubal dysplasia score were significantly higher in the genetic risk group than in controls (respectively 9.2 vs .3, p< 0.002, for ovaries and 7.6 vs 3.5, p< 0.007 for tubes). Increased ALDH1 expression was observed in pBSO compared with nBSO whereas expression patterns of Ki67, p53 and bcl2 were low at moderate in pBSO group. Interestingly, ALDH1 expression was low in non dysplastic epithelium, high in dysplasia and constantly low in the carcinoma found incidentally on pBSO. Genomic alterations were found in all of the dysplastic ovarian and tubal epitheliums.

Conclusion: The increased dysplasia score, the strong ALDH1 expression and the genetic alterations might be consistent with progression towards neoplastic transformation and could justify the use of the term “dysplasia”. Ovarian and tubal dysplasia may be a pre-malignant, non-invasive histopathological abnormality that could be an important step in early ovarian neoplasia. The ALDH1 activation in pBSO could be considered as a target for early diagnosis and prevention.
THE SAFETY OF CONSERVATIVE TREATMENT OF BORDERLINE OVARIAN TUMORS

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Background: Although primary conservative treatment for borderline ovarian tumors (BOTs) is associated with a higher risk of recurrence, it gives women the chance to have children in the future.

Aim: The aim of the study was to evaluate the safety of conservative surgery in women treated for BOT.

Material and methods: Of 196 patients treated surgically for BOTs at the Clinic of Gynecology of the Medical University of Gdansk between 1978 and 2006 a group of 66 women (33.7%) was selected in whom primary conservative surgery was performed.

Results: The stages of BOT, as recognized by FIGO, at which conservative surgery was performed were as follows: IA - 56 patients (84.8%), IB - 3 (4.5%), IC - 5 (7.6%), IIIC - 2 (3.1%). Primary conservative surgery consisted of unilateral cystectomy in 11 patients (16.7%), bilateral cystectomy in 3 patients (4.5%) and unilateral salpingo-oophrectomy in 52 patients (78.8%). In 24 of these a simultaneous partial resection of the other ovary was performed. After the primary surgical treatment 17 women (25.7%) became pregnant and gave birth to healthy children. Recurrence was observed in 10 patients (15.1%). Despite this one patient died, although the other two remain asymptomatic. The 5-year survival rate was 98.5%. The observation periods ranged from 40 to 384 months.

Conclusions: The high incidence of pregnancy after conservative therapy taken together with the low rate of recurrence of the disease constitutes evidence in support of the use of less radical surgical treatment for BOTs in young women who plan to have children.
ANTI-MÜLLERIAN HORMONE (AMH) IS A GROWTH INHIBITOR OF OVARIAN GRANULOSA CELL TUMORS

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Granulosa cell tumors (GCT) of the ovary, representing 5\% of malignant ovarian cancers, may recur even decades after primary diagnosis. Patients with a primary tumor of advanced stage or a recurrent tumor have a relatively poor prognosis, and targeted treatments for these patients would be desirable. Given that Anti-Müllerian Hormone (AMH) expression is downregulated in large GCTs, we hypothesized that AMH acts as a growth inhibitor for GCTs, similarly to ovarian carcinomas. We analyzed expression of AMH signal mediators (type I and II receptors, Smad1 and Smad5) in a panel of 92 GCTs, and utilized a GCT cell line (KGN) and primary GCT cell cultures to study the effects of exogenous rhAMH on this peculiar ovarian cancer. RT-PCR and/or immunohistochemistry analyses reveal that GCTs express type I AMH receptors ALK2, ALK3, and ALK6, and type II AMH receptor (AMHRII). In contrast to a mice model, showing that the lack of AMH signal mediators Smad1 and Smad5 leads to aggressive GCTs, we find that both of these genes are expressed in human GCTs, and that AMH activates (phosphorylates) Smad1 and Smad5 in cultured tumor cells. Finally, we find that AMH induces apoptosis in KGN and primary GCT cell cultures (n=8) as analyzed by caspase-3 activation assays and/or DAPI staining of apoptotic cells. In view of earlier findings that mice lacking AMH signal (mediators) develop GCTs and AMH is negative in large human GCTs, these data collectively suggest that AMH acts as a growth inhibitor by sensitizing GCTs to undergo apoptosis.
ROLE OF FROZEN SECTION DURING CONIZATION OF THE UTERINE CERVIX FOR THE EVALUATION OF HIGH GRADE CIN II-III

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Introduction: Determining the role of frozen section examination (FSE) of the cone specimen in the evaluation of the resection margin status and to rule out invasion in patients with high-grade cervical intraepithelial neoplasia.

Materials and methods: Twenty patients of High grade intraepithelial neoplasia, that had underwent conization biopsy and frozen section examination were studied in a cross sectional trial from March 2008 through September 2009. The results of permanent paraffin sections were compared with FSE.

Results: Among these twenty cases, 15 (75%) had the same results in frozen and permanent sections of cone biopsy specimens. Among the other 5 patients, 2 had higher grade CIN in frozen section, 2 showed a lower grad. Among these differences only one case was found in which the FSE result was CIN3 while the permanent section was invasive carcinoma which was of clinical importance and considered as significant. Eventually the Paired Sample T-test showed no significant difference in the results of the two groups of frozen and permanent section (P= 0.716, CI= 95%)

Conclusion: Frozen section evaluation of cervical cone biopsy specimens in patients with a diagnosis of CIN 3 is accurate, efficient, and cost-effective. Because of the great importance of missing even one case, further researches are highly recommended on this controversial subject.
SYNCHRONOUS PRIMARY CARCINOMAS OF THE ENDOMETRIUM AND OVARY

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The term synchronous tumors is applied when two or more tumors occur in a patient simultaneously. Among women with gynecologic cancer, the simultaneous presence of primary carcinomas of the endometrium and ovary is relatively uncommon.

The aim of the study was to analyze the clinicopathologic features and survival outcome of patients with synchronous primary carcinomas of the endometrium and ovary.

Between 1996 and 2005, 45 patients fulfilled the criteria of synchronous carcinomas of the endometrium and ovary and were included in the study. The medical records and the pathologic reports were retrieved. Kaplan-Meier survival analyses were performed and compared using the log rank test.

The incidence of synchronous primary endometrial and ovarian carcinomas was 3.3% in patients with endometrial carcinoma and 7.2% in patients with ovarian carcinoma. Median age of patients with synchronous primary endometrial and ovarian carcinomas at diagnosis was 52 years (range: 37-70 years). The majority of patients (64.4%) were premenopausal and (53.3%) nulliparous. Twenty-nine patients (64.4%) had similar (endometrioid/endometrioid) carcinomas in both the endometrium and ovary. There was no significant difference in survival outcome in patients who had similar histopathology and those who had dissimilar histopathology.

The correct classification of synchronous primary carcinomas of the endometrium and ovary is often problematic because of the frequent confusion with their metastatic counterparts. The majority of patients with synchronous primary carcinomas of the endometrium and ovary belonged to concordant endometrioid histopathology in the endometrium and ovary.

Keywords: Endometrial carcinoma, ovarian carcinoma, synchronous tumors
NOMOGRAM FOR 30-DAY MORBIDITY AFTER PRIMARY CYTOREDUCTIVE SURGERY FOR ADVANCED STAGE OVARIAN CANCER

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Objectives: Extensive surgical procedures to achieve maximal cytoreduction in patients with advanced stage epithelial ovarian cancer (EOC) are inevitably associated with postoperative morbidity and mortality. The current study aims to identify predictors of 30-day morbidity after primary cytoreductive surgery for advanced stage EOC and to develop a nomogram for individual risk assessment.

Materials and methods: All patients in the South Western part of the Netherlands who underwent primary cytoreductive surgery for advanced stage EOC between January 2004 and December 2007 were identified from the Rotterdam Cancer Registry database. All peri- and postoperative complications within 30 days after surgery were registered and classified according to the definitions of the National Surgical Quality Improvement Program (NSQIP). To investigate independent predictors of 30-day morbidity, a Cox' proportional hazard model with backward stepwise elimination was utilized. The identified predictors were entered into a nomogram.

Results: Two hundred ninety-three patients entered the study protocol. Optimal cytoreduction was achieved in 136 (46%) patients. 30-day morbidity was seen in 99 (34%) patients. Morbidity could be predicted by age (P = 0.033; OR 1.024), haemoglobin (P = 0.19; OR 0.843) and WHO performance status (P= 0.015; OR 1.821) with a for optimism corrected c-statistic of 0.62.

Conclusions: 30-day morbidity could be predicted by age, haemoglobin and WHO performance status. The generated nomogram could be valuable for predicting operative risk in the individual patient.
KRUKENBERG TUMORS OF THE OVARY - TEN YEARS OF OCCURRENCES

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Background: Krukenberg tumor is an uncommon ovarian metastatic tumor, which is mostly derived from a primary gastrointestinal tract tumor.

Aims: To characterize Krukenberg tumors who were diagnosed in the last ten years at our department.

Methods: We surveyed 13 clinic files of Krukenberg tumors diagnosed at the Gynecology Department of C.H.A.A. between 1999 and 2009.

Results: Mean age of the patients was 52 years. Pelvic pain was the most frequent onset symptom. Bilateral forms of the tumor were more frequent. The diagnosis of Krukenberg tumor preceded the diagnosis of the primary tumor in 4 cases (median time to diagnosis was 4 months). In 3 cases the primary tumor diagnosis was made per-operatively at the time of the anexectomy. Primary tumor remained unknown in 2 cases. Undifferentiated gastric adenocarcinoma with signet ring cells was the primary tumor in 9 cases and colon adenocarcinoma was the primary tumor in 2 cases. All patients undergo surgical or palliative medical treatment. The diagnosis was always histologic based on the presence of signet ring cells associated with a pseudosarcomatous stroma. Prognosis was always unfavorable. The mean survival time was 10 months.

Conclusions: Krukenberg tumor remains a mystery to clinicians. It’s an uncommon tumor with adverse outcomes. Although some measures were proposed to improve prognosis (prophylactic oophorectomy in patients with gastric cancer), none prove to improve the patients’ survival time.
EXPRESSION OF NUCLEAR FACTOR-KAPPA B FAMILY PROTEINS IN OVARIAN CANCER AND THEIR POTENTIAL LIKE PROGNOSTIC FACTORS

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Nuclear factor kappa-b (NF-kB) has been show to be elevated in some lymphoid malignancies and solid tumors, such as melanomas, lung, hepatocellular, breast, prostate, pancreatic, thyroid and ovarian carcinomas. The purpose of this present study was to determinate the expression of all NF-kB family members (p50, p52, c-REL, Rel-b, p65) and their association with clinicopathological parameters and prognosis in epithelial ovarian cancer (EOC). On immunohistochemistry 97 samples of ovarian tissue of EOC were evaluated. Elevated NF-kB p52 expression was significantly correlated with late FIGO stage, performance status, residual disease, histology and poor histological differentiation. Elevated NF-kB c-Rel expression was significantly correlated with poor histological differentiation, too. Elevated NF-kB p65 expression was correlated with age ≥65. We did not found significantly correlation between expression of NF-kB family members and overall survival or disease-free survival. Multivariate analysis not revealed that NF-kB family members was an independent prognostic factor in EOC.
IN VITRO BROMODEOXYURIDINE LABELING INDEX MAY BE VALUABLE AS A PROGNOSTIC FACTOR FOR PREDICTING RECURRENCE IN OVARIAN CANCER

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Background: To prospectively evaluate the value of in vitro bromodeoxyuridine labeling index (Brdu-li) as a prognostic factor in epithelial ovarian cancer and to assess its relationship with disease-free survival and to evaluate its possible associations with known prognostic factors of this disease.

Materials and methods: Ovarian fresh tissue biopsies were taken intraoperatively from the tumoral mass of consecutive 26 patients with ovarian cancer treated in a university hospital setting. The tissues were treated with Brdu monoclonal antibodies immunohistochemically to determine their Brdu-li. The correlation between Brdu-li and histology of the tumor, stage, presence of ascites, preoperative CA-125 levels, age and recurrence status of the patients were studied using Mann-Whitney U, spearman correlation, Kaplan-Meier and log-rank tests as appropriate.

Results: The mean age and median follow-up period of the patients were 59.3±13.3 years and 30 months respectively. The median Brdu-li was 6.1% (0-51.2%). None of the studied parameters had an association with Brdu-li values except the recurrence status. Brdu-li was significantly low in patients with recurrence (2.5%) when compared to patients without recurrence (33.5%) (p=0.01). In survival analysis, patients with low Brdu-li had a disease free survival of 12 months while patients with high values had 34.2 months (p=0.03).

Conclusion: Brdu-li, denoting cell proliferation rate, may contribute to standard prognostic factors in discriminating ovarian cancer patients with better disease free survival. This encouraging preliminary result awaits validation from larger prospective series.
ACCURACY OF INTRAOPERATIVE FROZEN SECTION ANALYSIS REPORTED AS BORDERLINE OR UNDECIDED IN EPITHELIAL OVARIAN TUMORS

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Objective: To assess the accuracy of intraoperative frozen section reported as borderline or undecided ovarian tumors.

Methods: Frozen section results (last three years) reported as undecided and borderline ovarian tumors were reviewed retrospectively. Frozen section and final histology results were compared.

Results: Totally 42 results were analyzed. Twenty two results were reported as borderline and 3(13.6%) cases were different diagnosis in final histopathologic examination. Diagnosis of borderline ovarian tumor was correlated in 19/22(86.3%) cases. In undecided frozen section results, 7/20(35%) cases were diagnosed as malignant ovarian tumors in the final histology. No borderline epithelial ovarian tumor was diagnosed in undecided results.

Conclusion: Intraoperative frozen section result reported as borderline are highly correlated with final histology. Also, possibility of malignant ovarian tumors are very high in unconclusive frozen section analysis.
GENETIC POLYMORPHISM OF NAT2 IN PATIENTS WITH OVARIAN CARCINOMAS

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Background: Single nucleotide replacement (points 481, 590 and 857) assigns an activity of NAT2 enzyme that allows segregating individuals as “fast” or “slow” acetylators. Polymorphism of NAT2 may be associated with predisposition to malignances.

Object: The results of genetic polymorphism investigation of NAT2 in patients with ovarian carcinomas are presented in the study.

Patients and methods: During the period from July, 2008 to September, 2009 214 patients were enrolled into the study. 100 of with ovarian carcinoma (study group) and 114 were selected as controls without malignances.

Results: Genotypes 481TT and 590AA that are associated with “slow” acetylation has been seen in 2.2 and 1.4 times were frequent in the control group compared with the study group. Depending on genotyping all the patients were separated on “fast” and “slow” acetylators. The “fast” ones had 3 dominant alleles in homozygous condition 481CC, 590GG and 857GG or those who have only one 3 mentioned genotypes in heterozygous condition. The comparative study demonstrated that in patients with ovarian carcinomas with “fast” acetylation the frequency of genotypes 481CC/590GG/857GG was significantly higher then control study (OR=8,51). The same was found for haplotype 481CT/590GG/857GA in “slow” acetylators in whom ovarian carcinomas were 6 times frequent.

Conclusion: According to the study the significant correlations of genotypes 481CC/590GG/857GG of NAT2 gene and ovarian cancer predisposition were found.
THE ROLE OF THROMBOCYTOSIS IN PREOPERATIVE ASSESSMENT FOR OVARIAN MASSES


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Aim: To evaluate the predictive value of thrombocytosis (platelet count > 400 x 10^9) in discriminating between benign and malignant ovarian masses.

Methods: This is a retrospective study performed in a gynaecological oncology centre in the United Kingdom between January 2007 and July 2009. 275 women with histologically confirmed ovarian masses were included in the analysis. Details of ultrasound findings, serum CA 125 levels, size of the ovarian mass, preoperative platelet count and final histology were recorded.

Results: 215 (78.2%) women were found to have benign masses and 60 (21.8%) women were diagnosed with ovarian malignancy. The mean diameter of the ovarian masses on ultrasonography was 9.95 cm (SD: 5.45 cm). The preoperative platelet count in women with ovarian cancer was higher than in women with benign ovarian mass (387.1x10^9 vs 303.4x10^9; p value < 0.001). We found a positive correlation (rho: 0.265) of thrombocytosis with ovarian cancer (p value < 0.001). The relative risk for ovarian cancer in the presence of preoperative thrombocytosis was 15.1. The sensitivity, specificity, positive predictive value and negative predictive value of thrombocytosis in differentiating between benign and malignant ovarian masses were 36 %, 96.4%, 69.2% and 87% respectively.

Conclusions: The presence of a normal preoperative platelet count in women with ovarian masses is associated with a low risk of ovarian malignancy. The platelet count may have a role if incorporated into the existing risk of malignancy indices.
DO DIFFERENT RISK MALIGNANCY INDICES PERFORM EQUALLY IN THE PREOPERATIVE EVALUATION OF PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN WITH OVARIAN MASSES?


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Aim: To compare the performance of three risk malignancy indices (RMI 1, RMI 2 and RMI 3) in discriminating between benign and malignant ovarian masses in pre- and postmenopausal women.

Methods: This is a retrospective study of 275 women with surgically confirmed ovarian masses in a gynaecological oncology centre in the United Kingdom over a 30-month period. We calculated the sensitivity, specificity, positive predictive value and negative predictive value of RMI 1, RMI 2 and RMI 3 to diagnose ovarian malignancy.

Results: Of the ovarian masses in the postmenopausal group, 68 were benign and 46 were malignant. An RMI 1 equal to or greater than 250 achieved a sensitivity of 73.9%, specificity of 85.2% and a positive predictive value of 77.2% for detection of ovarian malignancy. The respective values for RMI 2 were 82.6%, 70.5% and 65.5%; for RMI 3 the values were 73.9%, 83.8% and 75.5%. In the premenopausal group, 147 of the ovarian masses were benign and 14 were malignant. In premenopausal women, the sensitivity, specificity and positive predictive value for RMI 1 were 28.5%, 89.7% and 21.0% respectively; for RMI 2 were 28.5%, 89.1% and 20.0% respectively; for RMI 3 were 28.5%, 89.7% and 21.0% respectively.

Conclusion: The performance of the RMI 1, RMI 2 and RMI 3 in discriminating between benign and malignant ovarian masses is significantly poorer in premenopausal compared to postmenopausal women. We recommend that a different cut-off value for the RMI should be used in the premenopausal group of women.
MANAGEMENT OF METASTATIC NEUROECTODERMAL TUMOUR IN PREGNANCY

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Ovarian malignancy complicating pregnancy is a very rare event. Its management poses a dilemma to clinicians since either chemotherapy or surgical intervention can affect the pregnancy outcome and thus the fetus.

Here we present a case of a metastatic neuroectodermal tumour arising within an immature teratoma during pregnancy.

A 30 year old in her first pregnancy had a suspicious right adnexal mass detected on a routine ultrasound at 22 weeks gestation. She was also noted to have an enlarged supraclavicular lymph node which was biopsied. The resulting histopathology revealed an immature teratoma containing foci of neuroectodermal malignant tissue likely to have metastasised from the ovary.

Following multidisciplinary team discussion, it was decided that she receive neoadjuvant chemotherapy.

At 32 weeks gestation, she underwent an elective caesarean section and right oophorectomy. A live infant female was delivered in good condition with no congenital malformations. Histology from the right ovary confirmed the earlier diagnosis.

3 months after completion of chemotherapy, she underwent surgical resection of residual nodal disease and had second line chemotherapy with good response.

She remained well, with stable disease two years after initial presentation.

Paediatric follow up of her baby was unremarkable, with no issues of development.

This particular case demonstrates rare ovarian malignancy presenting with metastatic disease complicating pregnancy.

From the limited published literature, there is no established consensus of whether the maternal or fetal interests take precedence, this case highlights that potential conflict. We therefore recommend a multidisciplinary approach is essential in the management of these cases.
CHEMOSENSITIVITY TESTING: DO IN-VITRO RESULTS MIRROR EMPIRICAL RESPONSE RATES?

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Background and aims: Chemotherapy plays a key role in managing ovarian cancer. While platinum compounds are the most effective single agents in the primary setting, not all patients respond. Clear cell and mucinous carcinomas have significantly worse outcomes compared with other cell types. To evaluate the utility of a drug response marker to aid chemotherapy decision making, we determined whether tumors tested with ChemoFx® demonstrated this same response pattern.

Methods: 2,623 stage III/IV primary or recurrent epithelial ovarian, peritoneal, and fallopian tube cancers with known histologies and tested commercially with ChemoFx from August 2006-August 2009 were selected for analysis. Tumors were categorized as responsive(R), intermediate responsive(IR) or non-responsive(NR) based on in-vitro drug response.

Results: Of 2,172 assessable tumors, 1,503 were stage III/IV and 669 recurrent. 19% of primary and 28% of recurrent cancers were resistant to all chemotherapies tested, both platinum and non-platinum agents (p< 0.001). The in-vitro chemotherapy response rate (R + IR) to carboplatin and paclitaxel(CP) was 72% in primary and 60% in recurrent cancers (p< 0.001). For primary cancers, mucinous (53%) or clear cell (60%) had a lower response rate to CP as compared with serous (74%) tumors (p=0.018).

Conclusions: ChemoFx response rates to CP were consistent with expected population response rates. More aggressive histologic subtypes were less responsive to CP in-vitro. These data indicate the ChemoFx assay may provide tumor-specific information that can assist in chemotherapy decision making.
THE MALIGNANT TRANSFORMATION OF ATYPICAL ENDOMETRIOSIS
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Endometriosis is a common disease that rarely can undergo transformation into malignancy. Atypical endometriosis is supposedly the intermediate step in the transformation process but is not always identified on histology.

We present a case of endometriotic transformation into an ovarian malignancy in a background of atypical endometriosis.

A 33 yr old nulliparous woman presented to the gynaecology clinic with a year history of irregular bleeding and abdominal discomfort. Ultrasound revealed a 4cm endometrioma. Ca 125 was normal. The endometrioma was aspirated at laparoscopy due to extensive pelvic endometriosis.

At 3 month follow up repeat ultrasound showed recurrence of endometrioma, measuring 8cm. She then underwent laparoscopic ovarian cystectomy.

Histopathology of the cyst revealed a borderline endometrioid tumour arising in atypical endometriosis.

Given her age, she then had a fertility sparing staging laparotomy which confirmed early stage borderline ovarian tumour.

Consistent with the management of borderline tumours, she is under regular monitoring. 5 years after initial presentation she remains well with no evidence of recurrence.

Developing cancer from endometriosis is rare. In this case the evidence for malignant transformation is supported by the presence of atypical endometriosis.

The only unusual clinical finding in this case was the rapid recurrence and growth of her endometrioma. This may correlate with abnormal growth associated with carcinogenesis.

We suggest in women with a history of endometriosis, rapid alterations in clinical findings, such as a brief interval between surgery and recurrence, should be treated with suspicion.
LARCIST: A NEW PROPOSED METHOD FOR THE ASSESSMENT OF RESPONSE TO CHEMOTHERAPY IN ADVANCED OVARIAN CANCER PATIENTS

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Background and aims: Response to chemotherapy is an important predictive factor in advanced ovarian cancer (AOC) patients. A variety of approaches in measuring response to treatment with radiological (RECIST), serological (GCIG criteria) and combined metabolic/radiological (PERCIST) criteria have been elaborated. However, they do not always correspond to a clinical/surgical management of the disease. The aim of the study was to provide a more effective tool, based on a laparoscopic predictive value (PIV), to evaluate response to neo-adjuvant chemotherapy (NACT) in AOC patients.

Methods: Sixty AOC patients primary submitted to laparoscopic surgical exploration (S-LPS) and then NACT were included in the study if they had: i) complete/partial radiological or serological response, ii) stable radiological disease in the presence of serological response, iii) progressive serological disease but stable clinical and radiological disease. All patients were submitted to a second S-LPS. Laparoscopic Response Criteria in Solid Tumors (LARCIST) were calculated as the ratio between Δ-PIV (scoring gap between PIV at primary surgery and PIV at the time of IDS) and PIV at primary surgery.

Results and conclusion: A statistically significant correlation between LARCIST and RECIST criteria (p=0.0001), with an accuracy rate of 85% was observed. On the contrary, as far as GCIG criteria is concerned, no statistical correlation was found between the two methods. As expected, response to chemotherapy is a statistically significant predictor of PFS (p=0.002, p=0.02 and p=0.4 for LARCIST, RECIST, GCIG criteria, respectively). However, a more consistent correlation with the possibility of optimal cytoreduction has been observed for LARCIST criteria.
U.S. GOG 218 VS. EURO ICON7 - A COST ANALYSIS OF BEVACIZUMAB IN THE PRIMARY TREATMENT OF OVARIAN CANCER

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Objective: Recent results from GOG218 showed that the addition of bevacizumab (B) and maintenance bevacizumab (mB) (15mg/kg) to chemotherapy improved the outcome of ovarian cancer patients. The results of ICON7 with a lower dose Bevacizumab (ld-B) (7.5mg/kg) are pending. We evaluated the cost effectiveness of GOG vs. ICON trials.

Methods: Cost of drugs, rates of complication, and progression-free survival were assessed. Incremental cost-effectiveness ratio (ICER) per life-year saved (LYS) was established.

Results: Estimated cost of B (15mg/kg) is $6,450 and ld-B (7.5mg/kg) is $3,225 per cycle. Compared to GOG cost / cycle = [PC ($440) + B ($6450)] + $6,450/maintenance, ICON = [PC ($440)+ ld-B ($3,225)] + $3,225/ low dose maintenance was less. We estimated PFS to be 16 months with chemotherapy alone and 22 months with the addition of B. Of 600 patients, the GOG arm was $84.2 million vs. $43.5 million for ICON arm after adjusting for baseline estimates of PFS and bowel perforation risk. Assuming a 6 month improvement in PFS, the ICER was $270,900 per LYS for GOG arm, and $135,450 for ICON. If we assumed a 9 month additional PFS benefit associated with B, the ICER would be $180,600 for the GOG ARM and $90,300 for ICON arm. With a cost-effective ICER threshold of $100,000 per LYS, the ICON arm appears closest to being cost-effective.

Conclusions: In this economic model, our data suggest that a lower dose Bevacizumab, if proven to be effective, is more cost effective in the treatment of primary ovarian cancer.
SELECTED RARE TUMORS OF THE FEMALE REPRODUCTIVE TRACT AND PELVIC AREA - CLINICO-PATHOLOGICAL ANALYSIS OF SIX CASES AND LITERATURE REVIEW

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Introduction: The rarity of many neoplasms does not allow to define the optimal treatment. Knowledge of these tumors based on case reports and small series presentations. Recently, the immunohistopathological and genetic profile of tumors are evolving as a standard part of the diagnostic procedures. This novel approach pushes aside traditional descriptive definitions. Our review brings clinical and immunohistochemical information on six cases of very rare tumors in the female pelvic area helpful in the clinic.

Material and methods: Retrospective clinico-pathological profile of six cases of very rare tumors in female genital tract and pelvic area: liposarcoma globocellulare of the vulva, angiomyofibroblastoma of the vulva with sarcomatous transformation - to the best our knowledge, this is a second case described in the literature, leiomyomatosis intravenosum of the uterine with infiltration of the omentum and intestine surface, we also presented one case of gliomatosis peritonei, one case of PECOMa (clear cell myomelanocytic tumor of falciform ligament) ovarii and case of extra gastrointestinal GIST (gastrointestinal stromal tumor) of the omentum diagnosed in patient in whom carcinoma of the ovarium was suspected.

Conclusions: Some literature data and clinical observations suggest an increasing number of rare tumors diagnosis. In a lot of these cases precise and novel immunohistopathological and genetic diagnosis is a time and money consuming procedure, some of these rare cases may need histopathological recinsultation. An increasing literature data about rare tumors, central database may be helpful for physicians faced with patient with one of these tumors.
VITAMIN D RECEPTOR POLYMORPHISMS AND PROGNOSIS OF PATIENTS WITH EPITHELIAL OVARIAN CANCER


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Purpose: Recently, the vitamin D receptor (VDR) polymorphism FokI was demonstrated to be associated with susceptibility to ovarian cancer. We aimed to examine if VDR FokI polymorphisms influence the prognosis of patients with epithelial ovarian cancer (EOC).

Experimental design: VDR polymorphisms from FokI in 101 patients with EOC were genotyped by sequencing. Overall survival was compared between FokI single nucleotide polymorphism using Kaplan-Meier survival curves with log-rank tests and the Cox proportional hazard model adjusted for International Federation of Gynecology and Obstetrics stages, postoperative chemotherapy, histology, and existence of residual tumor. Hazard ratios, adjusted hazard ratios (AHR), and 95% confidence intervals (95% CI) were determined.

Results: The FokI C/C genotypes were associated with better prognosis compared with the C/T and T/T genotypes (log-rank test: P=0.008; AHR 0.16; 95%CI 0.05 to 0.57; P=0.004). At 30 months after surgery, 90% of patients with FokI C/C genotypes were still alive; in contrast, 66% of patients with C/T and T/T genotypes were alive. When cancer stage of patients was restricted to II - IV, 84% of patients with FokI C/C were still alive: in contrast, only 50% of patients with C/T and T/T genotypes were alive.

Conclusion: These results suggest that the VDR polymorphisms from the FokI genotype may be associated with improved prognosis of patients with EOC.
TRIPLE COLLISION TUMOR OF THE OVARY
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Collision tumors represent the coexistence of two or three adjacent but histologically distinct tumors, without histologic admixture in an organ. Collision tumors have been reported in various organs, but are rarely seen in the ovaries. Reported cases consisted of a benign mature ovarian teratoma and an ovarian cystadenoma or cystadenocarcinoma. Primary carcinoid tumors of the ovary, on the other hand, are uncommon, with a reported incidence of 0.3%. They are usually unilateral and are found in association with mature cystic teratoma, forming a solid nodule within it. Primary ovarian carcinoids rarely metastasize and are treated as ovarian tumors with low malignant potential. This is a rare case of a triple collision tumor of the ovary in a 63 year old multigravid who complained of a gradually enlarging abdominal mass. Total abdominal hysterectomy with bilateral salpingooophorectomy and complete surgical staging was performed. Histopathology revealed coexistence of a mucinous tumor of low malignant potential, carcinoid tumor, and mature cystic teratoma in the right ovary. The possibility of the occurrence of such collision tumors must always be kept in mind intraoperatively and during pathologic examination to avoid misdiagnosis of these cases.
SURGICAL MANAGEMENT OF ADVANCED OVARIAN CANCER: A 20-YEARS EXPERIENCE IN A TERTIARY GYNECOLOGIC ONCOLOGY UNIT

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Background and aims: Report data from 20 years experience in the management of advanced epithelial ovarian cancer (AEOC) in a tertiary gynecologic cancer unit.

Methods: Retrospective analysis of 419 stage IIIC-IV ovarian cancer patients treated with primary debulking surgery (PDS) or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) at the Catholic University at Rome and Campobasso, Italy.

Results and conclusion: Two-hundred eight patients (54.4%) underwent PDS whereas 191 patients (45.6%) underwent NACT and IDS. Median progression free survival and overall survival for the entire cohort was 19 months and 45 months, respectively. Patients undergoing PDS showed a better prognosis than those one treated with IDS in terms of PFS (p < 0.0037) and OS (p < 0.006). At PDS and IDS, patients with residual tumor (RT) = 0 had better prognosis with respect to patients with 0 < RT < 2. In multivariate analysis, the RT = 0 retained independent prognostic role for PFS and OS. Maximal surgical effort with complete cytoreduction should be considered the gold standard in the surgical management of AEOC. Patients in whom complete/optimal residual tumor at PDS is not achievable might be treated with NACT, followed by IDS.
PELVIC DISEASE IN PRIMARY ADVANCED OVARIAN CANCER: THE ROLE OF PERITONECTOMY OF DOUGLAS COMPARED WITH RECTOSIGMOID RESECTION

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Background and aims: The peritoneum of Douglas space and the rectosigmoid colon are frequently involved sites in patients with advanced ovarian cancer (OC). Peritoneectomy of Douglas'space (PDs) or rectosigmoid resection (RR) are two different surgical approach required to remove the pelvic disease. The aim of this study was to investigate the oncologic impact of this techniques in achieving optimal debulking.

Methods: We reviewed all patients undergoing pelvic surgery for OC at the time of primary cytoreduction, from 2004 to 2009.

Results and conclusion: There were 212 patients meeting the above criteria. Eighty-five (40%) patients were submitted to RR and in 71 (89%) of these patients the optimal residual disease was achieved, although the remaining one hundred twenty seven (60%) were managed with PDs and 115 (90%) were optimally debulked. The recurrence occurred in 57% of patients. Eighteen patients had pelvic recurrence in the subgroup of patients managed with the PDs, and all of them were submitted to secondary cytoreduction. The evaluation of oncologic outcome in terms of disease free survival (DFS) and overall survival (OS) not revealed significant statistical difference for the patients managed with the two surgical approach (median DFS was 16 months [RR] versus 15 months [PDs]; p 0.20. Median OS was 22 months [RR] versus 26 months [PDs]; p 0.15). The resection of pelvic tumor in patients with OC may require different surgical strategy depending by extension of the disease. The cytoreduction performed with RR appear to be comparable to PDs in terms of DFS and OS.
INTERVAL DEBULKING SURGERY AFTER NEOADJUVANT CHEMOTHERAPY USING INTRAPERITONEAL CHEMOTHERAPY FOR ADVANCED EPITHELIAL OVARIAN CANCER

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Objective: The objective of this study is to assess the impact of neoadjuvant chemotherapy (NAC) using intraperitoneal chemotherapy to interval debulking surgery (IDS) for patients with advanced epithelial ovarian cancer.

Methods: During April 2007 and March 2010, 26 patients histologically confirmed epithelial ovarian cancer received IDS after NAC using intraperitoneal chemotherapy. All patients received staging surgery. A Bard IP port system was placed before the abdomen was closed. We reviewed the medical records and extracted pertinent information.

Results: The median age of patients was 60 years (range 35-79). These patients included 23 epithelial ovarian carcinoma (stage II, 1; stage III, 13; stage IV, 9), 3 primary peritoneal carcinoma (stage II, 1; stage III, 1; stage IV, 1). There were 20 serous, 2 clear cell, and 4 other pathological type. All patients received neoadjuvant chemotherapy using intraperitoneal carboplatin and intravenous paclitaxel. The median cycles of neoadjuvant chemotherapy was 6 (range 3-8). Twenty patients (86.9%) achieved no residual status after IDS. The mean operating time and blood loss were 119 min (range 60-275) and 268 mL (range 5-11125), respectively. Only 1 patients (3.8 %) needed bowel resection.

Conclusion: Neoadjuvant chemotherapy using intraperitoneal chemotherapy may gain a rate of optimal surgery and reduce need for bowel resection.
HYPOXIA INDUCIBLE FACTOR 1-A EXPRESSION: ITS EFFECT ON PROGNOSIS AND RESPONSE TO TAXANE AND PLATINUM CHEMOTHERAPY IN OVARIAN CANCER

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Objectives: The objectives of this study were to measure hypoxia inducible factor-1α (HIF-1α) expression and to investigate the correlation between expression of hypoxia-inducible factor HIF-1α and progression-free survival and response to chemotherapy in epithelial ovarian cancer.

Methods: Expression of HIF-1α protein in 62 paraffin-embedded specimens of epithelial ovarian cancers was explored by immunohistochemistry. The correlation between the expression level of HIF-1α and clinicopathologic variables was evaluated by Student’s t-test and logistic regression analysis. Survival analysis was performed by Kaplan-Meier curves.

Results: HIF-1α expression was confirmed in 33 patients (53.2%). There were no significant relationships between HIF-1α expression and age, parity, FIGO stages, and histologic types. Expression of HIF-1α had a borderline relationship with optimal surgical reduction (P=0.08). In logistic regression analysis, there was no significant correlation between expression of HIF-1α and response to chemotherapy (P=0.999). However Expression of HIF-1α also had no significant relationship with progression-free survival (P=0.734).

Conclusions: This study suggests that HIF-1α expression has no impact on progression-free survival and response to chemotherapy in epithelial ovarian cancer.
NOVEL MARINE COMPOUNDS TO TREAT OVARIAN CANCER

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Ovarian cancer is the fourth most common gynaecological cancer world-wide and causes the highest mortality. Tyrindoleninone and 6-bromoisatin, two marine-derived compounds from muricid molluscs, have been shown to inhibit cell growth and induce apoptosis in non-reproductive cancer cell lines. We aimed to examine their effects on primary derived human granulosa cells from the ovary, and compare with the KGN granulosa cancer cell line.

Human granulosa cells, along with the KGN cells (10,000 cells/well) were exposed to the marine compounds (0.005-0.5mg/ml) for 4 and 24h. Cell viability was determined by the crystal violet (0.5%) assay and cell death by the caspase 3/7, LDH release and TUNEL assays.

Tyrindoleninone demonstrated the greatest cytotoxicity towards the KGN granulosa cancer cell line (EC₅₀ = 0.05mg/ml at 4 and 24h) in comparison to the primary granulosa cells (EC₅₀ = > 0.5mg/ml; 4 and 24h treatment). Caspase 3/7 enzymes were detected when the KGN cells were treated with tyrindoleninone (0.005mg/ml) at 4h. In comparison, caspase 3/7 enzyme activity was only significantly different to control in the primary granulosa cells at 0.1mg/ml tyrindoleninone. Tyrindoleninone induced apoptosis was confirmed in the KGN cells by fluorescent staining of DNA at 4h (0.05mg/ml) and 24h (0.005mg/ml).

In conclusion tyrindoleninone and 6-bromoisatin both demonstrated greater activity towards the granulosa cancer cell line, KGN in comparison to the primary granulosa cells. Tyrindoleninone was the most promising candidate because it was anti-proliferative and pro-apoptotic towards the KGN granulosa cancer cell line but did not significantly affect non-cancerous primary-derived granulosa cells.
HIGH THROUGHPUT DRUG SCREENING USING OVARIAN CANCER STEM CELLS IDENTIFIES NOVEL COMPOUNDS FOR OVARIAN CANCER THERAPY


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Background and aims: Ovarian cancer is one of the most common gynecological cancers. The high fatality-to-case ratio of ovarian cancer remains staggered in the past decades. Adding to our previous work in isolating ovarian cancer stem cells from human ovarian cancer tissues, the present study enriched ovarian cancer stem cells from cancer cell lines and discovered novel compounds preferentially targeting cancer stem cells.

Methods and results: Our previous work isolated ovarian cancer stem cells (OVCSC) from human ovarian cancer tissue using spheroid formation and characterized CD44+/CD117+ as surface markers. To explore the translational relevance of this cancer stem cell concept in ovarian cancer, we combined the dye-exclusion and spheroid formation methods to enrich OVCSC from ovarian cancer cell lines. The stem cells characteristics derived from this marker-free method were analyzed by various stem markers and validated by serial transplantation in immunocompromised mice. The OVCSC demonstrated chemoresistance. Loss of chemoresistance was noted as CSCs differentiate. High throughput drug screening using a chemical library of >1200 compounds discovered potential generic drugs preferentially targeting OVCSC derived from cell lines and human ovarian cancer tissues in vitro. The therapeutic effects were confirmed in animal models.

Conclusion: These results shed a new light on a better chance of survival for patients with ovarian cancer in the near future. A collaborated effort on the trial of these compounds is warranted. The paradigm shift from a stochastic model to cancer stem cell model has profound implications in cancer diagnostics and therapies.
LONG TERM FOLLOW-UP OF ADVANCED OVERIAN CANCER PATIENTES TREATED WITH BIWEEKLY PACITAXEL/CARBOPALTIN (TC) COMBINATION CHEMOTHERAPY

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Objectives: The objectives of this multicenter phase II study were evaluated effects of biweekly Paclitaxel (T) and Carboplatin (C) combination chemotherapy on response rate and toxicities in patients with epithelial ovarian cancer.

Methods: Patients with FIGO stage IIc-IV ovarian cancer received Paclitaxel 120 mg/m² and Carboplatin AUC 3 q2wks for up to eight cycles. Patients had to have an Eastern Cooperative Oncology Group performance status of 0-2 and to have received no chemotherapy. Informed consent was obtained from each patient before the start of therapy.

Results: Between March 2003 and April 2006, 29 patients were enrolled in 5 institutes, and evaluated for response and toxicity. The median age was 63 yrs (46-81 yrs). FIGO stage was IIc: 1 pts., IIib: 2 pts., IIic: 20 pts., IV: 6 pts., respectively. Overall response rate of 58.6% (5 CR and 12PR) was observed according to RECIST criteria, and 69.0% (20 of 29 pts) received up to 8 cycles or more. Median progression-free survival and overall survival was 24.4 and 59.1 mo, respectively (median follow-up time: 39.2 mo.). Toxicity was generally mild and reversible. Grade (G) 3 leukopenia (32.1%) and neutropenia (53.6%) were observed. The predominant G 3 nonhematologic toxicities were neuropathy (3.6%) and nausea (3.6%). No serious adverse events including pulmonary toxicity were observed.

Conclusions: Biweekly TC combination chemotherapy was effective and tolerable for patients with first line chemotherapy for ovarian cancer. This regimen will be considered as a treatment options in patients with chemonaive ovarian cancer.
DOES NEOADJUVANT CHEMOTHERAPY INCREASE THE NUMBER OF OPTIMALLY DEBULKED PATIENTS WITH ADVANCED OVARIAN CANCER? A RETROSPECTIVE STUDY

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Background: It’s recognized that complete debulking in advanced ovarian cancer is the main factor which significantly improves disease free and overall survival.

Aim: Of this retrospective analyses was to define if NACT could increase the number of optimally debulked patients with advanced ovarian cancer.

Methods: We evaluate the results of treatment in 275 patients with advanced epithelial ovarian cancer. All patients underwent primary exploration by open or laparoscopic approach. 134 patients was considered for primary cytoreduction at first exploration. Median age of patients in this group was 49.4±8.2 years. Other 141 patients with median age 58.3±5.3 years, were refered to recieve 3 cycles of NACT with following interval debulking surgery.

Results: Most frequent type of surgery in primary debulked group include total abdominal hysterectomy with BSO and omentectomy (n=91). 19 patients underwent additional pelvic and paraaortic lymph node dissection and resection of other organs in abdomen was performed in 24 cases. However, in these patients optimal and suboptimal debulking was achieved in 21.9% and 35% of patients, respectively. We found that the types of surgery were approximately the same in patients, operated after NACT: total abdominal hysterectomy with BSO and omentectomy was performed in 94 cases, lymph nodes and other organs were resected in 21 and 26 cases, accordingly. Optimal and suboptimal cytoreduction was achieved in 14.5% and 36.1% of cases. Progression free and overall survival were the same in both arms.

Conclusions: NACT failed to improve the number of optimally debulked patients in this retrospective study.
METHYLATION MARKERS IN FREE CIRCULATING DNA AS THE BASIS OF A BLOOD TEST FOR EARLY SEROUS OVARIAN CANCER

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Rationale: Serous ovarian cancer is typically diagnosed late in its clinical history, and the late diagnosis contributes to poor patient outcomes. One strategy in developing a test for early detection is to search for ovarian cancer specific methylation patterns in free circulating DNA, a DNA fraction which is found in blood and which is not associated with any population of cells. This DNA fraction is elevated in cancer patients and mirrors the molecular changes in the tumour. While the exact mechanism of its introduction into the blood circulation is unknown, it is believed to originate from cancer cells dying through necrosis or apoptosis.

Objective: The aim of this study was to evaluate methods of free circulating DNA extraction from plasma, and to optimise headloop PCR based detection of gene methylation.

Methods and results: Parameters considered include blood sample storage time and temperature, volume of plasma used as starting material, optimal DNA extraction and bisulphite conversion methods, and the effect of DNA fragmentation. Preliminary results show that free circulating DNA is present in control plasma at concentrations of approximately 1 ng/mL to 10ng/mL, and is fragmented in a regular pattern consistent with apoptosis. While blood storage times of 8 hours have no effect, storage for 24 hours or more prior to plasma fractionation leads to contamination of the plasma with leukocyte DNA.

Conclusions: Data obtained highlight the importance of sample storage and processing. These results are expected to contribute to the development of a clinically useful test for ovarian cancer.
THE CLINICAL SIGNIFICANCE OF EVALUATION OF PLEURAL EFFUSIONS IN PATIENTS WITH ADVANCED EPITHELIAL OVARIAN CARCINOMA AND PRIMARY PERITONEAL CARCINOMA


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Background and aims: To assess the clinicopathologic difference and survival outcomes in patients with little to moderate pleural effusions without cytological evaluation and patients with moderate to large pleural effusions with cytology-proven malignant diagnosed advanced epithelial ovarian carcinoma.

Methods: We conducted a retrospective review of the data from all consecutive patients with pleural effusions diagnosed advanced epithelial ovarian carcinoma from October 1999 through February 2009. Statistical analyses included the χ2 test and Kaplan-Meier curves with log-rank tests.

Results: Review of our patient database identified 40 patients with stage IIIc- IV ovarian cancer with pleural effusions: median age, 58.5 years (range, 41-77 years); 5-year overall survival, 17.2%. There were 13 patients classified as having stage IV disease by pleural cytology only, and the other 27 patients were classified as having stage IIIc disease without cytology examine. Patients with cytology-proven malignant pleural effusions were more likely to have pleural effusions and disease at relapse and at last follow-up (69.2% vs. 18.5%, P=0.004). However patients having stage IV disease by pleural cytology hadn't survival benefit when compared with patients having stage IIIc disease without pleural cytology (median survival, 17 months vs. 23 months; P>0.05).

Conclusions: The significance of cytology for patients with pleural effusions diagnosed advanced epithelial ovarian carcinoma and primary peritoneal carcinoma should need to be approached again. Further investigation is needed to define the staging system of ovarian carcinoma.
PREDICTION BY SERUM BIOMARKERS OF RESPONSE TO TREATMENT WITH PACLITAXEL AND CARBOPLATIN IN SEROUS CYSTADENOCARCINOMA OF THE OVARY

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Background: Combination chemotherapy by paclitaxel and carboplatin (TC) is commonly used in serous cystadenocarcinoma (SAC) of the ovary. The response rate for SAC is approximately 70 to 80%, however, most of SAC cases are diagnosed at advanced stages with massive ascites and pleural effusion. Thus, we attempted to explore serum biomarkers to predict response to TC for SAC.

Methods: Preoperative serum samples were obtained from 26 patients with TC responders; 5 case of complete response (CR) and 21 cases of partial response (PR), and TC non-responders; 13 patients with progressive disease (PD). Serum samples were analyzed by surface-enhanced laser desorption and ionization-time of flight mass spectrometry (SELDI-TOF MS). Single- and multi-variant analyses were performed to compare protein profiles in serum of responders and non-responders.

Results: Five biomarkers were selected in preliminary experiments. Four biomarkers declined in non-responders had molecular weight (MW) of 3263, 3278, 3299, and 3451 with significant (p< 0.001) difference compared to that in responders. A biomarker elevated in non-responders showed MW 8574 (p< 0.017) and, compared with responders, respectively. In a confirmatory experiment, similar results were obtained and the reproducibility was confirmed.

Conclusion: Significantly decreased four biomarkers and increased one biomarker in non-responders were found in preoperative sera, suggesting that these biomarkers may make prediction of response to TC possible. Using this biomarker profile, neoadjuvant chemotherapy with TC regimen would be more effectively selected for SAC cases.
HYPER-METHYLATION OF DAPK, E-CADHERIN AND BLU GENES AS BIOMARKER OF SURVIVAL IN OVARIAN SEROUS CARCINOMA

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Background and aims: To evaluate correlations between clinical outcome and chemo-response of patients with ovarian serous carcinoma and gene hyper-methylation.

Methods: Eighty-six patients with advanced-stage serous epithelial ovarian carcinoma were evaluated. Gene hyper-methylation was determined by methylation-specific polymerase chain reaction and capillary electrophoresis. Correlations between gene hyper-methylation and chemo-response, disease-free survival (DFS), and overall survival (OS) were investigated.

Results: The frequency of gene hyper-methylation were DLEC1 (68.8%), RASSF1A (48.8%), RUNX3 (37.2%), P15 (29.1%), E-cadherin (25.6%), BLU (25.6%), RARb (15.1%), DAPk (14.0%), and MGMT (1.2%). There was no significant difference in the frequency of gene hyper-methylation for histologic grading. Patients with gene hyper-methylation of DAPk, E-cadherin, BLU, or high-grade carcinoma had significantly shorter DFS in univariate analysis, but only DAPk hyper-methylation and high-grade carcinoma were significant in multivariate analysis. In combined gene hyper-methylation involving DAPk, E-cadherin, and BLU, patients with hyper-methylation in any one, two or all three genes had 1.59 (p=0.185), 5.88 (p=0.011), and 7.24-fold (p=0.001) higher risks of early recurrence, respectively, in the regression model. In contrast, none of these factors had significant influence on overall survival.

Conclusion: Combined analysis of promoter hyper-methylation in DAPk, E-cadherin, and BLU can be potential biomarkers for predicting disease recurrence in advanced ovarian serous carcinoma.
MICROARRAY ANALYSIS OF ONCOGENIC PATHWAYS IN ADVANCED SEROUS PAPILLARY OVARIAN CARCINOMA

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Background: The aim of this study is to identify important processes which could lead to possible candidates for targeted therapies in ovarian cancer.

Methods: Two publicly available microarray datasets of advanced stage (III and IV) ovarian cancer samples (N=244, N=122) were analysed for oncogenic pathways (AKT, BetaCatenin, E2F1, EGFR, ER, HER2, MYC, INFα, IFNγ, p53, p63, PI3K, PR, RAS, SRC, STAT3, TNFa, TGFβ) of which gene signatures were generated and validated by Gatza et al. (PNAS 2010). A VEGFA response gene signature was generated and validated based on in vitro experiments of VEGFA-stimulated HUVEC cells. These pathway gene signatures were correlated with clinicopathological findings and 3 prognostic gene signatures (Wound Response Signature, Genomic Grade Index and the Invasiveness Gene Signature).

Results: In both independent datasets, activation of BetaCatenin(R≥0.54), E2F1(R≥0.39), MYC(R≥0.35), p63(R≥0.35), PI3K(R≥0.20), RAS(R≥0.25) pathways were positively correlated with the 3 prognostic gene signatures (p< 0.001) while the EGFR(R≤-0.27) and HER2(R≤-0.26) pathway was negatively correlated (p< 0.003). Survival analysis confirmed reduced survival or time to progression for patients with an activated BetaCatenin(HR=0.78; p< 0.003), p63(HR=0.76; p< 0.034) and RAS(HR=0.48; p< 0.039) pathway. This was concordantly found in both datasets. Borderline significance was found for E2F1(HR=0.82; p< 0.07) and MYC(HR=0.70; p< 0.068) pathway.

Conclusions: Microarray analysis of two independent datasets showed that BetaCatenin, RAS and p63 pathway were consistently of prognostic value in advanced stage serous papillary ovarian cancer. Additional studies are needed.
IS THIRD-LINE CHEMOTHERAPY EFFECTIVE IN OVARIAN CARCINOMA?

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Purpose: Approximately two thirds of advanced ovarian cancer cases recur after primary surgery and chemotherapy, and treated with second-line or third-line chemotherapy. However, the efficacy of the therapies still remains unresolved.

Methods: The cases treated with third-line chemotherapy were retrospectively evaluated using medical records. Clinicopathologic factors affecting overall survival after third-line chemotherapy (3rd OS), and progression-free survival after third-line chemotherapy (3rd PFS) were investigated.

Results: Four hundred and ninety one ovarian cancer cases had primary debulking surgery or neoadjuvant chemotherapy followed by interval debulking surgery between 1984 and 2008 at our hospital. Among them, 101 cases (21%) received third-line chemotherapy, 21 stage I/II cases (21%) and 80 stage III/IV cases (79%). Histological subtypes were serous/endometrioid in 76 cases (75%), clear cell/mucinous/others in 25 cases (25%). Treatment-free interval from second-line chemotherapy (2nd TFI) was within 6 months in 76 cases (75%). Response was observed in 18 cases (18%); 3 complete response and 15 partial response. Median 3rd PFS was 3 months (range; 0M-31M), and median 3rd OS was 15.5 months (range; 1M-63M), respectively. Multiple regression analysis for 3rd OS revealed responses of primary and third-line chemotherapy were independent prognostic factors, and histological subtypes or stages or chemotherapeutic regimen were not prognostic factors.

Conclusion: Response to 3rd-line chemotherapy significantly improved 3rd OS, and histological subtypes or 2nd TFI of did not affect 3rd OS. The present study suggested responders to primary chemotherapy could be candidates to 3rd-line chemotherapy. Further larger studies are needed to confirm the results.
THE PROGNOSTIC IMPACT OF ANEMIA IN ADVANCED EPITHELIAL OVARIAN CANCER

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Purpose: To verify that anemia during chemotherapy could be used as an important prognostic factor for advanced epithelial ovarian cancer patients and assess the relationship between anemia and progression-free and overall survival.

Methods: Fifty-one patients with FIGO stage III and IV epithelial ovarian cancer who had received at least six courses of platinum/taxane-based systemic chemotherapy and achieved clinical or pathologic complete response were included. A new prognostic factor based on the duration of anemia was proposed and the impact of anemia on progression-free and overall survival was analyzed by a log-rank test and a Cox proportional hazard model.

Results: We propose that the Hb1020, the duration of hemoglobin (Hb) < 10 g/dL for 20% of the total duration of chemotherapy, is an optimal prognostic factor for epithelial ovarian cancer. The 5-year progression-free survival was 54.3% and 29.2% (p=0.045), and the overall survival was 91.1% and 43.3% (p=0.0103) in the groups above and below the Hb1020, respectively. With multivariate analysis using other well-known prognostic factors, the Hb1020 is still regarded as an independent prognostic factor of progression-free and overall survival.

Conclusion: Hb1020, based on the duration of anemia, not on the Hb levels of specific time points, is one of the important prognostic factors for progression-free and overall survival. By using Hb1020, we can administer more aggressive early treatment of anemia and improve the patient's survival.
PATERN OF IMMUNOREACTIVITY IN PRIMARY OVARIAN MUCINOUS ADENOCARCINOMA AT KING CHULALONGKORN MEMORIAL HOSPITAL

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Objectives: To study the pattern of cytokeratin 7 and 20 (CK7 and CK20) and CDX2 immunoreactivity including patient’s characteristics and histologic features in primary ovarian mucinous adenocarcinoma.

Methods: Eighty-seven cases of primary ovarian mucinous adenocarcinoma diagnosed at the King Chulalongkorn Memorial Hospital from 1999 to 2009 were reviewed for clinicopathologic features and immunohistochemical staining with CK7, CK20 and CDX2. The results were analyzed in correlation to the clinical characteristics.

Results: Mean age of the patients was 44.9 years (range 14-77 years). The tumors were unilateral in 87.4% with the mean size of 21.4 cm. Presence of both unilateral ovarian involvement and size ≥10 cm was observed in 85.1% of patients. Seventy-three cases (83.9%) were stage I. Microscopically, 95.4% of tumors were grade 1. Borderline components were present in more than half of cases. CK7+ and CDX2- were found in all cases, while CK20+ was found in only 34 cases (39.1%). There was no significant difference of clinicopathologic features, except for nulliparity, between cases with CK7+/CK20- and CK7+/CK20+. Worse prognosis was associated with advanced stage, suboptimal surgery, absence of borderline component, lack of confluent growth pattern, and bilateral tumors.

Conclusions: Immunoreactivity pattern in primary ovarian mucinous carcinomas was 60.9% CK7+/CK20- and 39.1% CK7+/CK20+, which was not associated with clinical prognosis. Majority of cases revealed unilateral ovarian involvement and size ≥10 cm. The diagnosis from clinical presentation, gross operative findings and H&E staining was practically used in most cases. However, immunohistochemical study was necessary in selected cases with atypical clinicopathologic features.
PHASE II TRIAL OF WEEKLY IRINOTECAN AND CARBOPLATIN FOR RELAPSED OVARIAN CANCER - A KANSAI CLINICAL ONCOLOGY GROUP STUDY

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Background: Irinotecan has shown favorable activities for patients with ovarian cancer (OC), thus a multicenter phase II trial was conducted to evaluate the activity and toxicity of irinotecan plus carboplatin in such a patient population.

Methods: Intravenous administrations of 60 mg/m² of irinotecan (Days 1 and 8) and carboplatin at an AUC of 5 mg・min/ml (Day 1), repeated every 21 days, were given to patients with either radiological or serological recurrent OC. The primary endpoint was response rate (RR) based on RECIST, while the secondary endpoints were adverse events (NCI-CTCAE ver 2.0) and progression-free survival (PFS).

Results: From 2005 to 2009, 40 patients were enrolled in the trial. Their median age was 59 years old (range, 33-78) and histological findings were serous (64%), endometrioid (18%), and others (18%). The number of previous regimens were 1 in 58%, 2 in 21%, and 3 or 4 in 21%. Overall RR was 25% (PR 13%, CR 13%) and median PFS was 6 months (range, 1-12) in patients with TFI < 6 months, while those were 53% (PR 20%, CR 33%) and 10 months (range: 7-16), respectively, in patients with TFI ≥6 months. Grade 3 or 4 toxicities encountered during the first cycle included G3/G4 neutropenia in 65% (12/14), G3/G4 thrombocytopenia in 48% (18/1), G3 febrile neutropenia in 5% (2), G3 nausea in 5%(2), G3 diarrhea in 5% (2), and G3 fatigue in 5% (2).

Conclusion: This regimen was useful as second-line chemotherapy because of its efficacy with controllable hematologic toxicity.
THE ROLE OF IL-6 AND OSTEOPONTIN IN DIAGNOSIS OF OVARIAN CANCER

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Ovarian cancer is a major death causes in women due to advanced stage diagnosis and also to the resistance to chemotherapy developed throughout the adjuvant treatment.

Purpose: The aim of the study was to quantify the serum levels of IL-6 and osteopontin in patients referred to surgery for ovarian cancer.

Material and methods: We have evaluated the serum levels of IL-6 and osteopontin by ELISA method in a group of 17 patients with ovary cancer and compared the results with a group of 13 patients without any ovarian pathology.

Results: The mean value of IL-6 in the ovarian cancer group was 47,217 pg/ml±41,4 and 5,09pg/ml±2,54 in the control group. The reference maximal value for IL-6 was 12,5pg/ml. 12 cases from the cancer group had higher (pathological) values. At ROC test, the minimum surface was of 0,917 which is very close of maximum value of 1. Hereby the marker is useful in detecting this condition. The mean value for osteopontin in the cancer group was 594,55±224,86ng/ml versus 36,72±25ng/ml in the control group. Se=Sp=1 for osteopontin, meaning ideal prediction of the disease.

Conclusions: The preoperatory levels of IL-6 and osteopontin are significantly higher in patients with ovarian cancer than in those with benign ovarian tumors. The dynamic assessment of these parameters - before and after surgery and also after two cures of chemotherapy - should provide us the opportunity of detecting new serum markers for the early prediction of cancer relapses, improving the management and the survival rates in these patients.
PROGNOSTIC DNA COPY NUMBER ALTERATION IN OVARIAN CANCER

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Ovarian cancer is the sixth most common gynecologic malignancy in women worldwide. The precise etiology of the majority of ovarian cancers is elusive. Due to its heterogeneity ovarian cancer, represented as a collection of distinct disease types, differ in disease progression, treatment response and disease-free and overall survival. Still there are no evident molecular or cytogenetic markers characterizing every histotype, disease stage or being reliable predictive factor. The importance of DNA copy number alterations has been demonstrated in many tumors. Hence we studied genomic alteration in 39 epithelial ovarian cancer (EOC) patients by the means of aCGH (array comparative genomic hybridization) using Nimblegen Human CGH 3x720K WG platform to find the likely chromosome region or particular gene responsible for clinical picture of disease.

We found copy number gains and high copy gains in region (chr3:169,750,345-171,315,444) on chromosome 3q26.2 to be strong predictive factor of advanced disease stage (FIGO III / IV; p=0.004), characteristic for progressive cases and being unfavorable survival factor (p=0.01). We indentified genes coded in this region: MECOM, TERC and MIR551B. Patients with (versus patients without) CN gains and high copy gains in 3q26.2 carried more numerous and diverse aberration (amplification and deletion) in their genome.

Amplification encompassing region in chromosome 3q26.2, coding genes TERC (telomerase gene) and MECOM (engaged in cell cycle) may be responsible for progression of EOC and may be consider as poor prognostic factor.
OVARIAN TISSUE CRYOPRESERVATION FOR GYNECOLOGICAL MALIGNANT TUMOR SURVIVORS

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Objective: Freezing of human ovary can not only preserve fertility for female, but also be used for future ovary transplantation to reserve hormone secretion of reproductive function. This study was to analyze indication and manipulullty of ovarian tissue cryopreservation for gynecological malignant tumor survivors.

Materials and methods: This is a retrospective study consisting of 9 young women. All of them suffered from gynecological malignancy and accepted surgery in our department. At the same time, they had a desire of fertility-sparing or preservation of ovarian function and wanted their ovarian tissue frozen for future usage.

Result: Characteristics of these nine women were seen in Table. Partial ovarian tissue was successful frozen for all of them except one person. The approach of freezing included slow speed and vitrification. The case 9 was a 14 year old with dysgerminoma. Both of her bilateral ovaries were involved by tumor cell, so oocyte freezing was taken for her. But unfortunately, it failed.

Conclusion: Ovarian tissue cryopreservation for gynecological malignant tumor survivors is easible.
PREDICTING OVARY MALIGNANCIES BY EVALUATING CA125+HE4 COMBINED WITH ROMA METHOD IN ADNEXAL MASSES

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Background and aims: Among all gynecologic cancers, clinical discussion is more focused on ovarian malignancies. They usually remain asymptomatic until metastasis; therefore include the most rates of mortality. If they were diagnosed in first stages, the chance of cure is about 90%. A method for early diagnosis of malignancy is evaluation two tumor makers: CA125 and HE4 combined before treatment of patients with adnexal masses.

Methods: In this study, all premenopause and postmenopause women (n=60) who had referred to Tumor and Gynecologic Clinics of Ghaem Hospital with diagnosis of ovarian masses (by sonography and clinical signs) were studied (1/1/09 to 1/1/010). Serum CA125 and HE4 were evaluated for prediction of the risk of ovarian malignancies before operation. All the patients underwent surgery and pathologic reports were compared to the results of ROMA.

Results: The range of age was 43-70 yrs (mean 56.5 yrs). 42 cases had ovarian cancer and 24 had benign masses. CA125 was positive in 65% of patients with malignancy and 40% with benign masses. HE4 was positive in 72% of cases with ovarian cancer and 18% with benign masses. Combination of CA125+HE4 had more sensitivity by ROMA method. Prediction value was 82% in malignant cases and 100% in benign cases.

Conclusions: Combining CA125+HE4 had high sensitivity and can be requested as a safe and successful method before surgery in women with adnexal mass. Therefore, we can design for choosing best treatment, selection of experienced surgeon and more equipped hospital.
INTRAOPERATIVE EVALUATION AT RISK-REDUCING SALPINGO-OOPHORECTOMY FOR BRCA1/2 MUTATION CARRIERS: A RADIOLOGIC, SURGICAL, AND PATHOLOGIC CORRELATION STUDY OF OPTIMAL INTRAOPERATIVE MANAGEMENT

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Background: Risk reducing salpingo-oophorectomy (RRSO) is effective in minimizing the risk of pelvic serous carcinoma in BRCA1/2 mutation carriers. A minority of RRSO specimens contain clinically occult carcinoma, typically detected only by special specimen processing and enhanced pathologic evaluation. It is possible that cysts or nodules visualized intraoperatively may predict the risk for occult cancer. This may affect intraoperative decisions.

Methods: 134 BRCA mutation carriers undergoing RRSO were studied retrospectively. Pre-operative pelvic ultrasound, intraoperative findings and gross pathologic findings were reviewed for presence of cysts or nodules. RRSO specimens were thinly sliced and entirely examined microscopically.

Results: Adnexal cysts were identified in 10% of intraoperative reports, 46% of ovarian gross pathologic exams, and 54% tubal/paratubal gross pathologic exams. Among 39 patients with pelvic ultrasound, 45% had adnexal cysts. No carcinoma was identified microscopically in any cyst. No adnexal nodules were reported by ultrasound; 1 tubal nodule was noted intraoperatively; gross pathologic detection of a nodule was reported in 16% ovaries and 6% tubes. Microscopically, carcinoma was diagnosed in 9% ovarian nodules (0.6 cm to 1.1 cm) and 25% of tubal nodules (0.6 cm to 1.2 cm). A total of 11 tubal/ovarian serous carcinomas were detected on microscopic examination, but only 36% of these cancers were visible intraoperatively as a nodule; the remainder were occult, microscopic cancers.

Discussion: There is no value to intraoperative evaluation of cysts in RRSO specimens however nodules larger than 0.5 cm may carry a small risk for carcinoma and detection intraoperatively may change surgical course.
A CASE OF ACUTE LYMPHOBLASTIC LEUKAEMIA MIMICKING AN OVARIAN MALIGNANT TUMOR


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On June 2009 a 50-years-old woman presented to our attention with abundant ascites, bilateral pleural fluid, increased serum of Ca125 level (> 500 U/ml) and an ovarian complex mass of 4 cm of diameter. Blood testing were within normal limit. The cytological report of the ascites and pleural fluid was positive for malignancy. The computer tomography scan of the abdomen showed a pelvic mass which was highly suspicious for an ovarian malignant tumor.

Because of her poor performance status, the patient was not a candidate for surgery.

Therefore, a neoadjuvant chemotherapy with paclitaxel and carboplatin for 4 cycles was performed and a partial response with reduction of abdomen and thorax fluid, a remarkable decreased of serum Ca125 level and a reduction of the pelvic mass was obtained. After approximately 15 days from the last cycle of chemotherapy the patient presented with dyspnea and the CT of the chest showed a bilateral pleural effusion. At that time an increment of white globules (42.000/µl) was also taken place, not answering to the antibiotic therapy.

Therefore an examination of peripheral blood and a bone marrow biopsy was undertaken. The results showed a diagnosis of acute lymphoblastic leukaemia and the patient succumbed for her disease 5 days later.

This case would show that cases highly suspicious for an ovarian malignancy may rarely mimic other malignancies such as an acute lymphoblastic leukaemia.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

CLINICAL SIGNIFICANCES OF GALECTIN-3 EXPRESSION IN OVARIAN CARCINOMAS

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Objective: Galectin-3 is β-galactoside-binding lectin and was characterized to regulate cell growth control, angiogenesis and tumor progression. We investigated the relation of galectin-3 expression and its clinical significances including roles of prognostic marker or therapeutic target in epithelial ovarian cancers.

Methods: We evaluated expression of galectin-3 by immunohistochemistry in 65 patients (49 serous, 12 endometrioid and 4 mucinous types) and investigated relationship with clinical characteristics including survival. Staining was scored based on intensity (IS 0-3) and proportion score (PS 0-100). We also examined the role of galectin-3 in ovary cancer cell line by inhibition with siRNA and additional effect with combination of paclitaxel.

Results: Galectin-3 cytoplasmic expression IS 2-3 group has a worse prognosis than IS 0-1 (P=0.038). Mean progression-free survival (PFS) was 4.8 and 1.6 months each. With respect to recurrence, strong staining group (IS 2-3) has a higher risk (P=0.046) and hazard ratio of strong group is 2.607 (CI 1.019~6.672). And in vitro experiment showed galectin-3 treated with siRNA shortened cancer cell survival compared with paclitaxel or siRNA alone.

Conclusion: Strong cytoplasmic expression of galectin-3 is associated with worse prognosis including PFS and recurrence. Therefore galectin-3 might be a prognostic marker. In vitro study, down-regulation of galectin-3 with specific siRNA potentiates growth-inhibiting effect of paclitaxel. It could be act as therapeutic target of epithelial ovary cancer.
IMPORTANCE OF CA 125 IN THERAPEUTIC MONITORING OF THE OVARIAN CANCER CASE REPORT


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In female patient (FP), P.M., 46 years after the gynecological operation (GO) was detected ovarian cancer PH-type gradus III. For them GO FP was suffering from unspecified gastrointestinal symptoms but in natural history existed often urinary infections and polycystic ovaria (45.y.). Determination of tumour marker CA 125 showed values in borders of referent values (RV < 35 U/mL), but in one moment the value was a 34.5 U/mL ! The FP had a some increased body mass index (BMI), increased S-Cholesterol increased activity of S-amylase (S-AMY), increased erythrocytes sedimentation rate (ESR) and increased S-CRP. For them one year ago (46.y.) often gynecological bleedings, bad hemato-hemostaseological parameters and explosively increase of the CA 125 till 118 U/mL (!!!) indicate to seriously gynecological examinations which introduce to radically GO (2). The patient was including in new chemiotherapeutic procedures (ChP) in our Institution (1). For them one year after ChP (47.y.) the values of the CA 125 was 4-7 U/mL (RV< 35 U/mL), BMI some increased still, S-Cholesterol=5.7 and the other laboratory parameters was in RV, except ESR=24 in first hour and

S-CRP = 5.3 (RV < 5.0). Our case, showed great importance of the CA 125 in therapeutic monitoring of the ovarian cancer. The CA 125 we determined by immunochemical method - ELFA technique, apparatus VIDAS, Company bioMerieux. Importance of the CA 125 is in monitoring of the breast cancer, too, with CA 15-3 and in malignant lymphomas, including male patients was showed some new reports.
PACLITAXEL CARBOPLATIN CHEMOTHERAPY FOR EPITHELIAL OVARIAN CANCER CURES SEVERE PSORIASIS OF 25 YEARS DURATION

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Background: We report the first case of epithelial ovarian cancer (EOC), whose severe psoriasis of long duration was surprisingly cured with standard paclitaxel and carboplatin chemotherapy, which was infused for her cancer.

Case report: 64 years-old postmenopausal patient presented with bloating and abdominal pain. Pelvic examination and computerized tomography (CT) showed 12 cm right adnexal mass, and ascites. Her history revealed 25 years of severe psoriasis that was unsuccessfully treated with various therapies including topical and narrowband UVB therapy. Her psoriasis was especially evident and resistant on her scalp, elbows, hands, fingers, and knees; while less severe on skin over coccyx, eyelids, and feet. On February 2007, she had complete cytoreduction to no residual tumor with hysterectomy, bilateral salpingooophorectomy, omentectomy, appendectomy, and bilateral pelvic and paraaortic lymphadenectomy. Final pathology depicted, serous papillary ovarian carcinoma, metastasizing to paratubal region, pelvic lymph nodes, uterosacral ligaments, peritoneum, omentum and malignant ascites. After first three courses of chemotherapy she realized that her long time accompanying psoriasis had gone completely. Later, at 16 months she developed an abdominal recurrence, which was successfully cytoreduced to no residual; she had additional paclitaxel and carboplatin chemotherapy. She is now alive with no sign of psoriasis 39 months after her first EOC diagnosis.

Conclusion: Besides being standard treatment for ovarian cancer, paclitaxel and carboplatin treatment might serve as a very effective treatment policy for severe psoriasis resistant to other standard treatment modalities; although optimum doses should be further studied.

Keywords: Psoriasis, ovarian cancer, paclitaxel, carboplatin, chemotherapy
PRIMARY OVARIAN LYMPHOMA. AN EXPANDED SURGERY IS NEEDED?

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Objectives: Report two cases of primary ovarian lymphoma in order to evaluate the surgical treatment and chemotherapy.

Materials and methods: We present two cases of patients aged 45 and 51 years who start clinic with a pelvic mass suspected of malignancy. In the first part, an expanded surgery is performed reaching the result of ovarian pathology with the biopsy, and the second is an intraoperative biopsy report of high-grade lymphoma which an hysterectomy plus double oophorectomy is performed due to ascendent colon affection.

Results: Both cases received chemotherapy with good response to treatment. Patients are alive and disease-free after a three years of follow-up.

Comments: The primary ovarian lymphoma is one of the most rare and obscure ovarian cancers. The incidence is most often between 40 and 50 years, being the most frequent one the lymphoma hodgkin B. Its most common presentation is in the form of ascites or ovarian mass and are usually unilateral. They usually have a greater than 80% survival rate at 5 years, with very good response to chemotherapy. They may appear as a primary neoplasm or secondary manifestation of a disseminated occult disease. Currently discussing the type of surgery to perform, or whether to perform an ovarian extended intervention or to submit only to tumor excision and then chemotherapy.
CLINICAL ANALYSIS AND MENTAGEMENT OF SWYER SYNDROME: ABOUT 7 CASES

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Introduction: Swyer’s syndrome is a distinct type of pure gonadal dysgenesis characterized by a 46 XY karyotype in female phenotypic patients. It shows an abnormality in testicular differentiation and is a risk factor for malignant gonadal transformation.

Patients and methods: We present the clinical sonographic and endocrine findings in 7 cases of phenotypic young girls with XY karyotype and gonadal dysgenesis. The treatment and the follow up are discussed.

Results: The mean age was 16.8 years. All patients presented with primary amenorrhea. One patient presented with acute pelvic pain. All patients had a normal height and weight except one. All patients had a female type external genitalia. Secondary sexual characters were merely developped in all cases. Ultrasonography showed a small uterus in all cases. The ovaries were not detected in 5 cases, they were described as hypoplastic in one case and a pelvic mass was noted in one case. FSH levels were high in all cases with a mean of 78.7 mIU/ml. The karyotype was 46 XY in all cases. A bilateral gonadectomy was decided. The surgical findings were steak fibrous gonads in 4 cases, gonads with different sizes in 2 cases and an ovarian tumor in one case. Histopathology showed fibrous ganads in 4 cases, a bilateral gonadoblastoma in 2 cases and a dysgerminoma associated to a gonadoblastoma in 1 case.

Conclusion: The risk of gonadal neoplasia is higt dictating early prophylactic removal of these dysgenesic gonads. The tumor that usually developes in Swyer’s syndrome is gonadoblastoma.
LAPAROSCOPIC SPLENECTOMY FOR SOLITARY SPLENIC RECURRENCE OF OVARIAN CANCER

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This report presents a patient in whom a solitary splenic metastasis was detected 5 years after diagnosis of stage IIIa ovarian cancer. The patient was a 54-year-old woman who was diagnosed with stage IIIa ovarian serous papillary cystadenocarcinoma in 2002. She underwent six-cycles postoperative chemotherapy, and exhibited no signs of recurrence in terms of clinical symptoms, tumor markers and imaging findings. In 2007, Her CA 125 was normal range and her clinical symptoms, pelvic examination was unremarkable. However, routine CT scan of pelvic and abdomen showed 3 * 2.5 cm lobulating contour splenic lesion that was not evident on previous CT scans. Also, PET-CT scan of whole body suggested hypermetabolic lesion at spleen. After pneumococcal vaccination, she underwent laparoscopic splenectomy and microscopy confirmed the splenic tumor to be of the same histologic type as the ovarian cancer. She received six cycles of paclitaxel-carboplatin. At present, she remains disease-free 24 months after the surgery.
INCREASED CIRCULATING HEPATOCYTE GROWTH FACTOR (HGF) LEVELS; AN INDICATOR OF EPITHELIAL OVARIAN CANCER AND POORER PROGNOSIS

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Aims: Elevated hepatocyte growth factor (HGF) levels have been found in fluids of benign and malignant ovarian cysts, and in ovarian cancer ascites. We therefore wanted to investigate whether serum HGF can distinguish benign from malignant ovarian tumors, and predict the outcome in patients with ovarian carcinomas.

Methods: We included 123 consecutive patients appointed for laparotomy due to a pelvic mass. Preoperative serum levels of HGF and CA 125 were analyzed with immunological methods. Immunohistochemical analyses of HGFα, HGFβ, and the receptor c-met were performed. The median serum HGF value in the benign tumor group was used as reference. For statistical analyses we used the Kruskal-Wallis and Mann-Whitney tests. Five-year survival of patients with advanced disease was analyzed with the Kaplan-Meier method.

Results: Sixty patients had ovarian carcinomas, 23 borderline tumors, and 40 benign ovarian tumors. The patients with carcinomas had significantly higher preoperative HGF and CA 125 levels than the patients with benign tumors (p=0.001, p< 0.001) and borderline tumors (p=0.02, p< 0.001). Patients with borderline tumors had higher CA 125 values than benign cases (p=0.005). We observed abundant HGFα, HGFβ and c-Met expressions in all ovarian tumors. Patients with advanced disease and preoperative serum HGF ≥ 2 SD above reference value had shorter survival than patients with advanced disease and serum HGF < 2SD above reference value (median survival 23 vs. 41 months respectively).

Conclusions: Elevated HGF in serum is an indicator of ovarian carcinoma, and high HGF levels indicate a poorer prognosis in advanced ovarian cancer.
CHEMOTHERAPY OR UPFRONT SURGERY FOR NEWLY DIAGNOSED ADVANCED OVARIAN CANCER: THE MRC CHORUS TRIAL

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Background: Most women with ovarian cancer are treated with surgery then chemotherapy even if they present with advanced disease. This standard approach was never investigated in a randomised clinical trial and there is debate regarding the optimum sequencing of these treatments. CHORUS together with the EORTC 55971 trial was designed to investigate this issue.

Methods: Women with newly diagnosed advanced ovarian cancer are randomised to standard treatment (immediate primary surgery followed by 6 cycles of platinum-based chemotherapy) or neoadjuvant chemotherapy (3 cycles of platinum-based chemotherapy either side of primary surgery). CHORUS is designed to demonstrate that the neoadjuvant arm is not inferior to the standard arm in terms of overall survival. It requires 550 patients and is designed to be analysed alone and in conjunction with EORTC55971.

Results: Recruitment from 74 sites in the UK and 3 sites in New Zealand will complete in Summer 2010; 25% of women had FIGO stage IV disease, 20% WHO performance status ≥2, the median age was 65. Full results of outcome measures are expected within 2 years. Baseline data on the final trial population, the numbers achieving surgery and survival in the trial overall are presented for comparison with EORTC55971.

Conclusion: We congratulate centres on their efforts in completing trial recruitment on schedule. Important follow-up information will be collected for a further two years before analysis. Results from CHORUS will be able to validate the conclusion of EORTC55971 and combined data will be able to exclude a difference of 6% in 3-year survival.
PRIMARY LYMPHOBLASTIC LYMPHOMA OF OVARY - CASE REPORT

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Background: Ovarian malignancies, the second common malignancy of women and a silent killer since screening tests are not welldefined. The Epithelial and gemcell tumors are common and Primary Lymphoblastic Lymphoma of ovary is still rare.

Case report: 51 year old multiparous female, still menstruating presented with the complaint of dull epigastric pain of 4 months duration. She had lost 6 kgs of weight over 2 months. No other menstrual or systemic disturbances in the past. Husband treated for carcinoma tongue recently (non consanguinous marriage). Neither she nor other family members had any major illness in the past.

Clinically she had an irregular, firm, non-tender mass in the lower abdomen 20cm X 15cm with unreachable lower border and mild anemia. No evidence of ascitis or lymphadenopathy. Pelvic examination confirmed the mass and healthy cervix.

Haematological investigations normal except thrombocytopenia - 61,000/cc, same in the peripheral smear. Imaging suggested multiple fibroid of uterus with right ovarian cyst 3.8cm X 4.7cm with non-specific features. Tumor markers negative.

With the diagnosis of huge myoma, with unexplained thrombocytopenia, surgery planned. With platelet transfusion peri and post-operatively, total hysterectomy with bilateral salpingo oopherectomy done. Other viscera appeared normal.

Post-operatively thrombocytopenia persisted. Bone-marrow aspirates revealed normal haemopoiesis and giant Mega karyocytes.

Histopathology with immunohistochemistry revealed primary B-cell lymphoblastic lymphoma of ovary with myoma. Lymphatics in myoma showing mets.

With the tumor board consensus, post-operative chemotherapy advocated.

Conclusion: Non-nodal manifestations of lymphomas especially as primary are rarely encountered and very few are reported in literature.
FACTORS ASSOCIATED WITH ENROLMENT IN OVARIAN CANCER CLINICAL TRIALS AND THE IMPACT ON OUTCOME

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Background: Previous studies have reported better outcomes when patients (pts) participate in clinical trials (CT), possibly due to exposure to active new agents, entry criteria restricted to better prognosis pts or adherence to strict best practice protocols. Enrolling pts in CT also improves cancer treatment, so understanding CT enrolment, and ways to improve this are important goals.


Results: 1095 pts were identified, 18% (n = 193) were elderly (>70 yrs). Stage breakdown was III (54%), I (26%), II (10%) and IV (10%). 862 (78.7%) pts had chemotherapy (79.5% < 70, 75.1% > 70 yrs, p=ns), 179 (20.8%) of these were treated on a CT. Participation increased over time, from 1986-1997 (15.8%) to 1998-2008 (24.2% p=0.003). Elderly pts participated less in CT (11.7% vs 22.6% p=0.002). Pts with higher stage (III & IV) disease were more likely to be enrolled versus stage I & II (26.5% vs 10.0% p< 0.001). Socioeconomic status did not impact participation. For stage III pts (n=489) there was a trend towards improved survival on CT (n=141) 3.8 versus routine treatment (n=348) 3.0 years, p=0.07. Overall the elderly pts benefited most from CT enrolment (median survival 3.5 versus 2.1 yrs, (p=0.02)). There was no difference in survival outcome when pts on the control arm (n=52) were compared to those not on trial (n=324). Multivariate analysis will follow.

Conclusions: A significant proportion of pts with ovarian cancer participate in CT. There was less participation among elderly pts, the group that benefited most. Inadequate treatment of elderly pts off study is one possibility that needs to be further explored.
INITIAL APPROACH TO BRCA1 GENE MUTATIONS IN EPITHELIAL OVARIAN CANCER

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Objective: To examine BRCA1 gene mutations in ovarian cancer and investigate the relationship between BRCA1 gene mutations and ovarian cancer.

Methods: BRCA1 gene testing was carried out on 76 DNA samples. 46 samples were ovarian cancer, in which, 40 samples were epithelial ovarian cancer. 11 of them were diagnosed with breast cancer and/or have family history with breast/ovarian cancer. 29 of them were sporadic epithelial ovarian cancer. 15 of 76 samples had at least one family relative suffered from breast or ovarian cancer. 15 women were used as normal controls. DNAs were exacted from blood sample by Genomic DNA extraction Kit before screening all BRCA1 coding sequence by PCR-SSCP. Alterations were confirmed by DNA sequencing. The amplified fragments of exon2 and exon3 which were not suitable for SSCP were sequenced directly.

Results: 16 cases of abnormal BRCA1 gene were found. 1 was frame shift mutation, 5 were missense mutation, 6 were synonymous mutation, while 4 were inserted within the intron sequence. BRCA1 gene in ovarian cancer patients was abnormal in 10 cases (21.7%), including 1(9%) in high-risk patients, 8(27.6%) in sporadic epithelial ovarian cancer patients, 1(16.7%) in none-epithelial ovarian cancer patients. 3(20%) mutations were found in family history group. No abnormality was found in the normal control.

Conclusions: There was some correlation between BRCA1 gene and ovarian cancer. Further analysis of BRCA1 gene testing and correct interpretation would be a significant breakthrough in ovarian cancer prevention. Analysis SSCP provides a path to BRCA1 testing in large sample studies.
CYTOKINE PROFILES IN OVARIAN CYST FLUID: CORRELATION WITH MALIGNANCY

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Background: Better insight in the interplay between ovarian cancer and the immune system is needed in order to improve immunotherapy in ovarian cancer. In the present study, we investigated cytokine profiles in cyst fluids of ovarian cancer patients, as a reflection of their immune status and compared the findings with the cytokine profile in benign cyst fluid.

Methods: Human Flow Cytomix Th1/Th2 11 Multiplex and TGF-β1 Simplex Kit and human CCL22 ELISA Kit were used for cytokine detection in 23 malignant and 20 benign ovarian cyst fluids.

Results: The pro-inflammatory cytokines IL-8 and IL-6 were both detected in malignant cyst fluids. However, only the presence of IL-6 correlated with malignancy whereas IL-8 was also found in benign cyst fluids, be it in significantly lower levels. IL-12p70 and IFN-γ (Th1-response), IL-4 and IL-5 (Th2-response) and IL-2 were generally absent in malignant samples and present in one third of the benign samples. Interestingly, immune suppressive chemokines TGF-β and CCL22 were also present in some benign samples while IL-10 was absent in all samples.

Conclusion: These results demonstrate that the expression of both IL-8 and IL-6 is upregulated upon malignant transformation. However, it is striking that only IL-6 is significantly associated with malignancy. The immune suppressive chemokines in benign cyst fluids illustrate that the suppressive status is already present in benign tumours. The total suppressive micromilieu that is created at full malignant transformation is demonstrated by the almost complete absence of cytokines like IL12, IL-4 and IFN-γ.
LONG TERM FOLLOW UP OF WOMEN WITH RECURRENT FIGO STAGE III OVARIAN CANCER: OVERALL SURVIVAL AND PROGNOSTIC FACTORS

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Background: Despite complete initial treatment, most patients with an advanced FIGO stage III ovarian cancer will experience a relapse. The purpose of our study were to determine overall survival of those patients and to identify factors predictive of poor outcome in a consecutive series of patients with a long follow up.

Methods: A retrospective study was performed on patients with a FIGO stage III ovarian cancer treated with primary surgery followed by intravenous platinum-based chemotherapy, with at least one relapse. The studied parameters were age, histological subtype, completeness of initial resection, disease-free period before the first relapse, localization of this relapse, clinical response to second-line chemotherapy, secondary cytoreductive surgery (SCS) and its completeness.

Results: From December 1990 to November 2004, 108 consecutive patients were included. Median overall survival from the first relapse was 15.5 months for the whole series, but 35 months for patient with an optimal SCS, and 13 months for patients with non optimal SCS or no SCS (p=0.006). In a multivariate analysis only age, disease-free period, the clinical presentation of the relapse, completeness of SCS and response to second line chemotherapy appeared to be independent prognostic factors.

Conclusions: Prognostic factors of ovarian cancer relapse are linked with the feasibility of a complete secondary surgery. Thus in the case of an ovarian cancer relapse after a disease free period of 6 months, an evaluation of the feasibility of a SCS must be performed in order to give the patient the best chance to experience its complete removal.
EXPRESSION OF COX AND VEGF-C IN PERITONEAL METASTASES OF OVARIAN SEROUS CARCINOMA AND THEIR RELATIONSHIP TO LYMPH NODE STATUS

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Background: Previous studies did not identify vascular endothelial growth factor-C (VEGF-C) expression and lymphatic vessels density (LVD) in primary tumor, as a significant variable predicting nodal metastases and overall survival in ovarian cancer patients. Possible relationship between cyclooxygenase -2 (COX-2) and lymphangiogenesis is not clear. The aim of our study was to evaluate COX-2 and VEGF-C expression in peritoneal metastases of serous ovarian carcinoma and their possible role in lymphangiogenesis and lymph node metastases as well as their correlation with clinicopathological parameters and overall prognosis in ovarian cancer patients.

Methods: Formalin-fixed, paraffin-embedded specimens from 61 patients with serous ovarian carcinoma, other than FIGO stage I, were selected. Tissue sections of primary tumors and their consecutive peritoneal metastases were immunohistochemically examined for VEGF-C and COX-2 expression. LVD was assessed in peritoneal metastases by counting peritumoral vascular spaces, immunostained by lymphatic endothelium marker D2-40.

Results: A highly significant correlation between high VEGF-C expression, but not COX-2 level, in peritoneal metastases and both LVD (P=0.0006) and positive lymph node status (P=0.002) were found. Combined high COX-2/VEGF-C expression in peritoneal metastases was associated with poorer survival of the patients (P=0.03). However, no association between COX-2 or VEGF-C, expressed by primary or metastatic tumors and clinicopathologic parameters were observed.

Conclusion: Our results suggest that VEGF-C levels of the peritoneal metastases, but not of the primary tumor, play an important role in lymphatic spread of ovarian serous carcinoma, other than FIGO stage I. COX-2 do not contribute to lymphangiogenesis and lymph node metastasis.
CYTOKINE PROFILE IN OVARIAN CANCER RELATED ASCITES FAVORS TUMOR SURVIVAL

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Background: Immunotherapy in the treatment of ovarian cancer has yielded promising results in fundamental and animal research in the past years. However, implementation in clinical practice remains poor. More insight in the immunological interaction between the tumor and the immune system is warranted in order to improve immunotherapy. In the present study we examined the cytokine profile in ascites as a reflection of the immune status of the patient.

Methods: Human Th1/Th2 11plex Flow Cytomix Multiplex, the FlowCytomix Human TGF-β1 Simplex Kit and human CCL22 ELISA kit were used for cytokine detection in 30 ovarian cancer related ascites samples. The samples were prospectively collected at our centre.

Results: Pro-inflammatory cytokines IL-6 and IL-8 are abundantly present in ascites. Moreover, IL-6 is the only cytokine present in all samples in high concentration levels. Furthermore, the immune suppressive chemokines TGF-β, CCL-22 and IL-10 are also detected in most samples. On the other hand, IL-12p70 and IFN-γ (Th1-response) and IL-4 and IL-5 (Th2-response) are mostly absent or only detectable in very low concentrations.

