ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

Management Considerations for the Surgical Treatment of Colorectal Cancer During the Global Covid-19 Pandemic

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Running title: Covid-19 and colorectal cancer

Word count (without abstracts, references, tables): 4712
Word count abstract: 250
References: 73

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ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

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The authors have not received any financial support for this manuscript.

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

Mini-Abstract

Surgical practice guidelines for colorectal cancer must be modified for the unprecedented COVID-19 pandemic as well as potential future outbreaks. Data to support delays in surgical care are limited. This review analyzes management recommendations and the strength of published evidence using the GRADE system to provide a rational basis for clinical decision-making.

Structured Abstract

Objective: The COVID-19 pandemic requires to conscientiously weigh "timely surgical intervention" for colorectal cancer against efforts to conserve hospital resources and protect patients and health care providers.

Summary Background Data: Professional societies provided ad-hoc guidance at the outset of the COVID-19 pandemic on deferral of surgical and perioperative interventions, but these lack specific parameters to determine the optimal timing of surgery.

Methods: Using the GRADE system, published evidence was analyzed to generate weighted statements for stage, site, acuity of presentation and hospital setting to specify when surgery should be pursued, the time and duration of oncologically acceptable delays, and when to utilize non-surgical modalities to bridge the waiting period.

Results: Colorectal cancer surgeries - prioritized as emergency, urgent with (a) imminent emergency or (b) oncologically urgent, or elective – were matched against the phases of the pandemic. Surgery in COVID-19 positive patients must be avoided. Emergent and imminent emergent cases should mostly proceed unless resources are exhausted. Standard practices allow for postponement of elective cases and deferral to nonsurgical modalities of stage II/III rectal and metastatic colorectal cancer. Oncologically urgent cases may be delayed for 6(-12) weeks without jeopardizing oncological outcomes. Outside established principles, administration of nonsurgical modalities is not justified and increases the vulnerability of patients.

Conclusion: The COVID-19 pandemic has stressed already limited health care resources and forced rationing, triage and prioritization of care in general, specifically of surgical interventions. Established guidelines allow for modifications of optimal timing and type of surgery for colorectal cancer during an unrelated pandemic.

Keywords

Colorectal cancer, Guidelines, Pandemic, Epidemic, Resource allocation, Surgery, Timing, Delay, Wait time, Chemotherapy, Radiation.

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

Introduction

The pandemic caused by the novel severe acute respiratory syndrome coronavirus SARS-CoV-2, or COVID-19, has led to a strain on healthcare resources. The staggering number of infections and associated mortality continue to increase with over 2.3 million confirmed cases and over one hundred fifty-thousand deaths by April 20, 2020.[1] In treating patients with cancer, unprecedented considerations extend beyond the individual's timely cancer needs or even acute individual illness due to COVID-19 infection and include, in the broader interest of all, pandemic control and resource management measures.[2] In 2019, nearly one hundred and fifty thousand new cases of colorectal malignancy were diagnosed in the USA, and the current pandemic stands to significantly alter treatment for these patients.[3] Standards of cancer care may have to be modified or trimmed in order to protect and prioritize the life of others. The optimal balance between the individual's needs and the necessity of the public to limit the spread of infection (including to the patients and health care providers) and to save bed resources and ICU capacity is subtle, agonizing, and uncharted territory.

In the early phase of the pandemic, ad hoc guidelines from various societies and governing bodies have emerged in quick sequence with the overarching goal to limit "elective surgical cases". The details of these recommendations are less well defined and are subject to rapid change as more specific knowledge evolves.

Using the GRADE system,[4] we therefore aimed at reviewing the published evidence regarding the recommended time frame of key interventions for colorectal cancer and the impact of variations thereof on the ultimate cancer-specific outcome. Basing our statements primarily on highly developed healthcare systems, our goal was to define those circumstances where timely surgery remains crucial as opposed to the ones where a delay or alternative treatment measures would appear justifiable and without measurable negative long-term impact for the individual while preserving essential resources for the public.

Current practice

Untreated, colorectal cancer progresses over time, and delay in care has been associated with worse outcomes. Guidelines recommend a short interval from symptoms to diagnosis with a benchmark of initiation of the first treatment within six weeks from diagnosis for 90% of patients.[5] Furthermore, the interval between surgery and adjuvant treatment should ideally be 4-6 but definitely less than 12 weeks. Timing of surgery for the primary tumor after neoadjuvant treatment, however, has been more controversial with a suggested range of 6-12 weeks after the last chemoradiation. Even less standardized is the timing and sequence of interventions for metastatic disease.