Conclusion: The cytokine network of ovarian cancer related ascites is rich in inflammatory cytokines and immune suppressive chemokines but generally lacks cytokines involved in specific and sustained immune responses. Our results suggest that pro-inflammatory cytokines, especially IL-6, may have a significant role in orchestrating malignant development in ovarian cancer. The production of the immune suppressive IL-10, TGF-β and CCL-22 together with IL-6 is acquired during malignant progression and facilitate tumor escape from immune elimination.
EXPRESSION OF THE LECTIN PATHWAY ACTIVATION FACTORS IN THE OVARIAN CANCER PATIENTS

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Mannan-binding lectin (MBL) and L-ficolin are important factors of the innate immunity. Both have an opsonic activity and activate complement through the lectin pathway in cooperation with MASP-2 serine protease. The serum source of these factors is liver. Several reports demonstrated an elevated level or activity of MASP-2 in sera of patients with colon cancer and increased expression in esophageal squamous cell carcinoma. The goal of the study was to investigate the extrahepatic synthesis of these factors in the female reproductive tract, benign ovarian tumors and the ovarian cancer cases. We have analyzed 17 cases of the benign ovarian tumors and 10 cases of the ovarian cancer. The mRNA expression of MBL, L-ficolin as well as MASP-2 was detected in the healthy ovary, but not in the oviduct or uterine tissue. The MASP-2 mRNA expression was higher in the ovarian cancer samples than in the tissue of benign tumors (p< 0.05). The immunohistochemistry showed an intensive MASP-2 staining of the ovarian cancer tissue. The ovarian MBL or L-ficolin mRNA expression did not differ significantly between patients with ovarian cancer and benign tumors (p>0.05). Moreover, no statistically significant differences were found in serum MBL concentrations, frequency of MBL deficiency as well as MBL-MASP-2 complex activities between both groups.

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LOW CD4/CD8 T-CELL RATIO’S IN ASCITES PREDICT A BETTER CA125 RESPONSE AFTER THREE CYCLES OF CHEMOTHERAPY IN OVARIAN CANCER

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Background: Increasing evidence suggests that ovarian cancer has the ability to escape the immune system by creating a highly immune suppressive environment in the peritoneal cavity. The presence of tumour infiltrating lymphocytes, regulatory T-cells and CD8+ T-cells in tumor tissue (Curiel, 2004) and in ascites (Giuntoli, 2009) have been correlated with prognosis in various studies.

Design: Ascites samples were prospectively collected from 35 primary advanced ovarian or peritoneal cancer patients (FIGO stage III and IV). The cells were isolated, frozen and after being thawed for analysis, stained with monoclonal antibodies tagged to several fluorophores. FACS analysis was performed on all samples. CD4/CD8 T-cell ratio’s and serum CA125 value after three cycles was available in 22 patients. Clinical data were collected prospectively.

Results: In accordance with published data CD8+, CD4+ T-cells and T-reggs were present in ascites in highly heterogeneous quantities. Survival data are not available for all patients yet. We found that low CA125 levels after 3 cycles of (neo-)adjuvant chemotherapy correlate with low (< 1.6) CD4/CD8 T-cell ratio’s (p< 0.03). We also observed significantly lower CD4/CD8 T-cell ratio’s in the group of patients with a complete response after the primary treatment (p< 0.05). No correlation was found between CD4/CD8 T-cell ratio and stage, differentiation and histological subtype of the tumor.

Conclusion: Low CD4/CD8 T-cell ratio’s in ascites predict a better CA125 response after three cycles of chemotherapy in ovarian cancer, which in turn predicts a better disease-free survival. Confirmation with survival data is needed.
QUANTITATION OF CIRCULATING TUMOR CELLS IN PATIENTS WITH EPITHELIAL OVARIAN CANCER

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The detection of circulating tumor cells (CTCs) may have prognostic and predictive value in solid cancers. No one of the previous papers aiming to detect CTCs in peripheral blood of epithelial ovarian cancer (EOC) patients has ever used an automated, standardized, and regulatory-approved system.

From 10/2009 to 05/2010, 36 patients with EOC were included in the study. Approximately 7.5 ml of peripheral blood were processed using the Cell-Search System (Veridex), which uses antibodies to epithelial cell adhesion markers and immunomagnetic capture. In 20 patients blood samples were obtained during chemotherapy for recurrent-advanced EOC, in 16 patients before debulking surgery and 9 of them had a second postoperative blood drawn. One patient had one blood draw preoperatively and three ones during chemotherapy.

CTCs were detected in 8 out of 20 patients (40%) with recurrent-advanced EOC (mean=4.7 CTCs/ml, maximum=26.1 CTCs/ml). Six out of 16 (37.5%) EOC patients showed CTCs presence before surgery (mean=2.2 CTCs/ml, maximum=11.8 CTCs/ml). Interestingly, the patient with 4 blood draws showed CTCs disappearance after 3 and 5 cycles of treatment, when she attained a complete clinical response.

Through an automated system we have demonstrated CTCs presence either in treatment-naive or in recurrent EOC patients. The disappearance of CTCs during the treatment, even if in only one patient, seems to be correlated with response to chemotherapy and may indicate a possible value of CTCs quantification as predictive marker. Further studies are warranted to validate these preliminary findings and to evaluate CTCs significance as an indicator of therapeutic decision making.
RISK OF MALIGNANCY INDICES IN DETECTION OF BORDERLINE OVARIAN TUMORS

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The aim of this study was to evaluate the ability of four malignancy risk indices (RMI1, RMI2, RMI3, and RMI4), to detect borderline ovarian tumors.

This is a retrospective of 50 women admitted to the Department of Obstetrics and Gynecology of Gulhane Military Medicine Academy and diagnosed as borderline ovarian tumor. To diagnose borderline ovarian tumors, the sensitivity, specificity, and positive predictive values of RMI1, RMI2, RMI3, and RMI4 are obtained.

This study confirms that, the accuracy of the RMI4 was better than RMI1, RMI2 and RMI3. The RMI4 at a cutoff level of 200 yielded a sensitivity of 56%, a specificity of 82%, a positive predictive value of 75.7%, a negative predictive value of 66.1%, and an accuracy of 69%.

We concluded that, in the discrimination between benign and borderline pelvic disease, risk of malignancy index 4 is useful and is able to identify borderline pelvic masses efficiently to optimize therapy.
SIGNIFICANCE OF SYSTEMATIC LYMPHADENECTOMY IN PATIENTS WITH MACROSCOPIC STAGE I EPITHELIAL OVARIAN CARCINOMA

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Background: The significance of systematic lymphadenectomy in patients with ovarian carcinoma is controversial.

Objective: To investigate the significance of systematic lymphadenectomy in patients with macroscopic stage I epithelial ovarian carcinoma.

Methods: Eighty-nine patients with macroscopic stage I epithelial ovarian carcinoma were treated in Peking University First Hospital from January of 1994 to December of 2005. They were divided into two groups based on whether they had undergone lymphadenectomy or not. Forty-five patients who had not undergone lymphadenectomy were assigned into the first group and the other forty-four patients who had undergone lymphadenectomy were assigned into the second group. The clinicopathological features were compared and factors associated with survival were identified.

Results: Nine patients were lymph node positive in the second group. The lymph node metastatic rate in patients with poor differentiated ovarian carcinoma was higher than those with well or moderate differentiated carcinoma. The 2, 5 and 10 year overall survival rate was 93.3%, 91.1% and 83.7% respectively in the first group, and that was 95.4%, 90.9% and 78.5% in the second group. The prognosis was not statistically different between the two groups. Cox regression analysis identified only stage was independent prognostic factor for the patients who had undergone systematic lymphadectomy. The prognosis in patients with stage I A, I B and I C is better than that in stage III C.

Conclusion: The lymph node excision could not improve the prognosis of these patients. The significance of second surgery for patients without surgical staging at first operation needs more investigation.
OVARIAN CANCER IN THE “DR. SALVATORVUIA” CLINICAL OBSTETRICS AND
GYNECOLOGY HOSPITAL ARAD DURING THE 2000-2009 PERIOD

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The present study about the frequency of ovarian cancer covers the 2000-2009 interval, the data being collected from the Histopathology Exams (HPE) registers. During the 2000-2009 period, 83,006 patients were admitted in our hospital and 16,063 HPEs were performed (19,35% of all patients). Ovarian cancer was discovered in 82 cases, representing 6,58% of all genital cancers (1246 cases).

The fragments sent to the histopathology departments were obtained by biopsies in 7 cases (8,54%) and from surgical specimens in 75 cases (91,46%).

Seventy-eight cases (95,12%) were primary ovarian cancers, while four patients (4,88%) had ovarian metastases (one with gastric, colic or mammary origin, one originating in the small intestine and two with unknown origin). Of the 78 primary cancers, 68 were carcinomas (87,18%), three were yolk-sac tumors (3,85%), two were tumors of the granulosa (2,56%), one was a disgerminoma (1,28%), one was a malignant mature cystic teratoma with carcinoma components (1,28%), one was a malignant immature teratoma (1,28%), one was a Seroli-Leydig tumor (1,28%) and one was an adenofibroma with a carcinomatous component (1,28%).

The mean age of the group was 51,46±14,28 years.

Ovarian cancer still remains a serious public health issue, thus demanding a well organized screening programme.
A PHASE 2 STUDY OF PEMETREXED IN COMBINATION WITH CARBOPLATIN IN PATIENTS WITH PLATIN-SENSITIVE RECURRENT OVARIAN OR PERITONEAL CANCER

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Background: Carboplatin (Cb)-based combinations are commonly used in PSOC. Pemetrexed at 500 mg/m² with carboplatin at an AUC of 6 was found feasible.

Aims: The primary objective was to determine overall response rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary objectives included progression free survival (PFS), overall survival (OS) and toxicity.

Methods: Patients with PSOC defined by recurrence >6 months after 1st-line therapy, measurable disease, ECOG PS 0-2, adequate organ function, age > 18 were eligible. In August 2008, protocol was amended to allow pts who had received 2 prior platin-based therapies. Cb AUC 6 was infused over 30 minutes, 30 minutes after a 10-minute infusion of pemetrexed 500 mg/m².

Results: Sixty-six patients were accrued (June 2007-Feb 2009). Sixty-one patients were eligible for response. ORR was 32.8% (95% CI = 21.3% to 46.0%). There were 20 responders (1 CR, 19 PR, 32.8%). Median PFS was 9.4 months (95% CI 8.3 to 11.1); 18.0% censoring. Median OS was not reached (censoring rate of 67.2%). 12-month survival rate was 86% (95% CI 74% to 93%). There was 1 drug-related death (sepsis). The most common G3/4 toxicities were nausea (6.1%), vomiting (6.0%), platin hypersensitivity (9.1%), neutropenia (39.3%), leukopenia (9.1%), and thrombocytopenia (24.2%).

Conclusions: Cb AUC 6 and pemetrexed 500 mg/m² is well tolerated. The activity seems to be in the range of the other proven carboplatin-based doublets in PSOC pts. Defining the platinum-based combination with the best therapeutic index would require a prospective phase III study.
TREATMENT OF BORDERLINE OVARIAN TUMOURS WITH GONADOTROPIN RELEASING HORMONE ANALOGUES

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Objectives: The aim of this prospective study was to evaluate the pathologic response to treatment with GnRH agonists in patients with prognostically negative borderline ovarian tumours.

Patients and methods: From 2003 to date, 7 were enrolled. All patients underwent laparoscopic conservative peritoneal staging and had at least one of the following negative prognostic factors: non-optimal cytoreduction, advanced stage, micropapillary feature, invasive peritoneal implants, microinvasive histotype. GnRH receptors were demonstrated in all surgical specimens. Treatment consisted in GnRH agonists given monthly for at least 3 months. After treatment, all patients underwent laparoscopy.

Results: Median age was 28 years (21-38 years); 86% of patients were nulliparous. Stage distribution was: 2 IC; 1 IIB; 1 IIIA; 1 IIIB; 2 IIIC. Macroscopic residual disease was present in 43% of cases, and other pathologic negative prognostic factors in 71%. Mean treatment time was 17 weeks (13-37). Treatment was well tolerated with patients reporting only mild hot flashes. All patients underwent laparoscopy after treatment. We observed 2 complete responses (28.5%), 2 partial responses (28.5%), 3 stable disease (43%). All patients but one had no macroscopic disease after surgery. Mean follow-up was 32 months (11-58). 2 patients relapsed, with a mean DFI of 26 months (6-51). All patients are currently alive without evidence of disease.

Conclusions: Prognostically negative borderline ovarian tumours don't have a definitive adjuvant therapy and GnRH analogues may be a viable option. Our preliminary study showed some objective response in 57% of patients, without a negative impact on quality of life.
EXPRESSION OF COX-2 AND VEGF-C IN PERITONEAL METASTASES OF OVARIAN SEROUS CARCINOMA AND THEIR RELATIONSHIP TO LYMPH NODE STATUS

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Background: Previous studies did not identify vascular endothelial growth factor-C (VEGF-C) expression and lymphatic vessels density (LVD) in primary tumor, as significant variable predicting nodal metastases and overall survival in ovarian cancer patients. Possible relationship between cyclooxygenase-2 (COX-2) and lymphangiogenesis is not clear. The aim of our study was to evaluate COX-2 and VEGF-C expression in peritoneal metastases of serous ovarian carcinoma and their possible role in lymphangiogenesis and lymph node metastases as well as their correlation with clinicopathological parameters and overall prognosis in ovarian cancer patients.

Methods: Formalin-fixed, paraffin-embedded specimens from 61 patients with serous ovarian carcinoma, other than FIGO stage I, were selected. Tissue sections of primary tumors and their consecutive peritoneal metastases were immunohistochemically examined for VEGF-C and COX-2 expression. LVD was assessed in peritoneal metastases by counting peritumoral vascular spaces, immunostained by lymphatic endothelium marker D2-40.

Results: A highly significant correlation between high VEGF-C expression, but not COX-2 level, in peritoneal metastases and both LVD (P=0.0006) and positive lymph node status (P=0.002) were found. Combined high COX-2/VEGF-C expression in peritoneal metastases was associated with poorer survival of the patients (P=0.03). However, no association between COX-2 or VEGF-C, expressed by primary or metastatic tumors and clinicopathologic parameters were observed.

Conclusion: Our results suggest that VEGF-C levels of the peritoneal metastases, but not of the primary tumor, play an important role in lymphatic spread of ovarian serous carcinoma, other than FIGO stage I. COX-2 do not contribute to lymphangiogenesis and lymph node metastasis.
MULTIPLE BOWEL PERFORATIONS ASSOCIATED WITH NEOADJUVANT CHEMOTHERAPY IN A PATIENT WITH ADVANCED EPITHELIAL OVARIAN CANCER

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Background: Bowel perforation is a rare complication of chemotherapy in patients with advanced or recurrent epithelial ovarian cancer. It may be due to necrosis of tumoral masses of involved bowel loops or may be correlated to a necrotizing enterocolitis during neutropenia. Few cases of colonic perforation as a serious side effect of taxane based chemotherapy have been reported previously.

Case: We present a 59 year-old woman, case of advanced epithelial ovarian cancer with extensive pelvic tumor and severe dense adhesions of small and large bowel to the huge pelvic tumor and a hard unresectable omental cake. Due to unsuccessful primary cytoreductive surgery, neoadjuvant chemotherapy was started. After second course of chemotherapy with carboplatin and paclitaxel, she developed spontaneous perforations of sigmoid colon, ascending colon and terminal ileum. To our knowledge, this is the first report of multiple spontaneous intestinal perforations with neoadjuvant chemotherapy for epithelial ovarian cancer.

Conclusion: Such life threatening bowel complication should be considered when deciding neoadjuvant chemotherapy in advanced epithelial ovarian cancer especially in patients with evidences of extensive bowel involvement with tumor.
THE SIGNIFICANCE OF SEROUS OVARIAN CANCER HISTOLOGY ON LYMPH NODE METASTASES

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Background: The aim of this retrospective study was to evaluate the incidence and the distribution of nodal metastases in relation to the histological subtypes (serous and non-serous) in epithelial ovarian cancer.

Methods: Patients were treated primarily with upfront surgery, including pelvic and para-aortic systematic lymph node dissection up to the level of the left renal vein, prior to any kind of chemotherapy administration. Dissected lymph nodes were meticulously marked according to their location in the pelvic and para-aortic regions. Patients were classified, according the tumor histology, into two groups; serous (including all cases of mixed histology with a serous component) and non-serous group.

Results: Inclusion criteria fulfilled 145 patients; 61 and 84 patients had serous and non-serous histology, respectively. Positive lymph nodes were found in 62.3% (38/61) and 13.1% (11/84) of patients in the serous and non-serous histology groups, respectively. There was no difference in positive node distribution between two regions (pelvic and para-aortic regions, including below and above the inferior mesenteric artery). The most common site for positive nodes was the para-aortic region with positive nodes in 81.6% (31/38) and 90.9% (10/11) of patients in serous and non-serous group, respectively.

Conclusions: Our results emphasize the predicting significance of epithelial ovarian cancer serous histology in lymph node metastases incidence. However, serous versus non-serous histology has no influence on positive lymph node distribution in the pelvic and para-aortic regions.
EARLY STAGE EPITHELIAL OVARIAN CANCER: WHAT DETERMINES THE OUTCOME?

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Background: We analyzed the data on women with early stage ovarian cancer to determine predictors of relapse and survival.

Methods: Between January, 1991 and November, 2008, 197 women were diagnosed to have FIGO stage I-II ovarian cancer. Patients' median age was 47 years (range, 14 to 78), stage I-79.2%, II-20.8%. Histopathology: serous -50.3%, mucinous - 23.9%, endometroid - 10.2%, clear cell- 4.6%, undifferentiated- 3% and adenocarcinoma, - 8.1%. Histologic grade I-II: 52.9% and grade III-47.2 %. Following surgery 47 women were advised observation, remaining received chemotherapy using either cisplatin + cyclophosphamide, n=79, paclitaxel + carboplatin, n=40 and carboplatin alone, n=31.

Results: 33 (16.8%) women relapsed at a median of 21 months. Stage (I vs II, p< .001), Grade (I+II vs III, p< .001), basal serum CA-125 (≤ 160 vs >160 U/ml, p< .007), Hb (≤10 vs >10 G/dl, p< .004), serum albumin (≤ 3.5 vs >3.5 G/dl, p< .002), residual disease (nil vs present, p< .0001) and low vs high risk, (p< .01) were important predictors of relapse. At a median follow up of 47 months, estimated 5 and 10 years survival is 90% & 85% for stage I and 73% & 54% for stage II, respectively. Corresponding figures for disease free survival at 10 years are 76% and 73%.

Conclusions: Present study confirm excellent outcome for women with early stage ovarian cancer. Identification of women, who can be spared of adjuvant chemotherapy based on molecular markers, would be possible areas of research in future studies.
A SUBGROUP WITH BRCA1 PROMOTER HYPERMETHYLATION IS ASSOCIATED WITH POOR DIFFERENTIATED, SEROUS, ADVANCED OVARIAN CANCER

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Objective: BRCA1 promoter hypermethylation and reduced expression of BRCA1 protein has been found in sporadic ovarian carcinomas, suggesting an epigenetic means of BRCA1 inactivation.

There is little evidence concerning tumor characteristics and survival data in ovarian cancer patients with BRCA1 hypermethylation. The objective of this study was to analyze a cohort of ovarian cancer patients for aberrant methylation in BRCA1 promoter region and to correlate the data on the BRCA1 methylation status with the clinical factors and also to analyze the impact of BRCA1 promoter hypermethylation on disease free and overall survival.

Methods: We determined the methylation status in BRCA1 promoter region in tumor tissues from 125 ovarian cancer patients and in tissue from 26 controls with benign ovarian neoplasms by using a methylation-specific real time PCR. All samples were obtained from the systematic Tumor bank Ovarian Cancer at Charité University Hospital, Berlin.

Results: BRCA1 hypermethylation was found in 12% of the ovarian cancer tissue and in none of the controls (p=0.001). All tumors with hypermethylation were serous adenocarcinomas diagnosed with advanced FIGO stage and 73.3% of them had high grading. The group with hypermethylation did not show any considerable difference in DFS and OS.

Conclusion: We confirmed the presence of a subgroup with high methylation in BRCA1 promoter region among ovarian cancer patients. BRCA1 hypermethylation was associated with poor differentiated, serous, advanced ovarian cancer.

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WEEKLY CLINICOPATHOLOGICAL MEETING: APPLICATION AND IMPACT ON MANAGEMENT OF OVARIAN CANCER

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Background: We analyzed the case records of patients reviewed in weekly clinicopathological (CP) meeting to determine the impact on overall management.

Patients and methods: Between 1st January, 2005 and June 30, 2009, 355 cases (out of 708 registered in the same period) were discussed in the weekly CP meeting. Clinical and radiological information was presented by clinical residents and Slides were discussed by pathology residents in presence of consultants. Reasons for inclusion of cases for discussion included- confirmation of diagnosis (27%), different tumor type in same patient (2.5%), tumor grading (2.3%), to confirm primary site of malignancy (31%), requested by pathologist (2.5%), rare diagnosis (5%) and review of immunohistochemistry in 5% of cases. A change in the pathological diagnosis was considered Major if it lead to a change in the treatment plan and Minor if treatment plan remained unchanged.

Results: There was a change in the treatment plan of 12 of 355 patients (3.4%). In 10 patients (2.8%), there was a minor discrepancy in the pathological diagnosis. Primary site of malignancy was identified as different (based on pathological findings alone) in 6 patients. In 6 cases, the meeting was inconclusive due to poor slide quality and inadequate tissue available.

Conclusion: A weekly clinic-pathological meeting helps in improving patient's management by improving diagnostic performance. It is also a good source of resident training. This should become routine in centers treating cancer patients.
CLINICAL OUTCOMES FOR MICROSCOPIC FALLOPIAN TUBE AND OVARIAN CARCINOMAS DIAGNOSED IN BRCA MUTATION CARRIERS UNDERGOING RISK-REDUCING SALPINGO-OOPHORECTOMY

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Objective: To evaluate overall clinical outcomes for microscopic fallopian tube and ovarian cancers diagnosed in patients with BRCA1/2 mutations undergoing risk-reducing salpingo-oophorectomy.

Methods: Cases of microscopic ovarian and fallopian tube cancers were identified by reviewing records for patients at M. D. Anderson Cancer Center (MDACC) that had undergone risk-reducing salpingo-oophorectomy (RRSO) due to germline BRCA1 or BRCA2 mutations.

Results: As of March 2010, 129 MDACC patients (73 women with BRCA1 mutations and 56 women with BRCA2 mutations) have undergone RRSO. In these 129 RRSOs, 7 microscopic cancers were identified (5.4%). Seven microscopic fallopian tube or ovarian cancers were identified in BRCA1 mutation carriers undergoing RRSO, zero cases were diagnosed in BRCA2 mutation carriers. Of these 7 cases, 6 cases of high grade serous carcinoma (HGSCa) and 1 case of microscopic ovarian serous carcinoma with low malignant potential were diagnosed. From 6 HGSCa cases, 4 cases involved the fallopian tube mucosa and one case was confined to the ovary. The sixth case involved HGSCa in peritoneal washings only. Six of the seven cases were followed with surveillance only. In the one case with positive peritoneal washings, chemotherapy was administered, followed by a negative second-look laparoscopy. With a mean follow-up time of 43.6 months (range 11 - 104 months), all of these women are currently without evidence of disease.

Conclusions: These cases illustrate that overall clinical outcomes are encouraging for microscopic ovarian and fallopian tube cancers in BRCA1 mutation carriers, even for patients that do not receive chemotherapy.
CLINICAL, PATHOLOGICAL AND BIOMARKER CHARACTERIZATION OF PATIENTS WITH ADVANCED OVARIAN CANCER ACCORDING TO THE AGE


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Objective: There are some studies suggesting that older patients diagnosed with ovarian cancer have worse outcomes. In this prospective study we analysed the correlation of age with clinicopathological parameters and the expression status of 7 biomarkers in five different age groups of patients with advanced ovarian cancer.

Methods: Tumour samples were collected prospectively from 91 selected women which undergone surgical interventions because of primary or recurrent ovarian cancer. Clinical data included patients´ age, FIGO-stage, histological grade, ascites and postoperative tumor residuals as relevant prognostic factors. For the immunohistochemistry a tissue microarray (TMA) was performed and the expression of Ki-67, HER-2/new, Estrogenreceptor (ER), Progesteronreceptor (PR), p53, CA 125 and VEGFR1 was investigated.

Results: Patients were divided into 5 groups: < 35 years, 36 - 50 years, 51 - 65 years, 66 - 75 years and > 76 years. No difference in survival was observed between the age groups. No significant difference in the expression levels of the analysed biomarkers were evaluated, where ER and CA 125 expression decreased in older patients and HER-2 and PR showed in generally a negative expression. No one of the investigated clinicopathological parameters and biomarkers correlated independently with survival in the overall study population.

Conclusion: In our study patients with advanced ovarian cancer have a similar clinicopathological characteristics, biomarker expression status and postoperative survival. Further studies on larger patients groups are needed to detect subgroups of ovarian cancers with different prognostic and predictive outcome according to the age.
RESEARCH ON BRCA1 /2 MUTATIONS IN PATIENTS WITH HEREDITARY OVARIAN CANCER AND PATIENTS WITH SPORADIC OVARIAN CANCER IN MAINLAND CHINA

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Objective: All exons of BRCA1/2 were analyzed by DHPLC+DNA direct sequencing in 39 patients with hereditary ovarian cancer and 32 patients with sporadic ovarian cancer to assess the prevalence of BRCA1/2 mutations and the clinical features in patients with ovarian cancer from different genetic background.

Results: The rate of pathogenic BRCA mutations was 28.2%, with 22.5% for BRCA1 and 5.6% for BRCA2 (P=0.004). The differences of BRCA mutation between patients with hereditary ovarian cancer and patients with sporadic ovarian cancer were statistically significant (41.0% vs. 12.5%, P=0.008). Sixteen different sites of pathogenic mutations were detected and 50% of them were novel. BRCA1 5589del8 was identified in three independent families and may be partial “founder effect” in Chinese people. Both exons 11 of BRCA1/2 have been found to be hotspots of germline mutations. In pedigree analysis, 11 out of 42 female members from the four families were detected to have pathogenic BRCA mutations. Some of them were unique for the family or were not reported in BIC database. The patients with ovarian cancer from these families had younger onset age, higher grades and advanced FIGO stages tumors, but better sensitivity to chemotherapy and longer disease-free survival intervals.

Conclusions: In mainland China, 28.2% of patients with ovarian cancer have BRCA gene mutation. The BRCA mutation rate of patients with hereditary ovarian cancer is higher than that in sporadic ones. BRCA1 gene may make greater impact on ovarian cancer in Chinese population. The patients with pathogenic BRCA mutations have better prognosis.
THE EFFICACY OF HYALURONIC ACID ON ADHESION FORMATION AND TUMOR RECURRENCE

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Aims: Perioperative peritoneal trauma activates a cascade of peritoneal defense mechanisms responsible for postoperative adhesion formation. The same cascade seems to play a role in the process of intra-abdominal tumor recurrence. The aim of the present study was to evaluate the efficacy of a hyaluronic acid solution on adhesion formation as well as on tumor recurrence after surgery in an ovarian cancer model.

Methods: Standardized peritoneal trauma was induced in 30 female SCID-mice (NOD.CB17-Prkdcscid/J) in the right abdominal wall. Ovarian carcinoma cell line SCOV3.ip was injected intraabdominally to induce specific tumorload. The animals were randomly assigned to 3 groups of 10 mice. One group was treated by intraabdominal instillation with hyaluronic acid, one with saline and another one received no instillate (control). After 21 postoperative days all animals were killed and relaparotomized. Areas of adhesion formation and tumor growth were measured by scores according to location and size. Tumor weight was gaged and tumor samples were taken for histological studies.

Results: Statistically significant differences were found between the treatment and the control groups for any adhesion parameter (ANOVA, p< 0.05). Adhesion scores were lower in mice treated with hyaluronic acid and saline compared to the control, with hyaluronic acid being more effective than physiologic saline. Concerning tumorload, hyaluronic acid and saline reduced tumor cell growth significantly (p< 0.05).

Conclusions: Hyaluronic acid is effective in reducing postoperative adhesions and in preventing tumor cell growth in an ovarian cancer model. It may be useful in gynaecological oncology.
EXPRESSION PROFILE AND MUTATION OF EGFR GENE IN EPITHELIAL OVARIAN CANCER

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Objective: To investigate the correlation between EGFR expression profile, EGFR gene mutation and clinicopathological characteristics, in order to provide evidence for the treatment of ovarian carcinoma with EGFR-TKIs.

Methods: The 96 patients with FIGO stage III and IV epithelial ovarian cancer were included, who were treated in Sun Yat-Sen University Cancer Center during Jan 2003 to April 2009. The EGFR expression was detected in paraffin-embedded cancer tissues with immunohistochemistry assay. For the cases with positive EGFR staining, real-time PCR was employed to detect EGFR gene mutation. The correlation between EGFR expression profile with gene mutation status and clinicopathological characteristics was analyzed by chi-square test.

Results: EGFR expression rate was 78.2% in all cases with different levels. Patients who were with stage III disease, with poor differentiated tumor, ascites cytology positive and underwent suboptimal cytoreduction presented high expression level of EGFR in their tumor tissues. Four specimens harbored tyrosine kinase domain mutation and were in-frame deletion of 15 nucleotides (2235del15; E746_A750del) in exon 19 of EGFR gene. These four patients with the mutation presented similar clinicopathological characteristics, they were older than 50 years at diagnosis and had FIGO stage IIIc, poor differentiated diseases with high expression level of EGFR.

Conclusion: In most cases with epithelial ovarian cancer, EGFR expression were positive. The old patients with high level of EGFR expression in advanced and poorly differentiated ovarian carcinomas are likely to harbor EGFR mutation E746_A750del, and they might have better response to EGFR-TKIs.
PLATINUM RESISTANT EPITHELIAL OVARIAN CANCER- ISSUES OF QUALITY OF LIFE AND COST-EFFECTIVE RATIO

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The treatment outcome the platinum potentially resistant recurrent epithelial ovarian cancer is often very poor. No work is done so far to observe benefit in terms of quality of life and cost-effective ratio of different mono therapy in second line setting in Indian patients.

From 2006 January to 2009 January, 35 platinum resistant advanced epithelial ovarian cancer cases were selected for a prospective study.

Both refractory (6 cases) and resistant cases (29 cases) were randomized to receive monotherapy of Inj gemcitabine (9 cases), Inj topotecan (9 cases), Inj Doxorubicin (8 cases), Inj Docetaxel (6 cases) or oral etoposide (3 cases). Response rate was highest in Doxorubicin (37%, 3 cases) followed by gemcitabine, topotecan and docetaxel (33.3%, 3 cases in each group). 1 case in Etoposide group was responder. There was no significant difference in PFS (4 to 7 months) or OS (10 to 17 months) in any of the groups. City Of Hope Quality of Life Instrument -- Ovarian Cancer Patient Version was used to calculate quality of life which was found to be better in doxorubicin and gemcitabine group. Quality adjusted life year (QALY) showed cost effective ratio (CER) to be best in etoposide followed by doxorubicin and gemcitabine group with incremental cost effective ratio (ICER) higher in gemcitabine than in doxorubicin in comparison to etoposide.

Doxorubicin was found to have best efficacy with good QoL and ICER. Molecular profiling may be important to increase PFS and OS as is done in recent Chinese study.
MANAGEMENT OF EXTRAVASATION IN OVARIAN CANCER PATIENTS RECEIVING TRABECTIDIN

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Trabectidin is a new antineoplastic agent, with proven activity against ovarian cancer and sarcomas, which has been recently introduced in clinical practice. Infusion modality, extravasation and following procedures are not yet well established. The aim of the present study is to report our experience with trabectidin extravasation in ovarian cancer patients.

Patients and methods: Between January and May 2010, 15 patients were treated with trabectidin at the Gynecologic Oncology Unit of the Department of Gynecology, Obstetrics and Neonatology of the University of Bari, as fifth line chemotherapy for recurrent ovarian carcinoma. The schedule used was 1.3 mg/mq trabectidin diluted in 1000 ml saline solution with antiemetic premedication with dexametasone and ondansetron.

Results: No patients developed allergic reaction to trabectidin. Four patients had infusion of trabectidin thorough a central porth and catheter, while 11 had infusion through a peripheric venous access. Among these patients 3 had drug extravasation, all at the first administration. In all cases trabectidin infusion was stopped, the vein was flashed with saline solution and 25 mg dexametasone. Ice cubes were applied on the skin and later, treatment was continued with a cortisonic cream applied twice daily for 10 days. Extravasation lesions resolved in all patients in the next 3 weeks without any sequelae. All these patients continued chemotherapy thorough a central access.

Conclusions: The administration of trabectidin is safe when given thorough a central access. Infusion thorough a peripheric vein should not be performed given the high risk of extravasation lesions, which anyway resolve with appropriate management.
THE CHANGES IN FOXP3+REGULATORY T CELL EXPRESSION BEFORE AND AFTER RECURRENCE OF OVARIAN CANCER


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Objectives: Epithelial ovarian cancer (EOC) is a devastating disease due to its high recurrence rate. Recently, there have been many studies on the relationship between cancer and immune system, especially on the role of regulatory T cell (Treg) in the development of cancer. Treg is a subsets of lymphocyte which control the immune reaction by inhibiting cytotoxic T cell response. Transcription factor Foxp3 has an important role in the differentiation of Treg. We evaluated the expressions of Foxp3+Treg in the primary and recurrent EOC tissue in order to elucidate the role of Treg in recurrence of EOC.

Materials and methods: Twenty two patients received both primary debulking and secondary surgery after recurrence at Asan Medical Center. Immunohistochemical staining was done with anti-Foxp3 antibody on the formalin-fixed and paraffin embedded pathology slides.

Results: Four patients(18%) showed increased expression of FoxP3 in the recurrent cancer tissues (Fig 1,2). 2 patients(9%) showed increased expression in the both of primary and recurrent cancer tissues. In the other 2 patients showed increased expression of FoxP3 in the primary cancer tissues only. Other 14 patients did not expressed FoxP3.

[Case no. 20. Primary cancer tissue : FoxP3 (-) ]

[Case no.20. Recurrent tissue : FoxP3 (+) (brown)]

Conclusion: We can assume that Treg has an effect on the recurrence of ovarian cancer. Further studies are required.
M2 MACROPHAGES IN THE ASCITES OF ADVANCED EPITHELIAL OVARIAN CANCER PROMOTE TUMOR PROGRESSION VIA STAT3 ACTIVATION

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Peritoneal macrophages are actively involved in the regulation of inflammation, immune response, and tumor growth in peritoneal cavity. Macrophages in the ascites from advanced epithelial ovarian cancer (EOC) are polarized to M2 immunosuppressive phenotype and involved in tumor progression by modulating the tumor microenvironment. However, the cell-to-cell interaction between peritoneal macrophages and ovarian cancer cells is still unclear. This study focused on the activation of signal transducer and activator of transcription 3 (Stat3) which is a critical signal transduction molecule at a point of convergence for numerous oncogenic signaling pathways as well as controlling the M2-polarization of macrophages. Immunohistochemistry using CD163 as a marker for M2 macrophages demonstrated that most macrophages in the ascites of EOC were polarized to the M2 phenotype. EOC ascites stimulated the proliferation of SKOV3 cells, a human ovarian cancer cell line, and immortalized human ovarian surface epithelial cells. It also induced the activation of Stat3 in THP-1 macrophages. In addition, the co-culture of M-CSF-primed M2 macrophages, but not GM-CSF-primed immature macrophages induced a strong Stat3 activation in SKOV3 cells. The expression of cyclin-D1 in SKOV3 cells was up-regulated by a co-culture with macrophages. The cyclin-D1 up-regulation in SKOV3 cells was significantly inhibited after blocking Stat3 by small interfering (si)RNA in the macrophages, thus indicating that Stat3-mediated M2 polarization of macrophages in the ascites is important for tumor cell survival. These results indicate that the cell-to-cell interactions between macrophages and EOC cells through Stat3 activation are positively involved in EOC progression.
PROGNOSTIC FACTORS AND REPRODUCTIVE OUTCOMES OF BORDERLINE OVARIAN TUMORS: A REVIEW OF 186 PATIENTS

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Objective: To determine the clinic pathologic characteristics of borderline ovarian tumors and to evaluate prognostic factors and fertility outcomes after conservative surgery.

Methods: A retrospective study included 186 patients with borderline ovarian tumors who were treated from 1990 to 2007 in Peking Union Medical College Hospital and were followed-up at least six months after surgery. The influence of clinic pathological characteristics upon recurrence and death were analyzed by independent sample t test, Chi-square test, Kaplan-Meier and Cox proportional hazard model.

Results: A total of 186 patients were enrolled. Median follow-up time was 44 months. One hundred and nine patients underwent conservative surgery, and seventy-seven patients underwent radical surgery. There were 31 relapses, only 3 of which died of disease. Multivariate analysis showed that surgery procedure, stage and pseudomyxoma peritonei was the independent prognostic factors affecting recurrence. Pregnant rate after conservative surgery is 36.4%.

Conclusion: The recurrence rate of conservative surgery was higher than that of radical surgery. However, conservative surgery is safe as it doesn’t lead to higher death rate.
CAVEOLIN-1 EXPRESSION IN LOW-MALIGNANT POTENTIAL (LMP) AND EPITHELIAL OVARIAN CANCERS (EOC)

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Background: Stromal Caveolin-1 (Cav-1s) may predict patient survival and disease recurrence in breast cancer patients. Epithelial and stromal Cav-1 expression in low-malignant potential (LMP; n=45) and ovarian cancers (EOC; n=89) has not been studied.

Methods: Cav-1, ER, PR, and EGFR expression was assessed by immunohistochemistry (IHC) in single slides. Epithelial Cav-1 (Cav-1e) expression was evaluated by H-score. Stromal Cav-1 (Cav-1s) expression was assessed as 0, negative; 1+, weak; 2+, moderate; 3+, strong. ER, PR, and EGFR expressions were evaluated per standard IHCs. Log rank tests and Wald tests were employed to assess the impact on survival based on Kaplan-Meier Product estimator and Cox Proportional Hazard Regression.

Results: Cav-1s was expressed (> +1) in 98% and 99% of LMP and EOC, respectively. Cav-1s was similarly expressed in serous and non-serous LMP cases (P=0.8). Cav-1s expression varied in serous (70%), mucinous (80%), endometrioid (64%), and other EOC (67%) cases. Cav-1e was found in 56% and 44% of LMP and EOC, respectively. Most serous LMP were Cav-1e, ER and PR positive while non-serous LMP were negative for these markers (P< 0.005). Cav-1e expression was similar in serous (45%), mucinous (47%), endometrioid (43%), and other EOC (44%) cases. In univariate analysis, PR+, ER+/PR+, Cav-1e+/ER+, and Cav-1e+/PR+ predicted good outcome (P< 0.05), but in the multivariate analysis, only grade, stage, performance status and ER+/PR+ predicted survival.

Conclusions: While Cav-1e expression varied in LMP and EOC, high Cav-1s was observed in both LMP and EOC cases with no value as a prognostic marker.
WHAT VALUE DOES THE RISK OF MALIGNANCY INDEX (RMI) HAVE IN PATIENTS WITH NON-SEROUS EPITHELIAL OVARIAN CANCERS?

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Introduction: The Risk of Malignancy Index (RMI) is widely used pre-operatively to distinguish patients with pelvic masses that are likely to be malignant from those that are likely to be benign. While RMI is well established for identifying serous cancers of the ovary, we wanted to examine whether it was able to perform well in patients who had clear cell and endometrioid histologies.

Methods: Retrospective case note analysis of 100 patients with clear cell and 100 with endometrioid adenocarcinoma of ovary between 2002 & 2008. The RMI1 score was calculated for each patient.

Results: A large proportion of cases were excluded due to missing data from notes and there were 33 cases of endometrioid adenocarcinoma (EAC) and 20 cases of clear cell cancer (CCC) analysed.

Using a cut-off of 200, the RMI correctly identified 27/33 EACs and 15/20 CCCs. This gives a sensitivity of 82% (95% CI: 66-99) for EAC and 75% (95% CI: 53-89) for CCC, comparable to previously published studies.

Conclusion: RMI1 appears to be able to identify cases of malignancy in both endometrioid and clear cell cancers of the ovary.
BRCA1- ASSOCIATED OVARIAN CANCER - CLINICAL FEATURES AND RESPONSE TO TREATMENT

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Introduction: Mutations of BRCA1 supresor genes increase the risk of the ovarian cancer from 1,5% to 25-50%. The literature data, regarding prognosis and chemosensitivity among those patients are conflicting. The most authors suggest better response for platinum-based chemotherapy, comparing to non-carriers.

Material and methods: Thirty eight BRCA1 mutation carriers were treated for ovarian cancer in Center of Oncology, Cracow Department between 2001 and 2008. Medium age of patients was 49 years. FIGO stage II ovarian cancer was found in 10(26,3%) patients, stage III in 26(68,5%) patients and stage IV in 2(5,2%) patient. The prevalent histological type of cancer was endometrial adenocarcinoma - 18(50%) of patients; the serous adenocarcinoma was diagnosed in 13(34,2%) patients. Complete debulking was achieved in 14(36,8%) patients; in 24(63,2%) patients residual disease was left in abdominal cavity. All 38 patients were treated with adjuvant platinum-based chemotherapy. Response to treatment was evaluated by physical examination, computed tomography and CA125 level.

Results: Complete response (CR) was obtained in 14(36,8%) patients, partial response (PR) in 17(44,7%) patients, stable disease (SD) in 2(5,3%) and progressive disease in 5(13,2%) patients. Overall response rate (ORR) was 86,8% in the study group. Medium time to progression (TTP) was 9 months.

Conclusions: The ovarian cancer advancement and histology in the study group was similar to others series, seen in the literature. However, earlier onset of the disease and better response for chemotherapy in HOC group were noticeable.
OUTCOME AND RISK FACTORS FOR RECURRENCE IN MALIGNANT OVARIAN GERM CELL TUMORS: A MITO-9 RETROSPECTIVE STUDY

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Aims: To investigate the outcome of patients with malignant ovarian germ cell tumors (MOGT) and to define the risk factors for recurrence.

Methods: A total of 123 patients with MOGT were retrospectively reviewed. Eighty-one patients had primary treatment in a MITO center, while the other 42 were referred for adjuvant chemotherapy or recurrence. The clinicopathologic characteristics were evaluated for association with relapse or death.

Results: Median age was 24 (range 11-76). Forty-nine (39.8%) had dysgerminomas, 35 (28.5%) had immature teratomas, 12 (9.8%) had mixed germ cell tumors, 26 (21.1%) had yolk sack tumors and 1 (0.8%) had embryonal carcinoma. FIGO stage was: 87 (70.7%) I, 3 (2.4%) II, 29 (23.6%) III and 4 (3.3%) IV. Fertility-sparing operation was performed in 92 patients while radical surgery was executed in 31 patients; 65.8% received adjuvant chemotherapy. Recurrence rate was 17.8% and the median time to recurrence was 9 months. Relapse rate was influenced by patient age (>45 years) (p=0.006), first treatment not in a MITO center (p=0.006) and positive peritoneal cytology (p=0.027). The 5-years overall survival rate was 88.8%, with a median follow up of 61 months. Non dysgerminomatous histology (p=0.033), yolk sack histology (p=0.001), capsular rupture (p=0.02), tumour on serosal surface (p=0.015), positive peritoneal cytology (p=0.024), advanced stage (p=0.004), age>45 (p=0.003), residual disease (p=0.018) have been found to affect the prognosis.

Conclusions: Prognosis of MOGT is excellent; non dysgerminomatous histology, yolk sack histology, tumor on surface and capsular rupture, positive cytology, advanced stage, older age, residual disease are the most important predictors of survival.
IS ADJUVANT CHEMOTHERAPY REQUIRED IN INCOMPLETELY SURGICALLY STAGED IA PURE OVARIAN DYSGERMINOMA (POD)? A MITO-9 RETROSPECTIVE STUDY

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Aims: Conservative surgery followed by platinum-based chemotherapy is considered the standard approach for POD, except for correctly staged IA. The aim of this study was to evaluate the outcome of IA POD patients with incomplete surgical staging in order to define the role of chemotherapy.

Methods: Data concerning primary treatment and recurrence were reviewed for 26 patients with stage IA POD treated in MITO centers.

Results: Median age was 22.5 years. Primary surgery was fertility sparing for 17 patients (65.4%) and radical surgery was performed in 9 patients due to older age or gonadal dysgenesis. Only five patients (19.2%) had complete surgical staging; 38.5% had lymph node dissection, 46.2% had peritoneal biopsies and/or omentectomy and 65.4% had peritoneal washing. Seven patients received adjuvant chemotherapy.

Overall recurrence rate was 11.5%; all recurrences occurred in the group submitted to incomplete staging procedure. No patients treated with adjuvant chemotherapy relapsed. One patient had pelvic recurrence, one relapsed in the abdominopelvic peritoneum and lymph nodes and the third recurrence was in peritoneum, lymph nodes and residual ovary. All patients with recurrence were cured by salvage therapy: 2 patients were treated by surgery plus chemotherapy and 1 only by chemotherapy. After a median follow-up of 100 months all patients are NED. Five patients opted for conception and delivered healthy infants, two with IVF with donor oocyte.

Conclusions: IA POD prognosis is excellent. Conservative surgery with a complete surgical staging is the gold standard. Patients with incomplete staging could undergo surgical restaging; chemotherapy should be reserved to relapse.
IS CLEAR-CELL EPITHELIAL OVARIAN CANCER A POOR PROGNOSTIC FACTOR?
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Objective: Compared with serous adenocarcinoma (SAC), clear cell carcinoma (CCC) often show chemo-resistance, which is suggested to lead to a poor prognosis. On the other hand, there have been several reports to indicate SAC and CCC had a similar prognosis. The present study is to compare the prognosis of the CCC with that of SAC who were treated at single Japanese hospital.

Methods: Between January 1984 and September 2008, a total of 457 ovarian cancer patients were treated at our hospital. Among them, 101 patients with CCC and 202 patients with SAC were identified. Overall survival (OS) and progression-free survival (PFS) were compared using the Kaplan-Meier method.

Results: Median age was 55 years for SAC and 52 years for CCC. Patients number of CCC were 65(65%) of stage I/II and 36 (36%) of stage III/IV, and those of SAC were 41(22%) of stage I/II and 159(78%) of stage III/IV, respectively. The cases who achieved complete surgery (RT=0cm) of the early-stage were 26 patients (63%) in CCC, and 54 patients (83%) in SAC (P=0.022). There were no significant differences of PFS and OS in stage I/II patients between CCC and SAC group. PFS and OS of stage III/IV CCC cases were poorer than those of SAC (p=0.006 and p<0.0001). Multivariate analysis showed that RT >1cm, histological type(clear), chemotherapeutic response (SD/PD) were independent predictors of poor prognosis of OS.

Conclusion: The present study confirmed PFS and OS of CCC patients were poorer in advanced-staged cases. However, early-staged CCC cases had a similar prognosis, compared with SAC.
DISPARITIES IN TREATMENT FOR EPITHELIAL OVARIAN CANCER IN A LARGE UNITED STATES POPULATION

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Background: Ovarian cancer (OC) is the deadliest gynecologic malignancy among women in the United States (U.S.). Previous studies have suggested that disparities in treatment exist among certain racial populations for OC, often leading to decreased survival.

Aim: The objective of this study is to identify demographic and clinical factors associated with not receiving standard treatment for ovarian cancer in a large U.S. population.

Methods: Demographic, treatment, health insurance, and provider information was collected for over 3000 women diagnosed with epithelial ovarian cancer in Northern California and New York State between 1998 and 2000. Factors associated with not receiving standard treatment for OC (surgery and chemotherapy according to stage-specific guidelines) were assessed using multivariate logistic regression modeling.

Results: A total of 2,382 women with epithelial OC were included in this analysis. Of these, 24% did not receive standard care. Demographic characteristics associated with not receiving standard care included black race (odds ratio [OR] 1.7, 95% CI 1.1-2.6), and increasing age (ages 65-79 yrs, OR=3.2, 2.1-4.7; ages 80+ yrs, OR=11.6, 7.2-18.5). Advanced stage was also associated with not receiving standard care. Additionally, women who did not have insurance (OR=3.6, 1.8-7.4) and those who had never seen a gynecologic oncologist (OR 2.4, 1.9-3.0) did not receive standard care.

Conclusions: Our results suggest that several disparities exist in OC care in the United States. These treatment disparities may be associated with decreased survival often seen in these populations. Further assessment is needed to determine causes for the lack of standard treatment in these populations.
FEASIBILITY OF MUSICAL PRAYER TO ENHANCE THE QUALITY OF SLEEP IN PERSONS WITH OVARIAN CANCER

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Background and aims: “Quality of Sleep” is a significant factor affecting the quality of life in cancer persons. This study aimed to test the feasibility of musical prayers in enhancing quality of sleep in persons with ovarian cancer.

Methods: A quasi-experimental research study was conducted on 10 ovarian cancer patients treated by chemotherapy. The patients were listening to musical prayers for about 45 minutes before sleeping for 27 days. Before and after intervention the instruments used to collect data were a demographic questionnaire, the Thai Depression Inventory (TDI), the Pittsburgh Sleep Quality Index (Thai version), and a semi-structured interview on the quality of sleep.

Results: Global sleep quality and perceived better sleep quality showed significantly (p < .05, p < .01) after listening to musical prayers. Sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication and daytime dysfunction also improved within the period of musical prayers, but without statistical significance. The patients were satisfied with musical prayers at the highest level. They also suggested the use of this program with other cancer persons in order to improve their quality of sleep.

Conclusions: The application of musical prayers to enhance the quality of sleep in persons with ovarian cancer should take into account the personal characteristics of each patient. Further study related to the most effective means of using musical prayers on persons with ovarian cancer at both the hospital and at home should be conducted.
Histone Deacetylase Inhibitors Anti-Tumour Activity and the Effect on ATP-Binding Cassette in Ovarian Carcinoma Cells

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Ovarian cancer is the cause of cancer mortality in female patients, and is a most malignant disease of worldwide importance, that ovarian cancer strongly requires novel treatment modalities. Histone deacetylase inhibitors (HDACi) are a new class of promising anti-tumor agent inhibiting cell proliferation and survival in tumor cells with very low toxicity toward normal cells. To study the effect of HDACi as chemotherapeutic drugs on human ovarian carcinoma cell lines.

Methods: The expressions of ATP binding cassette (ABC) transporter genes, multidrug resistance protein (MDR1) and multidrug resistance-associated proteins (MRP1 and 2), that have been proposed to influence the resistance of chemotherapeutic drugs, were determined.

Results: We show the HDACi Sodium Butyrate (NaB), suberoylanilide hydroxamic acid (SAHA) and Trichostatin A (TSA) strongly reduce ovarian cancer cells viability.

The anti-tumour activity reduced ovarian cancer cells viability of these HDACi was from 68.8% to 4.4%, both dose- and time-dependent. And HDACi induce the expression of MDR1 mRNA, but reduced MRP1 and MRP2 mRNAs expression.

Conclusion: HDACi are new anti-tumor agents for targeting highly malignant tumors such as ovarian cancer, as these agents display a strong toxicity toward aggressive ovarian cancer cells due to induce multidrug resistance protein (MDR1) and inhibit multidrug resistance-associated protein (MRP1 and 2).
DETECTION OF OVARIAN CANCER RECURRENCE AND RESPONSE TO THERAPY USING A CA125 AND HE4 DUPEX ASSAY

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Background: CA125 and HE4 are the only markers used for monitoring of ovarian cancer and are solely available as independent immunoassays. The aim of this research study was to determine preliminary feasibility of a combined duplex immunoassay (CA125 and HE4) for monitoring recurrence and response to therapy in ovarian cancer patients.

Methods: CA125 and HE4 assays were co-developed into a duplex Luminex assay capable of simultaneous quantification of both markers in a single well. The duplex assay was tested in a research study on twelve subjects monitored for ovarian cancer. Longitudinal serum samples included pre-surgical bleeds and time points ranging from one to twenty-four months post-surgery depending on clinical patient outcomes (n=68).

Results: For all patients, CA125 and HE4 dropped significantly (50%) within six months of the initial surgery. Eight of the twelve patients showed similar trends for both markers. Four patients showed variable changes of HE4 and CA125 markers across the monitoring period, two of which exhibited a rise in HE4 prior to CA125. Among five patients who experienced clinical recurrence or progression, three had parallel increases in both CA125 and HE4, one had normal levels of both CA125 and HE4 at recurrence, and one had a rise in HE4 levels three months prior to a rise in CA125.

Conclusion: Simultaneous detection of CA125 and HE4 in Luminex format is feasible for monitoring ovarian cancer patients. Use of both markers in a duplex format may provide a clinical benefit in identifying recurrence or response to therapy.
FEASIBILITY OF BEVACIZUMAB PLUS CHEMOTHERAPY IN HEAVILY PRE-TREATED OVARIAN CANCER PATIENTS. A RETROSPECTIVE STUDY

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Introduction: Patients with recurrent epithelial cancer of the ovary have a poor prognosis. As vascular endothelial growth factor (VEGF) is expressed in ovarian cancer, we assessed the efficacy and safety of combination of bevacizumab (a monoclonal antibody targeting VEGF) plus chemotherapy for heavily pre-treated ovarian carcinoma patients.

Methods: 43 patients with recurrent ovarian carcinoma were included. Treatment combined bevacizumab with paclitaxel, docetaxel, or other agents in 32 (74%), 10 (23%) and one (2%) patients, respectively.

Results: The median number of combined treatment was six cycles (range 1-29). The median number of prior chemotherapy regimen was three (range 1-13). The objective response rate (ORR) was 40% (16% CR and 24% PR). Clinical benefit (complete response (CR) plus partial response (PR) and stable disease (SD) lasting ≥ three months) was 74 % (CI95%: 46.7-77%). The median time to progression and overall survival were 3.8 months (range 0.2 -14.4 months) and 20.1 months (IC95%: 13.8-20.1) respectively. No toxic death was reported. Grade 3-4 toxicity occurred in 30% of patients. Gastrointestinal perforations and fistula occurred in 7% and 14% of patients, respectively.

Conclusions: The combination of chemotherapy and bevacizumab is active in resistant ovarian carcinoma, but gastrointestinal perforations and fistula are of concern. Further clinical trials are warranted to confirm these results in relapsed ovarian carcinoma.
OVARIAN CYSTS: WHEN TO OBSERVE, WHEN TO INTERVENE, AND WHEN TO REFER?
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Introduction: Ovarian cysts are common. The aim of clinical management is to optimize the treatment of malignant and premalignant cysts while minimizing intervention for cysts likely to resolve spontaneously.

Aim: The aim of this study is to compare actual practice with optimal practice for management of ovarian cysts.

Material and methods: A retrospective case note review of 175 women with ovarian cysts over 40mm was done. Patients were classified into low RMI (< 200) and high RMI (>200) based on CA125, menopausal status and ultrasound features. High RMI: 40% were premenopausal and 60% postmenopausal. In the postmenopausal group, 100% of the cases were referred to the tertiary centre as per guidelines. 81% of these women underwent primary surgery and rest had chemotherapy followed by delayed debulking. Histology revealed malignancy in 77% of the women; hence the referral pathway had 77% positive predictive value. In the premenopausal group, 45% had surgery, 55% were managed conservatively. Of all the patients who had surgery, 60% of the patients were referred to tertiary centre and the rest operated at North tees. Histology revealed borderline ovarian tumour in 1 patient and rest had benign pathology.

Conclusions: In postmenopausal women, ovarian cysts with RMI > 200 should be referred to a tertiary centre. Using the same criteria in premenopausal women involves referral of a larger number of benign cases. The standards for referral will undergo revisions and refinements over time. We enthusiastically await the release of better screening and diagnostic tests.
HEPATIC RESECTION IS A POTENTIAL TREATMENT FOR RECURRENT METASTATIC OVARIAN CARCINOMA OR PERITONEAL CARCINOMA

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Objective: The objective of this study was to investigate the validity of hepatic resection as a treatment option for hepatic metastasis in patients with recurrent epithelial ovarian cancer or peritoneal carcinoma.

Methods: We conducted a retrospective review of 40 recurrent ovarian carcinoma or peritoneal carcinoma patients with hepatic parenchymal metastasis who were treated at the Beijing Cancer Hospital from 1996 to 2009.

Results: In one hundred and fifty one recurrent ovarian carcinoma or peritoneal carcinoma patients, there were 40 patients with hepatic metastasis (median age 59 years; range, 41-78 years) during this period of time. Twelve patients with unilobar metastasis and less than 3 numbers of tumors were underwent hepatic resection for metastatic cancer. There was no significant difference between patients underwent hepatic resection and the patients accepted salvage chemotherapy in age, primary pathology type, tumor grade, the rate of optimal primary cytoreductive surgery and the serum CA-125 level at the liver metastasis (p>0.05). There were 7 patients recurrent in the 10 patients with microscopic negative margins. The median recurrent time was 11 months (range, 3-24) following the hepatic resection. The median overall survival time and cumulative 3-years survival rates after liver metastasis for patients who accepted optimal secondary cytoreduction including hepatic resection and those who obtained only salvage chemotherapy were 62 months (range, 9-76) vs. 14 months (range, 1-68) and 66.7% vs. 18.5%, respectively (p< 0.05).

Conclusion: Our findings suggest that hepatic resection should be attempted for selective patients with hepatic metastasis from ovarian carcinoma or peritoneal carcinoma.
NOVEL PLATFORM TECHNOLOGY FOR EFFICIENT UTILIZATION OF WATER INSOLUBLE DRUGS

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The bioavailability of water insoluble drugs remains a major limitation in its therapeutic use in all areas of medicine from cancer to autoimmune conditions. Research in the formulation of these compounds is intense, describing micelles, emulsions, and lipid vesicles for drug delivery. More recently, use of nanoparticles as carriers has generated interest, since nanoparticles achieve higher biodistribution, an essential element of therapy.

NUFS™ is a platform technology, that achieves a mean size particle in the range of 0.01~1 µm with a very stable output. The platform uses no toxic organic solvents and is based on widely used solid lipids, surfactants or bio-polymers. Moreover, NUFS™ provides the final process output as powder form that allows convenience in successive drug manufacturing steps.

We report here the in-vitro testing of paclitaxel and docetaxel formulated as nanoparticles using the NUFS™ platform on ovarian carcinoma cell lines, SKOV3 and ES2. At the doses used in-vivo the two nano-compounds are comparable to the parent compounds. Although the EC50 values for the two cell lines measured in vitro are higher than the respective parental compounds; it does not have any bearing in its therapeutic use; since the concentration used in vivo is much higher than the EC50 values. In fact, with better biodistribution, the nanoparticles will have better efficacy in vivo than their parental counterpart. In vivo biodistribution studies are now in progress.
HISTOPATHOLOGICAL CHANGES IN RESIDUAL CANCER BURDEN AFTER INTERVAL DEBULKING SURGERY ARE EFFECTIVE IN EVALUATING THE RESPONSE TO ADJUVANT CHEMOTHERAPY

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Objective: To study the clinical significance of histopathological assessment of residual cancer burden (RCB) of epithelial ovarian carcinoma (EOC) between primary (PDS) and interval debulking surgery (IDS) in evaluating the effectiveness of chemotherapy.

Methods: Thirty-eight EOC patients with suboptimal PDS with adjuvant chemotherapy were selected for this retrospective study and divided into pathologically negative (group A) and pathologically positive (group B) groups based on the histopathological examination. Patients in group B were further divided into groups B1, B2 and B3 based on the histological RCB results. The responses to chemotherapy evaluated by pathological examination of RCB vs. by CA125, recurrence patterns, and prognoses were analyzed.

Results: There was inconsistency between the pathological and CA125 methods in evaluating responses to chemotherapy. The clinical benefit rates evaluated by pathological assessment for groups A, B1, B2, and B3 were 100%, 100%, 100% and 0% respectively (P< 0.01), whereas the rates were similar when evaluated by CA125 (P>0.05). The median progression-free survival (PFS) in groups A and B was 36 and 6 months (P< 0.05); the median overall survival was 93 and 42 months (P< 0.05). There was no significant difference in recurrence rates between groups A and B, but there were significant differences in the rate of drug-resistant recurrence (28.6% vs. 72.2%, P< 0.05) and in median PFS of relapsed patients (19 vs. 4 months, P< 0.05).

Conclusion: The histopathological assessment of RCB between PDS and IDS may be used to evaluate and predict response to adjuvant chemotherapy in EOC.
THE PATTERN OF CA 125 CHANGES AS A PROGNOSTIC FACTOR FOR ADVANCED EPITHELIAL OVARIAN CANCER

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Objective: To investigate the pattern of CA 125 changes as a prognostic factor for advanced epithelial ovarian cancer.

Materials and methods: The medical records of the patients who were diagnosed with ovarian cancer and undertaken cytoreductive surgery followed by chemotherapy from 1998 to 2006 were retrospectively reviewed.

Results: Seventy nine patients were identified. Thirty two patients of 79 were diagnosed as stage III (29 patients) or IV (3 patients) epithelial ovarian cancer and enrolled the study. All patients were received combination chemotherapy minimum 3 cycles. The histologic type, grade, and postoperative CA 125 were not revealed as prognostic factors in survival of patients with advanced epithelial ovarian cancer. The CA 125 after 3rd cycle of combination chemotherapy completed was showed as a significant prognostic factor in those patients (p < 0.05).

Conclusion: The chemosensitivity is an important prognostic factor in survival of patients with advanced epithelial ovarian cancer.
OVARIAN GONADOBLASTOMA WITH DYSGERMINOMA COEXISTING WITH TUBAL ECTOPIC PREGNANCY IN A 15-YEAR-OLD GIRL WITH 46XX KARYOTYPE

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In disease of premenarcheal period, the clinician meets, as is well known, not infrequently with considerable diagnostic difficulties. Here we would like to present a 15-year-old girl with 46-XX karyotype who presented with irregular vaginal bleeding. The case turns out to be a tubal ectopic pregnancy coexisting with a small ovarian dysgerminoma in the setting of gonadoblastoma. A 15-year-old girl admitted to our emergency department with vaginal bleeding. Serum hCG level was 260 mIU/ml. Possibility of a malignancy was evaluated with radiologic and laboratory tests. MRI revealed no abnormality in the genitourinary system and tumor markers including LDH, ALP and alpha fetoprotein were all in normal limits. Then a right adnexal mass consisting of gestational sac measuring 32x28x15mm with a fetal pole but without cardiac activity was seen on the ultrasonography. 3 consecutive courses of Methotrexate 50 mg/m² were administered but the response was suboptimal. Exploratory laparoscopy was performed. On the left ovarian surface, there was an approximately 0.5 cm slight yellowish eminence. This area was excised. The serum hCG level was not detectable on the 3rd day. Pathologic examination of the specimen revealed dysgerminoma in the setting of gonadoblastoma. Diffuse hCG staining was shown by immunohistochemical analysis. Peripheral blood karyotype of the patient confirmed a 46 XX karyotype. To the best of our knowledge, this is the earliest diagnosis of an ovarian dysgerminoma in the setting of gonadoblastoma in a 46-XX girl coexisting with tubal ectopic pregnancy.
CA125 AS A PREDICTIVE MARKER FOR OPTIMAL INTERVAL DEBULKING SURGERY

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Background and aims: Neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) is a main treatment in patients with advanced ovarian cancer. But it is unclear whether IDS could be optimal or not actually even if it is evaluated preoperatively that optimal IDS is possible by CT, MRI and CA125.

This objective is to assess the ability of CA125 values to identify the patients of optimal IDS following NAC for advanced ovarian cancer.

Methods: 75 women diagnosed with ovarian cancer (six FIGOIIIA and 69 IIIC) between 1995 and 2009, who had serum CA125 levels >40IU/mL at pre NAC and treated with IDS following NAC, were retrospectively evaluated. After each NAC, CA125 measured times, and CA125 regression rate was calculated. Optimal IDS was defined as largest volume of residual disease < 1 cm in maximal dimension. The values of CA125 and patient and disease characteristics to predict optimal IDS were determined using univariate and multivariate analysis.

Results: On univariate analysis, CA125 regression rate from pre NAC to pre 2nd NAC and from pre NAC to pre 3rd NAC, and CA125 before IDS were significant (p< 0.01).

On multivariate analysis, CA125 before IDS was an independent predictor of optimal IDS (p< 0.01).

Determining the cut-off point of CA125 before IDS for optimal IDS by receiver operating characteristic curve, it was 20IU/mL.

Conclusion: In this retrospective study, It was shown to guess that the possibility of optimal IDS was high when CA125 before IDS was 20IU/mL or less.
IMMUNOREACTIVE SCORE OF EP-CAM MIGHT PREDICT SURVIVAL IN EARLY OVARIAN CANCER PATIENTS

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Background and aims: The epithelial cell adhesion molecule (Ep-CAM) is a well known adhesion molecule serving as a target for targeted therapies in ovarian cancer (OC) and prediction of breast cancer. Here, we studied a possible association between Ep-CAM expression and prognosis in patients with early OC.

Methods: All OC patients who were treated at our institution between the years of 1980 and 2003 with FIGO stage I-II, available follow-up information and OC tissue were enrolled in this study. Ep-CAM expression was assessed using an immunoreactive score defined by the product of a proportion score and intensity score. A score of 9 or 12 was considered as positive. SPSS 17 was used for statistical analysis.

Results: 103 patients entered this study. The median follow-up time was 74 months. Ep-CAM score was positive in 37%. Positive Ep-CAM score showed a negative impact on survival in early OC (HR 2.24; 95%CI, 0.90 to 5.57; p=0.083). Established clinical prognostic factors like FIGO stage (HR 2.97; 95%CI, 1.70 to 7.60; p=0.022) and histological grade were associated with decreased survival (HR 3.18; 95%CI, 1.11 to 9.10; p=0.031). Kaplan-Meier plot demonstrated an influence of Ep-CAM on 5 years survival rates (89.7% vs. 73.6%). Ep-CAM expression failed to show a significant association with survival of OC in multivariate Cox-regression analysis considering FIGO stage and histological grade (HR 1.844; 95%CI, 0.71 to 4.78; p=0.21).

Conclusions: Ep-CAM expression might be associated with survival in patients with early OC. Further studies with bigger cohorts are warranted to demonstrate this possible impact.
A GENE EXPRESSION PROFILE PREDICTS SURVIVAL OF PATIENTS WITH ADVANCED STAGE OVARIAN CANCER

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**Background:** Advanced-stage ovarian cancer patients are generally treated with platinum/taxane-based chemotherapy after primary debulking surgery. However, there is a wide range of outcomes for individual patients.

**Aims:** This study aimed to identify gene expression profile for predicting ovarian cancer recurrence.

**Methods:** Advanced-stage serous ovarian cancer tissues from 110 patients who underwent primary surgery and platinum/taxane-based chemotherapy were profiled using Agilent Whole Human Genome Oligo Microarray. Eighty-eight genes associated with progression-free survival (PFS) time were extracted by a univariate Cox model (p < 0.01), and regression coefficients of the genes were adjusted by ridge regression Cox model using 10-fold cross-validation. Then we developed the prognostic index for each patient based on the 88-gene expression profile with the estimated coefficients.

**Results:** Multivariate analysis showed that our prognostic index was independently associated with PFS time compared to other clinical factors in the discovery dataset (p< 0.0001). This predictive ability was validated using an external validation dataset (n = 87) by multivariate analysis (p = 0.0008). When we divided patients into the two groups (optimal and suboptimal groups) in each of the discovery and external datasets, the predictive power of our prognostic index was confirmed in each of the four strata from the two datasets.

**Conclusions:** Our prognostic index based on 88 genes was shown to be an independent predictor for PFS time. To improve predictive accuracy of the prognostic index toward clinical application for evaluation of the risk of recurrence in patients with advanced-stage serous ovarian cancer, large-scale multicenter.
OVARIAN CLEAR CELL ADENOFIBROMATOUS TUMOR OF BORDERLINE MALIGNANCY. A CASE REPORT

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Objective: Report of a case and review of the literature.

Material and methods: A 69-year-old female who was diagnosed with a cystic lesion in the left ovary during routine ultrasound examination (4cm × 3cm × 2cm). Total hysterectomy and bilateral salpingo-oophorectomy were performed.

Results: Macroscopically, the left ovary presented a unilocular cystic space of maximum diameter 4 cm with a smooth outer surface and a fleshy yellow-whitish nodule of the inner surface with a maximum diameter 2 cm. Microscopically the nodule was composed of varying-sized tubules lined by cuboidal epithelial cells with clear or eosinophilic cytoplasm and hobnail cells within dense fibrous stroma. The nuclei were large, bulbus and hyperchromatic or with prominent nucleoli. Mitoses and neoplastic invasion of the stroma were not observed. Neoplastic epithelial cells stained for cytokeratin 7 and AFP.

Conclusion: The diagnosis made was that of an ovarian clear cell adenofibromatous tumor of borderline malignancy. The patient 13 months after the surgery is in good health. Ovarian surface epithelial tumors with clear cell differentiation are characterized by cells with glycogen-rich cytoplasm or hobnail morphology. Even though clear cell adenocarcinoma is a well known entity that represents 6% of all epithelial ovarian tumors, benign and borderline malignancy clear cell tumors are very rare neoplasms.
OVARIAN CANCER: CLINICAL EXPERIENCE OF A 10-YEARS PERIOD
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Objective: This retrospective study, presents the cases of ovarian cancer, the therapeutical methods and their results of patients treated in our clinic at the time of period 2000-2009.

Materials and methods: Approximately 13,200 women, aged 18 - 80, examined in our gynaecology department. 138 found suffering from ovarian cancer cases that arrived in the Gynaecological Clinic of our Hospital were categorized depending on the histological type of disease, the clinical aspect of cancer, the methodology of confrontation of illness and the results of therapeutic effort.

Results: Diagnosis was based on the symptomatology, in the clinical examination, in the laboratorial methods (Ultrasonography, Computerized Tomography scan) and was confirmed with the histological examination of surgical material. Histologically, 28 were borderline tumours, 36 were serous cystadenocarcinomas, 14 were papillary serous carcinomas, 28 were mucinous cystadenocarcinomas, 13 were endometrioid tumours, 6 were endodermal sinus carcinomas, 3 were malignant Brenner tumour, 4 were thecoma, 6 were Krukenberg tumours. The mean age of patients was 64 years. The therapeutic confrontation was total abdominal hysterectomy and bilateral salpingooophorectomy, pelvic lymphadenection, omentectomy and appendicectomy and subsequent chemotherapy. The 5-year survival rate was about 40%.

Conclusions: Ovarian malignancies represent the greatest clinical and surgical challenge in gynaecological oncology. Epithelial cancers are the most common ovarian malignancies and patients have advanced disease at the time of diagnosis in more than two-thirds of the cases because they are usually asymptomatic until they have metastasized. It has the highest fatality-to-case ratio of all the gynaecologic malignancies.
LONG-TERM SURVIVAL IN A PATIENT OF OVARIAN JUVENILE GRANULOSA CELL TUMOR WITH PARAAORTIC LYMPH NODE METASTASIS

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Background: Juvenile granulosa cell tumors (JGCTs) are rare, representing only 5% of all granulosa cell tumors, and occur mostly in prepubertal girls. The advanced cases, which account for 3% of all JGCTs, are more aggressive and result in relapse and poor prognoses within a short period of time. Paraortic lymph node is an uncommon primary metastatic site in these tumors. Long term disease-free survival in the patients with advanced JGCTs is rarely reported.

Case: A 12-year-old girl suffering from a 21x18-cm right ovarian tumor with solitary paraaortic lymph node metastasis underwent unilateral salpingo-oophorectomy and lymph node resection. Peritoneal biopsies were free of tumor and there were no gross residual tumor nodules after the surgery. Alpha-inhibin was intensely positive in the ovarian tumor and paraaortic lymph node by immunohistochemical staining, consistent with a diagnosis of FIGO stage IIIC JGCT. The patient received four cycles of adjuvant chemotherapy consisting of cisplatin 75 mg/m² on day 1, bleomycin 15 mg on day 1-2, and etoposide 75 mg/m² on day 2-4, at 4-week intervals. She regained regular menstruation 5 months after chemotherapy. She has survived 9 years without recurrence.

Conclusion: A complete tumor resection and a cisplatin-based chemotherapy can achieve long-term control of advanced juvenile granulosa cell tumor with solitary lymph node metastasis.
REGULATORY T CELLS AND CYTOTOXIC T CELLS IN PATIENTS WITH OVARIAN CANCER
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Objective: The aim of our study was to compare the percentage of regulatory T cells and cytotoxic T cells in the peripheral blood and peritoneal fluid of ovarian cancer patients.

Methods: Flow cytometry was used to measure percentage of CD3, CD4, CD8 T-cells and measure the expression of intracellular marker Foxp3 on CD4+CD25+ obtained from peripheral blood (n=10) and peritoneal fluid (n=10) of ovarian cancer patients.

Results: The percentage of peripheral blood Tregs population was 1.1% (min.-0.4%, max.- 1.8% ). The percentage of peritoneal fluid Tregs population was 1,1% (min.-0.5%, max.-3.4% ). There was no significant difference between percentage of regulatory T cells in the peripheral blood and peritoneal fluid of ovarian cancer patients (p=0.16). The percentage of CD3 T-cells population was 4.6% (min.-2.3%, max-65.3%) in the peripheral blood and 64.5%; (min.-7.8%; max-83%) in peritoneal fluid. The percentage of CD3+ CD4+ T-cells population was 60.7% (min.-2.12%, max-72.6%) in the peripheral blood and in peritoneal fluid appropriately 50.7%; (min.-36.8%; max-79.3%). Finally the percentage of CD3+ CD8+ T-cells population was 30.4% (min-0.9%, max-45%) in the peripheral blood and 42.4%; (min-15.4%; max-61.1%) in peritoneal fluid.

Conclusion: Our results indicate that Tregs population is present in both, peripheral blood and peritoneal fluid compartment of ovarian cancer patients. No statistically significant differences between Tregs percentage in local and systemic environment were noticed.
BORDERLINE OVARIAN TUMORS: HOW DO PATIENTS ESTIMATE THEIR MALIGNANT POTENTIAL AND THEIR OVERALL PROGNOSIS?

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Background and aims: We assessed the personal evaluation of patients with borderline-ovarian-tumors (BOT), with special focus on fertility and the estimated risk of recurrence or death.

Methods: Sixty BOT-patients who underwent surgery between 01/2001 and 06/2009 in our institution answered within the regular follow-up an especially constructed 9-item questionnaire at the earliest 12 months after surgery. Aim was to assess their estimation regarding the malignant potential of BOT, the impact on future fertility, the risk of recurrence and death and the possible causes of the disease.

Results: Sixty BOT-patients (median-age:53.5years; range:27-76) were included in the present analysis. Four(6.7%) patients had a relapsed BOT. The vast majority of the affected women (n=39;65%) stated having no specific symptoms at initial presentation of the disease. Thirty-one women (51.7%) could not make any hypothesis about the possible cause of BOT. Only 10(16.7%) patients evaluated the malignant potential of BOT equivalent to that of a benign ovarian cyst, while 28(46.7%) and 20(33.3%) patients believed to carry the same or equivalent recurrence- and mortality-risk, respectively, like ovarian-cancer-(OC)-patients. In the subgroup of relapsed-BOT all patients estimated the grade of malignancy and the risk of recurrence and mortality equivalent to OC.

Conclusions: BOT-patients appear to correlate the malignant potential of borderline-disease with that of invasive-OC with an equivalent high risk of recurrence; they do not however expect to die of BOT. A more thorough and differentiated information about this rare disease is warranted for the better perception and understanding on the part of the affected patients.
MALIGNANT MIXED MULLERIAN TUMOR OF THE OVARY - CASE REPORT AND REVIEW

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Objective: To present a case of malignant mixed müllerian tumor (MMMT) of the ovary, a rare and aggressive ovarian malignant tumor with poor prognosis.

Case report: A 69-year-old woman was referred to Instituto Português de Oncologia (IPO) in Lisbon with complaints of pelvic pain and a firm palpable mass over her left flank of the abdomen. Physical examination, gynaecological ultrasound and computerized tomography showed a mass lesion in the left adnexal area. Ovarian cancer was suspected. Optimal surgery was performed, and final pathology revealed a MMMT of the ovary, predominantly serous, poorly differentiated, infiltrating the left bladder pillar and with extrinsic infiltration of the serosa, subserosa and muscle segment of the intestine. Chemotherapy using carboplatin and paclitaxel was administered postoperatively. After six cycles of chemotherapy, the patient referred severe abdominal pain predominantly in her lower abdomen. A computerized tomography revealed a pelvic mass with intestinal involvement, so the patient underwent exploratory laparotomy with excision of the lesion, consistent with pelvic recurrence of MMMT. After 2 months she died with renal, respiratory and intestinal complications

Conclusion: Aggressive surgical treatment followed by combination chemotherapy may result in improved progression free intervals for women with advanced ovarian MMMT. However, a major improvement in prognosis for this rare malignancy has not yet been achieved.
THE INVOLVEMENT OF THE APPENDIX IN OVARIAN MUCINOUS ADENOCARCINOMA

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Introduction: Surgical staging is central in the management of ovarian malignancy.

A complete staging procedure involves removal of the appendix especially as mucin secreting tumours metastasize to this site.

Aim: The purpose of this study is to assess the involvement of the appendix in ovarian mucinous adenocarcinoma.

Methods: A retrospective review of histology and case notes was undertaken on patients who had presented to our tertiary cancer centre over the previous 10 years.

Cases selected for analysis were primary ovarian mucinous adenocarcinoma. Mucinous tumours metastatic to the ovary were excluded.

Results: 18 cases were identified for the study. 12 cases (67%) were early stage and 6 cases late stage. The appendix was excised at primary surgery in 11 cases (61%). The appendix was described as grossly abnormal in 2 cases but only one of these of these cases had metastatic tumour. 61% suffered recurrence or progression of their cancer. The appendix was not involved in recurrent disease in any of the patients who had retained that organ.

Conclusion: In this study removal of the appendix was advantageous for just one patient. This suggests that excision of the appendix at primary debulking surgery may not be essential in the management of ovarian mucinous carcinoma. These findings should be investigated further using a larger study group.
DOES THE PRESENCE OF ENDOMETRIOSIS ALTER THE BEHAVIOUR OF CLEAR CELL CARCINOMA?

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Introduction: Clear cell carcinoma is one of the least common epithelial ovarian cancers and often occurs in association with endometriosis.

Aims: The purpose of this study was to compare the characteristics of clear cell carcinomas that had arisen with or without endometriosis.

Methods: A retrospective review of histopathology reports and medical records for patients that had presented to our cancer centre for the previous 10 years was performed. Cases selected were primary clear cell carcinoma of the ovary.

Endometriosis associated clear cell carcinoma (EACC) was determined by confirmation on histology or a recorded history of endometriosis.

Results: 66 cases were identified in total, 38 were categorised EACC and 28 were clear cell carcinoma without endometriosis (CC).

In the EACC group the mean age was 55 years while the CC group had a mean age of 59 years. 58% of the EACC group had early stage disease versus 61% in the CC group. The rate of recurrence was 68% and 57% and median time to recurrence was 11 months and 12 months in the EACC and CC groups respectively. The median survival time in the EACC group was 44 months, it was 39 months for the CC group. This difference was not statistically significant (p= 0.712).

Conclusion: In previous reports the presence of endometriosis has been shown to proffer a beneficial prognosis in ovarian cancer. In this analysis of clear cell carcinoma there is little difference in the biological characteristics of malignancies that have arisen with or without endometriosis.
EXPRESSION OF CXCR4 PREDICTS POOR PROGNOSIS OF PATIENTS WITH CLEAR CELL CARCINOMA OF OVARY

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Objectives: Recent reports have shown that CXCR4 are expressed in various solid tumors, and are involved in tumor development and metastasis. We examined the distribution and expression of this molecule in clear cell carcinoma of the ovary (CCC) to elucidate their clinical significance.

Methods: paraffin sections from CCC tissues (n=42) were immunostained with CXCR4 antibody and staining intensities were evaluated. The clinicopathological factors examined were age, FIGO staging, preoperative value of CA125, and residual tumor after cytoreductive surgery. Overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method, and multivariate analysis was completed using the Cox proportional hazard analysis.

Results: Of the 42 carcinomas, lower level of CXCR4 immunoexpression was observed in 21 (50.0%) cases (CXCR4_low group), and higher level of immunoexpression in 21 (50.0%) (CXCR4_high group). Five-year OS were significantly worse in CXCR4_high group than CXCR4_low group (OS; CXCR4_low group (90.2%), CXCR4_high group (50.3%), \( P =0.0002 \)). In addition, CXCR4_high immunoexpression significantly predicted a poorer PFS when compared with lower expression (5-year PFS; CXCR4_low group (90.5%), CXCR4_high group (36.2%), \( P < 0.0001 \)). Furthermore, the multivariate analyses including age, preoperative CA125 value, FIGO stage, and CXCR4 expressions revealed that CXCR4_high expression was independent prognostic factors for OS and PFS of patients with CCC in this study (OS, \( P = 0.0011 \); PFS, \( P = 0.0008 \), respectively).

Conclusion: Our current study suggested that the assessment of CXCR4 immunoreactivity may be a useful prognostic indicator and that CXCR4 may play a critical role in the progression of CCC.
MUCINOUS OVARIAN CANCER MARKER, MA2, PROMOTES CELL PROLIFERATION AND MIGRATION

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Ovarian cancer is a leading cause of death in women. Early detection of ovarian cancer is essential to decrease the mortality. However, early diagnosis of ovarian cancer is difficult due to lack of both clinical symptoms and good molecular diagnostic markers. Thus identification of good tumor biomarkers with potential clinical applications is urgent. To search for a biomarker for early detection of ovarian cancer, we identified mA2 from our systematic analysis of paired normal and ovarian tumor tissue cDNA microarray. We found a marked overexpression of mA2 mRNA and protein in early stage mucinous ovarian tumors compared to their normal ovary tissues and serous type ovarian tumors by western blot analysis and immunohistochemistry. To further explore the role of mA2 in ovarian tumorigenesis, stable 2774 human ovarian cancer cell lines overexpressing mA2 were established. Forced expression of mA2 in 2774 cells enhanced cell proliferation, migration, and invasion of ovarian cancer cells. Notably, mA2 protein can be detected in the serum of mucinous ovarian cancer patients by western blot and ELISA analysis. These results suggest that mA2 can be a potential biomarker for the diagnosis of mucinous ovarian cancer. It promotes cell proliferation and migration of ovarian cancer cells and may attribute to the progression of the mucinous ovarian cancer.
Primary fallopian tube cancer (PFTC) is very rare, it accounts less than 1% of all genital tract cancer in women and its management is similar to ovarian cancer. We report a case of squamous PFTC suspected by endometrial cytology in a 58-year-old multiparous patient with BMI of 38 and previous in situ breast cancer. After a 5 years regular follow up without symptoms, elevated CA 15.3 serum level was detected (281U/ml) with concomitant normal mammography. Subsequent Abdomen CT-scan revealed right pelvic mass, omental cake, peritoneal carcinoma and presence of a sierometra with linear endometrium. CA 125 and CA 19.9 were 52.9U/ml and 14.7U/ml respectively. No abdominal and pelvic masses were suspected at the abdominal, vaginal and rectal examination. Normal cervix and Pap smear. Endometrial fractional curettage revealed absence of cervical stenosis, no endometrial tissue but presence of serous fluid in the uterine cavity. Cytology underlined the presence of malignant squamous cells. Patient underwent laparoscopy to evaluate the citoriducibility: right fallopian tube was dilated, hyperemic with whitish, papillary and hard material leaking from the infundibular part with macroscopically normal omolateral ovary, omental cake, multiple peritoneal and ileo-mesenteric localizations. We proceeded to laparotomic extrafascial total hysterectomy, bilateral salpingo-oophorectomy, radical omentectomy and tumor debulking, with no residual disease. Histopathological examination documented a IIIC G3, adeno-squamous, PFTC. As ovarian cancer also PFTC diagnosis is usually made postoperatively but the direct communication of the tubes with the uterine cavity can help to reveal it and in 5% of case the diagnosis can be done preoperatively.
OVARIAN GERM CELL TUMORS: A 10-YEAR STUDY
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Background: The aim of this study was to evaluate the clinical presentation, management and outcome in patients treated for ovarian germ cell tumors at The Urmia Medical Science University - Motahhari hospital in a 10-year period.

Methods: The medical records of patients with histologically proven ovarian germ cell tumors operated from March 2000 to March 2010 were reviewed.

Results: One hundred seven women (mean age 29 years; 7-68 years) underwent ovarian operations. Eighty nine patients had mature teratomas and 18 had malignant tumours (7 dysgerminoma, 6 malignant mixed germ cell tumours, 2 Endodermal sinus tumor, 2 Immature teratoma and 1 dysgerminoma and Sertoli-Leydig cell tumor). Pain and an abdominal mass were the most frequent symptoms. Most patients with malignant tumors (9) were stage I, 5 were stage II, 4 stage III. Unilateral salpingo-oophorectomy was the most frequently performed procedure. Recurrence was observed in four patients with malignant tumors. Three patients, with malignant disease, died.

Conclusions: Ovarian germ cell tumours are common in young women. Conservative fertility-saving surgical treatment can be offered to young patients. With accurate staging, complete resection, and chemotherapy for malignant tumors, patients are expected to have excellent survival rates.
SMAC PEPTIDE POTENTIATES TRAIL OR PACLITAXEL MEDIATED DRUG-RESISTANT OVARIAN CANCER CELL DEATH IN VIVO

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Background and aims: Smac/DIABLO is a recently identified protein that is released from mitochondria in response to apoptotic stimuli and promotes apoptosis by antagonizing inhibitor of apoptosis proteins (IAPs). Our previous study had proved that transfection of Smac/DIABLO sensitizes drug-resistant tumor cells to TRAIL or Paclitaxel induced apoptosis in vitro, this study was designed to explore the effect of Smac peptide on human ovarian cancer xenograft models.

Methods: The cell-permeable, synthetic Smac peptides containing the four N-terminal residues essential for XIAP inactivation and its control peptides were synthesized. The abdominally and subcutaneously spread tumors in nude mice via inoculation of A2780 cells were established and were treated with Smac peptides, control peptides, TRAIL, Paclitaxel, Smac or control peptide +TRAIL, Smac or control peptide+Paclitaxel respectively. The xenograft tumor growth inhibition rate, pathology, apoptosis and biochemical assays were used to analyze their effects and possible mechanisms.

Results: Combined Smac peptide and TRAIL/ Paclitaxel therapy had a synergistic effect in the regression of established tumor xenografts than TRAIL or Paclitaxel treatment alone (P< 0.05), while Smac peptide alone had no effect. Notably, the combination of Smac peptide and TRAIL caused less damage in normal tissues and more apoptosis in tumor xenografts compared with the combination of Smac peptide and Paclitaxel (P< 0.05). Increased apoptosis was associated with the regulation of IAPs and caspase-3,9.

Conclusions: the N-terminal Smac peptide is a promising candidate for drug-resistant ovarian cancer combination therapy, and Smac/DIABLO may be the target for the development of novel class of anticancer drugs.
OVARIAN CANCER MORBIDITY IN TULA REGION (RUSSIA) WITHIN 10 YEARS

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Ovarian cancer and tumor-like ovarian mass is one of the most frequent disorders affecting the female sex organs. Ovarian cancer lies in the 7-th place in disease incidence and in the 5-th place as a cause of death among all cancer of all women in Russia. In Tula region (Russia) the morbidity of ovarian cancer was examined from 1999 to 2009. In the structure of gynecological morbidity ovarian cancer comes up to 4.3%. The ovarian cancer morbidity had grown up from 8.9% to 21.5% per 100000 population from 1999 to 2009 (14.6% increase). The morbidity rate of the I-II stadium had increased from 26% up to 35%, the rate of the III stadium had decreased from 49.3% to 32.5%, the rate of the IV stadium had increased from 24.7% up to 40%. For last 10 years a part of morphologically verified diagnosis has increased from 90.4% up to 92.6%. The mortality growth was from 6.4 to 11.4 per 100000 population (5% increase). A peak of morbidity was observed in women of 40-55 years old. For 10 years the morbidity growth had been observed in the age group 35-59 years. Five-year survival rate had decreased from 59.7% to 57%. In the I stadium it is 92%, II - 68%, III - 48%, IV - only 9%. Conclusion. In Tula region the ovarian cancer morbidity continued progress, the percentage of the ovarian cancer IV initial detection increased, it indicates that there problems of early diagnostics.
SURGICAL TREATMENT OF RELAPSING MALIGNANT OVARIAN TUMORS - SURGICAL EFFORT

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Background: Surgical treatment of relapsing malignant ovarian tumors is done with the purpose of survival improvement. The selection criteria for surgical treatment of relapsing malignant ovarian tumors have not been precisely defined yet. A small number of patients is suitable for surgical treatment.

Material and methods: This work has included 38 patients who had a surgery because of primary relapsing malignant ovarian tumor. All the patients had a hysterectomy with adnexitomy on both sides and paracolic omentectomy. Relapsing of the disease has been proved by increase of Ca125, clinical exam and MR examination. Indication for surgical treatment has been established on the basis of exclusive criteria: no ascit, no pleural effusion, no distant metastasis, no peritoneal carcinosis and systematic lymphadenomegaly, no tumor on more than three localisations. All the patients were in a good condition. Disease progression started in the period between 6 and 98 months later.

Results: Explorative laparotomy was done with 12 patients (31,6%). Optimal citoreduction was done with 20 patients (52,5%) and suboptimal citoreduction was done with 6 patients (15,5%). 10 patients had bowel resection and 1 patient had partial resection of urine bladder within optimal citoreduction.

Conclusion: Large number of patients had an explorative laparotomy - 31%. With 68% patients we did optimal or suboptimal citoreduction. Is it necessary to correct selection criteria, diagnostic procedures or surgical skill in order to reduce the number of exploration laparotomy - the question remains open.
DETECTION OF P16\textsuperscript{CDKN2A} GENE ALTERATIONS IN OVARIAN CANCER WITH FISH ANALYSIS

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The molecular events leading to the development of ovarian cancer are not well established. Defects of the “Rb/cyclin D1/p16 pathway” have been shown to play a critical role in the development of human malignancies. Especially gene p16/CDKN2A located on chromosomal region 9p21 is altered frequently in several types of cancer. To investigate both the presence of numerical abnormalities of chromosome 9 and p16 gene alterations in ovarian cancer we studied 28 cases by FISH technique. Numerical abnormalities of chromosome 9 were found in all of the cases studied. Polysomy 9 was detected in 12 cases while monosomy 9 in 8 cases. In 8 cases there were two cell populations, one with polysomy 9 and the other with monosomy 9. In all cases p16 gene deletion was observed. Among them, 25 cases presented deletion of p16 gene in a range between 21.43%-86.3% of the examined cells. Three cases carried deletion p16 gene in a proportion between 12.04%-19.49%. Numerical aberrations of chromosome 9 and p16 gene deletion are common findings in ovarian cancer. Despite suggesting the p16 gene in 9p chromosomal region plays a role in ovarian carcinogenesis, the presence of other oncogenes reflected by polysomy 9 participating in the neoplastic process could not be excluded. The utilization of molecular technologies that allow high throughput analysis of genes has provided new insights into gene expression profiles in ovarian cancer and may lead to the development of new biomarkers or novel therapies for this neoplasia.
DELETION (10)(p12) A NOVEL RECURRENT CHROMOSOMAL ABERRATION IN ADVANCED STAGE OF OVARIAN CANCER

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The identification of chromosomal abnormalities in malignant diseases is a useful strategy toward understanding specific molecular pathways and tumorigenesis. Most of the ovarian cancer cases described in the literature are characterized by complex chromosomal changes. However, non-random structural chromosomal aberrations with common chromosomal breakpoints have been reported in ovarian cancer. Since single chromosomal changes might be primary events implicated in the initiation or progression of the neoplastic process, the aim of the present study was to investigate the presence of simple structural chromosomal changes in ovarian cancer. Reviewing on ascetic effusions samples cytogenetically studied in our laboratory by direct culture of tumour cells and a G-banding technique, we found two cases with a diagnosis of ovarian cancer, which had a single chromosomal abnormality. Both cases presented an abnormal clone of cells with a deletion of chromosome 10p, del(10)(p12), as a sole anomaly. The significance of this chromosomal aberration in the development of the neoplastic process remains unknown. Therefore, it is necessary del(10)(p12) to be molecularly investigated in ovarian cancer. The documentation of more ovarian cancer cases with simple chromosomal abnormalities is considered of major importance facilitating the identification of candidate genes involved in the neoplastic process.
THE OUTCOME OF 3\textsuperscript{rd} LINE CHEMOTHERAPY IN PATIENTS WITH RECURRENT EPITHELIAL OVARIAN CANCER

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Background: Most Advanced epithelial ovarian cancer patients (EOC) respond to chemotherapy in the adjuvant or neoadjuvant setting. However, majority of the patients recur and require additional lines of chemotherapy.

Aim: To assess the outcome of 3\textsuperscript{rd} line chemotherapy in patients with recurrent EOC.

Methods: We retrospectively reviewed the medical records of women with recurrent epithelial ovarian, tubal and primary peritoneal cancer who received at least 3 lines of chemotherapy.

Results: Seventy patients who received 3\textsuperscript{rd} line chemotherapy were identified. Their median age was 66.2 (range: 41-84). The majority of the patients had serous carcinoma (82.9%), Stage III (85.7%) and grade 3 (81.4%) disease. Neoadjuvant chemotherapy was given to 40% of patients and optimal debulking was achieved in 58.6%. Third line chemotherapy consisted of various regimens. The most frequently given agent was Topotecan (19 patients, 27.1%). The response rate to 3\textsuperscript{rd} line chemotherapy was 28.6%. Complete and partial responses were achieved in 20% and 8.6% respectively. 31.4% of patients reached stable disease and 37.2% progressed. The median progression-free survival (PFS) was 3.9 months. Nevertheless, 32.8% and 17% of the women experienced long-term PFS lasting more than 6 and 12 months respectively. The median overall survival (OS) was 20.3 months. Both PFS and OS were significantly longer in platinum-sensitive patients. No significant differences in survival were observed with regard to optimal debulking or to neoadjuvant chemotherapy.

Conclusions: Third line chemotherapy seems to be worthwhile in EOC patients, mainly in platinum sensitive patients. In some women long-term PFS and OS are achieved.
DOES SELECTING THE FERTILITY-SPARING SURGERY IN YOUNG WOMEN WITH STAGE I OVARIAN CANCER LEAD TO A POORER SURVIVAL OUTCOME?

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Objectives: The purpose of this study was to compare the long-term survival of patients with stage I epithelial ovarian cancer (EOC) treated with fertility-sparing surgery (FSS), to those underwent radical surgery, including hysterectomy, bilateral salpingo-oophorectomy, and staging surgery.

Methods: After a central pathological review and search of the medical records from multiple institutions, a total of 572 stage I EOC patients (the FSS group; n=74, the radical group; n=498, respectively) were retrospectively evaluated in the current study.

Results: The median age of patients with the FSS group was 30 years (range: 12-40 years). The stage was IA in 36, IB in one, and IC in 37 patients. Nine patients experienced recurrence. Collectively, Five-year overall survival (OS) or progression-free survival (PFS) rates of both the FSS and radical group were as follows; (OS; 90.8 (FSS), 88.3% (radical/ under 40 y.o.), and 90.6% (radical/over 41 y.o.); PFS; 87.9 (FSS), 84.4% (radical/ under 40 y.o.), and 85.3% (radical/ over 41 y.o.), respectively). There was no significant difference in the OS between the FSS and the radical groups (OS, P=0.802; PFS, P=0.765, respectively). Moreover, stratifying to stage IA or IC, there were also no significant differences in DFS and OS between both groups.

Conclusions: Our data suggest that the patients who underwent FSS did not show poorer survival outcome compared to those underwent radical surgery in stage I EOC. FSS may be considered a treatment option in women with stage I EOC.
A NOVEL TREATMENT STRATEGY FOR OVARIAN GRANULOSA CELL TUMORS BASED ON IMMUNIZATION AGAINST ZP3

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Background: Ovarian granulosa cell tumors pose a therapeutic challenge with high mortality. We tested a novel strategy of immunotherapy against the zona pellucida glycoprotein 3 (ZP3), expressed in granulosa cell tumors.

Methods and aims: Transgenic mice expressing the Simian Virus 40T-antigen under the inhibin-promoter, presenting with ZP3 positive granulosa cell tumors, were treated with human ZP3 protein to induce T-cell mediated autoimmune oophoritis (IAO). Early immunization (at 2 mo of age) was expected to prevent tumorigenesis, and delayed immunization (at 4.5 mo) to eradicate existing tumors. Mice were immunized with 4-5 boosts at 3 weeks’ intervals, and the treatment effects were inspected 2 weeks after the last boost.

Results: Immunization reduced the ovarian tumor weight significantly in both treatment groups (by 86 and 75%, respectively; p< 0.001) in comparison to persistent tumor growth in controls (n=9-16/group). Significantly lowered tumor-produced progesterone and inhibin , and increased LH, supported the positive response. Liver metastases (n=4) were found in non-treated/vehicle-treated controls, but none following active immunization. Histological analyses confirmed that the ZP3 immunization prevented formation and abolished existing tumor cells by a mixed cellular/humoral immunological response.

Conclusion: These results prove the principle of active ZP3 immunization as a potential lead into the immunotherapy of ovarian granulosa cell cancer expressing ZP3.
THE ROLE OF TREG CELLS IN PATIENTS WITH OVARIAN CANCERS
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Background: Ovarian cancer is the 5th leading cause of death from malignancy in women and has the highest fatality to case ratio between all gynecologic malignancies. Regulatory T cells (CD4+CD25+FOXP3+Tcell) are a subset of T lymphocytes with great inhibitory impact on immune response. This study evaluates Treg cells in peripheral blood of epithelial ovarian cancer in comparison with healthy donors.

Materials and methods: 40 women suspicious of ovarian cancer (17 out of 40 included in study) and 20 healthy subjects were enrolled in the study. 6-8 cc blood was collected before operation. After processing and flowcytometric analysis prevalence of Treg was determined.

Results: The results indicate that Treg is significantly higher in ovarian cancer patients than healthy participants used as control group (5.7±3.1 versus 2.8 ±1.4,P=0.002). Anon significant increase of Treg in higher stages (III+ IV) than lower stages (I+ II) was observed (6.5 ±3.18 vs 4.44±2.69,P=0.2). Increase of Treg cells was also associated, although not significantly, with higher levels of CA-125(>100) than lower levels(≤100)(6.44±3.04 vs. 4.18±2.92,p=0.18).

Conclusion: Increase of Treg cells in ovarian cancers might be a response for immune compromization in cancer patients. Association of Treg cells with higher stages and increase of CA-125 tumor marker, although insignificantly, suggest the impact of Treg cell increase on the cancer progression and most likely patient survival. This finding suggests application of Treg cell -targeted immunotherapy for ovarian cancer patients.
PROGNOSTIC SIGNIFICANCE OF HUMAN EPIDIDYMIS PROTEIN 4 IN ENDOMETRIAL CANCER PATIENTS

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Background: To date, no good marker for screening or disease monitoring for endometrial cancer (EC) is available. In this study, HE4 serum (sHE4) levels in a panel of ECs and normal endometria (NE) were investigated, with the aim to test the correlation with clinicopathologic characteristics and the prognostic significance of this marker.

Methods: Pre-operative serum samples from 141 EC-patients (25 G1, 60 G2, 56 G3) and from 76 NE-patients were analysed for HE4 (HE4 EIA-assay, Fujirebio-Diagnostics) levels.

Results: sHE4 levels were significantly higher in EC-patients compared with controls, as measured by ELISA. sHE4 levels are significantly correlated with age ≥ 65, higher stage (III-IV vs ≥I-II), higher grade (G2/G3 vs G1), deeper myometrial invasion (M2 vs M0/M1) and lymph nodes involvement. Regarding the univariate survival analysis, considering the whole ECs cohort, high sHE4 levels were significantly correlated with decreased PFS, OS and DFS. If we restrict the analysis to G3-EC, high sHE4 levels had an independent prognostic value for DFS, PFS and OS in multivariate analysis.

Conclusions: This study highlights that HE4 is secreted at higher levels in serum of EC-patients compared with NE-controls. sHE4 levels could be associated with a more aggressive tumor phenotype. Since HE4 has shown an independent prognostic value for DFS, PFS and OS in G3-EC patients, its serum determination could be clinically useful in the attempt to identify patients at different risk of relapse before starting standard therapy.
CUTANEOUS MELANOMA METASTATIC TO THE OVARY: A CASE REPORT

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Background: Cutaneous melanomas rarely metastasize to the ovary. A case of malignant melanoma metastatic to one ovary occurring 8 year after wide local excision of the primary cutaneous lesion on the patient's back is reported.

Case report: A 28-year-old with woman had resection of a 3x3 cm (stage IV according to Clark) melanoma of the right shoulder with negative lymphnodes in 1999. The patient did well until June 2008 when she developed a 2 cm metastatic brain lesion that was resected. Whole brain irradiation was given and a CT scan of the abdomen revealed the presence of a 7 cm lesion on the left ovary. Total abdominal hysterectomy and bilateral salpingooophorectomy was performed and pathologic examination revealed a recurrent malignant melanoma in the ovary. The patient received chemotherapy but died in december 2009 for disseminated disease.

Discussion: This case illustrates the clinical variability and unpredictable biologic behavior of malignant melanoma and it is concluded that malignant melanoma metastatic to the ovary should be suspected in any patient who presents with an adnexal mass and has a history of malignant melanoma.
SPLENIC PELIOSIS IN ASSOCIATION WITH BENIGN OVARIAN TUMOUR (CASE REPORT)

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Peliosis is a term used to describe the presence of blood-filled cysts within the parenchyma of solid organs. It usually affects the liver (peliosis hepatis). Other organs such as the lungs, parathyroid glands, and kidneys may be affected. Isolated splenic peliosis (peliosis lienis) is a rare pathology. This is the first case to report isolated splenic peliosis in association with benign ovarian tumour.

A 66 year old female, presented with lower abdominal pain. An ultrasound scan suggested a complex ovarian mass, with a possibility of ovarian cancer. A CT scan confirmed the presence of a complex cyst with solid component. In addition there were multiple low attenuation lesions within the spleen. The CA125 was 12 U/ml. The differential diagnosis included advanced ovarian cancer with splenic metastasis or a lymph-proliferative disorder. An ultrasound guided biopsy of spleen was obtained. Histology showed reactive changes suggesting autoimmune thrombocytopenia, but the results were inconclusive. Platelet count was 146.

After discussion at Gynaecologic oncology multidisciplinary team meeting; debulking surgery was offered. Intraoperative findings showed enlarged spleen, and a 10 x 10 cm benign looking ovarian cyst with no evidence of spread. The gynaecologic concology team carried out a staging laparotomy including: peritoneal washings, total hysterectomy, bilateral salpingoophorectomy, omentectomy para-aortic lymphadenectomy and splenectomy.

The patient had a smooth post-operative recovery and discharged three days after surgery. Splenic histology showed a well circumscribed areas composed of blood filled cysts with intervening tissues showing fibrosis and neutrophil infiltration suggesting peliosis lienis. The ovary showed a benign Brenner tumour and mucinous cystadenoma.
PRIMARY OVARIAN CHORIOCARCINOMA PRESENTING WITH ACUTE ABDOMEN MIMICKING AN ECTOPIC PREGNANCY

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Pure ovarian choriocarcinoma is a very rare tumour. It is an aggressive tumour, carries a worse prognosis and usually chemoresistant compared to the gestational type\(^1\). The diagnosis is challenging and the clinical picture may be similar to benign conditions commonly seen during the reproductive age, such as ectopic pregnancy and ruptured ovarian cyst.

A 30 year old female, presented to our early pregnancy assessment unit (EPAU) with lower abdominal pain and a positive urinary pregnancy test, there were no signs of acute abdomen. A transvaginal scan examination revealed a left ovarian mass, and a thickened endometrium with no gestational sac seen. B-hCG and serum progesterone were checked. The levels were not conclusive and a plan was made to repeat B-hCG after 48 hours.

Two days later, she was admitted with severe lower abdominal pain. A provisional diagnosis of a ruptured ectopic pregnancy was made and the patient was taken to theatre for diagnostic laparoscopy. Operative findings showed what looked to be a ruptured ovarian cyst and active bleeding from the edges. Biopsy was taken from the bleeding ovarian tissues and edges were diathermised. The left fallopian tube looked healthy, absent right tube and ovary noted. Post operative recovery was uneventful.

Histology was inconclusive. The differential diagnosis was ectopic pregnancy versus a pure ovarian choriocarcinoma. Upon reviewing the slides at a tertiary centre and the diagnosis of ovarian choriocarcinoma was confirmed. Patient had exploratory laparotomy which included hysterectomy, salpingooophorectomy and assessment of peritoneal cavity followed by chemotherapy.
SMALL CELL CARCINOMA OF THE OVARY, HYPERCALCEMIC TYPE TREATED WITH CONSERVATIVE SURGERY

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Introduction: Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare neoplasm that typically occurs in young women. In two thirds of the patients the tumor is associated with asymptomatic paraneoplastic hypercalcemia. The diagnosis may be impeded and the neoplasm must be distinguished from other tumors with similar features. It is an aggressive malignancy with a poor prognosis and few long-term survivors. The overall 5-year survival rate is solely 10%.

Aim: To investigate the outcome of a young patient with SCCOHT treated with conservative surgery.

Case: A 23-year-old female patient was initially referred to our institute presenting a unilateral ovarian mass. She had primary conservative surgery with a left salpingo-oophorectomy, omentectomy, appendectomy and multiple biopsies. The definitive histological examination was a small cell carcinoma of the ovary, hypercalcemic type, stage IC. CA125, CA19.9 and CA15.3 were negative with asymptomatic hypercalcemia and positive HE4. She received six cycle of chemotherapy with ifosfamide, carboplatin and etoposide. Twelve months after the initial treatment CT scan revealed a retroperitoneal aortic relapse. A metastasectomy with sistematic aortic and pelvic lymphadenectomy was performed, followed by carboplatin and etoposide chemotherapy combination. After three cycle, PET/CT showed a recurrence of 5 cm close to the spleen. There was not evidence of pelvic disease.

Conclusion: Despite radical surgery and chemotherapy seem to have the most favorable results, the outcome remains extremely poor. In young patients conservative surgery, preserving uterus and one ovary, seem to be as feasible as the aggressive approach without compromising survival.
 IMPORTANCE TOPO I, TOPO II, MDR EXPRESSION LEVELS AT ADVANCED OVARIAN CANCER

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The study of level expression genes, which are take part in cytostatic metabolism, is very actual. The aim of our study was to estimate the importance TOPO I, TOPO II, MDR expression levels in advanced ovarian cancer (AOC). The research subject was the tumor tissues of 31 patients with AOC. These patients received treatment at the gynecologic department of National Cancer Center of N.N. Alexandrov from 2006 to 2008. Patient's histories, out hospital cards, operations protocols with histological verified diagnosis were analyzed. Oligonucleotide primers and probes were used for PCR to TOPO I, TOPO II, MDR genes. These primers have been synthesized by Applied Biosystems (USA). Kit for reverse transcription was used for receiving cDNA by High-Capacity cDNA Reverse Transcription Kit (Ambion, USA). Results. The mean age of patients with AOC was 57.6±10.1 years. 3-year overall survival patient with AOC was 50%. The disease progression more than 6 month after treatment was registered in 11 cases, less than 6 months after - in 20 cases. In first case - this is chemosensitive group, the second - chemoresistance group. There is no any statistically significance in studing groups at TOPO I, TOPO II, expression levels in AOC. But we estimated the correlation between expression levels of TOPO I, TOPO II (p< 0.0001). The high level MDR gene expression was estimated in tumor tissues of chemoresistance group patients (p< 0.05). Thereby, high level MDR gene expression in the tumor tissues of patients with AOC characterizes the progression disease more than 6 month after treatment.
HYTADID CYST CONCOMITANT WITH OVARIAN TUMOR IN POSTMENOPAUSAL WOMEN

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Aim: Hydatid disease is endemic in Asia. It involved predominantly liver. Occurrences in genital tract is very rare.

Case presentation: Two old women were refer to our clinic due to ovarian mass. At the time of exploratory laparatomy we had found ovarian tumor and concomitant with hydatic cyst in liver and omentum.

Discussion: Although hytadid disease distinguishable from tumors with imaging, but can result in difficulty of ovarian tumor diagnosis, so careful attention to it entity is necessary.

Keywords: Hytatid disease, ovarian tumor
THE PREDICTIVE VALUE OF PREOPERATIVE TRANSVAGINAL SONOGRAPHY IN THE STAGING OF TUMOR PATTERN IN OVARIAN CANCER CASES

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Objectives: A retrospective study was conducted to evaluate the predictive value of preoperative staging by transvaginal sonography (TVS) in ovarian cancer cases.

Methods: In 31 patients presenting with clinical signs and symptoms of ovarian cancer, preoperative systematic staging regarding tumor size (T), presence of ascites (A), peritoneal carcinomatosis (PC), bladder invasion (BI), intestinal invasion (II) as well as pelvic lymph node involvement (LN), were evaluated by TVS. Findings combining conventional ultrasound and Color Doppler imaging were compared to findings during the operation and final histology results.

Results: Preoperative staging was correctly achieved by TVS for T in 85%, for A in 98% (95% CI: 90-100), for PC in 94% (95% CI: 86-100), for BI in 98% (95% CI: 95-100), for II in 97% (95% CI: 91-100). The predictive value of TVS for LN was minor (9%, 95% CI: 6-25).

Conclusions: TVS is a sensitive noninvasive method for preoperative staging of suspected ovarian cancer regarding tumor size, ascites, invasion of adjacent organs and peritoneal carcinomatosis. It is not sensitive in the detection of malignant lymph nodes. The necessity of invasive or more elaborate diagnostic tools such as CT and MRI, cystoscopy, rectoscopy and diagnostic ascites punction can be reduced by systematic use of TVS.
CLINICAL CHARACTERISTICS OF LONG-TERM SURVIVORS OF ADVANCED EPITHELIAL OVARIAN CANCER

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Objectives: To review characteristics of women who are long-term survivors of advanced (stage III or IV) invasive epithelial ovarian cancer.

Methods: A retrospective chart review was performed of women who were diagnosed with advanced ovarian cancer between the years of 1988 and 1998 and who survived for at least 10 years after diagnosis. Age at diagnosis, family history of cancer, outcome of surgery (optimal versus suboptimal cytoreduction), time to first recurrence, and platinum sensitivity were examined.

Results: A total of 372 women in our practice were diagnosed with stage III or stage IV invasive epithelial ovarian cancer. Of these, 34 met the criteria of greater than or equal to 10 years survival and we had complete records for 12 women. Of these patients, 9 (75%) were perimenopausal (age > 50) at time of diagnosis, and 8 (67%) had no family history of cancer. 8 patients (67%) underwent an optimally cytoreductive surgery, while 4 (33%) were supoptimally cytoreduced. Of the 12 women, 7 (58.3%) had no subsequent recurrence following chemotherapy while the remaining 5 recurred at least 3 years (range 3-10 years) after their initial treatments. Of the 12 women, all had stage III disease and demonstrated either primary or recurrent sensitivity to platinum-based chemotherapy.

Conclusions: Women who are long-term survivors of ovarian cancer appear to have platinum sensitive disease with long duration to first recurrence or no recurrence at all. In addition, both optimal and suboptimal cytoreductive surgeries seem to afford a chance of a favorable prognosis.
NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGICAL CYTOREDUCTION IN STAGE IV OVARIAN CANCER: A RETROSPECTIVE CASE CONTROL STUDY

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Objective: To evaluate the role of neoadjuvant chemotherapy (NACT) followed by surgical cytoreduction in the management of stage IV epithelial ovarian cancer.

Methods: A retrospective case control analysis including 64 patients with stage IV ovarian cancer (excluding pleural fluid) was performed. Twenty-nine patients were treated with NACT (3 cycles of carboplatin/paclitaxel) followed by surgical cytoreduction and another 3 cycles of chemotherapy. In 35 patients, primary cytoreductive surgery followed by 6 cycles of chemotherapy, was applied. Response to NACT, optimal cytoreduction rate, progression-free interval (PFI) and overall survival (OS) were analysed.

Results: Diagnosis was established by ascitic fluid cytology, biopsies and CA-125 estimations. After NACT, a partial response occurred in 23 patients. No response was documented in 6 patients. Optimal cytoreduction could be achieved more extensively in the NACT group. At the median follow-up of 60 months, 5-year progression-free interval and overall survival were significantly worse in the NACT group.

Conclusions: A significant number of patients exhibit response to NACT. The degree of optimal cytoreduction is not the only factor affecting survival. Downstaging following NACT leads to higher optimal cytoreduction rates but does not prolong the PFI or OS in comparison to controls and it may have unfavorable effect on the prognosis.
LOW PREVALENCE OF GERM-LINE BRCA MUTATIONS IN EARLY ONSET OVARIAN CANCER PATIENTS

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Between years 2005 and 2009 we tested 143 ovarian cancer patients for the presence of germ-line BRCA1 or BRCA2 mutations. The aim of this retrospective analysis is to assess prevalence of BRCA mutations in certain indication groups and thus help for more appropriate indication to mutational analysis in Czech population.

Patients were indicated to mutational analysis due to early onset cancer (under 40), family history of breast and/or ovarian cancer or due to both reasons. The highest prevalence was, not surprisingly, seen among patients from families with more than 3 affected (breast and/or ovarian cancer) relatives - 83% and among patient from families with 3 affected relatives - 65.4%. Among patients with 2 first degree relatives affected with breast and/or ovarian cancer, the prevalence was 20%.

Although early onset ovarian cancer is thought to be indicator of possibility to harbor BRCA mutation, in our group of patients under 40, the prevalence was 7.1% (regardless family history) and only 1.85% after patients with family history were excluded from this group. There were no mutation detected in the subgroup of patients under 35 (patients with family history excluded).

We can conclude that family history is more precise indicator for possibility of harboring BRCA mutation than the age itself. Further studies are needed to investigate potential factors of hereditary susceptibility to ovarian cancer in young patients.

This work was supported by The Grant Agency of the Czech republic, project No. 301/08/P103.
RISK OF NASCENCY OF THE HYPERSENSITIVITY REACTIONS ASSOCIATED WITH CARBOPLATIN AND PACLITAXEL TREATMENT OF OVARIAN CANCER

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Background: While carboplatin hypersensitivity reactions (HSRs) are associated with IgE-mediated mechanism, paclitaxel related reactions are generally non IgE mediated.

The risk of HSRs to carboplatin increase with multiple cycles, total obtained doses of the drug and duration of PFI. The risk factors in association with severity of HSRs are still being discussed.

Methods: We retrospectively analysed 62 patients with ovarian cancer treated with carboplatin and/or paclitaxel from 1/2009 to 1/2010 (carboplatin=21, paclitaxel=8, carboplatin+paclitaxel=33).

Results: We recorded 11 HSRs (paclitaxel=2, carboplatin=9). 6 from 11 HSRs were severe (carboplatin=5, paclitaxel=1). Severe HSR to paclitaxel occurred after application of the few drops of the first infusion. Severe HSRs to Carboplatin occurred as demonstrated in Table 1.

Conclusion: Severe HSRs to paclitaxel are rare (< 1%) and usually obtained after few minutes of the first or second infusion and they are unpredictable. HSRs to carboplatin are expectables. Further studies are needed to identify the potential risk factors that may contribute to the development of carboplatin severe HSRs. If we define the risk factors of the development exactly, several HSRs we will be able to prevent the nascency of a severity of HSRs by changing the therapy or by using the desenzitization protocol.
ABERRANT HYPERMETHYLATION OF PROMOTER SITE IN TUMOR SUPPRESSOR GENES MAY BE THE MARKER FOR EARLY DETECTION OF OVARIAN CANCER

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Background: Over 60% of ovarian cancer cases are presented as advanced stages. The improvement in early diagnosis should bring the molecular medicine.

Aims: To evaluate methylation status of tumor-suppressor genes (RASSF1A, GSTP, E-cadherin, p16 and APC) in malign, border-line and benign ovarian tumors and find links between the development of ovarian malignancy and epigenetic DNA changes.

Methods: Tumor DNA from fresh tissue samples of ovarian tumors and controls was used. The methylation status of the promoter region of mentioned genes was determined by Methylation Specific Polymerase Chain Reaction (MSP).

Results: We examined 13 patients with epithelial ovarian cancer, 2 with border-line tumor, 12 with benign ovarian lesion and 7 with healthy ovarian tissue (controls). The MSP confirmed hypermethylated status of RASSF1A and GSTP gene only in malign ovarian tumors. Border-line and benign lesions exhibited preferentially hypermethylation in E-cadherin and p16 gene. The APC gene was hypermethylated in all groups. In ovarian cancer the most frequent hypermethylated gene was RASSF1A (46.2% cases) and p16 (38.5%), in border-line tumors E-cadherin (50%) and in benign ovarian tumors p16 (25%). The malign tumors exhibited higher number of methylated genes compared to border-line tumors (p< 0.05) and controls (p< 0.01). There were no associations with the type of ovarian cancer, tumor grade or disease stage.

Conclusion: The methylation of RASSF1A and GSTP may serve as useful molecular marker for early detection of ovarian malignancy.

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SET-UP OF AN OVARIAN CANCER BIOBANK WITHIN THE CONTEXT OF A MULTICENTRE INTERNATIONAL RANDOMISED PHASE 3 TRIAL (ICON7)

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**Background:** ICON7 is an international Medical Research Council sponsored two-arm multi-centre trial assessing the addition of bevacizumab to standard chemotherapy in patients receiving first-line chemotherapy for epithelial ovarian cancer. Currently there are no established biomarkers relating to the efficacy and/or toxicity of bevacizumab and the opportunity was taken to create a high quality central biorepository alongside the ICON7 trial. This was supported by a grant from F. Hoffmann-La Roche Ltd.

**Methods:** A multi-level approach was adopted to tailor sample collection to facilities and experience available at individual sites. An academic centre experienced in biobanking was chosen to co-ordinate sample collection. Biological samples were requested to be collected according to high quality SOPs, devised and validated locally.

**Results:** Overall samples were collected from 10 of 11 countries participating in the clinical trial. Of 1528 patients randomised, 772 patients consented to participate in sample collection. To date 471 whole blood samples, 228 serum/plasma samples and 422 tissue samples have been collected.

A high quality ovarian cancer biobank now exists with correlative clinical data. There is currently one proposal aiming to develop hypotheses relating to predictive biomarker profiles of bevacizumab efficacy. Other applications for use of this resource are currently requested for consideration.

**Discussion:** The development of the ICON7 biobank demonstrates the feasibility of developing a high quality biorepository alongside a clinical trial. To maximise success, careful planning is required alongside development of the clinical trial with multi-disciplinary engagement of laboratory and translational researchers, pathologists, sample co-ordinators and research nurses/sample processors.
THE THERAPEUTIC VALUE OF LYMPHADENECTOMY IN OVARIAN CANCER PATIENTS
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Although the assessment of regional lymph nodes status is the integral part of diagnostics in ovarian cancer patients, lymphadenectomy, as the routine procedure, is still the subject of controversy.

Aim: The assessment of the therapeutic value of lymphadenectomy in ovarian cancer patients.

Material: The retrospective analysis of 469 ovarian cancer patients, treated at Maria Sklodowska-Curie Memorial Cancer Centre, Gynecological Oncology Department in Warsaw, between 1998 and 2006, was performed. 211 patients were treated with surgery, according to the actual protocol, with pelvic and periaortal lymphadenectomy. The control group constituted 258 ovarian cancer patients, treated at the same time with surgery, but without lymphadenectomy. All patients were treated with complementary chemotherapy with paclitaxel and cisplatin.

Method: The multivariate Cox's analysis of clinico-pathological factors in aspect of the value of periaortal and pelvic lymphadenectomy was performed. Next, the survival Kaplan Meier's curves, using the log rank test, were compared.

Results: As the result of multivariate analysis, the statistically significant prognostic value of periaortal and pelvic lymphadenectomy, in aspect of the disease free survival (DFS), was demonstrated, p value = 0.018, HR = 0.69[0.51, 0.94]. As the result of the OS and DFS curves comparison, the difference was statistically significant in early ovarian cancer patients, relatively log rank test value: 0.01 and 0.005.

Conclusion: Periaortal and pelvic lymphadenectomy in ovarian cancer patients should be considered as part of the routine surgical procedure, especially for early ovarian cancer patients, but the future studies on this field are needed.
SPERM PROTEIN 17 VACCINATION REDIRECTS T-HELPER DIFFERENTIATION PROGRAM IN A MURINE MODEL OF OVARIAN CANCER

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Sperm protein (Sp17) is overexpressed in primary as well as in metastatic ovarian cancer (OC), at all disease stages. We used Sp17 as a target for CpG-adjuvated OC vaccine in the C57BL/6-ID8 animal model, obtaining enduring protection from OC development for both prophylactic and therapeutic purposes. This is the first time that a mouse counterpart of a cancer testis antigen (Sp17) was shown to be expressed in an OC mouse model, and that vaccination against this antigen significantly controlled tumor growth. We show that the vaccine breaks OC-induced immunologic tolerance, by boosting Th-17 and hampering T-reg cell differentiation. Further, our vaccine is the first reported effective prophylactic strategy that may be used for prevention purposes in high-risk OC women. The successful preclinical testing animal model presented here demonstrates that our strategy may represent a life-saving therapy in human OC treatment and prevention.
IS THERE SURVIVAL BENEFITS PERFORMING RETROPERITONEAL SYSTEMIC LYMPHADENECTOMY IN ADVANCED EPITHELIAL OVARIAN CANCER?

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Background: To estimate the survival impact of systemic retroperitoneal lymphadenectomy (SRL) in patients with advanced epithelial ovarian cancer (aEOC) with optimal cytoreduction.

Patients and methods: Demographic and clinicopathologic data were obtained from the Tokai Ovarian Tumor Study Group between 1986 and 2008. Survival curves were calculated using the Kaplan-Meier method. Differences in survival rates were analyzed using the log-rank test.

Results: A total of 180 patients had clinical pTIII-IV EOC (median age: 55 years, range: 18-84). Eighty-seven (48.3%) patients underwent systemic retroperitoneal lymphadenectomy (SRL). Five-year progression-free survival (PFS) rates of SRL and non-SRL group were 41.9 and 46.7%, respectively. In addition, Five-year overall survival (OS) rates of SRL and non-SRL group were 59.0 and 62.9%, respectively. Thus, SRL was not associated with improved PFS and OS in all patients (p=0.658 and p=0.853, respectively). Moreover, SRL did not improve the PFS and OS in those stratified with serous or non-serous histological type (PFS; \(p=0.672\) (serous), \(p=0.395\) (non-serous): OS; \(p=0.492\) (serous), \(p=0.622\) (non-serous), respectively). Furthermore, there was no significant difference in the ratio of positive lymph node metastases regardless of the completion of lymphadenectomy.

Conclusion: Our data suggest that patients with aEOC who underwent SRL did not show a significant improvement in survival.
CASE REPORT OF MASSIVE OVARIAN EDEMA: A BENIGN CONDITION THAT CAN MIMIC OVARIAN CANCER

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Background: Massive ovarian edema is a tumor-like enlargement of the ovary which probably results from an uncompleted torsion of the mesovarium. Although it is a benign and rare condition, it can be clinically misdiagnosed as ovarian cancer.

Aims: To describe a case of massive ovarian edema.

Case report: A 32 year-old white woman was admitted to Barretos Cancer Hospital with a suspected diagnosis of ovarian cancer. She had complained of abdominal pain, distention and vomiting for one month. The gynecologic examination showed a large and painful pelvic mass. The pelvic and abdominal computed tomographies demonstrated a voluminous ascites, and a pelvic complex cyst measuring 11 x 8 x 9cm (455 cm3), with thick wall and well delimited margins. A moderate left pleural effusion was observed in the chest computed tomography. Serum tumor markers values were: CA125 = 1,305U/ml; CEA < 0.2ng/ml; CA15.3 = 26.9U/ml. The patient underwent a left salpingooophorectomy for diagnosis and treatment. The ovarian mass was friable and well vascularized. Frozen-section analysis did not show any malignant disease. Definitive pathologic study reported a massive ovarian edema.

Conclusion: Massive ovarian edema, a benign condition, can mimic ovarian cancer, with important elevation on the levels of serum CA125 and Meigs’ syndrome.
CHARACTERIZATION OF THE CELLULAR IMMUNE RESPONSE IN WOMEN WITH OVARIAN CANCER

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Ovarian cancer presents late diagnosis and high mortality due to lack of sensitive and specific biomarkers and the rapid progression of this cancer, asymptomatic in early stages. The immune cells of the tumor microenvironment are dysfunctional and fail to control the tumor growth and may even promote the growth of cancer. Despite numerous attempts to correlate the degree and type of cellular infiltrate and the prognosis or survival of patients with ovarian cancer, there is no consensus about the real meaning of the leukocyte infiltrate in these cases. This study selected 36 patients: 10 women in the control group, 9 in the group of benign ovarian neoplasm and 17 in the group of malignancy. The serum levels of serum molecules surface expression of cells of the innate immune response with analysis by flow cytometry. More than 70% of patients with ovarian cancer presented advanced disease and values of CA125 changed. For the analysis found, there was a change between the groups for molecules expression in neutrophils CD80, CD69, CD62L, CCR3 and CXCR4. The molecules expressed by monocytes differences were found in the fluorescence intensity of HLA-DR and CD86 and CD80 expression. There was no statistical difference in the analysis of surface molecules of NK cells between groups. The results of these experiments showed alterations in the expression of some surface molecules of cells of the innate immune response between groups, which helps in the progression of carcinogenesis.

Keywords: Ovarian cancer, benign ovarian tumor, immune response, monocytes, neutrophils, NK cells
PRIMARY OVARIAN ENDOMETRIOID ADENOCARCINOMA: INCIDENCE AND CLINICAL SIGNIFICANCE OF MORPHOLOGIC AND IMMUNOHISTOCHEMICAL MARKERS OF MISMATCH REPAIR PROTEIN DEFECTS

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Background: Lynch syndrome (LS) screening algorithms in uterine cancer are improved by integrating pathologic variables such as morphology (tumor infiltrating lymphocytes (TIL), peritumoral lymphocytes (PTL)) and mismatch repair proteins (MMR) immunohistochemical abnormalities. Use of these markers to evaluate ovarian cancers has not been well studied. We assessed the incidence and clinical significance of TIL/PTL and MMR immunohistochemistry in primary ovarian endometrioid adenocarcinoma (OvEA).

Methods: 71 women with OvEA were studied. TIL was defined as 4 lymphocytes or more per high-power-field. PTL was defined as Crohn's-like peritumoral lymphocytic infiltrate. Immunohistochemistry for MMR proteins was performed using antibodies against MLH-1, MSH-2, MSH-6 and PMS-2 on tumor microarrays. Complete loss of tumor nuclear expression of 1 or more protein was defined as abnormal MMR.

Results: Among 71 OvEA, 9 (13%) had TIL, 2 (3%) had PTL, and 12 (17%) had abnormal MMR. Loss of both MLH-1/PMS-2 was most common (6/12), followed by loss of MSH-6 only (4/12). Young age (< 40 years) was not associated with TIL/PTL or abnormal MMR. There was no correlation between TIL/PTL and abnormal MMR: only 1/10 cases with TIL/PTL had abnormal MMR. No other morphologic features, such as tumor grade or stage, predicted abnormal MMR. Among 12/71 patients who died, 10 (80%) had normal MMR. Among 12 abnormal MMR patients, 10 were alive and 2 died.

Conclusions: Neither young age nor tumor morphology in ovarian endometrioid adenocarcinoma were associated with MMR status. Therefore, algorithms for LS-screening in ovarian cancer may differ from those proposed for uterine cancer.
CLINICAL IMPACT OF FDG-PET ON THE MANAGEMENT OF REFRACTORY AND RECURRENT OVARIAN CANCER

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Background and aims: This prospective study was study the clinical impact of FDG-PET on the management of refractory and recurrent ovarian cancers.

Methods: Patients were enrolled under any of the following criteria: (1) CT/MRI-undefined lesions in stage III/IV ovarian cancers with unsatisfactory decline of CA125 during first line chemotherapy. (2) Unexplained CA125 elevation after complete remission after primary surgery with or without chemotherapy (an increase with doubling of nadir level, at least one >35 U/mL or any two measurements > 35 U/mL at least 2 weeks apart). (3) For metabolic biopsy for interval or post-therapy surveillance CT/MRI-detected lesions that guided biopsy is not feasible. (4) A documented relapse or persistent tumor for curative salvage therapy. (5) Undefined lesion by surveillance CT/MRI with normal CA125. The findings of FDG-PET were compared with those of CT/MRI, or clinical status on follow-up. Clinical impacts were designated positive, negative, and no change.

Results: From Sep 2005 to Oct 2009, 63 patients were eligible to have 78 scans. 26 CT-guided biopsies were done. The median period of follow-up was 20.1 months (1.5 months - 52.3 months). To the date of last follow-up, 19/63 (30.2%) patients had no evidence of disease, 26/63 (41.3%) were alive with disease, 14/63(22.2%) died of disease. FDG-PET provided positive impact in 39.7% (31/78), negative impact in 7.7% (6/78) and no clinical impact in 52.6% (41/78) of all the scans.

Conclusions: FDG-PET combined with MRI-CT are beneficial to the clinical management for refractory and recurrent ovarian cancer.
CA125 VALUES: THREAT OR COMFORT TO OVARIAN CANCER SURVIVORS ON ACTIVE TREATMENT

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Objective: We examined ovarian cancer survivors' understanding of CA125, and identify whether perceptions of CA125 were related to objective CA125 values, depressive symptomatology, and quality of life.

Materials: Ovarian cancer patients with Stages III/IV disease undergoing first line or salvage chemotherapy within four weeks of enrollment were eligible. Measures included the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) to assess QOL, the Center for Epidemiologic Studies-Depression (CES-D) to assess depression, and two open-ended and five Likert scale questions to assess self-reported perceptions of CA125. The open-ended questions asked the patient to define the CA125, and the meaning or importance she placed on it. The questions examined perceptions of function, importance, threat, and meaning associated with CA125. CA125 values were obtained from medical record and CA125 trends were evaluated up to completion of the survey.

Results: Twenty two patients with Stages III/IV ovarian cancer were enrolled. Qualitative results of questions indicated that the majority of patients were able to clearly define the CA125 and articulate either threat or comfort associated with their CA125 values (98%). Ninety percent indicated that the CA125 value predicted their health status, and 71% stated that their mood was influenced by CA125 information. Further, rising CA125 values were significantly associated with depressive symptoms (p=0.007) and influenced patient-reported perceptions of the personal meaning of the CA125 (p=0.04).

Conclusions: Ovarian cancer survivors demonstrate a clear understanding of the CA125 value. Attributions or perceptions of health threat or comfort associated with CA125 information is significant, and may influence mood.
IS RISK MALIGNANCY INDEX A USEFUL TOOL FOR PREDICTING MALIGNANT OVARIAN MASSES IN DEVELOPING COUNTRIES?
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Introduction: Risk of malignancy index has been widely studied for prediction of malignant pelvic masses in western population, however, little is known regarding its implication in the developing countries. The objective of this study is to determine how accurately the RMI can predict the malignant pelvic masses.

Materials & methods: This was a retrospective review of charts conducted at The Aga Khan University Hospital, Karachi, Pakistan. Those patients who came to the Gynecological clinic between January 2004 to December 2008 with adnexal masses were identified by means of IDC-9CM coding system. The files of these patients were reviewed for collecting information related to demographic characteristics, ultrasound findings, menopausal status, CA 125 and histopathology. Patients with advanced stage disease were excluded. The RMI for each of these patients were calculated based on the standard formula.

Results: A total of 283 women were included in the analysis. When analyzing the individual parameters of RMI, the best predictor for malignancy was ultrasound with the sensitivity, specificity and positive likelihood ratio of 78.3%, 81.5% and 4.2 respectively. The positive likelihood ratio of RMI at the standard cut off value of 250 was 8.1 while at the cut off of 200; it was 6.8 with comparable sensitivity and specificity.

Conclusion: RMI is a sensitive tool in predicting malignant adnexal masses. A cut off of 200 may be suitable in developing countries for triaging and early referrals to tertiary care centers.
EXTENDED CYTOREDUCTION OF TUMOR AT PORTA HEPATIS WITH EPITHELIAL OVARIAN CANCER BY INTERDISCIPLINARY TEAM APPROACH

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Objective: The objective of this study was to describe the development and experience for resection of tumor at porta hepatis in patients with ovarian cancer by interdisciplinary team approach.

Methods: From August 2007 to June 2009, 11 women underwent extended cytoreductive surgery involving resection of tumor at porta hepatis by hepatobiliary surgeons for 2 primary and 9 recurrent ovarian cancer cases.

Results: Tumor resection at porta hepatis was required in 7.1% of the patients (11/155) during the study period. Median tumor size of porta hepatis was 2.0 (range, 0.7–4) cm. All visible tumors at the porta hepatis were completely resected with co-operation of hepatobiliary surgeons. Optimal cytoreduction was achieved in all patients. There was no significant morbidity related to tumor resection of porta hepatis and mortality associated with surgery. Disease-free survival ranged from 1-21 months with median follow-up of 8 months (range, 3-21 months).

Conclusion: Tumor at porta hepatis could be resected in patients with ovarian cancer by interdisciplinary team approach with hepatobiliary surgeons.
“INTRAPERITONEALISM” IN CHEMOTHERAPY (IPCT) OF OVARIAN CANCERS

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Introduction: Ovarian cancer is known for late stage disease. An attempt was made to improve effectiveness of available chemomolecules and hope for satisfactory survival in late stage inoperable disease. This was possible with Intraperitoneal (IP) chemotherapy and its pharmacokinetic fundamental basis that provides high concentration topical effect in addition to systemic effect. Although many chemotherapeutic regimen were tried in this attempt, but only survival data of stage III epithelial tumors treated with SCAP is presented.

Aim:

- To utilize best of bioavailability of drug through topical application.
- To improve efficacy of drugs by chemo-chemosensitization.
- To achieve improved survival and TDP times in stage III ovarian tumors.

Methods: Stage III ovarian epithelial tumour patients divided in two groups

Group I received: Intraperitoneal Cis Platinum preceded by IP 5 FU and followed by IP Adriamycin. Endoxan 500mg given intravenously on Day1 & Day5. Such three courses were given preoperatively and six courses all together in operable or inoperable cases. Group II received all four drugs by systemic route in same sequence.

Results:

1. Quick palliation and pain relief, ascitis control achieved with rapid fall of CA-125
2. Improved disease progression free rates and Improved debunking operability.
3. Lesser Systemic Side effects.

Conclusion: Late stage ovarian tumours can be greatly benefited by intraperitoneal chemotherapy. Logically this method is advocated with view of topical and bioavailability of the drug for much prolonged period. Palliation is much quicker with IP administration. There is improvement in survival as well as treatment to disease progression time.
THROMBOCYTOSIS IN OVARIAN CANCER: EFFECT ON PLASMA PROTEIN PROFILES AND SURVIVAL

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**Background:** Thrombocytosis is present in a wide range of malignancies with its clinical significance remaining unclear. Our study looks into thrombocytosis in epithelial ovarian cancer (EOC) to evaluate the prognostic role of thrombocytosis as part of a prognostic index and to identify mediators of thrombocytosis.

**Method:** Using a high through-put Luminex immunoassay, plasma levels of 41 proteins were measured in samples from 62 chemo-naive EOC patients newly diagnosed from 2000 to 2009. We developed a prognostic index named mPIEPOC (modified Prognostic Index in Epithelial Ovarian Cancer) based on and platelet count and the PIEPOC index (Teramukai et al). The mPIEPOC for each variable are: Stage Ic (+0), II-IV(+2); Grade 1(+0), 2/3/not known(+1); Histology mucinous/clear cell (+1), endometrioid(-1); Residual disease none/microscopic(+0), other(+2); Performance status 0(+0), 1/2(+1), 3/4(+2). We also assessed the relationship between proteins and thrombocytosis using Pearson correlation and the prognostic performance of the mPIEPOC relative to PIEPOC using Cox regression analyses.

**Results:** Eleven plasma proteins showed a significant correlation between platelet counts and plasma protein levels (p< 0.05). These were syndecan1, leptin, Notch Homolog, CA125, HE4, ESM1, TNFRSM21, CFS1R, mesothelin isoform 3, LYPD3, and osteopontin. The mPIEPOC model demonstrated a better prediction of PFS compared to PIEPOC (p=.005).

**Conclusion:** Our data indicates that the mPIEPOC performs better as a prognostic score than PIEPOC. We have also identified several candidate proteins that may represent critical mediators of thrombocytosis in EOC. They have the potential to elucidate the mechanisms of thrombocytosis in EOC and warrant further investigation.
PREDICTIVE VALUES OF THE ULTRASOUND PARAMETERS, CA-125 AND RISK OF MALIGNANCY INDEX IN PATIENTS WITH OVARIAN MALIGNANCY

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Study: 115 patients, divided into: group-A(n=41)-ovarian malignancy; group-B(n=74)-benign ovarian tumor, evaluated for CA-125, MRI and US regarding sensitivity, specificity, positive and negative predictive values (PPV, NPV respectively).

Results: The patients of group A were older (p<0.05). CA-125<35U/ml was predominant in group B (p<0.001); CA-125>35 in group A (p<0.001); no differences for CA-125(35-130U/ml). CA-125<35U/ml showed high NPV, sensitivity and specificity, CA-125>35U/ml only specificity. Regarding US, only presence of ascites showed PPV>70.0%. The NPV>70.0% we noted for: size<6cm, solid structure, clear distinguish ability from surround tissue, unilaterality, absence of the ascites, smooth margins, capsules≤2mm, absence of septum/papillary vegetation≤2 mm, low density liquor; sensitivity>0.700 for: uni-laterality, rugged margins, capsule>2mm, septum/papillary vegetation>2 mm, high density liquor; specificity>0.700 for: sizes≥6cm, cystic structure, clear distinguish ability from surround tissue, absence of the ascites, smooth margins. The MRI showed only high NPV for MRI<200(76.8%). Additionally analyzed MRI in correlation of CA125 increased its predictive values: 1.high NPV and sensitivity(81.6%, 0.818, respectively) for MRI< 200; and high NPV and specificity(86.7%, 0.755, respectively) for MRI>200 with CA125< 35U/ml; 2.high PPV and specificity(75.0%, 0.929, respectively) for MRI< 200; and high sensitivity(0.750) for MRI>200 with CA125 of 35-130U/ml; 3.high specificity(0.714) for MRI< 200; high sensitivity(0.944) for MRI>200 with CA125>35U/ml.

Conclusions: CA-125 and US, as single criteria were not accurate. MRI is good indicator in correlation with CA-125. The situation with CA-125(35-130U/ml) (high PPV for MRI< 200) confirmed our suspicion that this group could be confounding regarding the nature of tumor.

Keywords: Ovarian tumor, CA125
HOW LONG? HOW TO TREAT RECURRENT OVARIAN CANCER

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**Background:** Ovarian cancer is increasing rapidly in Japan as Western World. Most patient present with advanced disease. Unfortunately, majority will relapse after initial therapy. The median time to relapse is 12 to 18 months and the median survival of women with advanced ovarian cancer is 3 to 4 years. It means that most patients will need second or more therapy including phase study or surgery or radiation or other.

**Methods:** We reviewed charts that received chemotherapy in our hospital during 2 years (2007 to 2008) of recurrent ovarian cancer patients.

**Results:** In this period, we did 1669 courses of chemotherapy for ovarian cancer. Of these, 288 courses were for recurrent 28 cases. In recurrent cases, median number of course was 1 to 100 (median 28). The number of regimen was 1 to 5 (median 2.5). Mean age was 40 to 79 y.o (median 55). Survival time was 1 to 140 M (median 24.5). The number of regimen was more than 9. Nine of 28 patients had more than 30 courses of therapy after recurrence. One patient had more than 100 courses. Another case had breast, ovary, endometrial cancer had recurrence at lung and bone and controlled for 6 years with radiation, chemotherapy and bisphosphonates.

**Conclusion:** To treat recurrent patients, we have no good guidelines. Tumor Dormancy Therapy (Takahashi, Kanazawa Univ. Japan), and Metronomic chemotherapy (Folkman and Kerbel) are getting topic. To treat advanced or recurrent cancer, do not give up and do not hang on too much.
THE ROLE OF SECONDARY SURGICAL DEBULKING IN RELAPSED OVARIAN CANCER. A RETROSPECTIVE STUDY

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In order to evaluate the role of secondary surgical debulking, we retrospectively analyzed 244 consecutive patients affected by relapsing epithelial ovarian cancer treated in our Institutions.

108/244 patients were submitted to secondary cytoreduction (SCS) plus chemotherapy while the remaining patients were treated with chemotherapy alone. Patients eligible for SCS were more frequently affected by single or localized relapse, platinum sensitive, preoperatively considered “optimally debulkable” (i.e. to no residual disease) at the time of the diagnostic work-up. Patients submitted to SCS showed better prognosis (median OS: 60.4 Vs. 50.4 months; p=0.014). Among them, those with limited disease (1 or 2 sites) experienced the longest median OS, compared to patients treated with chemotherapy alone (median OS:70.2 Vs. 50.9 months; p< 0.0001). Within the “surgical” group, the completeness of surgical debulking significatively impacts prognosis (median OS: 79.6 months for optimal debulking Vs. 37.6 months for sub-optimally; p< 0.0001). The best results were observed in platinum-sensitive patients (median OS: 90.1 months for optimal debulking Vs. 47.3 months for sub-optimally; p< 0.0001). The OS advantages have been observed in platinum-sensitive patients only with a gradient of efficacy depending on the PFS (13-18; 19-24; > 24 months; median survival: 41 Vs. 59 Vs 75 months). The platinum “highly-sensitive” patients (PFS>24 months) with limited disease treated with SCS and second line platinum-based chemotherapy showed the best prognosis: median OS 139 Vs 67.6 months (patients not submitted to surgery).

In our series patients with platinum resistant/refractory disease did not show any survival advantage when submitted to a SCS.
BORDERLINE TUMORS: DIAGNOSIS AND MANAGEMENT: ABOUT 15 CASES

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Background: Borderline ovarian tumors (BOTs) are rare entities with excellent prognosis depending on tumor stage and presence of invasive implants. Since their discovery in 1929, they inspired confusion, apprehension and disagreement.

Aim:

- Identify epidemiological, clinical and therapeutic particularities of borderline tumors of the ovary.
- Study the different surgical approaches for borderline tumors of the ovary.
- Assess the value of frozen section in this pathology.

Methods: This is a retrospective study of 15 patients operated for borderline tumor of the ovary and collected at the department A of the center of maternity and neonatology in Tunis.

Results: The average age of our patients was 38 years. Pelvic pain was the main circumstance of discovery, it accounted for 50% of the cases. The discovery was fortuitous in 40% of the cases. Ultrasound has shown purely cystic tumors in 70% of cases and solido-cystic ones in 30% of cases. The surgery was conservative whenever possible (12 cases). Histological examination concluded to 60% cases of serous tumor, 26.6% of mucinous tumor, 6.6% of endometrial tumor and 6.6% of mixt ones. All the patients were classified as stage I. Three spontaneous pregnancies were diagnosed after surgical treatment. In 2 patients, surgery was performed for recurrence.

Conclusion: Borderline ovarian tumors require a systematic surgical evaluation to verify or exclude extrapelvic tumor lesions and allow further clinical relevant differentiation between invasive and noninvasive implants. The laparoscopy is of great use in the management of this pathology and the conservative treatment is the more appropriate one.
A CASE OF PORTAL VENOUS GAS WITH SEPTIC SHOCK IN A PATIENT TREATED WITH IRINOTECAN FOR OVARIAN CANCER

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Portal venous gas is a rare complication, especially during chemotherapy. We present a case of portal venous gas with septic shock in a patient treated with irinotecan for ovarian cancer.

A 57-year-old woman with ovarian cancer (FIGO stage IIIc) received 6 cycle of paclitaxel and carboplatin followed by debulking surgery. Pathological examination showed serous adenocarcinoma.

She underwent adjuvant chemotherapy of weekly irinotecan(60mg/m2) for residual tumor from the 17th day after the surgery. She had a fever after the 2 cycles of weekly irinotecan, and suffered from lower abdominal pain. An abdominal CT scan demonstrated portal vein gas, intraperitoneal free air and pneumatosis intestinalis. Given a high index of suspicion for intestinal perforation, she had a surgery emergently for exploration revealing necrosis of residual tumor in omentum without any evidence of intestinal perforation. She dropped into septic shock after the surgery and required intensive care for one week.

The portal venous gas, intraperitoneal free air and pneumatosis intestinalis were disappeared in the abdominal CT on the 9th day after the surgery. A colon fiber revealed a mucosal ulceration of descending colon.

Mucosal injury of bowel wall by irinotecan might have caused bacterial translocation and presented with portal venous gas and septic shock. This case report is the first description of portal venous gas and septic shock in a patient treated with single agent irinotecan for ovarian cancer.
EXTREME DRUG RESISTANCE (EDR) ASSAY DIRECTED THERAPY OF PLATINUM RESISTANT OVARIAN CANCER

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Objective: To investigate Extreme Drug Resistance (EDR) assay guided chemotherapy in recurrent platinum resistant ovarian cancer.

Study design: A total of 34 patients (pts) with recurrent platinum resistant ovarian, primary peritoneal, or fallopian tube cancer were identified in this IRB approved retrospective single institutional study. Of these, 29 had adequate EDR results for analysis in our study. RECIST criteria were used to assess response.

Results: A median of 2 (range 1-5) separate lines of chemotherapy was used prior to platinum resistance. Using the EDR results to treat patients with recurrent disease resulted in, 24% response rate (RR) (7% complete response CR, 17% partial response PR) and 31% stable disease, with 45% of pts with progression. The median progression free survival (PFS) was 3.6 months (95% CI 2.7-4.5) and median overall survival (OS) was 12.9 months (95%CI 12.1-13.9). For comparison, 10 phase 2 co-operative group trials for recurrent platinum resistant disease, with reported response rates and survival data were identified on pub med. Analysis of these 10 studies showed an overall response rate of 13%, (CR 4%, PR 9%), 42% stable disease, 37% progression, and 8% with non-evaluable disease. The median PFS of the 10 studies was 3.3 months, the median overall survival was 10 months.

Conclusion: Our study has a higher response rate than the 10 phase 2 trials reviewed and also yields a similar PFS and OS.
HE4 - NEW TUMOR MARKER
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**Objectives:** Aim of this study was to compare the new tumor marker HE4 with CA 125 and to evaluate its sensitivity for primary diagnostics and for disease progression.

**Methods:** The following tumor markers (HE4, CA 125, TK, TPS and Monototal) were analyzed in two groups of patients. The first group included 80 patients with ovarian cancer and the second control group included 250 patients with the following diseases: malignant non-ovarian cancer diseases in small pelvis, benign gynecological diseases, endometriosis, pregnancy, chronic kidney and liver diseases, heart insufficiency, non-cancer ascites. The sensitivity of these markers are always expressed at 95% specificity.

**Results:** In the group of patients with ovarian cancer we found significantly higher values of HE 4, CA 125, MT and TK (p< 0.001). HE 4 showed the highest sensitivity (73%), while CA 125 and TK were both at 64% sensitivity. The combination of HE 4 and TK had the highest sensitivity at 80%.

In the group of patients with chronic kidney diseases both markers expressed false positivity almost at 100%, other diseases showed false positivity of HE4 at 5 - 15% cases, but CA 125 in 30 -75 % cases

**Conclusions:** HE4 is an appropriate marker for the primary diagnosis and follow-up of ovarian cancer. It expresses a minimal false positivity and it is currently possible to use it for routine clinical practice.

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MOLECULAR PATHOGENESIS OF OVARIAN SEROUS CARCINOMA WITH PSAMMOMA BODIES; INTERPRETATION OF LONG-TERM ONCOLOGICAL OUTCOMES

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A two-grading system in which ovarian serous carcinomas are subdivided into low-grade and high-grade tumors has been proposed on the basis of recent molecular pathogenesis findings. Low-grade tumors, unrelated to TP53 mutations, show favorable prognosis in a slow step-wise process, whereas high-grade tumors, related to TP53 mutations, contribute to poor prognosis. Ovarian serous carcinomas with excessive psammoma bodies behave like the low-grade tumors. However, their etiology and prognostic significance remain obscure. The objective of the present study was to evaluate the characteristic features and potential relevance of psammoma bodies to the clinical outcome of 44 patients with serous carcinomas with long-term follow-up. The 5- and 10-year survival rates were significantly different between the serous carcinomas with less than 5% area of psammoma bodies and those at least 5% area (p< 0.01). All tumors with at least 5% area were both diploid and immunohistochemically negative for TP53 mutations. All patients with those tumors, including eight with FIGO stages III or IV disease, survived more than 5 years and their 10-year survival rate was 76%. In multivariate analysis using clinical parameters, the apparent existence of psammoma bodies was an indication to view low-grade serous carcinomas with long-term survival. Our results suggested that the formation of psammoma bodies is associated with increased apoptotic tumor cell death related to normal TP53 function. The pathological findings of psammoma bodies might contribute to the consideration of pathogenesis and to the development of prognostic prediction rules for serous carcinomas.
THE TEST OF MULTIPLEX PANEL FOR OVARIAN CARCINOMA

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Objectives: In our commercially available xMAP multiplex panel specifically designed for ovarian cancer was tested for the measurement of serum levels of tumor biologic activity markers: Macrophage Migration Inhibitory Factor (MIF), prolactin (PRL), CA 125, leptin, osteopontin (OPN) and IGF-II.

Methods:

1) Control group 0: patients with benign ovarian cyst

2) Pathology group 1: patients with ovarian carcinoma stage III-IV.

Serum levels of biological activity markers were measured by Beadlyte Human cancer Biomarker Panel kit from Millipore-Upstate (US) and Luminex 100 instrument (Luminex corp.,US). Simultaneously, levels of CA 125, TK, TPS, HE4 and Monototal were measured by routine immunoanalytic methods.

Results: From the multiplex markers, the best ROC characteristics were observed for CA 125, IGF II and OPN. HE4 marker had the best ROC characteristics from all measured. In the multiplex panel, significant differences (Wilcoxon test) in marker levels between groups were founded only for CA 125 (higher level in carcinoma), OPN (higher level in carcinoma) and IGFII (lower level in carcinoma).

Conclusion: Multiplex analysis enables an easy simultaneous measurement of multiple markers and could enable the use of scoring system in the future. We would like to confirm the right choice of analytes and the system of results interpretation for multiplex panel in larger patient cohorts and to evaluate the possibilities of use in diagnosis of ovarian cancer stage I-II in further studies.
CLINICOPATHOLOGICAL ANALYSIS OF OVARIAN CANCER ARISING FROM ENDOMETRIOSIS
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Objectives: Endometriosis, which causes dysmenorrhea and dyspareunia, is frequently detected along with ovarian cancer, especially clear cell and endometrioid subtypes. It is not identified that endometriosis-associated ovarian cancer is a specific entity compared with ovarian cancer not associated with endometriosis. We have therefore evaluated the clinical manifestations of ovarian cancer based on the co-existence of endometriosis.

Methods: A retrospective analysis was conducted on 7 patients who had been treated for our hospital. Using medical records, the clinical features and laboratory findings were analysed.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

THE IMPACT OF STAGING LAPAROSCOPY FOR CLINICALLY EVIDENT OVARIAN MALIGNANCY ON TREATMENT STRATEGY

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Background: We represent a retrospective analysis in patients, admitted to University Medical centre Ljubljana, Dpt of Ob/Gyn, with clinical evidence of advanced ovarian malignancy, where laparoscopy was performed as staging procedure in order to evaluate its impact on treatment strategy.

Material and patients: 2 years retrospective analysis of 35 patients with clinical signs of advanced ovarian malignancy, where laparoscopy was proposed as a diagnostic and staging procedure. Records from surgical protocols, intraoperative and postoperative treatment strategy are presented.

Results: Ascites together with elevated tumour markers, with or without pelvic or abdominal mass were the most common clinical sign in population studied. In 29 cases histopathology revealed ovarian cancer and metastatic disease in 6 cases. Laparoscopic staging included evaluation of omental infiltration, peritoneal and diaphragmatic carcinosis, mesenteric and bowel infiltration, and liver superficial metastasis as well as amount of pelvic disease. According to laparoscopic staging, three major treatment strategies were revealed: conversion to laparotomy for debulking and adjuvant chemotherapy (N=14), postponed laparotomy and debulking for creation of relevant oncologic team (N=5): and neodjuvant chemotherapy (N=10). In neodjuvant subgroup of patients the primary peritoneal cancer was predominating. Laparoscopic procedures in last two subgroups were: unilateral or bilateral adnexectomy (N=14); omental biopsy (N=8), peritoneal biopsy (N=11); and cytology specimen (N=15).

Conclusion: Laparoscopy as a staging procedure can have a certain impact on treatment strategy in advanced ovarian cancer. Its predictive value on resectability is still open, but it can distinguish patients with primary peritoneal disease. enabling early start of neoadjuvant chemotherapy.
THE ROLE OF CA 125 AND A NEW TUMOR MARKER HE4 IN THE DISCRIMINATION OF ADNEXAL MASSES

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Objective: To understand and verify the usefulness of HE4 as tumor marker in benign-malignant separation of pelvic masses by comparing with CA 125 levels.

Methods: A prospective study of patients with adnexal masses admitted to Zeynep Kamil Hospital from June 2008 to May 2010. Serum samples were obtained preoperatively from women undergoing surgery for adnexal mass. The samples were analyzed for both CA 125 and HE4 levels and compared with final pathologic diagnosis. Chi-square, Mann-Whitney U, logistic regression and area under the curve analysis were used for statistical significance.

Results: 110 patients were enrolled in the study. 76 had benign and 34 had malignant disease. There were statistically significant differences between HE4 and CA 125 levels of malignant and benign adnexal masses (p=0.0001, p=0.0001). In logistic regression analysis HE4 prolonged its statistical significance (p=0.012) while CA125 failed (p=0.277). In our group the sensitivity, specificity, positive likelihood ratio at 35 U/ml CA 125 level was 59.4, 75 and 2.37 respectively. For HE4, 41pM was determined as cut-off value, which had sensitivity, specificity, positive likelihood ratio of 70.6, 88.2 and 5.96. When ROC curves were drawn the AUC of HE4 was 0.820 and of CA 125 was 0.726 which showed bare supremacy of HE4 in determination of malignant disease.

Conclusion: HE4 is a new but useful marker in determining adnexal masses. Arisen levels of HE4 is a better guide for the determination of malignant masses than CA 125, especially for epithelial ovarian tumors. But it needs more studies to prove itself.
WHOLE ABDOMEN RADIATION FOR PALLIATION OF PLATINUM RESISTANT OVARIAN CANCER

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Whole Abdomen Radiation (WAR) has not been examined prospectively in the palliative setting for ovarian cancer (OVCA). We report the outcome of a cohort of 10 patients treated for palliation of platinum resistant disease using WAR as part of an ongoing prospective study of toxicity and outcomes using contemporary diagnostic criteria including PET/CT and Ca 125 as markers of response.

Retrospective reports suggest that RT provides effective palliation for patients with recurrent/chemo-resistant disease, with symptomatic response rates of up to 80%.

Method: All patients were consented to a RCT of anti-emetic therapy using ondansetron 8mg PO twice daily with either aprepitant or placebo after PET/CT confirmation of recurrence within the abdominal cavity only. CT planning with cine-loop confirmation of diaphragm excursion was used to ensure dose distribution of a minimum of 25Gy/20 fractions to the whole abdomen with concurrent in-field boost to bulk disease sites.

FBE, biochemistry symptoms and performance status were monitored weekly.


CTCAE toxicity: 4 grade 3/4 acute non-haematologic (nausea or fatigue), 1 grade 4 acute haematological toxicity (lymphopenia).

Nausea was absent in 3 patients, intermittent in 5 and 2 persistent. 1 patient required a pause.

Median time to progression 3.7 months, median overall survival 8.8 months.

Imaged response rates: PR 3, SD 3 and PD 3. CA125 response 70%.

Failure sites: 4 abdominal, 2 abdomen and distant and 4 distant only.

Conclusion: WAR offers end-stage OVCA patients active and useful palliation with acceptable toxicity.
TOLERABILITY OF PLD/OXALIPLATIN REGIMEN IN HIGH RISK OVARIAN CANCER PATIENTS

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Objectives: To show the safety profile of treatment with pegylated liposomal doxorubicin (PLD) and oxaliplatin treatment in high risk ovarian cancer patients who experienced myelotoxicity (principally neutropenia) during first line chemotherapy with carboplatin and paclitaxel.

Methods: Medical records of patients with relapsed ovarian cancer treated with PLD/Oxaliplatin at the IOV/IRCCS, Padua University between 2002 and 2008.

Results: A group of 16 patients who developed myelodepression and other toxicities of grade 3-4 during first line chemotherapy with carboplatin/paclitaxel, were selected for this retrospective study. Among these, 5 patients were found to have pathogenic mutation in BRCA1 and 6 were defined as high risk for breast and/or ovarian cancer. Patients had developed mainly grade 3-4 neutropenia and grade 1-3 thrombocytopenia as major toxicities during first line chemotherapy with carboplatin and paclitaxel. Following disease progression, PLD/oxaliplatin treatment was administered at 30-35 and 70 mg/m², respectively, over 2 days, every 4 weeks.

Conclusions: Regression and stabilization of bone marrow suppression and no allergic reactions were seen with PLD/oxaliplatin treatment. Estimated median overall survival was 51.2 months. PLD/oxaliplatin chemotherapy did not give hematological toxicity and was active in this set of pretreated frail patients. We suppose that positive family history and/or a BRCA1/BRCA2 mutation could be a predictor of response to PLD/Oxaliplatin and a protective factor for patients who experienced bone marrow fragility.
IMRT IN THE TREATMENT OF SMALL-VOLUME RELAPSE OR RESIDUAL IN PRE-TREATED OVARIAN CANCER PATIENTS: A PILOT STUDY

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Aim of this study was to evaluate the role of selective irradiation in the management of small-volume recurrence or persistence of OC.

Patients: 10 pts (age 30-56) with one/two sites of OC residual or relapsed after chemotherapy (CT) have been considered for RT. Previous lines of CT ranged from 2 to 5, and time to progression (TTP) from 1 to 12 months. Sites of disease were abdominal wall (2), pelvis (5), supraclavicular (2), torax (2), inguinal (1). RT in IMRT modality was given to a total dose of 25-50 Gy.

Results: In all pts a clinical response was achieved. 5 pts had a complete response (CR) (lymph nodes, abdominal wall), 5 had a partial response (PR) >50%. The toxicity was very mild. The TTP ranged from 4 to 37 months (median: 13). 7 pts showed progression of disease (PD) in sites different from irradiation field, and 3 pts had PD also in irradiated sites. One patient (refractory) died without further CT. 2 platinum-resistant pts did not showed response after the next systemic CT. 6 pts underwent to further lines obtaining a clinical response (still ongoing). One pt is actually free from relapse.

Conclusion: The improvement of CT encourages in proposing patients for several, consecutive CT lines. The chance to obtain control of small lesions preserving time and QOL should be considered. In this very limited sample of patients the RT preserves QOL and doesn’t seem to affect the efficacy of further CT.
MORBIDITY AND MORTALITY ANALYSIS OF UPPER ABDOMINAL SURGERY FOR GYNECOLOGICAL CANCERS

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Background: Upper abdominal surgery may increase the rates of debulking and therefore it improves the survival. However, morbidity and mortality of upper abdominal surgery for gynecological cancers have not been investigated properly.

Objective: To analyse intraoperative and postoperative morbidity and mortality of upper abdominal surgery in patients who underwent cytoreductive surgery.

Method: Between February 2007 and May 2010, 375 patients with ovarian carcinoma, primary peritoneal carcinoma, tubal carcinoma operated in Baskent University School of Medicine were analysed retrospectively.

Results: Upper abdominal surgery was performed in 23% of the patients. 19% of the patients who underwent upper abdominal surgery required 2 or more upper abdominal organ resection. Splenectomy, Diaphragmatic resection/stripping, cholecystectomy was performed in 53 (62%), 11(13), 4 (5%) patients. Splenectomy plus diaphragmatic resection was most commonly performed concomitant operation. Mean operation time was 156 ± 63 min. Mean intraoperative total blood loss was 373 ± 386 ml (100-4500). Of all patients, 18% required ICU admission postoperatively. Among the patients who underwent upper abdominal cytoreduction, ICU admission rate was 25 %. Intraoperative great vessel injury and diaphragmatic perforation were seen in 4 and 2 patients, respectively. Only 1 patient re-operated due to bleeding. Surgical mortality was 1.02 (n=4). Incisional complication (6.9%), ileus (6.4%), pulmonary (5.6%) complication were most common complications among the patients. Other GIT complications including fistula and bowel perforations was the another common complication in this cohort.

Conclusion: In order to reach maximal cytoreduction rates, upper abdominal surgery can be performed with acceptable morbidity and mortality.
AQUAPORIN-1(AQP1) EXPRESSION IN SEROUS EPITHELIAL OVARIAN CANCERS AND ITS RELATIONSHIP WITH CONVENTIONAL PROGNOSTIC FACTORS

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Objective: This study was designed and performed with purpose of detecting AQP1 expression level and determining the significance of AQP1 expression level on prognosis with comparing conventional prognostic factors.

Method: The AQP1 expression levels, IMD and AQP1/IMD ratio in 55 cases with primary serous epithelial ovarian cancers were measured by semiquantitative immunohistochemical method.

Results: AQP1 protein was strongly expressed in the membrane of microvessels and small vessels in all primary serous epithelial ovarian tumors. AQP1 expression was observed in the membrane of interstitial cells of ovarian cancer and in tumor cells in a few cases. It was not observed in the cytoplasm of tumor cells. A statistically significant difference was not found between FIGO stage I-II and FIGO stage III-IV for AQP1 expression (p>0.05). A positively correlated relationship was not detected between expression of AQP1 and IMD and between expression of AQP1 and ascites volume (p>0.05). A statistically significant difference was also not found between groups which are compared according to ascites volume, ascites cytology, lymph node metastasis, lymphovascular space invasion (LVSI), preoperative CA125 levels and performance status for AQP1 expression levels, IMD and AQP1/IMD ratio (p>0.05).

Conclusion: In contrast with previous similar studies in the literature, the relationship between AQP1 expression levels and FIGO stage, lymph node metastasis or ascites volume was not found to be statistically significant in this study. The low number of early stage cases may have had an influence on these results.
TERTIARY CYTOREDUCTIVE SURGERY VERSUS THIRD LINE CHEMOTHERAPY FOR RECURRENT OVARIAN CANCER. A PROSPECTIVE STUDY

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Surgical cytoreduction remains a debated approach for recurrent ovarian cancer. This study wants to assess the role of tertiary cytoreductive surgery in recurrent ovarian cancer patients.

Between 2000 and 2003, a prospective study was carried out on ovarian cancer patients treated with surgery or third line chemotherapy for secondary disease recurrence. Only platinum-sensitive patients after adjuvant first line chemotherapy previously subjected to secondary cytoreduction followed by chemotherapy with no residual disease were enrolled. Patients with unresectable disease or peritoneal carcinosis were treated by chemotherapy.

Fourteen (64\%) of 22 patients underwent tertiary cytoriduction (SG) whereas 8 (36\%) received third line chemotherapy (CG). Median time to second disease recurrence was >12 months for both SG and CG. In the SG, 4 (28.6\%) patients achieved RT3 >2cm, 4 patients (28.6\%) RT3 between 1 and 2cm, and 6 (48.8\%) patients obtained no macroscopic disease (RT3 = 0). Intraoperative and postoperative complication occurred in 3 (21.4\%) and 2 (14.3\%), respectively. At univariate analysis, significant difference in OS was found between SG patients with RT = 0 at Tertiary cytoreduction (median OS 29 months) and CG patients (median OS 12 months) (p=0.0086). In SG, significant difference was found in OS between patients who had secondary peritoneal recurrence versus those in which the peritoneum was not involved (13 vs 30 months, p=0.001). Fisher’s exact test showed that only the absence of peritoneal recurrence (p=0.009) and RT1 = 0 at first surgery (p=0.0029) were able to influence tertiary cytoreductive outcome (RT3 = 0).

Tertiary cytoreduction is safe and effective, with a low rate of complications and should be considered in patients with secondary ovarian cancer recurrence with no evidence of peritoneal disease, who achieved no traceable disease at first surgery (RT1 = 0) obtaining greatest benefit in OS with surgery respect Chemotherapy approach.
MALIGNANT PERITONEAL MESOTHELIOMAS

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Background: Primary malignant peritoneal mesothelioma is a rare tumor with a poor prognosis and optimal treatment approach has not been clearly identified.

Method: This is retrospective analysis of 12 patients treated for malignant peritoneal mesothelioma in one institution from January 2007 to June 2009.

Results: Mean age of the patients was 57 years. Main presenting symptom was abdominal distention. Primary cytoreductive surgery followed by chemotherapy was performed in all patients. In 6 patients completeness of cytoreductive score below 2 was achieved. In average there were 5 chemotherapy cycles received (p=0.005). There were 5 cases with concomitant pleural involvement. As a first line chemotherapy most often was used cisplatin in combination with pemetrexat (ALIMTA) or cisplatin with gemcitabine. Disease free survival of 4.4±1.0 months after completing particular treatment and overall 5-year survival of 21.5±4.2 months was observed.

Conclusion: Treatment strategy for malignant peritoneal mesothelioma should involve a multimodality approach which includes maximal cytoreductive effort followed by chemotherapy. Further studies are needed to reach clear conclusions.
UMBILICAL METASTASIS (SISTER MARY JOSEF’S NODE) IN ADVANCED OVARIAN CANCER: A CASE REPORT

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Aim: Sister Mary Josef’s nodule (SMJN), is a metastatic cutaneous umbilical tumor from intra-abdominal malignancies, mainly of gastrointestinal tract and female genital tract. Umbilical metastases are a rare occurrence, in about 1 to 3% of patients with abdominal-pelvic disease. Ovarian carcinoma is the most common origin (34%) in women with cancers of gynecological origin.

Material: We present 1 case of umbilical metastasis in a 64-year-old woman, with advanced endometrioid ovarian carcinoma stage IV. She was treated with optimal debulking surgery followed by 6 courses of chemotherapy (paclitaxel and carboplatin) every 3 weeks. Postoperative follow-up was regular. Four years after the initial operation, a para-aortic lymphatic block was found in the abdominal computed tomography (CT) without any symptoms or signs. She followed a multi-agent chemotherapy (gemcitabine-liposomal doxorubicin). After 2 years she presented with several neurologic symptoms and a single brain metastasis with surrounding edema was found by magnetic resonance scan (diameter < 3cm) during the work-up for the symptoms and was treated with gamma-knife radiosurgery (GKR) with successful outcome.

Results: After 13 months of follow-up a umbilical metastasis (SMJN) was found any symptoms as a sign of advanced recurrent ovarian cancer with widespread peritoneal dissemination. The patient until now is alive (4 months after diagnosis) and treated with chemotherapy (oral etoposide).

Conclusions: SMJN is a rare manifestation of a variety of advanced malignancies and majority of patients present at a late stage and many harbor distant metastases. It is associated with very poor outcome and is generally inoperable.
MANAGEMENT STRATEGIES IN OLDER PATIENTS WITH ADVANCED OVARIAN AND PRIMARY PERITONEAL CANCER

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Background: Seventy percent of women with ovarian or peritoneal cancer in our region have FIGO stage III or IV disease at diagnosis. Despite improvements in overall survival, the mortality remains high. The optimal strategy for the use of chemotherapy and surgery in these patients remains the subject of debate. We aimed to identify the current management strategies employed and the subsequent outcomes in our older population.

Method: Data were gathered from the notes of a random sample of 250 patients with advanced ovarian or peritoneal cancer. All patients presented via the regional Specialist Gynaec-Oncology MDT between January 2006 and July 2009. The data included patient characteristics, management strategies and survival.

Results: Forty-one percent of our sample were seventy years or older. The median survival in patients receiving chemotherapy for ovarian cancer was significantly lower in these older patients (14 months v 28 months). They were less like to receive dual therapy with carboplatin and paclitaxel than those younger than seventy years (15% versus 61% of those receiving chemotherapy). Patients under the age of seventy who received dual therapy had a significantly better median survival than those receiving single agent carboplatin (34 months versus 17 months, p= 0.001). This difference was lost in the older patient group (16 months versus 14 months, p= 0.04).

Conclusion: A significant proportion of patients with advanced ovarian cancer are over seventy years at presentation. They appear to represent a distinct clinical group. Further investigation is warranted to clarify the optimal chemotherapeutic management strategy.
BRAIN METASTASIS IN GYNECOLOGIC CANCERS: ANALYSIS OF 12 PATIENTS

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Background: Most common site for distant metastasis are lungs, liver, spleen and distant lymph nodes for gynecological cancers. Brain is an unusual site for metastasis of gynecological cancers.

Objective: To analyse 12 patients with brain metastasis arise from gynecologic cancers.

Material and method: 12 cases with various kinds of gynecologic malignancies were retrospectively analysed.

Results: Ovarian carcinoma was the most common (n=6,50%) gynecologic cancers metastasing to brain. While cervical cancer, primary peritoneal cancer, vulvar cancer, malign mixed mullerian tumor had one patient with brain metastasis (8,3%), two patient with endometrial cancer developed brain metastasis (16,6%). All of them were high stages at initial diagnosis except one patients with Ic endometrial cancers. Overall mean survival was 27.7 (range 2.3 to 79) months for whole group . Mean survival was 41.4 (range 27 - 79 ) months for six ovarian cancer patient.

At the time of brain metastases developed, CA-125 levels found to be elevated through all patients no matter what kind of cancer they had except one patient with cervical cancer. Mean CA-125 level was 202 IU/ml. Overall there are no difference found on mean survival between surgical resection, radiation therapy and medical therapy application to patients with brain metastasis (p:0.859) and it was found as 2.2 months for all 12 patients.

Conclusion: Although ovarian carcinoma is the most common primary for brain metastasis in this series it can be seen in all kind of gynecologic cancers.
HER2 PROTEIN OVEREXPRESSION IN OVARIAN CANCER- AN ASSOCIATION WITH OTHER PROGNOSTIC FACTORS

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Introduction: The HER2 proto-oncogene encodes a protein with tyrosine kinase activity that functions as a growth factor receptor. Significance of HER2 expression/amplification in ovarian carcinomas is not clear enough. The purpose of this study was to determine the rate of HER2 protein overexpression in ovarian cancer, and to detect if any associations exist between HER2 status and histological type, grade, tumor stage and patients age.

Material and methods: A total of 34 cases of ovarian cancer were included in this study. The immunohistochemistry was used to determine the HER2 protein overexpression in tumor tissue. Strong membrane reaction detected in more than 10% of tumor cells was considered a positive result.

Results: Positive expression of HER2 protein was found in 5 (14.7%) cases. All HER2 positive ovarian cancers were diagnosed in stage III (p< 0.05). Out of total 5 HER2 positive tumors, four (80%) were of serous type, and one (20%) of the serous-mucinous type. In the group of mucinous and endometrial tumors no positive HER2 expression was detected (p=0.05). HER2 overexpression was seen in 7.7% of tumors grade III and in 33.3% of grade II. All well differentiated carcinomas were HER2 negative (p>0.05). Patients with positive HER2 expression were 65 years old on average, whereas for those with HER2 negative status the average age was 56 (p>0.05).

Conclusion: Positive expression of HER2 protein in ovarian cancer is significantly correlated with an advanced stage of tumor disease and could represent a factor of poor prognosis.
THE IMPACT OF 2ND TO 4TH LINE THERAPY ON SURVIVAL OF RELAPSED OVARIAN CANCER AFTER PRIMARY TAXANE/PLATINUM BASED THERAPY

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Background: Despite maximum efforts at primary therapy most patients with advanced ovarian cancer will relapse. Data about used regimen and outcome of relapsed patients in further therapy lines are unclear, especially for 3rd and 4th line therapies.

Material and methods: An exploratory analysis was performed to describe the 2nd to 4th line chemotherapy regimens used and their potential effects on survival. This analysis was based on individual patients data from 3373 patients from three prospectively randomized trials (Ovar 3,5,7) between 1995 and 2002 investigating platinum/taxane-based primary chemotherapy regimens. Descriptive statistics was applied.

Results: 2393 of 3373 patients had at least one relapse. A total of 1973 patients died in the observation period until 2007. In 2074 patients at least one treatment was reported after first-line therapy. Overall 4962 treatments were documented. Most of them were chemotherapy regimens. 3825 chemotherapy cycles were administered in 1937 patients mostly as single agents (55 %) vs. 20% combination therapies. Mostly platinum based polychemotherapy (24%) as 2nd line followed by topotecan (22%) and platinum monotherapy (16%) was given. Therapies were in the 3rd line: topotecan 24%, PLD 16%, gemcitabine 7%, platinum 8%; in 4th line: topotecan 13%, PLD 16%, gemcitabine 14%, platinum 11%. Combination therapy became less frequent in higher lines: 3rd 17%, 4th 12%.

Conclusion: Monotherapies were the preferred treatment options after 2nd line treatment, despite a higher than expected use of combination therapy. Survival gain by 4th line therapy is limited. Studies at this stage of disease should focus on other endpoints like symptom control than classical objectives.
GIANT STRUMA OVARII MIMICKING ADVANCED STAGE EPITHELIAL OVARIAN CARCINOMA

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Background: Struma ovarii is a monodermal tumor originating as small cystic structures from the ovaries. Usually it is found with elevated tyroglobulin levels and without any clinical symptom coincidentally after surgical resection.

Objective: To present a patient with giant pelvic mass accompanying elevated CA-125 levels and ascites.

Case report: A 52 year old woman complaining with abdominal distension and pain with an elevated ca125 level of 1424 and an accompanying giant mass measured 22x17 centimeter in size came to our clinic. Because of its malignancy mimicking size and view on explorative laparatomy she underwent a complete surgical cytoreduction. The pathology report was struma ovarii. On follow up her ca125 levels turn back to normal ranges. Ascites resolved with removal of the mass.

Conclusions: Although all of these symptoms can be tought as they are barely representing a malignant disease, it is possible that those can be related with a benign disorder such as struma ovarii and it is known that combination of struma ovarii and elevated CA-125 has rarely been reported. This is one of the ten cases published in the English literature from 1990 so far.
FIRST EXPERIENCE OF SURGICAL TREATMENT IN ADVANCED OVARIAN CANCER AFTER INTRAPERITONEAL APPLICATION OF THE TRIFUNCTIONAL ANTIBODY CATUMAXOMAB

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Background & aims: Intraperitoneal (i.p.) treatment with the trifunctional-antibody Catumaxomab is a novel promising option in patients with advanced-ovarian-cancer (OC). No data exist regarding the surgical experience after such a treatment. Aim of our present study was to evaluate the surgical outcome of OC-patients, previously treated with catumaxomab i.p., with special focus on the associated morbidity.

Methods: We conducted a retrospective evaluation of all (n=9) OC-patients operated in our institution between 01/2007 and 03/2010, who have been previously treated with catumaxomab-i.p within the multicenter-trials “IP-CAT-OC-02” (n=6) or “CASIMAS” (n=3). Surgical outcome, intraoperative adhesions and operative morbidity were assessed as recorded in the operation-protocols and interview with the gynaecologic-oncologic surgeons.

Results: Nine patients (FIGO-stage:IIII-IV; mean-age:63; range:49-77) were included in the present analysis. Mean time elapsed between catumaxomab-treatment and surgery was 187 days (range:8-481). Mean operation-time was 168 minutes (range:69-258). The indications for surgery were as follows: 3 patients due to anastomotic insufficiency after primary-tumordebulking, 2 patients due to secondary-tumordebulking, 3 patients due to ileus in recurrent-OC and 2 patients for restoring intestinal-continuity. One patient was re-operated twice. At surgery 7 patients (77.8%) presented massive adhesions, while 3 patients (33.3%) developed repeated postoperative abscesses. Four out of the 5 patients (80%), operated due to recurrent OC, presented intraoperatively massive tumor-load with severe peritoneal-carcinosis, but none of them had ascites>500ml.

Conclusions: Catumaxomab-i.p. appears to be associated with reduced amounts of ascites in recurrent-OC despite severe peritoneal-carcinosis. Surgery after catumaxomab-i.p. seems to be feasible, however larger prospective evaluations are warranted to assess long term clinical outcome.
CA-125 IN STEROID CELL TUMOR

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Hirsutism can be defined as an excessive male-pattern hair growth, typically caused by a state of hyperandrogenism. It can be associated with the signs of virilisation, such as breast atrophy, increased muscle bulk, deepening of voice, clitoromegaly and increased libido.

We describe the case of a 44 years old woman with an steroid cell tumor, NOS (not otherwise specified), of the ovary. This is a rare tumor of the ovary which raises differential diagnosis with many disorders causing hyperandrogenism.

The patient had a 5 month history of hirsutism, amenorrhea, spotting and choking. The physical examination showed a masculinised obese female with acne and hair growth on face, arms, back, chest and abdomen. Laboratory analysis results were in the range of normality. A transvaginal ecography showed a left adnexal mass with 12 cm f. The mass presented two components: solid and cystic, with papillas, septums and low resistance vascularisation. Liquid free in the peritoneal cavity was found too. The value of CA-125 was studied, with result of 2087.3 U7ml, and a TAC evidenced the ovarian mass and ascitis, but no peritoneal or bowel implants.

The patient underwent laparotomy with intraoperative anatomopathologic study, with the result of functional steroid cell tumor. A total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, appendicectomy, and peritoneal biopsies were performed. Three years after the treatment the patient remains alive and free of disease.

A very interesting element of this case is a very high level of CA-125, never described as associated to this type of tumor.
DRUG RESISTANCE/SENSITIVITY IN VITRO AND CLINICAL OUTCOMES IN OVARIAN CANCER PATIENTS

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Objective: To compare drug resistance/sensitivity in vitro in solid tumor and ascitic fluid using the MTT assay with the clinical outcomes in ovarian cancer patients.

Methods: MTT - (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) chemo-sensitivity assay was performed in 66 ovarian cancer patients. Progression-free survival, histologic subtype, grade and stage were correlated with MTT assay results. Tested chemotherapeutic agents were cisplatin, carboplatin, paclitaxel, topotecan, gemcitabin and etoposid.

Results: The incidence of drug resistance in vitro to the tested chemotherapeutic agents were gemcitabin 59,0%, etoposid 53,0%, paclitaxel 26,5%, carboplatin 38,6%, topotecan 10,8% and cisplatin 8,4%. The incidence of drug sensitivity in vitro were topotecan 56,6%, cisplatinum 54,2%, carboplatinum 16,9%, gemcitabin 10,8%, paclitaxel 15,7%, etoposid 7,2%. We found differences in the frequencies of resistance/sensitivity to chemotherapeutic agents in vitro and histologic subtypes and grade of epithelial ovarian cancer. No significant differences in stage and drug resistance sensitivity in vitro were noted. Patients whose tumors exhibited in vitro platinum resistance had significantly shorter progression free survival.

Conclusion: Patients with tumor demonstrating in vitro resistance to carboplatin and cisplatin had significantly higher risk for progression of disease when treated with standard platinum-based regimens. This study found a significant association between in vitro drug resistance to platinum compounds and clinical outcomes of the evaluated group of patients. This study was supported by the Ministry of Health in Czech Republic 9737.
OVARIAN CARCINOSARCOMA

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Carcinosarcomas (also called malignant mixed müllerian tumor or sarcomatoid carcinoma or malignant mixed mesodermal tumor) are a relatively rare gynecologic tumors that occur throughout the female genital tract, most commonly in the uterus. Ovarian carcinosarcomas are reported to represent less than 2% of ovarian malignancies. Histologically, carcinosarcomas are epithelial tumors that are comprised of both a carcinomatous and sarcomatous component.