Depending on tumor location (rectum vs colon) and stage, treatment modalities include surgery, chemotherapy/immunotherapy, and radiation. While surgery remains the principal treatment for curative intent, the standard sequence of modalities and the extent of surgery may require modification depending on the acuity of presentation or the presence of an underlying pan-colonic disease (e.g., hereditary cancer syndrome, inflammatory bowel disease). Settings of metastatic cancer are highly variable, and surgery is reserved for either acute disease complications or for the comparably small subgroup of patients who, despite the spread of disease, are considered potentially curable.

Governing Mandate During a Global Pandemic

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

Hospital bed availability and resources are impacted by the pandemic and need to be conserved. Prior to COVID-19, the region of Lombardy in Italy had an intensive care unit capacity of nearly 720 beds; in the first two weeks in March 2020, 16% of COVID-19 positive patients required ICU admission,[6] varying from 6.6% to up to 40%.[7, 8] The Italian hospital capacity quickly reached its limits consistent with an exponential increase in the number of patients requiring ICU care. In fact, some mathematical models predicted up to 14,500 patients in Italy requiring ICU admission.[6] Similar projection have been made for the United States.[9] These estimates highlight the need to reserve and allocate hospital beds and staff including physicians, nurses and respiratory therapists.[10] Further complicating perioperative care, blood banks have reported critically low reserves with greater hesitance of the public to donate blood.[11]

Rationing, triaging, and prioritization of surgical interventions is necessary, but the details remain a fluid field for discussion. The American College of Surgeons and governing bodies in the USA and around the world have advised to cancel elective surgical cases, especially those requiring postoperative admission to the hospital.[12-14] Separating elective from urgent or emergent cases relates to their deferability only and should by no means be interpreted as a statement about the necessity of these surgeries. Decisions may vary and become more restrictive as the overall state of the crisis progresses through different phases *(see Table 1,* adapted from the American College of Surgeons *COVID-19 Guidelines for Triage of Colorectal Cancer Patients)*:[15]

- Phase 1 (semi-urgent setting): hospital resources are not exhausted and the COVID-19 trajectory is not in a rapid escalation phase
- Phase 2 (urgent setting): hospitals are seeing many COVID-19 patients; ventilator capacity and blood bank resources are limited.
- Phase 3 (pandemic crisis): all hospital resources are used at or above maximal capacity and primarily directed towards treatment of COVID-19 patients.

In Phase 1, urgent and emergent cases can and should be undertaken. Examples include obstructing or nearly obstructing cancers as well as local or loco-regional colon cancers and early stage rectal cancers with no role for neoadjuvant therapy; in addition, rectal cancers with incomplete response to neoadjuvant therapy or selected surgeries for metastatic locations should proceed if they otherwise risk falling out of the recommended window of opportunity for surgery and more chemotherapy is deemed nonbeneficial.

In Phase 2, all but true or looming emergency colorectal surgery cases should be delayed.

In Phase 3, rationing becomes more severe and operations are restricted to acute emergencies; but even emergency cases must be limited to those with a high potential of recovery with surgery when death or significant morbidity would result without surgery.

Surgical Considerations Based on Cancer and Patient Characteristics

Apart from the distinction between rectal and colon cancer, factors influencing surgical timing include the acuity of presentation, the cancer stage and tumor biology, the extent and complexity of a surgical intervention, the feasibility of bridging non-surgical interventions, and the patient's performance status and

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

risk constellation with and without COVID-19 infection. It has become evident that an active COVID-19 infection in the perioperative period is associated with excessive mortality.[16]

1. Acuity of Presentation

Statement: Acute life-threatening complications related to the primary tumor or metastatic disease warrant surgical treatment unless a patient is terminal and has no further treatment options (GRADE 1B: strong recommendation, moderate quality evidence).

Acute presentations related to the primary tumor or recurrent/metastatic disease include obstruction, perforation with acute sepsis, or life-threatening bleeding. If left untreated, these conditions invariably lead to death. Immediate definition of the goals of care is important and primarily based on the comprehensive assessment of the probability of success. Advanced directives and code status should be included, but even in patients with metastatic cancer, code status is documented in only 20% of patients.[17] Unless treatment is considered futile, surgery remains the appropriate lifesaving approach albeit with a significant morbidity and mortality. There are a myriad of surgical interventions (e.g. resections, diversion, lavage, stent placement) or interventional radiology procedures to tailor to the individual situation.[18] Compared to emergent surgery, colorectal stenting leads to a higher rate of minimally invasive surgery and of primary anastomosis (64.9 vs 55%, p = 0.003), lower stoma necessity (45.5% vs 62%, p = 0.02) and no significant difference in overall complications.[19, 20] The short-term benefits of stenting may come at the cost of a small negative impact on 5-year overall and disease-free survival rates.[21]

COVID-19: Turnaround time for COVID-19 testing by serology or PCR continues to decrease.[22] As the surgical intervention cannot be delayed, health care workers should take protective measures as if the patient tested positive, especially in communities where the disease is prevalent. Transfer to another center is generally not recommended. In the interest of saving time and resources, diversion or source control without complex reconstructive efforts might be prudent.

Statement: Subacute or chronic complications related to the primary tumor or metastatic disease should be addressed on an urgent basis by either resection or a temporizing intervention (GRADE 2B: Weak recommendation, moderate quality evidence).

Subacute presentations may result from occluding or penetrating disease and include pending obstruction, contained perforation with smoldering sepsis or fistulization, or recurrent severe bleeding episodes that require multiple transfusions. Non-surgical management in lieu of a surgical intervention may misuse valuable blood products or carry a high risk of future perforation or complete obstruction, both of which are associated with a higher morbidity and mortality than (semi-)elective surgery. The surgical armamentarium mirrors the one for elective surgeries and includes resection, diversion, or less common stenting. Particularly in rectal or metastatic cancer, where there is a role for neoadjuvant or palliative treatment prior to definitive resection, a proximal diversion offers advantages. A meta-analysis comparing proximal diversion first versus primary resection showed a permanent colostomy rate of 6% vs. 22% ($p<0.001$).[23] For non-metastatic colonic lesions, an immediate resection with or without diversion is the treatment of choice as neoadjuvant chemotherapy with few exceptions (T4 tumors) is not considered

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

standard.[24] The FOxTROT and the PRODIGE 22 trials as well as newer data with checkpoint inhibitors are showing promising results and may change that paradigm.[25-27]

COVID-19: A subacute presentation is historically managed by surgery to expedite chemotherapy treatment, if indicated, and obtain source control. Considering the need to conserve and reallocate resources during the global pandemic, interventions ought to be prioritized. If possible, less-invasive treatments to avert the immediate emergency (diversion, stenting) should be considered. Chemotherapy or radiation are not prudent alternatives in midst of a looming perforation/obstruction. However, transfer of stable patients to hospitals with more available resources is a valid approach.

2. Colon Cancer

Statement: Local and loco-regional colon cancer is best treated with primary surgical resection (GRADE 1B: Strong recommendation, moderate quality evidence).

The National Comprehensive Cancer Network (NCCN) recommends that resectable colon cancer without evidence of metastatic disease undergo upfront resection.[24, 28] 5-year survival rates for local, locoregional and metastatic colon cancer patients are 90%, 71% and 14%, respectively.[29] Adjuvant chemotherapy is recommended for stage III and selected stage II disease.[24] Neoadjuvant treatment for non-metastatic colon cancer is subject to further research. The timing of the surgical intervention should be within 6 weeks of the diagnosis,[5] but given the slow growth pattern, the impact of delays is not fully quantified.[30, 31]

COVID-19: Minor delays in surgical resection are unlikely to influence oncological outcomes. In hospitals with active COVID-19 burden, priorities should shift towards treating COVID-19 infected patients until capacity and resources allow for elective, but oncologically urgent cases (Table 1, category IIB). Delays beyond 6-8 weeks should be avoided as they may have a negative impact on overall survival.[32] Reassignment of such patients to hospitals with more available resources and equal cancer expertise is a valid approach.

Statement: Colon cancer arising within polyps does not represent an urgent situation (GRADE 2C: Weak recommendation, weak quality evidence).