We present a case of a 56 years old patient who started with increase of abdominal perimeter and decreased appetite. The patient was cachectic and showed a distended abdomen and free ascites. Bimanual examination showed a mass in Douglas, irregular, hard and no mobile. Ultrasonography showed a mixed solid-cystic mass greater than 20 cm, with atypical vascularization, and moderate to severe ascites. Ca 125 was increased. The patient was operated for a suspected ovarian cancer in stage III, and a cytoreductive surgery was performed, with no residual tumor. The final pathology result reported carcinosarcoma (malignant mixed tumor müllerian) with epithelial component type papillary serous carcinoma and sarcomatous heterologous component type rhabdomyosarcoma in the right ovary, which infiltrates the uterine serosa. The patient began chemotherapy after surgery (6 cycles of Taxol and Carboplatin), and one month after treatment was admitted to hospital for peritoneal carcinomatosis secondary to abdominal mass with intestinal obstruction and subsequent death, 6 months after surgery.

In conclusion, the ovarian carcinosarcomas are rare and very aggressive, especially when diagnosed in advanced stages, and thus the diagnosis in early stages is considered the main prognosis factor.
Brenner tumors is a rare neoplasia, that account for only 1 to 2% of ovarian tumors. Most of them are benign, but there are a small percentage of malignant Brenner tumors, including the case presented. It is a tumor from the epithelium ovarian surface, which reminds morphologically to the bladder's transitional cells epithelium. The transitional cells tumors are composed by epithelial elements similar to those observed in the urothelial carcinomas and do not present any component of benign or borderline Brenner tumor associated.

We present a case of a 41 years old woman with amenorrhea since approximately 8 months. Ultrasound examination showed a solid-cistic right adnexial tumor, 52 mm Ø, with excrescences, and in Doppler, a simple cyst on right ovary with restrictive vascularization. The patient was proposed for surgery. The biopsy informed about serous papilar carcinoma, therefore an extended surgery was realized. The definitive microscopic examination informed about bilateral serous papilar carcinoma, poorly differentiated, associated to malignant Brenner tumor.

In spite of being diagnosed in early stages, this case stands out for its poor prognosis. It is important to differ between benign and malignant Brenner tumor, since prognosis and treatment are radically different. It is also important to recognize the microscopy and immunohistochemistry characteristics of Brenner tumor and transitional cell ovarian tumor, in order to be able to separate them from the ovarian metastasis from urothelial tumors. In spite of being diagnosed in early stages, this case stands out for its poor prognosis.
HIGH PREOPERATIVE PLASMA CONCENTRATION OF HE4, SUPAR AND CA125 DISCRIMINATE BETWEEN BENIGN AND MALIGNANT OVARIAN TUMORS

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Objective: To evaluate the plasma level of HE4, soluble urokinase plasminogen activator (suPAR) and CA125 as discriminators between malignant and benign ovarian tumors.

Material & methods: HE4, suPAR and CA125 were measured in preoperative plasma samples obtained from 302 patients with adnexal lesions. Using ELISA analyzes HE4, CA125 and time-resolved fluorescence assays TR-FIA 2 measuring suPAR(I-III) and the cleaved suPAR(II-III). Tumors were classified as benign (n=207), borderline malignant (n=25), well (G1, n=14), moderately (G2, n=13), and poorly differentiated malignant (G3, n=43).

Results: The area under curve (AUC) to discriminate between malignant (borderline and invasive tumors) and benign ovarian tumors using the product of HE4, suPAR(I-III)+suPAR(II-III) and CA125 was AUC 0.91 (CI 95% 0.87-0.95). In order to discriminate between invasive (malignant) vs. non-invasive (borderline and benign) ovarian tumors the product of HE4, suPAR(I-III)+suPAR(II-III) and CA125 resulted in AUC 0.94 (CI 95% 0.90-0.98).

Conclusions: The product of HE4, suPAR(I-III)+suPAR(II-III) and CA125 is a very good pre-operative plasma indicator to differentiate between malignant and benign ovarian lesions.
OVARIAN LUTEOMA. DIFERENCIAL DIAGNOSIS OF ADNEXIAL MASS IN PREGNANCY

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Ovarian luteoma is a tumor formed by nodes of hyperplasia of luteal cells, which occurs during pregnancy and involutes during puerperium. Only about 100 cases are described. We present a clinical-pathological case and discuss the differential diagnosis of an adnexal mass during pregnancy.

26 years old patient, primipara. She entered the hospital at the 37 week of gestation, with suspected diagnosis of adnexal mass. Tumor markers were: AFP 97.5 UI/ml and Ca-125 57.8 UI/ml. Ultrasound shows heterogeneous mass, 12-14 cm, with low resistance pheripheral vascularization. At 40 weeks of gestation a cesarean section was performed because of fetal risk. Mobile, smooth, encapsulated, 12-14 cm ovarian tumor was found. A month later right salpingo-oophorectomy was performed, with intraoperative study demonstrating benign process. Final microscopy examination (with immunohistochemical techniques) reported ovarian luteoma in involution. After 2 years the patient had a new pregnancy that ended in vaginal birth, and there was no new adnexial pathologies.

The ovarian luteoma is a rare disease that occurs between 30 and 40 years, 80% in multiparas. Most of women are asymptomatic and often incidental findings in cesarean section or post-partum LTB. 25% of women show virilization and 70% of female fetuses have elevated testosterone and other androgens. The differential diagnosis must be based on the ultrasound and tumor markers. The identification of this entity is very important, in order to consider expectant attitude, since most of these tumors regress during the postpartum without needing aggressive therapies.
THE CT ENHANCING FRACTION PREDICTS RESPONSE TO NEO-ADJUVANT CHEMOTHERAPY IN PATIENTS WITH HIGH GRADE SEROUS OVARIAN CARCINOMA

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\textbf{Background:} Pre-chemotherapy CT enhancing fraction (EF) has been proposed as a simple predictive and prognostic imaging biomarker. We correlated the EF prior to neo-adjuvant chemotherapy for high grade serous carcinoma (HGSC) of the ovary with response, PFS and OS.

\textbf{Methods:} The pre-chemotherapy EF of patients with HGSC from the CTCR-OV01 study were evaluated at four separate CT Hounsfield Unit (HU) thresholds of 50, 60, 70 and 80. Response was assessed after 3 cycles of chemotherapy by CA-125 and CT. Tumours were stratified into 2 groups using median EF as the cut point (EF 'high' or EF 'low'). Logistical regression was used to analyse radiological and CA-125 response. Cox regression analysis was used for PFS and OS analysis.

\textbf{Results:} 13/47 patients were evaluable. 2/13 had only an ovarian/pelvic mass, 4 peritoneal disease, and 7 had both. Nine patients received paclitaxel and four received carboplatin for the first three cycles. Pairwise analysis of matched ovarian and peritoneal disease did not show any significant difference in EF. Results for ovarian/pelvic and peritoneal disease were therefore summed. Patients with 'low' EF showed a better CT (p=0.038 for both EF 50 and 70 HU thresholds) and CA-125 response. There was a trend towards improved overall survival in the 'low' EF group at the EF 60 HU threshold (p=0.064).

\textbf{Conclusion:} In this study, pre-chemotherapy EF predicted CT response to neo-adjuvant chemotherapy. Potential applications include EF based stratification of patients to primary surgery or interval debulking surgery. Larger confirmatory studies are required.
MODIFIED OUTPATIENT REGIMEN OF INTRAVENOUS / INTRA-PERITONEAL PACLITAXEL AND CISPLATINUM FOR OPTIMALLY DEBULKED STAGE III EPITHELIAL OVARIAN CANCER

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Background: IV/IP P+C have proven to have superior overall survival compared to IV P+C in EOC. GOG 172 required inpatient admission with 42% completion rate. We evaluated a modified outpatient IV/IP regimen (P 135 mg/m2 IV over 3 h, d 1, C 75 mg/m2 IP d 2 and P 60 mg/m2 IP d 8) to assess completion rate, clinical response, and toxicities.

Materials and methods: Eligible patients treated with modified IV/IP regimen were evaluated. Data were collected and analyzed.

Results: 53 patients were identified. Mean age was 59.8 (36-79). Most common stage, grade, histology were IIIC, III and serous. 64% completed 6 cycles. Complete clinical response was 83%. Mean follow up was 28 m (1-91). 55% were alive at last visit. Mean PFS was 22 m (1-72). Mean pre and post CA125 were 2296 IU (20-26000) & 34 IU (3.5-246). 49% received consolidation with IV (P), 54% completed 12 cycles. Toxicities were GI (N/V) 22%, 11% G 3-4, neuropathy 9%, 1.8% G 4, abdominal pain 11%, 4% G 3-4, catheter complications 7.5%, 1 requiring replacement. Fever, infection, hand and foot syndrome, fatigue at 3.7%, DVT /CVA 2%, neutropenia 19%, anemia 15%, 3.7% G 3-4, thrombocytopenia 7.5%, 2% G 3-4. 1 died of sepsis. 7.5% required dose reduction. Only 11/262 cycles were missed due to toxicity.

Conclusions: Modified regimen allows for a higher completion rate than inpatient regimen with acceptable and lower toxicities with favorable clinical response. Further investigation of this modified regimen is warranted.
OVARIAN LYMPHOMA

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Ovarian lymphoma can be primary or secondary manifestation of disseminated disease. The primary ovarian lymphoma is extremely rare, only 0.5% of all NHL (No Hodgkin Lymphoma) and 1% of ovarian malignancies.

We report the case of a 45 years old patient with a probable ovarian tumor. Five months ago she presented postprandial epigastric pain, intestinal changes and weight loss. The high Endoscopy was normal. Abdominal ultrasound showed an hypoechoic structure in right adnexal, 93x69 mm, with low resistance vascularization, and free peritoneal fluid. TAC showed a 52 x 45 mm solid right adnexal mass and ascites. Tumor markers were normal.

Surgery was performed, finding abundant peritoneal fluid, with negative cytology. 8 cm solid tumor was observed in right ovary, and left Falopian tube had tumoral appearance. Cerebroid solid implants (0.5-3cm) was found involving omentum, meso and intestinal package. Abdominal hysterectomy was performed, with bilateral salpingo-oophorectomy, omentectomy, pelvic and paraaortic lymphadenectomy, and resection of two small bowel pieces and many tumors in meso and intestinal serosa.

Microscopic examination revealed diffuse large B-cell lymphoma. The patient started chemotherapy, and after six cycles complete remission was achieved. After 3 years, the patient is alive and free from disease.

Primary ovarian lymphoma is extremely rare, debuted as ovarian masses or ascites, with few systemic symptoms. The origin is due to the presence of B and T lymphocytes in the ovarian stroma, cortical, follicles and corpus luteum. 15% have only ovarian involvement. Survival in this patients are long after oophorectomy.
NEOADJUVANT CARBOPLATIN, PACLITAXEL (NACT) FOR ADVANCED STAGE (AS) EPITHELIAL OVARIAN CANCER (EOC) COMPARED TO SURGICAL CYTOREDUCTION (USC) FOLLOWED BY CP

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Background: To determine if AS EOC patients evaluated by gynecologic oncologists and believed not to be surgically cytoreducible (SC) to ≤ 1 cm diameter of residual disease (RD) had a different PFS and OS with NACT (CP) followed by cytoreductive surgery compared to (AS) EOC patients believed to be SC to ≤ 1 cm RD with USC followed by CP.

Methods: 221 USC patients (Stage IIIC - 169, IV - 52) and 95 NACT patients (Stage III - 40, IV - 55) treated between 1996 and 2009 were retrospectively reviewed. NACT patients received a median of 6 C and P cycles (AUC 6) (175 mg/M²) prior to surgery. All NACT patients had imaging findings compatible with AS non-optimally SC EOC and pathology consistent with EOC.

Results: The PFS and OS for Stage IIIC NACT patients (median 32.5 mos. and 47.5 mos.) was not different than USC patients (median 19.5 and 45.7 mos.; p=0.099 and 0.918). The PFS and OS for Stage IV NACT patients (median 15.6 and 25.8 mos.) was not statistically different than USC patients (median 13.0 and 48.5 mos.) (p=0.841 and 0.701). Patients who had no postsurgical RD (NACT 72.8%, USC 43.8%) had statistically improved OS and PFS compared to those with residual tumor. Stage IIIC NACT patients had significantly less postoperative hospitalization (5.9 vs. 8.5), blood loss (487 vs. 909 cc), transfusions (0.6 vs. 1.4) than USC patients.

Conclusions: NACT is an appropriate option for AS EOC patients who appear to be non-optimally SC with surgery.
COMPARATIVE STUDY OF INTRAPERITONEAL CHEMOTHERAPY ASSOCIATED GRADE 3 / 4 TOXICITIES AFTER PRIMARY VERSUS INTERVAL SURGICAL DEBULKING

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Objective: To compare the incidence of grade 3/4 toxicity during intraperitoneal chemotherapy following primary versus interval debulking surgery.

Methods: Ovarian cancer patients treated with IP chemotherapy were identified from prospective ovarian cancer database. Study patients were stratified by their primary treatment (upfront surgery vs. neoadjuvant chemotherapy). The IP regimen administered was similar to GOG 172 protocol. NCIC criteria were used to diagnose grade 3 / 4 toxicities. Chi square analysis was used to assess significance between categorical variables. All p values less than 0.05 were considered statistically significant.

Results: Thirty-three patients were included in the study analysis. Sixteen patients had primary surgery. The total number of IP cycles administered was 134. The median number of IP cycles administered was 3 following neoadjuvant chemotherapy and 6 following primary surgery. Patients receiving IP chemotherapy after neoadjuvant chemotherapy reported significantly more fatigue (p=0.038). Although not statistically significant, patients treated with IP chemotherapy after primary surgery reported more hematologic toxicity (p=0.06) and abdominal pain (p=0.08). There was no significant difference in terms of needs for dose reduction, use of day 8 paclitaxel, dose delay, grade 3 or 4 neurologic / nausea / metabolic toxicities, or the presence of IP port complications with respect to when IP chemotherapy was initiated.

Conclusion: Significant fatigue is more commonly observed in patients receiving IP chemotherapy after neoadjuvant chemotherapy while abdominal pain and hematologic toxicity occur more frequently during IP treatment after primary surgery. Toxicity data can potentially be used to plan for optimal IP delivery and patient counseling.
FACTORS INFLUENCING UPTAKE OF RISK REDUCING SALPINGO-OOPHORECTOMY (RRSO) IN WOMEN AT HIGH RISK OF FAMILIAL OVARIAN CANCER

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Objective: To evaluate factors influencing uptake of risk-reducing salpingo-oophorectomy (RRSO) in women at 'high-risk' for ovarian cancer.

Methods: Prospectively collected data from women attending a tertiary high-risk familial gynaecological cancer clinic between March-2004 and November-2009 were analysed. Risk management options discussed include RRSO, participation in a national screening trial, as well as lifestyle and reproductive issues. Statistical analysis was undertaken using SPSS 12.0.1.

Results: Of 2193 women seen in clinic, 1639 from breast and/or ovarian cancer families had a high (≥10%) estimated life-time risk for ovarian cancer. 318(19.4%) high-risk women opted for RRSO and 1151(70.3%) for screening. 170(10%) were < 35years and deferred decision making. Women undergoing RRSO were older (median age 49.9, IQR 12.5years) than those opting for screening (median age 42.3, IQR 13.1 years) (p< 0.0005). Having a BRCA1/2 mutation, postmenopausal status, personal history of breast cancer, and family history of breast cancer only, was significantly associated with increased RRSO uptake (p< 0.0005) on univariate analysis. While, family history of breast and ovarian cancer (p=0.035), and ovarian cancer < 50years (p=0.004) was significantly associated with screening. Parity and Jewish ethnicity were not found to influence decision making. The only factors found to significantly influence RRSO uptake on multivariable regression analysis were age, BRCA mutation status and a personal history of breast cancer (p< 0.0005).

Conclusions: Various factors affect RRSO decision making in high-risk women. Women who are older, carry a BRCA mutation and have had breast cancer themselves are more likely to opt for surgery over screening.
EPIDIDYMAL TISSUE PRESENTING IN A PHENOTYPIC MOSAIC FEMALE WITH A MALIGNANT MIXED GERM CELL TUMOR OF THE OVARY

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Background: Turner Syndrome is a disorder caused by partial or complete X chromosome monosomy. 20-40% of patients are noted to have a mosaic component. The presence of Y chromosome fragments is seen in about 6% and is known to increase the risk of virilization, dysgenetic gonads, and gonadal tumors. It has been hypothesized that a gene on the pericentromeric region of Yp known as the gonadoblastoma locus on the Y chromosome (GBY) predisposes to these tumors.

Methods: A 23 year-old phenotypic female presented complaining of oligomenorrhea and increasing abdominal girth. Clinical exam revealed a large pelvic mass, clitoromegaly and poorly developed breasts. Elevated tumor markers were: β-hCG of 433 mIU/mL, AFP of 54,419 ng/mL, and LDH of 1377 IU/L. Surgical staging found a conglomerate mass that incorporated a hypoplastic uterus and long tubular cervix together with the left adnexa. The right adnexa contained a streaked ovary.

Results: Histologic examination revealed a malignant mixed germ cell tumor: dysgerminoma 50%, embryonal carcinoma 40%, malignant teratoma 5%, and yolk sac tumor 5% with metastasis to a high para-aortic lymph node (FIGO stage IIIC). Pathology also showed a sex cord duct remnant compatible with epididymis. Karyotype was 46,X,+mar[75%]/45,X[25%]. Using FISH analysis, the marker chromosome appeared to be derived from the Y chromosome.

Conclusion: To our knowledge, this is the first case to report malignant mixed germ cell tumor with true hermaphroditism, given the presence of epididymal tissue, in a mosaic Turner Syndrome. Further study of the GBY locus is warranted in these patients.
HIGH CUMULATIVE DOSES OF PEGYLATED LIPOSOMAL DOXORUBICIN ARE NOT ASSOCIATED WITH CARDIAC TOXICITY IN PATIENTS WITH OVARIAN CANCER

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Objective: The purpose of this study was to determine the cardiac safety of pegylated liposomal doxorubicin (PLD) in patients receiving high cumulative doses of PLD.

Patients and methods: A retrospective chart review of patients with ovarian cancer treated at Oregon Health & Science University from 2003 through 2009 who received cumulative doses of PLD \( \geq 400 \) mg/m\(^2\) was performed.

Results: Twenty-two met the inclusion criteria. The mean age at initiation of PLD therapy was 62 years. The cumulative dose range of PLD was 400-1,280 mg/m\(^2\). The mean cumulative number of cycles of PLD given was 11.6 (range 10-28). Multigated acquisition (MUGA) scans were obtained after 4 doses of PDL in all patients. The mean baseline ejection fraction was 65%. Serial follow-up MUGA scans were performed on 8 patients. No significant decrease in their ejection fraction in any of the patients and 2 of the 8 patients had an increase in their left ventricular ejection fraction of 1 and 2%. There were no treatment interruptions or discontinuations due to cardiac toxicity.

Conclusion: Cumulative doses of PLD \( \geq 400 \) mg/m\(^2\) are not associated with clinically evident cardiac toxicity in ovarian cancer patients.
RADIOTHERAPY IN RECURRENT AND PERSISTENT OVARIAN CANCER: LONG-TERM OUTCOMES

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Published management guidelines make either no or scant mention of the role of radiotherapy in the management of women with ovarian cancer. There have been few recent publications on this topic.

Between 1976 and 2009, 813 women with ovarian malignancy were managed in the principal author's practice. Sixty-eight patients (8.4%) received radiotherapy (RT) with or without chemotherapy for treatment of recurrent disease (58 patients) or persistent disease (9). Tumours included epithelial carcinomas (61) and non-epithelial malignancies (7). Treatment was given with palliative intent to approximately one half of the patients and with curative intent in the other half in whom RT encompass the known extent of tumour. Localised tumour was debulked where possible and in patients undergoing laparotomy a surgical re-staging was performed.

Twenty-two patients are currently alive from 0.3 to 25.4 years after treatment of their recurrence. Fifteen have no evidence of disease at 4.1 to 25.4 years (median 9.3 years). All had localised recurrence in the central pelvis/vaginal vault (6 cases), pelvic sidewall (3), sigmoid colon wall (2), brain (1), cervical lymph node (1), inguinal node (1) and abdominal wall (1). One long-term survivor has required surgery for obstructive radiation enteritis.

These data suggest that RT has a role in the salvage treatment of a small proportion women with recurrent or persistent ovarian malignancy. Clinicians should be on the lookout for the apparent solitary recurrence during follow-up. Pooling of data from multiple centres will further define the role of RT in the second-line treatment of ovarian malignancy.
PREDICTIVE FACTORS IN RELAPSED OVARIAN CANCER FOR COMPLETE TUMOR REDUCTION


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Background: The role of secondary cytoreductive surgery in ovarian cancer is not well defined. Although several authors reported a survival benefit for patients who underwent secondary cytoreduction, it remains uncertain which subjects with recurrent ovarian cancer are suitable for further surgery.

Aims: To search prognostic factors for complete tumor reduction in patients with relapsed ovarian cancer.

Methods: All patients with first relapsed ovarian cancer who underwent secondary cytoreduction at our center between 10/2000 and 04/2006 were included and analyzed within TOC -databank. Predictive factors were searched by logistic regression following the Cox-Regression Model. Variables examined (stepwise model) were age, ascites, small and big bowel metastasis, peritoneal carcinomatosis, tumor localization, FIGO stadium, tumor grade, histology and platinum-based chemotherapy response/sensitivity.

Results: 177 consecutive patients (pts) were analyzed. Median age was 55 years and median follow-up 10.8 months (range 0.0-65.0 months). 79 patients (44.6%) were macroscopic disease free after surgery. 118 (67.8%) pts were previously platinum sensitive.

Variables as ascites ( < 500ml ) (OR=0.3; 95% CI 0.1-0.8 p< 0.05), small bowel metastasis (OR=0.22; 95% CI 0.07-0.71 p< 0.05), tumor spread in upper abdomen (OR=0.33 CI 95% 0.1-0.9 p < 0.005), serous tumor histology (OR 5.8 95% CI 1.2-28.1) and platinum sensitivity (Platinum-resistant OR 0.1 95% CI 0.06-0.5 p< 0.01) were seen to be prognostic significant factors in Cox-regression equation. Age was no significant.

Conclusions: Variables as ascites, bowel metastasis tumor spread in upper abdomen, tumor histology and platinum- sensitivity may be prognostic factors for complete cytoreduction in relapsed ovarian cancer.
CLINICAL OUTCOME OF CONSERVATIVE SURGERY FOR BORDERLINE OVARIAN TUMORS WITH NONINVASIVE IMPLANTS AND STAGE I DISEASE

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Objective: We analysed retrospectively to evaluate recurrence and the 5 year overall survival rate in patients with borderline ovarian tumor with non-invasive implant and stage I disease received conservative surgery.

Materials and methods: A retrospective review was performed on patients with borderline ovarian tumor received conservative surgery (n = 52) at the Department of Obstetrics and Gynecology, Paik hospital from Jun. 1996 to Dec. 2005. All data were analyzed using Kaplan-Meier method and long-rank test.

Results: Mean follow-up duration is 90 months. Recurrence rate for borderline ovarian tumor with non-invasive implant and stage I disease received conservative surgery was 5.7%. The 5 year overall survival rate for the conservative surgery group was 97%. Recurrence rate and the 5 year overall survival was no significant difference in between for the conservative surgery group and radical surgery group (p < 0.01).

Conclusion: In borderline ovarian tumors with noninvasive implants and stage I disease, conservative surgery may be safe therapeutic option.
NRF2 SIGNALING - A POTENTIAL MECHANISM FOR CISPLATIN -RESISTANCE IN OVARIAN CANCER

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Background and aims: Nrf2 used to be recognized as an important transcriptional regulator of antioxidant response element (ARE) for the cellular adaptive response to toxic insults. Recent data show some chemo-resistant cancer cells have elevated level of Nrf2. In this study we want to find the link between Nrf2 signaling pathway and cisplatin-resistance in ovarian cancer.

Methods: Ovarian cancer cells A2780cp, A2780, SKOV3 and Hey were cultured. Nrf2 siRNA was transfected into A2780cp and A2780 cells. Cells were treated with cisplatin at varied level of concentrations for 72hr. Western-blot was used to investigate Nrf2 protein level, while SRB was used to investigate the effect of cisplatin on cellular viability. FCA was used to detect the apoptosis rate in cells.

Results: A2780 and Hey cells were shown to be cisplatin-sensitive, while A2780cp and SKOV3 cells were demonstrated as cisplatin-resistant. The Nrf2 protein was highly expressed in A2780cp and SKOV3 cells and was shown in significantly low level in A2780 and Hey cells. Treatment with Nrf2 siRNA decreased cell resistance to cisplatin. Increasing apoptosis rate was also found in cells treated with Nrf2 siRNA.

Conclusion: The Nrf2 protein play a certain role in platinum-resistance in ovarian cancer cells. Nrf2-ARE signaling pathway may be the key chain linking a variety of mechanisms for chemo-resistance, and ovarian cancer cells may regain chemosensitivity through genetic engineering on this pathway.
SYMTOMATIC TREATMENT OF ASCITES WITH IP-CHEMOTHERAPY IN ADVANCED RELAPSING OVARIAN CANCER SEEMS EFFECTIVE AND SAFE

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Background: Ovarian cancer is a dreaded disease since it is usually diagnosed in an advanced stadium due to its often mild symptoms. More prevalent in Sweden, Norway and Denmark than in the rest of the world, ovarian cancer affects approximately 750 Swedish women every year. In advanced recurrent ovarian cancer one of the most distressing symptoms for many patients is ascites, causing pain, nausea and dysnoea. Mostly treatment is initiated with systemic chemotherapy, but eventually, ascites will start to refill the abdomen and necessitate frequent laparocenteses. This study intended to assess the effect of intraperitoneal treatment with anti-cancer drugs (cisplatin and mitoxantrone) on ascites.

Methods: Records of 27 patients with symptoms from ascites and treated with intraperitoneal cisplatin and/or mitoxantrone at the oncologic clinic in Lund between 2005 and 2009 were included in the study. To achieve a more homogenous group of patients only the 20 diagnosed with confirmed diagnosis of ovarian cancer were included in the analysis. The interval between laparocenteses before and after intraperitoneal treatment was measured and prolongation of the interval was registered as response.

Results: After 10 out of 18 treatments with mitoxantrone and after 5 out of 7 treatments with cisplatin a prolongation of the interval between laparocenteses was obtained, revealing a response rate of 60 %.

Conclusion: Although not statistically significant, a majority of the patients had a decrease in ascites production after treatment. According to available records the treatment seemed safe. However, additional follow up including records of adverse events is warranted, if palliative treatment for ascites with intraperitoneal chemotherapy should be considered a well documented alternative.
PROGNOSTIC FACTOR IN THE PATIENTS OF EARLY-STAGE (PT1/PT2) CLEAR CELL CARCINOMA OF THE OVARY

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Background: Advanced clear cell carcinoma (CCC) of the ovary are poor prognosis tumor because of resistance for conventional platinum based chemotherapy. But in early stages, it is not uncertain that retoroperitoneal lymphadenectomy and adjuvant chemotherapy can contribute to improving the prognosis of the patients.

Aims: To evaluate prognostic factors in the patients with early-stage (pT1/pT2) CCC of the ovary.

Patients / methods: We analyzed 55 cases of CCC of the ovary between 2003 and 2009.

16 Patients were stage Ia,,30 stage Ic, 9 stage II. 44 patients underwent systematic retroperitoneal lymphadenectomy (pelvic and para-aortic). 35 received adjuvant chemotherapy. Survival analysis was estimated by Kaplan-Meier methods, and prognostic factors were evaluated using a Cox regression model.

Results: Retoperitoneal lymphnode metastasis were observed 4.5% (2/44). Lymphnode recurrences were observed 36.4% (4/11) in patients without lymphadenectomy. 5-year progression free survival rate was 80% in patients with lymphadenectomy and 37% in without (p=0.0006). In analysis of prognostic factor, systematic retoperitoneal lymphadenectomy (HR:0.19 p=0.0088) and positive for peritoneal cytology (HR:4.3 p=0.047) were independent prognostic factors. Tumor capsule ruptured at the laparotomy and adjuvant chemotherapy, tumor size, CA125 value did not influence progression free survival.

Conclusion: Systematic retroperitoneal lymphadenectomy improve the outcome of the early stage CCC of the ovary.
A PHASE II STUDY OF BEVACIZUMAB IN COMBINATION WITH DEFINITIVE CHEMORADIOThERAPY IN UNTREATED PATIENTS WITH LOCALLY ADVANCED CERVIX CARCINOMA


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Background: RTOG 0417 was a phase II study exploring the safety and efficacy of bevacizumab added to chemoradiotherapy.

Methods: Eligible patients with bulky IB-IIIB disease were treated with weekly cisplatin (40 mg/m2) chemoradiotherapy. Bevacizumab was administered at 10 mg/kg IV Q2 weeks for 3 cycles during chemoradiation. Primary outcome was treatment-related serious adverse events (SAEs), defined as any grade ≥ 4 vaginal bleeding or thrombotic event, or grade ≥ 3 arterial event, GI bleeding or bowel/bladder perforation, or any treatment-related death. Treatment-related AEs included all SAEs and grade 3 or 4 GI toxicity persistent for > 2 weeks despite medical intervention, grade 4 neutropenia or leucopenia persisting for > 7 days, febrile neutropenia, grade 3 or 4 other hematologic toxicity and grade 3 or 4 GI, renal, cardiac, pulmonary, hepatic or neurologic AEs. Adverse events were scored using CTCAE v 3.0 criteria (MedDRA version 6.0).

Results: 60 patients were accrued from 28 institutions, 49 were evaluable. Median follow-up was 10 months. Median age was 45, and most patients were FIGO IIIB (63%) with a Zubrod performance status of 0 (67%). There were no treatment-related SAEs. 15 patients (31%) experienced protocol specified treatment-related AEs, most common were hematologic (12/15, 80%). Nonhematologic treatment-related AEs included one report each of anorexia, dehydration, depression, syncope, and proctitis. There was one case each of grade 3 vaginal hemorrhage and grade 3 thrombosis.

Conclusions: Bevacizumab given concurrently with standard pelvic chemoradiotherapy for locally advanced cervical cancer is feasible and safe.
PHASE II STUDY OF VEGF-TRAP IN RECURRENT/METASTATIC GYNECOLOGIC SOFT-TISSUE SARCOMAS. TRIAL OF PMH, CHICAGO AND CALIFORNIA CANCER PHASE II CONSORTIA


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Background: Uterine sarcomas represent 3% approximately of uterine malignancies. Leiomyosarcomas (LMS) is the commonest. Carcinosarcoma (CS) is now generally considered a poorly differentiated epithelial cancer. There are no effective systemic therapies available against these tumors for recurrent disease after failure of chemotherapy. Vascular endothelial growth factor (VEGF) over-expression in uterine sarcomas correlates with poor outcome, thus targeting VEGF is a rational therapeutic approach. We have conducted a phase 2 study in patients with metastatic or recurrent LMS/CS of the uterus with a VEGF-Trap (Aflibercept), a decoy-soluble receptor.

Methods: Patients with recurrent/metastatic gynecologic sarcomas were recruited. Patients received single agent Aflibercept at a dose of 4mg/kg IV every two weeks. Imaging was repeated every 8 weeks. Primary objectives are objective response and disease stabilization, as measured by incidence of progression-free survival at 6 months.

Results: Study has completed the accrual. 63 patients (41 LMS and 22 CS) were included. 37 LMS and 18 CS patients are evaluable for response assessment. Adverse effects which were grade 3 or higher in >10% of patients were hypertension, fatigue and abdominal pain. Possibly related deaths were seen in 2 patients (infection and cerebral hemorrhage). Best responses with LMS: Progressive disease (PD) 24/37(60%), stable disease (SD) 11/37(29.7%), with SD > 24 weeks in 4/37(10.8%). CS group; PD: 17/18(94.4%), SD: 1/18(5.6%) no prolonged SD seen. Median TTP was 1.8(95% CI: 1.6-3.6) and 1.6(95% CI: 1.1- 1.7)(LMS/CS) months respectively.

Conclusions: VEGF-Trp has demonstrated at best moderate stable disease in LMS and no activity in the carcinosarcoma group.
PRIMARY UTERINE EXTRA NODAL NON-HODGKIN LYMPHOMA CASE REPORT

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Background: Primary extra nodal Non-Hodgkin Lymphoma account for 25 to 35% of Non-Hodgkin lymphoma. The most extra nodal organ involvement with Non-Hodgkin lymphoma is gastrointestinal tract and skin. Primary female genital tract non-Hodgkin lymphoma is very rare especially in uterus and about 0.5% has reported. We report another case of uterine lymphoma.

Case report: A 31 years old woman was presented with non specific lower abdominal pain and weight loss since six months ago that had aggravated recently. All radiographic studies were normal except the last pelvic ultrasound showed a mass in the uterus. Total abdominal hysterectomy and bilateral oophorectomy and resection of small part of small and large bowels near the uterus were done. The pathology was malignant large B cell lymphoma; full thickness myometrium was involved. Muscular layer of large intestine was involved. Both adenexes were free of tumor. IHC demonstrated LCA, CD20 and Ki 67 (60%) positive. Pathology reviewed and confirmed diagnosis. Spiral CT scan of chest, abdomen and pelvis after surgery was negative. Bone marrow aspiration and biopsy was normal. Patient was treated with 8 courses chemotherapy with R-CHOP and radiotherapy.

Discussion: Since primary extra nodal non-Hodgkin lymphoma in uterus is rare use of immunohistochemistry profile could be very valuable in differential diagnosis of malignant tumors of female genital tract.

Conclusion: Although Non-Hodgkin lymphoma of uterus is a rare condition it should be considered as differential diagnosis of gynecological malignancies. Because if it properly diagnosed could result in good outcome.

Keywords: Non-Hodgkin lymphoma, extra nodal lymphoma, immunohistochemistry
ENDOMETRIAL SQUAMOUS CELL CARCINOMA. A CASE REPORT

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Objective: The aim of our study is to present the clinicopathologic findings of a case with squamous cell carcinoma of the endometrium.

Case: A 72-year-old postmenopausal patient presented in our Department with vaginal bleeding and hypogastric pain. The ultrasound showed a thick endometrium measuring 11 mm. She underwent dilatation and curettage which revealed squamous cell endometrial carcinoma. She underwent hysterectomy with bilateral salpingo-oophorectomy which confirmed the diagnosis. The histological study showed an atrophic uterus. The cervix was normal while the endometrial cavity and the uterine wall were infiltrated by a well-differentiated squamous cell carcinoma that infiltrated focally the whole thickness of the uterus. The cervical transformation zone presented mature squamous cell metaplasia which did not reach the endometrial cavity. Immunohistochemical study showed positivity for HPV types 31-33 and negativity for p-53 suppressor gene, C-NEU oncogene or EGFR expression. The patient underwent adjuvant pelvic irradiation. She is followed-up every six months and 40 months after surgery is free of disease.

Conclusion: Squamous cell carcinoma of the endometrium is an extremely rare malignancy of the genital tract. Its identification in the endometrium without coexisting cervical squamous cell carcinoma or adenocarcinoma of the endometrium confirms the diagnosis.
ABNORMAL PAPANICOLAOU SMEARS DURING PREGNANCY

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Aim: Pregnancy provides a valuable opportunity to screen women for cervical cancer. The objective of our study is to study the cytopathologic findings of pregnant women and their management.

Methods: This is a retrospective study of 34 cases with abnormal Papanicolaou smear findings during the period January 2004 - December 2008.

Results: The mean age of our patients was 29 years (20 - 43 years). 23/34 women were smokers, whereas 9/34 had a history of abnormal Papanicolaou before pregnancy. The cytologic findings in the beginning of pregnancy were: 2/34 ASCUS, 1/34 ASC-H, 25/34 CIN I and 6/34 CIN II-III. Colposcopy was performed in all the patients. Women with histological diagnosis of CIN underwent colposcopy every 8 weeks and they were evaluated after delivery. At delivery 3/34 patients had ASCUS, 13/34 CIN I and 7/34 CIN II-III. We recorded 1 progression of CIN I to CIN II-III, 13 persistent CIN I and 11 regressions to normal findings. Women with persistent postpartum CIN II-III underwent cone biopsy. No invasion was suspected during pregnancy or postpartum.

Conclusion: The nine-month period of pregnancy is a short enough time to allow expectant management in women with abnormal Papanicolaou smear until their delivery.
CUTANEOUS METASTASIS FROM GYNAECOLOGIC MALIGNANCIES

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Background: Gynecological malignancies commonly metastasize to contiguous structures and other sites intra-abdominally. We report four post-menopausal females with peri-umbilical (sister Joseph's nodule) metastatic lesions from uterine tumours.

Materials & method: Patients' tissue biopsies were fixed in 10% formalin, processed in paraffin wax and stained with Haematoxylin & eosin, PAS and mucicarmine.

Result: Four females, aged 50, 65, 70 and 72 years were seen. They presented with cutaneous peri-umbilical nodules of 3-6 months duration. Clinical examination revealed respectively right matted axillary and inguinal lymphadenopathy, ulcerated nodule with a 16 weeks uterine mass, vaginal discharge & bleeding with a fungating cervical mass and a year history of total abdominal hysterectomy secondary to endometrial carcinoma. Histologic sections from the nodules in three cases showed pigmented skin overlying malignant columnar cells having hyperchromatic nuclei and abundant amphophilic cytoplasm growing in focal papillary, cystic and glandular patterns in a fibromyxoid stroma. They were diagnosed metastatic adenocarcinoma from the endometrium. Biopsies of the nodule and cervical mass in the third female showed malignant non-keratinizing squamous cells.

Conclusion: There is a rise in the incidence of gynecological malignancies and over 80% cases of endometrial cancer are seen in postmenopausal females at the time of diagnosis. Metastasis usually spread to contiguous pelvic structures, while distant metastasis affects the lung, liver, bone and CNS. Cutaneous spread, though uncommon occurs in the head and neck region, particularly the scalp. However, in advanced disease or late presentation as seen in our patients, a high index of suspicion should be entertained.
AN INVESTIGATION OF THE INFLUENCE OF ESTROGEN BINDING TO ITS RECEPTOR-Α ON THE INVASIVENESS OF AN ENDOMETRIAL CARCINOMA HEC-1B

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Objective: The aim of this study is to explore the influence of estrogen binding to its receptor-α on the invasiveness of an endometrial carcinoma HEC-1B cells.

Methods: Validated ERα-siRNA was transfected into human endometrial carcinoma cell line, HEC-1B cells. The RT-PCR and Western blot were used to examine the efficiency of down-regulation. Invasive capability of HEC-1B cells with 17β-estradiol before and after ERα RNAi were detected by Matrigel cell invasion assay. Messenger RNA and protein expression and zymographic activities of MMP-2, MMP-9, TIMP-1 and TIMP-2 were measured by RT-PCR, Western blot and gelatin zymography, respectively.

Results:
1. The mRNA and protein expression levels of ERα in HEC-1B cells were significantly reduced after transfection with ERα-siRNA (knocked down by 67% and 72% respectively).

2. The invasive capacity of HEC-1B cells under the influence of 17β-estradiol was significantly inhibited by ERα siRNA (P< 0.05). The mRNA and protein levels of MMP-2 and MMP-9 were remarkably decreased (P< 0.05) after transfected with ERα-siRNA, whereas the expression levels of TIMP-1 and TIMP-2 were increased.

Conclusion: 17β-estradiol regulates the expression of MMPs/TIMPs and influences invasive capacity of the endometrial carcinoma cells via ERα

Keywords: Endometrial carcinoma; Estrogen receptor alpha (ERα); Matrix Metalloproteinases (MMPs); Tissue Inhibitors of MMPs (TIMPs); RNA interference (RNAi)
THE EFFECT OF BEVACIZUMAB (VEGF MONOCLONAL ANTIBODY) WITH OR WITHOUT CLASSIC CHEMOTHERAPEUTICS IN ENDOMETRIUM CARCINOMA CELL CULTURE

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Endometrial carcinoma is the most common malignancy of the female genital tract in industrialized countries. Although most endometrial carcinomas are detected at low stage, there is still a significant mortality from the disease. About 75 % of the patients present limited disease, confined to the uterus that can be cured by surgery. However, one third of the patients will need systemic treatment because of metastatic or relapsing disease. Vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis in endometrial cancer growth. Preclinical studies have shown that a humanized variant of monoclonal antibody against VEGF, Bevacizumab, has shown promising activity in many non-gynecologic human solid tumors. Invitro tests have been used to determine the cytotoxic and apoptotic effects of agents which are the main topic of our study (cisplatin, doxorubicin, bevacizumab). Cytotoxic effect was determined by the standard MTT assay and apoptosis by DAPI staining, caspase-3 in Ischikawa cell culture. Based on these informations, the aim of our study is to determine the effect of a antiangiogenic agent Bevacizumab with or without classic chemotherapeutics which used in one of the most common gynecologic malignancy and use these informations in our clinical practice. In vitro cytotoxicity and apoptosis tests against Ishikawa cells indicated that the triad drug combination showed a higher inhibition than a single and dual drug combination, which holds a promise for multidrug combination.

Keywords: Endometrial carcinoma, MTT, DAPI, Ischikawa, Apoptosis.
BETA-ARRESTIN 2 MODULATES RESVERATROL-INDUCED APOPTOSIS AND REGULATION OF AKT/GSK3B PATHWAY IN HUMAN ENDOMETRIAL CANCER CELLS

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Background and aims: Endometrial cancer is the fourth most prominent cancer among all feminine cancers in the world. Resveratrol, an antioxidant found in food products, is emerging as a novel anticancer agent. However, the mechanism(s) by which resveratrol exerts its effects on endometrial cancer are unknown. We previously reported that β-arrestin 2 plays a critical role in cell apoptosis. The role of β-arrestin 2 in resveratrol modulation of endometrial cancer cell apoptosis remains to be established.

Methods: Human endometrial cancer cells HEC1B and Ishikawa were transfected with β-arrestin 2 RNA interfering (RNAi) plasmid and β-arrestin 2 full length plasmid respectively. The cells were then exposed to differing concentrations of resveratrol. Apoptotic cells were detected by TUNEL assay. Expression of total and phosphorylated Akt (p-Akt), total and phosphorylated glycogen synthase kinase 3 beta (p-GSK3β), and caspase-3 were determined by Western blot analysis.

Results: Our data demonstrate inhibition of β-arrestin 2 in HEC1B cells increases the number of apoptotic cells and caspase-3 activation. Additionally β-arrestin 2 exerted an additive effect on resveratrol-reduced levels of p-Akt and p-GSK3β. Overexpression of β-arrestin 2 in Ishikawa cells decreased the percentage of apoptosis and caspase-3 activation and attenuated resveratrol-reduced levels of p-Akt and p-GSK3β. Taken together, our studies demonstrate for the first time that β-arrestin 2 mediated signaling plays a critical role in resveratrol-induced apoptosis in human endometrial cancer cells.

Conclusion: Resveratrol primes endometrial cancer cells to undergo apoptosis by modulating β-arrestin 2 mediated Akt/GSK3β signaling pathways.
SURVIVAL AND DISEASE RELAPSE IN SURGICAL STAGE 1 ENDOMETRIOID ADENOCARCINOMA OF UTERUS AFTER ADJUVANT VAGINAL VAULT BRACHYTHERAPY (VVBT)

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Introduction: Advanced age, deep myoinvasion, whole cavity or isthmic tumors, poor differentiation, and lymphvascular space invasion (LVSI), increase recurrence risk and adversely effect survival in stage 1 uterine endometrioid adenocarcinoma.

Objectives: To ascertain survival, failure patterns, salvagibility, and correlate adverse histopathology to recurrences in these patients.

Methods: We reviewed 162 patients of surgical stage 1 uterine endometrioid adenocarcinoma at increased risk of recurrence, who were treated with surgical staging, and adjuvant high dose rate VVBT.

Results: Mean patient age was 58.9 years. Surgical stage 1C had 54.3% patients, while rest were 1B. Grade 2 tumors were seen in 53.7% and grade 3 in 21.61%. Mean follow up was 52.9 months with maximum of 11.5 years. Five and ten year survival was 94% and 89% respectively. There were 9 (5.56%) recurrences. Stage 1C had 77.78% while stage 1B had 22.22% recurrences, the median time being 19 months. Initial three years had 77.78% relapses. There was no recurrence in grade 3 tumors with 100% five year survival for 1CG3. Age, LVSI, tumor volume and location, were not significant parameters in surgical stage 1 patients who failed. One patient had isolated pelvic failure while pure distant relapse occurred in 5 patients. Three patients failed at both locoregional and distant sites. Vault recurrence coupled with distant metastasis occurred in one patient. Three (33.33%) recurrences, all with limited relapse sites, were salvaged with mean survival of 71.33 months. Median survival after recurrence was 5 years.

Conclusion: Excellent survival rates, acceptable morbidity and mostly distant recurrence was seen.
THE EFFECTIVENESS OF LEVONORGESTREL RELEASING INTRAUTERINE SYSTEM (LNG-IUS) IN THE TREATMENT OF ENDOMETRIAL HYPERPLASIA IN KOREAN WOMEN

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Background and aims: Levonorgestrel releasing intrauterine system (LNG-IUS) has been shown to treat patients with non-atypical & atypical endometrial hyperplasia successfully in many western studies. Our purpose was to examine the effectiveness of LNG-IUS in the treatment of Korean women with endometrial hyperplasia.

Methods: We conducted a prospective observational study of 12 women diagnosed with endometrial hyperplasia and treated with LNG-IUS insertion between February 2007 and August 2009 at the Department of Gynecology of Gangnam CHA hospital, College of Medicine, CHA University. Baseline endometrial biopsies were done before insertion of LNG-IUS, and outpatient follow-up endometrial biopsies were undertaken at 3-month intervals after insertion of LNG-IUS. We investigated the regression rate and the time to regression.

Results: Four patients had simple hyperplasia without atypia, 7 patients complex hyperplasia without atypia, and just 1 patient complex atypical hyperplasia. Complete regression of endometrial hyperplasia was achieved in all cases (100%, 12/12), with the significant proportion (66%, 8/12) achieving it within 3 months. The mean duration to regression was 4.5 months. All cases had regression within 9 months. In the case of complex atypical hyperplasia, the regression was attained at the ninth month after insertion of LNG-IUS. The mean follow-up duration was 12 months (3 months~ 27 months). As long as LNG-IUS was maintained, the endometrial hyperplasia did not recur.

Conclusion: LNG-IUS appears to be as highly effective in treating Korean women as in western women with endometrial hyperplasia.
THE CORRELATION OF LOWER UTERINE SEGMENT INVOLVEMENT WITH LYMPH NODE METASTASIS IN ENDOMETRIAL CARCINOMA: A RETROSPECTIVE ANALYSIS

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Objective: To determine the relationship between lower uterine segment involvement (LUSI) and lymph node metastasis in surgically staged endometrial carcinoma patients.

Study Design: A retrospective analysis was done on all patients diagnosed with endometrial carcinoma from April 1999 to February 2008. Patients who underwent complete surgical staging and found to have lower uterine segment involvement were included. Slides were reviewed by a single pathologist. The primary endpoint was the presence of nodal involvement. Comparison/association of the different variables under study was done using the following test statistics: Chi-square test, Fisher Exact test and logistic regression. Odds ratios (OR) with 95% confidence interval were calculated.

Results: A total of one hundred and ninety-nine patients (199) were included in the review. Forty-five (45) were found to have lower uterine segment involvement, sixteen (35%) of which had nodal metastasis. Out of the 154 patients without LUSI, sixteen (10%) were found to have nodal metastasis (p=0.0001). Both for univariate and multivariate analysis, lower uterine segment involvement, lymphovascular space invasion and deep myometrial invasion were found to be predictive of nodal spread.

Conclusion: Lower uterine segment involvement may be an important predictive factor of lymph node metastasis for endometrial cancer patients with epithelial type of endometrial cancer.
ASSESSMENT OF GROSS EXAMINATION AND FROZEN SECTION OF UTERINE SPECIMEN IN ENDOMETRIAL CANCER PATIENTS

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Subject: The accuracy of intraoperative gross visual examination of myometrial invasion of uterine specimen has been evaluated in several studies with controversial results. The intraoperative frozen section (IFS) analysis is used to identify patients at high risk for pelvic and para-aortic nodal metastasis in order to avoid lymphadenectomy in low risk patients. However, there is still some controversy concerning the efficiency of IFS. The aim of this study was to evaluate the accuracy and validity of frozen section diagnosis and gross examination of uterine specimen compared to the final histological results in patients with endometrial cancer.

Methods: The study group comprised of 31 patients with a pre-operative histopathological diagnosis of endometrial carcinoma. Comprehensive surgical staging were performed in all patients. Intraoperative gross examination with frozen section analysis was performed. Lymphadenectomy was performed in all patients. The uterus together with removed lymph nodes were stored and subjected to final pathologic diagnoses.

Results: Gross examination accurately identified microscopic invasion of myometrium in 86.6% of the patients with 88.9% sensitivity, 85.7% specificity and negative and positive predictive value of 72.7% and 94.7%. The kappa was 0.70 (p< 0.0001) with a 95% CI 0.432-0.968. Frozen section in 90% of cases was correctly reporting final histopathological myometrial invasion with sensitivity 88.9%, specificity 90%, positive and negative predictive value 80% and 94.7% respectively .The kappa was 0.76 (p< 0.0001) with a 95% CI 0.51-1.009.

Conclusion: These data confirms the previous reports for the accuracy of gross examination and frozen section diagnosis in early stage and low grade tumors.
ENDOMETRIOID ENDOMETRIAL CANCER AND OVARIAN SEX CORD TUMOR WITH ANNULAR TUBULES IN WOMAN WITH PEUTZ-JEGHERS SYNDROME AND MULTIPLE PRIMARY CANCERS

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**Background:** Peutz-Jeghers syndrome is a rare syndrome which is inherited in a dominant manner. It is characterized by hamartomatous polyps of the gastrointestinal tract and hyperpigmented macules of the oral mucosa. It is characterized by an increased risk of developing neoplasms in the gastrointestinal tract, pancreas, breast and genital system. Women with Peutz-Jeghers syndrome almost always have an ovarian sex cord tumor with annular tubules and often present a minimal deviation adenoma malignum of the cervix.

**Case:** We present a case of a 58-year-old patient with Peutz-Jeghers syndrome and history of multiple malignancies (thyroid, breast and colon cancer). She presented with metrorrhagia in our department. The dilatation and curettage revealed endometrial adenocarcinoma. The patient underwent total abdominal hysterectomy with bilateral oophorectomy. The histologic examination showed an endometrioid endometrial adenocarcinoma developed in atypical endometrial hyperplasia. The histologic examination of the right ovary revealed a sex cord tumor with annular tubules, measuring 3 cm.

**Conclusion:** Sex cord tumors with annular tubules in patients with Peutz-Jeghers syndrome are usually small, bilateral benign tumors of the ovaries which have common characteristics with granulosa cell tumor and Sertoli cell tumor. Hyperestrogenism is a rather common finding with development of estrogen-dependent lesions.
DETECTION OF SUGAR CHAINS OF GLYCOPROTEINS EXPRESSED BY NORMAL ENDOMETRIUM AND UTERINE ENDOMETRIAL CANCER(WELL-DIFFERENTIATED AND POORLY-DIFFERENTIATED) WITH THE LECTIN ARRAYS

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Objective: Sugar chains of glycoproteins or glycolipids on the cell membrane are known to be involved in recognition between cells and in cell and differentiation, and thus are attracting attention in the fields of reproductive medicine and oncology. In the present study, we analyzed the expression of glycoprotein sugar chains in the normal endometrium and the endometrial cancer(well-differentiated and poorly-differentiated), and searched for sugar chains that were specifically expressed in each case.

Materials: The materials were cultured cells derived from uterine cancer, as well as resected endometrium and uterine cancer tissues. We analyzed the profile of sugar chains with lectin arrays containing 40 immobilized lectins and detected sugar chains by fluorescent labeling of membrane proteins extracted from the cultured cells and tissues. Then we compared the profile obtained from cultured cells derived from uterine cancer, the normal endometrium, and the endometrial cancer(well-differentiated and poorly-differentiated).

Results:

1. There were differences in the expression of glycoproteins recognized by UEA-1 (α-fucose), SSA and SNA(sialic acid), and BPL and ACA (β-galactose) between the cells derived from well-differentiated and poorly-differentiated uterine cancer.

2. The lectin profile was useful to differentiate normal endometrium from endometrial cancer.

Conclusions: Sugar chains on the cell membrane showed changes of expression due to carcinogenesis of the endometrium and differentiation of cancer cells. It was suggested that analysis of the sugar chain profile expressed on the cell membrane in various gynecological cancers with lectin arrays may help us to assess the characteristics of tumors(malignancy, sensitivity to anticancer drugs, sensitivity to irradiation, metastatic potential, and invasiveness).
A QUALITY CONTROL STUDY OF LYMPH NODE EVALUATION IN ENDOMETRIAL CANCER

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Objective: To analyze the reported lymph node counts of uterine cancer patients enrolled on GOG protocol 210 for discrepancies between surgeons, histology prosectors and pathologists.

Materials and methods: This is a retrospective review of uterine cancer patients who underwent a formal staging procedure while enrolled on GOG Protocol 210. All patients required an abdominal hysterectomy or laparoscopic-assisted vaginal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy, with the specimen separated by the following regions: external iliac, obturator, common iliac and periaortic. Lymph node counts were analyzed by surgeon, histology prosector, and pathologist.

Results: There were 78 patients enrolled on GOG 210 during the study period. Of these, 72 (92%) patients met inclusion criteria. A total of 2,397 lymph nodes were counted, with an average total number of lymph nodes dissected per patient of 33 (STD=9.04). Surgeons A, B, and C had an average lymph node count of 32, 33, and 35, respectively (p=0.66). Prosectors 1 through 4 dissected an average of 34, 33, 28, 35 lymph nodes, respectively (p=.091). There were 2 pathologists with > 10 cases. Their mean lymph node counts were 35 and 30, respectively with no significant difference in mean node (p=0.079).

Conclusion: This systematic review did not identify a discrepancy in nodal count between surgeons, prosectors or pathologists at our institution. The methods used may be helpful in structuring interdepartmental reviews for completeness of nodal dissections in cases where surgical intent has been standardized.
CLINICAL IMPLICATIONS OF POSITIVE PERITONEAL CYTOLOGY IN ENDOMETRIAL CANCER

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Background: In 2009, a revised FIGO staging for endometrial cancer were released in which peritoneal cytology had been removed from the staging system. To date there is no definitive consensus on the prognostic significance of positive peritoneal cytology alone in endometrial cancer.

Objectives: To evaluate the clinical significance of positive peritoneal cytology in patients with endometrial cancer.

Methods: The records of 315 patients with endometrial cancer treated at Cancer Hospital, Fudan University between January 1996 and December 2008 were reviewed.

Results: All patients underwent surgery and 256 (81.3%) had full surgical staging. 206 (65.4%) were stage IA, 26 (8.3%) were stage IB, 21 (6.7%) were stage II, 19 (6.0%) were stage IIIA, 2 (0.6%) were stage IIIB, 23 (7.3%) were stage IIIC, and 18 (5.7%) were stage IVB. Peritoneal cytology were positive in 30 (9.5%) patients. Three-year OS and RFDSS were 93% and 85.5%, respectively. Positive peritoneal cytology was associated with a higher rate of serosal involvement, cervical involvement, adnexal involvement, or omental involvement ($p<0.05$). Positive peritoneal cytology, surgical stage, and myometrial invasion were significantly associated with a worse OS in multivariate analysis ($p<0.05$).

Conclusion: Our data showed that positive peritoneal cytology was a prognostic factor for patients with endometrial cancer. Patients with positive peritoneal cytology had a higher rate of serosal involvement, cervical involvement, adnexal involvement, or omental involvement. Therefore, full surgical staging were necessary for patients with positive peritoneal cytology.

[Survival curve]
ENHANCED EXPRESSION OF SULFATIDES IN THE WELL-DIFFERENTIATED TYPE OF HUMAN ENDOMETRIAL ADENOCARCINOMA

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It has been well recognized that the poorly differentiated (diff) type of human endometrial adenocarcinoma(Emca) shows faster progression and more refractory to therapy than the well-diff type. To examine the molecular backgrounds on the morphological and cell biological properties between the well- and the poorly diff types, we quantitatively determined glycolipids(GSL) in the cancerous tissues. No significant difference was observed in the amounts of the neutral GSL belonging to the globo-series, and GM3 ganglioside. Also, a mode of the expression of tumor-associated GSL, LeY and sialyl Lea, was not correlated with the diff types. However only a difference between them was observed in the expression of sulfatides. By TLC-immunostaining, sulfatide was revealed to be frequently expressed in the well diff types. The altered expression of sulfatide was also proven to be due to the expression of GalCer sulfotransferase gene. Since sulfatide has been shown to be expressed in association with the gland formation at the luteal phase of normal uterine endometrium, our observation might be indicated that sulfatide is involved in the formation of the well-diff phenotypes of Emca.
EFFICACY OF SYSTEMATIC LYMPHADENECTOMY FOR SURVIVAL IN PATIENTS WITH NON-ENDOMETRIOID ENDOMETRIAL CANCERS


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Background: Non-endometrioid endometrial cancer is a clinically and pathologically distinct subtype of endometrial cancer. Because it is less common than the endometrioid subtype, its optimal treatment strategies have not yet been determined, making evidence-based management difficult. The aim of this study was to determine whether systematic lymphadenectomy improves overall survival compared to no systematic lymphadenectomy in non-endometrioid endometrial cancer.

Methods: The authors retrospectively reviewed the medical records and pathological findings of 112 patients who underwent surgical staging for non-endometrioid endometrial cancer from 2000 to 2006 in Korea.

Results: Systematic lymphadenectomy was performed in 71 patients. Pelvic lymph node metastases were identified in 31% and 14.6% patients who underwent systematic pelvic lymphadenectomy and no lymphadenectomy, respectively. After adjusting for risk factors, there was no significant difference in overall survival (odds ratio (OR) = 0.69; 95% confidence interval (CI), 0.29-1.67) between patients who did or did not undergo systematic lymphadenectomy. On multivariate analysis, patients with lymph node metastasis had higher risk of death (OR = 3.11; 95% CI, 0.97-10.00) than did patients with no lymph node metastasis.

Conclusion: Although systematic lymphadenectomy did not affect overall survival in patients with the non-endometrioid subtype, it has the potential benefit of providing prognostic information and acting as a guide for further adjuvant treatment.
RECURRENT PATTERNs AND PROGNOSIS OF LOW-GRADE ENDOMETRIAL STROMAL SARCOMA AND THE POTENTIAL OF TYROSINE KINASE-INHIBITING THERAPY

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Purpose: Low-grade endometrial stromal sarcoma (ESS) is a rare uterine malignancy. The current treatment approaches yield unsatisfactory results, and potential therapeutic targets need exploration.

Methods: We reviewed the electronic medical records of 74 patients with low-grade ESS who had been treated at The University of Texas M. D. Anderson Cancer Center between 1995 and 2006. Using immunohistochemistry, we tested the expression of targets in paraffin-embedded tissue samples taken from 13 of the patients.

Results: Forty-seven patients (64%) had a recurrence, and 16 (22%) had died of their disease at last follow-up. The 10-year progression-free survival (PFS) rate was 43% (median PFS duration, 108 months), and the overall survival (OS) rate was 85% (median OS, 288 months). Patients who received hormonal therapy had an overall response rate of 27%; another 53% had stable disease, with a median time to progression of 24 months. No complete response or partial response was observed among patients who received radiotherapy or chemotherapy. In the paraffin-embedded specimens we tested, C-Abl was expressed universally. Expression of PDGF-α, PDGF-β, VEGF, and c-Kit was detected in 33%, 36%, 54%, and 8%, of specimens, respectively. EGFR and HER-2 were not detectable in any specimens.

Conclusions: Our study confirms that low-grade ESS is a hormone-dependent malignancy, with hormonal therapy showing a higher efficacy and longer response duration than chemotherapy and radiotherapy. The universal expression of c-Abl among the samples we tested suggests that c-Abl may be therapeutically targeted in low-grade ESS with a tyrosine kinase inhibitor such as imatinib mesylate.
THE INFLUENCE OF EARLY DIAGNOSIS OF ENDOMETROID ENDOMETRIAL CANCER ON DISEASE STAGE AND SURVIVAL

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Objective: To evaluate whether the presence of symptoms or their duration are associated with disease stage and survival of patients with endometroid endometrial carcinoma (EEC).

Patients and methods: The data of 220 women with EEC extracted from the patient’s records included the history, surgical note, pathology reports and clinical follow-up. The patients were stratified into three groups. Group (1): 42 patients who were asymptomatic at the time of diagnosis and in whom endometrial histological evaluation was performed solely to ultrasonographic suspicion. Group (2): 95 patients with a history of irregular bleeding or postmenopausal bleeding of up to 3 months duration. Group (3): 83 patients whose symptom duration exceeded 3 months.

Results: The median age of the patients was 63 years (range 27-90). 190 patients were stage I, of which 47 had deep myometrial invasion; 20 were stage II, 8 were stage III and 1 was stage IV. 150 had FIGO grade 1, 41 had grade 2 and 27 patients had grade 3 tumors. There was no significant increment difference between groups 1 through 3 with regard to the proportion of patients with deep invasion in stage I (21%, 24%, 26%, \(p=0.84\), respectively) with grade 3 tumors (10%, 13%, 14%, \(p=0.42\), respectively) or with advanced stage (12%, 14%, 15%, \(p=0.92\), respectively). Survival analysis demonstrated no significant trend toward better survival with earlier diagnosis (\(p=0.172\)).

Conclusions: Early diagnosis of EEC cancer is not significantly associated with less advanced disease and survival advantage.
A PHASE II TRIAL OF COMBINATION THERAPY WITH PACLITAXEL, CARBOPLATIN AND MEGESTEROL ACETATE FOR ADVANCED STAGE/RECURRENT ENDOMETRIAL CARCINOMA (NCT00584857)

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Objective: To determine overall survival (OS), progression-free interval (PFI), and toxicity in patients with advanced stage or recurrent EMCA treated with combination paclitaxel, carboplatin, and megestrol acetate (Megace).

Methods: Patients with Stage III-IV or recurrent EMCA were enrolled between 10/2004 and 4/2008 and received paclitaxel (175 mg/m²) and carboplatin (AUC 6) every 21 days for 6 cycles and Megace 40 mg orally four times daily for up to 5 years in the absence of recurrence or progression. Dose reductions were based on grade 3/4 hematologic toxicity. Survival data was calculated from time of study enrollment.

Results: 28 patients were evaluable: 20 (71%) patients with stage III/ IV disease and 8 (29%) with recurrent disease. Three patients with recurrence received prior radiation. Median OS was 36.3 months (4.7 - 49.5). Median PFI was 31.9 months (2.3 - 49.5). After a median 28.2 months of follow-up, 14 patients (50%) were NED, 4 were AWD, and 9 were DOD. One patient died without evidence of disease. Twenty-three patients completed 6 cycles of chemotherapy. Ten patients experienced a dose reduction. Myelosuppression was common with 13 patients (48%) experiencing grade 3/4 neutropenia, and 9 patients (33%) experiencing grade 3/4 anemia. There were no episodes of febrile neutropenia. Three patients had a deep vein thrombosis. One patient experienced a pulmonary thromboembolus.

Conclusion: Combination therapy with paclitaxel, carboplatin, and Megace had excellent activity. The addition of hormonal therapy to cytotoxic chemotherapy is safe and may improve survival. Myelosuppression is common, but can be managed with colony-stimulating factors.
THE INSULINE-LIKE GROWTH FACTOR SYSTEM AND ENDOMETRIAL CANCER WITH METABOLIC SYNDROME

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Aims: The aim of the study was to assess the levels of insulin-like growth factors I (IGF-I), insulin-like growth factor binding protein-3 (IGFBP-3) and IGFBPs specific protease PAPP-A in tumors of endometrial cancer patients (pts.) with metabolic syndrome.

Methods: The concentrations of IGF-I, PAPP-A and IGFBP-3 in tumors were determined by hard-phase immunoenzymatic analysis (R&D Systems, USA). Results were analyzed in relation to ER, PR and PTEN expressions (immunohistochemistry) and hormonal-metabolic disturbance. A total of 54 pts. were enrolled (23 endometrial cancer pts. with metabolic syndrome, 11 endometrial cancer pts. without metabolic disturbance and 20 endometrial hyperplasia pts. with metabolic syndrome).

Results: The levels of IGF I, PAPP-A and IGFBP-3 were significantly higher in endometrial cancer pts. compared to those observed in endometrial hyperplasia pts. The maximum levels were found in the group of endometrial cancer pts. with metabolic syndrome. Multiple correlations between IGF-system values and anthropometric, clinical parameters and hormonal-metabolic disturbance were revealed in endometrial cancer pts. with metabolic syndrome. The IGF-I level was significantly higher in PTEN-positive tumors than in PTEN-negative tumors. The PAPP-A level was higher in receptor-positive tumors than in receptor-negative tumors, p< 0.05.

Conclusion: Thus, the data obtained were indicative of IGF-system activation in endometrial cancer pts. with metabolic syndrome. The relationship between the IGF-I and PAPP-A levels and PTEN, ER and PR expressions in endometrial tumor as well as the relationship between IGF-system values and signs of metabolic syndrome (anthropometric, clinical and hormonal-metabolic) were revealed.
PROTEASOME ACTIVITY AND SUBUNIT COMPOSITION IN ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CANCER WITH METABOLIC SYNDROME

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Background and aims: Proteasomes are the main components of the system required for the protein degradation. They play a great part in processes of degradation of own protein in cell and are involved in cell division, differentiation, immune response.

Material and methods: The group of patient was presented by 33 people with endometrial cancer and 15 patients (pts) with endometrial hyperplasia. Total proteasome activity, 26S and 20S proteasome activity were determined by the hydrolysis of fluorogenic peptide Suc-LLVY-AMC. 26S and 20S proteasomes were obtained by the ammonium sulfate adding. Content of proteasome subunits was investigated by Western blotting.

Results and conclusions: The high total proteasome activity and activity of 26S and 20S proteasome was revealed in endometrial cancer. The change of proteasome activity was correlated with the decreased content of a1a2a3a5a6a7 proteasome subunits and increased content of LMP2, LMP7 и PA28b proteasome subunits. The pts with endometrial hyperplasia and metabolic syndrome had the decreased in 2,4 mal 26S proteasome activity in comparison with the group of pst without metabolic syndrome. The total proteasome activity and 26S proteasome activity were higher in 2 and 1,3 mal, consequently, in endometrial cancer pts in comparison with ones without metabolic syndrome. The development of endometrial cancer against a metabolic syndrome background was accompanied the decreased content of PA28b proteasome subunit. The metabolic syndrome is associated with the significant disbalance of proteasome activity in endometrial hyperplasia. The development of endometrial cancer with metabolic syndrome leads to the modified proteasome subunit composition.
MONITORING OF ENDOMETRIAL K-RAS MUTATION IN TAMOXIFEN-TREATED PATIENTS WITH BREAST CANCER

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Aim: A high incidence of endometrial K-ras mutations has been reported in Tamoxifen (TAM)-treated patients with breast cancer. We examined the changes in the frequency of endometrial K-ras mutations after the cessation of TAM treatment.

Methods: DNA was extracted from fresh cytological or polypectomy samples of the endometrium in 28 patients who had undergone TAM treatment of breast cancer. Mutations were detected by an enriched polymerase chain reaction-enzyme-linked minisequence assay (Sumitomo Metal Industry, Inc, Tokyo, Japan). K-ras codon 12 mutations were monitored in these 28 patients.

Results: An initial examination detected endometrial K-ras mutations in 13 of the 28 patients. However, repeated examinations performed after cessation of TAM treatment did not detect endometrial K-ras mutations in any of these 13 patients. No endometrial K-ras mutation has been detected in repeated examinations performed for these patients for over more than 2 years since the cessation of TAM treatment. In addition, the 15 patients who did not have endometrial K-ras mutations in the initial examination did not demonstrate them in repeat examinations.

Conclusion: The cessation of TAM treatment may reduce the risk of developing endometrial cancers through K-ras mutations.
IMMUNOLOGICAL RESPONSE AFTER THERAPEUTIC VACCINATION WITH WT1 mRNA-LOADED DENDRITIC CELLS IN A PATIENT WITH END STAGE ENDOMETRIAL CARCINOMA

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Background and aims: Wilms' tumor gene 1 (WT1) is a highly ranked immunotherapeutic target. Since it is expressed in uterine cancer, WT1 immunotherapy seems an attractive treatment option in this group of patients.

Methods: A HLA-A2.1 positive 46-year-old woman with end stage serous endometrial cancer received 4 weekly injections of WT1-RNA-loaded mature dendritic cells. Response was measured clinically (CT scan), biochemically (CA125) and immunologically (WT1-specific T cells).

Results: Our patient showed WT1 positivity in 10% of her tumor cells and diffusely in the intratumoral endothelial cells on biopsies taken from the recurrent disease. After 2 vaccinations, CA125 started to decrease and a 2.5-fold increase of circulating WT1-specific T cells was observed. The treatment was feasible, and there were no treatment-related side effects. However, the patient - suffering from diffuse disease - became again progressive and died 8 months later.

Conclusion: This is the first patient with a WT1 positive endometrial carcinoma, who received immunotherapy with dendritic cells loaded with WT1 RNA, resulting in a vaccine-specific T cell response.
Vaginal Hysterectomy as a Treatment Option in Patients with Endometrial Cancer and Significant Co-Morbidities

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Background: The objective of this study is to ascertain the presence of extra-uterine spread in radiologically early stage and grade endometrial cancer. This could be the basis for offering vaginal hysterectomy as an alternative to primary radiotherapy in women with significant medical co-morbidities in whom laparotomy will be contraindicated.

Materials and methods: A retrospective cohort study assessing patients with clinically early stage endometrioid adenocarcinoma of the endometrium. 542 endometrial cancer cases were identified, of these 439 were endometrioid type. surveillance data were collected from hospital records Postoperative histopathological findings served as a reference standard.

Results: Of the 439 cases treated during the study periods; 415 patients had an MRI pre-operatively imaging, 14% of these cases showed signs of extra-uterine spread. MRI staging was then compared with the histopathology staging; the latter was taken as the gold standard. In 8% of the cases where no spread seen on MRI; the disease was actually spread outside uterine corpus mainly to the cervix and pelvic lymph nodes. The sensitivity, specificity, positive predictive value and negative predictive value for MRI were 56, 93, 60, and 92 respectively for predicting early stage disease.

Conclusions: The risk of adnexal metastasis is less than 1% in clinically early stage disease and highly unlikely if MRI suggests disease is confined to the inner half of the myometrium and low grade disease. We suggest that vaginal hysterectomy might be a safe alternative to laparotomy in treatment of radiological early stage disease in medically compromised elderly patients.
CASE REPORT LEIOMYSARCOMA WITH LYMPHATIC DISSEMINATION OF RETROPERITONEAL LEIOMYOMATOSIS

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Objective: Uterine leiomyosarcoma constitutes 1-2% of uterine malignancies. We present a case of a 60-year-old postmenopausal woman who developed leiomyosarcoma with lymphatic dissemination of retroperitoneal leiomyomatosis, from previous hysterectomy state for smooth muscle tumors of uncertain malignant potentials (STUMP).

Materials: In Sep 2009, a 60-year-old woman returned 37 months of initial operation later with overman’s fist sized pelvic mass. She was initially treated with hysterectomy, both adnexectomy and paraaortic lymph node biopsy without postoperative adjuvant therapy. Her final tissue pathology showed STUMP, intramural myoma with no coagulative tumor necrosis, diffuse high cellularity and focal high mitotic areas.

There were paraganglioma and reactive lymphoid hyperplasia in paraaortic lymph nodes. Ultrasound exam of the pelvis revealed 5x6 cm sized solid mass in pelvic cavity. The whole body PET-CT showed several masses with abnormal FDG uptake in pelvic cavity. The CA 125 was 28.29. The explorative laparotomy was performed.

Results: The intraperitoneal cavity was clear. There were several sized multiple myomas along major vessels in retroperitoneum. There was 6x7 cm sized, necrotic hemorrhagic mass in pelvis. The frozen and permanent histology reported that excised retroperitoneal masses along major vessels were multiple leiomyomas and the midline pelvic mass was epithelioid leiomyosarcoma. She had an uneventful postoperative course. She had three cycles of chemotherapy with adriamycin, cisplatin, ifosfamide and mesna, followed by pelvic irradiation. She has no evidence of recurrence at present.

Conclusions: STUMPs are rare but sometimes behave as sarcoma. After initial surgical excision, STUMPs may need postoperative adjuvant therapy to reduce relapse.
DOES POSTOPERATIVE RADIOTHERAPY PROVIDE ANY SURVIVAL ADVANTAGE OVER OBSERVATION IN STAGE IC ENDOMETRIAL CANCER AFTER COMPREHENSIVE SURGICAL STAGING?

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Aims: We aimed to compare postoperative radiotherapy and observation for survival and recurrence rates in stage IC endometrial carcinoma patients who underwent comprehensive surgical staging.

Methods: Fifty-seven stage IC endometrial cancer (according to FIGO 1988 staging system) patients who underwent surgical staging including lymphadenectomy were included in this study. Twenty cases (35%) received postoperative radiotherapy (in 19 cases external pelvic, in 1 case vaginal radiotherapy) and 37 (65%) were observed without additional therapy. Two groups were compared for survival and recurrence rates.

Results: Mean follow-up for the radiotherapy and observation groups were 52.05 (median, 55; range 4-84) and 38.71 (median, 25; range: 2-84) months, respectively. 5-year disease free survival rates for the radiotherapy and observation groups were 91% and 63%, respectively and 5-year overall survival rates for the radiotherapy and observation groups were 90.0% and 80.8%, respectively. Both of disease free and overall survival rates were similar between two groups (p=0.124, p=0.416, respectively). One (5%) of the 20 patients in the radiotherapy group and 4 (10.8%) of the 37 patients in the observation group had recurrences and there was no statistical significance for the recurrence rates (p>0.05). There were no significant differences among following four groups: irradiated grade 1-2 patients, observed grade 1-2 patients, irradiated grade 3 patients and observed grade 3 patients (p=0.468).

Conclusion: Comprehensive surgical staging might minimize the unfavorable role of deep myometrial invasion and grade. After surgical staging, postoperative observation without radiotherapy may be an appropriate approach in stage IC - all grade endometrial carcinoma.
CLINICAL OUTCOMES OF UTERINE SARCOMAS AND THE ROLE OF ADJUVANT TREATMENT
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Aims: Uterine sarcoma cases were evaluated retrospectively to determine prognostic factors affecting survival.

Methods: Women with uterine carcinosarcoma (CS) and leiomyosarcoma (LMS) were included in this study.

Results: In total, 69 patients were evaluated. 61% of patients had uterine CS, 32% had LMS and 7% had endometrial stromal sarcoma (ESS). Owing to the small number, ESS cases were excluded from analyses. The mean age was 60.53 (range 27-83 years). Primary treatment was surgery in all cases. 18% LMS and 36% CS cases underwent combined chemotherapy and all combinations were containing platinium. Adjuvant pelvic radiotherapy was applied to 50% LMS and 45% CS cases. Most of the LMS cases were in stage 1-2 compared with CS group. Estimated 5-year overall survival in all cases, CSs and LMSs were 50.5%, 47%, and 57.7%, respectively. There is no significant difference between LMS and CS groups for overall survival (p>0.05). Patient survival rates were 54.6% with median 20 and mean 33.2 months follow-up in entire group. A total 53.1% of the patients were recurred in mean 20 months. 59% of all recurrences were seen outside of the pelvis. Stage of disease, adjuvant chemotherapy and residual disease after primary surgery were revealed as strong prognostic factors.

Conclusions: This study demonstrated that most of the uterine sarcoma recurrences have occured outside of the pelvis. Adjuvant combined chemotherapy may be suitable to prevent distant recurrences especially in uterine CS cases. Improvements in adjuvant treatment modalities may provide better outcome in these poor survived tumor groups.
TWO METHODS EVALUATION OF ENDOMETRIAL SAMPLING IN POSTMENOPAUSAL UTERINE BLEEDING

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Background and aims: Endometrial malignancy must be ruled out in the presence of post menopausal bleeding. The best diagnosis strategy for diagnosis of endometrial carcinoma in patients with postmenopausal bleeding still remained controversial. The aim of this study was to compare Novak curettage and dilatation & curettage (D&C) in post menopausal bleeding.

Methods: A prospective collective study was performed on 140 post menopausal women referred to hospital for abnormal bleeding. After pelvic exam, four-site endometrial biopsy with Novak curette was performed without anesthesia in each patient. Then endometrial sampling, "dilatation and curettage" (D&C) was performed on all cases with anesthesia. Endometrial histopathologic findings were compared with each other.

Result: The women’s mean age was 54.2 $\pm$ 3.3 years (range, 42-80). Of 140 cases of post menopausal bleeding, 2.8% (4) was endometrial carcinoma and 67.1 % (94) was benign condition in both methods. Endometrial hyperplasia was 17.1% (24) with Novak curettage and 18.6% (26) with D&C, (P= 0.755). Novak curettage sampling was inadequate for histological diagnosis in 13.5% versus D&C in 11.4 %; (P=0.714).

Conclusion: Our data indicated that Novak curette was a good and safe sampling device in outpatients for diagnosis of postmenopausal bleeding. It is known that simple outpatient sampling device (Novak curette) is as reliable as D&C in women with postmenopausal bleeding.

Keywords: Post menopausal bleeding, Novak curettage, Dilatation & Curettage (D&C).
FEMALE SEX HORMONAL EFFECTS ON CLUSTERIN EXPRESSION AND PACLITAXEL RESISTANT IN ENDOMETRIAL AND BREAST CANCER CELL LINE

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Clusterin is a heterodimeric glycoprotein that is synthesized in a wide variety of tissues. We have investigated the regulation of Clusterin expression under the female sex hormones in endometrial and breast adenocarcinoma cell lines. And we compared Clusterin expression according to the hormone levels and the paclitaxel resistance. The expression levels of Clusterin in endometrial adenocarcinoma cell lines (KLE, ECC) and breast adenocarcinoma cell lines (MDA MB 231, BT474, T47D) were validated by performing western blotting. And the correlation between Clusterin expression levels and the IC\textsubscript{50} of paclitaxel was tested. Also we evaluated the paclitaxel-sensitivity under the female sex hormones (Estradiol, Progesterone). After transfection of Clusterin siRNA, we evaluated their effect on paclitaxel-sensitivity by XTT assay. Among the female sex hormones, the effect of Estradiol pronounced Clusterin expression in both endometrial and breast adenocarcinoma cell lines whatever they have hormonal receptor or not. These data suggest that Clusterin expression is tightly regulated by estrogen in endometrial and breast adenocarcinoma cell lines. There may be a complex mechanism of regulation of Clusterin expression in the normal and cancerous endometrium.
STRATEGIES IN THE HISTOLOGIC DIAGNOSIS OF LOW-GRAGE GLANDULAR ENDOMETRIAL NEOPLASM

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Background and aims: Histological diagnosis of well differentiated endometrioid adenocarcinoma (WDA) has been challenging over the years. Considering the impact of this diagnosis on treatment and follow-up of the patient, in this review, we have discussed and evaluated the most useful of the proposed histological criteria for diagnosis of WDA and its distinction from mimic lesions.

Method: Diagnostic criteria for WDA are proposed regarding histologic features predicting the presence of myometrial or endometrial stromal invasion by proliferating glands, or aggressive behavior.

Results and conclusions: Most useful diagnostic histological features in WDA, such as cribriform, labyrinthine, and confluent glandular patterns, and stromal desmoplasia are highlighted. Presence of these features differentiates WDA from mimics and justifies aggressive treatment.
THE PROGNOSTIC ROLE OF DNA PLOIDY IN ENDOMETRIAL CANCER

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Aims: The aim of the study was to relate the changes of nuclear DNA content with the clinical stage of disease and tumor grade.

Methods: The study group included 26 endometrial cancer patients divided according to the prognosis into the “low risk disease” (FIGO stage Ia, Ib) group (n=10, 38%) and “high risk disease” (FIGO stage Ic, II, III) group (n=16, 62%). Parafin-embedded samples of tumor tissue were examined by flow cytometric ploidy analysis. The findings were evaluated in respect to the clinical stage of the disease and tumor grade.

Results: Aneuploidy was found in 8 (31%) from all 26 patients. In all but one patients there was tetra or more ploidy in main sternline cancer cells, in the last hypoploidy was found. In the group of “low risk disease” aneuploid tumor cells were found in 4 from 10 patients (60%) while only 4 from 16 patients (25%) with the advanced stage of the disease had aneuploid tumors. In the group of 22 patients with well and moderately differentiated tumor (grade I, II) aneuploidy was found only in 2 patients (9%) while in patients with poorly differentiated tumor (grade III) the aneuploidy was found in 50%.

Conclusions: Aneuploidy was found in 50% in patients with prognostically unfavourable grade III tumors. No positive correlation was found between aneuploidy and the clinical stage of disease.

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ENDOMETRIAL CYTOLOGY IS USEFUL TO DETECT THE EARLY STAGE ENDOMETRIAL CANCERS

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Objective: The diagnosis of early stage endometrial cancer can lead to a good prognosis for patients. The purpose of our study is to prove the accuracy of endometrial cytology in the diagnosis of early stage endometrial cancers, as compared to that of endometrial biopsy.

Materials and methods: From 2000 to 2008, 1,077 patients with endometrial cancer underwent operation in our hospital. Among them, we could review preoperative cytology and biopsy specimens of 870 endometrial cancer cases. For endometrial cytology, direct aspiration, or brush method, was performed. For endometrial biopsy, endometrial sampling was performed. For histologic review, operation materials were also examined.

Results: There were 197 cases (22.6%) of the early stage (FIGO1988 stage Ia) endometrial cancer among the 870 cases. The positive rate of endometrial cytology and biopsy of all the stages of endometrial cancers were 80.2% and 95.5% respectively, with respect to the early stage only, the positive rate of endometrial cytology and biopsy were 74.2% and 93.4% respectively. Endometrial cytology, as compared with biopsy, was more useful when the histologic diagnosis was serous or clear cell adenocarcinoma, which led to poor prognosis. As a diagnostic method, endometrial cytology is less painful than endometrial biopsy.

Conclusion: Positive rate of the endometrial cytology was comparable to that of the biopsy in early stage endometrial cancers. Therefore, endometrial cytology is useful to, and a preferred method for, early detection of endometrial cancers.
EXPRESSION OF PTEN AND BETA-CATENIN AND THEIR RELATIONSHIP WITH CLINICOPATHOLOGICAL FACTORS IN ENDOMETRIAL CANCER

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Aim: To investigate rates of expression of PTEN and beta-catenin and their relationship with clinico-pathological factors in endometrial cancer.

Materials and methods: Full-staged 125 patients were operated and managed in Cerrahpasa Medical Faculty, Gynecologic Oncology Division between January 2000 and December 2008. Clinical and pathological data were obtained from patient files and pathology records. Four tissue sections prepared from tumoral tissue of each patient were stained by immunohistochemically for PTEN and beta-catenin. All data were evaluated in Excel 2007 database and SPSS 16.01. Fisher and x² tests were used for statistical comparisons.

Results: Immunohistochemical staining of PTEN and beta-catenin were positive in 63% and 64% of all cases, respectively. Beta-catenin expression was observed in 69% and 27% in endometrioid and non endometrioid groups, respectively (p=0.001). PTEN expression was encountered in 52% and 70% of low-grade (grade I) and high grade (grade II and III) cases, respectively (p=0.034) in whole group. Also PTEN expression increased significantly as MI increased (p:0.05). There was a limited relation between MI and beta-catenin expression (p:0.063). Tumor recurrence and disease related mortality were observed in 13 and 6 cases respectively during median follow-up of 45,7±28,4 months.

Conclusion: PTEN expression was seen more then 50% of patients with endometrioid and non-endometrioid endometrial cancer. But beta-catenin expression was detected nearly ¼ of non-endometrioid group. There were significant relationships between depth of MI, tumor volume and tumor grade and pten expression in whole group. But there was no significant relation between beta-catenin expression and pathological prognostic factors.
NOVEL CHEMOEMBOLIZATION USING CALCIUM-PHOSPHATE CERAMIC MICROSPHERE INCORPORATING TNP-470, AN ANTI-ANGIOGENIC AGENT FOR UTERINE SARCOMAS

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Aims: The purpose of the present study was to develop a new method of chemoembolization to improve the therapeutic effectiveness and safety profile of cancer treatment. A chemoembolization approach was designed for human solid tumors using resorbable calcium-phosphate ceramic microspheres loaded with an agent anti-angiogenic to tumor vasculature in vivo.

Methods: The human uterine sarcoma cell line, FU-MMT-3, was used in this study because this tumor is aggressive and also exhibits a poor response to radiotherapy or any chemotherapy currently used. The calcium-phosphate ceramic microspheres loaded with TNP-470, an anti-angiogenic agent, were injected into FU-MMT-3 xenografts in nude mice three times per week for 8 weeks. The treatment using TNP-470-loaded microspheres suppressed tumor growth, compared to treatment with TNP-470 alone, microspheres alone, and the control.

Results: The mean tumor weight after treatment using TNP-470-loaded microspheres was significantly lower than that after treatment with microspheres alone. These ceramic microspheres were remarkably embolized in tumor microvessels as well as in the feeding arteries and a significant reduction of intratumoral vascularity was also demonstrated following treatment with TNP-470-loaded microspheres. Severe loss of body weight was not observed in any mice treated with TNP-470-loaded microspheres, compared to treatment with TNP-470 alone.

Conclusions: These results suggest that targeting tumor vasculature in human uterine sarcoma using calcium-phosphate microspheres might be more effective and safer than the physicochemical action of treatment that employs anti-angiogenic agent alone. This new chemoembolization method incorporating an anti-angiogenic agent may contribute to the effective treatment of locally advanced or recurrent solid tumors.
A NOVEL BIOMARKER, “AMINOINDEX” FOR EARLY DETECTION OF ENDOMETRIAL CANCER USING PLASMA AMINO ACID PROFILE

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**Background and aims:** Plasma amino acid profile could change depending on metabolic states, and changes in plasma amino acid concentrations have been reported. The previous report suggests that “AminoIndex”, a novel biomarker based on plasma amino acid profile, can be useful for early detection of several cancers. The diagnostic performance of “AminoIndex” in patients with endometrial cancer was evaluated to reveal the superiority to CA125.

**Methods:** Amino acid levels in plasma were measured using liquid chromatography and mass spectrometry for 88 patients with endometrial cancer, 122 patients with gynecologic benign disease without malignancy, and 264 age- and BMI-matching controls. Univariate analysis was performed to detect changes of several plasma amino acid levels in patients with endometrial cancer. For multivariate analysis, we applied multiplexed model based on plasma amino acid profile, “AminoIndex”, to discriminate between patients with endometrial cancer and control subjects and tested the diagnostic performance compared with CA125.

**Results:** Several plasma amino acid levels significantly changed in endometrial cancer patients. The areas under the Receiver Operating Characteristic (ROC) curves to distinguish endometrial cancer from controls and patients with gynecologic disease without malignancy were 0.93 and 0.79 respectively. The areas under the curves for “AminoIndex” were higher than those for CA125. In addition, the area under the ROC curve for early stage endometrial cancer is 0.90.

**Conclusions:** We describe the novel multiplexed plasma biomarker, “AminoIndex”, which is a useful tool with high accuracy and disease-specificity for early detection of endometrial cancer compared with CA125.
ENDOMETRIAL CANCER. PROGNOSTIC SIGNIFICANCE OF RELAPSE RISK CLASSIFICATION BASED ON PRE-INTRAOPERATIVE FINDINGS

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The aim of this study was to determine whether a pre-intraoperative prognostic classification of endometrial cancer (EC) patients may accurately predict the patient’s risk of relapse. Prognostic factors achievable before and during surgery (histotype, grade, myoinvasion, cervical spread, abdominal spread) were utilized to classify patients in low risk (endometrial adenocarcinoma, grade 1-2, myoinvasion < 50%, no evidence of abdominal spread), and in intermediate/high risk (serous papillary and clear cell, grade 3, myoinvasion > 50%, cervical invasion, abdominal spread). Risk classification obtained pre-intraoperatively was compared with the classification obtained from definitive surgical-pathological assessment. 118 consecutive patients with EC treated with surgery entered the study. Pre-intraoperative risk assessment correctly identified risk classification in 113 (96%) patients; sensitivity, specificity, PPV and NPV were 98%, 94%, 93%, and 98%, respectively. Median follow-up was 37 months (range 6 - 93); 12 (10%) patients relapsed (median time 14 months, range 3 - 60). Relative risk of relapse was higher in intermediate/high risk patients with both classifications (pre-intraoperative RR: 2.62, CI 0.74 - 9.25; surgical-pathological RR: 3.63, CI: 0.93 - 14.21). 5-years DFS according to pre-intraoperative assessment was 89% and 80% for low-risk and intermediate high-risk patients (p = 0.08), respectively; and according to definitive assessment was 91% and 79% for low-risk and intermediate/high risk patients (p = 0.029), respectively. This classification selected low-risk patients with high sensitivity and high NPV, and was able to identify patients with risk of relapse < 10%. The knowledge of the prognostic estimate may strengthen the surgeon choice when tailoring surgery.
USE OF BISPHOSPHONATES ASSOCIATED WITH LOWER RISK OF MAJOR GYNECOLOGICAL CANCERS

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Background: Bisphosphonates have been shown to be associated with reduced risk of developing breast cancer. The association between the use of bisphosphonates and the risk of developing gynecological cancers has not been reported yet.

Methods: The Cancer in the Uterus and Ovary Study is a case-control study of consecutive gynecological cancer cases cared for at Carmel Medical Center in Haifa, Israel and age/clinic/ethnic-group matched population controls. Use of bisphosphonates was assessed in 270 endometrial and ovarian cancer cases and their matched controls using data from prescription computerized records which were available for 100% of the participants.