The rate and time of progression through different stages in the adenoma-carcinoma model remains speculative. Except in high-risk genetic constellations, progression is thought to occur on the order of years. Mathematical modeling based on Indiana and Minnesota data have estimated the times of disease progression as 3.4 years from in-situ to local, 3.5 years from local to regional, and 0.9 years from regional to distant disease.[33] Whether the presence of an area of invasive cancer remains confined within a polyp depends, among other factors, on the gross configuration of the polyp. Access to lymphovascular structures is more concerning in sessile than in pedunculated polyps. The risk of nodal metastases in the absence of high-risk features of the polyp is as low as 1% for a Haggitt level 1 cancerous polyp, but may be as high as 25% with SM3 invasion or adverse features.[34]

COVID-19: Both the American College of Surgeons and the Society of Surgical Oncology suggested that surgery should be deferred for all cancers within polyps and for all early stage disease.[35] However, this recommendation lacks an objective distinction between a “cancer within a polyp” versus a “cancer” and in that sense may be at variance with the previous statement. The specifics of the target lesion and the

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

completeness of any preceding endoscopic excision should be clarified. High-risk lesions be managed as stated in the previous section and treatment expedited if resources are available.

3. Rectal Cancer

Statement: Stage I rectal cancer does not benefit from chemoradiation and is best treated with surgery (GRADE 1A: Strong recommendation, high quality evidence).

According to the NCCN guidelines, stage I rectal cancer should proceed upfront with a transabdominal oncological resection, or – in highly selected cases of T1 tumors – a transanal local excision.[36] Cure rates with surgery alone are greater than 90%. The only stage I rectal cancer where neoadjuvant chemoradiation may be beneficial is for a low T2N0 rectal cancer where neoadjuvant therapy in conjunction with a local excision may allow for sphincter preservation. However, this approach has a reduced overall survival rate and exposes the patient to a significant incidence of adverse effects associated with chemotherapy and radiation .[37]

COVID-19: Stage I rectal cancer should undergo surgery within 6-8 weeks from the time of diagnosis. Longer delays may result in tumor upstaging with an associated increased risk of local recurrence and complications and a decrease of sphincter preservation. Replacement of surgery by chemoradiation would not be considered a valid choice solely for the purpose of gaining time. Reassignment of such patients to hospitals with more available resources and equal expertise in management of rectal cancer is a valid approach.

Statement: Stage II/III rectal cancer should be treated with neoadjuvant chemoradiation (GRADE 1A: Strong recommendation, high quality evidence).

Locally advanced rectal cancers that are T3/T4 or show evidence of lymphadenopathy, but no distant metastases, should undergo neoadjuvant chemoradiation. The multimodality treatment either in short course, standard long course, or total neoadjuvant chemoradiation has been associated with decreased local recurrence rates and potentially long-term survival. Furthermore, there is a 15-25% complete pathological response rate with standard neoadjuvant treatment, which is increased with total neoadjuvant chemoradiation up to 38%.[38, 39]

Surgery should be scheduled within 6-12 weeks after the last radiation. in the setting of protracted chemoradiation and 1 week after radiation in the setting of short course radiation therapy. In settings where surgery is feasible and where institutional resources are strained, short course radiation therapy may be considered more appropriate as it reduces the strain on health care, reduces costs, and limits potential patients and staff exposure to COVID-19 by reducing treatment visits. Short course radiation has resulted in similar outcome as protracted radiation in randomized clinical trials.[40] In the setting where total neoadjuvant therapy is considered, the combination of capecitabine and oxaliplatin would be preferable over FOLFOX as it reduces potential hospital visits, is associated with decreased bone marrow suppression, and decreases the need for clinical resources by eliminating the needs for infusional 5-FU therapy via a central indwelling catheter.

Rectal cancer surgery following pelvic radiation is fraught with higher incidence of complications. In the ROLARR trial comparing laparoscopic with robotic low anterior resection for rectal cancer, the overall

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

complication rate was about 30% with anastomotic leaks in about 10% of patients.[41] In this trial, the average postoperative length of stay was 8 days, regardless of approach. This hospital length of stay is nearly double the average hospitalization required for colon cancer resections.

COVID-19: Neoadjuvant and particularly total neoadjuvant treatment represent the accepted standard and afford the patient a planned delay in surgical treatment. Furthermore, the window between completion of chemoradiation and surgery allows for some flexibility in scheduling.

4. Metastatic Colorectal Cancer (Stage IV)

Statement: Patients with metastatic disease should be maintained on systemic treatment (GRADE 1B: strong recommendation, moderate evidence).