Results: Bisphosphonates were used by 30% of the ovarian cancer controls and 23.2% of the endometrial cancer controls but only by 13.6% of the ovarian cancer cases and 9% of the endometrial cancer cases. When analyses were restricted to women using the drug for one year or more prior to diagnosis, the use of bisphosphonates was associated with a significantly marked reduction in risk of endometrial cancer, and similarly of ovarian cancer. The association with endometrial cancer remained significant after adjustment for age, fruit and vegetable consumption, sports activity, family history of endometrial cancer, ethnic group, BMI, HRT use, number of pregnancies. The current number of participants with ovarian cancer is too small to evaluate the association between bisphosphonates and disease in a multivariate model.

Conclusions: The use of bisphosphonates for more than one year was associated with a major reduction in the risk of endometrial cancer and possibly also of ovarian cancer.
ROLE OF OMENTECTOMY AND APPENDECTOMY IN THE MANAGEMENT OF ENDOMETRIOD ENDOMETRIUM CANCER


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Introduction: The main treatment for endometrial cancer is surgery. Omentectomy and appendectomy is not included in the recommendations for primary treatment of endometrium cancer. The value of omentectomy and appendectomy for the treatment of endometrial carcinoma is unclear. We tried to investigate if it is necessary to add omentectomy and appendectomy to the surgical staging of endometrioid endometrium cancer.

Methods: 189 patients out of 299 women who had undergone surgery for endometrial cancer at the Zekai Tahir Burak Women's Health Education and Research Hospital between June 2005 and June 2009 were investigated retrospectively. In all patients a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, infracolic omentectomy and appendectomy was performed. Age, grade, myometrial invasion, cervical and adnexial involvement and positive peritoneal cytology, lymph node, omentum and appendix involvement were investigated.

Results: Of the 189 patients, the mean age of the patients were 50.46±9.47. Of all patients 92% had a disease limited to uterus and 8% had extraperitoneal disease and 87.2% of the patients had stage I disease. There was only one omental metastases and no appendix metastasis in all stages.

Conclusions: We decided that omentectomy and appendectomy is unnecessary unless there is suspicion of gross metastases during intraoperative examination.

Keywords: Endometroid endometrium cancer, omentectomy, appendectomy.
RISK FACTORS FOR POSTOPERATIVE LOWER-EXTREMITY LYMPHEDEMA IN ENDOMETRIAL CANCER SURVIVORS WHO HAD TREATMENT INCLUDING LYMPHADENECTOMY

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Objective: The aim of this study was to determine the incidence rate of lower-extremity lymphedema after systematic lymphadenectomy in patients with uterine corpus malignancies and to elucidate risk factors for this type of lymphedema.

Methods: A retrospective chart review was carried out for all patients with uterine corpus malignant tumor managed at Hokkaido Cancer Center between 1991 and 2007. Patients who did not undergo lymphadenectomy as a treatment or died of cancer/intercurrent disease were excluded from this study. All living patients included in this study had hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy and their medical records were reviewed. We identified patients with postoperative lower-extremity lymphedema (POLEL). Logistic regression analysis was used to select the risk factors for POLEL.

Results: Of 286 patients evaluated, 103 (37.8%) had POLEL. Multivariate analysis confirmed that adjuvant radiation therapy (OR=5.2, 95% CI= 2.1-12.7), resection of more than 31 lymph nodes (OR=2.6, 95% CI= 1.4-4.9), and removal of lateral suprainguinal lymph nodes (OR=6.1, 95% CI= 1.3-28.2) were independent risk factors for POLEL.

Conclusion: Adjuvant radiation therapy should be avoided in patients who undergo systematic lymphadenectomy if an alternative postoperative strategy is possible. Although reducing the number of resected lymph nodes is not appropriate from a therapeutical point of view, elimination of lateral suprainguinal lymph node dissection may be helpful in reducing the incidence of POLEL. The clinical significance of lateral suprainguinal lymph node dissection need to be investigated by a randomized controlled trial.
RACIAL DISPARITY IN THE OUTCOME OF PATIENTS WITH EARLY STAGE UTERINE ENDOMETRIOID CARCINOMAS

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Objective: To compare treatment and patients outcome based on race (African American AA vs. Caucasian C) in a cohort of patients with early stage (FIGO I &II) type I endometrial cancer

Materials and methods: Using the institutional database at Henry Ford Hospital, we identified patients with early stage endometrioid adenocarcinoma. Data on patients’ demographics, tumor characteristics, treatment and recurrence were collected from the records. Kaplan Meier survival analysis and log-rank test were performed to evaluate difference in recurrence by prognostic factors. Multiple regression analysis was done to determine the independent prognostic significance of the factors analyzed.

Results: 655 patients were included (AA 180, C 477). AA patients were 2.2 times more likely to have grade 3 lesions compared to C patients (p < 0.01). There was no difference in lower uterine segment involvement or angiolymphatic invasion between AA and C. Similarly there was no difference in the number of lymph nodes resected (mean, SD- 9.1, 5.9), or the percentage of patients who had postoperative radiation (36%). After a median follow-up of 5.1 years, the rate of recurrence was 7%. Regression analysis showed that race, grade and stage independently impacted the risk of recurrence. AA patients had 2x-increased risk of recurrence compared to the C patients (p= 0.023).

Conclusion: Race is an independent prognostic factor in a large cohort of patients with type I endometrial cancer treated uniformly in one institution. Future studies need to focus on racial differences in tumor biology beyond histologic grade and host response to treatment.
PREOPERATIVE CA 125 LEVEL AS A PREDICTOR FOR METASTASIS AND SURVIVAL IN ENDOMETRIOID ENDOMETRIAL CANCER

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Objective: To determine relationship of preoperative CA 125 level with an increased risk of metastatic disease, recurrence and death in endometrial cancer patients.

Material and methods: The patients with endometrial adenocarcinoma of all stages who underwent primary surgery were reviewed. Multiple variables were abstracted from the data, including demographic characteristics, CA 125 level, postoperative histopathologic results and progression free survival (PFS) and overall survival (OS) rates.

Results: Ninety seven patients with endometrial carcinoma were analysed. If the CA 125 level cut-off value is defined as 35 IU/ml, likelihood of disease related death could be predicted with 70% sensitivity and 83% specificity rates, these later rates were 60% and 84% for progression and 75% and 84% for lymph node metastasis (LNM), respectively. There was a significant relation in CA 125 level with increase in stage, grade and depth of myometrial invasion (MI). Cervical stromal involvement, positive peritoneal cytology, and LNM associated with significantly higher mean of CA 125 levels. Five year PFS and OS rates were significantly better in CA 125 < 35 IU/ml group compared with ≥ 35 IU/ml group (88% versus 57%, p=0.0001 and 92% versus 70%, p=0.001, respectively)

Conclusion: CA 125 levels and extension of disease are highly correlated according to our results and elevated CA 125 levels seem poor prognostic factor for recurrence and death.
LAPAROSCOPIC RADICAL SURGERY FOR ENDOMETRIAL CANCER IN RECENT 3 YEARS IN OUR HOSPITAL

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Objective:

2. Evaluation of validity and radicality of the operation.
3. Assessment of contribution to patients' QOL in peri-surgical period.

Methods:

1. 20 Patients of endometrial cancer with low-risk factors have been underwent for the Laparoscopic surgery (LS) from 2007 May to 2010 Jan. in Hokkaido Cancer Center. Other 20 patients subjected to abdominal open surgery (AS) in the same period was compared with LS by the operation time, blood loss, number of excised lymph nodes and complications.

2. Standard operation procedure was semi-radical hysterectomy, removal of bilateral adnexes, pelvic lymph-adenectomy and para-aortic lymph-adenectomy to the level of renal vein, for both LS and AS.

Results:

1. Operation time was 473.6 min vs 380.6 min (LS vs AS).

Blood loss was 236.8ml vs 1095ml, showing significant reduction in LS group.

2. Number of excised lymph nodes were, 31.7 vs 37.9 in pelvis, 10.9 vs 14 in para-aorta, indicating no significant difference.

3. After the operation, incidence of ileus were relatively lower in LS (5 vs 8.3%), and shorter stay in hospital was remarked also in LS (16.1 vs 20.5 days after the operation).

Conclusions: Laparoscopic surgery for endometrial cancer can be done with the same safety and radicality to the open abdominal surgery.

Laparoscopic surgery has superiority in the contribution to the QOL comparing with the open abdominal surgery.
THERAPEUTIC IMPACT OF PARA-AORTIC LYMPHADENECTOMY IN PATIENTS WITH HIGH-RISK, EARLY STAGE AND ADVANCED STAGE ENDOMETRIAL CARCINOMA

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Background: Recently, two prospective randomized trials on pelvic lymphadenectomy failed to show any therapeutic benefit for pelvic lymphadenectomy in endometrial cancer. However, they did not clarify whether complete, systematic lymphadenectomy, including the para-aortic lymph nodes, should be part of surgical therapy for high-risk patients.

Methods: A comparative cohort study with 815 patients was conducted at two tertiary centers to clarify the survival effect of para-aortic lymphadenectomy in endometrial carcinoma between January 1984 and June 2004. Surgery at one institute included both pelvic lymphadenectomy (PLX) and para-aortic lymphadenectomy (PALX), while at the other PLX alone was routinely performed. We selected 215 patients with high-risk, early stage and advanced stage endometrial carcinoma. A total of 125 patients underwent PLX+PALX and 90 patients underwent PLX alone. Patients included in the study were recommended to receive adjuvant therapy either with radiotherapy or chemotherapy.

Results: The survival rate in the PLX+PALX group was significantly better than that in the PLX alone group for patients who had adjuvant therapy (p=0.0006). Multivariate analysis confirmed that Age, histology, lymph node metastasis, type of lymphadenectomy, and type of adjuvant therapy were independent prognostic factors.

Conclusion: PALX and chemotherapy improved the survival of patients with high-risk, early stage and advanced stage endometrial carcinoma. A randomized trial aiming to validate the therapeutic effect of lymphadenectomy in endometrial cancer should include PALX and focus on patients with high-risk, early stage and advanced stage endometrial carcinoma.
COMPARISON OF SURGICAL OUTCOMES AND COMPLICATIONS FOR CLINICAL STAGE I ENDOMETRIAL CANCER: LAPAROSCOPY VERSUS LAPAROTOMY

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Objective: To compare operative outcomes and complications for endometrial cancer in patients undergoing staging via laparoscopy (LSC) versus laparotomy.

Methods: A retrospective study for patients surgically managed for clinical stage I endometrial cancer from 2004-2009. Operative complications including urologic, vascular, gastrointestinal injuries, hospital admission and unplanned ICU admission were compared between the groups. Surgical variables were also reviewed. Standard statistical tests were utilized.

Results: Eighty-six patients were identified (50 LAP and 36 LSC) with similar age, race and BMI. Utilizing a composite score for all complications, LSC patients had a significantly decreased complication rate (17% vs 42%, p = 0.018). Five of 36 LSC (13.8%) patients had their surgery converted to a LAP. The 2 groups had similar rates of intra-operative injuries. Although LSC surgery was longer (281 min vs. 202 min, p =.0015), patients had fewer ICU admissions (LSC 0% vs. 16%, p = 0.02), less EBL (339 cc vs. 558cc, P < 0.001), lower rates of blood transfusion (LSC 5.6% vs. LAP 24%, p =0.037) and a shorter hospital length of stay (2 vs. 5 days, p =0.0002). There were no differences in lymph node yields.

Conclusions: LSC staging for clinical stage I endometrial cancer resulted in longer operative time but was associated with fewer ICU admissions, fewer blood transfusions, and shorter hospital stays. Prolonged operative time as compared to published experience is potentially secondary to unique factors in our relatively low volume center. Nonetheless, favorable complication and conversion rates were noted.
THE VALUE OF THE NEW FIGO STAGING SYSTEM ON THE PROGNOSIS OF UTERINE SARCOMA

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Background and aims: To determine the value of the new staging system established in 2008 for prognostic stratification of uterine sarcoma.

Method: Eighty five patients treated for uterine leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS) at Yonsei University Health System from 1989 to 2009 were retrospectively reviewed. The prognostic value of both previous and revised FIGO staging as well as age, BMI, menopausal status, cell type, tumor size, lymph node status, myometrial invasion and treatment modality were assessed using univariate (log-rank test) and multivariate (Cox regression) analysis.

Results: The studied cohort consisted of 41 (48.2%) leiomyosarcoma (LMS) and 44 (51.8%) endometrial stromal sarcoma (ESS). During a median follow up of 56.6 months (range 0.7-265.2), 26 patients died. Forty two (65%) out of 64 eligible patients were reclassified by the new staging system. Among 64 patients, 45 patients with lesions limited to uterine corpus were divided into stage IA (n= 13) and IB (n= 31). Univariate analysis demonstrated significant difference in disease free survival (DFS) between stage I and other stages in both staging systems (P < 0.001). Age, menopausal status, tumor size, and cell type were significantly associated with DFS. In multivariate analysis, ESS cell type and revised FIGO stage (I and II) were independent prognostic factors with hazard ratio of 0.15 (95% CI: 0.03-0.88, P= 0.035) and 5.32 (95%CI: 1.81-15.63, P=0.002), respectively.

Conclusion: The new staging system is more valid than the previous system in terms of its ability to stratify prognosis in patients with LMS and ESS.

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Introduction: Uterine sarcoma was staged previously according to the 1988 FIGO staging system for endometrial adenocarcinoma. However, the 2009 staging system for uterine sarcoma has been developed recently. The purpose of this study was to compare the survival between traditional and new FIGO staging system.

Materials and methods: The medical records of uterine sarcoma patients received primary treatment at King Chulalongkorn Memorial Hospital during 1999 to 2007 were reviewed. The survival curves were generated by Kaplan-Meier method. Comparison of survival between groups was assessed by the log-rank test.

Results: Twenty eight patients were included. The incidence of uterine sarcoma was 1% and 5.2% of all gynecologic cancers and uterine cancer, respectively. A comparison between these two staging systems showed that four patients (14.3%) were down-staged and none were upstaged. The 5-year disease-free survival (DFS) and overall survival (OS) were 36.0% and 45.5%, respectively. Age, parity, histology, tumor size, lymph node dissection, and adjuvant treatments were not significant prognostic factors. Patients with early stage had significantly longer survival than those with advanced stage. Median DFS in early stage according to both FIGO staging system were equally account for 58 months. Mean OS were 91 months and 83 months, respectively. Median DFS in advanced stage were 9 months and 7 months, respectively. Median OS were 12 months and 10 months, respectively. There was no difference on survival between these two staging systems.

Conclusion: Stage is the only independent prognostic factor. However, there was no difference on survival between these two staging systems.
PAX2 EXPRESSION IN ENDOMETRIAL HYPERPLASIA AND CARCINOMA

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Background: PAX2 is a member of the pair box (PAX) gene family, consisting of nine members, PAX1-PAX9, each encoding a nuclear transcription factor. PAX2 is involved in the proliferation and growth of endometrial cells and tumors indicating a role in carcinogenesis. However, there are limited studies about PAX2 expression in endometrial hyperplasia and carcinoma.

Objectives: This study examines the Pax-2 expression in endometrium, aiming to help in the differential diagnosis between atypical hyperplasia and well differentiated endometrioid adenocarcinoma, knowing the major problem in inter observer variability.

Material and methods: Immunohistochemical analysis of Pax-2 expression was performed on 57 endometrial specimens: 18 non atypical hyperplasias, simple or complex (SH/CH), 13 atypical hyperplasias (CAH) and 26 endometrioid carcinomas (EC) grade I and II. We estimated only nuclear staining, using a semi-quantitative method as follows: 0= 0% 1+=5-25%, 2+=26-50%, 3+=51-100%

Normal endometrial glands, as were uniformly strong positive, were served as positive control.

Results: Pax-2 was uniformly expressed in normal endometrium (atrophic or functional). Non-atypical hyperplasia’s epithelial nuclei were positive in 16 cases (88,9%, 2+ or 3+) while only in 4 cases of CAH (30,76%). Mainly, mild to moderate Pax-2 expression was demonstrated in 8 endometrioid carcinomas ( 30,8%, 4:1+ , 3:2+, 1:3+).

Conclusions: Though PAX2 expression may reflect varying responsiveness to steroid hormones, unfortunately its levels are same between CAH and EC, therefore the use of PAX2 as a tool in the differential diagnosis is limited.
CLINICAL UTILITY OF SERUM TUMOR MARKERS IN WOMEN WITH MALIGNANT MIXED MULLERIAN TUMORS OF THE UTERUS

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Objectives: Since there are no available data in the literature to determine the clinical usefulness of serum tumor markers in the management of Uterine malignant mixed mullerian tumors (MMMTs), the purpose of our study was to evaluate the practical utility of serum tumor markers in patients with MMMTs.

Methods: Twenty one patients (mean age 67.8 years, SD=7.6 years) with surgically staged MMMT between 2003 and 2008 were identified.

Results: Preoperative values of CA125, CA19-9, CA15-3, CEA and a-FP were available in 21, 17, 18, 20 and 6 while upper the normal limit were for 7 (33.3%), 2 (11.8%), 6 (33.3%), 2 (10%) and 1 (16.7%) patients respectively. Postoperative values of CA125, CA19-9, CA15-3, CEA and a-FP were available in 7 (33.3%), 5 (23.8%), 4 (19%), 6 (28.6%) and 2 (9.5%) patients respectively. Preoperative values of CA125, CA19-9, CA15-3, CEA and a-FP did not correlate significantly each other. Preoperative mean values of CA125 and CA19-9 increased with stage (p for trend < 0.05). Women with MI over 50% tend to have greater values of CA19-9 and significant greater values of CA15-3 (13.4±4 vs. 23.5±9.4, p=0.035). The proportion of women with CA15-3 over 22 was significant greater in women with MI over 50% (54.5% vs. 0%, p=0.038).

Conclusion: Preoperative CA125 and CA19-9 elevation are markers of extrauterine disease. Also, preoperative values of CA19-9 and CA15-3 may determine deep MI in women with MMMTs. Tumor markers may be clinically useful in the management and disease surveillance of patients with MMMTs.
THE EFFICACY OF UTEROBRUSH SYSTEM IN THE DETECTION OF ENDOMETRIAL PATHOLOGY

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Aim: The aim of our study was to compare the results of endometrial brush cytology and histopathologic examination of patients with endometrial abnormalities.

Methods: This is a prospective study evaluating the efficacy of the Uterobrush method in the detection of endometrial abnormalities such as polyps, hyperplasia and malignancy. Endometrial cytology was performed during the period January 2009 to April 2010 in all the symptomatic patients that underwent dilatation and curettage. The collected samples were smeared directly onto a glass-slide and a ThinPrep buffer. Cytologic features were evaluated according to the criteria of Tao. The main objective was to evaluate the efficacy of Uterobrush method, in terms of Area Under Curve in ROC curve graphs comparing the results of cytologic and histopathologic examination. For all statistical methods a significance level of 5% was used.

Results: The sample of the study consisted of 100 women aged 55.8 years (range 38-78 years). Fifty-five patients were postmenopausal. 92% of the samplings were performed by trainees. Endometrial carcinoma was diagnosed cytologically in 8/9 patients (88.9%), whereas endometrial polyps were diagnosed in 5/34 patients (14.7%). All the patients with simple hyperplasia were correctly diagnosed, whereas the diagnosis of complex hyperplasia with or without atypia was correct in 85.7% and 100% of patients, respectively. Regarding endometrial carcinoma the sensitivity, specificity, positive and negative predictive values were 88.9%, 100%, 100% and 98.9%, respectively.

Conclusion: Uterobrush is a reliable direct intrauterine sampling for detecting endometrial abnormalities especially endometrial carcinoma and hyperplasia, but not polyps.
PREOPERATIVE PREDICTION MODEL OF LYMPH NODE METASTASIS IN ENDOMETRIAL CANCER

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**Background:** We aimed to develop a preoperative prediction model identifying the low-risk group for lymph node metastasis in endometrial cancer.

**Methods:** In 110 patients who underwent preoperative magnetic resonance image (MRI) and serum CA-125 test, logistic analysis was performed to identify predictors. The coefficients obtained from logistic regression were used to construct scoring system, and receiver operator characteristic (ROC) curve was created.

**Results:** Lymph node metastases were found in 14 of 110 patients (12.7%). After multivariate logistic regression analysis, histologic grade, preoperative CA-125 levels, disease extent, and myometrial invasion assessed by MR were selected as viable predictors. The scoring system was internally validated using bootstrapping \((P < 0.001)\), and ROC curve yielded the area under the curve of 0.902. The patients with the score of 0 or 1 (57.3%) was identified as a low risk group and no nodal metastasis was observed among them (negative predictive value 100%, 95% confidence interval = 94.3% to 100%).

**Conclusion:** The current study suggests that preoperative prediction system to identify the risk of lymph node metastasis is feasible. This model may be useful in preoperative counseling about cost and benefit of systemic lymph node dissection.

[ROC curve of scoring system]
LEVONORGESTREL-IUD: AN ELEGANT TREATMENT-OPTION OF ENDOMETRIAL (PRE) MALIGNANCY IN CASE OF SERIOUS CO-MORBIDITY

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Standard treatment-options of endometrial (pre)-malignancies are oral (high-dose) progestogens or hysterectomy with bilateral salpingo-oophorectomy. However, serious co-morbidity (dementia, cardiopulmonary/vascular/ diabetic/hypertensive disease etc.) with advanced age and/or morbid obesity may exclude standard treatment.

The Levonorgestrel-releasing-Intra-Uterine Device (LNG-IUD, Mirena® Bayer Schering Pharma, The Netherlands), providing very high concentrations of progestins to the uterine mucosa, has been successfully used to treat endometrial (atypical) hyperplasia and endometrial adenocarcinoma without the disadvantages of oral progestogens or surgery.

LNG-IUD treatment results of our first 11 patients, diagnosed with endometrial (pre)malignancy and medically unfit for standard treatment, are presented.

No progression into endometrial malignancy, nor progressive disease was observed during follow-up. Bleeding was absent or minimal, acceptable for all patients.

**Conclusion:** The LNG-IUD appears an effective minimal-invasive treatment-option for patients diagnosed with an endometrial (pre)malignancy in case of serious co-morbidity, morbid obesity or very old age, excluding standard (high-dose) oral progestogen or surgical treatment.
ASSOCIATIONS BETWEEN INTRATUMORAL LYMPHATIC MICROVESSEL DENSITY (LMVD) AND CLINICOPATHOLOGIC FEATURES IN ENDOMETRIAL CANCER

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Introduction: Lymph node metastasis in endometrial cancer significantly decreases survival rate. Associations between intratumoral lymphatic microvessel density (LMVD) and classical pathological factors may help elucidate pathways of lymphangiogenesis leading to identification of drug targets for endometrial carcinomas.

Methods: Fifty-seven patients with endometrial carcinoma diagnosed between 2000 and 2008 underwent complete surgical staging and evaluation of intratumoral LMVD and other histologic variables. Lymphatic microvessels were identified by immunohistochemical staining using monoclonal antibody against human podoplanin (clone D2-40) and evaluated by counting the number of immunostained lymphatic vessels in 10 hot spot areas at 400X magnification.

Results: The mean number of lymphatic vessels counted in all cases ranged between 0 and 4.7. The median value of mean LMVD was 0.5, and defined the cut-off for low and high LMVD. We identified low intratumoral LMVD in 27 (47.4%) patients and high LMVD in 30 (52.6%) patients. Low intratumoral LMVD was associated with poor outcome, miometrial and adnaexal infiltration, and cervical and peritoneal involvement. No association was seen between LMVD and age, FIGO staging, histological type, vascular invasion, or lymph node involvement.

Conclusion: Low LMVD was associated with miometrial and adnaexal infiltration, cervical and peritoneal involvement. No association was seen between LMVD and age, FIGO staging, histological type, vascular invasion, or lymph node involvement. High intratumoral LMVD was then associated with good outcome.
COST EFFECTIVENESS OF LAPAROSCOPIC VERSUS ABDOMINAL HYS TERECTOMY IN EARLY STAGE ENDOMETRIAL CANCER

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Objective: To investigate the cost-effectiveness of total laparoscopic hysterectomy (TLH) versus total abdominal hysterectomy (TAH) in early stage endometrial cancer.

Methods: A multicentre RCT, including 26 proven skilled laparoscopic surgeons in 21 hospitals in the Netherlands. Patients with clinical stage I endometrioid adenocarcinoma or complex atypical hyperplasia were randomized (2:1) for TLH or TAH. In total 275 patients were required to detect a significant difference of 15% in major complication rate between TLH and TAH (80% power; α=0.05). The primary effect measure was major complication rate, as assessed by an independent panel. Costs were evaluated from a societal perspective including operative procedure costs, hospital stay and costs incurred during the postoperative period over a three months time horizon. Analysis was by intention-to-treat.

Findings: In total, 283 patients were randomized (TLH n=187; TAH n=96). The major complication rate was 14.6% in the TLH group versus 14.9% in the TAH group (p=0.95). The intra operative major complication rate during TLH (2.7%) was lower than during TAH (4.3%) (NS). Conversion to laparotomy occurred in 10.8% of the laparoscopic procedures. Total costs were €3,453 for a TLH and €3,577 for a TAH. An amount of €3,700 will be saved per additional major complication-free patients in case of performing TLH instead of TAH.

Interpretation: TLH is cost effective when compared to TAH. Therefore and due to comparable safety, TLH should be recommend as the standard surgical procedure in early stage endometrial cancer, on the condition of "skilled surgeons".
EXPLORATION OF BIOMARKERS FOR LYMPH NODE METASTASIS IN PATIENTS WITH ENDOMETRIAL CANCER USING EXON-EXPRESSION MICROARRAY


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Objective: To predict possibility of lymph node metastasis using primary cancer tissue preoperatively, we explored putative biomarker genes of node metastasis in patients with endometrial cancer.

Patients and methods: mRNAs were extracted from primary cancer tissues of patients underwent hysterectomy, bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy in Hokkaido University Hospital from August 2001 to April 2010. Affymetrix Exon Microarray (Santa Clara, CA) sorted out transcripts showing significantly different expression between node-negative and node-positive groups. To validate microarray results, realtime PCR with Taqman(R) Gene Expression Assays (Applied Biosystems, Foster City, CA) were employed. Twenty-seven and 61 mRNA samples with endometrioid adenocarcinoma were used for microarray and realtime PCR, respectively. For statistical analyses of microarray results, ArrayAssist 5.0 (STRATAGENE, La Jolla, CA) was used and t-test was carried out to test statistical significance consecutively. Realtime PCR data were also analyzed statistically with t-test.

Results: Expression levels of 6 transcripts, KIAA1641/ANKRD36, VPS13A, ZNF577, CROP (cisplatin resistance-associated overexpressed protein), MALAT-1 (metastasis-associated lung adenocarcinoma transcript 1) and TIMP3 (tissue inhibitor of metalloproteinase 3) showed significant differences between node-negative and node-positive groups in microarray analyses. For the validation, realtime PCR narrowed down 6 candidates to 4 upregulated transcripts in node-positive samples; KIAA1641/ANKRD36, VPS13A, CROP and MALAT-1. Interestingly, immunostaining intensity for CROP in paraffin-embedded carcinoma tissues corresponded to mRNA expression levels of realtime PCR analyses.

Conclusion: We have identified 4 upregulated transcripts in primary cancer focus of node-positive endometrial cancer. They might be the putative node-positive biomarkers in endometrial cancer.
SYMPTOMATIC PELVIC LYMPHOCYSTS AFTER BILATERAL PELVIC LYMPHADENECTOMY FOR GYNECOLOGICAL CANCER

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Introduction: Symptomatic lymphocysts are not unusual (7.5-10\%) following bilateral pelvic lymphadenectomy after gynecological cancer surgery.

Objectives: The aim of the study was to determine the incidence of symptomatic lymphocysts after pelvic lymphadenectomy, risk factors, correlation with symptoms and treatment methods.

Methods: This was a 3-year retrospective study of 119 patients who have undergone bilateral pelvic lymphadenectomy for gynecological cancer between Jan 2007 - Dec 2009 in our Department. Identification was initially made by palpation and confirmed by CT or US.

Results: Eleven (9.24\%) patients presented between 2\textsuperscript{nd} - 24\textsuperscript{th} postoperative week with either pelvic pain (36.3\%), fever (27.3\%) or lymphedema (36.3\%). Nine had unilateral (mostly on the left side, 6) or bilateral (2) lymphocysts max diameter 4-11 cm.

Five lymphocysts were found after type III hysterectomy and bilateral pelvic/paraortic lymphadenectomy for cervical cancer (5/23, 21.73\%), 1 after lymphadenectomy for ovarian cancer (1/24, 4.16\%) and 5 after surgical staging for endometrial cancer (5/72, 6.94\%). In 5 of these cases drains were used after laparotomy.

Histology showed positive lymph nodes in only 2 cases while the total number removed was >14 in all cases (14-32, average 19.2).

Regression was achieved with conservative treatment: antibiotics in 5 cases, needle aspiration under radiologic guidance with (4/6) or without (2/6) tube insertion - for 7-92 days, average 58.5 - . All patients were asymptomatic within 6 months from diagnosis.

Conclusions: Symptomatic lymphocysts can at times complicate pelvic lymphadenectomy but they usually regress spontaneously or with conservative treatment.
HIGHER INCIDENCE OF ENDOMETRIAL CANCER IN YOUNG WOMEN IN SINGAPORE COMPARED TO OTHER CENTERS. KK HOSPITAL EXPERIENCE. AN UPDATE

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Objective: Endometrial cancer ranks 4 in gynecologic malignancies in Singapore. Literature quotes 5 to 15% of women are premenopausal. The objective of this study was to conduct a large clinical and pathologic review of endometrial cancers diagnosed in women aged younger than and up to 50 years who are not attained menopause.

Methods: We conducted a retrospective cohort study of patients with histologically confirmed endometrial cancer treated in our center from Jan2000 to Dec 2009. Clinical characteristics and pathologic information obtained from the medical records.

Results: 33.9% (431/1270) of all patients with endometrial adenocarcinoma were aged up to 50 years. The mean age at diagnosis was 43 years (range 23-50 years). Sixty nine percent (297/431) were in staged as stage 1 Cancer. Only 11% (48/431) were in advanced stage 3 and 4 cancer. 8.8% of cancers were detected in women younger than 40 years.

Conclusion: We found that proportion of women with endometrial cancer under the age 50 years was considerably high in Singapore.
PREOPERATIVE SERUM CA-125 IS HELPFUL IN THE CLINICAL MANAGEMENT AND PROGNOSTICATION OF UTERINE PAPILLARY SEROUS CARCINOMA PATIENTS

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Objective: Uterine papillary serous carcinoma (UPSC) is a highly malignant subtype of endometrial adenocarcinoma. Typically, 40-70% of clinical stage I UPSC patients are upstaged at the time of surgery due to extra-uterine spread. A specific preoperative test or tumor marker that can discriminate between early and advanced stages of UPSC disease will help in management and planning, in counseling of the patient and in prognostication. The purpose of this study was to determine the utility of preoperative serum CA-125 measurement as a prognostic factor for survival and as a predictor of extra-uterine disease specifically in UPSC patients.

Method: In this retrospective multi-centre study, histopathology was independently revised by four expert gyneco-pathologists. 66 patients constituted the study population.

Results: A preoperative CA-125 cut-off value of 45 U/mL provided the best sensitivity and specificity for extra-uterine disease (74.5% and 75.0% respectively). Overall survival was significantly shorter in UPSC patients with preoperative CA-125 > 45 U/mL (median 9 months) compared to the group with preoperative CA-125 level ≤ 45 U/mL (median 38 months) (P< 0.001). Multivariate regression model showed FIGO stage and CA-125 as the only variables significantly associated with survival (P=0.012 and P=0.024 respectively). Patients with a preoperative CA-125 > 45 U/mL had a 4.24 times greater risk of death from UPSC disease.

Conclusion: Preoperative serum CA-125 correlates with stage of disease and an elevated CA-125 level was associated with a dismal survival. This could have implications in the clinical management and prognostication of UPSC patients.
INSULIN IN ENDOMETRIAL CARCINOMA CHEMOTHERAPY: A BENEFICIAL DESIGN AND NOT A PROBLEM

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Objective: Study already proved the expression of insulin receptor in endometrial cancer cell and found that insulin can promote the proliferation and inhibit the apoptosis of endometrial carcinoma cells. However, for these endometrial cancer patients complicated with diabetes, we often have to use insulin to control blood glucose. To investigate the effect of insulin or insulin combined with chemotherapeutic drugs on the proliferation and apoptosis of endometrial carcinoma cells; aim to determine the efficacy and safety of insulin in endometrial cancer therapy.

Methods: Ishikawa and Hec-1A cells were treated with insulin and/or paclitaxel. Cell proliferation was assessed by MTT assay; Cell cycle analysis and cell apoptosis were detected by flow cytometry (FCM); Survivin gene expression was analyzed by RT-PCR.

Results: In a certain range of working concentration and action time, insulin can mildly augment cell proliferation and the percentage of S phase cell in endometrial cancer (Ishikawa/Hec-1A) cells; Insulin combined with paclitaxel (combined group) can significantly inhibited cell proliferation (Ishikawa 69.38%±2.32% VS 40.31%±4.52%; Hec-1A 64.11%±6.33% VS 45.89%±3.27%) and increase cell apoptosis compared with paclitaxel alone (paclitaxel group). Survivin gene expression also significantly decreased in combined group than paclitaxel group.

Conclusions: Insulin can mildly augment cell proliferation and presented chemotherapy sensitivity in endometrial cancer cells. Insulin should be able to safely and efficiently use in endometrial cancer therapy.
NEUROENDOCRINE CARCINOMA OF THE ENDOMETRIUM - CASE SERIES AND A SYSTEMATIC REVIEW OF THE LITERATURE

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Objectives: Neuroendocrine carcinoma of the endometrium (NECE) is a rare disease with very little published on clinical features, prognostic factors or treatment. We report our experience and a review of the literature.

Materials and methods: All patients with NECE diagnosed between January 1990 and December, 2007 identified from tumor registry and gynecological oncology databases at McGill University Health Centre comprised this series. A search on PUBMED and MEDLINE was carried out for the literature review.

Results: Eleven cases were encountered. The median age of the patients was 76 years. All presented with perimenopausal or postmenopausal bleeding. Two patients were Stage Ib, one Stage IC, one Stage IIA, and the other seven were diagnosed in advanced stages (III or IV). Two patients were pure neuroendocrine small cell histology type, 2 were pure large cell and, the other 7 had mixed type of adenocarcinoma with small cell carcinoma. Seven patients were treated by radical surgery, and 5 of them received adjuvant chemotherapy or radiotherapy. The remaining patients received only palliative radiation/chemotherapy or refused further treatment. The median survival was 9 months (range: 0.1 - 84). Only two patients, both of whom were stage IB are alive without evidence of disease at 2 and 7 years following surgery alone or surgery and adjuvant radiotherapy, respectively. The other patients died of their disease.

Conclusion: NECE is a rare and aggressive disease presenting in late stages with poor prognosis despite surgery and adjuvant chemotherapy and radiotherapy. Early stage is the most important prognostic factor.
USE OF ESTRADIOL-PROGESTIN THERAPY ASSOCIATES WITH INCREASED RISK FOR UTERINE SARCOMAS

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Objective: An evaluation of the effect of postmenopausal estradiol-progestin therapy (EPT) on the risk of uterine sarcoma.

Methods: All Finnish women (> 50 years of age) who had in 1994-2008 used EPT for at least 6 months (n=243,566) were identified from the national Medical Reimbursement Registry. Their incidence of uterine sarcoma (stromal and leiomyosarcoma) was compared to that in the background population with aid of the Finnish Cancer Registry.

Results: A total of 78 uterine sarcomas were encountered in the EPT cohort; 47 (61%) were leiomyosarcomas, 24 (31%) stromal sarcomas and 7 (8%) other uterine sarcomas. The ever EPT use (> 6 months) was associated with a significant elevation in the risk of all uterine sarcomas combined (standardized incidence ratio [SIR] 1.6, 95% confidence interval [CI] 1.3-2.0). The SIR for stromal sarcoma was 1.4 (CI 0.9-2.1) and for leiomyosarcoma 1.8 (CI 1.4-2.4). EPT use for 5 years or longer was accompanied with higher risk elevations for all uterine sarcomas combined (SIR 2.0, CI 1.5-2.8) for stromal sarcoma 1.5 (CI 0.9-2.1) and for leiomyosarcoma (SIR 3.7, CI 2.2-5.8). The mode of progestin use (sequential or continuous) seemed not to markedly affect the risk of sarcoma.

Conclusion: The use of EPT in postmenopausal women is accompanied with a modest elevation in the risk of uterine sarcomas. Due to the rarity of this cancer, about 10,000 women must have been exposed to EPT for at least 5 years before one additional sarcoma case would appear.
DESCRIBE THE TEN YEAR EXPERIENCE WITH TRACHELECTOMY AT THE LAHEY CLINIC FOUNDATION, INCORPORATED

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Objective: To document the increasing rate of trachelectomy between 2000-2004 compared to 2005-2009 at Lahey Clinic Medical Center. Chart review to determine patient demographics, indications, operative approach and pathology findings was performed.

Study design: Institutional Review Board Approval was obtained for retrospective chart review of all trachelectomy surgery performed at Lahey Clinic.

Results: Twenty-five trachelectomy surgeries were performed at Lahey Clinic between 2000 and 2009, three procedures during 2000-2004 and the remaining twenty-two from 2005-2009. The indications for the initial subtotal hysterectomy (STH) were uterine fibroids 32% (7/22), pelvic pain 18% (4/22), abnormal bleeding 18% (4/22), endometrial hyperplasia 9% (2/22), pelvic organ prolapse 4.5% (1/22), endometriosis 4.5% (1/22), and intraoperative hemorrhage 9% (2/22). The abdominal, laparoscopic (+/- robotics) and vaginal route for surgery was 77%, 18%, and 4.5% respectively. The most common indication for trachelectomy was pelvic pain accounting for 32% of all cases. 23% of patients had either complex endometrial hyperplasia (1), endometrial carcinoma (2), or leiomyosarcoma (2). Other indications for trachelectomy included cervical dysplasia (14%), pelvic mass (14%), cervical prolapse (9%), cyclic bleeding (4.5%), and metastatic cancer (4.5%).

Conclusion: A seven fold increased rate of trachelectomy is reported between 2005-2009 relative to 2000-2004. After pelvic pain, the most common indication for trachelectomy was non-cervical cancer or precancerous pathology arising in the uterine fundus suggesting that proper patient pre-operative screening and intra-operative pathology exam of the fundus is critical in reducing the rate of the subsequent trachelectomy.
LIPOSOMAL DOXORUBICIN (LD) AND CARBOPLATIN (CP) IN PRIMARY ADVANCED OR RECURRENT ENDOMETRIAL CANCER - A PHASE-II-TRIAL OF AGO AUSTRIA

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**Introduction:** Endometrial carcinoma with recurrence or advanced stage at diagnosis carries a poor prognosis. Chemotherapy is used more frequently, consisting of cisplatin/doxorubicin/paclitaxel, if tolerated, or the doublet of carboplatin/paclitaxel. These are the results of the first 23 patients from an ongoing trial of LD and CP in patients with primary advanced or relapsed endometrial cancer. Primary endpoint is RR (response rate).

**Methods:** 39 patients will be recruited in this trial. All patients should receive 60mg/m\(^2\) LD and CP AUC 5 for 6-9 cycles or until progression. A first analysis was planned after 23 patients to ascertain activity of the regimen. Activity was defined to be present if \(\geq 7\) responses occur.

**Results:** At baseline, 11 (48%) patients had stage I tumor, 1 (4%) stage II, 6 (26%) with stage III and 5 (22%) patients with stage IV. 5 (22%) tumors with grade I, 11 (48%) grade II and 6 (26%) grade III tumors were diagnosed. Of the first 23 patients 7 (30%) had primary advanced, 16 patients (70%) recurrent disease. Tumors were found to be adenocarcinomas in 18 (79%), serous papillary carcinomas in 3 (13%) cases, clearcell- and mixed mullerian carcinomas in 1 (4%) case each.

RR was defined as best response during therapy. Of the first 23 patients, we observed no complete response, but partial response in 11 (48%) patients.

**Discussion:** After stage I of this trial, due to a RR of 48% the protocol is considered to be active and the trial will be continued.
EXPRESSIONS OF ANGIOTENSIN II TYPE I RECEPTOR AND MIR-155 IN ENDOMETRIAL CANCER AND THEIR CORRELATIONS WITH PATIENT SURVIVAL

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MicroRNA-155 (miR-155) is one of the micro RNAs (miRNA) most consistently involved in neoplastic diseases, and it is known to repress the angiotensin II type 1 receptor (AGTR1). This study investigated the expressions of miR-155 and AGTR1 and their correlations with clinicopathologic factors and prognosis in patients with endometrial adenocarcinoma. Expressions of miR-155 and AGTR1 were evaluated in 13 endometrial adenocarcinoma specimens and six normal endometrial samples using real-time PCR. Histologic sections of formalin-fixed, paraffin-embedded specimens from 86 primary endometrial tissues were stained for AGTR1. Disease-free survival (DFS) and other clinicopathologic characteristics were analyzed according to the expression of the receptor. miR-155 level was increased, and mRNA level of AGTR1 was decreased in endometrial carcinoma tissue compared to those of normal endometrial tissues (P = .0254 and P = .0125, respectively). Of the 86 cases that underwent immunohistochemical analysis for AGTR1, six of ten (60.0%) normal endometrium, 11 of 14 (78.6%) endometrial hyperplasia, and 27 of 62 (43.5%) endometrial carcinoma tissues were scored as AGTR1-positive (P = .051). AGTR1 expression was negatively correlated with myometrial invasion (P = .003) and predicted a significantly favorable disease-free survival (P = .019), though it was not an independent prognostic factor (HR = 0.16, 95% CI 0.02-1.28, P = .084). In this study, we demonstrated the expressions of miR-155 and AGTR1 in endometrial adenocarcinoma. Our findings suggest that assessment of AGTR1 status may provide clinically useful prognostic information in patients with endometrial carcinoma.
RISK FACTORS IN WOMEN 40 YEARS OF AGE AND YOUNGER WITH ENDOMETRIAL CARCINOMA

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Objective: To identify and compare risk factors among endometrial cancer patients < 40 years of age, postmenopausal women with the same malignancy and women < 40 years without malignancy.

Population: Endometrial cancer patients < 40 years (study group, n=40), postmenopausal women with the same malignancy (positive control, n=40) and women < 40 (negative control, n=40) without endometrial cancer.

Methods: Study was conducted from 1988 to 2009. Clinical history, treatment and follow-up of the patients were evaluated. Factors studied included age, histology, stage, grade, lymph-vascular space involvement, body mass index, cytology, lymph node status, parity, smoking, family history, diabetes mellitus, hypertension, endometrial hyperplasia, recurrence and survival.

Results: Nulliparity and smoking were significantly related with endometrial cancer in the study group compared to positive controls (p=0.001 and p< 0.01 respectively). BMI >30, presence of endometrial polyps and hyperplasia with atypia increased endometrial cancer risk in the study group compared with negative controls (p=0.006, p=0.001, p< 0.001 respectively). History of irregular menstruation cycles implying possible polycystic ovarian syndrome and cancer in the family were significantly observed in the study group compared to both controls. Stage, grade, myometrial invasion, lymphovascular space involvement and lymph node status were comparable between study and positive group.

Conclusion: Clinicians should always keep in mind the possibility of endometrial cancer in a young woman presenting with irregular vaginal bleeding, especially when smoking, nulliparity, obesity and history of unstable menstruating cycles are reported.
MULTIMODALITY TREATMENT WITH CARBOPLATIN AND TAXOL IMPROVES SURVIVAL IN ADVANCED STAGE UTERINE SEROUS CARCINOMA

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Objective: To evaluate the clinical and treatment characteristics affecting survival in patients with advanced stage uterine serous carcinoma (UPSC).

Methods: All patients with Stage III-IV UPSC diagnosed 1/95-12/08 at a tertiary referral center were retrospectively identified. Patients underwent either neoadjuvant chemotherapy or primary surgical cytoreduction. Adjuvant treatment included platinum-based chemotherapy and/or pelvic, vaginal, or whole abdominal radiation. Kaplan-Meier and Cox regression analyses were performed.

Results: Seventy-three UPSC patients met criteria with a mean age of 68.7 years. Median follow-up was 23.3 months with 67.1% optimally debulked. Four patients received neoadjuvant chemotherapy, 27 postoperative chemotherapy, 20 sequential chemoradiation, 6 radiation only (2 whole abdominal), and 16 no further treatment. Sequential chemoradiation was associated with a superior progression free (33.9 months vs 11.7 and 17.3 months, p< 0.01) and overall survival (37.3 months vs 17.7 and 33.1 months, p< 0.01) compared to chemotherapy or radiation alone. In those optimally debulked, adjuvant carboplatin and taxol led to an improved overall survival (37.3 vs 23.3 months, p=0.04), and the combination of carboplatin and taxol was associated with a better overall (27.3 vs 13.6 months, p=0.03) but not progression free survival (16.9 vs 8.8 months, p=0.07) when compared to other platinum-based regimens. On multivariate analysis, only the utilization of carboplatin and taxol and postoperative radiation independently predicted survival outcome.

Conclusion: Adjuvant chemoradiation, particularly with carboplatin and taxol, allows for the most favorable outcome in advanced stage UPSC. However, given the poor prognosis in these patients, newer synergistic treatment modalities still need to be investigated.
COMPARISON OF HER2/NEU AND CA125 AS A ROLE FOR TUMOR MARKER IN OVARIAN CANCER

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Background: The HER2/neu proto-oncogene is 1 of 4 epidermal growth factor receptor-related receptors. The HER2/neu gene is located on chromosome 17q21 and activated by amplification and overexpression of the wild-type gene. We attempted to decide role of HER2/neu and CA125 as a tumor marker by evaluating serum HER2/neu protein and CA125 in ovarian cancer patients.

Materials and methods: Serum was collected from 52 patients diagnosed as ovarian cancer (n=21), recurrent ovarian cancer (n=5) and benign ovarian tumor (n=26) from 2004 to 2006 at the department of Obstetrics and Gynecology, Kosin university hospital. We measured the serum levels of HER2/neu and CA125. To analyse statistical significance, we used SPSS program. Correlation between HER2/neu and CA125 was analyzed, and independent-samples T-test and non-parametric test were performed to examine the statistical significance of HER2/neu and CA125 between ovarian cancer group and recurrent ovarian cancer group and between ovarian cancer group and benign ovarian tumor group.

Conclusion: No significant correlation between HER2/neu and CA125 in ovarian cancer is observed, and also it would be difficult to use HER2/neu as a independent tumor marker. As serum HER2/neu protein is expected to play a role in early prediction of a recurrent ovarian cancer, additional evaluation is thought to be needed.
MICROARRAY ANALYSIS OF THE GENES INVOLVED IN ENDO METRIAL CARCINOGENESIS: UP-REGULATION OF LIPOCALIN2 IN NEOPLASTIC ENDOMETRIA, AND ITS FUNCTIONAL RELEVANCE

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Background: Endometrial carcinoma often arises from normal endometrial glandular cells via a precursor, atypical endometrial hyperplasia. However, the genetic changes involved in this carcinogenetic process are not fully understood.

Methods: Differentially expressed genes were selected from glandular cells of normal proliferative phase endometria, endometrial hyperplasia and endometrial carcinoma using laser-captured microdissection (LCM) and microarray.

Results: The microarray analysis revealed a total of 51 genes to be up-regulated, and 23 genes to be down-regulated in neoplastic endometrial epithelia. We focused on lipocalin2 (LCN2), which showed the largest magnitude of up-regulation. Immunostaining for lipocalin2 confirmed a stepwise increase in its expression in endometrial hyperplasia and carcinoma. The subcellular distribution of lipocalin2 was both cytoplasmic and nuclear, despite reports that lipocalin2 is a secretory protein. Treatment of endometrial carcinoma cells with 5-azacytidine increased the expression of lipocalin2, suggesting the expression to be controlled by methylation of the promoter. The forced expression of lipocalin2 resulted in the enhanced cell proliferation and invasion in vitro.

Conclusions: The expression of lipocalin2 increased with the endometrial carcinogenesis, and accumulation of the protein conferred biological aggressiveness to endometrial carcinoma cells. These results suggest lipocalin2 to be a novel target in the treatment of endometrial carcinoma.
OUR INITIAL EXPERIENCE WITH ROBOTIC SURGERY FOR UTERINE CANCER IN SOUTH EAST ASIA (SEA)

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Aims: Robotic surgery overcomes many of the difficulties associated with standard laparoscopy. We describe our experience of the first 21 cases of robotic assisted endometrial cancer staging in our institution, the first SEA centre to conduct robotic gynaecologic oncologic surgery.

Method: A retrospective chart review was performed for all the women with uterine cancer who had undergone robotic surgery, analyzing patient characteristics, surgical-pathologic data and surgery-related complications. The surgeries were performed utilizing the da Vinci® surgical system (Intuitive Surgical, Sunnyvale, CA) with 3 arms and 4 ports. Standardized instrumentation and similar cuff closure techniques were used.

Result: The mean age was 57.1 and body mass index was 26.7. 42.9% had medical comorbidities and 28.6% had previous abdominal surgeries. The mean docking time is 11 min, console time is 194 min and total operation time is 274 min. Robotic total hysterectomy and bilateral pelvic lymph node dissection was done for all except 3 cases. Estimated blood loss was < 150mls in all cases and length of stay was 2.9 days. The average node count was 14.7. The most common histological cell type was endometrioid and most of the tumour was grade 1. None of the cases were converted to open. One case of recurrence at the vaginal vault seeded with tumour from the primary surgery was treated successfully with vault radiotherapy.

Conclusion: Robotic staging for uterine cancer appears to be a feasible and safe procedure and can be performed with an acceptable complication rate.
LOW RISK STAGE I ENDOMETRIAL CARCINOMA: PROGNOSTIC FACTORS AND OUTCOMES

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Objectives: The aim of the study is to evaluate clinical features of patients with low risk stage I endometrium cancer, who received adjuvant therapy or followed with observation only and to analyse the effects of known prognostic factors in this group of patients.

Methods: 246 patients (median age: 53, range: 31-77) with low risk stage I endometrial cancer, who were just followed postoperatively (156 patients) or received adjuvant radiotherapy (90 patients) between 1996 and 2007 were reviewed retrospectively.

Results: Local recurrence was detected in four patients, distant metastasis occurred in seven patients and two patients had both local recurrence and distant metastasis. 83.3% of recurrences were on the vaginal stump. Five and ten year local control and overall survival (OS) rates are 97.6%, 97.6% and 96.4%, 93.5% in the observation and adjuvant therapy groups respectively, whereas distant control rates are 96.7% and 96.3%. In multivariate analysis only age and lymphovascular invasion (LVI) were found to affect OS and disease-free survival.

Conclusions: LC and OS rates are high in the low risk group of patients, however current adjuvant therapies did not improve the outcomes. Age over sixty years and presence of LVI have negative effects on outcomes in this group of patients.
ADIPONECTIN TO LEPTIN RATIO AS A PREDICTOR OF ENDOMETRIAL CANCER

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Aim: To evaluate the adiponectin to leptin ratio as a predictor of endometrial cancer.

Material and methods: 98 women aged 29-88 years old were included in the study. Females who were diagnosed with endometrial cancer confirmed postoperatively in histopathology constituted the investigated group (n=54). The controls (n=45) were healthy subject in similar age. Plasma leptin concentrations were measured using a commercial human leptin radioimmunoassay kit (Linco Research, Missouri, USA). Plasma adiponectin concentrations were measured using a commercial human adiponectin ELISA kit (B-Bridge International Inc., Sunnyvale, USA). The adiponectin to leptin cut-off point was set at the level of 1,5 based on the observation of the adiponectin-leptin ratio distribution in the studied population.

Results: The median plasma leptin concentration was significantly higher in investigated group compared with controls, whereas reversed correlation were observed in the adiponectin levels (19.5ug/ml vs 13.35ug.ml and 11.29ug/ml vs 17.21ug/ml, respectively). The adiponectin and leptin concentrations as well as adiponectin to leptin ratio were significantly correlated with the risk of endometrial cancer (Spearman Rank: 0.44, -0.21 and 0.34, respectively). The adiponectin to leptin ratio below 1.5 was negatively correlated with endometrial cancer risk - Spearman Rank: 0.24, p level < 0.002. The adiponectin to leptin ratio had a sensitivity and specificity of 81% and 59%, respectively, with a positive and negative predictive value of 62% both.

Conclusions: The adiponectin to leptin ratio below 1.5 might be an important predictor of the endometrial cancer risk. However, further investigation on larger population of women is essential.
PULMONARY AND SPLENIC SARCOIDOSIS MIMICKING RECURRENCES OF ENDOMETRIAL CANCER

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Sarcoidosis is a multisystem granulomatous disease. According to its imaging profile it can be confused with benign or malignant tumors specially in patients with suspicious recurrent gynecologic cancer. We report the case of a 49 years old Caucasian woman who had a total abdominal hysterectomy, bilateral salpingo-oophorectomy and peritoneal cytology in 2006 for Stage IB Grade 1 adenocarcinoma of the endometrium. Follow up with CT and Positron Emission Tomography (PET) scans of lungs, abdomen, and pelvis revealed extensive mediastinal adenopathy and multiple space occupying splenic and hepatic lesions worrisome for metastatic disease. The patient underwent a laparotomic splenectomy and pathology report showed sarcoidosis.

This case demonstrates that sarcoid-like lesions are a potential cause of confusion in patient with endometrial cancer because they may be misinterpreted as metastatic disease. This case underlines the need for careful evaluation of patients with apparently recurrent cancer, as therapy could be altered or initiated on this wrongful presumption.
A CASE OF ENDOMETRIOID ADENOCARCINOMA CONSIDERED TO BE OCCURRED FROM BROAD LIGAMENT

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Intra pelvic malignant tumors arising from mesonephric duct, paramesonephric duct are rare and only a few cases has been reported. They are classified as broad ligament tumors and are clinically treated like ovarian carcinomas. The present case is a 52-year-old woman, who complained of pain and feeling of a tumor mass in the lower abdominal. Laboratory investigation showed elevated serum markers, CA19-9 at 992U/ml and CA 125 at 2248U/ml. From the MRI findings, ovarian cancer was strongly suspected. On laparatomy, the uterus was found to be slightly enlarged and both ovaries, fallopian tubes were normal. An isolated tumor measuring 16x10x4cm was seen on the right side of urinary bladder in vesicouterine pouch, in continuity with surrounding fatty tissue, without significant adhesion.

On gross examination, this intrapelvic tumor weighed 1400gm, was partly solid and partly multilocular cystic. The histopathological diagnosis was endometrioid adenocarcinoma. Since the fimbria of fallopian tube was seen in close proximity, the tumor was considered to have originated from tissue surrounding the fallopian tube. Furthermore, both adnexae showed presence of endometriosis raising its possible association with malignant transformation.

Another solid tumor was noted inside the uterine body on the luminal side. Histologically, the tumor was diagnosed as endometrioid adenocarcinoma, grade 1, with depth of invasion limited to superficial half of myometrium. Extension to uterine cervix or exposure to parametrium and bilateral adnexae was not seen. Vascular invasion was noted.

Based on clinical and histological findings, the tumors were considered to have concomitant but multiple primary origin.
PROGNOSTIC SIGNIFICANCE OF TETRASPANIN CD151 IN POOR PROGNOSIS ENDOMETRIAL CANCER

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Purpose: To evaluate the prognostic significance of Tetraspanin CD151 expression in a cohort of poor prognosis endometrial cancers of diverse histological type along with Estrogen Receptor (ER), Progesterone receptor (PR), p53 and Her-2 expression in the same samples.

Background: CD151 is a small membrane protein that regulates cell migration and facilitates cancer metastasis. High CD151 expression is associated with poor prognosis in breast, pancreatic and colorectal cancer, and in prostate cancer it is a better prognostic factor than histological grading. Type II endometrial cancers account for 10% of all endometrial carcinomas but are responsible for 50% of cancer recurrence. Identification of novel targets in this group may help improve therapy.

Patients and methods: After complete surgical staging of 156 patients with type II endometrial cancer a tissue microarray was constructed and tested for ER, PR, p53, Her-2 and CD151 expression. 132 (85%) datasets were complete for analysis.

Results: Expression of CD151 was significantly stronger associated with uterine papillary serous and clear cell carcinoma than with grade 3 endometrioid carcinoma, sarcoma or MMMT (p < .001). In univariate and multivariate analysis however, only age, stage and histological type were of prognostic value for disease-specific survival (p = .001; < .001 + .002 resp.) and progression-free survival (p = .001; < .001 + .008 resp.). CD151, HER-2, p53, ER and PR were not prognostic for survival.

Conclusion: CD151 appears to be a biomarker significantly associated with UPSC and clear cell endometrial cancer but fails to predict survival in this patient cohort.
GLOBAL DNA METHYLATION IN BLOOD LYMPHOCYTES IN HUMAN UTERUS AND BREAST CANCERS

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Background: DNA methylation is an epigenetic mark that plays important role in cancerogenesis. Lymphocytes are known to take part in the defence mechanism against cancers. It has been shown that the number of natural killer cells significantly decreases in noninvasive uterine carcinomas, whereas in G3 tumours their quantity is high.

The aim of the study was to check if there are any changes in total DNA methylation of peripheral blood lymphocytes (PBL) in patients with recognized gynecological malignancies.

Methods: PBL were isolated from venous blood of hormonally non-treated, non-cancerous female patients (10) and 36 with geniatal tract and breast cancers (endometrial n=21, breast n=8, cervical n=7). After the lymphocytes isolation DNA isolation has been performed: Lymphocytes using Qiagen RNA:DNA kit, uterine cancer tissues using conventional phenol-chloroform method. The radioactivity of the labeled spots of 5-methyldeoxycytidylic acid and deoxycytidylic acid measured by bio-imaging analyzer in a quan mode and/or by Cerenkov counting. The m5dC content was expressed as a ratio: (m5dC/m5dC+C)x100%.

Results: The mean 5methyldeoxycytidine level in lymphocytes of breast cancers was 3.3+/−0.14 and was significantly lower in comparison to patient groups with genital tract malignancies (p< 0.005). There was no dependance of total DNA methylation in lymphocytes between cervical (3.71+/−0.13) and endometrial cancer groups (3.64+/−0.08);(p< 0.3). m5dC levels recognized in lymphocytes (3.58+/−0.07) was higher than those in endometrial tissue (3.32+/−0.09) of the same cancerous patients (p< 0.038), however without any correlation.

Conclusions: Our investigations revealed that m5dC levels in PBL are statistically higher in uterine and cervical cancers compared with breast cancer and healthy patients tissue.
EFFECTIVENESS AND LIMITATIONS IN THE PRESERVATION OF THE UTERUS IN YOUNG PATIENTS WITH ENDOMETRIAL ADENOCARCINOMA TREATED WITH MEDROXYPROGESTERONE ACETATE

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Aims: To determine the effectiveness and limitations of medroxyprogesterone acetate therapy in young women with endometrial adenocarcinoma in preserving their uterus.

Methods: 7 patients with endometrial carcinoma were treated with high-dose medroxyprogesterone acetate alone as primary therapy and their clinical responses evaluated by hysteroscopy guided endometrial biopsy and additional laboratory clinical tests.

Results: 4 of the 7 cases (57%) with grade I adenocarcinoma responded initially to medroxyprogesterone acetate. The median length of treatment required for regression was 29 weeks. 2 patients who initially responded relapsed. 6 patients are alive without evidence of disease as of December 2005 (10 to 48 months, median; 2 years and 11 months) and one is continuing medroxyprogesterone acetate therapy as a final follow-up. One patient was lost to follow-up. One patient have conceived having two healthy infants.

Conclusion: Treatment of endometrial carcinoma with high-dose medroxyprogesterone acetate is effective and could be an alternative to hysterectomy, although the successful rate is limited.
ENDOMETRIAL POLYPS - RISK OF PREMALIGNANT AND MALIGNANT PATHOLOGY

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Aims: To evaluate the risk of premalignant and malignant pathology among endometrial polyps.

Methods: Among 124 patients seen in outpatient department, 31 had endometrial polyps. All patients had endometrial sampling for pathohistological assessment. To determine the malignant potential among polyps, we compared the pathohistological findings of the polyps (cases) with non-polypoidal specimens (controls).

Results: Out of 31 polyps histologically proved, 26 (83.8%) were benign, 3 (9.68%) had hyperplasia, and 1 (3.2%) were associated with malignancy. Hyperplasia was more frequent in endometrial specimens with polyps than in those without (9.68% vs 4.3%), but the incidence of carcinoma in the two groups was the same (3.2% vs 3.2%).

Conclusions: In abnormal uterine bleeding, hyperplasia was more common in women with endometrial polyps compared to those without polyps. The incidence of carcinoma was not associated with endometrial polyps.
COMPARISON OF KAI 1 PROTEIN EXPRESSION IN STEROID POSITIVE AND NEGATIVE ENDOMETRIAL CANCER

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Background: The specific mechanisms facilitating the invasive growth of endometrial cancer remain obscure.

Aim: The aim of this study was to evaluate the expression of KAI 1 protein in respect to present/absent steroid receptors.

Methods: The expression of KAI 1 protein, ER and PR was estimated by using immunohistochemical staining in 100 endometrial cancers, taking into account clinical and pathological factors of tumors.

Results: The expression of KAI 1 protein, ER and PR was observed in 60%, 46%, 51% of endometrial cancers respectively.

Taking into account endometrial cancer clinical stage, the expression of KAI 1 protein and steroid receptors was observed incomparable percentage of cases. There was no significant correlation between the expression of examined markers and the cancer cell differentiation.

The study revealed the significant correlation between KAI 1 protein expression and PR immunohistochemistry (p=0.01).

The relationship immunophenotypes of endometrial cancer and clinicopathological features shown that KAI 1/ER or KAI 1/PR positive cases were often present in FIGO stage IA-IB, whereas KAI 1+/ER- and KAI 1+/PR- immunophenotypes were associated with advanced stage of cancer.

Conclusions: This study shows that ER- positive expression doesn't suppress the expression of KAI 1 protein.

In conclusion, positive correlations between KAI 1 protein and PR may suggest, that progesterone protective activity in endometrial cancer may be intensified by capable of inhibiting the metastatic process of KAI 1 protein. That suggestion may be useful in indentifying low-risk patients, who don't need an intense oncology surveillance.
MULTICELLULAR SPHEROIDS OF EPITHELIAL ENDOMETRIAL CANCER: CHARACTERISATION AND APPLICATION FOR ANTI-CANCER DRUG SCREENING

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Multicellular spheroids of cancer cells generated in vitro are considered to resemble the physiological origin of tumours. Hence spheroids may provide substantial advantages for study over traditional monolayer cell culture on plastic, cell architecture and heterogeneity of cell population may be more useful.

**Aim:** We are characterising and utilising multicellular spheroids of epithelial endometrial cancer cells and investigating the effects of chemotherapeutic agents.

**Methods:** First, endometrial cancer cell lines (Ishikawa, RL95-2, KLE and EN-1078D) were cultured within 3D matrigel. Second, cancer cell lines were cultured on a non-adhesive surface to form “microtumours”. Third, monolayer cultures were performed. Cell growth, proliferation and metabolism and protein expression, and production of vascular endothelial growth factor (VEGF) were determined. The inhibitory effects of conventional and targeted chemotherapeutic agents, including doxorubicin, cisplatin, paclitaxel, tyrphostin AG1478, LY294002 and natural compound EGCG, were investigated.

**Results:** Following 8 days of culture in 3D matrigel, the well differentiated cell line (Ishikawa) formed central lumen with well defined apical and basal regions. β4-integrin was located at the basal region of Ishikawa cells whereas β4-integrin was diffusely stained in RL95-2, KLE and EN-1078D cells. Proliferation of cells in 3D matrigel was less than for cells grown in a monolayer. The level of VEGF production was dramatically reduced in 3D matrigel. Chemotherapeutic agents had substantially less effect on microtumours.

**Conclusion:** Our findings suggest that multicellular spheroids (“microtumours”) of endometrial cancer cells may offer great potential for investigating novel pathways which regulate drug resistance resembling **in vivo** tumours.
EFFECT OF THE TYPE OF HYSTERECTOMY ON PROGNOSIS IN CLINICAL STAGE I ENDOMETRIAL CANCER

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Objective: To determine whether clinical outcomes show a benefit from an extended hysterectomy in patients with early endometrial cancer.

Methods: We reviewed the medical records of 101 patients with endometrial cancer with clinical stage I disease. All the patients were surgically staged and two types of hysterectomy, simple hysterectomy (SH) or extended hysterectomy (EH) were performed by surgeon's preference. The postoperative pathology findings, recurrence rate and disease free survivals between two groups were compared.

Results: Sixty-six patients and thirty-five patients underwent SH and EH, respectively. At subsequent surgical staging, seven patients (10.6%) in the SH and four (11.4%) in EH group were upgraded to stage II or III disease. The surgical and pathological features were not different between the groups. Though recurrence rate was lower in EH (9.09% for SH vs. 2.86% for EH), it shows no statistical significance (P=0.241). The five-year disease free survival (88.2% for SH vs. 96.0% for EH) showed no statistically significant difference between groups, either (P=0.242).

Conclusions: Compared to the simple hysterectomy, an extended hysterectomy did not have any prognostic benefit in clinical stage I endometrial cancer. Until the therapeutic role of the extended hysterectomy is determined by further studies with larger sample size, the simple hysterectomy remains the treatment of choice in patients with early endometrial cancer, and surgeons should not perform type of extended operation without definite evidence of it.
PREOPERATIVE SERUM LEPTIN LEVELS IN PATIENTS WITH ENDOMETRIAL CANCER AND ITS CORRELATION WITH PROGNOSTIC VARIABLES

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Background and aims: Since leptin is believed to be a key player in carcinogenesis, a study is designed to investigate the relationship between leptin levels and endometrial cancer.

Methods: A study including 30 patients with endometrial cancer and 30 healthy controls was carried out between November 2008 and July 2009 in Hacettepe University Hospital. All patients with endometrial cancer underwent a complete surgical staging procedure including lymphadenectomy. Preoperative leptin levels of endometrial cancer patients and healthy controls were compared. The relationship between leptin levels and stage, grade, histological type and lymph node status of endometrial cancer cases were evaluated.

Results: The mean serum leptin levels were 16.9 ng/ml among endometrial cancer cases and 19.0 ng/ml among controls (p=0.32). Of endometrial cancer cases, the mean leptin level was found to be 15.8 ng/ml for stage I and 18.5 ng/ml for stage II-IV disease (p=0.34). The figure was 17.7 ng/ml for endometrioid and 13.2 ng/ml for nonendometrioid type of tumor (p=0.24). The mean leptin levels of 16.3 ng/ml for grade I and 19.9 ng/ml for grade II-III tumors were observed (p=0.07). The cases with positive and negative lymph nodes had leptin levels of 20.2 ng/ml and 16.1 ng/ml, respectively (p=0.30).

Conclusions: Serum leptin levels in endometrial cancer patients were similar to healthy controls. Leptin did not show any significant correlation with stage, grade, histological type and node metastases in endometrial cancer.
P53 SIGNATURE IN ENDOMETRIAL POLYP - SEROUS CARCINOMA SEQUENCE

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Alteration of p53 is an early event in the development of endometrial serous carcinoma (ESC). Recently, a group of benign-looking endometrial glands with p53 overexpression which is designated p53 signatures (p53S) has been reported in the surrounding endometrium of ESC. To evaluate the presence of p53S in endometrial polyp - ESC sequence.

The p53, estrogen receptor (ER) and Ki-67 expressions were immunohistochemically examined in 63 atrophic endometriums (AEs), 52 postmenopausal endometrial polyps (PEPs) and 4 ESCs developing in PEPs. The overexpression of p53 was divided into two types: p53 positive endometrial gland (p53PG) and P53S showing weak and strong overexpression of p53, respectively.

No p53PG and p53S were found in 63 AEs. P53PG and P53S were found in 12 and 5 of 52 PEPs, respectively. P53S was essentially associated with P53PG in the surrounding endometrium. Both P53PG and P53S were found in the surrounding endometriums of 4 ESCs. The ER expression was found in all of AEs and PEPs. P53PG and P53S of PEPs showed the positive ER expression and low labeling index of Ki-67. The immunohistochemical attitude of P53PG and P53S in the surrounding endometriums of ESCs showed the same as that of P53PG and P53S of PEPs except one ESC. Four ESCs showed overexpression of p53, negative expression of ER and high labeling index of Ki-67.

P53S is suggested to be the precancerous lesion of ESC in endometrial polyp - ESC sequence. Loss of ER expression may be important for progression from P53S to ESC.
PREOPERATIVE DIAGNOSIS OF UTERINE SARCOMA
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Background: Uterine sarcoma is a relatively rare disease. However, has a poor prognosis. It is difficult to make the differential diagnosis from uterine myoma, and because it is almost always impossible to make a definite diagnosis preoperatively when uterine sarcoma is suspected, as matters now stand it is ultimately necessary to perform surgery. In this study we assessed the preoperative clinical and imaging findings in cases in our hospital in which uterine sarcoma was suspected.

Methods: We retrospectively assessed the clinical findings, blood examination findings, and diagnostic imaging findings, in the 30 cases in which surgery was performed in our hospital between January 2006 and March 2010 because of suspicion of uterine sarcoma.

Results: The final diagnosis was uterine sarcoma in 11 cases. The mean resistance index (RI) value in the 20 cases in which RI was measured by Doppler ultrasonography was 0.38 (0.20-0.70), and in the sarcoma cases among them it was 0.29 (0.22-0.40). Of the 14 cases in which uterine sarcoma was suspected based on the MRI findings, the diagnosis was actually uterine sarcoma in 8 (57.1%).

Conclusions: While it is important to avoid unnecessary surgery as much as possible when making the diagnosis of uterine sarcoma, it is also true that missing the diagnosis when it should have been made is unacceptable. Thus, it will be necessary to improve the accuracy of differential diagnosis and to build up evidence for preoperative diagnosis by accumulating additional data.
VORINOSTAT HISTONE DEACYLASE INHIBITOR INDUCES APOPTOTIC ACTIVITY IN ENDOMETRIAL CANCER

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Introduction: A correlation between components of the insulin-like growth factor (IGF) system and endometrial cancer risk have been shown in several studies. The antitumour action of vorinostat (Merck Oncology), a histone deacetylase may involve changes in the expression of specific genes via acetylation of histones and transcription factors.

Aim: The aim of this study was to establish whether vorinostat can modify the expression of specific genes related to the IGF-IR signaling pathway and revert the transformed phenotype.

Methods: Human endometrioid Ishikawa (Type I) and serous papillary (USPC-2; Type II) endometrial cancer cell lines were treated with vorinostat in the presence or absence of IGF-I.

Results: Vorinostat increased IGF-IR phosphorylation, and BRCA1, pTEN, and p21 expression, and reduced Sp1 and p53 protein levels in Ishikawa cells. Vorinostat up-regulated the expression of total IGF-IR, p21 and down-regulated the expression of total AKT, BRCA1, Sp1, p53, and pTEN in USPC-2 cells. Of interest, IGF-IR activation was associated with a major elevation in IGF-IR promoter activity. In addition, vorinostat treatment induced apoptosis in both cells lines and abolished the anti-apoptotic activity of IGF-I in the absence or presence of humanized monoclonal anti-IGF-IR antibody, MK-0646 (Merck Oncology).

Conclusions: In summary our studies demonstrate that vorinostat exhibits a potent pro-apoptotic effect in Type I and Type II endometrial cancer. The mechanism of action of vorinostat, at least in the specific context of endometrial cancer, is most probably an IGF-IR independent mechanism. Future studies will address the molecular nature of these biological effects.
APPLICATION OF NARROW BAND IMAGING (NBI) FOR HYSTEROSCOPY OF ENDOMETRIAL LESIONS


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Objective: Narrow band imaging (NBI) for detection of blood vessels and microstructures on the mucosal surface is of interest in gastrointestinal endoscopy. We performed flexible hysteroscopy using NBI for outpatients and investigated the significance of this method for endoscopic diagnosis of endometrial lesions.

Methods: Of patients who visited our hospital for suspected lesions in the uterine cavity between April and December 2009, 68 underwent a hysteroscopy with NBI. Based on the pathological diagnosis, we compared the accuracy of the diagnosis of lesions by NBI with that of 209 cases examined by conventional hysteroscopy in 2008. We also compared the sensitivity and specificity of atypical endometrial hyperplasia (AEH) or carcinoma between NBI and conventional hysteroscopy.

Results: The diagnosis with NBI hysteroscopy was consistent with the pathological diagnosis in 58 of the 68 cases, giving an accuracy of 85.3%. The accuracy of NBI was significantly higher than the accuracy of 70.8% obtained with the conventional hysteroscopy. Regarding the sensitivity and specificity for AEH or carcinoma between NBI and conventional hysteroscopy, the sensitivity and specificity of NBI were 100% and 84.6%, respectively, while those of the conventional hysteroscopy were 82.6% and 85.1%, respectively. The sensitivity of NBI was significantly higher than that of the conventional hysteroscopy.

Conclusion: Our results show that a hysteroscopy using NBI has increased accuracy and sensitivity for detection of AEH and carcinoma. These findings suggest that NBI is useful for diagnosis of endometrial lesions.
THE INCIDENCE OF LYMPH NODE METASTASIS IN CASES OF ENDOMETRIAL CANCER

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Background: Endometrial cancer is the most frequent of gynecologic neoplasm. The staging is being done surgically, and the prognosis is worst in cases with lymph node metastasis.

Aim: A prospective study of the incidence of the lymph node metastasis in cases of endometrial cancer.

Materials and methods: 567 patients with endometrial cancer (8 with carcinosarcoma) were treated surgically at our department (2004-2009). Before the operation the clinical stages detected were as: Stage I - 427 patients, Stage II - 95 patients, Stage III - 44 patients and Stage IV - 1 patient.

Results: In 430 cases (75%) a lymph node dissection was performed. In 144 cases (33,5%) a pelvic lymph node metastasis was detected. 59 patients (40,9%) were staged as Stage I, 75 patients (52,1%) - as Stage II and 10 patients (7%) - as Stage III had metastases.

After surgical staging from 427 patients with Stage I (IA and IB) only 368 remained, 59 were staged as IIIC1 - with positive pelvic lymph nodes, from 95 patients with Stage II only 20 remained, and 75 were staged as IIIC1 - with positive pelvic lymph nodes.

After surgical staging the cases in Stage III increased from 44 to 178.

Conclusions: Because of the surgical staging 134 patients were restaged and were treated with the necessary radiation and chemotherapy. Our results suggest that pelvic lymph node metastasis can often be found.
INTEROBSERVER REPRODUCIBILITY OF ASSESSMENT OF PTEN LOSS BY IMMUNOHISTOCHEMISTRY IN ENDOMETRIAL CARCINOMA

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PTEN is a tumor suppressor that negatively regulates the AKT signaling pathway. PTEN loss occurs in >50% endometrial tumors and has been implicated in endometrial carcinogenesis. As AKT pathway inhibitors enter clinical trials, gynecologic pathologists must accurately identify endometrial cancer patients who may benefit from these new forms of targeted therapy. This is a cross-validation study of PTEN immunohistochemistry performance and interpretation between two major cancer centers.

Two batches of endometrial carcinomas, each consisting of 59 cases from both cancer centers, were immunostained for PTEN (Dako, 6H2.1) and scored at each institution. IHC staining categories were designated as positive (>90% of tumor with diffuse cytoplasmic staining), negative (< 1% of tumor cells staining) and heterogeneous (distinct positive and negative foci).

The overall agreement was 89.1% with a kappa value of 0.821 (95% CI, 0.697-0.944) for the first batch of cases and 77.1% with a kappa value of 0.601 (95% CI, 0.447-0.755) for the second batch. Since tumors with negative and heterogeneous staining would have complete or partial PTEN protein loss and therefore activation of the AKT pathway, a second analysis was performed to disregard any scoring discrepancies between the two centers involving these groups. For the first batch, the overall agreement was 95.2% with a kappa value of 0.922 (95% CI, 0.837-1.000), and 84.9% with a kappa value of 0.749 (95% CI, 0.603-0.895) for the second batch.

We conclude that the assessment of PTEN protein loss in endometrial tumors is highly reproducible through the use of standard immunohistochemical techniques and simple scoring criteria.
QUALITY OF LIFE AND SEXUAL FUNCTIONING IN ENDOMETRIAL CANCER SURVIVORS

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Background: Recent evidence suggests equivalent efficacy in terms of local control for adjuvant vaginal brachytherapy (VBT) compared to external beam radiotherapy after surgery in patients with intermediate-high endometrial cancer. The objective of this study is to compare the quality of life (QoL) and sexual function of women with endometrial cancer that were treated with either surgery alone or surgery in combination with postoperative VBT.

Methods: Women were interviewed at least 5 years after initial treatment for endometrial cancer. QoL was evaluated by using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and the cervical cancer module, CX-24. Sexual function was evaluated by using the Female Sexual Function Index (FSFI). Eligible women had early stage disease, were currently disease-free, and had undergone surgery and adjuvant VBT, but neither external beam radiotherapy nor systemic treatment. This study group were then compared using univariate and multivariate analyses with an age-matched control group comprising of endometrial cancer patients without adjuvant VBT.

Results: Fifty-five patients (29 surgery+VBT and 26 surgery without VBT) were included for analysis. With respect to QoL, univariate and multivariate analyses did not show significant differences between the study group and controls. Likewise, in terms of sexual function statistical analyses did not show significant differences between patients with VBT and controls on any of the outcome measures in the FSFI questionnaire.

Conclusion: Adjuvant VBT after surgery does not seem to have a significant impact on quality of life and sexual function in endometrial cancer survivors.
OVER-EXPRESSION OF ESTROGEN RECEPTOR-RELATED RECEPTOR Α IN ENDOMETRIAL CARCINOMA CELLS MAY PROVIDE AN ER-INDEPENDENT MECHANISM TO RESIST THE ENDOCRINE THERAPY

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Objective: Estrogen receptor-related receptor α (ERRα) was identified as a nuclear transcription factor closely related to estrogen receptor α (ERα) and reported to compete with ERα in an estrogen-independent manner. To discuss the role of ERRα in the endometrial carcinoma cells treated with endocrine therapy, this study was performed.

Materials and methods: Plasmid pSG-hERRα-1 was transiently transfected into the endometrial carcinoma cell lines Ishikawa (ER-positive) and HEC-1A(ER-negative). Quantitative PCR and Western-Blot were performed to analysis the alternation of mRNA and protein expression of hERRα. After transfection, the Ishikawa and HEC-1A cells with over-expression of hERRα. The XTT-cell growth curve and cell cycle flow cytometry analysis were performed in the cancer cells treated with tamoxifen and pure anti-estrogen ICI 182,780. Induced by high dose tamoxifen or ICI182,780.

Results: After transfection, the cell lines were detected an increasing expression of hERRα in mRNA levels and protein levels. A decreasing expression of hERα was observed in the cells with over-expression of hERRα. Over-expression of hERRα markedly increased the number of S-phase cells and decreased the G0-G1 phase cells in ERα-negative HEC-1A cells.Moreover, analyzed by flow cytometry, the cells Ishikawa and HEC-1A with over-expression of hERRα achieved a resistance to the cell apoptosis induced by high dose of tamoxifen (SERM) or ICI 182,780.

Conclusion: In endometrial carcinoma cells, over-expression of hERRα may provide an ER-independent molecular mechanism to resist the anti-cancer endocrine therapy on the basis of repressing ER function. hERRα may be the next endocrine therapy target in hormone-related cancer.
A STUDY OF ENDOMETRIUM OF PATIENTS WITH ABNORMAL UTERINE BLEEDING AT GUANGZHOU CHINA

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Objective: To know the causes for the abnormal uterine bleeding in Women at Guangzhou China and to compare the histopathological findings between the pre-menopausal and postmenopausal women.

Methods: A descriptive study of patients who have had vaginal bleeding during the period from September 2005 to March 2010 seen at Department of Gynecology of Sun Yat Sen University the Third Affiliated Hospital, Guangzhou, China (SUMS). Eighty-four women (aged 39 years and above) having abnormal vaginal bleeding managed at SUMS.

Results: A total of eighty-four patients were studied. Majority (53.5%) of them were postmenopausal ladies presenting with abnormal vaginal bleeding. The age range was 39 to 66 years, with an average of 52.2. Only 37% had pathological bleeding including malignancy and about 16.6% of all had malignancies. Malignant diseases were found in 7.7% cases in the pre-menopausal ladies whereas it was 24.3%, three times higher, in the post-menopausal ladies.

Conclusion: Endometrial cancer occurred with increasing frequency with increasing age in this study. So, a thorough work-up is needed for the perimenopausal/postmenopausal women presenting with an abnormal vaginal bleeding especially to rule out malignancies.

Keywords: Curettage, endometrial cancer, postmenopausal bleeding, hysterecscopy, biopsy
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HYALURONAN SYNTHASES (HAS1-3) AND HYALURONIDASES (HYAL1-2) IN THE ACCUMULATION OF HYALURONAN IN ENDOMETRIAL CARCINOMA

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Background: Hyaluronan accumulation correlates with the degree of malignancy in many solid tumor types, including endometrial carcinomas. To elucidate the mechanism of hyaluronan accumulation, we examined the expression levels of the hyaluronan synthases (HAS1, HAS2 and HAS3) and hyaluronidases (HYAL1 and HYAL2), and correlated them with hyaluronan content and HAS-3 immunoreactivity.

Methods: A total of 35 endometrial tissue biopsies from 35 patients, including proliferative and secretory endometrium (n=10), post-menopausal proliferative endometrium (n=5), complex atypical hyperplasia (n=4), low grade (n=8) and high grade (n=8) adenocarcinomas were studied by real-time RT-PCR, and cytochemistry for hyaluronan and HAS1-3.

Results: The mRNA levels of HAS1-3 (HAS1 very low), were not consistently changed, while the immunoreactivity of all HAS proteins was increased in the cancer epithelium. HAS3 mRNA, but not HAS3 immunoreactivity, was increased in post-menopausal endometrium compared to normal endometrium (p=0.003). The median of HYAL1 mRNA was 10-fold and 15-fold lower in both low-grade and high-grade endometrial cancers, as compared to normal (p=0.004-0.006), and post-menopausal endometrium (p=0.002), respectively. HYAL2 mRNA was also reduced in cancer (p=0.02) and correlated with HYAL1 (r=0.8, p=0.0001). There was an inverse correlation between HYAL1 mRNA and the epithelial hyaluronan staining intensity (r=-0.6; P=0.001).

Conclusion: The results indicated that HYAL1 and HYAL2 were coexpressed and significantly downregulated in endometrial cancer and correlated with the accumulation of hyaluronan. While immunoreactivity for HASs increased in the cancer cells, tumor mRNA levels for HASs were not changed, suggesting that reduced turnover of HAS protein may also have contributed to the accumulation of hyaluronan.
HIGH PROTEIN EXPRESSION OF IGF-1R AND BRCA1 IN UTERINE SEROUS PAPILLARY CARCINOMA (USPC)

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Introduction: The aim of this study was to evaluate the effect of BRCA1 on IGF-1R protein expression in uterine serous papillary carcinoma (USPC) paraffin blocks, and in USPC-derived cell lines.

Methods: BRCA1 and IGF-1R immunohistochemistry on paraffin blocks (35 uterine and 17 metastasis) were performed. The patients were examined for the three predominant Jewish germline BRCA1-2 mutations. In addition, USPC1 and USPC2 cell lines were transiently co-transfected with an IGF-1R promoter construct driving a luciferase reporter gene, along with a BRCA1 expression plasmid. USPC2 cells were transiently and stably transfected with a BRCA1 expression plasmid, and levels of endogenous IGF-1R were evaluated by western immunoblotting.

Results: Positive immunostaining for BRCA1 was identified in all the samples with strong staining in 71% of them. 33/35 (94%) were stained positively for IGF-1R. No difference in BRCA1 and IGF-1R staining intensity was noted between BRCA1-2 mutation carriers and non carriers. Interestingly, metastatic tumors were stained more intensely for BRCA1 compared to their primary tumor site (p=0.041) and more intensely with borderline significance for IGF-1R (p=0.069). Results from the co-expression experiments revealed that BRCA1 expression led to a 35% and 54% reduction in IGF-1R promoter activity in the USPC1 and USCP2 cell lines, respectively. Results from western immunoblotting showed a decline in the levels of p-IGF-1R both in transiently and stably transfected cells and also a decline in p-AKT levels.

Conclusions: Our data showed a high protein expression of BRCA1 and IGF-1R in USPC. Moreover, BRCA1 suppresses IGF-1R gene expression and IGF-1R activity.
THE INFLUENCE OF CERVICAL INVASION ON LYMPH NODE MAPPING IN STAGE III ENDOMETRIAL CANCER

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Introduction: To investigate whether cervical invasion changed lymph node (LN) metastases distribution in endometrial cancer.

Methods: The patients were staged according to the FIGO 1988. Forty-six patients underwent systematic bilateral pelvic and para-aortic lymphadenectomy up to left renal vein were enrolled. For inclusion in the study, patients had to have at least 10 LN removed from the para-aortic region and at least 15 LN removed from the pelvic region.

Results: In 23 cases, there was tumor invasion into cervix and 4 had glandular involvement, while 19 had both glandular and stromal invasion. The tumor spread to para-aortic LN in 26 cases, and to pelvic LN in 41 cases. The most invaded region was the obturator, and the least was the presacral. The mean number of dissected LN was 62.9. Patients with and without cervical invasion were similar in terms of factors affecting LN metastasis, except age. The mean age of patients with cervical metastases was younger. When the distribution of the LN metastasis in each region was examined, tumor spread to the cervix was only associated with increased external iliac LN metastasis (21.7 vs. 60.9; p=0.07).

Discussion: When endometrial cancer has spread to the cervix, there is a different spread pattern through the cervical lymphatic network. The presence of cervical invasion significantly increases the rate of metastases to the external iliac LN and changes the pattern of the disease in the pelvic region.
APPLICATIONS OF INTRA-OPERATIVE FROZEN SECTION (IOFS) IN THE MANAGEMENT OF ENDOMETRIAL CANCERS

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Background and aims: Staging and diagnosis of stage-I endometrial cancer by imaging and histology prior to hysterectomy may be improved by IOFS. The aim of this study was to assess the impact of IOFS on the intraoperative surgical management of suspected or early stage endometrial cancers and to identify women requiring pelvic lymphadenectomy (LND).

Methods: Women with presumed stage-I disease or suspected endometrial cancer were selected prior to hysterectomy. The tumour type, grade & depth of invasion were assessed by IOFS. Confirmed Stage-I cancers with intermediate/high-risk factors (≥grade-2, ≥50% myometrial invasion or poor histological sub-types) and those with higher stages on IOFS had LND. Accuracy of IOFS was documented and changes to management plan recorded.

Results: Thirty three women had IOFS. Median age was 55 years (31-83 range). Indications for IOFS were staging (46%), diagnosis (33%) or both (21%). Sensitivity for cancer diagnosis with IOFS was 92%, specificity 89%, negative predictive value 89% and positive predictive value 95.7%. The overall accuracy rate was 91% for diagnosis. Grade/stage were correct in 88%. There were 23 endometrial cancers, 1 metastatic tumour and 9 endometrial hyperplasias.

One third of women would not have had correct treatment if IOFS was unavailable. Following IOFS, 4 women avoided LND while 7 women had LND. 1 had positive lymphnodes on histology.

Conclusion: Assessment by IOFS is accurate in diagnosing endometrial cancer and to identify women with Stage-I endometrial cancers who may benefit from LND.
FACTORS AFFECTING LYMPH NODE METASTASES IN ENDOMETRIAL CANCER

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Introduction: To investigate the factors affecting lymph node (LN) metastases in endometrial cancer.

Methods: The patients were staged according to the FIGO 1988. The patients underwent systematic bilateral pelvic and para-aortic lymphadenectomy up to left renal vein were enrolled. For inclusion in the study, patients had to have at least 10 LN removed from the para-aortic region and at least 15 LN removed from the pelvic region. Based on these criteria, 149 patients were enrolled.

Results: The disease stage varied between IA-IVB. LN involvement was present in 31 (20.8%) cases. Pelvic and para-aortic metastases were detected in 26 and 17, respectively. Univariate analysis revealed that age, cell type, lymphovascular space invasion (LVSI), presence of cervical invasion, ovarian involvement, fallopian tube involvement, peritoneal spread and myometrial invasion depth affected the para-aortic and pelvic LN metastases. LVSI, cell type, myometrial invasion depth, peritoneal spread, fallopian tube spread and age were identified as independent risk factors for para-aortic LN metastases. LVSI, cell type, myometrial invasion depth, cervical invasion, peritoneal spread and ovarian metastases were independent risk factors for pelvic LN metastases.

Discussion: All surgical and pathological risk factors examined, except grade and tumor size, affected LN metastases in endometrial cancer. However, the factors affecting LN metastases were not identical for pelvic and para-aortic LN. Fallopian tube invasion and age were specific for para-aortic LN metastases, while cervical invasion and ovarian metastases were specific for pelvic LN metastases.
ISOLATED PARA-AORTIC LYMPH NODE METASTASES IN ENDOMETRIAL CANCER
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Introduction: The surgical-pathological risk factors in patients with endometrial cancer with isolated para-aortic lymph node (LN) metastases were analyzed.

Methods: The cases were staged according to the FIGO 1988. The 207 patients underwent systematic bilateral pelvic and para-aortic lymphadenectomy up to left renal vein were enrolled.