In the United States, nearly a quarter of colorectal cancer patients are diagnosed with metastatic disease.[42] In select patients, surgical resection of metastatic colorectal cancer is potentially curative. This typically follows neoadjuvant cytotoxic chemotherapy combined with targeted therapies or immunotherapy. Patient performance status influences the choice of chemotherapy and is a critical selection parameter for surgery. In a phase III trial comparing FOLFOXIRI and FOLFIRI, FOLFOXIRI was associated with partial response in 58% of patients and progression-free survival of 9.8 months.[43] The most aggressive cytotoxic medications for colorectal liver metastases achieve a durability of 9-12 months. Other phase II and III clinical trials for colorectal liver metastases have shown similar 10-month progression-free survival as first line agents *(Table 2)*.[43-48]

For resectable colorectal liver metastases, perioperative chemotherapy with 6 cycles of FOLFOX4 has been shown to improve progression-free survival.[49] However, long-term follow-up showed no significant difference in overall survival.[50] In most resectable liver metastatic disease, there is some room for an individualized plan that is not bound to a strict time frame. One may opt to complete the intended total systemic therapy up to 12 cycles prior to a planned surgical intervention which allows for some flexibility. If surgical intervention is still not attainable due to resources, most of these patients may be maintained on maintenance therapy (fluoropyrimidine with or without bevacizumab) until surgery is feasible. However, there are patients who would be unfavorably affected by a delay. The decision-making process therefore must be individualized and be based on the patients' extent of disease, tumor responsiveness, ability to continue chemotherapy, and the risk of increased post-operative complications in the setting of protracted pre-operative systemic therapy. For example, patients with unresectable metastatic disease that are converted to resectable disease through aggressive systemic therapy may have a short window only for optimal curative-intent surgical intervention. These patients should be triaged to surgery in a more pressing manner.

COVID-19: Treatment planning must carefully consider surgical timing and the fact that not all patients can tolerate chemotherapy, as studies have shown nearly 80% grade 3 and 4 toxicities *(Table 2)*. While chemotherapy may be continued in some to delay surgery, a surgical resection should be expedited in patients with a short window of opportunity and a risk of disease progression. The risk of COVID-19 infection related to immunosuppression from chemotherapy must also be considered.

5. Performance Status

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

Statement: Preoperative evaluation of performance status and operability should be used to deselect patients unfit for major surgery (GRADE 1B: strong recommendation, moderate evidence).

Preoperative evaluation of patients undergoing colorectal cancer surgery is traditionally focused on decreasing complications, costs and mortality, reducing delays and cancellations, and improving patient satisfaction.[51] Postoperative complications in laparoscopic colorectal surgery are significantly increased in patients with ASA greater than 2.[52] The ASA classification and the Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM) have both been validated to predict postoperative mortality in multiple colorectal surgical populations, highest in those requiring emergent surgery for malignant bowel obstruction.[53] Programs such as Enhanced Recovery After Surgery (ERAS) have decreased hospital length of stay, but patients still occupy a hospital bed for an average of three days following laparoscopic, and four days following open partial colectomies.[54, 55]

COVID-19: Active COVID-19 disease in the perioperative period has been associated with poor outcomes and high mortality.[16] Surgery for such individuals should be avoided regardless of other criteria to proceed. Real-time preoperative COVID-19 testing will allow for reducing the number of patients unknown to have active disease. Patients with major comorbidities (higher ASA) need to be stratified as to the benefit and timing of surgery. Comorbid conditions as well as the treatments as such, be it surgery, chemotherapy, immunotherapy, or radiation, are likely to increase the patients' vulnerability to the COVID-19 and may trigger a more severe course.

6. Cancer dynamics

Statement: The cancer growth pattern is comparably slow with a long doubling time but may accelerate in metastatic disease (GRADE 1B: strong recommendation, moderate evidence).

Tumor growth is affected by the genetic profile, the micro- and macroenvironment, as well as the host response. In vitro analysis of colorectal cancer cell lines showed doubling times as fast as 24 hours in ideal conditions.[56] Clinical observation of colorectal cancer using surveillance contrast enema studies has estimated doubling times to be 92 to 1,032 days.[57] Tumor characteristics including differentiation influence disease stability and progression. Complex mathematical models have attempted to characterize this stochastic process.[33, 58] Shorter doubling times of colorectal liver metastases below 45 days was a risk factor for early recurrence and poor prognosis.[59] Histopathologic features including differentiation, lymphovascular and perineural invasion are associated with faster and more aggressive growth potential and worse prognosis.[60]

COVID-19: Cancer dynamics should be considered when deciding to postpone surgery. Tumors with poor differentiation or known genetic mutations may have a more immediate negative impact from delays in care.