Results: There were LN metastases in 23.2% of cases. Isolated para-aortic LN metastases were present in 6 patients (2.9%). The cell type was endometrioid in 5 patients. Cervical invasion was identified in 2 patients. In 3 of 4 patients with no cervical invasion, the myometrial invasion depth was greater than 1/2; in the other patient serosal invasion and tubal metastases were present. In 3 of these 4 patients with no cervical invasion, lymphovascular space invasion (LVI) was present. Peritoneal cytology was positive in one patient, who also had serosal infiltration, cervical stromal invasion and LVI. LVI was present in 5 patients. In the patient without LVI the myometrial invasion depth was greater than 1/2. None of these patients, with LVI, had ovarian metastases, but one had fallopian tube metastases. The myometrial invasion depth was greater than 1/2 or serosal invasion was present except for one patient. In the patient with less than 1/2 myometrial invasion, the grade was 3, the cell type was clear cell and cervical invasion was present. The grade was 1 in two, 2 in two, and 3 in two cases.

Discussion: The patients with isolated para-aortic lymph node metastases had at least one risk factor.
DETAILED ANALYSIS OF ENDOMETRIAL CANCER PATIENTS WHO UNDERWENT RESECTION OF UPPER AND LOWER PARA-AORTIC NODES DURING A LYMPHADENECTOMY


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Introduction: In this study, the para-aortic lymph node status of patients with endometrial cancer was analyzed.

Methods: The seventy-eight patients with endometrial cancer enrolled in this study. Lymph node status was evaluated during the lymphadenectomy, with the inferior mesenteric artery used as the border between the upper and lower regions of the para-aortic region.

Results: The mean number of resected lymph nodes was 14.4 for upper region and 10.1 for lower region. Lymphatic involvement rate was 14.1% in upper region and 6.4% in lower region. In 27.3% of the patients with metastatic lymph nodes in the upper region, there were no metastases detected in the pelvic lymph node. Endometrioid-type histology was reported for 72.7% of patients with upper region metastases and for 40% of patients with lower region metastases. Patients with a grade of 1 didn’t have metastases detected in the lower region, yet metastases were detected in the upper region. In 9.1% of patients who had metastases in the upper region and in 20% of patients who had metastases in the lower region, myometrial invasion was not detected.

Discussion: The number of metastatic pelvic lymph nodes site, cell type, grade and the depth of myometrial invasion the upper and lower para-aortic regions could be distinguished into two different clinical conditions. However, due to the small number of cases evaluated in this study, additional case studies are needed to confirm these findings.
VAGINAL HYSTERECTOMY AS AN ALTERNATIVE METHOD OF TREATMENT OF ENDOMETRIAL CANCER

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The aim of the study was a clinical analysis of vaginal hysterectomy as an alternative method of surgical treatment in a selected group of patients with endometrial cancer.

28 vaginal hysterectomies were performed due to endometrial cancer in Dept. of Gynecology and Gynecologic Oncology Medical University of Gdansk between 1983 - 2008. The following parameters were analysed: age of patients, number of deliveries, coexisted internal diseases, previous surgical treatment, weight and BMI, histologic type and clinical stage of neoplastic disease, myometrial and cervical invasion, intra- and postoperative complications.

Results: The youngest patient was 42 years old, the oldest - 82 years old. 27 women (96,4%) were postmenopausal and 1 woman (3,6%) was premenopausal. The most of patients delivered 2 or 3 times. In a 92,9% of the analysed group (26 patients) coexisted internal diseases were found. The most of patients was obese or pathologic obese (between 72 and 230 kilograms): 60,5% of them weigh over 100 kilograms. Adenocarcinoma was typically detected. only endometrial lesion or myometrial invasion less then ½ was detected in over the half of the analysed group. In all group 3 cases of superficial cervical invasion and 1 case of coexisted cervical cancer were found. 11 patients (39,3%) operated between 1983 - 2007 are still living. 7 patients (25%) died 2 or 3 years after surgical treatment. The history of 10 patients (35,7%) is unknown.

Conclusion: Vaginal hysterectomy can be an alternative method of the surgical treatment of endometrial cancer in a selected group of patients.
HEALTH-RELATED QUALITY OF LIFE OUTCOMES WITH ROBOTIC SURGERY FOR ENDOMETRIAL CANCER: TIME TO STRAY FROM THE MIDLINE?

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Objective: Reported benefits of robotic surgery (RS) include decreased hospital stay, blood loss, and complications when compared to laparotomy for endometrial cancer. To date, there are no prospective reports on quality of life (QoL) between the two groups. The objective of this study was to assess measures of health-related (HR)QoL outcomes in women undergoing RS or laparotomy for endometrial cancer.

Methods: Twenty-seven patients underwent surgery for endometrial cancer and completed HRQoL assessments were identified. Initial assessment was conducted pre-operatively and follow-up assessment was conducted at least four months after the initial assessment. Eight subscales of the Medical Outcomes Study-Short Form 12 were used to assess HRQoL. Analysis based on surgical approach was performed and data compared with ANOVA. Repeated-measures ANOVA tested the group differences in QoL change from pre- to post-operative time controlling for age and BMI.

Results: Median age was 57 years and 93 % had stage I disease. Eighteen patients underwent laparotomy and 9 underwent RS. There was no significant difference between groups in socio-demographics, stage, or adjuvant treatment. Significant decreases in physical functioning (p=0.02), bodily pain (p=0.03), and social functioning (p=0.05) were seen after laparotomy. Interestingly, patients undergoing RS experienced improvements in these HRQoL indicators.

Conclusions: Patients undergoing RS for endometrial cancer experience significantly improved outcomes in bodily pain, physical and social functioning scores compared to laparotomy patients. Though larger studies are required, these results suggest that the improved HRQoL outcomes with RS should be considered when selecting the surgical approach for patients undergoing endometrial cancer surgery.
FAILED CONSERVATIVE TREATMENT OF SYNCHRONOUS PRIMARY CANCER OF ENDOMETRIUM AND OVARY IN YOUNG WOMAN: A CASE REPORT

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A case of well differentiated endometriod adenocarcinoma of the endometrium with a synchronous endometriod and clear cell adenocarcinoma of both ovaries was reported.

Recently, a 28-year-old woman presented with vaginal bleeding was diagnosed to have only FIGO stage IaG1 (FIGO 2000) cancer of the endometrium. High dose progestin was used for conservative treatment after counseling.

After 3 months of treatment, 15 cm bilateral ovarian tumors later diagnosed as FIGO stage IIc ovarian cancer (mixed endometriod and clear cell adenocarcinoma) were detected, and later surgically removed. The patient then was started on Paclitaxel/Carboplatin combination chemotherapy for 6 cycles after surgery.

The synchronous cancers of endometrium and ovary are usually presented in woman with median age of 50 with obesity, diabetes, and hypertension. These low grade tumors and better prognosis are the norm in contrast to our case with clear cell component and higher stage of ovarian cancer in young lean Thai woman. The prognosis of cases from literature is surprisingly good due to early stage detection of endometrial and ovarian cancer. Good result is usually obtained even after total abdominal hysterectomy and bilateral oophorectomy.

Keywords: endometrial cancer, ovarian cancer, synchronous tumor of endometrium and ovary.
PROGNOSTIC SIGNIFICANCE OF LYMPHO-VASCULAR SPACE INVASION AND NODAL INVOLVEMENT IN INTERMEDIATE AND HIGH RISK ENDOMETRIAL CANCER PATIENTS

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Purpose: The aim of this analysis was to assess whether Lympho-vascular space invasion and nodal status provide incremental prognostic value compared with traditional prognostic factors in intermediate and high risk endometrial cancer patients treated with primary surgical staging and adjuvant radiotherapy.

Materials and methods: Prognostic factors considered were FIGO stage, grade, histology, fractional myometrial invasion, nodes, LVSI, age and type of adjuvant radiotherapy. In addition 4 new pair-wise groups using various combinations of LVSI and nodal status were also created for analyses. A pair with negative nodes and negative LVSI was used as the reference category. All other combinations were compared against this in using multivariable analyses.

Results: Three hundred and twenty four patients were available for analyses. The mean follow-up was 4.8 years. At 5 years, failure free survival rate was 79.8%. Eighty three percent of patients with endometrioid histology were alive and free from disease at 5 years compared with 69.8% patients with serous/clear cell histology. In multivariate model only three factors, patients with LVSI and positive nodes (P=0.004, HR- 8.8), LVSI and negative nodes (P=0.000, HR- 4.9) and age (p=0.025, HR- 1.02) were significant predictors for relapses.

Conclusion: The traditionally used prognostic factors did not add to the predictive abilities for relapses in this series. A simplified model that uses nodal and LVSI status along with age has equal prognostic predictive abilities as a full model and can be used in simplifying the staging and patients selection for clinical studies of high risk endometrial cancer patients.
ISOLATED PARA-AORTIC LYMPH NODES METASTASES IN PATIENTS WITH ENDOMETRIAL CARCINOMA UNDERGOING EN BLOC PELVIC LYMPHADENECTOMY

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Background: Regional lymph nodes evaluation is necessary for the adequate surgical staging of endometrial carcinoma, however, only limited information is available about the requirement for and value of para-aortic lymph nodes adenectomy.

Aims: To describe the incidence of isolated para-aortic lymph nodes metastases in patients with negative pelvic lymph nodes undergoing en bloc pelvic lymphadenectomy.

Methods: All medical records of patients with endometrial carcinoma experienced en bloc pelvic lymphadenectomy in our institution between 01/01/2000, and 12/31/2008 were identified. The incidence of isolated para-aortic lymph nodes metastases was defined as the number of patients with at least 1 positive para-aortic node and negative pelvic nodes by the number of patients who experienced en bloc pelvic lymphadenectomy with at least 1 para-aortic node dissected.

Results: Among the 739 patients surgically treated at our institution between 1/00 and 12/08, 501 patients (67.8%) received en bloc pelvic lymphadenectomy. Thirty-one patients among those 205 patients with para-aortic lymph nodes dissection experienced nodal metastases, 12(5.9%) with pelvic nodal metastases, 12(5.9%) with pelvic and para-aortic nodal metastases, and the other 7(3.4%) with isolated para-aortic nodal metastases. In patients without para-aortic lymph nodes dissection, 33 patients (11.1%) had positive pelvic lymph nodes.

Conclusions: Though, the incidence of isolated para-aortic lymph nodes metastases is low, para-aortic lymphadenectomy should be regarded as an investigated protocol for endometrial carcinoma. Further studies major in identification of patients with high risk isolated para-aortic nodal metastases are urgently needed.
TRANSVAGINAL ULTRASOUND EXAMINATION OF MYOMETRIAL INFILTRATION BY ENDOMETRIAL CANCER

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Objective: To determine the accuracy of preoperative transvaginal ultrasound in the examination of myometrial invasion in endometrial patients.

Methods: 48 patients with endometrial cancer were assessed preoperatively by transvaginal ultrasound to evaluate the depth of myometrial infiltration. Subsequently, the patients were operated and, with use of the frozen section and the standard paraffin section, the hysterectomy specimens were evaluated for the depth of myometrial infiltration. The results of transvaginal sonography were compared with the histopathological results.

Results: In the diagnosis of myometrial invasion, the ultrasound sensitivity was 100%, specificity was 82%, negative predictive value was 100%, positive predictive value was 56% and the accuracy reached 85%.

Conclusion: By the assessment of the depth of myometrial invasion in patients with endometrial cancer, the preoperative transvaginal ultrasound provided an acceptable accuracy when compared with the standard paraffin section. This technique may be useful in the preoperative management of patients with endometrial cancer and helpful in the decision whether or not to perform the pelvic and paraaortic lymphadenectomy.
IMMUNOHISTOCHEMICAL EXPRESSION OF SYNUCLEIN-γ, ER, PR, MMP-2, MMP-9 AND GLUT-1 IN EARLY AND ADVANCED ENDOMETRIOID TYPE ENDOMETRIAL CANCER

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Objective: To evaluate the differences in immunohistochemical expression of malignancy related proteins in early(EEE) and advanced(AEE) stage endometrioid type endometrial cancer.

Methods: A tissue microarray was constructed using formalin-fixed, paraffin-embedded tissue, including 23 EEEs and 18 AEEs. Tissue array sections were immunostained with antibody of synuclein-γ, ER, PR, MMP-2, MMP-9 and GLUT-1. The staining intensity and area extent of the immunohistochemical reactions were evaluated using the semi-quantitative scoring system. The data were analyzed by spearman's correlation test, nonparametric, Mann-Whitney tests, the Kaplan-Meier and log-rank test.

Results: Synuclein-γ and MMP-2 expression were higher in AEEs, although they were not statistically significant (P=0.51, P=0.45). MMP-2 was not expressed in EEEs and expressed in 3 of 18 AEEs. ER and PR were overexpressed in EEEs (P<0.05, P<0.05). MMP-9 and GLUT-1 were overexpressed in AEEs (P=0.02, P=0.01). ER (score ≤5 versus >5) and PR (score ≤7 versus =8) expression was positive relationship with survival outcome (P<0.01, P=0.04).Synuclein-γ(score = 0 versus >0) and GLUT-1 (score ≤7 versus =8) did not show any differences in survival rate (P=0.54, P=0.48).

Conclusion: In this study, the expression of synuclein-γ and GLUT-1 was not a prognostic factor but the role of ER and PR as prognostic factors was reconfirmed. MMP-9 was considered to be an important factors but MMP-2 was less related with tumor progression of endometrioid endometrial carcinoma.
THE INCIDENCE OF PARAAORTIC LYMPH NODE METASTASIS IN PATIENTS WITH SURGICALLY STAGED ENDOMETRIOID UTERINE CANCER: A MULTICENTER, RETROSPECTIVE KOREAN STUDY

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Aim: To describe the incidence of paraaortic lymph node metastasis (PALNM) in patients with surgically staged endometrioid uterine cancer.

Methods: We retrospectively reviewed the medical records and pathological findings of histologically proven endometrioid uterine cancer patients who underwent surgical staging including both pelvic and paraaortic lymphadnectomy, and the removal of at least ten pelvic nodes from 2000 to 2006 in Korea.

Results: Of 685 surgically staged endometrioid uterine cancers, 283 patients both pelvic and paraaortic nodes retrieved during surgery and identified by pathology. The incidence of overall lymph node metastasis was 17.7% (50 women) and 30 (10.6%) women had at least positive paraaortic lymph nodes. Twenty-six (56.5%) of pelvic node-positive women had also PALNM. Only 4 (1.7%) women had positive paraaortic nodes with negative pelvic node (isolated PALNM). Final grade for these cases were grade 1 of 3 women, and grade 3 of 1 woman. Multivariate logistic analysis identified that positive pelvic nodes (OR=31.4, 95% CI=7.0-141.8) and tumor grade (OR=5.2, 95% CI=1.0-25.5) were significant predictors of PALNM. The incidence of PALNM in relation to number of positive pelvic nodes was as follows: isolated PALNM 1.7% (4/237 women), 1 positive pelvic node 33.3% (4/12), 2 positive pelvic nodes 50.0% (6/12), and 3 positive pelvic nodes or more 72.7% (16/22).

Conclusion: Even though positive pelvic node and tumor grade can predict PALNM, isolated PALNM occurs about 1.7% of surgically staged endometrioid uterine cancers in both a low and high grade tumor.
SIGNIFICANCE OF THE SUVMAX AND GLUT-1 EXPRESSION TO DETERMINE TUMOR AGGRESSIVENESS IN CLINICAL STAGE I ENDOMETRIAL CANCER

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Background: The objectives of this study were to evaluate the value of $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) for estimating tumor aggressiveness in endometrial cancer, and to evaluate correlation between aggressiveness and expression of glucose transporter-1 (GLUT-1).

Methods: $^{18}$F-FDG PET/CT was performed on 43 patients with clinical stage I endometrial cancer. $^{18}$F-fluorodeoxyglucose uptake was quantified by calculating the SUVmax and the GLUT-1 expression status obtained by immunohistochemistry.

Results: The mean SUVmax of the primary tumor in the 43 patients was 8.55±5.04. The mean SUVmax and GLUT-1 expression in stage IB and stage IC were significantly higher than those in stage IA (P=0.001; P=0.003). The mean SUVmax was 6.81±4.55 in grade 1, 10.92±4.61 in grade 2, and 15.35±1.34 in grade 3, respectively (Grade 1 vs grade 2 and 3; P=0.005). The mean GLUT-1 expression was 1.17±0.94 in grade 1, 2.00±0.94 in grade 2, and 3.00±0.00 in grade 3, respectively (Grade 1 vs grade 2 and 3; P=0.017).

Conclusions: The tumor aggressiveness, such as myometrial invasion or tumor grade, had a positive correlation with the SUVmax and GLUT-1 expression in clinical stage I endometroid type endometrial cancer.
Abstracts presented at the 13th Biennial Meeting of the International Gynecologic Cancer Society

FERTILITY CONSERVATION IN A WOMAN WITH A UTERINE ADENOSARCOMA

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Background: Uterine adenosarcoma with sarcomatous overgrowth (ASSO) is a rare variant of uterine sarcoma. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is considered standard treatment. We present a reproductive-age woman with an ASSO, who was offered ovary-preserving surgical treatment.

Case: A 32-year-old nulliparous patient with metrorrhagia was diagnosed with an ASSO on histology following dilatation and curettage of the uterus. The tumour was confined to an endometrial polypoid mass; no evidence of disease was detected in the accompanying curettings. One month previously an open myomectomy led to benign histology. A hysteroscopy done prior to the hysterectomy failed to produce clinical or histological evidence of disease. Following a literature review the multi-disciplinary meeting decided for ovary-preserving surgery with adjuvant chemotherapy. A total hysterectomy with unilateral salpingo-oophorectomy followed. The patient underwent egg-collection and freezing before she had the operation and the chemotherapy. She is currently disease-free and clinically well 3 years post hysterectomy. She does not suffer from menopausal-type symptoms. She has not used her frozen eggs yet.

Conclusion: Diagnosis and management of uterine adenosarcomas especially in fertility-wishing patients can be challenging. The scarcity of literature on the fertility-sparing surgical management of these tumours allows the clinicians to offer complex management options.
IMPACT OF TUMOR MORCELLATION DURING SURGERY ON THE OUTCOMES OF PATIENTS WITH UTERINE LEIOMYOSARCOMA


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Objective: The aim of this study was to analyze the impact of tumor morcellation on the outcomes of patients with uterine leiomyosarcoma.

Methods: A total of 64 patients with uterine leiomyosarcoma were included in this retrospective analysis. The outcomes were compared between patients who underwent upfront total abdominal hysterectomy without tumor morcellation (Group A, n=43) and who underwent surgical management including tumor morcellation (Group B, n=21).

Results: There were no differences in age, parity, body mass index, tumor size and FIGO stage between the two groups. In group B, 4 patients underwent myomectomy, 1 patient underwent vaginal hysterectomy, and 16 patients underwent laparoscopic-assisted vaginal hysterectomy as a first operation. Of them, 4 patients underwent second operation. There was no difference in 5-year disease free survival rate (61% and 57%, P=0.809) and overall survival rate (60% and 69%, P=0.335). Patients in group A had peritoneal sarcomatosis more frequently at recurrence, whereas patients in Group B had distant metastasis more frequently at recurrence.

Conclusion: Tumor morcellation during surgery in patients with uterine leiomyosarcoma had little impact on survival outcomes. However, it was associated with peritoneal sarcomatosis more frequently at recurrence.
UTERINE MÜLLERIAN ADENOSARCOMA: THE CLINICOPATHOLOGIC REVIEW OF 9 CASES IN A SINGLE CENTER, KOREA

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Objectives: To analyze clinicopathologic features of uterine müllerian adenosarcoma(UMAS) which was very rare malignancy of uterus.

Methods: We, retrospectively, reviewed 9 patients with UMAS which were diagnosed at Asan Medical Center, Seoul, Korea from January 1998 to February 2010.

Results: Clinical characteristics of 9 patients were shown below.

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age(year)</th>
<th>Menopause</th>
<th>Initial Symptom-Impression</th>
<th>Initial CA-125</th>
<th>Operation</th>
<th>Stage</th>
<th>Adjuvant Treatment</th>
<th>Final Status(follow-up months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>no</td>
<td>Vaginal bleeding-Submucosal Myoma</td>
<td>11.3</td>
<td>TAH BSO omental biopsy</td>
<td>1A</td>
<td>none</td>
<td>NED(3months)</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>no</td>
<td>Vaginal spotting-Submucosal myoma</td>
<td>not checked</td>
<td>Hysteroscopic mass excision</td>
<td>1A</td>
<td>none</td>
<td>NED(11months)</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>no</td>
<td>none-Submucosal myoma</td>
<td>4.9</td>
<td>LAVH RSO PLND PALND</td>
<td>1A</td>
<td>ifosphamide cisplatin 4cycles</td>
<td>NED(19months)</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>no</td>
<td>none-endometrial polyp</td>
<td>4.6</td>
<td>LRH BSO PLND</td>
<td>1A</td>
<td>none</td>
<td>NED(42months)</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>yes</td>
<td>none-Submucosal myoma</td>
<td>9.2</td>
<td>TAH BSO PLND PALND</td>
<td>1A</td>
<td>5040cGy in whole pelvis</td>
<td>NED(51months)</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>no</td>
<td>Vaginal bleeding-Submucosal myoma</td>
<td>9.7</td>
<td>TAH BSO PLND</td>
<td>1A</td>
<td>none</td>
<td>NED(55months)</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>no</td>
<td>none-Submucosal myoma</td>
<td>2.9</td>
<td>LAVH</td>
<td>1A</td>
<td>Adriamycin cisplatin 3cycles</td>
<td>NED(131months)</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>no</td>
<td>Vaginal bleeding-Submucosal myoma</td>
<td>12.3</td>
<td>LAVH BSO PLND</td>
<td>2</td>
<td>none</td>
<td>NED(57months)</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>yes</td>
<td>none-Pelvic mass</td>
<td>25.7</td>
<td>mass excision. IVC RA thrombectomy</td>
<td>4</td>
<td>none</td>
<td>NED(&lt;1month)</td>
</tr>
</tbody>
</table>

After median follow-up of 42 months(range 1-131), no recurrence was occurred.

The pathologic results were as follows. The mean tumor size of the largest dimension was 8.52cm(range 0.8-14cm). Three patients had special pathologic features; endometrial stromal sarcoma component, focal sex-cord like elements, and sarcomatous overgrowth. Myometrial invasion were in two, cervical involvement in one. No one had lymphovascular involvement. The median value of mitosis was 3/HPF (range 0-7). All had mild pleomorphism.

Conclusion: Irrespective of adjuvant treatments, the prognosis of UMAS would be good after surgical treatment if tumor is confined to the uterus.
KI-67 AS A STRONG PROGNOSTIC INDICATOR IN ENDOMETRIAL STROMAL SARCOMA

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Background: To search potential molecular therapeutic target and molecular prognostic marker in patients with endometrial stromal sarcoma (ESS).

Methods: Using tissue microarray of 42 patients with ESS, immunohistochemical study was performed on estrogen receptor (ER), progesterone receptor (PR), C-kit, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), epidermal growth factor (EGFR), Her-2/neu, p53, p16 and ki-67. Clinicopathologic data of each patient was obtained from their medical records. Survival analysis was performed using Kaplan-Meier method and Cox’s regression model.

Results: The expression rate of ER, PR, C-kit, VEGFR, PDGFR, EGFR, Her-2/neu, p53, p16 and ki-67 in ESS was 66.7%, 84.4%, 77.8%, 26.7%, 100%, 0%, 0%, 13.3%, 44.4% and 53.4%, respectively. In univariate analysis, ER expression was associated with significantly longer recurrence free survival (DFS, 55% vs. 78%, P = 0.043) and overall survival (OS, 61% vs. 100%, P = 0.001), and ki-67 expression was strongly associated with significantly shorter RFS (89% vs. 50%, P = 0.002) and OS (100% vs. 76%, P = 0.016). In multivariate analysis, these were also strong indicators for prognosis.

Conclusion: The use of ki-67 as a prognostic indicator is strongly recommended. Besides ER and PR, further evaluation on the C-kit and PDGFR as a potential therapeutic target for ESS is suggested.
MORPHOLOGICAL, MOLECULAR AND GENETIC CHARACTERISTICS OF ENDOMETRIAL MALIGNANT TRANSFORMATION STAGES: ENDOMETRIAL HYPERPLASIA (EH), ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA (EIN), ENDOMETRIAL ADENOCARCINOMA (EAC)

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The aim of the study was to investigate morphological, molecular and genetic characteristics of different stages of endometrial malignant transformation.

The study was performed on endometrial samples obtained via D&C from 17 women of reproductive age with combination of changes in samples: 5 foci of simple EH, 5 foci of complex EH without atypia and 5 of complex EH with atypia, 3 foci with EIN and 3 samples of EAC. Immunohistochemical analysis was performed on serial paraffin sections with monoclonal antibodies PTEN, Ki-67, EGFR (Lab Vision) and FISH analysis was made with HER2/CEP17 probe (Zytovision, Zytolight SPEC HER2/CEP17 dual color probe).

Immunohistochemical analysis revealed gradual loss of PTEN in the sequence simple EH-complex EH without and with atypia-EIN-EAC. Cases with atypical complex EH showed clones of cells both PTEN positive and negative, whereas in EIN and EAC PTEN negative clone was predominant. Ki-67 expression was significantly higher in normal proliferative endometrium (62%) compared to EH with and without atypia (respectively 34% and 38%). EGFR was low in all types of EH and appeared only in EIN and EAC. FISH analysis indicated absence of amplification both HER2 and CEP17.

Conclusion: Endometrial malignant transformation is characterized by gradual changes in cell clones positive and negative for PTEN. Thus at the stage of complex EH with atypia and even in well differentiated EAC policlonality of cells is preserved. Obtained results show that Ki67, EGFR and HER2/CEP17 can't be used as single markers for differential diagnosis of EH, EIN and EAC.
CHARACTERISTICS AND SURVIVALS OF ENDOMETRIAL CANCER PATIENTS ACCORDING TO THE PRIOR 1988 AND THE NEW 2009 FIGO STAGING SYSTEMS

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Aims: To compare characteristics and survivals of endometrial cancer (EMC) patients according to prior FIGO 1988 and current 2009 staging.

Methods: Clinico-pathological data of EMC patients who had primary surgical treatment from 1992 to 2008 were collected. The new applied and prior assigned FIGO staging were compared. Survivals of patients according to prior and new staging were compared.

Results: Data from 261 patients was reviewed. Mean age was 55.4 ± 9.9 years. Radiation was the most common adjuvant therapy after surgery, 92/103 patients (35.5%). Progression and recurrences occurred in 34 patients (17 for each event) while 47 died (18.1%). Comparing the prior and current staging, early stage I-II was commonly found in both systems. Stages were the same in 82 patients (31.7%), lower in 176 (68%), and higher in one (0.4%). After a median follow-up of 57.5 months, 5-year progression-free, cancer-specific and overall survivals according to the prior and new systems were similar in stage III-IV. Survivals of the new stage I A (from 16-prior stage IA, 124-IB, 12-IIA, and 1-IIIA) and stage IB (from 31-IC and 8-IIA) were worse than those of prior stage IA or IB. Survivals of the new stage II patients (11-IIB) were the same as prior stage IIB.

Conclusions: The “new” FIGO staging system for endometrial cancer in Thai patients treated at a large academic urban medical center resulted in lower stage in a large number of patients. Survival trends were worse in the new stage I and remained similar in the other stages.
CLAUDIN LOSS FROM THE SITE OF TIGHT JUNCTIONS IN ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA AND ENDOMETRIAL ADENOCARCINOMA

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Claudines are the major tight junction components and they may reflect the cells' proliferation and differentiation ability. They are localized in cell membrane where they are involved in tight junction constitution.

The aim of the study was to investigate tight junctions in endometrial intraepithelial neoplasia (EIN) and endometrial adenocarcinoma (EAC) based on immunohistochemic claudin detection.

Materials and methods: The study was performed on endometrial samples obtained via D&C of 17 women. Morphological and immunohistochemical analysis was performed on serial paraffin sections with monoclonal antibodies PTEN, Ki-67, Claudine 3 and 5 (Lab Vision).

Morphological analysis of 17 women revealed combination of changes in samples: 5 foci of simple endometrial hyperplasia, 5 foci of complex endometrial hyperplasia without atypia and 5 of complex endometrial hyperplasia with atypia, 3 foci with EIN and 3 samples of EAC. The diagnosis of EIN was made based on abundance of parenchyma and lack of stroma (more than 50 %) and presence of atypical cells and immunohistochemical loss of PTEN. Immunohistochemical analysis showed significant decrease of membrane localization of claudin expression in tight junction sites in endometrial complex hyperplasia with severe atypia and nearly full absence in EIN and EAC to high claudine expression in cell membranes in simple endometrial hyperplasia and complex endometrial hyperplasia without atypia.

Conclusion: Obtained data indicate claudine loss from tight junction sites in sequence of endometrial malignant transformation. Thus claudine loss in membrane may be suggested to be early predictor of EIN and EAC.
CLINICO-PATHOLOGICAL INCLUDING HORMONAL RECEPTORS EXPRESSION AND SURVIVALS OF YOUNG ENDOMETRIAL CARCINOMA PATIENTS: A CASE CONTROL STUDY

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Objective: To compare clinico-pathological features including hormonal receptors and survivals of young endometrial carcinoma (EMC) patients with older patients.

Methods: Young EMC patients aged < 45 years treated in the institution from 1992 to 2008 were identified as cases. Controls were patients aged > 45 years who had operation on the nearest dates of the cases with a 3:1 ratio. Clinico-pathological data and survivals of case and control were compared.

Results: Mean ages of 41 cases and 123 controls were 40.4 ± 3.7 years and 58.4 ± 8.3 years, respectively. Cases were significantly different from controls in terms of: nulliparous (58% vs 25%), low grade tumors (49% vs 14%), positive PR expression (93% vs 61%), less medical illnesses (57% vs 74%) and nodal metastases (3% vs 21%) and marginal significant for early stages (90% vs 75%) and endometrioid histopatholgy (100% vs 91%). Adjuvant therapy was given in 29% of cases and 46% of controls. From a median follow up of 51 months, cases had significantly lesser events of progression and recurrences (5% vs 19%), cancer-related deaths (2% vs 16%), and all deaths (5% vs 23%) with significantly longer 5-year disease-free, cancer-specific and overall survivals than controls by univariable analysis: 97.2% vs 79.6% (p= 0.023); 97.1% vs 83.2% (p=0.020); and 93.1% vs 78.8% (p= 0.005). Stage, histopathology, hormonal receptors, and Her2/ neu were significant prognostic factors by multivariable analyses.

Conclusions: Young Thai EMC patients had more favorable clinico-pathologic features than older patients, with significantly longer survivals by univariable analysis.
HIGH BMI IS SIGNIFICANTLY ASSOCIATED WITH POSITIVE PROGESTERONE RECEPTOR STATUS AND CLINICO-PATHOLOGIC MARKERS FOR NON-AGGRESSIVE DISEASE IN ENDOMETRIAL CANCER

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Introduction: Endometrial cancer incidence is increasing in industrialized countries. High body mass index (BMI, kg/m²) is known to increase the risk for disease. We wanted to investigate if BMI is related to clinical phenotype, receptor status in primary tumor and disease outcome in endometrial cancer.

Materials and methods: BMI was calculated for 989 patients treated for endometrial carcinoma at Haukeland University Hospital during 1981-2009. Comprehensive clinical and histopathological data, treatment, and complete follow-up were collected. Estrogen- and progesterone receptor status (ER and PR) was assessed by immunohistochemistry (n=440) and qPCR in fresh tumors (n=151). Associations were assessed by Pearson Chi-square and Mann-Whitney tests, and Kaplan-Meier- and Cox’ analyses for survival estimation (SPSS 17.0).

Results: High BMI was associated with low FIGO stages (p< 0.001), endometrioid histology (p=0.01), low/intermediate grade (p=0.02), and high expression of PR estimated by immunohistochemistry (p=0.009) and qPCR (p=0.01). ER status was not related to BMI. Univariate survival analysis for postmenopausal women identified a 5% higher disease specific 5-year survival rate for women with high BMI (BMI ≥ median value of 26.3) compared to women with BMI < median value (p=0.067, borderline significance). Cox multivariate analysis showed no independent prognostic impact of BMI.

Conclusion: High BMI was significantly correlated with markers for non-aggressive disease and positive PR status in endometrial carcinoma. Postmenopausal women with high BMI showed a tendency to better prognosis, but this effect disappeared in multivariate analysis. The role of PR in endometrial carcinogenesis in obese women needs to be further studied.
PROGNOSTIC INDICATORS IN ENDOMETRIAL STROMAL SARCOMAS AND UNDIFFERENTIATED ENDOMETRIAL SARCOMAS

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Background: Endometrial stromal sarcomas (ESS) have been traditionally divided into low/high grade but the World Health Organization (WHO2003) has changed the definition. Since 2003, many studies still used the old criteria and few focused on WHO2003-defined ESS low grade (ESS-LG) and undifferentiated endometrial sarcomas (UES).

Patients and methods: We reviewed in 91 tumors (previously classified as ESS low and high grade) the diagnostic WHO2003 criteria, CD10 positivity and JAZF1/JAZZ fluorescence in situ hybridisation. In the ESS-LGs, the prognostic value of clinico-pathological features were studied.

Results: There were 68 ESS-LGs and 23 UES with median follow-up of 79 (range: 20-474) and 36 (5-329) months. The recurrence and death rates were 5/68 (7%) and 1/68 (1.5%) in the ESS-LG and in the UES patients 13/23 (57%) and 12/23 (52%) (P < 0.0001, Hazard Ratio=HR=10.5 for recurrence; P < 0.0001, HR=45.3 for death). In the ESS-LG, ovary saving-surgery-or-not (P < 0.0001, HR=10.4) and MAI (0-3 versus >3, P=0.005, HR=8.6) had independent prognostic value. Other frequently used MAI thresholds, age, stage, tumor diameter and vessel invasion were not prognostic. In patients without ovary-saving operation (n=61), 0/53 with MAI 0-3 recurred, contrasting 2/8 (25%) with MAI>3 (P=0.003) and 1 of these 2 recurrence patients died (P=0.02). In patients with ovary saving (n=7), 3 (43%) recurred but none died and MAI had no additional prognostic value.

Conclusion: The WHO-2003 criteria for ESS-LG and UES are prognostically strong. In ESS-low grade, ovary-saving operation and mitotic activity >3 are associated with increased recurrence risk.
PROGNOSTIC FACTORS AND TREATMENT OUTCOMES IN PATIENTS WITH OPERATED ENDOMETRIAL CANCER: ANALYSIS OF 674 PATIENTS AT A SINGLE INSTITUTION

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Background: Endometrial carcinoma is the most prevalent gynecologic tumor in developed countries. The aim of the present study was to evaluate the clinical characteristics of the patients with endometrial cancer.

Methods: Six hundred and seventy four patients, who had received post-operative therapy were retrospectively investigated. Of the cases, 186 were only monitored, whereas 43 received intracavitary radiotherapy (ICRT) and 54 received external radiotherapy (ERT). Two hundred fifty nine patients received both external and internal radiotherapy (RT). Eight patients received chemotherapy (CT), whereas 24 patients received both CT and RT.

Results: Statistical analyses revealed that age, menopausal status, tumor histology, stage, grade, tumor diameter, myometrial invasion, lymphovascular space invasion (LVI), positive abdominal fluid for tumor cells, omental involvement, adnexal involvement and the type of the therapy significantly affected both the overall survival (OS) and disease-free survival (DFS). Survival was poor in the patients over 60 years of age, who had advanced tumor higher than stage 2a and more differentiated than grade II and who had myometrial invasion larger than 50%.

Conclusion: Age is the most important factor associated with local relapse while survival was affected by age, grade, myometrial invasion and stage in operated endometrial cancer.
PROGNOSIS OF INTERMEDIATE- OR HIGH-RISK STAGE I ENDOMETRIOID CARCINOMA WITH MODIFIED RADICAL HYSTEROECTOMY

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Background: Studies have suggested that postoperative external-beam pelvic radiotherapy and/or vaginal brachytherapy significantly reduce the local-regional recurrence of stage I endometrial cancer, but morbidity with treatment is more common. Finding a treatment that can decrease the local-regional recurrence without significantly affecting survival and therapy-associated complications is urgent.

Aims: To determine whether modified radical hysterectomy (MRH) could improve local-regional cancer control without incurring significant complications in patients with stage I endometrioid carcinoma.

Methods: We reviewed the medical records of patients with intermediate- or high-risk stage I endometrioid carcinoma (grade 1 with deep myometrial invasion, grade 2/3 with any invasion) underwent MRH at Fudan University Shanghai Cancer Center between 1996 and 2008. The Kaplan-Meier method was used to time-to-event analyses, with recurrence and death as end points.

Results: A total of 246 women with intermediate- or high-risk stage I endometrioid carcinoma underwent MRH + bilateral salpingo-oophorectomy + peritoneal cytology ± pelvic and/or para-aortic lymphadenectomy. Forty-six patients (18.7%) received postoperative adjuvant therapy (external-beam pelvic radiotherapy or chemotherapy, or both). After a median follow-up of 26 months (3-149 months), 10 cases relapses were observed. The 3- and 5-year cumulative local-regional recurrence rates were 1.2% and 2.5%, respectively. The 5-year overall survival rate was 97.2%. Surgical-associated morbidity was 8.5%.

Conclusions: The results compared favorably with other results of postoperative adjuvant therapy. MRH is a viable and perhaps preferable option for patients with intermediate- or high-risk stage I endometrioid carcinoma. Randomized clinical trials are urgently needed to address the utility of MRH in this situation.
OVARIAN PRESERVATION IN YOUNG PATIENTS WITH EARLY STAGE ENDOMETRIAL CARCINOMA

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Background and aims: Ovarian preservation in young patients with endometrial cancer is highly controversial. The purpose of this study was to determine the frequency and risk factors of ovarian metastasis and to assess the feasibility of ovarian preservation in young patients with early stage endometrial carcinoma.

Methods: Clinical and pathological data of 991 patients with endometrial carcinoma surgically treated in our hospital from 1996 to 2007 were retrospectively reviewed. Follow-up information of patients with ovarian preservation was obtained.

Results: Ovarian metastasis was detected in 76 (7.67%) of 991 patients who underwent primary surgical treatment. The independent risk factors of ovarian metastasis were non-endometrioid histology, lymph node metastasis, and deep myometrial invasion. No ovarian metastasis was found in patients under the age of 45 with no known risk factors. One or bilateral ovaries were selectively preserved in 25 patients (age range 22-42 years). All the patients with ovarian preservation were stage I A with grade 1 or grade 2 endometrioid histology. A thorough surgical staging including hysterectomy, pelvic lymphadenectomy, peritoneal washings and biopsy of the ovaries was conducted to confirm the absence of known risk factors in all the patients with ovarian preservation. The follow-up was 27 to 144 months. All the patients with ovarian preservation were living with no recurrence.

Conclusions: Hysterectomy with ovarian preservation could be the treatment of choice for young patients with early stage endometrial carcinoma if a thorough surgical staging is conducted with the confirmation of the absence of predictable risk factors. Close follow-up is essential.
LYMPHADENECTOMY VERSUS NO LYMPHADENECTOMY IN ENDOMETRIAL CARCINOMA: A RETROSPECTIVE ANALYSIS OF 410 PATIENTS


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Objective: Pelvic lymph nodes are the most common site of extraperitoneal spread in clinical early-stage endometrial cancer. International Federation of Gynecology and Obstetrics has mandated surgical evaluation of lymph nodes in endometrial cancer since 1988; however, the clinical impact of lymphadenectomy has never been addressed.

Design: We reported a retrospective analysis in order to evaluate whether pelvic systematic lymph dissection improves overall and progression-free survival compared with no lymphadenectomy.

Method: From 1991 through 2008, patients with endometrial carcinoma were evaluated using a log-rank statistic and a Cox multivariable regression analysis. All statistical tests were two-sided.

Results: Of the 410 patients with a diagnosis of endometrial carcinoma, 390 underwent primary surgery. Of those who underwent surgery, 285 had endometrioid histology. One hundred and ninety (190) patients had surgery with no lymphadenectomy, whereas 95 had surgery with lymphadenectomy. Only 4 women revealed positive nodes. Median number of removed nodes was 14 in the lymphadenectomy group. The 5-year survival rate of 90% and 86% was achieved, respectively, for lymphadenectomy and no lymphadenectomy ( p=0.501).

Conclusions: Although systematic pelvic lymphadenectomy significantly improved surgical staging of women with clinical early-stage endometrial carcinoma by detecting a higher rate of patients with positive nodes, it did not improve overall survival.
NON Puerperal UTERINE INVERSION SECONDARY TO A MIXED MULLERIAN TUMOUR OF THE CORPUS

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Inversion of the uterus was not well understood before the time of Hippocrates (460-370 BC). There are descriptions of such a condition in the Hindu system of medicine (2500-2600 BC), and passages in literature to support this. Inversion of the uterus is a rare clinical problem, most often encountered as an obstetric emergency during the puerperium. Non-puerperal uterine inversion is a diagnostic challenge where accurate diagnosis is essential before treatment. This clinical condition is a rare occurrence in gynaecology and is so infrequent that its incidence has not been estimated in literature. It has been mainly associated with benign tumours of the uterus such as submucosal fibroids, with uterine sarcomas and endometrial carcinomas being the least common causes of uterine inversion. We report a case of a post menopausal woman who presented with a non puerperal uterine inversion secondary to a malignant mixed mullerian tumour associated with a heterologous component of rhabdomyosarcoma.
PHOTODYNAMIC DIAGNOSTICS OF A PATHOLOGY ENDOMETRIUM AFTER INTRAUTERINE APPLICATION OF 5-AMINOLEVULINIC ACID

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Objectives: Now one of the most actual problems in oncogynecology is revealing tumours at early stages of development.

In fluorescence diagnosis 5- aminolevulinic acid (5-ALA), a stimulator for the production of cellular protoporphyrin IX (PPIX), was used for the detection of tumour lesions of microscopical dimensions.

Study design/patients and methods: 101 patients: was spending fluorescence hysteroscopy. Ten milliliter of a 3% 5-ALA - solution at PH = 4.0 was instilled into the uterine cavity of 101 women before hysteroscopy. The fluorescence induced was measured by fluorescence hysteroscopy: STORZ-D-LIGHT system (STORZ, Germany) after 2 hours instillation. It was made targeted biopsies from places of a fluorescence endometrium.

Results: Comparison of fluorescence and morphological research has revealed a true fluorescence endometrial at patients 21 atypical hyperplasia, 61 - endometrial adenocarcinoma. At 19 patients it is noted fluorescence endometrial and polyp endometrial is diagnosed.

Conclusion: The given method allows reveal not only poorly appreciable at traditional hysteroscopy research the centers of a cancer endometrial but also the latent microscopic tumoral centers (up to 1 mm) on sites, it would seem not changed mucous to specify their topography and to receive targeted biopsies from these places.

Researches in the given direction proceed.
ASSESSMENT OF MYOMETRIAL INVASION, HISTOLOGIC TYPE AND GRADING IN ENDOMETRIAL CANCER BY TRANSVAGINAL ULTRASOUND AND PREOPERATIVE SAMPLING. A MULTICENTER STUDY

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Objective: Preoperative knowledge of myometrial infiltration and histopathological parameters is frequently used to direct different treatment interventions in patients with early endometrial cancer. We aimed to assess the value of preoperative histopathological parameters obtained from an endometrial sampling, and the value of transvaginal ultrasound (TVU) in the preoperative prediction of myometrial invasion.

Methods: In this prospective multicenter study, we collected histopathological data and ultrasound from 367 consecutive women with endometrial cancer, coming from 25 different centers. TVU was performed by the team of gynecologists sonologists in every hospital, using FIGO stage I categories (less than 50%, more than 50%). The preoperative data were correlated to postoperative results.

Results: A total of 293 patients had both a preoperative biopsy and postoperative histological assessment. Only 172 (58%) cases showed concordance between preoperative and final histological grade, 85 (20%) cases were upgraded to a higher grade or were diagnosed as rare histologic type. A total of 340 patients had both preoperative and postoperative infiltration assessment. 215 patients had prediction of infiltration ≤50%, 48 of them had infiltration >50% on final evaluation (positive predictive value 77.7%); 125 patients had prediction of infiltration >50%, 55 of them had infiltration ≤50% on final evaluation (positive predictive value 56%).

Conclusions: Preoperative tumor grade and type don't accurately predict final histologic result. The accuracy of TVU in detecting myometrial invasion in our multicenter experience, is similar to the one observed in several monocenter studies in literature. TVU seems to be a simple, fast, reliable and reproducible technique.
A CASE REPORT OF PELVIC LIPOSARCOMA IN A WOMAN PREVIOUSLY TREATED WITH HYSTERECTOMY


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Uterine liposarcoma is a rare neoplasm generally encountered in the sixth decade of life and belongs to the group of mesenchymal tumours. It is usually a relatively well-circumscribed, inhomogeneous, soft-tissue mass that contains a variable amount of fat. A mass that is predominantly solid with one or more focal lipomatous regions is most likely a lipomatous uterine tumor. The presence of an invasive lipogenic component identifies an otherwise nonspecific lipomatous pelvic mass as a liposarcoma.

We reported a 53 year-old woman who received a wide excisional surgery and adjuvant chemotherapy for a skin melanoma in 1999. In 2003 she had a subtotal abdominal hysterectomy and bilateral ovariectomy for uterine fibromatosis and then, in 2007, she removed a lipoma at the right thigh. On February 2010 due to the presence of pain in the right lower abdomen, she was referred to our Institution. A CT scan of the abdomen and pelvis demonstrated a well-encapsulated mass in which was a predominant density of fat. Pelvic ultrasound showed a 8 cm solid mass with irregular walls, inhomogeneous echostructure with a poorly defined echogenicity and anaechoic areas. All the mass had a poorly vascularised and was situated close but without infiltration to the right iliac vessels. She underwent a laparotomy with removal of the mass and histological examination revealed a uterine liposarcoma.

This case shows an extremely rare occurrence of uterine liposarcoma and it would like to remind that also in patients who had a previous hysterectomy this disease can be found.
IMPORTANCE OF OPTIMAL CYTOREDUCTION IN ADVANCED STAGE ENDOMETRIAL CANCER CASES

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Aim: The management of advanced stages of endometrial cancer remains controversial. This study was aimed to analyse the treatment results of stage III-IV endometrial cancer cases.

Methods: A total of 67 patients with stage 3-4 endometrial cancer which were treated with primary surgery were evaluated in this retrospective analyze. Overall survival (OS) and progression-free survival (PFS) according to clinical, surgical and histopathologic features were evaluated.

Results: Estimated mean OS and PFS were 59 and 55 months, respectively, for the entire group. Optimal cytoreduction (OCR), described as removing all macroscopic disease was the most important prognostic factor for survival rates. Estimated mean OS in patients with OCR was 63 months while 15 months in patients without OCR (p< 0.001). Hormone therapy, chemotherapy, radiotherapy or their various combinations in adjuvant treatment did not affect survival. Local and distant recurrences occurred with the similar rates and recurrence localizations were not affected from adjuvant treatment modalities. Cervical involvement, paraaortic lymph node involvement and no pregnancy history had worse survival effect.

Conclusions: To improve survival in advanced endometrial cancer cases, all macroscopic disease should be resected. Type of adjuvant therapy has not altered survival rates.
IMMUNOHISTOCHEMICAL MARKERS IN ENDOMETRIAL HYPERPLASIA AND ENDOMETRIOID CARCINOMA

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The aim was to analyze the immunological-histochemical pattern in normal, hyperplastic and neoplastic endometrium in order to improve the daily used diagnostic methods.

Materials and methods: 421 women with histologically confirmed diagnosis of endometrial hyperplasia (EH) and endometrioid carcinoma treated between 2007 and 2009 at the Gynecological Department, Riga Hospital No.1 Latvia were used in this study. Immunhistochemical reactions for evaluation of cell proliferation (Ki-67), apoptosis (M30) and tumor suppression (PTEN protein expression) were performed at paraffin embedded curettage endometrial tissue samples.

Results: In case of simple EH the proliferative endometrium showed variation of M30 expression from 13.8 ± 2.15 to 14.8 ± 1.36 cells/field of vision, but in cases of atypia this expression decreased and revealed variation from 6.2 ± 0.57 to 8.9 ± 1.96 cells/field of vision. The lowest M30 expression was observed in case of adenocarcinoma (1.6 ± 0.65 cells/field of vision. Additionally performed TUNEL confirmed the same tendency.

There were 978, 968 and 918 PTEN-positive cells per 1000 glandular epithelial cells in case of simple EH, EH with atypia and endometrioid carcinoma, respectively.

Conclusions: There was immunohistochemically confirmed reduction of apoptotic (using M 30 and TUNEL markers) and cell proliferation rates along with an elevation of severity of atypical endometrial lesions. PTEN protein expression was higher in simple EH comparing with atypical hyperplasia and endometrioid carcinoma. Immunohistochemically detected markers are of a greater value comparing with standard histopathological findings used for estimation of endometrial lesions.
THE PREVALENCE OF THE UTERINE CANCER IN POST MENOPAUSAL PERIOD

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Aims: Prevalence of the types of uterine cancer concerning the women in post menopausal period.


Results: The study included a number of 55 patients diagnosed with uterine cancer: 36 (65.45%) cervical cancer and 19 (34.54%) endometrial cancer and uterine sarcoma. Histopathological exam find that there were 24 cases (43.63%) diagnosed with adenocarcinoma, 23 cases (41.81%) with epidermoid squamous carcinoma, 1 case (1.81%) with papillary carcinoma, 1 (1.81%) with sarcoma and 6 (10.9%) with other histopathological forms.

The patients investigated in our clinic were between 51 and 85 years old, each clinical form of uterine cancer having a peak of incidence (6\(^{th}\) decade for the endocervical form and 7\(^{th}\) decade for the endometrial one). The staging of the uterine cancer in the moment of the diagnosis revealed a number of 11 cases (20%) in stage I, 25 cases (45.45%) in stage II, 15 (27.27%) in stage III and 4 (7.27%) in stage IV.

Conclusions: The increasing prevalence of the uterine cancer and the fact that it is diagnosed until extreme ages and many times in advanced stages should determine us to adopt new strategies of investigation and follow-up for the women in post menopausal period and treat it as a major medical problem.
OUTCOME OF INVESTIGATION FOR VAGINAL BLEEDING IN POSTMENOPAUSAL WOMEN UNDER THE AGE OF 50 YEARS

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Aim: The aim the study was to evaluate the outcome of the investigation in postmenopausal women younger than 50 years presenting with vaginal bleeding.

Methods: This prospective cross sectional study conducted at a gynaecological oncology centre in the United Kingdom from 2006 to 2010, collected and analysed data regarding clinical characteristics of postmenopausal women under the age of 50 years presenting with vaginal bleeding.

Results: A total of 3895 postmenopausal women were investigated with vaginal bleeding during the study period. 228 (5.85%) women were younger than 50 years. In the group younger than 50 years, median age was 47 years (range: 35-49 and mean body mass index was 27.5 (range: 18-49). The incidence of diabetes was 2.6% and hypertension was 5.7%. 48 patients were using hormone replacement therapy preparations. 29 (12.71%) patients were diagnosed previously with breast carcinoma. 17 patients were receiving Tamoxifen at the time of referral (mean duration: 3 years; range 1-5). Mean endometrial thickness measurement of ultrasonography was 4.8 mm (range: 1.2-28). Atrophic endometrium was suggested by ultrasonography in 108 cases (47.3%). Further investigation showed benign endometrium in 108 cases (47.3%), benign polyps in 3 cases (1.3%), endometrial hyperplasia in 4 cases (1.7%), and endometritis in one case (0.4%). No cases of endometrial cancer were diagnosed.

Conclusions: Our results show that no cases of endometrial cancer are diagnosed in women younger than 50 years presenting with postmenopausal vaginal bleeding. We recommend that investigation should still take place in this group, however not necessarily on an urgent basis.
FAILURE TO PERFORM AN OFFICE-BASED ENDOMETRIAL BIOPSY FOR THE EVALUATION OF POSTMENOPAUSAL WOMEN WITH VAGINAL BLEEDING - CAUSES AND MANAGEMENT

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Aim: The aim of this study is to identify the failure rate to perform an outpatient endometrial biopsy in women with postmenopausal vaginal bleeding, to determine the causes for failure and analyse the outcome of subsequent investigations.

Methods: This prospective study was conducted at a gynaecological oncology centre in the United Kingdom. Women presenting with postmenopausal vaginal bleeding were evaluated using transvaginal ultrasound. When endometrial thickness measured equal to or greater than 5 mm, an endometrial biopsy using a Pipelle device was performed.

Results: 486 women were seen reviewed in the clinic during the study period. The overall incidence of endometrial cancer was 7.6%. In 225 (46.3%) women, endometrial thickness was either not visualised or measured greater than 5 mm and a Pipelle biopsy was attempted. Biopsy was not possible in 45 (20%) women. Causes for failure to perform the outpatient endometrial biopsy were: cervical stenosis (20 women), discomfort during the examination (2 women) or difficult examination (10 women). In 11 cases the ultrasound appearance was suggestive of an endometrial polyp and women were referred for hysteroscopy. When a Pipelle biopsy was not performed, subsequent hysteroscopy revealed: 16 (35.5%) cases of benign endometrial polyps, 15 (33.3%) cases of endometrial cancer, 13 (28.8%) cases of benign endometrium and 1 (2.2%) case of complex atypical hyperplasia.

Conclusion: We observed a significantly higher (P=0.0001) incidence of endometrial cancer in the group of women where the attempt to perform an outpatient endometrial biopsy failed. Further evaluation by hysteroscopy should always be performed.
POSTMENOPAUSAL VAGINAL BLEEDING IN WOMEN WITH HISTORY OF BREAST CANCER

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Aim: The objective of this study is to assess if a history of breast cancer increases the risk of developing endometrial cancer in postmenopausal women presenting with vaginal bleeding.

Methods: This prospective cross-sectional study conducted over a 4-year period in a gynaecological oncology centre in the United Kingdom analysed the outcome of the investigation for postmenopausal bleeding in women with a history of breast cancer.

Results: Of a total of 3895 women investigated for postmenopausal vaginal bleeding, 258 (6.6%) were previously diagnosed with breast cancer. The median age in the group of women with history of breast cancer was 60.5 years (range: 35-97) and the median body mass index was 27 (range: 14-50). Mean endometrial thickness measurement on transvaginal ultrasonography was 7.1 mm. 143 (55.4%) women were using Tamoxifen. Duration of Tamoxifen use varied from 1 to 11 years. Investigation showed 167 (64.7%) cases of benign endometrium, 62 (24%) cases of benign endometrial polyps, 23 (8.9%) cases of endometrial cancer, 4 (1.5%) cases of endometrial hyperplasia and 1 (0.4%) case of bladder cancer. The incidence of endometrial cancer in women using Tamoxifen was 7.8% and in the group that did not use Tamoxifen was 10.2%. The incidence of endometrial cancer in the group of women without a history of breast cancer was 4.9%.

Conclusion: A history of breast cancer increases the incidence of endometrial cancer in postmenopausal women presenting with vaginal bleeding regardless of the use of Tamoxifen.
BENIGN METASTASIZING LEIOMYOMA. SHOULD IT REALLY BE CONSIDERED AS BENIGN? A CASE REPORT

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Background: Uterine leiomyomas are the most common benign gynecological tumors affecting at least 25% of premenopausal women. Occasionally they may appear in any smooth muscle organ creating an extraterine tumor of no or low malignant potency. The pathogenesis of benign metastasizing leiomyomas (BML) is not clear though some reports suggest its similarity to endometriosis spread. They may appear as genitourinary tract tumors, distant metastases (e.g. lung or stomach) or disseminated peritoneal and intravenous leiomyomatosis. Nevertheless BML is recurrent, locally aggressive and devastating disease so the patients do not consider this as benign.

Case report: In the spread of six years a 40-year-old patient has been operated six times on recurrent BML. The sites of BML included the bladder, urether, lung, vaginal vault after hysterectomy and retroperitoneal pelvic tumor. All those tumors were resected and TAH/BSO was performed. The pathology report diagnosed BML with the presence of estrogen and progestin receptors. Hormonal therapy was then introduced with GNRH analogues which was not sufficient to stop metastasizing as it caused the need for the resection of the retroperitoneal tumor. Although no malignant cells were recognized in any postoperative specimen we consider this case of BML as clinically aggressive as it led to hydronephrosis, subileus and premature menopausa.

Conclusions: BML is bizarre and rare disease which management is difficult and frequently unsuccessful. It often relapses and destroys the metastasizing organs so the question arises if it is still benign.
EARLY-ONSET ENDOMETRIAL CANCER IN METROPOLITAN DETROIT, MICHIGAN: A 20 YEAR REVIEW

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Background: Endometrial cancer, the most commonly diagnosed female cancer in the US, is primarily diagnosed in postmenopausal women; however, age at diagnosis is an important biological variable as it often impacts treatment.

Methods: Endometrial cancer cases were identified from the Metropolitan Detroit Cancer Surveillance System, between 1988 and 2007. Differences in tumor characteristics, treatment and survival were examined by age at diagnosis. Chi-square tests were used to assess differences in distribution of clinical and demographic variables. Cox proportional hazards models were used to assess the risk of death.

Results: 6,034 women diagnosed with endometrial cancer during this period, including 202 ages 20-39, 628 ages 40-49, and 5204 age 50+. 30% of women under the age of 40 were African American (AA), higher than expected given that 25% of the population in metro-Detroit is AA. Among young (< 40 yrs) AA women, 50% of the tumors were of non-endometrioid histology. Young women are more likely to present with stage I tumors, compared to patients ages 40-49 (p-value=0.01). 18% of young women did not receive surgery, compared to 7% of women ages 40-49 (p-value< 0.0001) and 12% of women over 50 (p-value=0.01). AA race is a negative predictor of survival for all patients, but particularly for those under 40 (HR=4.22, 95% CI: 1.87-9.52) compared to their white counterparts, after adjusting for other prognostic factors.

Conclusions: Race is an independent predictor of poor prognosis, particularly among young women. These results highlight the importance of examining early-onset endometrial cancer in multi-ethnic populations.
RELATIONSHIP OF PREOPERATIVE HIGH CA-125 LEVELS WITH CLINIC AND PATHOLOGIC PROGNOSTIC FACTORS IN ENDOMETRIUM CANCER

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Endometrium cancer is the most prevalent female genital cancer. In this study, the relationship of preoperative high CA-125 levels with clinic and pathologic prognostic factors in endometrium cancer cases were investigated.

The relationship between preoperative CA-125 levels and clinicopathologic parameters were investigated on 114 patients diagnosed as endometrium cancer and operated on between January 2006-June 2009 in Izmir Atatürk Training and Research Hospital 3rd Obstetrics and Gynecology Clinic. Average age, menopausal status, body mass index, endometrial thickness by transvaginal USG, preoperative CA-125 levels, tumor types, histologic grades, surgical-clinical stage, positive peritoneal fluid cytology, myometrium invasion and its degree, omentum metastasis and grades were evaluated. For CA-125, two cut of points were evaluated: 20 IU/mL and 35 IU/mL.

Both cut of points of CA-125 results (20 and 35 IU/mL ) of endometrium cancer patients were significantly associated with tumor grade , invasion to more than half of the myometrium, omentum metastasis, positive peritoneal fluid cytology and positive lymph nodes. In addition, pre- and post-menopausal status and other clinical parameters did not have a significant association with CA-125 levels.

For patients with endometrium cancer, preoperative CA-125 measurement (both cut points of 20 and 35) can be utilized as an important factor determining bad prognostic factors and extent of the disease. However, it is not suitable to be used as a sole prognostic factor.
DEMographic factors associated with stage at Presentation in endometrial cancer

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Introduction: The survival rate for endometrial cancer has increased steadily over the past two decades, however the main determinant of survival is stage at diagnosis. There is evidence from other cancer types that delay in diagnosis is associated with demographic factors, in particular older age, ethnicity and socio-economic status.

Methods: A review of all women undergoing surgery for endometrial cancer between 2007 and 2009. Stage of disease at presentation was analysed with respect to age at diagnosis, ethnicity, social deprivation scores and tumour histology.

Results: In total 359 were treated during the 3-year study period. The median age of the cohort was 67 years (range 38-93 years). Patient ethnicity was available in 297 cases, 18.2% of the patients were non-white. The majority of women were in the most socially deprived category (43.5%) and 58.2% of the tumours were endometrioid-type. Tumour type (endometrioid/non-endometrioid), ethnicity and social deprivation were not associated with stage at presentation. Women over the age of 70 were significantly more likely to present with advanced disease (stage 2\textsuperscript{+}) as compared to women under the age of 70 years in the endometrioid tumour group, 52.8\% versus 35.8\% (p=0.004). No difference between age and stage at presentation was seen in the non-endometrioid histology group (p=0.111). White ethnicity in the endometrioid group was significantly associated with advanced disease at presentation as compared to non-white ethnicity, 46.5\% versus 23.1\% (p=0.026).

Conclusions: Early stage at presentation in endometrioid endometrial cancers is associated with younger age and non-white ethnicity in our patient population.
COMPARISON OF THE SURGICAL AND PATHOLOGIC FACTORS OF ENDOMETRIAL CANCER PATIENTS WITH OR WITHOUT PARA-AORTIC LYMPH NODE METASTASES

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Introduction: To investigate the surgical and pathological risk factors of endometrial cancer patients with isolated pelvic lymph node (LN) metastases compared with patients with para-aortic +/- pelvic LN metastases.

Methods: The cases were staged according to the FIGO 1988. Forty-six patients underwent systematic bilateral pelvic and para-aortic lymphadenectomy up to left renal vein were enrolled. For inclusion in the study, patients had to have at least 10 LN removed from the para-aortic region and at least 15 LN removed from the pelvic region, or, if fewer than 10 were removed from the para-aortic region, metastases were found.

Results: The mean age of patients was 59.6. Forty cases had pelvic and 27 had para-aortic LN metastases. Nineteen cases had only pelvic, six had only para-aortic and 21 had pelvic and para-aortic LN metastases. The mean number of LN removed was 61.7. The surgical risk factors were similar between the groups, except the presence of lymphovascular space invasion (LVI). LVI was detected in 84.2% of cases with para-aortic LN metastases, but in only 50% of cases in which metastases were isolated pelvic LN metastasis (p= 0.035).

Discussion: The surgical and pathologic factors affecting prognosis didn't differ, except for LVI, in patients with para-aortic LN metastases compared with patients with isolated pelvic LN metastases.
A PROSPECTIVE CLINICO PATHOLOGICAL STUDY OF CARCINOMA ENDOMETRIUM

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Aims: To study the clinico-pathological profile of Ca. Endometrium with type of treatment modality and pattern of recurrence at one year follow up.

Material & methods: 110 cases of Ca. endometrium from Jan 2005 to Dec 2007 who presented at Mohan Dai Oswal Cancer Treatment & Research Foundation, Ludhiana were studied.

Results: The mean age at diagnosis was 55.8 years. 86% were post menopausal. 13.3% patients were nulliparous. 5.4 % (6) patients were known cases of Ca. breast on treatment with tamoxifen. Ultrasound scan was the radioimaging procedure in (76%). Endorette biopsy was used for endometrial sampling in 92 patients. D & C in 21 patients. Endometroid adenocarcinoma was the common histopathological type seen in 80% cases (88). Adenosquamous in 4, Clear cell carcinoma in 4. On final histopathological co-relation 75% patients showed same histology on specimen while histopathological differentiation was upgraded 8 cases and down graded in 11 patients.

On clinico-pathological staging majority of the patients were stage I- 76% with maximum in stage I B. Surgery was the primary modality of treatment in 106 patients. 4 patients underwent radiotherapy because of medical reasons and advance stage of disease. At 2 year follow up 94.5% patients were disease free. Distant recurrence occurred in 2 patients and loco regional recurrence in 4 patients. All the patient were alive at 1 year follow up.

Conclusion: Endometrial cancer is disease of post menopausal women. Early diagnosis is possible due to presence of symptoms with good long term results.
TISSUE AND PLASMA PROTEIN MARKER PATTERNS OF ENDOMETRIAL CANCER


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Endometrial cancer (EC) is the second spread cancer of women in Western Europe and Northern America. There is no screening developed for early detection of EC and its precursors.

Aim: To identify cancer-specific tissue and blood plasma marker protein patterns for objective diagnostics of early EC.

Clinical material: Blood plasma and tumor biopsies from EC patients, endometrium biopsies and plasma from non-cancer individuals.

Methods: 2-DE of tissue and low-abundant blood plasma proteins (AurumKit, BioRad), analysis of 2-DE by SameSpot, MALDI-TOF MS, measurement of DNA-ploidy, immunohistochemistry.

Results: 128 differentially expressed tissue proteins were identified. They are markers of malignant transformation, proteins that specifically differentiate genomically stable and unstable EC, proteins that differentiate EC and cervical cancer, and proteins that characterize non-malignant tissues. Among identified proteins are markers of prognostically unfavorable EC, and changes in their expression is detectable on the level of atypical hyperplasia of endometrium. By analysis of low-abundant blood plasma proteins 18 marker proteins of EC were identified, and by their different expression patterns EC can be detected and differentiated from cervical cancer.

Conclusions: Proteins differentially expressed in tissue of EC include patterns that are typical for genomically stable and unstable subtypes and changes in their expression are detectable in atypical hyperplasia of endometrium. EC can be detected and differentiated by blood plasma protein expression patterns.
OUTCOME OF PATIENTS WITH UTERINE SEROUS CARCINOMA (USC) USING THE REVISED FIGO STAGING SYSTEM

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Objective: Our aim was to evaluate the prognostic significance of the revised 2009 FIGO staging criteria in patients with USC.

Materials and methods: We retrieved clinical and histopathologic data on women with USC from two large academic centers. Age, race, stage, myometrial invasion, angiolymphatic invasion and adjuvant therapy were analyzed using Kaplan-Meier and Cox regression models.

Results: 161 patients were included. Three year survival was 82\% for revised stage I, 60\% for stage II, 41\% for stage III, and 16\% for stage IV. Survival was not significantly different comparing 1988 FIGO stage I or II to 2009 FIGO stage I or II. All 1988 FIGO stage III or IV patients maintained the same stage category using 2009 FIGO criteria. New FIGO stage, age, myometrial invasion, angiolymphatic invasion and administration of chemotherapy all remained independent predictors of survival on multivariate analysis (p< 0.05). Race was not a prognostic factor for either classification. Interestingly, out of 37 patients without myometrial invasion, 7 were found to have advanced surgical stage (III/IV).

Conclusions: In patients with USC, patients' survival was not changed using the 2009 FIGO staging system. The relatively high percentage of patients without myometrial involvement having advanced stage disease is concerning.
PATTERNS OF FAILURE IN STAGE III/IV UTERINE SEROUS CARCINOMA AFTER ADJUVANT RADIOTHERAPY AND CARBOPLATIN/PACLITAXEL CHEMOTHERAPY

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Purpose/objective(s): To evaluate patterns of failure and survival outcomes in women with Stage III/IV Uterine Serous Carcinoma (USC) treated with adjuvant chemotherapy and radiotherapy.

Materials/methods: A pooled analysis of 37 patients was identified following surgical staging between July 2002 and June 2009 at two institutions. Adjuvant therapy consisted of 6 cycles of carboplatin/paclitaxel chemotherapy, and involved field radiotherapy (45Gy) to the pelvis ± para-aortic (13 patients) ± HDR vault brachytherapy (32 patients).

Results: 29 patients had Stage III and 8 had Stage IV disease. 25 patients had LVSI, and 22 had pathologically positive nodes. Median follow-up after surgery was 31 months (6.7-88.3). 16 patients recurred (43%), the majority being extra-pelvic initial site (12/16). The median time to recurrence was 23.8 months (7.4-68.8). Distribution of the extra-pelvic failures included: carcinomatosis (5), nodal recurrence (3 retroperitoneal, 1 supraclavicular), hepatic (4), skeletal (2), and pulmonary (2); some patients had multiple initial sites of failure. Only 3 patients (8.1%) initially recurred within the pelvic radiation field. 3 patients with retroperitoneal nodal recurrences did not receive para-aortic radiation therapy. Median disease-free and overall survival was 62.3 months and 76.6 months, respectively.

Conclusions: Surgery and adjuvant radiotherapy resulted in favorable local control for this cohort of patients with advanced stage serous uterine cancer; however, a significant number of patients relapsed distantly, predominantly with carcinomatosis, retroperitoneal and hepatic metastasis. High rates of distant failure suggest a need for improved systemic therapy, while retroperitoneal nodal failures suggest a greater role for extended field radiotherapy.
PRESURGICAL STUDY AND LYMPHADENECTOMY IN ENDOMETRIAL CANCER SUBTYPE ENDOMETRIOID


Hospital Virgen del Camino, Pamplona, Spain

Aims: Analyze indications of lymphadenectomy in endometrial cancer subtype endometriod based on presurgical study

Methods: We make an study of 310 patients diagnosed and treated of endometrial cancer subtype endometriod in Virgen del Camino Hospital during the period 2004-2009. In 17 cases the nodes turned out to be positives, that is 5.48%. We make a descriptive analysis of characteristics of such patients respect of histological grade of biopsy and the percentage of tumoral infiltration based on the Nuclear Magnetic Resonance or in the intrasurgical anatomopathologic study.

Results: First of all we compare the histological grade of biopsy with tumoral infiltration based on the Nuclear Magnetic Resonance:

<table>
<thead>
<tr>
<th>Biopsy grade RMN Infiltration</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infiltration</td>
<td>1/85</td>
<td>0/16</td>
<td>0/15</td>
</tr>
<tr>
<td>Infiltration &lt;50%</td>
<td>1/33</td>
<td>0/16</td>
<td>1/5</td>
</tr>
<tr>
<td>Infiltration &gt;50%</td>
<td>3/62</td>
<td>2/44</td>
<td>7/20</td>
</tr>
</tbody>
</table>

[Biopsy grade. RMN Infiltration]

Secondly another comparation would be the histological grade of biopsy with tumoral infiltration based on intrasurgical anatomopathologic study:

<table>
<thead>
<tr>
<th>Biopsy grade AP Infiltration</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infiltration</td>
<td>0/38</td>
<td>0/13</td>
<td>0/3</td>
</tr>
<tr>
<td>Infiltration &lt;50%</td>
<td>2/99</td>
<td>0/29</td>
<td>1/15</td>
</tr>
<tr>
<td>Infiltration &gt;50%</td>
<td>3/31</td>
<td>2/28</td>
<td>5/11</td>
</tr>
</tbody>
</table>

[Biopsy grade. AP Infiltration]

Conclusions: We have probed that exist many patients with favourable presurgical prognosis factors (tumoral grade and miometrial infiltration) who have lymph node metastasis. So not doing the lymphadenectomy in these patients would affect to their diagnosis and treatment to increase the survival index.
DNA PLOIDY IN ENDOMETRIAL CARCINOMA - A COMPARISON OF PREOPERATIVE VS. POSTOPERATIVE AND PARAFFIN-EMBEDDED VS. FRESH/FROZEN SAMPLES EVALUATION

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¹Dept. of Gynaecology and Obstetrics, ²Dept. of Pathology, ³Dept. of Histology and Embryology, ⁴Dept. of Tumour Biology, ⁵Dept. of Oncology, 3rd Faculty of Medicine of Charles University, Prague, Czech Republic

Background: DNA ploidy is a strong independent prognostic factor in endometrial carcinoma patients. Although usually evaluated after surgical treatment, it can help to select high-risk patients at the time of diagnosis for complete surgical staging. Fresh/frozen tissue examination is not so time consuming compared to paraffin-embedded tissue procedure; unfortunately fresh samples are often not available. The aim of the study is

1) to evaluate the accuracy of DNA ploidy preoperative vs. postoperative evaluation;

2) to compare the results from fresh/frozen vs. paraffin-embedded tissue.

Methods: We studied prospectively a population of endometrial carcinoma patients treated in our institution in 2009/2010. DNA ploidy was evaluated from preoperative biopsy and postoperative specimens (both fresh/frozen and paraffin-embedded).

Results: We analyzed 51 patients of average age 67.8; 42 endometroid and 10 non-endometroid histopathology; 9 of G1, 25 of G2 and 17 of G3 disease. 23.1% of tumours were identified as DNA aneuploid by postoperative analysis. There was no significant difference between postoperative vs. preoperative and fresh/frozen vs. paraffin-embedded samples.

Conclusions:

1) Preoperative evaluation of DNA ploidy in endometrial carcinoma is as accurate as postoperative one. It could be add to diagnostic procedure for selection of patients with high risk of extrauterine disease/recurrence.

2) Evaluation of DNA ploidy from paraffin-embedded samples is as accurate as from fresh/frozen tissue. Both methods can be used depending on tissue samples availability.

Acknowledgement: This is a first part of 3-year study of DNA ploidy in endometrial cancer patients supported by Ministry of Health of Czech Republic (IGA MZ CR NS9975-4/2008).
FERTILITY-SPARING TREATMENT FOR EARLY STAGE ENDOMETRIOID ENDOMETRIAL ADENOCANCER

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Aim: To investigate the efficacy of fertility-sparing treatment for endometrial cancer.

Materials and methods: Nine patients with endometrial adenocarcinoma who were treated conservatively from 2006 to 2010 were enrolled in this retrospective study. The median age was 35 (33-43). All patients had grade I tumor. On transvaginal USG, myometrial invasion was not detected at 5 patients. Endometrial polyp was found in one patient and < ½ myometrial invasion was suspected in 3 patients. MRI confirmed the < ½ myometrial invasion in 2 patients. One patient was treated with progestin 30 mg/d for 8 months. Eight patients were treated with megestrol acetate 160 mg/d for 5-7 months. The mean treatment duration with megestrol acetate was 5.6 months. Furthermore 6 of the megestrol acetate using patients were also had LNG IUS.

Results: Complete remission was achieved in 6 of the 9 patients (%66). Pregnancy achieved in 2 of the 4 patients who wanted to conceive. Five of them underwent to hysterectomy. Three patients were operated because of tumor persistence and 2 with patient desire. Five out of 6 patients responded completely had LNG IUS application during the follow up period, disease free-interval is 50 months for one patient, 14 months for 2 patients and 22 months for 1 patient, respectively.

Conclusion: Fertility-sparing treatment with progestin can be considered as a good therapeutic option in patients with well-differentiated early-stage endometrioid endometrial adenocarcinoma who wish to preserve their fertility. LNG IUS application additional to megestrol acetate may be increase the response rate.
PITFALL IN THE DIAGNOSIS OF ENDOMETRIAL CANCER ARISING FROM UTERINE ADENOMYOSIS: REPORT OF A CASE

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Background: The development of cancer from adenomyotic foci is a relatively rare occurrence. The diagnosis is often delayed because of the absence of tumor involvement of the eutopic endometrium.

Case: A 64-year-old postmenopausal woman presented with irregular vaginal bleeding and dull abdominal pain. Hysteroscopy was negative and hormonal treatment was continued. No improvement occurred. Nine months later, endometrial biopsy revealed an atrophic endometrium and hydrosalpinx suggested an endometrial polyp of 14 x 7 mm with a regular thin endometrium and an inhomogeneous myometrium. Ten months after the initial symptoms, hysteroscopic excision of the endometrial polyp was performed. Pathological examination could not detect a polyp, but showed fragments of a well differentiated endometrioid endometrial carcinoma with squamous differentiation (so-called “adenocanthoma”) invading the myometrium. A laparoscopic assisted vaginal hysterectomy with bilateral salpingo-oophorectomy, pelvic lymphadenectomy and peritoneal cytology was performed. Pathologic examination revealed a stage IB (according to the revised staging of the International Federation of Gynaecology and Obstetrics of 2009) well differentiated endometrioid endometriumcarcinoma with prominent squamous differentiation originating from nodular adenomyosis. This localisation was responsible for the diagnostic delay of twelve months.

Conclusion: This report confirms the diagnostic difficulty of endometrial cancer arising from uterine adenomyosis.
RESULTS OF THE AGO STUDIES ON OPERATIVE APPROACHES IN THE CARE OF ENDOMETRIAL CANCER IN GERMANY FROM 2006 AND 2009

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\(^1\)Obstetrics and Gynecology, University Hospital Mainz, Mainz, \(^2\)Obstetrics and Gynecology, GPR, Ruesselsheim, \(^3\)AGO, Scientific Board Uterus, Germany

Background and aims: In 2006 and 2009 the AGO explored common therapeutic approaches of endometrial carcinoma (EC) in Germany. Here we present the findings concerning laparoscopy (LSC), pelvic and paraaortic lymphadenectomy (LNE) and frozen section (FS).

Methods: A questionnaire was sent to 500 German gynaecological departments in 2006 (775 in 2009). The results were compared to each other and to the guideline of AGO. To describe associations between this results and the departments' number of beds (NB) or number of cases of EC (NC) we calculated quartiles and Pearson's chi-square test.

Results: 258/775 (33.3%) responses in 2009 and 179/500 (35.8%) in 2006 were available. LSC was performed more often in 2009 as in 2006 (21.1% vs. 11.4%, p=0.012). LSC is more often used by NB>69 and NC>29 as by NB< 40 and NC< 16 (2006: 8.1% (NB< 40) vs. 34.7% (NB>69), p=0.01). Pelvic LNE was performed according to guideline in 2009 and 2006. In 2009 paraaortic LNE was conducted roughly according to guideline independently of NB and NC. In 2006 paraaortic LNE wasn’t conducted according to guideline in NB< 40 and NC< 16 (69.5% (NB< 40) vs. 95.5% (NB>69), p=0.011; 85.2% (NC< 16) vs. 97.1% (NC>29), p=0.004). In 2009 69.5% (2006: 66.5%) used FS to estimate myometrial infiltration and 62.4% (2006: 65.7%) decided intraoperatively on the performance of LNE.

Conclusions: This evaluation enabled us to describe the common therapeutic approach in the care of EC in Germany. Further studies are warranted to determine a possible impact on patients' outcome.
THE APOPTOTIC AND CYTOTOXIC EFFECTS OF CYCLOOXYGENASE (COX) ENZYME BLOCKER-NIMESULID AND CISPLATIN COMBINATION ON ENDOMETRIAL CANCER (ISHIKAWA) CELLS

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Introduction: Endometrial carcinoma is one of the most common gynaecologic cancers in the world. Both single-agent and combination chemotherapy regimens have antitumor activity in disseminated and recurrent endometrial carcinoma. The aim of this study is to investigate the effects of cisplatin, nimesulid and cisplatin, nimesulid combination on Ishikawa cells with different methods.

Material and methods: To evaluate the effects of cisplatin, nimesulide and cisplatin-nimesulide combination on cell proliferation of endometrial carcinoma cells, we initially treated Ishikawa cells with escalating concentrations for 24 and 48 h. Cell proliferation was estimated by MTT assay. Upon these assay results we further, identified cells undergoing apoptosis by morphologic analysis of cells staining with DAPI and JC-1, and also by Caspase-3 colorimetric assay.

Results: Our results showed that these drugs and especially nimesulid/cisplatin combination inhibited cellular proliferation in a dose and time dependent manner. We next investigated whether drugs and combination induces cell death through an apoptotic mechanism. DAPI staining was used after cells treated with cisplatin, nimesulid and with their combination for 24 h. Apoptotic bodies increased dose-dependently with cisplatin-nimesulide combination. We also assessed mitochondrial membrane potential with JC-1 dye for the same concentrations. Next, caspase-3 activity were determined in cells exposed to same concentrations of drugs. All results were compatible with MTT assay.

Discussion: Cisplatin-nimesulide combination exhibits the cytotoxic activity on Ishikawa cells through apoptosis. Since nimesulid also exhibits anti-tumor activities by inducing cancer cell apoptosis and inhibiting cancer cell proliferation, our findings suggest that cisplatin and nimesulid combination may represent a new class of chemotherapeutic agents.
DESCRITIVE ANALYSIS OF LYMPH NODE METASTASIS IN ENDOMETRIAL CANCER


Hospital Virgen del Camino, Pamplona, Spain

Aims: Describe percentage of lymph node metastasis in our environment

Methods: We make an study of series of endometrial cancer treated cases treated in Virgen del Camino Hospital in Pamplona (Spain) during the period 2004-2009

Results:

In this diagram we analyze lymph node metastasis following hystologyc type with this results.

[Diagram 1]

Finally we analyze pelvic and paraaorty lymph node metastasis remarking that in 44% of cases exists paraaortal nodes affection with no consequences in pelvic nodes. Or with another words in 75% of paraaortal lymph node metastasis there is no pelvic affection. Such affection is reflected in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Pelvics negatives</th>
<th>Pelvics Positive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ParaAo Positive</td>
<td>15 (75%)</td>
<td>5 (25%)</td>
<td>20</td>
</tr>
<tr>
<td>ParaAo Negative</td>
<td>0</td>
<td>14 (100%)</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>15 (44%)</td>
<td>19 (56%)</td>
<td>34</td>
</tr>
</tbody>
</table>

[Contingence table ParaAo-Pelvics nodes]

Conclusions: Lymph node metastasis and hystologyc subtype is the most important prognosis factor in endometrial cancer. Therefore the importance of individual treatment with or without lymphadenectomy. By not doing so the patients wouldn’t be properly diagnosed and treated.
PREOPERATIVE MRI ASSESSMENT OF DEPTH OF MYOMETRIAL INVASION IN ENDOMETRIAL CANCER: DOES MDM REVIEW IMPROVE ACCURACY?

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Background: Assessment of myometrial invasion (MI) by magnetic resonance imaging (MRI) is used to triage patients with low grade endometrioid adenocarcinoma of the endometrium. Patients with <50% myometrial invasion are managed by general gynaecologists, and those with >50% are offered staging in the gynaecological oncology unit. MRIs are reviewed by specialist gynaec-radiologists at multidisciplinary (MDM) review.

Aim: To evaluate the accuracy of preoperative MRI in assessment of MI by general and specialist radiologist.

Method: 50 patients with Grade 1 and 2 endometrioid endometrial carcinoma underwent hysterectomy in 2009 at Auckland hospitals. MRI was performed pre-operatively and the depth of MI was assessed as either < 50% or >50%. The MRI prediction of the depth of MI by referring radiologists and MDM radiologists were noted separately, and compared to the final histology.

Results: 41 patients had < 50% invasion, and 9 patients had >50% invasion on final pathology. MRI assessment by the referring radiologist showed 46 patients had correct diagnosis of depth of MI; the sensitivity, specificity, and accuracy were 78%, 95%, and 92% respectively. MRI assessment by the MDM radiologists, 43 patients had correct diagnosis; the sensitivity, specificity and accuracy were 78%, 90% and 88% respectively.

Conclusion: Our data suggests that preoperative MRI assessment of depth of MI has good correlation to final histology. There is good correlation between initial radiology report and specialist MDM review. Omitting secondary review could streamline patient care pathway, without compromising accuracy.
PROGNOSIS AND IMPACT OF ADJUVANT TREATMENT OF UTERINE CARCINOSARCOMA

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CHUM, Montreal, QC, Canada

Objective: Carcinosarcomas are aggressive tumours and constitute 4% of uterine malignancies. The aims of this study were to determine prognostic factors and outcomes based on different treatment modalities.

Methods: This is a retrospective study of 86 cases of uterine carcinosarcoma in a single institution between December 1982 to June 2008. Medical records of all patients were reviewed, and information on demographics, tumour characteristics, recurrence and survival were obtained.

Results: The median follow-up was 17 months (1-250). The most common presenting symptoms were abnormal vaginal bleeding (88%), and pain (7%). Stage I was present in 51% of the patients, stage II 6%, stage III 22% and stage IV 21%. Fifty one percent had no adjuvant treatment, 34% had radiotherapy alone, 3% had chemotherapy alone and 12% had radiotherapy and chemotherapy combination. In this study, 52% of cases had recurrent disease with a mean time of recurrence of 8 months. Mean survival were respectively 46, 13, 20 and 7 months for stage I, II, III and IV (p<0.0001). Patients with stage II, III and IV had a mean survival of 11 month when they had no adjuvant treatment, 15 months with single adjuvant treatment, 22 months with chemotherapy and radiotherapy combination (p=0.015). The difference in survival between adjuvant treatment for stage I were 37, 41 and 100 months respectively but not statistically significant (p=0.1).

Conclusion: Our results confirm the aggressive behaviour of uterine carcinosarcoma. The combination of chemotherapy and radiotherapy seems to be the best adjuvant treatment.
ESTIMATING THE RISK OF ENDOMETRIAL CANCER - A CLINICAL PREDICTION ALGORITHM BASED ON PATIENT CHARACTERISTICS

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¹Obstetrics and Gynaecology, Norfolk and Norwich University Hospital NHS Foundation Trust, ²School of Medicine, Health Policy & Practice, University of East Anglia, ³Lawson Road GP Practice, Lawson Road Surgery, Norwich, ⁴Obstetrics and Gynaecology, Addenbrookes Hospital, Cambridge, UK

Aim: The study aimed to develop an algorithm to predict the risk of endometrial carcinoma in postmenopausal women presenting with vaginal bleeding.

Methods: This prospective study collected the data from 3047 women presenting with postmenopausal bleeding. Data regarding the presence of risk factors for endometrial cancer was collected and univariate and multivariate analysis were performed.

Results: The age distribution ranged from 35 to 97 years with a median of 59 years. 149 women (5% of total) were diagnosed with endometrial carcinoma. Women in the endometrial cancer group were significantly more likely to be older, have higher body mass index, recurrent episodes of bleeding, diabetes, hypertension, or a previous history of breast cancer. An investigator best model selection approach was used to select the best predictors of cancer and using logistic regression analysis we created a clinical prediction rule for endometrial cancer. The calculated score of the algorithm can vary from a value of 0 to 9. A value of equal to or greater than 3 achieved a sensitivity of 81.9% (95% CI, 74.7%-87.7%) and specificity of 50.1% (95% CI, 48.2%-51.9%) while a score of equal to or greater than 5 had a sensitivity of 67.8% (95% CI, 59.6%-75.2%) specificity was 74.1% (95% CI, 72.5%-75.7%). The overall predictive ability measured by the area under the ROC curve was 0.76.

Conclusion: The combination of clinical information with our investigation tool in women with postmenopausal vaginal bleeding allows the clinician to calculate a predicted risk of endometrial malignancy and prioritise subsequent clinical investigations.
FERTILITY SPARING TREATMENT (FST) IN ENDOMETROID ENDOMETRIAL CANCER G1 (EC) AND COMPLEX HYPERPLASIA WITH ATYPIA (CHA). OUR EXPERIENCE

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¹Oncology Unit, University of Buenos Aires, Buenos Aires, ²Fertility Unit San Isidro, San Isidro, ³Obstetrics and Gynecology, University of Buenos Aires, Buenos Aires, Argentina

Objective: to evaluate the efficacy and fertility outcome of FST

Materials: Twelve patients were included. Mean age was 27 (23-40).

All patients were submitted to hysteroscopy and pathological specimens were evaluated by the same pathologist.

Seven patients were diagnosed with EC and 5 with CHA.

Hormonal treatment was medroxyprogesterone acetate 500 mg/day VO. A hysteroscopy was performed after three months. Patients with stable or progressive disease discontinued treatment. Patients with partial response were reevaluated every three months with the same criteria. When complete response was achieved treatment was extended for three more months.

Results: There were no cases with stable or progressive disease. Treatment time was less than a year in all cases.

Seven patients wanted to get pregnant after treatment, 6 achieved pregnancy. Time to pregnancy was 12 to 36 months. Five pregnancies had healthy term newborns, one have had spontaneous abortion.

Three patients relapsed, one after 12 months; it was a EC and relapsed with the same pathology. The second patient, with a EC relapsed as CHA after 24 months; the third one with CHA relapsed with the same pathology after 48 months. All relapses received surgical treatment.

Conclusions: Hormonal treatment may be an acceptable alternative for women with EC and CHA in reproductive age desiring to preserve their fertility potential. Early diagnosis of recurrence may be warranted by close follow up.
AGE RELATED INCIDENCE AND DIFFERENTIAL DIAGNOSIS OF POSTMENOPAUSAL VAGINAL BLEEDING


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Aim: The aim of this study is to identify the causes of vaginal bleeding in postmenopausal women. Also, we attempt to estimate the age related incidence of postmenopausal vaginal bleeding in a defined geographical area.

Methods: The study was conducted at a gynaecological oncology centre in the United Kingdom, between February 2006 and May 2009. Patients were investigated according to established evidence based departmental guidelines.

Results: During the study period 3047 women were referred with postmenopausal vaginal bleeding. In 1356 women (44.5%) the endometrial thickness measured less than 5 mm on transvaginal ultrasound scan. Benign histology was found in 1144 women (37.5%). Benign endometrial polyps were the cause of bleeding in 10.1% of the cases. The incidence of endometrial cancer in our study population was 5%. The incidence of postmenopausal vaginal bleeding peaks at the age of 55 to 59 years (25.9/1000 postmenopausal women/year) and declines thereafter.

Conclusion: This is the first population-based estimation of the incidence of genital tract bleeding amongst postmenopausal women in the United Kingdom. The results of this study could be used to inform clinical practice when counselling postmenopausal women with vaginal bleeding.
PROGNOSIS OF SURVIVAL IN 104 CASES OF PAPILLARY SEROUS AND CLEAR CELL ENDOMETRIAL CARCINOMAS

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Objective: This study aims to identify patients' characteristics and factors independently associated with recurrence and survival of uterine papillary serous (UPSC), uterine clear cell carcinoma (UCCC) and mixed type.

Materials and methods: We retrospectively retrieved 104 cases of UPSC and UCCC managed in our institution from 1998 to 2008. A variety of clinicopathological factors were recorded. Multivariable Cox regression was performed to examine the associations of parameters with survival.

Results: There were 64 UPSC, 27 UCCC and 12 mixed endometrial carcinomas. Mean age was 66.3 (range 34-91) and median follow up time was 36 months. Seventy four patients (71.5%) were at stage I and II (early), while 30 (28.8%) were at stage III and IV (advanced). Overall 36 patients (34.6%) died. Multivariable analyses revealed that >50% of miometrial invasion (p< 0.001), positive omentum (p< 0.001) and advanced stage (p=0.003) were all poor prognostic factors affecting recurrence and survival. Adjuvant therapy was administered in 84.62% of the patients consisting of only chemotherapy in 42, chemoradiation in 24 and radiation in 23. There were 27 recurrences; 18 distant and 9 locoregional. Recurrence and survival were not influenced by age, histological type, tumor size, LVSI, positive cytology, presence of ascites, adjuvant therapy or menstrual history.

Conclusion: Three factors seem capable of independently modifying survival of patients with UPSC or UCCC. Depth of miometrial invasion spread of the disease in the omentum and stage. Prospective studies are needed in order to determine exact prognostic factors.
TOTAL LAPARO-ENDOSCOPIC SINGLE SITE SURGERY (LESS) HYSTERECTOMY IN LOW-RISK EARLY ENDOMETRIAL CANCER: TECHNIQUE AND PRELIMINARY RESULTS

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Dept. Obstetrics and Gynecology, Catholic University of the Sacred Heart, Roma, Italy

Background and aims: To present our initial experience with laparo-endoscopic single site surgery (LESS) in the surgical treatment of early-stage endometrial cancer patients.

Methods: Between July 2009 and February 2010, 15 consecutive low-risk early endometrial cancer referred to the Division of Gynecologic Oncology of the Catholic University of the Sacred Heart of Rome were enrolled in the study. All patients underwent total LESS hysterectomy. Intra- and early post-operative outcomes were collected.

Results and conclusion: Median age was 57 (42-68) and median BMI was 24 (21-30). Median operative time was 120 minutes (range 85-155) and median estimated blood loss 20 ml (range 10-180). Larger skin and fascial incision required by LESS approach was 2.5 cm (median 2.2 cm; range 2.0-2.5). No laparoscopic/laparotomic conversion was registered, and no additional port insertion was necessary. Median ileus was 16 hours (range 12-20) and median time to discharge was 1 (range 1-2) day. All patient conveyed complete satisfaction towards cosmetic result and post-operative pain control. LESS can represent a safe and adequate surgical option for hysterectomy in early-stage endometrial cancer patients, with the potential to further decrease invasiveness of the conventional laparoscopic approach.
CORRELATION OF 18-FDG UPTAKE IN PET/CT WITH CLINICOPATHOLOGICAL FEATURES AMONG 5 CASES OF RECURRENT LOW GRADE ENDOMETRIAL STROMAL SARCOMA (LGESS)

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¹Obstetrics and Gynecology, ²Pathology, ³PET Center, Hyogo College of Medicine, Nishinomiya, Japan

Background: To date, there is only one known case report of detection of low grade endometrial stromal sarcoma (LGESS) by 18-FDG-PET/CT. LGESS comprises a rare group of gynecologic malignancies and relapse-free intervals following a hysterectomy have been reported to widely range from 3 months to 23 years.

Methods: We assessed the correlation of 18-FDG uptake by recurrent LGESS with the interval following previous surgery (disease-free interval, DFI), CT and MRI diffusion imaging findings, and immunohistochemical findings (Ki-67, p53, ER, PR, GnRH-R) using specimens obtained from five LGESS cases during surgery or biopsy following PET/CT.

Results: Table. MRI diffusion imaging showed apparent tumors in all five cases.

Conclusion: There was a tendency for 18-FDG uptake and positive Ki-67 findings in LGESS.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV max early/late</td>
<td>1.2/1.7</td>
<td>2.1/2.1</td>
<td>1.8/2.3</td>
<td>3.0/3.8</td>
<td>5.3/NA</td>
</tr>
<tr>
<td>DFI</td>
<td>7 years</td>
<td>6 years</td>
<td>9 months</td>
<td>9 years</td>
<td>10 months</td>
</tr>
<tr>
<td>Site of recurrence</td>
<td>pelvic LN</td>
<td>uterus</td>
<td>sigmoid</td>
<td>pelvic LN</td>
<td>pelvic LN</td>
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<tr>
<td>Ki-67 (%)</td>
<td>1</td>
<td>10</td>
<td>50</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>ER (%)</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>PR (%)</td>
<td>30</td>
<td>70</td>
<td>60</td>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

[18F-FDG uptake and clinicopathological findings]
SECOND CYTOREDUCTIVE SURGERY FOR TREATMENT OF RECURRENT ENDOMETRIAL CANCER

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Background: Cytoreductive surgery for recurrent endometrial cancer (EC) was not widely accepted. Recent data revealed a positive association between survival and satisfied cytoreduction for patients with recurrent EC.

Objectives: To determine the survival significance of second cytoreductive surgery for patients with recurrent EC.

Methods: All patients with recurrent EC treated at Cancer Hospital, Fudan University between January 1995 and January 2010 were reviewed.

Results: Altogether 70 patients underwent second cytoreductive surgery with median recurrence interval of 16 months (3-372). Median age at recurrence was 56 years (31-75). All patients were restaged by FIGO stage 2009. 38 patients (54.3%) had no residual disease after the surgery, 15 patients (21.4%) with residual disease less than 1 cm, and 17 (24.3%) >1 cm. 33 patients (47.1%) had single recurrence, and 37 (52.9%) had multiple. 24 patients died during follow-up. 5-year overall survival and progression free survival were 36.8% and 21.6%, respectively. Single recurrence, tumor < 6cm, and early initial FIGO stage were associated with satisfied cytoreductive surgery (residual disease < 1 cm). Residual disease >1cm, distant recurrence out of pelvis, low histology grade, and age > 56 years were significantly associated with a worse OS in multivariate analysis (p< 0.05).

Conclusion: Satisfied cytoreductive surgery and regional recurrence were associated with prolonged overall survival for patients with recurrent EC. Patients with single recurrence, small tumor size, and early FIGO stage were more likely to achieve satisfied cytoreductive surgery and benefit from it.

[Survival Curve on residual disease]
INTRAOPERATIVE ASSESSMENT OF MYOMETRIAL INVASION AND HISTOLOGICAL GRADE IN ENDOMETRIAL CANCER USING REVISED FIGO STAGING SYSTEM

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Objectives: The objective of this study is to assess the value of intraoperative frozen-section diagnosis for myometrial invasion and histological grade in endometrial cancer using the revised FIGO staging system.

Methods: The records of 303 patients of endometrial cancer who underwent surgery with intraoperative diagnosis at the Osaka University Hospital between January 1999 and December 2008 were reviewed. Intraoperative frozen-section diagnosis was retrospectively analyzed for the accuracy rates of myometrial invasion and histological grade compared with preoperative prediction by MRI and endometrial curettage.

Results: When using the previous FIGO staging system, the accuracy rate of intraoperative frozen section for the diagnosis of myometrial invasion was 77%, while the accuracy rate of preoperative prediction by MRI was 54%. However, for myometrial invasion, using the revised FIGO staging system, the accuracy rate of frozen section was 87% and preoperative prediction by MRI was 82% respectively. The accuracy rate of intraoperative frozen section for the diagnosis of histological grade was 71%, whereas the accuracy rate of preoperative prediction by endometrial biopsy was 68% respectively.

Conclusion: Although intraoperative frozen-section diagnosis is more accurate than preoperative prediction by MRI in the previous FIGO staging system. There is no significant difference between value of intraoperative diagnosis and preoperative diagnosis in the revised FIGO staging system. The accuracy of intraoperative frozen-section, however, trend to better than preoperative procedure by MRI and endometrial biopsy. Thus intraoperative frozen-section diagnosis is useful for directing primary operative management.
CPG ISLAND HYPERMETHYLATION OF WNT INHIBITORY FACTOR-1 (WIF-1) AND E-CADHERIN (CDH1) IS ASSOCIATED WITH RECURRENCE AND PROGNOSIS OF ENDOMETRIAL CANCER

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Objectives: To investigate promoter methylation status of WIF-1, E-cadherin and PTEN genes and discuss the different molecular characters of type I and type II endometrial cancer.

Methods: Methylation-specific PCR (MSP) was performed to detect the promoter methylation status and immunohistochemistry (IHC) to detect protein expression of E-cadherin, PTEN and β-catenin genes.

Results: 105 patients included 81 type I and 24 type II cases, with median age of 57. The frequency of promoter methylation of WIF-1, E-cadherin and PTEN genes was 26.7% (28/105), 27.6% (29/105) and 18.1% (19/105), respectively. The methylation frequency of endometrial tissues was higher than that of corresponding normal tissues (P< 0.05). E-cadherin promoter hypermethylation was associated with pathological subtypes (type I and type II EC), WIF-1 promoter methylation was correlated with FIGO stage, and PTEN promoter methylation was correlated with p53 expression (P< 0.05). Reduced E-cadherin expression was observed in 60.0% (63/105) of the cases, being more frequent in type II cases, more advanced stage and carcinomas of deep myometrial invasion (P< 0.05). Abnormal β-catenin expression was observed in 29.5% (31/105) of the cases, being more frequent in type I EC (P< 0.05). In univariate analysis, patients with WIF-1 promoter methylation, E-cadherin promoter hypermethylation, and reduced PTEN expression were associated with worse prognoses in type I patients and reduced E-cadherin expression associated with worse prognoses in type II patients (P< 0.05).

Conclusions: There were different molecular characters between type I and type II EC, including more E-cadherin promoter hypermethylation and reduced E-cadherin expression in type II and more abnormal β-catenin expression in type I.
PROGNOSTIC FACTORS IN PATIENTS WITH UTERINE SARCOMA: DATA FROM A SINGLE INSTITUTION IN BRAZIL


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Background: Uterine sarcomas comprise less than 1% of gynecologic tumors. Classic prognostic factors include tumor resection, local recurrence or metastatic disease. The ideal adjuvant treatment for uterine sarcoma is not a consensus.

Aims: To evaluate the prognostic factors in patients with uterine sarcoma.

Methods: Retrospective cohort study including patients with uterine sarcoma from a Brazilian cancer center between 2000 and 2008. Kaplan-Meier was applied for overall survival (OS) analysis.

Results: The casuistic was composed by 62 women with uterine sarcoma: 23 with endometrial stromal sarcoma (37.5%), 20 with leiomyosarcoma (32.3%), 15 with carcinosarcoma (24.2%), and 4 with adenosarcoma (6.5%). Hysterectomy was performed in 54 women (87.1%), adjuvant radiotherapy in 36 (58.1%) and postoperative adjuvant chemotherapy in 8 (12.9%). Five-year OS rates were respectively 91.3%, 83.0%, 46.9% and 50.0% (log-rank: p=0.059). Regarding the final stage, the 5-year OS rates were significantly different (p< 0.006): stage I (n=34; 88.1%), stage II (n=6; 100.0%), stage III (n=7; 37.5%) e stage IV (n=13; p=50.0%). There was no significant difference in 5-year OS rates according to: surgical margins (p=0.290), tumor size (cut-off: 10 cm; p=0.399), capillary embolisation (p=0.898), perineural invasion (p=0.169), necrosis (p=0.328), postoperative radiotherapy (p=0.314) and adjuvant chemotherapy (p=0.499). High grade tumors had worse prognosis (p=0.037), as well as tumors with adjacent organ invasion (p=0.032).

Conclusion: In this univariate analysis, negative prognostic factors for uterine sarcoma were FIGO stage, histological grade, histological type and invasion of adjacent organs.
UTERINE SMOOTH MUSCLE TUMOURS OF UNCERTAIN MALIGNANT POTENTIAL (STUMPS) - A REPORT OF FIVE CASES

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Background: STUMPs are rare tumours that cannot be histologically diagnosed as unequivocally benign or malignant. There were only limited case reports in the literature and their clinical behaviors are not well understood.

Aims: To evaluate the pathologic features and clinical behaviors of 5 cases of uterine smooth muscle tumours with uncertain malignant potential.

Methods: From 2001 to 2008, five cases of uterine smooth muscle tumours with either tumour cell necrosis or cellular atypia were studied. The clinical and pathological findings were reviewed.

Results: Patient’s age ranged from 39 to 62 years (mean, 47 years). All but one patient were at pre-menopausal state. The presenting symptoms were menorrhagia in 4 patients, intermenstrual bleeding in 2 patients and postmenopausal bleeding in 1 patient. The size of tumours ranged from 4 to 15cm (mean, 7.2cm). Tumour cell necrosis was present in 4 cases, one of which had very focal cellular atypia also. Focal moderate-to-severe cellular atypia was present in one case, without significant mitotic figure or tumour cell necrosis. Three patients had hysterectomy performed. Two patients underwent hysterectomy and bilateral salpingo-oophorectomy. Follow-up periods ranged from 24 to 108 months (mean, 78 months). No recurrence of tumour was detected and all patients were alive at last follow up.

Conclusion: Our reported cases of STUMPS appeared to be clinically benign when hysterectomy was performed. However, longer follow up and larger case series especially those underwent fertility sparing myomectomy would help in studying its behavior.
A PRIMARY STUDY ON THE EXPRESSION OF TRPV6 GENE IN ENDOMETRIAL CARCINOMA

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Objective: In recent years, many studies found the calcium channel TRPV6 (transient receptor potential vanilloid 6) overexpression in some hormone related tumors such as prostate cancer and breast cancer, and also affect their development. However, the expression of TRPV6 in endometrial cancer is rarely reported. In this study, the expression of TRPV6 in endometrial cancer was detected and its relationship with clinicopathological features was analyzed respectively.

Methods: The expression of TRPV6 protein were detected in endometrial carcinoma, atypical endometrial hyperplasia and normal endometrial with immunohistochemistry and real-time quantitative PCR.

Results:

(1) TRPV6 expression was mainly located in the membrane and cytoplasm of endometrium. The positive rate of TRPV6 expression was 77% in endometrial cancer. It was significant lower than that in premenopausal normal endometrium (100%) and atypical endometrial hyperplasia (100%) (P < 0.05). Real-time quantitative PCR results also showed that the expression of TRPV6 was lower in endometrial cancer tissues than that in normal endometrial tissue (p < 0.05).

(2) TRPV6 expression in endometrial cancer was related to the menopausal status. The expression of TRPV6 was lower in postmenopause patient (71.8%) than that in non-menopause ones (89.5%).

(3) TRPV6-positive expression was higher in the cases of cervical involvement.

Conclusions: The expression of TRPV6 in endometrial cancer is lower than the normal endometrium, and TRPV6-positive tissues are trend to have more cervical involvement. It suggests that calcium channel protein TRPV6 has relationship with endometrial cancer.
A PRIMARY STUDY ON THE EXPRESSION OF ESTROGEN RECEPTOR A36 IN ENDOMETRIAL CARCINOMA

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Objective: Estrogen receptor α36 (ERα36) is a new type of estrogen receptor. The aims of this study are following:

(1) Exploring the expression of ERα36 in endometrial carcinoma tissues.

(2) Analyzing the relationship between the expression of ERα36 and clinicopathologic characteristics in endometrial carcinoma and exploring the clinical significance of ERα36 in endometrial carcinoma.

Methods: 73 cases endometrial carcinoma, 20 cases normal endometrial tissues and 9 cases atypical endometrial hyperplasia tissues were selected and ERα36 protein expressions were detected by immunocytochemistry methods. The correlations between ERα36 protein expression and many clinicopathologic characteristics and disease-free survival (DFS) were also studied.

Results:

(1) The rate of positive expression of ERα36 in endometrial carcinoma tissues was 32.9%, which was significant lower than that of in normal endometrial tissues (85%) and atypical hyperplasia endometrial tissues (77.8%).

(2) The expression of ERα36 had no correlation with ER, and it can express in ER negative endometrial carcinoma tissues.

(3) ERα36-negative tissues were inclined to cervical involvement (24/49) and were significantly different with ERα36-positive ones

(4) DFS of the patients with ERα36 positive expression was poorer than that of with ERα36-negative expression.

Conclusions:

(1) The expressions of ERα36 in endometrial carcinoma tissues are significantly lower than those in normal endometrial tissues or atypical endometrial hyperplasia tissues.

(2) ERα36 expression has no correlation with ER expression, which also expresses in ER negative endometrial carcinoma tissues.

(3) ERα36-negative patients are inclined to cervical involvement; while ERα36-positive patients have poorer DFS.
UTERINE CANCER INCIDENCE AND PROGNOSIS AMONG INDIGENOUS AND NON-INDIGENOUS WOMEN IN QUEENSLAND AUSTRALIA, 1997 TO 2006

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Background and aims: Overall, Indigenous Australians have poorer health than non-Indigenous Australians and poorer cancer survival. The prognosis for Indigenous people with specific cancers varies however, and the incidence and prognosis for uterine cancer are largely unknown. We therefore have compared incidence of uterine cancer, diagnosis, treatment and survival between Indigenous and non-Indigenous women in Queensland, Australia.

Methods: Incidence rates were based on all Indigenous women registered with uterine cancer between 1997 and 2006. Treatment and survival rates were based on a subset of Indigenous women, frequency-matched on age and location with non-Indigenous cases, treated in public hospitals between 1998 and 2004. Data were obtained from hospital records and the National Death Index.

Results: Incidence of uterine cancer was higher for Indigenous women (SIR 1.83 95%CI 1.40, 2.35). There were no differences in stage at diagnosis or tumour morphology between 38 Indigenous and 36 non-Indigenous women in the study subset. Indigenous women were significantly more likely to have comorbidities, especially diabetes (58% versus 17%). Percentages who received cancer treatment were similar (95% and 92%) and on follow-up (median approximately 120 months for both), 8 (21%) of the Indigenous women died compared to 10 (28%) non-Indigenous. The adjusted Hazard Ratio for cancer survival was 0.36 (95%CI 0.09, 1.44).

Conclusions: Despite higher rates of uterine cancer, Indigenous women were as likely to receive cancer treatment and had similar or better survival than their non-Indigenous counterparts within Queensland public hospitals. Prevention is therefore the key to control of this cancer in Indigenous Australians.
IMPACT OF HISTOCHEMICAL MARKER EXPRESSION PROFILES ON SURVIVAL OF ENDOMETRIAL CANCER PATIENTS

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\textbf{Aim:} Of this study was to evaluate the influence of different prognostic markers on survival indexes in endometrial cancer patients.

\textbf{Methods:} Expression of estrogen (ER) and progesterone (PR) receptors, epidermal growth factor receptor (EGFR) and proliferative activity marker (Ki67) was evaluated in tumor tissues. 73 patients with endometrial adenocarcinoma were enrolled.

\textbf{Results:} Overall survival in patients with positive staining for ER and PR was 98.6\% and 91.2\%, respectively. Negative results for ER in tumor tissue resulted in 23\% decreasing of 5-year survival. The decreasing in survival indexes was 2 folds less in cases with negative PR. 5-year survival rate was 78.3\% in these patients. The difference in survival rates between ER/PR positive and ER/PR negative patients was found to be significant: 96.2\% vs. 76.8\%, accordingly (p< 0.05). Patients with negative EGFR stains (0 and 1+) demonstrated better survival than patients with positive EGFR results (2+): 81.6\% and 71.3\%, respectively. However, the difference was not significant. Hyper expression of EGFR resulted in extremely poor survival rates (50.0\%). We also found a 23\% difference in DF survival indexes in patients according to Ki67 expression (80.8\% vs. 57.9\%). Further increasing of proliferative activity of tumor (Ki67 >34\%) was associated with poor survival (p< 0.05).

\textbf{Conclusions:} Positive ER/PR staining have shown it’s significant prognostic value and should be used routinely if available. Despite the significant influence of EGFR and Ki67 on survival their hyper expression were not common in our series, but this data suggests evaluation of possible use of targeted chemo agents.
PATTERN OF FAILURES AND PROGNOSTIC FACTORS IN TYPE 2 ENDOMETRIAL CARCINOMA: A SINGLE INSTITUTION RETROSPECTIVE STUDY

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Background and aims: To evaluate pattern of failures and prognostic factors in women with Type 2 endometrial cancer (EC) focusing on histological subtype and adjuvant treatment.

Methods: Between 1997 and 2009, 80 patients out of 603 consecutive cases of EC (13.2%) had Type 2-EC (41 papillary serous, 21 clear cell, 11 undifferentiated and 7 adenosquamous). Six patients were not eligible for missing data. 74 (100%) patients underwent hysterectomy and BSO, 36 (48.6%) lymphadenectomy. FIGO stages were as follows: I=34 (46.0%), II=12(16.2%), III=24(32.4%), IV=4(5.4%). 24 patients (32.4%) received no adjuvant treatment, 22(29.7%) chemotherapy, 15 (20.2%) radiotherapy, 13 (17.5%) chemo-radiotherapy as adjuvant treatment. Kaplan Maier method and Log rank test were used to assess survival prognostic factors. Multivariate Cox-proportional hazard model was generated.

Results: The 5 year survival rate was: 88.9% in stage I, 75% in stage II, 52% in stage III and 40% in stage IV. No survival difference was found by different histotypes (p=0.274). 15 patients relapsed: 11 (73.3%) had distant site recurrences, 4 (26.6%) loco-regional recurrences irrespective of post surgical management. Stage, LVSI, nodes and omental metastasis, positive peritoneal cytology had prognostic significance at univariate analysis. On multivariate analysis, LVSI (p=0.01), myometrial infiltration (p=0.01) and stage (p< 0.001) were independent prognostic factors.

Conclusions: Type 2 endometrial cancer is rare and differs from Type 1 especially for the high frequency of distant metastasis. The pattern of failures supports the use of systemic adjuvant treatment. A multicentric study is needed to better define appropriate management for these kind of malignancies.
THE ANALYSIS OF QUALITY OF LIFE AND CORRELATION FACTORS IN ENDOMETRIAL CANCER PATIENTS

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Objective: The purpose of this study is to assessing the quality of life of the patients with endometrial cancer after treatment, to provide a reference for improving the quality of life of patients.

Methods: Endometrial cancer patients after surgical treatment were interviewed by telephone or outpatient follow-up, including general socio-demographic characteristics and their quality of life by EORTC-QLQ-C30 and EORTC-QLQ-OV28 questionare.

Results:

(1) 221 patients finished the assessment, the response rate was 82.7%.

(2) Patients treated by surgery + hormonal therapy(n=87) had better physical function, role function, global health status and less frequent fatigue than patients treated by surgery alone (n=36), and their physical function, role function were better than patients received surgery and radiotherapy/chemotherapy (n=43); but their perimenopausal symptoms are multiple than patients with surgery + hormonal therapy + radiotherapy/chemotherapy(n=55); patients with surgery + hormonal therapy + radiotherapy/chemotherapy, their physical function are better than those treated with surgery alone.

(3) The quality of life had correlation with histological type, surgical stage, recurrence and complications

(4) Patients age and educational level have certain impact on the quality of life except marital status of patients.

Conclusion:

(1) For stage I endometrial cancer patients, treated by surgery combinded with hormone therapy may result better quality of life, while the patients treated by surgery alone may have lowest quality of life.

(2) For stage II-IV, patients treated with surgery and radiotherapy/chemotherapy had better physical function than that in patients treated by surgery alone.

(3) Patients age is positively correlated with emotional function.
UTERINE SARCOMA - OUR EXPERIENCE

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The vast majority of malignancies of the uterine body are endometrial carcinomas and only about 4% will be uterine sarcomas. The lesion originates from the stroma of the uterine lining or from the uterine muscle cell.

Aim: To estimate the incidence of uterine sarcoma in our clinic between 2004 - 2009 and the management of these cases.

Material and methods: We analised the symptoms, the mode of diagnosis, the treatment and the histologic types at our patients.

Results: We present 22 cases of uterine sarcoma. Median age of women was 59 years, range 38-75 +/- 4 years. 8 cases had mixed mullerian tumors (uterine carcinosarcoma), 7 had endometrial stromal sarcoma (4 low grade and 3 high grade) and 7 leiomyosarcoma. Unusual or postmenopausal bleeding was at 17 patients and at other 5 patients we palpated abdominal tumors (4 with uterus of 13-16cm and 1 with uterus of normal dimensions but at the fundus of uterus it was a tumor of 25cm). Only two women took long-term tamoxifen for breast cancer in their history. According to FIGO classification, Stage I, III A and IV tumors were identified in 12, 8 and 2 patients respectively. Standard treatment option was surgery for 20 cases. After surgery, treatment with chemotherapy was recommended for 4 patients.

Conclusions: Incidence of uterine sarcoma increased in the last years. Prognosis for leiomyosarcoma depends on dimensions of it. The 5-year relative survival rate for endometrial stromal sarcoma is better than for leiomyosarcoma.
SURVIVAL OUTCOME OF WOMEN WITH SYNCHRONOUS CANCERS OF THE ENDOMETRIUM AND OVARY: A 10 YEAR RETROSPECTIVE COHORT STUDY

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Introduction: Synchronous occurrence of endometrial and ovarian tumors is uncommon, and they affect less than 10% of women with endometrial or ovarian cancers. The aim of this study is to describe the epidemiological and clinical factors; and survival outcomes of women with these cancers.

Method: This is a retrospective cohort study in a large tertiary institution in Singapore. The sample consists of women with endometrial and epithelial ovarian cancers who sought care from the institution, and who were followed up over a period of 10 years from 2000 to 2009. Patients with borderline or germ cell ovarian tumors were excluded. The epidemiological and clinical factors include age at diagnosis, histology types, stage of disease.

Results: A total of 75 patients with synchronous cancers were identified. 59 patients met the inclusion criteria. Follow up period ranged from 3 months to 9.2 years with mean follow up of 4 years. The incidence rate for synchronous cancers is 8.7% of all epithelial ovarian cancers and 4.9% of all endometrial cancers diagnosed over this time frame. Mean age at diagnosis was 51 years old. About half of the women (55%) were premenopausal, 54% had endometrioid histology for both endometrial and ovarian cancers. The majority of the women (78%) presented at early stages of 1 and 2. The 5 years cumulative survival rate was at 84%.

Conclusion: In our cohort, we found that women afflicted with synchronous cancer of the endometrium and ovary were younger, with early stages of cancer and had a favorable prognosis.
MULTIMODALITY THERAPY FOR PATIENTS WITH MALIGNANT MIXED MULLERIAN TUMORS OF THE UTERUS

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**Introduction:** The role of adjuvant therapy in the management of patients with malignant mixed Mullerian tumors (MMMT) of the uterus has not been well defined.

**Objective:** To assess the outcome of planned multimodality therapy for patients with apparent early stage disease.

**Methods:** This is a followup study of 66 patients diagnosed with MMMT of the uterus between the years 1987 till 2007 who were offered treatment according to a standard protocol. The protocol consisted of removal of the uterus, fallopian tubes and ovaries and surgical staging followed by tailored radiation therapy and chemotherapy, consisting of cisplatin and epirubicin. Staging was reclassified according to the new FIGO 2008 system.

**Result:** The mean follow-up for patients was 55.87 months (range, 2-244 months), meanwhile the mean time to death from disease diagnosis was 20.61 months (range, 2-114 month). Overall 5 years survival was 66.6 %. Using Kaplan-Meier survival analysis, there was significantly better survival outcome in patients who received both chemotherapy and radiation as adjuvant therapies in comparison with the group who received one or none of these protocols (p< 0.001). Interestingly in analysis of adjuvant therapy outcome in patients who had expired, there was no significant difference found with radiotherapy treatment where as adjuvant chemotherapy significantly improved survival of this group (respectively p=0.9 and p< 0.001).

**Conclusion:** In this study, MMMT patients who underwent surgical staging and aggressive adjuvant radiation and chemotherapy had an excellent survival rate.

**Keywords:** Malignant Mixed Mullerian Tumors, Survival, Surgical staging, chemotherapy, radiation therapy.
UTERINE EMBRYONAL RHABDOMYOSARCOMA (SARCOMA BOTRYOIDES) IN A 13 YEAR-OLD GIRL SUCCESSFULLY TREATED CONSERVATIVELY WITH HYSTEROSCOPIC RESECTION AND CHEMOTHERAPY

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Background and aims: We report a case of uterine rhabdomyosarcoma in a young patient, successfully treated with a combination of hysteroscopic surgery and chemotherapy.

Case report: 13 year-old girl presented with bleeding and a protruding mass of 10x15 cm through her vagina. Ultrasound revealed normal sized ovaries. Upon vaginal examination the cervix seemed normal despite being dilated by the mass; the mass was clamped behind internal os and removed on June 2008. As final pathology revealed rhabdomyosarcoma, hysteroscopy was performed and the base of the tumoral lesion was resected along with some surrounding normal endo-myometrium. Abdominal and pelvic magnetic resonance imaging (MRI), Positron emission tomography and computerized tomography (PET-CT) was negative for metastases. After a detailed discussion with the patient and her family, they decided to go on with conservative treatment in the form of long-term chemotherapy and regular follow-up with dilatation & curettage, and imaging studies. She had weekly vincristine, actinomycin, cyclophosphamide (VAC) chemotherapy for 10 months; endometrial biopsies every three months and imaging studies were all negative for malignancy. After 23 months of follow-up she is healthy and completely free of disease.

Conclusion: Although two years without recurrence is not much time, it seems possible that select very young patients with uterine isthmic rhabdomyosarcoma might be considered for conservative treatment in the form of surgery and chemotherapy.

Keywords: Uterine rhabdomyosarcoma, sarcoma botryoides, conservative treatment, hysteroscopy, hysteroscopic resection, young patient
THE ACCURACY AND REPRODUCIBILITY OF “NON-THREE-LAYER” ULTRASOUND IN PREMENOPAUSAL WOMEN WITH ABNORMAL BLEEDING: A PROSPECTIVE STUDY

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Background and aims: To prospectively evaluate the diagnostic accuracy of the “non-three-layer” transvaginal ultrasonography (TVU) criteria for biopsy recommendation in premenopausal women that we have previously established in a retrospective study, and evaluate the reproducibility.

Methods: 146 consecutive patients underwent TVU combined with aspiration biopsy. The abnormal findings so called “non-three-layer” criteria were either diffuse or focal hyperechoic texture regardless of a three-layer; three-layer-like or non-laminar appearance; and linear irregularities. TUV findings were recorded and compared with final diagnoses of histopathologic evaluation. Sensitivity, specificity, positive and negative predictive value, likelihood ratio, inter and intraobserver reproducibility were calculated.

Results: Histologically abnormal endometrial histology found in 117 patients (80.1%) as carcinoma (2), EIN (2), polyp (101), endometritis (4) and hormonal disorders (8). The sensitivity and specificity of TVU in detecting histological abnormality using “non-three-layer” criteria were 97.4% and 93.1% with a positive and negative predictive value of 98.3% and 90.0%. The intraobserver reproducibility was excellent (weighted κ=0.96) and interobserver reproducibility between different gynecologists was good (weighted κ=0.64 and 0.67).

Conclusions: TVU using our diagnostic criteria is an excellent initial diagnostic tool with high accuracy for determining the necessity of endometrial biopsy in premenopausal women with abnormal bleeding. We achieved over 95% sensitivity and over 90% specificity with a good degree of reproducibility. We recommend TVU using “non-three-layer” criteria during the proliferative phase combined with endometrial aspiration biopsy when necessary in the workup of premenopausal women with abnormal bleeding as a perfect initial diagnostic procedure.
MORBIDITY AND MORTALITY OF THE SURGICAL TREATMENT OF THE OLDEST OLD WOMEN WITH ENDOMETRIAL CANCER

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Objective: Despite the fact the endometrial cancer commonly occurs in elderly women, little is known about the perioperative outcomes of women > 80 years of age treated surgically.

Methods: An analysis of women > 65 years of age with endometrial cancer who underwent hysterectomy with or without lymphadenectomy between 1998-2007 and registered in the Nationwide Inpatient Sample was performed. Patients were stratified by age: 65-69, 70-74, 75-79, 80-84, and ≥ 85 years of age. Multivariable logistic regression models were constructed to examine morbidity and mortality based on age while adjusting for confounding variables.

Results: A total of 25,698 women including 3789 aged 80-84 and 2024 ≥ 85 years of age were identified. Compared to women 65-69 years of age, those ≥ 85 were more likely to have perioperative surgical complications (12% vs. 17%) (adjusted OR=1.53; 95% CI, 1.34-1.76), postoperative medical complications (24% vs. 34%) (adjusted OR=1.69; 95% CI, 1.52-1.89), require a transfusion (6% vs. 10%) (adjusted OR=1.86; 95% CI, 1.55-2.24) and have a longer length of stay (3.8 days vs. 5.0 days) (adjusted OR=1.66; 95% CI, 1.44-1.88). Perioperative mortality was 0.4% in women 65-69 years of age compared to 1.6% in those ≥ 85 (p< 0.0001). Adjusting for other prognostic variables, women ≥ 85 were more than three and a half times more likely to die during hospitalization (OR=3.64; 95% CI, 2.23-5.99).

Conclusion: The complication rate associated with the surgical treatment of endometrial cancer is significantly higher in women > 80 years of age even after accounting for medical comorbidities.
ADJUVANT PACLITAXEL AND CARBOPLATIN IN PATIENTS WITH COMPLETELY OR OPTIMALLY RESECTED CARCINOSARCOMAS (MIXED MESODERMAL TUMORS) OF THE UTERUS


Gynecology, Tohoku University, Gynecology, Miyagi Cancer Center, Sendai, Gynecology, Yamagata University, Yamagata, Gynecology, Hirosaki University, Hirosaki, Gynecology, Keio University, Tokyo, Gynecology, Kanagawa Cancer Center, Yokohama, Gynecology, Kure Medical Center/Chugoku Cancer Center, Kure, Gynecology, Kumamoto University, Kumamoto, Gynecology, Fukushima Medical University, Fukushima, Gynecology, Nagoya University, Nagoya, Gynecology, Akita University, Akita, Gynecology, Fukuoka University, Fukuoka, Gynecology, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Gynecology, Nagoya City University Hospital, Nagoya, Gynecology, Tsuboi Hospital, Koriyama, Gynecology, Shikoku Cancer Center, Matsuyama, Gynecology, Ryukyu University, Naha, Gynecology, JA Hiroshima Hospital, Hiroshima, Gynecology, Tottori University, Yonago, Gynecology, Nagasaki Municipal Hospital, Nagasaki, Japan

Objectives: To determine progression-free survival (PFS) and overall survival (OS) in women with completely or optimally resected carcinosarcoma of the uterus treated with adjuvant paclitaxel (P) and carboplatin (C) (TC), and to assess the toxicity of this regimen.

Methods: We conducted a phase II study of P 175 mg/m2 plus C AUC 6 intravenously, every 3 weeks, until 6 cycles in patients (pts) with histologic confirmation of carcinosarcoma.

Results: A total of 51 pts were entered into the study between March 2006 and September 2009. The median age of the pts treated was 61 years (range: 32-81). All patients received TAH + BSO and pelvic-paraaortic lymphadenectomy was added with 30 pts (58.8%). Forty-eight pts (94.1%) were completely resected. Twenty-one (41.2%) pts were stage I, 3 (5.9%) were stage II, 22 (43.1%) were stage III, and 5 (9.8%) were stage IV. Thirty-three pts (64.7%) had homologous tumors and 18 (35.3%) had heterologous tumors. Forty pts (78.4%) were administered with 6 courses. PFS and OS were 78.9% and 74.8%, respectively. The most frequently observed grade 4 toxicities were neutropenia seen in 34 pts (66.7%), anemia in 5 (9.8%), and thrombocytopenia in 2 (3.9%). Two pts developed neutropenic sepsis, but manageable. There were 10 progress/recurrent pts (19.6%, 2: stage I, 7: stage III, and 1: stage IV).

Conclusions: Adjuvant TC in pts with completely or optimally resected carcinosarcomas of the uterus is tolerable. In the absence of concurrent controls, the impact on PFS and OS is unclear.
FEASIBILITY OF NEW BRACHYTHERAPY DEVICE FOR TREATMENT OF CERVICAL AND UTERINE CARCINOMA

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**Purpose:** This study evaluates the feasibility of a new brachytherapy treatment device for cervical and uterine carcinoma.

**Materials and methods:** The intracavitary device is a single unit with three lumens. It is inserted in collapsed form, resembling a curved tandem 3mm in width. When released two peripheral lumens expand away from the central tandem filling the uterine horns. The expansion allows multiple hdr source dwell positions and dose modulation for uterine conformity and normal tissue sparing. The device was inserted into a freshly harvested uterus and scanned in a GE CT scanner. Dose coverage was evaluated with BrachyVision (Varian) treatment planning by examining the uterine volume covered by 100%, 150%, and 200% of the prescription dose.

**Results:** The device was successfully implanted and expanded properly. The coverage for the fully loaded device (all three lumens) was approximately equal to the centrally loaded (single strut) at ~ 98% of the target volume. However, the multi-lumen loading showed a decrease in tissue receiving more than the prescribed dose with V150 of 63% compared to 68% and V200 of 41% compared to 44%.

**Conclusions:** The multi-lumen gynecologic device is clinically feasible and demonstrates high dose conformity by allowing multiple dwell positions juxtaposed to the endometrial tissue target area and minimizes areas of unnecessary dose. Additional data is being collected comparing various single lumen tandem placements with the tri-lumen device in additional specimens.
UTERINE CANCER IN THE “DR. SALVATORVUIA” CLINICAL OBSTETRICS AND GYNECOLOGY HOSPITAL ARAD DURING THE 2000-2009 PERIOD

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The purpose of this study is to examine the frequency of uterine cancer in our hospital during the 2000-2009 interval, the data being collected from the Histopathology Exams (HPE) registers. During the 2000-2009 period, 83,006 patients were admitted in our hospital and 16,063 HPEs were performed (19,35% of all patients). Uterine cancer was discovered in 392 cases, representing 31,46% of all genital cancers (1246 cases).

Most cases (372 or 94,90%) were represented by carcinomas, seventeen patients (4,34%) had sarcomas and there were also three cases of carcinoma combined with sarcoma (0,76%). The fragments sent to the histopathology departments were obtained by biopsies in 239 cases (60,97%) and from surgical specimens in 153 cases (39,03%).

The mean age of the group was 61,71±9,06 years.

Uterine cancer, although less aggressive, still remains a serious public health issue in Romania as many cases are discovered too late.
ECHOSIMIOTICS OF MICROINVASIVE ENDOMETRIAL CANCER
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The basic group was represented by 59 patients with microinvasive endometrial cancer (cancer within the mucous layer or with 5mm invasion). The average of control group was 48 patients with endometrial cancer (EC) with infiltration in miometrium more than 5mm but within 1/3 of its thickness.

The whole research was carried out with the consideration of three growth types of microinvasive EC I type - 18 patients with multiple focuses with underlying hyperplasia of all endometrium. II type - 22 patients with one tumor focus surrounded by hyperplastic endometrium. III type - 19 patients with one tumor focus with underlying mucous layer atrophy.

Obviously the true dimensions of the tumor can be definable only with the III type M echo 8.0 + 4.7mm; volume 4.2cm3). With the II type (M echo 10.5 + 5.3 mm; V5.8cm3) and to a large scale with the I type (M echo 14.5 + 6.7mm; V 8.8cm3) the sonography shows both the tumor itself and the surrounding hyperplasia of mucous layer.

Clearly the using of panoramic or virtual hysteroscopy in combination with sonography allowed in 57.9% of cases in III type and 45.5% in II type accurately defined the tumor focus with average volume 1.06sm3 , which indicates on microinvasive process.

Thus, the usage of the full range of modern ultrasound technologies and the possibility of morpho-echographical parallels allowed us correctly evaluate the option of infiltrative growth in 92.4% of cases. Moreover the differentiation of microinvasive cancer reached 88.7%. 
MANAGEMENT OF EARLY STAGE ENDOMETRIAL CANCER USING THE DA VINCI SYSTEM: 
THE BELGIAN EXPERIENCE

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Objective: We report the multicentric Belgian experience of early stage endometrial malignancies managed with robotic-assisted laparoscopic.

Materials and methods: From september 2007 to may 2010, seventy three patients with presumed early stage endometrial cancer were managed with the da Vinci system in six Belgian cancer centers.

Results: Among the 73 patients operated on for endometrial carcinoma, the median age and BMI were 69 years (range: 49-92) and 27 kg/m\textsuperscript{2} (17-46), respectively. Histology types were represented by endometrioid (n=68, 93\%), serous (n=2, 3\%), carcinosarcoma (n=2, 3\%), mucinous (n=1, 1\%) histologies. Pelvic lymphadenectomy was performed in 63 patients (86\%) and the median nodal count was 19 (range: 8-54). The mean estimated blood loss was 90 ml (range: 20-1000). Median operative time (skin to skin) is 265 min (70-400). We report no conversion to laparoscopy nor to laparotomy. The mean hospital stay was 4 days (2-19). Per-operative complications included three lymphocysts, two vaginal dehiscences, one cystitis, one compartment syndrome and post-operative complications were one recurrent epilepsy, one DVT. After a median follow-up of 20 months, one patient died of disease (serous histology, no staging and no adjuvant due to advanced age). Four patients experienced local/regional recurrences and are actually alive.

Conclusions: This series reports the initial multicentric Belgian experience with the da Vinci for the management of early stage endometrial cancer. It supports the feasibility and safety of this surgical approach. Staging rate is high and blood loss, hospital stay, complication rate are low. Longer follow-up is needed to confirm oncologic outcomes.

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ASSESSMENT OF RISK FACTORS OF LYMPH NODE METASTASIS IN ENDOMETRIAL CANCER

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Objective: Assess the risk factors associated with node involvement.

Study desing: In the period 1990-2008 a total of 265 endometrial cancers were treated in the Institut Universitari Dexeus. Rate of myometrial invasion, tumour grade, node involvement are analyzed.

Results: 86% of tumours were endometrioid. Among those with endometrioid histology, lymphadenectomy was not performed (NL) in 85 cases (37.2%), whereas pelvic lymphadenectomy (PL) or pelvic-aortic lymphadenectomy (PAL) was carried out in 84 (36.84%) and 59 patients (25.87%), respectively. In NL patients the overall disease-free survival (DFS) rate at five years was 92.8%. In the PL group, node involvement was observed in 2.4% of cases and the five-year DFS rate was 92.3%. Among PAL patients, 18.6% showed node involvement (72.7% positive pelvic nodes and 63.6% aortic). Aortic involvement was present in 5.9% of cases when there was no pelvic disease, whereas in the presence of positive pelvic nodes the rate of aortic involvement was 50%. The DFS rate at five years was 93.6%. Referring to the risk factors, when infiltration was >50% of the myometrium, lymph node involvement occurred in 37% of cases and G3 tumors in 45.5%.

Conclusions: Node involvement is more commonly observed in cases with >50% myometrial invasion and G3, accounting for 25% of cases that can be considered as at-risk patients. When node involvement is present it is equally distributed between the pelvic and aortic levels. As node involvement is a predictive factor for distant metastasis, the 25% of patients considered to be at risk should undergo pelvic and aortic lymphadenectomy.
RETROSPECTIVE REVIEW OF 187 WOMEN TREATED FOR CARCINOSARCOMA BETWEEN 1970 AND 2008 AT GROOTE SCHUUR HOSPITAL, CAPE TOWN, SOUTH AFRICA

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Background: Carcinosarcoma is a rare uterine cancer with a poor prognosis. Management is controversial and usually involves surgery. Additional radiation and/or chemotherapy are of uncertain benefit. The study was undertaken to document the outcome of treatment of carcinosarcoma, comparing the different treatment approaches used at our institution during the period under review.

Methods: The records of 186 women treated between 1970 and 2008 were retrieved and analyzed for demographic data, pathology, treatment modalities and survival.

Results: The median age was 67 years (range 31 - 86). The stage distribution was 68 (36.4%) for stage I, 29 (15.5%) for stage II, 58 (31%) for stage III and 32 patients (17.1%) for stage IV. Forty six women did not undergo surgery (advanced disease in 33, medically inoperable in 6, and no reason found in 7 patients). Of the 33 patients with advanced disease, 15 received pelvic radiotherapy only, and 18 were treated symptomatically. The mean survivals for these patients were 9.8 and 3.9 months respectively. One hundred and forty women underwent standard surgery in the form of hysterectomy and bilateral salpingo-oophorectomy. Of these patients, 83 were found to have stage I and II. There was no apparent benefit when surgery alone was compared with surgery followed by adjuvant treatment with radiotherapy and/or chemotherapy, either in overall survival or disease free interval.

Conclusion: From our data, we could find no evidence of a survival benefit with the addition of adjuvant treatment after surgery for early stage carcinosarcoma. Radiotherapy can palliate symptoms in advanced disease.
SYSTEMATIC PELVIC AND PARAORTIC LYMPHADENECTOMY IN ENDOMETRIAL CANCER: LYMPH NODE METASTASIS PATTERN AND IDENTIFICATION OF PREDICTIVE FACTORS FOR LYMPH-NODE STATUS

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¹Gynecology and Gynecological Oncology, Dr. Horst Schmidt Kliniken, Wiesbaden, ²Gynecology and Gynecological Oncology, Charité Campus Virchow-Klinikum, Berlin, Germany

Background: Endometrial cancer is surgically staged since 1988; however, there is a controversy and debate about the indication and extent of lymphadenectomy, and in particular, the role of a complete bilateral infrarenal paraaortic nodal dissection.

Methods: We analysed retrospectively the data from two major gynaecological-oncology centres in Germany. Included were patients with endometrial cancer treated between 1998 and 2008 with any of the following risk factors: myometrial space invasion > 50%, G3, histological type II. All patients received a surgical staging including systematic pelvic and para-aortic lymphadenectomy.

Results: 128 patients were included, 77 patients (60.2%) had T1-Status. The median number of removed pelvic and paraaortic lymph nodes was 29 (1-66) and 21.5 (2-63), respectively. 27 patients (21.1%) had positive lymph nodes. 14 patients (10.9%) had positive pelvic and para-aortic lymph nodes; 6 patients (4.7%) presented with only para-aortic positive lymph nodes and 7 patients (5.5%) had only positive pelvic nodes.

48.1% of the affected para-aortic lymph nodes were above the level of the inferior mesenteric artery. Multivariate analysis revealed that only the T-Status (P-Value: 0.041) was a significant risk factor for N1-status. Not significant were age, histology and grading.

Conclusion: Para-aortic lymphadenectomy cannot be abandoned in the staging of high-risk endometrial cancer. The extension of dissection should always be above the level of the inferior mesenteric artery up to the renal veins. The future prospective trial (ECLAT) will investigate the prognostic effect of full lymphadenectomy in high risk patients.
DIAGNOSTIC VALUE OF ENDOMETRIAL CYTOLOGY FROM DIRECT SAMPLING BY BRUSHING

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Background: The purpose of the current study was to examine the diagnostic value of cytology from direct endometrial sampling by brushing.

Methods: In our institution starting from Jan 01 2008 to May 15 2010, 359 women (age 26-87, mean 56 years, 204 postmenopausal) underwent endometrial brushing in an outpatient setting. 251 patients had abnormal uterine bleeding, 50 had asymptomatic endometrial thickening (>4 mm), the others needed preoperative controls for other reasons or were treated with tamoxiphen, or had atypical glandular cells on pap-smear. Cytologic slides were obtained by filtration (fig.1).

![Figure 1]

A sample large enough to prepare cell-block for histology was obtained in all cases (fig.2).

![Figure 2]

Results: Patients defined the technique rather painless. In 15% of the cases the sample was non diagnostic. The cases were categorized as non-pathologic (negative) and pathologic (atypical hyperplasia and carcinoma) (table 1).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for atypical cells</td>
<td>273 (76%)</td>
</tr>
<tr>
<td>Presence of atypical cells</td>
<td>27 (7.5%)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>56 (15%)</td>
</tr>
</tbody>
</table>

[Tab. 1. Cytological diagnosis]

The correlation between samples obtained by brushing and histology on biopsy or surgical specimen was possible in 95 cases. The diagnostic concordance was 92%. 22/25 pathologic cases were correctly diagnosed. 3 cases of carcinoma were underdiagnosed, 2 cases of reactive changes were overestimated and in 2 cases of neoplasia the sample was inadequate. Sensitivity was 92%, specificity 96%, positive predictive value 95%, negative predictive value 94%.

Conclusions: Endometrial direct sampling in an outpatient setting is well tolerated. This procedure allows also cell-blocks preparation. The endometrial cytology is less expensive and invasive than other procedures and therefore it could be effectively used in the detection of endometrial malignancies or atypical hyperplasias in symptomatic women.
TAXAN-PLATINUM BASED CHEMORADIATION IN ENDOMETRIAL CANCER III-IV PRIMARY TREATMENT

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Background: Endometrial cancer (EC) Stage III - IV patients’ prognosis is very poor with more than 40% rate of one-year morbidity.

Purpose: To evaluate the significance of taxan-platinum (TP)-based chemoradiation in EC III-IV disease control.

Materials and methods: 25 pts., 38 - 73 y.o, EC T2b-3cNo-1Mo-1 underwent chemoradiation after radical surgery.

9 pts (36%) with ovarian metastases (T3a) received only brachytherapy (BT), Co-60, Ir-192 HDR TD 30Gy to vaginal cuff and adjuvant 3-9 cycles of TP (paclitaxel 175mg/m2, carboplatinum AUC 5-6). In 16 pts. (64%) T2b-T3b BT HDR and external beam irradiation (EBRT) 18MeV were performed concomitantly with 4-6 cycles of TP, pelvis only (TD 30-34Gy to center, TD 44-46Gy to pelvic LN) in N0 pts. In N1 pts. paraaortic LN were irradiated TD40Gy additionally or simultaneously with pelvic RT and cycles of TP. No specific prevention for gastro-intestinal (GIT) or urinary complications, G-CSF (Leucostim®, Biocard, Moscow, Russia) 600mcg weekly to prevent predicted hematological toxicity, no severe complications during the treatment.

Results: In 24 months 22 pts (88%) are still alive, no evidence of progression in 15 (60%) pts. Local recurrences - 4 pts (16%), LN recurrences - 2 pts. (8%), distant metastases - 4 pts. (16%), GIT (I-II - 56%, III - 4%), thrombocytopenia (I-II - 24%, III-4%) were the most common early complications. Fibrosis III in 1 (4%)pts. and surgically treated intestinal stenosis in 1 (4%)pts. - the most severe late complications.

Conclusion: TP-based individually planned chemoradiation can be considered effective and tolerable in EC III-IV primary treatment.
CHANGING PATTERNS OF RADIOTHERAPY FOR POST OPERATIVE ENDOMETRIAL CANCER 2000-2008

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Background: Since 2000, practice patterns for post operative radiation of endometrial cancer patients have changed from external pelvic radiation to vaginal brachytherapy.

Purpose: The objectives of this study were to identify endometrial cancer patients referred for radiation from 2000-2008 and to quantify the changing proportion of patients receiving pelvic radiation (PRT), vaginal brachytherapy (VB) or both (PRT + VB).

Methods: This is a retrospective review of tumor registry data from University of Iowa Hospitals and Clinics (UIHC). Patients with endometrial cancer were sorted to identify those referred for radiation. The first 50 patients (2000-2002) and the last 50 patients (2007-2008) on the list were compared. Patients were excluded if they were not treated, had definitive radiation, metastases, or a non-epithelial tumor. The remaining patients were compared for the proportion treated with PRT, VB or both.

Results: The proportion of patients referred for radiation remained stable at approximately 30 %. Of the first 50 patients, 20 were excluded (6 definitive, 1 metastasis, 6 sarcomas, 7 refusals). Of the last 50 patients, 20 were excluded (8 definitive radiation, 4 metastases, 8 sarcomas). In the early group (2000-2002) 1/30 patient received VB (3.3%), 22/30 received PRT (73.3%) and 7/30 received PRT + VB (23.3%). In the later group (2007-2008) 24/30 received VB (80%), 4/30 received PRT (13.3%), and 2/30 received PRT + VB (6.7%).

Conclusions: The primary treatment modality for post operative endometrial cancer patients has changed from pelvic radiation to vaginal brachytherapy. This may have significant implications for resource utilization.
EVALUATION OF RISK FACTORS AND PROGRESSION HISTORY IN WOMEN WITH RECURRENT POSTMENOPAUSAL BLEEDING

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Introduction: Postmenopausal bleeding increases risk of endometrial cancer by 64 fold. There is 10% risk of endometrial cancer amongst postmenopausal bleeding women if the USS thickness is < 4 mm and the cervix is normal then further investigation is unnecessary (RCOG) . The management of women returning with further episodes of PMB is uncertain. It is also not known for how long a negative scan or benign histological report is protective in relation to future endometrial cancer development.

Method: - We looked retrospectively at records of women diagnosed with endometrial cancer from 2004 to December 2008 to develop a strategy for the group of women who continued to present to our PMB clinic.

We identified women who presented to PMB more than once and subsequently developed endometrial cancer. We identified 23 women amongst our service.

Results: Total no of patients with endo.cancer was 470 .23 patients were identified in recurrent PMB group of 225 attenders. The average mean presentation from the last benign pathology to cancer was 40 month( 4mth-15 yr). The time lapse from first presentation to cancer averaged 49 mth(4mth-15 year).Raised BMI > 30 was consistent in 18 women.

Conclusion: Most women were diagnosed on their first presentation. The change to malignancy usually appears to take at least one year. Patients presenting with PMB for a second time should be re investigated in the same manner as those who present for the first time Endometrial cancer may result from continuous endogenous endometrial stimulation.
PERSONALIZING ENDOMETRIAL CANCER TREATMENT BASED ON ERCC1 AND CLASS III β-TUBULIN: RESULTS FROM AN IMMUNOHISTOCHEMICAL STUDY

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Background: The expression of the excision repair cross-complementation group 1 (ERCC1) and class III β-tubulin correlates with resistance to platinum and taxanes in non-small cell lung cancer.

Material & methods: 149 patients received platinum-based chemotherapy, with or without paclitaxel. Patients were divided into 2 groups: group A (n=33), patients with early stage endometrial cancer treated with adjuvant chemotherapy. Group B (n=116), primary advanced or recurrent cases. Immunohistochemistry was used to analyse the expression of ERCC1 and class III β-tubulin. The findings were correlated with clinical outcome, including RECIST-criteria, recurrent free- and disease specific survival.

Results: The mean age of 149 patients was 64 years (range 31-84). Distribution of histopathological subtypes was as follows: 44(30%) endometrioid, 92(62%) serous/clear cell and 13(8%) carcinosarcomas.

<table>
<thead>
<tr>
<th>Group A (n=33)</th>
<th>Response Rate (n(%))</th>
<th>Recurrence (n(%))</th>
<th>DOD (n(%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCC1 positive</td>
<td>2/11(18)</td>
<td>2/11(18)</td>
<td></td>
</tr>
<tr>
<td>ERCC1 negative</td>
<td>6/20(30)</td>
<td>5/22(23)</td>
<td></td>
</tr>
<tr>
<td>β-tubulin positive</td>
<td>2/6(33)</td>
<td>2/7(29)</td>
<td></td>
</tr>
<tr>
<td>β-tubulin negative</td>
<td>1/2(50)</td>
<td>1/2(50)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group B (n=116)</th>
<th>ERCC1 positive</th>
<th>12/25(48)</th>
<th>12/19(63)</th>
<th>13/25(52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCC1 negative</td>
<td>35/91(38)</td>
<td>52/79(66)</td>
<td>54/91(59)</td>
<td></td>
</tr>
<tr>
<td>β-tubulin positive</td>
<td>25/52(48)</td>
<td>26/43(61)</td>
<td>25/52(48)</td>
<td></td>
</tr>
<tr>
<td>β-tubulin negative</td>
<td>10/18(56)</td>
<td>10/15(67)</td>
<td>10/18(56)</td>
<td></td>
</tr>
</tbody>
</table>

[The clinical outcome in relation to the expression]

Conclusion: In contrast to theoretical assumptions, the expression of ERCC1 and class III β-tubulin did not predict sensitivity to cytotoxic treatment and patient outcome in endometrial cancer.
THE KIT GENE IN ENDOMETRIAL CARCINOMA: AN IMMUNOHISTOCHEMICAL AND MUTATIONAL ANALYSIS

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Objective: Since the outcome of recurrent disease of endometrial carcinoma is cumbersome, the development of target treatment strategies is critical. We evaluated KIT, a receptor tyrosine kinase, to determine a potential role for imatinib mesylate in the treatment of endometrial carcinoma.

Material & methods: Immunohistochemical analysis for KIT expression was performed on paraffin sections from 45 patients: 30 primary and 15 recurrent tumors. Fifteen primary cases were available for mutation analysis.

Results: Histopathological distribution of paraffine embedded tissue was as follows: 30 type I and 15 type II endometrial carcinoma. Histopathological distribution of fresh frozen tissue was as follows: 8 type I and 7 type II. Cases did not show KIT expression nor mutations in mutational hot spot exons of KIT gene.

Conclusion: Based on the absence of KIT expression or mutations, endometrial carcinoma is unlikely to respond to imatinib mesylate.
THE WEEKLY PACLITAXEL-CARBOPLATIN REGIMEN IN PATIENTS WITH PRIMARY ADVANCED OR RECURRENT ENDOMETRIAL CARCINOMA

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Gynecological Oncology, University Hospitals Leuven, Leuven, Belgium

Objective: To evaluate the response of weekly paclitaxel/carboplatin (TC) in patients with primary advanced or recurrent endometrial cancer.

Methods: Eighteen cycles of paclitaxel (60mg/m$^2$) and carboplatinum (AUC 2.7) were administered weekly. Response rates were evaluated according to RECIST criteria.

Results: TC weekly was administered to twenty-six patients. Median age was 61 years (range 40-80). Main histopathologic types were serous/clear cell (n=13) and endometrioid (n=9). Patients were divided into 2 groups: chemo-naïve group (n=16)(group1) and a group with previous chemotherapy (n=10)(group2).

Response for group1 was as follows: 8(50%) partial remission (PR), 1(6%) stable disease (SD) and 7(44%) progressive disease (PD). Response for group2: 3(30%) PR and 7(70%) PD. Median progression free survival (PFS) for group 1 was 8 months(range5-9). At time of analysis 50% of patients were still alive after median follow up of 12 months(6-18). PFS for group 2 was 8 months(6-10).

Overall 390 weekly treatments were administered. Due to grade 4 bone marrow toxicity, treatments needed to be adjusted: 78(20%) dose reduction (AUC 1.3-2), 62(16%) dose delay, 4 (1%) were not administered and 4 (1%) were changed to paclitaxel/cisplatin. Twenty-one patients (84%) needed treatment adjustment due to toxicity. Neutropenic fever occurred in 1patient (4%). The most common non-hematological toxicities were grade1-2 fatigue (92%) and grade2 nausea (38%) of patients. 8% suffered from grade2 neural toxicity.

Conclusion: TC weekly is active in primary advanced or recurrent endometrial cancer, especially in chemo-naïve patients. Treatment modifications due to toxicity were frequent but similar as for the previously tested 3-weekly and dose-dense regimen.
THE ROLE OF ADJUVANT CHEMOTHERAPY IN SURGICAL STAGE I-II SEROUS ENDOMETRIAL CARCINOMA AND ENDOMETRIAL CARCINOSARCOMA: A COLLABORATIVE STUDY

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Objective: To assess the benefit of adjuvant chemotherapy in early stage type II endometrial cancer (serous (S), clear cell carcinoma (CC)) and carcinosarcomas (CS). This study evaluates the impact of adjuvant chemotherapy on recurrence and survival for early stage type II endometrial cancer.

Material & methods: Patients diagnosed with surgical stage I-II S-CC and CS after comprehensive surgical staging were retrospectively collected. This was defined as lymphadenectomy of >11 nodes harvest and exploration of the upper abdomen, with or without omentectomy. Groups with (group A) and without (group B) platinum-based chemotherapy were compared.

Results: We identified 73 patients with a mean age of 66 years (range 48-88). The upper abdomen was not explored in 4 women, who currently are without evidence of disease.

Group A consisted of 36 patients (25 S-CC and 11 CS). Nine (25%) systemic recurrences (6 S-CC and 3 CS) were observed. Group B existed of 37 patients (29 S-CC and 8 CS) of which eleven (30%) showed systemic recurrence (8 S-CC and 3 CS). The median recurrence free survival was 21 months (range 13-51) for group A versus 7 months (range 1-59) for group B (p=0.058). Five patients (14%) of group A and nine (24%) of group B died of disease after a median follow-up of 29 months (range 20-59) and 17 months (range 4-64) respectively (p=0.153).

Conclusion: Recurrences in early stage type II endometrial cancer occur irrespective of adjuvant chemotherapy. Prospective randomized intergroup trials only can address the benefit of adjuvant chemotherapy in early stage high risk endometrial cancer.
THIRTEEN-YEAR EXPERIENCE OF 832 PATIENTS WITH ENDOMETRIAL CANCERS FROM A CHINESE INSTITUTION

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\textbf{Background and aims:} The aim of this study was to describe our experience of endometrial cancer.

\textbf{Methods:} A retrospective analysis was performed on a series of 832 endometrial cancers treated in Fudan University Shanghai Cancer Center between 1995 and 2008.

\textbf{Results:} The mean age of the patients was 55 years (26-85). Seven hundred and eighty cases (93.8\%) underwent primary surgery. According to the FIGO staging 2009 criteria, 659 (79.2\%) cases were classified as stage I, 63 (7.6\%) stage II, 59 (7.1\%) stage III and 51 (6.1\%) stage IV. Distribution of tumor grade was as follows: grade 1, 269 (32.3\%); grade 2, 363 (43.6\%); grade 3, 154 (18.5\%). The commonest histological subtype was endometrioid carcinoma (85.1\%), followed by uterine papillary serous carcinoma (UPSC) (5.4\%). Modified radical hysterectomy and lymphadenectomy was performed in 79.6\% and 60.7\% of the patients respectively. The median number of lymph nodes dissected was 18 (1 to 47). Lymph node metastasis was found in 20.0\% of Type-II carcinomas and 11.0\% of Type-I carcinomas (P=0.035), with the highest in UPSC (42.8\%). Postoperative radiotherapy and chemotherapy was performed in 20.0\% and 30.2\% of the patients respectively. The 5-year disease-free survival and overall survival in Type-I carcinomas was 84\% and 91\%, significantly higher than in Type-II carcinomas (49\% and 60\%, p=0.000).

\textbf{Conclusions:} Majority of endometrial cancers in Chinese population presented at early stage and had a favorable prognosis. Lymphadenectomy was necessary in the management of Type-II endometrial cancers. Some clinical trials are ongoing to improve the poorer prognosis in Type-II carcinomas.
CLINICOPATHOLOGIC CLEAR CELL ENDOMETRIAL CANCER’S STUDY

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Objectives: Clear cell endometrial cancer is an uncommon but important disease because of its aggressive behavior. Furthermore, prospective, randomized studies are either too difficult or impossible because of the small number of patients. The objective of this review is to study the clinicopathological factors of this entity.

Material and methods: We reviewed cases of endometrial cancer in HUC between 1994 and 2009, a total of 175 cases, of which, 13 were found to be clear cell carcinomas, surgery and treated in our hospital. They were followed the same until April 2010. We also reviewed the diagnostic and therapeutic management of this tumor.

Results: Clear cell histology was diagnosed in 7.4% of cases. This tumor occurs mainly in postmenopausal, mean age at diagnosis of 68 years. The first clinical sign was postmenopausal metrorrhagia in 69% of cases.

The diagnosis was made in early stages in all cases, surgical treatment was performed optimal surgery: 63%), followed by adjuvant radiotherapy in 92% plus adjuvant chemotherapy in 30% of cases. Recurred in more than 50% of patients (pelvic at 23% and 31% with metastases) who were treated only with chemotherapy, in 57% of cases. 3 out of 13 patients died.

Conclusions: Women with clear cell carcinoma require complete surgical stratification. Adjuvant chemotherapy should be considered part of treatment. It is suitable care and long-term monitoring after treatment, because of the high rate of recurrence.
BRAIN METASTASES ASSOCIATED WITH ENDOMETRIAL CANCER: A SERIES OF 18 CASES
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Objective: Less than 100 cases of brain metastases from endometrial cancer (EC) have been reported in the literature. In this study, we report our experience in the management of brain metastases (BM) from EC.

Methods: We retrospectively analyzed EC cases treated at Mayo Clinic during the time interval 1984-2001, to identify patients who developed primary BM (i.e. BM either at the time of diagnosis of EC or as primary site of recurrence).

Results: Among the 1,632 patients operated at Mayo for EC, 14 (0.86%) developed primary BM. Including 4 referred cases, the clinical outcome of 18 patients was assessed. In two (11.1%) cases, the diagnosis of BM was made at presentation of EC; in the others, median time to recurrence was 5 (range 1-57) months. All patients had symptoms associated with their BM. Median survival after the diagnosis of BM was 5.5 (range 0-118) months. Multiple brain lesions and the presence of extra-cerebral dissemination at diagnosis of BM were significant predictors of poor prognosis. Overall survival was 64 (7-118) months in patients with single BM without extra-cerebral involvement (N=6), vs. 3 (0-28) months in the other 12 patients (p=0.009). Considering the 6 patients with solitary BM without extracerebral spread, 5 of them had complete surgical excision (± chemotherapy or radiation) with a median survival of 82 months.

Conclusions: Less than 1% of patients develop primary BM from EC. The presence of solitary BM without extra-cerebral spread is associated with improved survival when treated with complete surgical excision.
ADJUVANT RADIOTHERAPY FOR ENDOMETRIAL CANCER STAGE IB HISTOLOGICAL GRADES 1 AND 2: COMPARISON BETWEEN TREATMENT REGIMENS

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Objectives: To compare the rates of Overall Survival (OS), Disease-free Survival (DFS) and Toxicity in different techniques of postoperative radiotherapy for stage IB endometrioid adenocarcinoma of endometrium, histological grades 1 and 2.

Methods: A before and after trial was performed, and 133 women with a minimum follow-up of 5 years were included. Teletherapy (Tele group), with 22 patients treated from 1988 to 1996, with a 10 MV linear accelerator, average dose 46.2 Gy. Low dose rate brachytherapy (LDRB group) was performed between 1992 and 1995, in 19 women, with an insertion of Cesium 137, at a 60 Gy dose. Fourteen women operated between 1990 and 1996 did not receive radiotherapy (NO RT group). High dose rate brachytherapy was performed in 78 patients (HDRB group), from 1996 to 2004, in five weekly 7 Gy insertions, prescribed at 0.5 cm from the vaginal cilinder. Results The 5-year disease-free survival was 94.6% for the HDRB group, 94.1% for the LDRB group, 100% for the tele group and NO RT groups (p=0.681). The 5-year overall survival was 86.6% for the HDRB group, 89.5% for the LDRB group and 90% for the tele group and NO RT groups (p = 0.962). Grades 3-5 late toxicity was 5.3% in LDRB group and 27.3% for the tele group (p < 0.001).

Discussion: Patients submitted to adjuvant teletherapy showed very high toxicity, which contra-indicates that treatment for those patients. There may be a role for adjuvant HDRB, but randomized controlled trials are still needed to evaluate its benefit.
THE STUDY OF MORPHOLOGICAL CHARACTERISTICS OF BLOOD CELLS IN WOMEN WITH UTERINE TUMOURS

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Background and aims: Analysis of morpho-structural characteristics of blood cells is important step in diagnosis of pathology and gives possibility to evaluate the gravity of the disease. The aim of the study was to investigate morpho-structural characteristics of blood cells (erythrocytes, lymphocytes and thrombocytes) in women with uterine tumours.

Methods: The object for investigation was blood of patients with uterine benign (myoma, age of 40-46) and malignant (uterine cancer, age of 50-65) tumours. Ultrastructural observation of blood cells was held by electron microscopy (Tesla, Zchech, BS-500) with rapid pressure.

Results and conclusions: The obvious changes of blood cells (erythrocytes, lymphocytes, thrombocytes) morpho-structural indexes have been revealed in case of uterine cancer - giant young cells, segmentation of nucleus, picnotic and segmented nucleus, great number of citoplasmic inclusions, increased granulation, membrane outgrowths.

These changes sharply reflect the alterations that take place in parallel with hormonal imbalance. The changes in structural characteristics of blood cells can be used for evaluation the gravity of given pathology.
STAGING SYSTEMS IN UTERINE SARCOMAS. CAN THE NEW STAGING SYSTEM PREDICT THE SURVIVAL AND PROGNOSIS?

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Objective: International Federation of Gynecology and Obstetrics (FIGO) designed a new staging system in 2009 for uterine sarcomas. We want to evaluate the new staging system for overall survival and prognosis in this retrospective study.

Method: We analysed 115 patient with the diagnosis of uterine sarcomas in two centers between 1988-2009. Data were collected from patients files. We used SPSS 18 for statistical analysis.

Results: The mean age was 58.11(± 11.21). The mean gravida was 3.87(±2.11), the mean parity and abortion was 3.10 (±1.77) and 0.77 (±1.18) respectively. The most common two type postoperative diagnosis from the pathological specimens were malign mixed mullerian tumor (32.8%) and liomyosarcoma (32.7%). For FIGO 1988 classification endometrial stromal sarcomas (high grade) accounted 11.5 % and also low grade stromal sarcomas accounted 11.5% of all uterine sarcomas in our study. Smooth muscle tumors of uncertain malignant potential(STUMP), adenosarcomas, undifferentiated endometrial sarcomas was 4.4%, 3.5% and 2.7% respectively. Totally 106 patients could be staged with both staging systems(FIGO 1988 and FIGO 2009). Number of the patients that the clinical stage remained unchanged was 63 (59.43%). Only one patient's clinical stage got advanced stage for FIGO 2009. The number of the patients had lower stage for FIGO 2009 was 42 (39.62%). We evaluated overall survival for every stage of sarcomas there were no statistical difference between two groups.

Conclusion: New staging system(FIGO 2009) for uterine sarcomas doesn't suggest a better prediction for survival rates than previous staging system(FIGO 1988) although significant number of cases(39.62%) have changes in new staging system.
THE REGULATION OF BUB1 EXPRESSION IN ENDOMETRIAL CARCINOMA CELL WITH ESTROGEN AND PACLITAXEL

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Objective: The spindle checkpoint protein kinase Bub1 performs a crucial function for correct chromosome segregation during mitosis. However, the signal pathway of Bub1 involving the tumorigenesis is not clear in endometrial carcinoma. The purpose of this study is to explore the regulation of Bub1 expression in endometrial carcinoma cell with estrogen and Paclitaxel.

Methods: The high differentiated endometrial adenocarcinoma cells (Ishikawa cell line) were cultured in DMED/F12 supplemented with 10% FBS or phenol red-free DMED/F12 supplemented with 5% dcFBS. After the cells were stimulated with estradiol (E2), the expression of Bub1 was detected by real-time quantitative PCR. Then, Paclitaxel was added to Ishikawa cells at different time, and real-time quantitative PCR was also used to detect the expression of Bub1.

Results: Bub1 mRNA expressed in Ishikawa cell line. 17β-E2 could decrease the expression of Bub1 mRNA in Ishikawa cell. Dose-response experiments revealed maximal estradiol stimulation at 10\(^{-8}\) mol/L. After Ishikawa cells was treated with serum-free culture, Paclitaxel could also significantly decreased the expression of Bub1 mRNA (\(P < 0.05\)). While without adjuvant treatment, Paclitxel significantly increased the expression of Bub1 mRNA (\(P=0.02\)).

Conclusion: Bub1 expression is regulated by estradiol and Paclitaxel. Deregulated Bub1 expression may contribute to chemotherapeutic efficacy of Paclitaxel.
FERTILITY-SPARING COMBINED HYSTEROSCOPIC AND MEDICAL TREATMENT OF ATYPICAL ENDOMETRIAL LESIONS IN YOUNG WOMEN


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Background and aims: To assess safety and effectiveness of combined hysteroscopic and medical treatment of atypical endometrial lesions in young women to preserve their fertility.

Methods: In the Department of Gynaecology and Obstetrics of “Federico II” University of Naples 14 patients (mean age 32.6±3.5 yrs) with a diagnosis of atypical polypoid adenomyoma (APA) (n=4), atypical endometrial hyperplasia (AEH) (n=6) and well differentiated (G1) endometrial cancer (EC) (n=4) were enrolled in a prospective study. For all patients were excluded cancer invasion and metastases. All patients were treated with hysteroscopic resection of endometrial atypical lesions preserving the basal endometrial layer. Furthermore a levonorgestrel releasing intrauterine system (LNG-IUS) was inserted in all patients. GnRH analogues for 6 months were also administered to 2 of those 4 patients with a pre-treatment diagnosis of EC.

Results and conclusion: At 24 months of follow up no patient had a progression of the endometrial disease. Ten patients had a complete remission (CR) with normal functional endometrium. Two patients had a partial response (i.e. a regression of endometrial carcinoma to atypical hyperplasia). No recurrence was detected at the follow up. Four out of the 10 patients with a diagnosis of CR had a pregnancy after LNG-IUS removal and 6 patients decided to continue contraceptive LNG-IUS treatment. Hysteroscopic resection of endometrial atypical lesions preserving the basal endometrial layer, followed by medical treatment, is a safe and effective treatment, in young women desiring to preserve their fertility.

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<th>Treatment (2)</th>
<th>Treatment response (3)</th>
<th>Follow up (24 months) (4)</th>
<th>Pregnancy</th>
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[Patient's diagnosis and treatment details.]
FERTILITY-PRESERVING HIGH-DOSE MEDROXYPROGESTERONE ACETATE (MPA) THERAPY FOR 4 YOUNG PATIENTS WITH GRADE 2 ENDOMETRIOID ADENOCARCINOMA


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Objective: Fertility-preserving therapy with medroxyprogesterone acetate (MPA) is administered to young patients with endometrial cancer of grade 1 endometrioid adenocarcinoma (G1). We experienced 4 patients with grade 2 endometrioid adenocarcinoma (G2), who were estimated to have no myometrial invasion and strongly desired to preserve fertility. We report and assess MPA therapy for G2.

Patients and methods: Since 2006, we administered MPA (600mg/day) to 4 patients with G2 with solid growth part in 5 to 20 percents area of total tumor volume at Keio University Hospital. All cases showed positive immunoreactivities for PgR. After 4 months of oral administration, D&C and/or TCR (transcervical resection) were performed. When residual disease existed, an additional 2 months oral administration followed by D&C were repeated. After tumor disappeared, careful follow-up was performed every 3 months with endometrial cytology and biopsy as well as transvaginal ultrasound. We compared treatment outcomes with those of 62 cases of G1 who similarly received MPA therapy.

Results: Tumor disappearance was noted in all cases; however, the average time required for tumor disappearance was 394 days (224-671) compared with 112 days in G1 (p < 0.05). During the follow-up period (496-1053 days), one patient became pregnant and delivered; however, the remaining 3 patients recurred within the endometrial cavity as either atypical endometrial hyperplasia or G1. Times to recurrence were, 493 days, 496 days, and 130 days.

Conclusions: Effects of MPA treatment for G2 may be lower than those for G1. Based upon these data, it may be difficult to readily indicate MPA therapy for G2.
MATRIX METALLOPROTEINASE-1 AND -9 PROMOTER POLYMORPHISMS AND ENDOMETRIAL CARCINOMA RISK IN A JAPANESE POPULATION

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Objective: Several studies have demonstrated association between matrix metalloproteinases (MMP) gene polymorphisms and various cancers. The object of this study was to investigate whether the MMP-1 and MMP-9 gene promoter polymorphisms are associated with endometrial carcinomas in a Japanese population.

Methods: We compared the allele frequencies and genotype distributions of single nucleotide polymorphisms in the promoter regions of MMP-1 (-1607 1G/2G) and MMP-9 (-1562 C/T) in 107 endometrial carcinoma cases and 213 controls using polymerase chain reaction-restriction fragment-length polymorphism analysis.

Results: The allele frequencies of MMP-1 -1607 2G and MMP-9 -1562T were 64.0% and 10.7% in the cases and 70.0% and 16.7% in the controls, respectively. No significant differences in the allele frequencies or genotype distributions were found between cases and controls for the MMP-1 -1607 1G/2G polymorphism. However, a small but significant difference in the allele frequency of the MMP-9 -1562T allele was noted between cases and controls (P = .046; odds ratio [OR] =1.01; 95% confidence interval [CI], 1.01 to 2.73). Stratification by histology revealed a significant difference in the frequency of the MMP-9 -1562T allele between endometrioid carcinoma cases (10.2%) and controls (P =.043; OR = 1.76; 95% CI, 1.02 to 3.03); we did not find a significant difference in the frequency of the MMP-9 -1562T allele between non-endometrioid carcinoma cases (13.2%) and controls.

Conclusions: These results suggest that the MMP-9 -1562 C/T polymorphism may be associated with susceptibility to endometrioid carcinoma in the Japanese population.
ASSOCIATION STUDY OF VASCULAR ENDOTHELIAL GROWTH FACTOR GENE POLYMORPHISMS IN ENDOMETRIAL CARCINOMAS IN A JAPANESE POPULATION

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Objective: Vascular endothelial growth factor (VEGF) is one of the most potent endothelial cell mitogens and plays a critical role in angiogenesis of endometrial carcinomas. Several studies have demonstrated positive associations between VEGF gene polymorphisms and several carcinomas. In this study, we investigated whether VEGF gene polymorphisms are associated with endometrial carcinomas in a Japanese population.

Methods: The allele frequencies and genotype distributions of VEGF -460 C/T, +405 G/C, and +936 C/T polymorphisms were examined in 105 endometrial carcinomas and 179 controls using PCR-RFLP analysis. An association of these polymorphisms with three year-disease free survival was evaluated using Kaplan-Meier method.

Results: No significant differences in the allele frequencies and genotype distributions of VEGF -460 C/T (P=0.54, 0.90), +405 G/C (P=0.31, 0.17), and +936 C/T polymorphisms (P=0.46, 0.24) were observed between endometrial carcinoma patients and controls. There were no significant differences in the frequencies of haplotype -460 T/+405 C between patients and controls. Furthermore, VEGF -460 C/T, +405 G/C, and +936 C/T polymorphisms were not associated with three year-disease free survival of endometrial carcinoma patients.

Conclusions: Although limited by sample size, our study did not demonstrated any evidence that VEGF -460 C/T, +405 G/C, and +936 C/T polymorphisms are associated with an increased risk of endometrial carcinomas in Japanese women.
DETECTION OF THE MUCIN GENES (MUC1, MUC3, MUC4, MUC13, MUC15) IN NORMAL AND NEOPLASTIC ENDOMETRIAL TISSUES

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Background: Mucins are large and heavily O-glycosylated proteins expressed by epithelial tissues. The alterations in mucin expression or glycosylation are thought to contribute to the pathogenesis of cancer. Previous studies have shown an association of MUC1 with poor prognosis and MUC2 and MUC5AC with a mucinous phenotype. However, the expression of other mucins in endometrial carcinomas has not been documented.

Methods: A total of 15 samples, 8 of normal endometrium (5 proliferative and 3 secretory) and 7 of endometrial endometrioid adenocarcinomas were analyzed. The expressions of mucin genes, MUC1, 3, 4, 13, and 15, were determined by quantitative RT-PCR.

Results: Normal and neoplastic endometrial tissues expressed almost all studied mucins except MUC4. There is no significant difference in the expression of MUC1 and MUC15 between the normal and cancerous tissues. Endometrial carcinoma showed a less expression of MUC3 and MUC13 than normal tissues, and there was a decrease in expression of MUC13 with increasing cancer stage.

Conclusions: These observations suggest a relationship between mucin gene expression and the pathogenesis of endometrial endometrioid cancers. Additional investigation of MUC3 and MUC13 in endometrial cancers may lead to new approaches for early detection and therapy.
EFFECT OF PERI-OPERATIVE ALLOGENEIC BLOOD TRANSFUSION ON THE RISK OF RECURRENCE IN ENDOMETRIAL CANCER PATIENTS

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Objective: To evaluate the effects of perioperative blood transfusions on the prognosis of patients with endometrial cancer.


Results: Women who received allogeneic blood donations (n=27) and patients who did not need any transfusion (n=331) were compared for disease-free and overall survival. The surgical standard procedure included peritoneal washing cytology, total hysterectomy (n=358), bilateral adnexectomy (n=350) and pelvic lymphadenectomy (n=227). The groups were homogeneous in term of age, BMI, previous abdominal surgery, type of surgery, operative time, lymph nodes count and hospital stay. The median (range) estimated blood loss was higher in the transfusion group, 450 mL (100-2000 mL), than in the no transfusion group, 150 mL (10-1000 mL). Median (range) follow up was 32.7 months (1-120 months). A higher incidence of major postoperative infections (4/27 vs 4/331; p=0.0015) was observed in transfused patients. Factors significantly associated with the risk of recurrence at univariate analysis were: age>65 years (p=0.043), non-endometrioid histotype (p=0.0001), grade 3 (p< 0.001), stage>1 (p< 0.0001), allogeneic transfusion (p=0.0046). After multivariate analysis, blood transfusion remained significantly associated with recurrence (OR:3.21,CI95%:1.10-9.35), as well as grading (OR:3.51,CI95%:1.42-8.71) and stage (OR:5.77,CI95%:2.48-13.73).

Conclusions: The use of allogeneic blood transfusion is associated with a higher risk of recurrence. We hypothesize that this could be due to a transitory perioperative immunodepression that promotes the spread of neoplastic cells.
OUTCOMES OF LAPAROSCOPIC TREATMENT FOR ENDOMETRIAL CANCER IN OVERWEIGHT AND OBESE PATIENTS

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Obesity, a relevant risk factor for endometrial cancer, has been traditionally considered a relative contraindication to laparoscopy. Our aim was to compare overweight and obese patients to normal-weight patients treated by laparoscopy in terms of surgical and oncologic outcomes in a large prospective cohort of consecutive patients.

All endometrial cancer patients admitted at our Institution since 2002 were offered laparoscopic hysterectomy and pelvic lymphadenectomy. Only patients with absolute anesthesiologic contraindications were refused laparoscopic approach. We compared the intra- and post-operative outcomes and survival of patients with BMI≥25 and ≥30 with those of women with BMI< 25.

A total of 167 patients were treated by laparoscopy: 45, 122 and 62 had a BMI < 25, ≥25 and ≥30 respectively. Median (range) nodal count was 17 (10-39), 18 (6-36), and 17 (9-35), in the three groups, respectively. Operative time and blood loss were similar among groups. Intra-operative complications occurred in 3 (6.6%), 1 (0.8%), and 1 (1.6%) patients in the three groups, respectively (p=0.06 for normal-weight vs. overweight).

Eight (18%) women developed post-operative complications among normal-weight vs. 18 (15%) overweight (p=0.63) and 10 (16%) obese patients (p=1.00). Disease-free and overall survival were comparable among the three different groups.

This is the largest series on the use of laparoscopy in overweight and obese patients with endometrial cancer. The study design, including all consecutive patients, demonstrates that the minimally invasive approach does not affect operative and survival outcomes even in women with BMI>30, and should not be considered contraindicated in this group of patients.
LARGE-CELL NEUROENDOCRINE TUMOR OF THE UTERUS: A CASE REPORT
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Neuroendocrine tumor is a rare malignancy, and its occurrence in the female reproductive organs is even more uncommon. When it involves the gynaecological tract, it most frequently arises in the gonads and cervix. Large cell neuroendocrine carcinoma of uterine corpus is extremely infrequent.

A 54-year-old nulliparous woman, was admitted to our department for abdominal pain and vaginal bleeding. The ultrasound examination showed a large size uterus. Chest X-ray was normal. Surgical exploration identified massive involvement of the uterine corpus enlarged to the size of a 16-week pregnancy. The tumour was friable and irregular on the uterine surface. Cervix and ovaries had normal appearance. There was no evidence of peritoneal carcinomatosis. The patient underwent abdominal hysterectomy, bilateral salpingo-oophorectomy, total infracolic and gastrocolic omentectomy, partial peritonectomy and lymphadenectomy (52 pelvic and 24 lombo-aortic lymph-nodes were removed). The pathology report revealed a large cell neuroendocrine carcinoma of the uterus with involvement of pelvic and lombo-aortic lymph-nodes. Proliferation index (Ki67) was 70%. Few days after surgery the patient had malaise without fever; blood exams revealed leukocytosis and an increased C-reactive protein. Blood cultures were negative. Empirical antimicrobial therapy was administered. CT examination demonstrated pulmonary and intra-peritoneal relapses. Adjuvant therapy was not performed for poor clinical conditions. The patient died of disease after one month.

Large-cell neuroendocrine carcinomas are rare conditions, with fast growing activity. Prognosis is generally poor. Therapy should include radical surgery and chemotherapy. Early diagnosis and consequent therapy are recommended. More experience should be registered to increase knowledge about this cancer.
PELVIC LYMPHADENECTOMY, SILS VS ROBOT

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The Single incision laparoscopic surgery starts to belong to our daily practice even in oncologic surgery. We started perform single incision treatment of endometrial cancer in February 2010, having at the moment about 10 cases of pelvic lymphadenectomy. 7 patients have been operated of hysterectomy bilateral oophorectomy and pelvic lymphadenectomy for endometrial cancer stage 1a/1b. We have compared our results, in term of bleeding, nodes and OR., to the literature of robot surgery in treatment of endometrial cancer. The aim of the study was to evaluate the advantage of the use of this new approach to the gynaecologic oncologic surgery analyzing the operating time, the cost of the technique, use of drugs, the hospitalization and the pain, despite to the expensive use of robot. The single incision laparoscopic surgery, finds frankly the place in the treatment of endometrial cancer.
MANAGEMENT OF RECURRENT ENDOMETRIAL CANCER BASED ON THE TREATMENT FREE INTERVAL

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Objectives: Current chemotherapy for endometrial cancer is commonly consisted of doxorubicin, taxane, and platinum (Pt). However, no consensus on Pt readministration has been established for endometrial cancer, unlike for ovarian cancer. In this study, we examined the response to Pt readministration in recurrent endometrial cancer.

Methods: The subjects were 34 patients with recurrent endometrial cancer who received Pt readministration after surgery and chemotherapy including Pt in our hospital. Refractory patients were defined as those in whom the response to initial chemotherapy was PD. The correlation between the treatment free interval (TFI) and response rate was examined, and clinicopathological factors that affected the therapeutic effect of Pt readministration were identified.

Results: Of the 34 cases, 13 were defined as refractory, 6 had TFI < 6 months, and 15 had TFI > 6 months. After Pt readministration, 11 cases (32.4%) were responsive (CR + PR) and 23 (67.6%) were non-responsive (PD + SD). The response rate was significantly higher for cases with TFI > 6 months (66.7%) than those with TFI < 6 months (5.3%). In addition, overall survival (OS) was significantly longer for cases with TFI > 6 months than those with TFI < 6 months (p=0.029).

Conclusions: In Pt readministration for recurrent endometrial cancer, the response rate and OS were significantly improved in cases with TFI > 6 months, suggesting the effectiveness of Pt readministration in these cases. Present data may be useful to establish new management for recurrent endometrial cancer based on Pt sensitivity.
THE VALUE OF IN VITRO BROMODEOXYURIDINE LABELING INDEX AS A PROGNOSTIC FACTOR IN ENDOMETRIAL CANCER

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Background: To prospectively evaluate the value of in vitro bromodeoxyuridine labeling index (Brdu-li) as a prognostic factor in endometrial cancer and to evaluate its possible associations with known prognostic factors of this disease.

Materials and methods: Endometrial fresh tissue biopsies were taken intraoperatively from the pathologic specimens of consecutive 42 patients with endometrial cancer treated in a university hospital setting. The tissues were treated with Brdu monoclonal antibodies immunohistochemically to determine their Brdu-li. Age, histology of the tumor, grade, stage, degree of myometrial invasion, preoperative CA-125 levels, presence of lymphovascular space invasion and adjuvant radiotherapy, follow-up period and outcome of all patients were noted. The association between these parameters and Brdu-li was studied using Mann-Whitney U, spearman correlation, Kaplan-Meier and log-rank tests as appropriate.

Results: The mean age and mean follow-up period of the patients were 59.0±10.7 years and 43.0±12.9 months respectively. Endometrioid type was the most common histology (78.6%). Stage I disease was encountered in 79% of the patients. There were four recurrences (two stage 3 and two stage 1 non-endometrioid) during follow-up. Mean Brdu-li was measured to be 7.13% (0.139%). Brdu-li values were not significantly different in any of the studied parameters (p>0.05). Brdu-li also did not show any correlation with disease-free survival (p=0.24).

Conclusion: Brdu-li failed to show any association with known prognostic factors in endometrial cancer. The prognostic value of Brdu-li in endometrial cancer seems to be limited.
PROXIMAL-TYPE EPITHELIOID SARCOMA OF THE UTERINE CORPUS. A CASE REPORT

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Objective: Report a case of this rare sarcoma to this anatomical region.

Materials and methods: A 49-year-old woman was investigated for a 2 month history of low grade fever, anemia, moderate weight loss and elevated inflammation markers. Ultrasound suggested the presence of a 34x36x40 mm intramural leiomyoma located at the left cornu uteri. A strongly positive tuberculin skin reaction, lead to anti-TBC therapy and a total body scan with Ga-67 citrate was undertaken in order to localize potential sites of active extrapulmonary TBC. The scan revealed intense focal tracer uptake in the pelvic area corresponding to the site of uterine leiomyoma, strongly suggestive of malignancy. The patient underwent total abdominal hysterectomy and pelvic lymphadenectomy.

Results: A spherical tumor (36x40mm) was observed, located at the fundus and anterior wall of the uterine corpus, characterized by necrosis and poor circumscription. Histopathologically, diffuse and partially multinodular growth of epithelioid neoplastic cells was noted. Immunohistochemically positivity to vimentin, cytokeratins, EMA and CD34, whereas negativity to S100 protein, desmin, SMA and HMB-45. Morphologic and immunohistochemical data were consistent with proximal-type epithelioid sarcoma(ES) of the uterine corpus. The patient is currently under chemotherapy and she is free of metastatic disease 8 months upon hysterectomy.

Conclusions: Proximal-type (ES) is a malignant mesenchmal neoplasm of undetermined lineage. This aggressive tumor is most frequently located in the soft tissues of pelvis and perineum. In our case was located within the uterine corpus. Thorough review of the English literature revealed no documented cases of ES in this specific anatomic site.
ENDOMETRIAL CARCINOMA IN MONTENEGRO

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Objective and methods: To analyze the development of the number of endometrial cancer cases and those who died of the disease in Montenegro. We used data on the number of cases and deaths over a ten year period (1998 - 2007).

Results: In Montenegro 406 women developed endometrial cancer in that period, which is 28.47% of all cancers affecting the female genital organs. The average morbidity (Mb) rate were from 4.7/100000 - 20.0/100000. The trend suggests significant growth. The average mortality (Mt) rate was 3.3/100000 (2.2 - 4.7/100000). The trend suggests slight decrease. The majority of cases were aged between 60 and 69 years (37.57%).

Conclusion: Endometrial carcinoma is second malignant disease of the female genital organs in Montenegro and accounts for 28.47% (cervical cancer is the most frequent). Morbidity rate of the endometrial carcinoma suggests significant growth, but mortality rate shows slight decrease as a result of good treatment algorithm. There is also need to establish central registry of malignant diseases in Montenegro.
DELAYS IN TREATING ENDOMETRIAL CANCER IN THE SOUTH WEST OF ENGLAND


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We measured delays in diagnosing and treating all cases of uterine cancer over 3 months in the Autumn of 2009 in the South West of England. There were 142 women with a new diagnosis of endometrial cancer and all 15 hospitals prospectively collected information on a structured data collection sheet.

The main outcome measures were time lines in the uterine cancer pathway. There were delays in treatment at all stages of the NAEDI pathway. When unknowns and not applicables were excluded, 52% of women took more than a month and 12% waited more than 6 months to see their GP from the onset of symptoms. Almost half said that they had no idea that abnormal bleeding was a symptom of cancer. Only a quarter of women had treatment within 31 days from the outpatient visit to first definitive treatment and 18% waited more than the target of 62 days for their treatment.

The delays due to medical care are appreciable but probably have little impact on outcome statistics. However, enough women delayed presenting to the GP to cause serious concern. If this was reflected across the country, approximately 1000 women per year would conceal their symptoms by at least 3 months and 600 would wait more than over 6 months. It is now time to invest in public education.
THE EXPRESSION OF GLYOXALASE IN ENDOMETRIAL CARCINOMA AND ITS EFFECT ON CELL PROLIFERATION AND APOPTOSIS

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The aim is to investigate the expression of glyoxalase I (GLO-I) in endometrial carcinoma tissues and cell lines as well as its effects on endometrial carcinoma cell proliferation and apoptosis. Ishikawa cellular protein and mRNA in comparison with normal endometrium. Spectrophotometer was applied to measure GLO-I activity in normal endometrium, endometrial carcinoma and paraneoplastic tissues. Positive rate was reached to 75.86% (22/29 cases) in endometrial carcinoma tissues and no expression was shown in normal endometrium tissues (0/19 cases), showing a significant difference with P < 0.01. The average value of < 2.0 IU/mg indicated that GLO-I was low in activity in normal endometrium and paraneoplastic tissues while the average value of < 92.3 IU/mg indicated that GLO-I was remarkably high in activity in endometrial carcinoma tissues. After Ishikawa cell was transfected by GLO-I siRNA, GLO-I mRNA expression was lower than negative and blank control groups, with their respective expression values of 0.25±0.06, 0.93±0.10 and 1.0 showing a significant difference (P< 0.01). There was no significant difference (P>0.05) in GLO-I mRNA expression between negative and blank control groups. Deregulating GLO-I gene expression could significantly decrease the capability of Ishikawa proliferation (P = 0.028) leading to its apoptosis. Compared with negative group (1.16±1.45%) and blank group (1.41±1.62%), apoptosis rate in GLO-I siRNA group (6.74±2.63%) was significantly higher (both P values < 0.01). Inhibition of GLO-I gene expression may promote endometrial carcinoma cell death and can restrain its proliferation. GLO-I may play an important role in the pathogenesis and development of endometrial carcinoma.
L1-CAM REVEALS NON-ENDOMETRIOID HISTOLOGY IN A SET OF 101 ENDOMETRIOID ENDOMETRIAL CARCINOMAS

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Objectives: Endometrial carcinomas are classified in two subtypes. Type I are endometrioid endometrial carcinoma's (EEC's), associated with hyperplastic endometrium and good prognosis. Type II represents non-endometrioid endometrial carcinoma (NEEC) and poor prognosis. However, about 20% of the individual cases does not fit within this dualistic model: EEC's associated with poor clinical outcome. L1-CAM is a molecular marker associated with aggressive tumor behavior in endometrial carcinoma. The aim of this study was to identify clinical-pathological features of L1-CAM positive EEC.

Methods: In 103 patients with EEC diagnosed in the RUMCN between 1993 and 2008 L1-CAM status was determined. From these patients clinical-pathological data were collected. The histological slides were revised by two pathologists on histological type, differentiation grade and nature of pre-existing endometrium. Two patients were excluded because histological materials were missing.

Results: In 101 EEC patients 19 tumors were L1-CAM+. However, after revision of the histological slides 13 of the L1-CAM+ tumors were serous- or mixed carcinomas. In the L1-CAM+ tumors 94,4% was grade 3 compared to 67,1% in the L1-CAM- tumors. Five-year-survival-rate was 51,5% in the L1-CAM+ group and 80,8% in the L1-CAM- group (p=< 0,01). Carcinoma was associated with atrophic endometrium in 61,1% and 12,0% respectively (p=< 0,01).

Conclusion: In this study of 101 EEC's 18,8% was L1-CAM+. A large part of these tumors were found to be NEEC's (serous- and mixed carcinomas) after revision. Furthermore, L1-CAM+ patients had poor clinical outcome. L1-CAM could be a useful marker to distinguish NEEC from EEC, and to predict aggressive behavior.
LAPAROSCOPY VERSUS LAPAROTOMY FOR TREATMENT OF ENDOMETRIAL NEOPLASIA IN OBESE PATIENTS

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Objective: We examined the feasibility of performing laparoscopic hysterectomy in obese women with a Body Mass Index (BMI) > 30 and endometrial neoplasia.

Methods: A BMI matched sample from a three year retrospective chart review provided data from women in each of 2 hysterectomy cohorts - 66 in the abdominal (TAH) cohort and 40 in the laparoscopic (TLH) cohort. Patient characteristics were compared to ensure baseline similarity between TAH and TLH. An analysis of variance technique was used to compare mean differences between the two cohorts.

Results: The mean BMI was 39.9 and 39.2 for the TAH and TLH cohorts respectively. We found no statistically significant differences for age, parity, number of prior abdominal surgeries. Significant differences were noted for length of hospital stay (mean vs. 0.756 days, p=0.000), intra operative blood loss (mean 376 vs 200 mL, p=0.000) and number of post operative complications (0.56 vs 0.05 p=0.000), all in favour for TLH. No significant differences were noted for intra operative complications (mean 0.09 vs 0.23, p=0.18). Operative time was longer for the TLH cohort (119 vs 140 min, p=0.005).

Conclusions: Previously described advantages for a minimally invasive approach are confirmed in a cohort of obese patients. Length of hospital stay, blood loss, and number of post operative complications were significantly lower for laparoscopically treated patients. The additional operative time of 19 min., while statistically significant, is of probably of marginal clinical importance. Laparoscopy appears safe and feasible for treatment of endometrial neoplasia in obese women.
A NEW TREATMENT OF LUNG METASTASES FROM UTERINE SARCOMA: HYPERTHERMIC PERFUSION WITH ANTICANCER DRUGS IN ISOLATED LUNG

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In patients with multiple lung metastases from uterine sarcoma, recurrence is common after complete pulmonary resection and systemic chemotherapy. Loco-regional hyperthermic chemotherapy could play a major role in this setting, achieving high local drug's concentrations and limiting systemic toxicity. Rationale of the study is the sterilization of micrometastases eventually not diagnosed at the time of metastasectomy. We therefore report the feasibility, the local and systemic toxicity of this therapy and present preliminary data on its effectiveness. Among the group of patients undergoing this type of therapy, only three patients presenting pulmonary metastases arising from uterine sarcoma were included in this report; these three patients, examined in detail in this preliminary experience, underwent multiple metastasectomy associated to hyperthermic perfusion. Tumor Necrosis Factor and Melphalan, which proved to be effective in the treatment of loco-regional sarcomas of the limbs, have been chosen as chemotherapeutic agents. Surgical resection was classified R0 in all cases. Leakage from the perfusion circuit to the systemic circulation has been consistently less than 7%. We had no perioperative mortality and any significant systemic toxicity. Reduction of respiratory parameters appears to be consistent with the proportion of lung parenchyma resected. The absence of significant chronic parenchymal injury was confirmed by transbronchial biopsy (small interstitial fibrosis). In conclusion hyperthermic lung perfusion with TNF and Melphalan is feasible, proved so far limited systemic and local toxicity and deserves further evaluation as a treatment of pulmonary metastatic uterine sarcomas.
ACCURACY OF PREOPERATIVE DIAGNOSIS OF GRADE 1 ENDOMETRIAL ADENOCARCINOMA BY D&C

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Background: To determine the accuracy of preoperative diagnosis of grade 1 endometrial cancer to correctly predict final post-hysterectomy FIGO grade.

Materials and methods: A total of 754 patients with endometrial cancer treated in a university hospital between 1992 and 2009 were reviewed to identify preoperative FIGO grade 1 cases. All cases were pathologically reviewed and surgically treated in our institution. Data about pre- and postoperative histology, grade, FIGO stage, tumor diameter, lymph node dissection, and demographic characteristics of the patients were recorded. Fisher-exact and Chi-square tests were used as appropriate.

Results: We identified 268 cases with preoperative diagnosis of grade 1 endometrial cancer by D&C. Median age of the patients was 57 years (range:23-87). Sixty-seven of these women were postmenopausal. Final pathology showed FIGO grade was greater in 20.8% of patients (46 [17.1%] were grade 2 and 7 [2.6%] were grade 3). Clear cell or serous histology was encountered in 3 patients. The new FIGO stage distribution was as follows: 61.5% stage 1A, 22.7% stage 1B, 7.3% stage 2, 8.1% stage 3, and 0.4% stage 4. In 176 patients who underwent lymph node dissection, 10 patients had metastasis (5.7% [9 pelvic, 1 para-aortic]).

Conclusion: Preoperative D&C diagnosis of grade 1 endometrial cancer correlates with final grade in 75% of cases. An upgrade in postoperative pathology may be expected in more than 20% of these patients, placing them at high risk. The rate of underlying serous or clear cell adenocarcinoma based on preoperative grade 1 histology is around 1.1%.
SURGICAL TREATMENT OF ENDOMETRIAL CANCER ELDERLY PATIENTS (≥ 65 YEARS)
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Objective: The study analyze operability, short-term morbidity and mortality in women aged 65 and older affected by endometrial cancer.

Methods: The study cohort consisted of 124 consecutive patients with histological diagnosis of endometrial cancer.

Patients' clinical data included age at diagnosis, body mass index, ASA status and comorbidities, surgical procedures, FIGO stage, histologic type, tumor grade and number of dissected lymph-nodes, occurrence of operative and early postoperative complications, post-operative hospital stay, and long-term disease-specific survival.

Patients were divided into two groups according to age at diagnosis: those < 75 years of age and those ≥ 75 years of age.

Results: All patients were submitted to primary surgery with the exception of 3 patients.

Factors affecting significantly the choice of type of intervention were age, BMI, and the presence of comorbidities. Serious postoperative complications occurred only in 3 patients. The rate of perioperative complications was significantly higher for the older group. No women died during the perioperative period. In a logistic regression model, age >75 ys but not age > 80 ys, chronic lung disease and performing lymphadenectomy correlated with a higher probability of perioperative morbidities.

Long-term disease-specific survival is significantly shorter only for women aged 80 and more.

Conclusions: Geriatric patients tolerate gynecologic surgery with minimal morbidity as well as the younger ones so that elderly patients should not be denied surgical treatment, hysterectomy at minimum.
DEVELOPMENT OF MICE MODEL FOR INQUIRY INTO THERAPEUTIC TARGETS: AN ANTICANCER EFFECT OF DIENOGEST ON ENDOMETRIAL NEOPLASM

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Objective: Hormonal therapy is employed as a conservative treatment among young women with endometrial well-differentiated endometrioid adenocarcinoma as well as complex atypical hyperplasia. However, the therapy with medroxyprogesterone acetate (MPA) occasionally has a serious adverse effect of thrombosis. Therefore, novel agents with fewer side effects would be desirable. Dienogest, a synthetic progestin with lower incidence of thrombosis, has been studied as a possible treatment for endometriosis. However, its anticancer activity still remains unknown because of lack of experimental models for endometrial carcinoma. We have already developed a novel mouse-model that mimics the human endometrial neoplasm. In this study, we investigated the anticancer effect of the dienogest on endometrial neoplasm using Pten^{loxP/loxP} mouse based on conditional Pten deletion in the endometrium.

Methods: The Pten^{loxP/loxP} mice were injected with MPA and dienogest subcutaneously to evaluate the anticancer effect against endometrial neoplasm which developed in the Pten deficient endometrium. One week after the injection, the histopathological analysis was performed.

Results: One of 8 (12.5%) and 1 of 6 (16.7%) mice treated with MPA and dienogest showed the endometrial neoplasm, respectively. In contrast, it was revealed in 5 of 6 (83.3%) mice treated without progestins. As the result, the both progestin-treatments significantly decreased the neoplasm, comparing with no treatments.

Conclusions: The treatments of dienogest as well as MPA possessed a potent anticancer activity against the endometrial neoplasm in the mice model. The present study demonstrated that dienogest with fewer side effect might be a more useful therapeutic agent for human endometrial neoplasm.
CERVICAL SARCOMA WITH AN INHUMOHISTOCHEMICAL GIST PROFILE

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Objectives: Present a rare case of uterine sarcoma with an immunohistochemical GIST profile due to its rareness and therapeutical implications.

Clinical case: A 68 years old patient, who went through a subtotal hysterectomy with double aneexectomy 16 years ago due to uterine miomatosis. Intervened in our center in 2006 of a pelvic mass, uterine stump dependant, affecting the small intestine loop and informed in the pathology report as an uterine leiomiosarcoma grade II (immunohistochemistry (+) for actine, caldesmon and CD 117), the c-KIT test wasn’t made due to unavailability in our center, receiving radiotherapy and brachitherapy. In 2008, in the follow up studies, in the ct scan a 4 cms pelvic mass is discovered, confirmed by MRI and surgical resection of the mass and serose implants is performed, near the previous anastomosis. A dark tumor is resected, of 4.8 cms X 3.6 cms X 2.4 cms, soft consistency, with a cystic cavity of 2.1 cm with hematic material. The pathology report informs of sarcoma with an immunohistochemical profile similar to GIST, C-kit (+), CD-117 (+) and vimentine, caldesmon and prot S-100 (+), having to modify the pathology report to GIST. The patient was treated with IMATINIB (glivec). Neither recurrence nor metastasys have been reported in the 2 years after surgery.

This case is a sample that tumors with similar characteristics as the gastrointestinal stroma may occur at the cervix being a cause of confusion at diagnosis and with a possible target therapy with the monoclonal anti C-KIT (imatinib).
SURGICAL AND SURVIVAL OUTCOMES OF ENDOMETRIAL CANCER TREATED WITH LAPAROSCOPIC STAGING SURGERY

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Objective: To evaluate the surgical and survival outcomes of endometrial cancer treated with laparoscopic staging surgery.

Materials and methods: A longitudinal study of prospectively registered patients of histologically proved endometrial cancer undergoing laparoscopic staging surgery (LSS) in Chang Gung Memorial Hospital from June 1995 to April 2008.

Result: Total 104 patients, with mean±SEM age 51.57 ± 0.98 years and mean body mass index 26.76 ± 0.54 Kg/m2, were included, which consists of 88 stage-I, 3 stage-II, and 13 stage III patient. Mean operation time was 186.6 min, and mean blood loss was 235.7 mL. The medium number of lymph node removed was 16. The medium hospital stay was 6.1 days. Intraoperative complication was noted in 2 patients as ureteral injury, 1 as bladder injury, 1 as bowel injury and 1 as vascular injury and 4 patients were noted with post-operative complications. 3 patients had recurrence to the date of this report. The overall 5-year survival rate was 94.11±3.27%; however, the disease-free survival rate was 92.97±2.9%.

Conclusion: Our results of LSS were compatible to those of other groups using laparotomy staging surgery in the world and has demonstrated favorable longterm survival outcomes and perioperative morbidity. LSS is an ideal option for surgical treatment of endometrial cancer in experienced laparoscopists.
PROGNOSTIC FACTORS AND RADIOTHERAPY (RT) TOXICITY STAGES I-II ENDOMETRIAL CARCINOMA (EC): A POPULATION-BASED STUDY IN TARRAGONA PROVINCE (SPAIN)

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Purpose: To evaluate prognostic factors and RT toxicity for Stages I-II EC in Tarragona Province (Spain).

Materials and methods: A retrospective population-based review was conducted on 232 patients (pts) with EC treated between 1997 and 2000, 173 of them (74.6%) were stages I-II. Multivariate analysis of variables were performed for disease-free survival (DFS), overall survival (OS), and RT toxicity (RTOG).

Results: Mean age: 62.56 years (35-88). Median follow-up: 74 months (2-183). FIGO Stage (S): 11% IA, 48.6% IB, 23.1% IC, 10.4% IIA, 6.9% IIB. Pathology: endometrioid 75%, papillary 2.3%, serous 2.3%, clear-cell 3%, sarcoma 5.2%. Grade (G): 37.6% G1, 39.3% G2, 17.9% G3. Treatment: 1) Surgery in all patients (86% abdominal, 14% vaginal, 50.3% lymph nodes dissection (41% pelvic and paraaortic). 2) RT in 57.1%: 43.6% external beam radiotherapy (EBI) and brachytherapy (BT), 11.4% BT alone, 2.1% EBI alone. 3) Chemotherapy in 7.5% & Hormonal treatment in 2.3%. Grade 3 & 4 toxicity: 7 (4%) pts, 4 early & 3 late. Relapses: 10/173 (5.8%) loco-regional recurrence. Metastasis: 14/173 (8%). Survivals at 5 years: 1) OS in all stages was 86.7%; and 83% and 89.6% for SI and SII, respectively. 2) DFS was 84.9% for all pts. 3) LRFS was 86.2% for all pts. Multivariate analysis: significant prognostic factors for good outcome were lymph nodes dissection and radiotherapy.

Conclusions: Our results suggest that survivals, RT toxicity and relapse were similar to the other reported series. Predictors of good outcome were lymph nodes dissection and radiotherapy treatment.
DEFINITION OF SURVININ (BIRC5A) IN ENDOMETRIUM BY MEANS OF TEST SYSTEM «PEPTOSURVIM»

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Objectives: Survivin is a key regulator in the antiapoptotic network, and overexpression of survivin has been reported in endometrial hyperplasia and cancer. This study investigated the expression of survivin (BIRC5a) in endometrium by means of test system « Peptosurvim» for revealing of presence of an oncologic pathology.

Patients and methods: Endometrial hyperplasia tissue samples from 30 women were examined for changes in survivin expression. All women have been parted on four groups. I group - 5 patients at whom according to morphological research of a endometrial pathology it is not taped, II group - 10 women with a endometrial hyperplasia (simple or complex) without atypia, III group - 5 persons with a atypical endometrial hyperplasia (simple or complex), IV group - 10 patients with low-grade endometrioid cancer.

Middle age of patients was 47,8 years.

Results: In our research it is shown that survivin expression in normal endometrium ( group I) is present at the quantity which is on the verge of sensitivity of our diagnostic set. In samples with a endometrial hyperplasia (simple or complex) without atypia ( group II) and a atypical endometrial hyperplasia (simple or complex) ( group III) an obvious difference in an survivin expression it is not taped. In samples with low-grade endometrioid cancer observed overexpression of surviving.

Conclusion: Thus overexpression of survivin is the detector of an oncologic pathology in endometrium.
EXPERIENCE WITH STAGES III-IV ENDOMETRIAL CARCINOMA (EC): A POPULATION-BASED STUDY IN TARRAGONA PROVINCE (SPAIN)

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Purpose: To evaluate outcome, failure patterns, prognostic factors and RT toxicity for Stages III-IV EC in Tarragona Province (Spain).

Methods and materials: A retrospective population-based review was conducted on 232 patients (pts) with EC treated between 1997 and 2000 from different gynaecological Department and in a single oncologist institution with RT Units. 39 of them (17%) were stages III-IV. Multivariate analysis of variables were performed for disease-free survival (DFS), overall survival (OS) and RT toxicity (RTOG).

Results: Mean age: 64.01 years (40-82). Median follow-up: 53 months (2-149). FIGO Stage (S): 43.6% IIIA, 7.7% IIIB, 20.5% IIIC, 15.4% IVA, 12.8% IVB.

Pathology: endometrioid 46.2%, papillary 7.7%, serous 2.6%, sarcoma 23.1%. Grade (G): 17.9% G1, 35.5% G2, 15.4% G3.

Treatment:

1) Surgery 87.2% (79.5% abdominal, 5.1% vaginal).

2) RT in 86.2%: 62.1% external beam radiotherapy (EBI) and brachytherapy (BT), none of them BT alone, 24.1% EBI alone.

3) Chemotherapy in 22.5% & Hormonal treatment in 25.7%.

Grade 3 & 4 toxicity: 3 (8%) pts, 1 early & 2 late.

Relapses: 8/39 (20.5%) loco-regional recurrence S-III: 18.5%, S-IV: 30.0%.

Survivals at 5 years:

1) OS in all stages (III-IV) was 59.8%; and 76.0% and 20.0% for SIII and SIV, respectively.

2) DFS (III-IV) was 54.2%; 68.2% (SIII) and 20.0% (SIV). LRFS (III-IV) was 52.1%; 66.6% (SIII) and 13.3% (SIV).

Conclusions: Our results suggest that survivals, RT toxicity and relapse were similar to the other reported series. The chemotherapy treatment can have an important role to improve overall survival in advanced stages endometrial carcinoma.
A COMPARISON OF ENDOMETRIAL SAMPLING METHODS ON ENDOMETRIAL CANCER GRADING

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Objective: The purpose of this study is to compare the effectiveness of Pipelle biopsy and curettage (as preoperative endometrial sampling types) in detecting endometrial tumors and to find out the accurate histological type and degree, which directly impacts patients' survivals.

Study design: In total 187 preoperative samples and postoperative hysterectomy specimens, of which 159 were obtained through curettage and 28 through Pipelle biopsy were examined. The Kappa statistic which examines the coherence between the two results was used.

Results: In detecting the endometrial malignancy, the sensitivity levels for curettage and pipelle biopsy were 93.1 % (148/159) and 89.3 % (25/28) respectively. The concordance between preoperative histologic findings and postoperative pathologic results was 138 of 148 (93.24%) for curettage and 22 of 25 (88 %) for Pipelle biopsy. The Kappa statistic was calculated as 0.65 for curettage and 0.62 for pipelle biopsy. These values were in between the substantial agreement. Preoperative endometrial samples which show concordance in finding out both the histological type and degree, with postoperative pathological findings were 110 out of 148 (74.32 %) for curettage and 21 out of 25 (84 %) for Pipelle biopsy. There was a moderate agreement for curettage (Kappa statistic was 0.47) and substantial agreement for pipelle biopsy (Kappa statistic was 0.61).

Conclusion: Pipelle biopsy has better agreement between the grade of the preoperative sample and the tumor grade at final histologic diagnosis compared with curettage. In conclusion Pipelle biopsy, which is a minimally invasive outpatient procedure, may be beneficial option in detecting endometrial tumors.
A SURVEY OF PRACTICE PATTERNS REGARDING THE MANAGEMENT OF COMPLEX ATYPICAL ENDOMETRIAL HYPERPLASIA (CAH) AMONG GYNECOLOGIC ONCOLOGISTS

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Background: The management of CAH varies considerably. The objective of this study was to assess gynecologic oncologists' management practice patterns in patients with biopsy-proven CAH.

Methods: Following IRB approval, the Society of Gynecologic Oncologists full membership email list was queried. SurveyMonkey online software was utilized; 688 surveys were sent. Surveys were open between 12/2009-4/2010. All authors were blinded to the anonymous survey responses.

Results: 216 of 688 (31%) surveys were completed. There were 104 academic (48.1%), 68 private/community practice (31.5%), 37 hybrid (community/private with teaching affiliation - 17.1%), 5 military (2.3%), and 2 industry (0.9%). The majority based staging on pathologic factors assessed by frozen or gross examination. (Table 1) When performing intraoperative consultations, many would only perform staging with high grade or myometrial invasion. (Table 2)

Conclusions: CAH possesses a risk of underlying endometrial cancer. Despite this, the majority of gynecologic oncologists do not perform a staging procedure when referred a patient with CAH.
CD1A AND S100 POSITIVE DENDRITIC CELLS IN HUMAN ENDOMETRIAL CANCER

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Objective: To study whether the tumor infiltration by CD1a and S100 positive dendritic cells could be a prognostic marker for endometrial cancer.

Materials and methods: 58 human endometrial carcinoma specimens were collected from Peking University People's Hospital and paraffin sections were made and HE stained routinely. Immunohistochemistry method was used to identify the CD1a+ and S100+ antigen-expressing dendritic cells.

Results: Among the 58 patients with endometrial carcinoma, 32 cases belong to FIGO I and 26 cases belong to FIGO III. CD1a and S100 positive dendritic cells were found around the tumors. Seldom positive cell infiltrated the tumors. The expression of CD1a in moderately differentiated tumors was significantly higher than that in poorly differentiated ones (P< 0.05). And the expression of CD1a in FIGO III tumors was significantly higher than that in FIGO I ones (P< 0.05). The expression of CD1a was positively related to S100 protein.

Conclusions: The number of CD1a and S100 positive dendritic cells increased as the stage of the tumor increased, reflecting an overall higher leukocyte density in higher stage tumors. However, a possible trend for less dendritic cell activation in higher stage cancers was noted, raising the intriguing possibility that this might be a relevant prognostic factor, to be confirmed in a larger study.
FROZEN SECTION ON PATIENTS WITH PREOPERATIVE DIAGNOSIS OF COMPLEX ATYPICAL HYPERPLASIA

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Introduction: The prevalence of concurrent endometrial cancer (EMCA) in women with complex atypical hyperplasia (CAH) on preoperative biopsy is greater than 40%. Aim of the study is to evaluate the sensitivity and specificity of frozen (FS) section in predicting EMCA in patients with preoperative diagnosis of CAH.

Materials and methods: Retrospective review of 39 patients with preoperative diagnosis of CAH who underwent hysterectomy and bilateral salpingooophorectomy with FS analysis of the uterus was performed. Preoperative diagnosis was based on specimens collected either through EMB or through D&C. Intraoperative diagnosis was compared with diagnosis on permanent section (PS) to evaluate for sensitivity, specificity, positive and negative predictive values in predicting EMCA.

Results: At FS 18 (46.2%) patients were diagnosed with EMCA, 1 (2.7%) patient was diagnosed with carcinosarcoma (CS), 2 (5.2%) patients were diagnosed with CAH, 18 (46.2%) of the patients were diagnosed with other benign conditions. On PS 21 (53.8%) patients were diagnosed with EMCA, 2 (5.2%) patients were diagnosed with CS, 6 (15.4%) patients were diagnosed with CAH, 9 (23.1%) patients were diagnosed with other benign conditions. Of the 6 patients diagnosed with CAH at PS none was detected on FS. The patients diagnosed with CAH on FS were diagnosed with EMCA and CS on PS. Sensitivity and specificity for detecting EMCA or CS were 87% and 100% respectively. The PPV was 100% and NPP was 84.2%.

Conclusion: FS had has good sensitivity and specificity in predicting gynecologic malignancy on PS in patients with preoperative diagnosis of CAH.
PATIENTS WITH EARLY-STAGE UTERINE PAPILLARY SEROUS CANCERS MAY BENEFIT FROM ADJUVANT PLATINUM-BASED CHEMOTHERAPY

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Objective: Uterine papillary serous carcinoma is an aggressive subtype of endometrial cancer. We studied survival outcomes in patients with stages I/II UPSC.

Materials: A retrospective, multi-institutional study of patients with stages I/II UPSC was conducted. Patients underwent surgical staging followed by either observation, adjuvant platinum-based chemotherapy or radiation therapy. Statistical analyses were performed using the Kaplan-Meier and Cox proportional hazards regression methods. Quantitative data was analyzed using Student's t test, while Fisher's exact test was used for categorical data.

Results: Thirty nine women were diagnosed with stage I (30) or II (9) UPSC, with the median follow-up of 42 months. Of the 19 patients who did not receive adjuvant therapy, 7 developed recurrences and 5 died of their disease. Of the 10 patients with Stage IA UPSC who did not receive adjuvant therapy, 3 developed recurrences and expired. Of the 7 patients who underwent RT, 2 developed distant recurrences and expired. Of the 13 patients who underwent CT, one developed vaginal recurrence. The 5-year overall survival and progression free survival rates were 75% and 65% in observation, 63% and 63% in RT and 100% and 91% in chemotherapy groups. There were improvements in OS and PFS in patients who received CT compared to those who did not (p = 0.04 for OS and p = 0.05 for PFS).

Conclusions: Patients with stages I/II UPSC are at significant risk for distant recurrence and poor survival. Platinum-based adjuvant chemotherapy may decrease recurrence rate and improve survival in women with early and well-staged UPSC.
CORRELATION BETWEEN PREOPERATIVE D&C AND POSTOPERATIVE PATHOLOGY IN MALIGNANT MIXED MULLERIAN TUMOR OF THE UTERUS

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Background: To retrospectively determine the spectrum of D&C results for definitive postoperative diagnosis of malignant mixed mullerian tumor (MMMT).

Materials and methods: A total of 754 patients with endometrial cancer treated in a university hospital between 1992 and 2009 were reviewed to identify postoperative MMMT cases. All cases were pathologically reviewed and surgically treated in our institution. Data about pre- and postoperative histology, grade, FIGO stage, tumor diameter, lymph node dissection, presence of lymphovascular invasion and demographic characteristics of the patients were recorded. Fisher-exact and Chi-square tests were used as appropriate.

Results: We identified 33 cases with definitive diagnosis of MMMT. Mean age of patients were 67.1±8.4 years (range 49-88). Seventeen of the patients had a correct preoperative diagnosis of MMMT in their D&C specimens (52%). While in the rest, endometrioid adenocarcinoma was the most common D&C diagnosis (36.4% [7 were G3]). In one patient, no epithelial component was seen in biopsy therefore preoperative diagnosis was a sarcoma. In 25 patients who underwent lymph node dissection, there were 3 lymph node metastases (12%). Lymphovascular space involvement was present in 61% of cases.

Conclusion: Final postoperative diagnosis of MMMT is usually not correlated with preoperative D&C result. In up to 50% of these patients, preoperative pathology mostly reported an underlying endometrioid adenocarcinoma. The reason for this is the absence of sarcomatous elements in D&C specimens.
RELIABILITY OF PREOPERATIVE DIAGNOSIS OF SEROUS CARCINOMA OF ENDOMETRIUM

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Background: To evaluate the accuracy of preoperative diagnosis of serous endometrial cancer to correctly predict final post-hysterectomy report.

Materials and methods: A total of 754 patients with endometrial cancer treated in a university hospital between 1992 and 2009 were reviewed to identify preoperative serous adenocarcinoma cases. All cases were pathologically reviewed and surgically treated in our institution. Data about pre- and postoperative histology, grade, FIGO stage, CA-125 levels, tumor diameter, lymph node dissection, and demographic characteristics of the patients were recorded. Fisher-exact and Chi-square tests were used as appropriate.

Results: We identified 36 cases with preoperative diagnosis of serous cancer by D&C. Mean age of the patients was 63.2±10.7 years (range 38-85). Mean preoperative CA-125 levels were 73.2 IU/ml. In 69% of the cases, CA-125 levels were elevated above 35 IU/ml. D&C correctly predicted serous cancer in 61% of the patients. The final pathology turned out to be endometrioid in 9 (1 grade 1, 8 grade 2/3), clear cell in three, mixed epithelial in two and malignant mixed mullerian tumor in one patient. Of the 25 patients who underwent lymph node dissection, there were 2 pelvic lymph node metastases; and lymphovascular space invasion was positive in 50% of cases.

Conclusion: Preoperative D&C diagnosis of serous cancer correlates with final pathology in 61% of cases. In about 33% of these patients final pathology after hysterectomy may turn out to be a clear cell or an endometrioid adenocarcinoma which mostly are of high risk types.
HOW CA-125 IS AFFECTED BY CHEMOTHERAPY IN PATIENTS WITH UTERINE CANCER: THE BRITISH COLUMBIA CANCER AGENCY EXPERIENCE

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Background: Endometrial Cancer is the most common gynecological malignancy. Preoperative CA-125 levels predict nodal involvement and are associated with poor outcome. No data is available on the predictive value of changes in CA-125 levels in patients receiving platin/taxane chemotherapy for newly diagnosed advanced disease.

Objectives: To assess the response of CA-125 to chemotherapy in women with newly diagnosis of advanced endometrial cancer.

Methods: A retrospective analysis of patients with endometrial cancer who were treated at a single institution between 1995 and 2006. The upper limit of normal for CA-125 was 35mUI/ml. Progression-free survival (PFS) was calculated for each event. Univariable, multivariable and a decision-tree analysis were performed.

Results: 181 patients were included in the study. Significant factors upon univariable analysis were: age≥60, increasing stage/substage, papillary serous histology, presence of residual disease, grade 3, increasing depth myometrial invasion, CA-125 level at initiation of cycle #3 and pre-operative CA-125 ≥35 mUI/ml. Multivariate analysis identified grade 3, presence of residual disease and CA-125 after cycle #3 ≥24mUI/ml. In the decision-tree analysis CA-125 ≥24mUI/ml at cycle #3 was the most important independent predictor: 31/32 relapsed if above this value and 45/89 if below it.

Conclusions: Abnormal CA-125 levels in patients with endometrial cancer are associated with poor outcome. CA-125 level at the third cycle of chemotherapy correlates with outcome and is the most important predictive factor. Prospective data is necessary to confirm these findings.
MUTATION OF K-RAS GENE IN CARCINOGENESIS OF ENDOMETRIAL CARCINOMA

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Background: Two types of endometrial carcinoma are distinguished with respect to biology and clinical course: type I- endometroid and type II- non-endometroid /serous, clear cell/ carcinoma.

Molecular data from multiple studies support the hypothesis of different pathway in the development of type I and type II carcinomas. The most frequent genetic alteration in endometroid carcinoma is PTEN inactivation, microsatellite instability and mutation of K-ras and beta-catenin. Mutation of p53 gene is the most frequent alteration in non-endometroid carcinomas.

K-ras protooncogene encodes a membrane GTPase and is related to tumor growth and differentiation. Mutations of K-ras gene are present in about 10-30% of endometroid carcinomas, predominantly found in exon 1 (codons 12 and 13).

Methods: A case control study. PCR analysis is performed to detect K-ras mutation in a group of patients with I. stage endometroid carcinoma and patients with normal endometrium as a control group.

Results: Preliminary results show presence of K-ras gene mutation in approximately 20% of specimens with endometroid carcinoma.

Conclusion: Data support the importance of K-ras mutation in pathogenesis of endometroid carcinoma.

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HYSTEROSCOPY IN DETECTION OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN

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Objectives: The aim of our study is to compare the hysteroscopic and histological findings in women admitted at our clinic with postmenopausal bleeding.

Material and methods: 145 patients aged 48-62 years were included in the study. None of them with recent hormonal therapy or any malignancy in the past. The patients underwent diagnostic hysteroscopy and endometrial sampling for histological analysis. Hysteroscopy was successfully completed in 142 women.

Results: In 28 cases hysteroscopically was evident endometrial cancer and all of them were confirmed with histological analysis. Hysteroscopic finding in only 4 cases (2.8%) was suggestive of atrophic endometrium and atypical hyperplasia, but the histology revealed endometrial carcinoma. Although histological analysis is necessary for the final diagnosis and treatment, hysteroscopy proves to be a safe and powerful technique in the management of abnormal uterine bleeding.
MALIGNANCY RISK OF ENDOMETRIAL POLYPS IN POSTMENOPAUSAL WOMEN

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Objectives: The malignancy risk of endometrial polyps in postmenopausal women was correlated with the presence or absence of abnormal uterine bleeding.

Material and methods: Retrospective study comprised 125 postmenopausal women who presented with endometrial polyps at diagnostic hysteroscopy between 2005 and 2009. They were divided into two studying groups according to the presence or absence of abnormal postmenopausal uterine bleeding. 47.8% were without and 52.2% with postmenopausal uterine bleeding. Transvaginal ultrasound revealed: abnormal endometrial thickness in 64.0% in asymptomatic vs. 57.7% in the group with postmenopausal bleeding, endometrial polyps in 37.9% vs. 32.9%, endometrial carcinoma in 1.3% vs. 0.8%, and submucosal myomas in 0.9% vs. 2.0%. In all the cases the polyps were hysteroscopically resected. Histologic analyses showed mucous polyps in 92.2 of asymptomatic women compared to 81.7% of those with bleeding, while endometrial carcinoma was seen only in the cases with anamnestic data for bleeding (18.3%). The malignancy risk within endometrial polyps in postmenopausal women varies with the presence of vaginal bleeding, and is minimal in asymptomatic women.
ULTRASONOGRAPHY IN PREOPERATIVE ASSESSMENT OF MYOMETRIAL INVASION IN PATIENTS WITH ENDOMETRIAL CANCER

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Objective: The aim of this study was to compare the diagnostic performance of ultrasonography (US) with that of magnetic resonance imaging (MRI) in estimation of myometrial invasion.

Methods: 54 patients with endometrial cancer were included. Ultrasonography and MRI were performed before surgery. All patients had complete staging procedures, including peritoneal cytologic analyses. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined for US and MRI.

Results: The concordance rates of myometrial invasion for US and MRI were 82.4% and 81.1%, respectively. The sensitivity, specificity, PPV, and NPV for identification of deep myometrial invasion were 64.7%, 87.7%, 61.1%, and 89.3% on US and 70.6%, 84.2%, 57.1%, and 90.6% on MRI. Two patients (2.7%) were found to have positive results for malignant cells on peritoneal cytologic analyses.

Conclusions: Although MRI is sovereign and powerful diagnostic method, ultrasonography appears to be a useful preoperative method for predicting myometrial invasion.
MYXOID AND FIBROUS ENDOMETRIAL STROMAL SARCOMA OF THE UTERUS: A REPORT OF TWO CASES

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Background: Myxoid and fibrous endometrial stromal sarcoma (MFESS) of the uterus is extremely rare. During the period of 1998-2009 in our hospital, two patients verified MFESS.

Case 1: A 64-years-old woman presented for a checkup. An enlarged uterus was palpated. We could not make a diagnosis on the preoperative curettage. Total hysterectomy and bilateral salpingo-oophorectomy was performed. The tumor was 10cm in diameter and they have a yellow-white homogeneous appearance with foci of necrosis. And the metastasis was found surface of rectum. On microscopic examination, the myxoid matrix and fibrous component were seen. It was no significant cytological atypia and 5 mitoses per 10 HPFs. At the surface of rectum, it was only an ingredient of ESS. There is no evidence of recurrence for three years after operation.

Case 2: A 58-years-old woman presented for irregular vaginal bleeding. An enlarged uterus was palpated. The diagnosis on preoperative curettage was given as sarcoma for atypical spindle cell. Total hysterectomy and bilateral salpingo-oophorectomy was performed. The tumor of endometrial polypoid was 5cm in diameter. It was an abundant myxoid matrix and fibrous component were seen. And the typical morphologic features of endometrial stromal sarcoma (ESS), low-grade were focally present. After 2.5 years, recurrence occurred in an ileum. It was the typical morphologic features of ESS and it was resistance for chemotherapy.

Conclusion: We have extremely rare cases of MFESS, these were stained positive CD10 and negative α-smooth muscle actin by immunohistochemistry.
A RETROSPECTIVE STUDY OF UTERINE SARCOMA OVER A PERIOD OF 8YRS AT A ONCOLOGY CENTER IN NORTHERN INDIA

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Introduction: Uterine sarcoma is a rare malignant tumour of the uterus. Most often the diagnosis is made on post operative histopathology of the specimen.

Methods: From January 2000 to December 2008 - 42 cases of uterine sarcomas were registered at our centre.

Observation: The age group ranged from 30 to 85 yrs. Most (83.3%) of the patients had Irregular bleeding P/V or post-menopausal bleeding. Abdominal mass was palpable in 9/33 patients (27.2%). Histopathologically mixed mullerian tumour(carcino-sarcoma) was seen in 31 (73.8%). Leomyosarcoma in 6 cases (14.28%), Endometrial stromal sarcoma in 5 cases (11.9%). 7 patients had prior radiotherapy - in 6 extra-pelvic radiation and one pelvic radiation for ca cervix. 35 cases underwent surgery at Oswal Hospital and 9 cases were referred for further management after surgery done out-side. 2 patients underwent 2nd surgery at our center where earlier myomectomy had revealed leomyosarcoma. Total abdominal hysterectomy and bilateral salpingoophrectomy was done in 7 patients. In 28 patients surgical procedure done was- TAH with BSO with retroperitoneal lymphadenectomy/sampling ± infracolic omentectomy. Patients who underwent surgery outside - 4 patient had vaginal hysterectomy, 2 patients had myomectomy, 3 patient had total abdominal hysterectomy and B/L salpingoophrectomy. Post operative adjuvant therapy was given in 25 (59.5%) patients. Radiotherapy was given in 11 patients and chemotherapy in 14 patients...11 patients had progressive disease while on treatment. At 12-18months follow up 10/42 patients showed recurrence.

Conclusion: Uterine sarcomas though rare are aggressive tumors of uterus. Pre-operative diagnosis is difficult with overall poor survival.
INHIBITORY EFFECT OF ROSIGLITAZONE BOMBINED WITH CISPLATIN ON THE GROWTH OF ENDOMETRIAL CARCINOMA IN NUDE MICE

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Objective: To investigate the synergistic effects of rosiglitazone (ROZ) and cisplatin on the growth of human endometrial cancer cell line KLE xenografted to nude mice.

Methods: KLE cells were transplanted into nude mice to form study model. When the models were established, they were randomly divided into 6 groups: control group(A), cisplatin1mg/kg(B), cisplatin3mg/kg(C), ROZ50 mg/kg(D), cisplatin1mg/kg+ROZ50 mg/kg(E), cisplatin3mg/kg+ROZ50 mg/kg(F). Cisplatin was given by intraperitoneal injection every two days; ROZ was intragastric administration every day. During the period of observation, the volumes of the transplanted tumors were measured every 4 days. The tumor growth inhibitory rates of each group were calculated. Moreover, the curves of BALB/c- nu mice growth were drawn. After 38 days, BALB/c-nu mice were euthanized and xenograft tumors were measured. The expression of NF-κB and PTEN protein in subcutaneous tumors were determined by immunohistochemical method with image analysis system.

Results: Significant differences in tumor inhibitory rates were found between the treatment groups and the control group(P< 0.05). The tumor inhibitory rate of B, C, D, E, F 5 group was 24.41%, 43.34%, 49.67%, 78.02%, 84.78%, respectively, and the combination group showed synergistic effect on inhibiting the growth of the xenografts with a q value of 1.19. Contrary to control group, the expression of subcutaneous tumor NF-κB was down-regulated and PTEN was obviously up-regulated by rosiglitazone and its combination with cisplatin.

Conclusion: Rosiglitazone could enhance inhibition of the growth of endometrial tumor by combination with cisplatin.

Keywords: Endometrial neoplasms; Rosiglitazone; Cisplatin; Mice, nude
FOLATE RECEPTORS IN LEIOMYOSARCOMA: A PROMISING TARGET FOR DIRECTED CHEMOTHERAPY

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Background: While normal cells obtain folate through the reduced folate receptor, cancer cells can develop folate receptors that function through endocytosis and can be used for targeted delivery of folate bound chemotherapy. These receptors are often present in both ovarian and endometrial cancers and might represent a target in leiomyosarcoma.

Methods: Utilizing an antibody to the folate receptors, staining was performed on primary uterine leiomyosarcoma tumors. Renal tubules were used for positive controls and skeletal muscle for negative controls. Tumors demonstrating 2+ or 3+ staining were reported as positive.

Results: Nineteen patients with leiomyosarcoma were identified over a 10 year period. The mean age of the patients was 58.7 years. Overall, the mean follow-up period was 25.8 months. Fifteen patients recurred at a mean of 5.7 months and 10 patients died with a mean survival 24.2 months. Strong folate staining was noted in 10/19 tumors (53%) with a diffuse staining pattern in 7 (37%) and a focal pattern in 3 (16%). There was no difference in staining patterns with respect to age, mitotic index, recurrence, disease free survival, or overall survival.

Conclusions: The folate receptor is present in approximately half of leiomyosarcomas and may represent a rational therapeutic target for chemotherapy against this tumor type.
THE FOLLOW UP OF EARLY STAGE ENDOMETRIAL CANCER - IS IT WORTHWHILE?

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Objectives: To determine the incidence of recurrences in early stage endometrial cancer patients in relation to resources utilised.

Methods: A retrospective case note review of stage 1 endometrial cancer patients between 1995 - 2005 in the South East of Scotland.

Results: There were 228 Stage 1 A and B (pre 2008) endometrial cancer patients.

In the 53 patients with stage 1A disease, the average number of follow up visits was 6 and no recurrences were detected.

Conclusions: All 53 stage 1 A (pre 2008) endometrial cancer patients in this study were cured surgically and had no evidence of recurrence. On average each had 6 follow up appointments, totalling 318 for this group. Each clinic appointment generated three letters (General Practitioner, Surgeon, Notes), nearly 1000 letters to be typed, posted, read and filed.

A large percentage of endometrial cancer patients are obese and it is clearly documented repeatedly that these examinations are difficult and of limited clinical significance.

Following full analysis of the stage 1 B outcomes, the significance of the FIGO staging changes will become evident. It may be that a group of patients, formerly 1A, could be confidently told of surgical cure and no requirement for follow up. This could save not only money but also consultant time and most importantly end unnecessary patient anxiety.
THE ROLE OF D2-40 (PODOPLANIN) AS A MARKER FOR LYMPH VESSEL INVASION IN PRIMARY ENDOMETRIAL CANCER

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Background: Lymph node metastasis (LN+) plays a key role in the spread of endometrial cancer and predicts prognosis. Tumors confined to the uterus show LN+ in up to 30%. The evaluation of lymph vessel invasion (LVI) as marker for LN+ is of great importance. D2-40, a monoclonal antibody might be able to increase the detection rate of LVI compared to conventional Haematoxylin-Eosin (H.E.) staining. The aim of this study was to evaluate the eligibility of D2-40 for prediction of LN+.

Methods: Immunohistochemical staining with D2-40 was performed on paraffin-embedded tumors of 182 patients with endometrioid adenocarcinoma. Slides were screened for the presence of LVI. Correlation with clinico-pathological features was assessed. Treatment modalities and patients follow-up were available.

Results: Immunostaining with D2-40 significantly (p=0.001) increases LVI detection compared to conventional H.E. staining. LVI was identified by D2-40 (D2-40-LVI+) in 53/182 (29.1%) of tumor specimen as compared to 34/182 (18.3%) by H.E. (H.E.+LVI). D2-40-LVI+ was detectable in 90% of the nodal positive tumors and (p=0.001) predicted significantly LN+. Furthermore, D2-40 was the only independent prognostic factor for patients overall survival (p< 0.01) considering tumor stage, LN+, H.E.-LVI and tumor differentiation.

Conclusion: Our study demonstrated the superiority of D2-40 staining for LVI in endometrial cancer. D2-40-LVI+ was a strong predictor for LN+ and prognostic relevant parameter. Further studies on large patient groups are required to evaluate the clinical role of D2-40-LVI+ in endometrial cancer. These studies have to be focused on patients in which lymph node dissection could be omitted without worsening outcome.
ROBOT-ASSISTED LAPAROSCOPIC STAGING OF ENDOMETRIAL CANCER IN TAIWAN

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Objective: The objective of the study was to evaluate perioperative and early postoperative outcomes of a robotic surgery program in endometrial cancer.

Materials and methods: The surgeries were performed with the da Vinci system (Intuitive Surgical, Inc.). We collect data retrospectively including docking times, operative times, estimated blood loss, length of hospital stay, lymph node yields, and complications.

Results: Six patients with early-stage endometrial cancer underwent robotic-assisted staging laparoscopy from July 2007 to December 2009. The median lymph node count was 24.8 (range, 9 to 30). Mean operating time was 200 minutes (range, 143 to 261). The average estimated blood loss was 178 mL. No conversion was required, no intraoperative or postoperative complications occurred. All patients in this group were alive and free of disease at the time of last follow-up. To date, we are the first institute to perform robotically-assisted staging laparoscopy for endometrial cancer in Taiwan.
SURVIVAL OF WOMEN WITH UTERINE LEIOMIOSARCOMA: A SINGLE INSTITUTION EXPERIENCE


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Objective: To evaluate the survival of women with uterine leiomiosarcoma from a Single Academic Institution.

Methods: Data from hospital charts and from follow up visits on 28 women with diagnosis of uterine leiomiosarcoma were collected from 1983 to 2009. Survival curves with Kaplan Meyer methods was also performed.

Results: We collected 28 women with diagnosis of uterine leiomiosarcoma; the median age was 54 years with most of them were in menopause.

16 women of 28 (57.14%) presented with FIGO stage I, 2 women of 28 (7.14%) with FIGO stage II, 2 women of 28 (7.14%) with FIGO stage III and 8 women of 28 (28.57%) with FIGO stage IV.

The main symptoms were: the presence of myoma at diagnosis that showed to be a leiomiosarcoma at the final histological report (32.14%), vaginal bleeding (17.86%), ascites (7.14%) and pain (3.57%).

26 patients of 28 underwent a complete surgery which included total abdominal hysterectomy and bilateral annexectomy, whereas 2 of 28 underwent a conservative surgery with the only removal of the myoma.

The median overall and progression free survival of the 28 women was 33 months (1-113) and 20 months (1-95), respectively. The patients who underwent miomectomy had a median progression free survival of 8 months.

Conclusions: Leiomiosarcoma of the uterus is a very aggressive disease which should be treated with a complete surgery. Our results confirmed the data presented in the literature.
EXPRESSION OF PHOSPHO-MTOR AND MAPK IN ENDOMETRIAL CARCINOMA

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Background-aim: Endometrial carcinoma is the most frequent malignancy of the female genital tract. The MAPK and PI3K/AKT/mTOR pathways are frequently activated in various tumor types but data on endometrial cancer are limited. The purpose of our study is to investigate the expression of MAPK and mTOR in endometrial carcinoma.

Methods: The medical records of our hospital were retrospectively reviewed to identify the patients who underwent surgery for endometrial carcinoma in our Department from 1995 to 2010. Cases with available tissue blocks were reviewed and immunohistochemical reactions for MAPK and phospho-mTOR were performed in a representative tissue block of each case. The expression of each marker was assessed by calculating the H-score in neoplastic and adjacent non-neoplastic tissue. The data were correlated with clinicopathological parameters by statistical analysis.

Results: MAPK was expressed in 74.3% (75/101) of carcinomas and in 38.7% (24/62) of non-neoplastic tissue. m-TOR was expressed in 75.8% (75/99) of carcinomas and 76.6% (49/64) of non-neoplastic tissue. MAPK expression was increased and m-TOR expression was decreased in carcinomas compared to non-neoplastic tissue, changes that were statistically significant (p< 0.000) for both markers by Wilcoxon analysis. No significant associations were noted between the expression of the markers and histologic type, grade and stage.

Conclusions: The increased MAPK expression in endometrial carcinomas compared to the adjacent non-neoplastic tissue suggests activation of this pathway in this tumor type. This finding merits further investigation and confirmation, particularly in light of targeted therapies. m-TOR expression requires further investigation, particularly in relation to PTEN expression.
AUDIT OF UTERINE SARCOMAS AT THE UNIVERSITY OF BENIN TEACHING HOSPITAL, BENIN-CITY, NIGERIA

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Background: Uterine sarcomas account for 3-4% of all uterine malignancies. The investigators observed an increase in the rate of uterine sarcomas and decided to investigate this trend.

Objective: To determine the incidence of uterine sarcomas and other associated clinico-pathological factors.

Methodology: This was a retrospective study in which all cases of Uterine sarcomas (Leiomyosarcoma, Carcinosarcoma, Adenosarcoma and Endometrial stromal sarcoma) were reviewed from 2005 to 2009. Details of clinical presentation and findings, investigation reports, operative findings and Histological types were obtained.

Results: A total of 12(18%) cases of uterine sarcomas out of 67 uterine malignancies occurred over the study period. When considered on an annual basis, in 2005 there was an 11% incidence of uterine sarcomas, with 2006-2008 recording incidences of 7%, 8% and 14% respectively. In 2009 it rose sharply to 66% that is 6 out of a total of 9 uterine malignancies. Majority 9(75%) were leiomyosarcomas, while the remaining 3(25%) were carcinosarcomas. 5(55%) of the leiomyosarcomas occurred in premenopausal women between the ages of 31-40 years, while 1(33%) of carcinosarcomas was in a premenopausal woman.

Conclusion: An increasing rate of uterine sarcomas was observed and found to occur in particularly younger women; however there is a need to confirm the trend by increasing the study period.
INTRAOPERATIVE LYMPHATIC MAPPING WITH 99MTC IN PATIENTS WITH ENDOMETRIAL CANCER INCREASES THE RATE OF LYMPH NODES RETRIEVAL

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Background: Pelvic lymphadenectomy is an imperative part of surgical treatment in certain patients with endometrial cancer. As the procedure increases patient’s morbidity, the concept of sentinel lymph node mapping was established. However, there still will be concerns related to residual cancer cells in remaining lymph nodes overlooked during surgery.

Aims: To compare the extent of retrieved lymph nodes (LNs) during surgery with and without using radiocolloid for lymphatic mapping in patients with intermediate risk-type of endometrial cancer.

Methods: Preoperatively the volume of 30-90 MBq technetium-99 m-labelled nanocolloids was injected into subendometrial layer underlying tumor under ultrasound guidance in 18 patients with endometrial cancer type IA,G3-IIA,G1-3. The operation was performed from 60-90 minutes after the isotope application. The LNs were identified by direct observation, palpation and radioactive counts using the handheld gamma counter. The number and location of nodes were recorded and compared with the lymph nodes specimens after conventional, radiotracer free pelvic lymphadenectomy (n=41).

Results: Feasibility of radioisotopic detection of 99mTc was 100%. No drainage failure, isotope activity deficiency or problems with LNs location occured. The highest activity (MBq) was noticed in interiliac region. The mean number of harvested LNs in patients operated with and without 99mTc lymphatic mapping with was 20.8 (range 10-32) and 13.5 (interval 6-20,p=0.0001), respectively.

Conclusion: Intraoperative pelvic lymph node detection with technetium-99m is feasible in patients with endometrial carcinoma and enhances chances for removing hidden metastases via increasing number of harvested lymph nodes. *Work was supported by the CEPV grant co-financed from EC sources.
DOWN-REGULATED PROGESTERONE RECEPTOR A AND B COINCIDING WITH SUCCESSFUL TREATMENT OF ENDOMETRIAL HYPERPLASIA BY THE LEVONORGESTREL IMPREGNATED IUD

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The main objective of the present study was to investigate whether regression of endometrial hyperplasia observed after three months of treatment with levonorgestrel impregnated intrauterine device (LNG-IUS) was sustained after six months and whether these effects were still occurring synchronously with extinguished expression of progesterone receptors and increased apoptosis. In a retrospective population-based study 41 patients with low and medium risk endometrial hyperplasia were included. Treatment response comparing response to LNG-IUS (N=25) and standard per oral medroxyprogesterone (MPA) (N=16) was evaluated. Expression of PR-A, PR-B, ER-alfa, ER-beta, Bcl-2, BAX, Caspase-3 and MT (metallothioneine) was investigated by immunohistochemistry, results evaluated by a semi-quantitative H-score. Result demonstrated that all the LNG-IUD treated patients had therapy response after six months. PR-A and PR-B in glands were almost extinguished for IUD users compared to the oral group (PR-A P= 0.0001, PR-B P=0.0006). Estrogen receptors were also reduced (ER-alfa P= 0.002 ER-beta P= 0.03). Co-existent changes in apoptosis were differently modulated in glands and stroma, significantly different for the two treatment groups (Bcl-2 P=0.03, BAX P=0.0001, Caspase-3 P=0.0001, MT P=0.037). Bcl-2 was significantly different in glands (P=0.01) and stroma (P=0.03) in responders and non-responders to oral therapy. LNG-IUS conclusively demonstrates sustained treatment effect after six months in endometrial hyperplasia. The clinical effect is accompanied by almost extinguished PR-receptors in glands coinciding with modulation of apoptosis. Maintained high levels of Bcl-2 in glands and low levels in stroma are related to progestin resistance. The results strongly indicate that progestins activate non-classical initiated signaling pathways.
HIGH GRADE ENDOMETRIAL STROMAL SARCOMA OF THE UTERUS

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Background: Endometrial stromal sarcoma (ESS) is a rare uterine malignancy characterized by cells resembling proliferative-phase endometrial stroma. The tumor is classified into low grade (LGESS) and high-grade (HGESS) based on mitotic rate. HGESS is characterized by more than 10 mitoses and poor prognosis.

Aim: To analyze the prognostic factors in high grade endometrial stromal sarcoma in 8 patients were evaluated retrospectively.

Material & method: Eight cases with histologically proven HGESS were treated between 2007-2010 at Department of Gynecologic Oncology, Ankara Baskent Univercity Hospital were retrospectively analysed. Tumor size, mitotic count, tumor stage, menopausal status, age and histologic grade have been reported to have prognostic significance in various studies. Standard treatment is total hysterectomy and bilateral salpingo-oophorectomy.

Result: Mean age of the 8 patients was 48,8 (range 23-65 years). Four patients (%50) were premenapozal, two of them were nulliparous. Four patients were (%50) postmenapozal. Mean gravida and parity were 2.88 and 2.33. Mean number of resected lymph nodes was 48. Mean number of mitosis was 19 ±2.75% of the patients received IMA based chemotherapies. Recurrences were seen in 37.5% (n=8) of the patients. 50% (n=4) of the recurrent patients were died within 6 and 25 months.

Conclusions: HGESS may demonstrate very aggressive clinical behaviour despite the aggressive surgical management and chemotherapeutic approach. Management strategies of HGESS should be re-evaluated.
THE SUME LEVELS OF 8-HYDROXY-2'-DEOXYGUANOSINE IN ENDOMETRIAL AND OVARIAN NEOPLASMS

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Background: Genetic stability and its maintenance is very important for DNA replication processes in all forms of life. Recently increased attention has been paid to the importance of reactive oxygen species (ROS) in all the steps of carcinogenesis.

The aim of the study was to check if there are any changes in the quantitation of 8-hydroxy-2'-deoxyguanosine in analyzed blood serum derived from patients diagnosed with endometrial and ovarian cancers.

Methods: Whole blood samples were drawn from the antecubial vein of healthy post menopausal, non cancerous patients (7), with diagnosed endometrial cancer (15) and ovarian cancer (12) patients. Serum has been analyzed using Trevigen HT 8-oxo-dG ELISA Kit. Absorbance wavelength at 450nm has been measured twice after dilution of anti-8-oxo-dG. Calculation y=a+bx+cx², where y is the average absorbance measurement of the sample, x is the log of 8-oxo-dG concentration in ng/ml and a, b, c are coefficients, has been performed to determine 8-oxo-dG concentrations.

Results: The average 8-oxo-dG sume levels measured in ng/ml in blood serum of endometrial cancer patients was 167.47(+-71.76), and was statistically significant higher in comparison with group of ovarian cancer patients 43.44(+-16.94) (p< 0.0001). There were no dependance between endometrial cancer and control groups 155.29 (+/-63.65)(p< 0.75).

Conclusions: Our investigations revealed that levels of 8-oxo-dG measured in blood serum is statically higher in uterine cancer in comparison with ovarian cancer.
CLINICAL CHARACTERISTICS OF PATIENTS IN CASE OF ENDOMETRIAL HYPERPLASIA (EH)
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The aim was to analyze the patient's complaints, symptoms, anamnesis, objective investigation data, histological findings and further recommendations in case of endometrial hyperplasia.

Methods: 421 patients with histologically confirmed diagnosis of endometrial hyperplasia and endometrioid carcinoma treated between 2007 and 2009 at the Gynecological Department, Riga Hospital No.1, Latvia were included in the analysis partially retrospectively, partially prospectively.

Results: The average age of the patients was 44.77 years (SD ± 8.9). Only 16.6% of patients (n=70) were already postmenopausal. The most common clinical symptom in 63.2% cases (n=266) was bleeding. The mean duration of bleeding was 17.1 days. In the 30.9% of cases (n=130) there were no complaints, the examination was initiated based on ultrasonographic data. From the total amount of the patients the EH relapse was diagnosed in 30.9% (n=130) of cases, were 20% of women (n=26) underwent the dilatation & curettage more than once in the past. Ultrasound data were available in 67% of cases (n=282), from them 45.7% (n=129) were performed in hospital. In 10.5% of patients in the family anamnesis there were some gynecological malignancies. It is to stress that only 37% of patients (n=156) obtained some therapy after confirmed EH diagnosis (hysterectomy or hormonal treatment).

Conclusions: The average time of bleeding is more than 2 weeks before the woman consults the doctor. The relapse rate is 30.9% high. Closer attention should be paid to the suitable drug treatment with subsequent histological endometrium control in order to prove the EH regression and to prevent relapses.
THE ROLE OF MULTIDISCIPLINARY TEAM MEETINGS IN MANAGEMENT OF ENDOMETRIAL CANCER

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Background: Multidisciplinary team (MDT) meetings have been shown to significantly improve cancer staging accuracy. Central-review of pathology and imaging is not a requirement for endometrial cancer according to government guidelines; but is regarded as good practice.

Objective: We decided to evaluate the influence of MDT meetings on the histological type, grade of tumour and magnetic resonance imaging (MRI) staging for endometrial cancer.

Methods: Over 15 months, all new cases of endometrial cancer within the Greater Manchester and Cheshire cancer network were prospectively registered. Only women who had biopsy and imaging performed and reported in the local hospital, which were reviewed at the MDT were included in this study. The final stage, type and grade as determined from the surgically resected specimen were considered to be the gold-standard.

Results: MR scans of 59 women and endometrial biopsy samples of 61 women were reviewed at the MDT.

Histopathology: In 74%, concordance in the tumour type was noted between local, MDT and final results. Individually, local pathology was accurate in 74% and MDT pathology in 82% of cases.

Imaging: In 56%, concordance between local, MDT MRI staging and final histopathological staging was noted. Individually, both local and MDT staging were equally accurate at 61%.

Discussion: Despite an increase in the delivery of cancer services via the MDT method, there is little evidence for its direct effect on the quality of patient care. Since MDT decisions play an important role in the overall outcome, we believe quality assurance of these meetings is mandatory.
CURRENT STATUS OF CLINICAL MANAGEMENT IN ENDOMETRIAL CANCER: A NATIONAL SURVEY OF THE NORTH-EASTERN GERMAN SOCIETY OF GYNAECOLOGIC ONCOLOGY (NOGGO)

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Background & aims: Optimal treatment strategies for the management of endometrial cancer (EC), especially regarding the extent of systematic lymphadenectomy and the choice of adjuvant treatment remain controversial. To design prospective trials to improve the clinical outcome of patients with endometrial cancer, insights from the current clinical practice are absolutely necessary. Therefore we conducted the present survey about current status-quo of the surgical and medical management of EC in Germany.

Methods: A validated 11-item-questionnaire regarding surgical and adjuvant procedures of EC was sent to 915 German gynaecological departments as part of a cross-sectional-study between 05/2009 and 08/2009.

Results: A total of 316 questionnaires were returned and evaluated: 5.7% from university hospitals, 26% from hospitals for maximum medical care and 68% from hospitals for basic medical care. 5% of the clinics reported never performing a lymphadenectomy in EC, 38% do so in selected cases and 57% at a regular basis. 5% of the clinics perform a lymphadenectomy up to the common-iliac-artery, 7.4% up to the inferior-mesenteric-artery and 86% up to the renal-veins. The most common risk factors to indicate a lymphadenectomy were: high grading (95%), non-endometrioid-histology (91%), lymphovascular invasion (74%), blood-vessel invasion (61%) and tumor-diameter>2cm (56%). 56.5% indicate radiation for stage III/IV and 42.5% will indicate chemotherapy alone.

Conclusions: This is the largest cross-sectional study in a Western country about the treatment strategies in EC. The heterogenous approaches reported by the hospitals reflect the current treatment dilemma regarding lymph-node evaluation and adjuvant treatment. Further studies are urgently needed.
MANAGEMENT OF SIMPLE ENDOMETRIAL HYPERPLASIA: QUESTIONNAIRE SURVEY AND LITERATURE REVIEW

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Introduction: Simple endometrial hyperplasia is a relatively common condition. There is no uniformity in the management of simple endometrial hyperplasia and no guidance for the management. Although there is a very high rate of spontaneous regression (80% in cases without atypia), therapy should be instituted since some patients may progress to cancer.

Material and methods: A simple questionnaire survey was designed which consisted of two clinical scenarios with a number of options for initial management, follow up and subsequent management of persistent simple endometrial hyperplasia. This was sent to all the consultants in the West Midlands.

Results: 70% of the consultants contacted returned the questionnaire. 9 of the respondents did not practice gynaecology. Of the remaining answers there was a wide variation of practice. In postmenopausal women with simple endometrial hyperplasia most respondents preferred the insertion of a Mirena IUS or repeat pipelle in 6 months. Most preferred not to follow up the asymptomatic patients or to see them after 6 - 12 months. For premenopausal women majority preferred insertion of a Mirena IUS. If repeat pipelle showed no hyperplasia and the patient was asymptomatic, most surgeons preferred not to follow up the patients or to see them after 6 - 12 months.

Conclusion: The results of this survey demonstrates a lack of uniformity in the treatment and follow up options for both premenopausal and post menopausal endometrial hyperplasia. The authors hope to stimulate a regional discussion and debate and formation of a regional treatment protocol for this common condition.
UTILITY OF NARROW BAND IMAGING TARGETED BIOPSIES IN THE CONSERVATIVE MANAGEMENT OF ENDOMETRIAL ATYPICAL HYPERPLASIA

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Introduction: Narrow band imaging (NBI) is a novel endoscopic technique able to enhance the accuracy of diagnosis by using narrow band width filters in a red-green-blue sequential illumination system. The light penetration depth depends on the wavelength used: the blue filter is designed to correspond to the peak absorption spectrum of hemoglobin so that NBI allows appreciation of the mucosal pattern and surface microvasculature simply through an on-off switch located on the head of the endoscope. This technology has recently been introduced in the evaluation of endometrial lesions.

Methods: Six young women with atypical hyperplasia underwent resectoscopic treatment under NBI visualization system followed by megestrol acetate administration for six months.

Results: The conservative surgery was effective since transvaginal ultrasound and diagnostic hysteroscopy with NBI targeted biopsies at 3, 6, 9 and 12 months after surgery were negative for atypia or progression.

Conclusions: NBI allows a clear visualization of microvascular architecture, helping in identifying suspected areas, even if small, with thick and irregular microvessels for targeted surgery. This method, under a close post-surgical follow-up, might represent a novel technical option in treating those women with atypical hyperplasia who wish to preserve fertility.
Mortality and Morbidity Associated with Surgery for Endometrial Cancer in Women ≥70 Years


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Objective: The gold standard treatment of endometrial cancer is surgery. However, this disease often occurs in older women with comorbidities. Our objective was to determine the treatment options offered at our institution to elderly women with endometrial cancer, analyze the surgical (30-day) mortality and morbidity and determine any predictors of poor outcome of surgical treatment.

Study methods: This is a retrospective analysis of women ≥70 years with endometrial cancer treated at McGill University Health Centre between 1991 and 2006.

Results: Of the 354 women ≥70 years identified with endometrial cancer, 302 (85.3%) were treated surgically and formed the study group. The median age of the patient was 76 years (range 70-92); 16.4% had 0 co-morbidities, 53.9% had ≥2 and 26.2% had ≥3. The median post-operative hospital stay was 5 days, (range 2-44). Although 20.5% experienced surgical morbidity, only 6.3% had high grade complication and 1.3% died from surgery-related complications. Increasing age or stage of disease did not significantly influence morbidity. On univariate analysis, obese patients were significantly more likely to develop severe/life threatening complications (19% vs 6.9% p=0.011), and so were those with coronary artery disease (CAD), (25% vs 6.6%, p=0.005). On multivariate analyses, CAD remained an independent risk factor for severe/threatening morbidity (OR 3.51 (95% CI 1.22-10.14)).

Conclusion: This study, the largest series on this subject, suggests that surgery which is known to be associated with the best long-term survival rates for endometrial cancer in women ≥70 years, has acceptable treatment related mortality and morbidity, except in women with CAD.
ACCURACY OF PRE-OPERATIVE ENDOMETRIAL BIOPSY AND MAGNETIC RESONANCE IMAGING IN PREDICTION OF HISTOLOGICAL TYPE, GRADE AND STAGE OF ENDOMETRIAL CANCER

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Background: The prognosis of endometrial cancer depends on a number of factors including tumour grade, stage, LVSNI and nodal-status. Endometrial cancer although ideally staged surgically (FIGO), evaluation with imaging before surgery has been suggested as an alternative to surgical-staging.

Objective: The objective was to assess the sensitivity, specificity and accuracy of pre-operative endometrial biopsy for tumour-grade and type and staging derived from magnetic resonance imaging (MRI) in women diagnosed with endometrial cancer.

Methods: Data was prospectively collected over 12 months from 15 hospitals in the Greater Manchester and Cheshire cancer-network. Pre-operative endometrial biopsy and MRI staging was compared to the final histopathological result of the surgical specimen, which was considered to be the gold-standard.

Results: Pre-operative biopsy result was available for 218 and MRI staging for 211 women. The sensitivity and specificity for endometriod and non-endometriod pathology were 95, 50% and 61, 97% respectively. Sensitivity and specificity for low-grade(G1) and high-grade(G2/3) disease were similar at 81 and 82% respectively. When assessed for MR stage IA/IB (old FIGO), IC, II and III disease, the sensitivity and specificity were 77, 81%; 76,87%; 83,92% and 68, 94% respectively. The overall accuracy for pathology, tumour-grade and MRI staging when assessed on a scale from 0-1 ranged between 0.79 - 0.92, considered to be 'almost perfect'.

Discussion: Our study confirms good accuracy of pre-operative biopsy and MRI staging for endometrial cancer. This additional knowledge has clinical advantages and also helps in preoperative counselling of patients, planning place of surgery, theatre schedules, personnel, and adjuvant treatment.
THE CONSIDERABLE FACTORS TO REQUIRE ENDOMETRIAL BIOPSY IN TAMOXIFEN-TREATED BREAST CANCER PATIENTS


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Objective: The possible carcinogenetic effect of tamoxifen on endometrium in patients with breast cancer has received world-wide attention. We investigated considerable factors to decide that the endometrial biopsy was necessary to a tamoxifen-treated breast cancer patient.

Methods: We selected 327 patients who received one or more endometrial biopsy during tamoxifen treatment based on breast cancer. We reviewed their medical and histopathological records and analyzed their clinical features according to pathologic results.

Results: Patients have evaluated their endometrium with transvaginal ultrasonography (TVS), usually every 6 months. Endometrial biopsy was performed 1-7 times to each patient if endometrial thickness was 5 mm or more, consistent with prior reports, or abnormal vaginal bleeding was shown. They had experienced abnormal vaginal bleeding in 32.1% and mean endometrial thickness was 12.3 mm (SD, ±6.9 mm). The period from beginning tamoxifen to endometrial biopsy was very diverse. Pathologically, endometrial polyp was most common (26%) and cancer/precancerous lesions were proven in 8.0%; endometrial cancer in 2.4%, endometrial hyperplasia in 4.9%, and atypical polyp in 0.9%. Patients with cancer/precancerous lesions showed significantly larger endometrial thickness and more often abnormal vaginal bleeding than the other patients (18.8±9.7 mm vs. 11.7±6.4 mm) (93.5% vs. 26.2%). The duration of administering tamoxifen was not associated with pathologic result.

Conclusions: We evaluated the relation between considerable clinical factors and pathologic results in patients received the endometrial biopsy during tamoxifen treatment. Further studies are required to establish the standard endometrial thickness, which is needed to decrease endometrial biopsies in tamoxifen-treated breast cancer patients.
A STUDY OF EXPRESSION AND PROMOTER METHYLATION OF RUNX3 IN ENDOMETRIAL CANCER TISSUE AND CELL LINE

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Objective: The aim of study to investigate expression and promoter methylation of RUNX3 in endometrial cancer tissue and cell lines.

Methods: Thirty endometrial cancer tissues and two endometrial cancer cell lines (HEC1-alpha, Ishikawa) were used in this study. We performed reverse transcription-polymerase chain reaction (RT-PCR), methylation specific PCR and immunohistochemical staining to reveal related mechanism. The methylating agent, 5-aza-2'-deoxycytidine (ADC) was used in the HEC1-alpha cell line to reverse the methylation status.

Results: Loss of RUNX3 expression was observed in 40%(12/30) of the endometrial tissue and HEC1-alpha cell line. Hypermethylation of RUNX3 promoter was observed in 53.3%(16/30) and HEC1-alpha cell line. Tumor grade and stage were statistically correlated with loss of RUNX3 expression. The expression was augmented by treatment of 5-aza-2'-deoxycytidine (ADC).

Conclusion: This study suggested that loss of RUNX3 expression induced by hypermethylation of RUNX3 promoter is an important mechanism in endometrial carcinogenesis. This data may have potential significance in developing not only prognostic marker but also therapeutic agent for endometrial cancer.
FIRST CASE REPORT OF A HIGHLY MALIGNANT UTERINE PECOMA EXPRESSING ESTROGEN AND PROGESTOGEN RECEPTORS: POTENTIAL FOR A NEW THERAPEUTIC MODALITY

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Introduction: Perivascular epitheloid cell neoplasms (PEComas) comprise a growing family of related tumours without a known normal cell variant. Very few malignant uterine PEComas have been reported in the literature and most of these showed only locally aggressive behaviors. We found five reports of systemic metastases, mostly years after diagnosis. Treatment of metastatic PEComa is problematic and usually consists of systemic chemotherapy.

Case report: We report a case of highly aggressive uterine PEComa in a very young woman aged 21 years. The tumour recurred locally within months after surgical resection and metastasized to the lungs within three months. The local recurrence was removed again surgically, confirming the absence of lymphatic spread and the patient currently receives systemic chemotherapy for her metastatic disease.

Histology: Histology revealed some of the features of malignancy and special immuno-histochemical staining confirmed tumour classification. The tumour was strongly positive for Actin and HMB-45. Due to the tumour behavior, the dilemma of systemic therapy and the origin of the tumour, hormone receptor analysis was performed. The tumour expressed strong estrogen receptor positivity and also progestogen receptor positivity.

Conclusion: We report one of very few highly malignant and metastatic uterine PEComas in the existing literature. This is the first report of sex hormone receptor positivity in this very rare neoplasm. Clinical experience with hormonal therapy in rare uterine tumours is currently limited. In view of these results, we consider this option worth exploring.
PTEN-LOSS AND NUCLEAR ATYPIA OF EIN IN ENDOMETRIAL BIOPSIES CAN PREDICT THE EXISTENCE OF A CONCURRENT ENDOMETRIAL CARCINOMA

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Aim: To evaluate whether nuclear atypia or PTEN-loss in EIN could help to predict in curettage material, the prevalence of concurrent carcinoma in hysterectomy specimens.

Materials and methods: This retrospective study included women diagnosed with endometrial hyperplasia (simple or complex) and underwent hysterectomy within 12 weeks from the initial diagnosis without interval treatment. Curettage slides were reviewed by three experienced pathologists and only cases that fulfilled the criteria of EIN were used for analysis. For each case, the nuclear atypia and the immunohistochemically detected expression of PTEN were evaluated. The hysterectomy slides were also reviewed and the findings were used in the subsequent analysis.

Results: Out of 83 cases that were enrolled in the study, 33 (39.76%), had a concurrent endometrial carcinoma. Nuclear atypia in EIN cases with a final histology of endometrial cancer was found in 31 out of 33 cases (93.94%) but only in 27 out of 50 benign cases (54%). There was no PTEN-loss in 8 out of 33 EIN cases (24.24%) that proved to be cancer and 22 out of 50 EIN cases (44%) that proved to be benign. Either atypia or PTEN-loss or both were found in 33/33 (100%) cancer cases and in 39/50 (78%) benign cases; this difference was statistically significant (Fisher exact test, p< 0.05).

Conclusion: PTEN-loss, as an independent variable, was not found to be a predictor of endometrial cancer in the final histology. However, biopsies presented with EIN, featuring nuclear atypia and recognized as PTEN-null are more likely to be finally diagnosed with endometrial cancer.
**MELF INVASION IN ENDOMETRIAL CANCER AS A RISK FACTOR FOR LYMPH NODE METASTASIS**

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**Aim:** To investigate whether the microcystic, elongated and fragmented (MELF) pattern of myometrial invasion encountered in certain endometrioid endometrial carcinomas can be considered as a risk factor for lymph node metastasis.

**Materials and methods:** 351 cases of total abdominal hysterectomy and bilateral salpingo-oophorectomy with/without lymphadenectomy or lymph node sampling, performed for endometrioid endometrial adenocarcinoma were enrolled in the study. The existence of MELF invasion, vascular invasion, fibromyxoid stromal reaction and lymph node metastasis were recorded. Immunohistochemistry for endothelial and epithelial markers was performed on selected cases.

**Results:** MELF invasion was identified in 20 (10.81%) and 13 cases (13.13%) treated without and with lymphadenectomy respectively. All of these cases were either well or moderately differentiated carcinomas, stage IA to II (without considering lymph node status). Positive lymph nodes were detected in 7/13 MELF positive (53.84%) and in 6/86 MELF negative cases (6.97%) This observation was statistically significant. Out of the 7 MELF positive tumours with lymph node metastasis, 3 cases exhibited intravascular tumour emboli while 4 showed a fibromyxoid stromal reaction.

**Conclusion:** MELF pattern invasion was found to be statistically related to lymph node metastasis. Nevertheless, further studies are needed in order to evaluate the clinical significance of this observation.
ESTROGEN REPLACEMENT INDUCES A UNIQUE GENE EXPRESSION PROFILE IN OVARIAN CANCER THAT DIFFERS FROM BREAST CANCER

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Objectives: Estrogen replacement therapy (ERT) increases risk of ovarian cancer but not breast cancer. We sought to contrast ERT regulated genes in human ovarian cancer vs. human breast cancer.

Methods: Athymic nude mice received xenografts of human ovarian cancer cells (ER\textsuperscript{+} PEO4, or ER\textsuperscript{-} 2008). 17\textbeta-Estradiol (E2)-releasing pellets were implanted subcutaneously for 7 weeks; then continued or withdrawn for 4 weeks. Intraperitoneal ovarian tumors were harvested and cDNA hybridized to Affymetrix gene chip microarrays. Significant differences were ANOVA p < 0.05 and expression difference >1.2 fold. Data were compared to published ERT-regulated genes in breast cancer.

Results: A significant increase in volume of ER\textsuperscript{+} PEO4 intraperitoneal disease with E2 was confirmed by quantitative imaging. E2 withdrawal decreased expression of progesterone receptors (PR) without decreasing tumor proliferation. Three ERT responsive gene classes were defined: Class A (↓2008, ↓ Control (C) PEO4, ↑ERT PEO4); Class B (↑2008, ↓C PEO4, ↑ ERT PEO4); Class C (↑ C PEO4, ↓ ERT PEO4). Class A genes (146) included PR. Class B genes (152) included caveolin, CD44 and fascin 1, which have known roles in ovarian cancer; palladin was novel. Surprisingly, ERT-regulated genes in ovarian and breast cancers minimally overlap: only 6.8% (10/146) of class A genes and 9.9% (15/152) of Class B ovarian ERT-regulated genes overlapped with ERT-regulated breast cancer genes.

Conclusions: ERT induces a unique gene expression profile in ovarian cancer cells that lacks significant overlap with breast cancer genes. Novel selective estrogen response modifiers for ovarian cancer need to be developed.
CURCUMIN ENHANCED THE ANTITUMOR EFFECT OF HERPES SIMPLEX VIRUS THYMIDINE KINASE IN HUMAN BREAST CANCER THROUGH MODULATION OF ANTI-APOPTOTIC PATHWAY

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Background and aims: Suicide gene therapy using herpes simplex virus thymidine kinase (HSV-TK)/ganciclovir (GCV) has shown to be a potential strategy for cancer treatment. However, GCV-mediated cytotoxicity relies on the replicating ability of the targets. In this study, we investigated whether curcumin, a chemopreventive drug, potentiates the antitumor effect of HSV-TK/GCV using an orthotopic human breast cancer model.

Methods: We used MDA-MB-435s cell line stably transfected with HSV1-tk and luciferase (luc) genes to study the anti-proliferation effect of combination therapy. The in vitro surviving fraction was measured by SRB assay. The expression of antiapoptosis-related proteins was examined by Western blotting. The in vivo therapeutic efficacy of GCV, curcumin, and GCV+curcumin was evaluated in NOD/SCID mice bearing MDA-MD-435s/tk-luc orthotopic tumors using bioluminescent imaging.

Results and conclusions: The results showed the synergistic killing effect of combination therapy on MDA-MB435s/tk-luc cells through inhibition of Bcl-2 and Cyclin D1 expression at early time points. The tumor growth rate of the combination group was significantly lower than that of GCV alone (p<0.05) after day 22. Curcumin alone resulted in a slight, but no significant tumor regression as compared with the control.

![Graph showing in vivo tumor growth curves](image-url)

We concluded that HSV-TK gene therapy combined with curcumin could be a potential strategy for breast cancer treatment.
HIGHLY EFFECTIVE RISK STRATIFICATION BY HUMAN PAPILLOMAVIRUS TESTING IN WOMEN WITH ABNORMAL CERVICAL CYTOLOGY; 17.5 YEARS PROSPECTIVE COHORT STORY

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Aims: To evaluate the long-term cumulative incidence of cervical intraepithelial neoplasia grade 3 or carcinoma (CIN3+) following an abnormal cytological result (mild to moderate and severe dyskaryosis) and determine the additional value of human papillomavirus (HPV) testing.

Methods: 353 women with abnormal cytology referred to a Dutch gynaecological outpatient clinic between 1990 and 1992 were followed until December 2009 for CIN3+.

Results: The median follow-up was 17.6 years. During follow-up 31.4% (111/353) developed CIN3+. Women with mild to moderate dyskaryosis had a risk for CIN3+ of 26.6% (79/297) and women with severe dyskaryosis of 57.1% (32/56). The vast majority (107/111, 96.4%) of CIN3+ lesions were detected within 5 years of the first abnormal smear, hereafter their risk is similar to the general population (1.8%). Among women with mild to moderate dyskaryosis, HPV-testing at baseline discriminated significantly for CIN3+. A negative HPV-test decreased the risk to 2.6% (3/114) whereas the risk increased to 41.5% (97/183) if a positive test result was detected (RR 15.78, 5.10 to 48.84). In women with severe dyskaryosis HPV testing at baseline did not have clinical benefits (RR 3.04, 0.52 to 17.79).

Conclusions: Women with abnormal cytology have an increased risk to develop CIN3+ for the first 5 years after detection. Hereafter their risk is similar to women in the general population. For women with mild to moderate dyskaryosis an additional HPV-test at baseline is very distinctive to identify women at risk for CIN3+, whereas women with severe dyskaryosis should always be referred for colposcopy.
DIAGNOSTIC PERFORMANCE OF CONTRAST ENHANCED CT AND FDG-PET/CT IN THE ASSESSMENT OF LYMPH NODE METASTASIS IN OPERABLE CERVICAL CANCER

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Background: Pre-operative knowledge of lymph node status in early stage cervical cancer may lead to a better selection of patients for radical surgery. Conventional imaging modalities i.e. CT or MRI have low sensitivity in predicting nodal metastasis. PET-CT combines the anatomic detail from CT with metabolic information from PET and shown to be superior to CT alone.

Aim: To determine the accuracy of pre-operative PET/ CT and CE-CT scan for detecting lymph node metastases in operable cervical cancers compared with histopathologic results from systemic lymphadenectomy.

Methods: Fifty operable cervical cancer patients (up-to FIGO stages-IIA) were studied prospectively. CE/CT abdomen & pelvis and whole body PET/CT were done preoperatively. All patients underwent pelvic and low para aortic lymphadenectomy. Each nodal group was labeled as per anatomical location (obturator-internal iliac, external iliac, common iliac and low para-aortic) and evaluated separately on histopathology. Histopathology was considered the gold standard.

Results: Primary tumor was FDG avid in all cases with gross disease. The median number of nodes removed was 22 (8-43). Twenty three percent patients had positive nodes. Nodal station-based analysis showed that the sensitivity, specificity, positive predictive value and accuracy of PET/CT for detecting nodal metastases were 52.4%, 99.0%, 78.6% and 95.8% while corresponding values for CE/CT were 47.6%, 97.6%, 58.8% and 94.1%, respectively.

Conclusions: Both CE/CT and PET/CT have low sensitivity in predicting lymph node metastasis in patients with operable cervical cancer. The PPV of PET/CT is higher than CE-CT. Therefore a positive PET/CT may be useful for treatment planning.
EVALUATION OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED CERVICAL CANCER AND ANALYSIS OF RISK FACTORS

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Objective: Neoadjuvant chemotherapy (NACT) is becoming the therapeutic trend for young cervical cancer patients. In order to evaluate the short-term effect of NACT in locally advanced cervical cancer (LACC), to study the effect of NACT on risk factors of postoperative recurrence, this paper sums up clinical, pathological and follow-up data of patients with LACC in West China second hospital during past two years.

Method: From 2008 to 2009, 414 patients with FIGO stage I B2- II A (tumor > 4 cm) were assigned to receive either NACT followed by surgery or radical surgery directly.

Results: Patients had poorer situation in NACT+Surgery group than in Surgery group like Anemia (36.1% vs 15.6%, P=0.00) and local lesion (5.5±0.91cm vs 4.9±0.58cm, P=0.00) before therapy. The overall clinical response rate was 89.6%. The effective rates of squamous cell carcinoma and adenocarcinoma were 89.4% and 83.3% respectively. The clinical response was only associated with FIGO stage (P=0.04). The rate of positive pelvic lymph nodes metastasis (25.4% vs 47.6%, P=0.03) and deep stromal invasion > 1 / 2 (68.0% vs 90.5%, P=0.03) in complete and partial response patients was lower than that in stable response ones. Besides, 78.5% of effective patients underwent additional therapy, while 95.2% of ineffective patients did (P < 0.05). Two-year disease-free rate and two-year survival rate in NACT+Surgery group were 95.4% and 96.0%, in Surgery group were 96.9% and 96.2% (P>0.05).

Conclusion: NACT has a satisfactory effect on LACC. The clinical response is only related to FIGO stage. NACT can decrease risk factors of the effective patients, so these patients have less opportunity for postoperative supplementary therapies.
OBESITY: A PREDICTIVE FACTOR OF SIGNIFICANT DISEASE FOLLOWING A DIAGNOSIS OF CERVICAL GLANDULAR DYSKARYOSIS?

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Introduction: Obesity is considered an important cause of several malignancies. Whilst its role in increasing the risk of cervical adenocarcinoma is well documented, its role in the risk of significant disease following a smear reported as cervical glandular dyskaryosis has been identified in a small retrospective study. With rising incidence of obesity and improved screening methods, the incidence of cervical glandular dyskaryosis has risen in the UK with significant disease outcomes. This leads to an increase in use of diagnostic and therapeutic resources and manpower.

Objectives: To determine whether obesity should be considered as a predictive factor of significant disease following a diagnosis of cervical glandular dyskaryosis?

Methods: A review of available literature and results of studies presented at an international meeting.

Results: A rising incidence was observed in other studies with data collected over significant time periods (4 - 10 yrs) at a recent scientific meeting - British Society for Colposcopy and Cervical Pathology. Adedipe et al (2009) identified an incidence of 0.601% (higher than quoted) and a positive predictive value of cervical smears in identifying disease in a general population at 57.1%, which rose to 75% within the subgroup of women with BMI>25.

Conclusion: A BMI> 25 should be recognized formally as a significant predictive factor for presence of disease following cervical glandular dyskaryosis. This aids the clinician's ability to deliver care. More research is needed into identifying the type of obesity (as determined by waist -hip ratio) and time-period of obesity that is associated with significant disease.
FORTY YEARS REVIEW FOR THE TREATMENT OF VAGINA CARCINOMA: AN INSTITUTIONAL EXPERIENCE

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Objective: To evaluate clinical outcome, prognostic factors and treatment modalities for vaginal carcinoma.

Material and methods: 105 patients with vaginal carcinoma treated in Sun Yat-Sen University Cancer Center between July 1969 and March 2009 were selected, which included 13 patients with cancer of vagina stump. 46 were at stage I disease (FIGO staging), 24 at stage II, 14 at stage III and 8 at stage IV disease. 83 patients had squamous cell carcinoma, 17 had adenocarcinoma, 2 had clear cell carcinoma and 3 had undifferentiated carcinoma. All cases were divided into five groups according to the treatment modalities that included radiation therapy only (group 1), surgery only (group 2), the combination of radiation and adjuvant chemotherapy (group 3), the combination of surgery and adjuvant radiation or chemotherapy (group 4), chemotherapy only (group 5).

Results: The 5-year survival rate was 46.7%(49/105) in all cases, 55% (22/40) in group 1, 33.3% (3/9) in group 2, 18.2% (4/22) in group 3, 69.0% (20/29) in group 4 and 0% (0/5) in group 5. The patients who were given a combined treatment with surgery and adjuvant therapy (group 4) had a better prognosis (P<0.001). Multivariate analysis revealed that FIGO stage, tumor size and superficial lymphnode enlargement were the independent prognostic factors (P<0.05).

Conclusion: Treatment modality was not correlated to the survival of patients with primary vaginal carcinoma. However, the better prognosis may be achieved by combined therapy with surgery and adjuvant therapy.