Statement: Limited delay in cancer treatment does not cause worse oncological outcomes (GRADE 2C: weak recommendation, weak quality evidence).

Data regarding delays of surgical intervention for stage I–III is limited and contradictory. Some studies have shown worse 5-year survival if surgery was delayed more than 40 days whereas others showed no difference at 30, 60 or even 90.[30, 32] Observational data on this topic are not fully conclusive. For early stage

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

(I-II) colorectal cancers, several studies suggested no disadvantage to delay treatment within 2-3 months. For stage III colon cancer, there was an inverse relationship between treatment delay and survival and recurrence, which persisted on multivariate analysis.[31]

COVID-19: Studies regarding delay of surgery for resectable and curable colorectal cancer is not-surprisingly difficult to extrapolate. Delays of 30 days appear to have no negative influence, beyond 45 days, the data are more limited, and contain little information about upstaging of the tumor.

Intervention Options and Timing of Delays

Statement: Surgery during the current pandemic presents significant risks for the patient, providers, and community at large (GRADE 1C: strong recommendation, weak quality of evidence).

There is emerging evidence that developing symptomatic COVID-19 during the perioperative period is associated with a very high morbidity and a mortality of over 20%.[61] Even for patients with asymptomatic or early COVID-19 infection, exposure to general anesthesia (even for low-risk surgery), may precipitate respiratory failure and death.[16] COVID-19 positive patients should have surgery delayed for 14 days if at all possible or at least have the least-invasive life-saving procedure. COVID-19-negative patients can be treated safely within the context of available healthcare resources but may have increased exposure risk during a hospital stay through diminished social distancing in the act of delivering care.

Surgeons and perioperative staff are subject to exposures. Instant and universal COVID-19 testing of hospital and specifically surgery patients will reduce but not eliminate that risk. Endotracheal intubation is considered an aerosolizing procedure and warrants minimizing personnel and following an optimal sequence while being equipped with the highest standards of personal protective equipment including filtering facepiece respirators (aka N95 mask).[62, 63] Gastrointestinal endoscopy including colonoscopy and minimally invasive surgery with positive pressure pneumoperitoneum are also considered aerosolizing procedures. Upon release of gas from laparoscopic or robotic trocars, aerosolized viral particles could pose a risk for inoculation.[64] The risk of transmitting aerolized virus is feared but not quantitated. Out of an abundance of caution, the same standards for PPE apply.[65-68] Surgeons gaining early experience in Italy and China have recommended liberal use of suction to divert gases from the peritoneum, maintaining low insufflation pressure, and considering open rather than laparoscopic or robotic approaches to some higher risk cases.[64] Mitigation efforts include the use of constant negative pressure or electrostatic smoke evacuators. The choice to use an open incision, however, should be balanced with the risks of remaining in the hospital longer than with minimally invasive surgery.

As surgeons are confronted with the difficult decision of whether to proceed or delay surgery for colorectal cancer, alternative or adjunctive maneuvers should be considered. Prioritizing management approaches that avoid inpatient hospitalizations or higher risk operations.

Non-surgical Modalities to Consider

Statement: Non-surgical modalities are indicated for neoadjuvant treatment of locally advanced rectal cancer or and palliative treatment of metastatic colorectal cancer (GRADE 1A: strong recommendation, high quality of evidence).

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

There are well defined roles for neoadjuvant, adjuvant and palliative therapies. As the COVID-19 pandemic continues to spread, the judicious expansion of non-surgical therapies could be employed to delay surgical interventions in order to (A) reduce hospital occupancy and conserve resources for a possible upsurge of COVID-19 patients, (B) prevent perioperative complications related to a COVID-19 positive patient, and (C) reduce mutual exposures of patients and health care workers.

Recently, two trials have looked at the efficacy of neoadjuvant chemotherapy in the treatment of stage II/III colon cancers. The FOxTROT trial, presented at the 2019 ASCO Annual Meeting, randomized stage III colon cancer patients to 6 weeks of neoadjuvant FOLFOX followed by surgery and 18 weeks of adjuvant FOLFOX to a control group of surgery with 24 weeks of adjuvant FOLFOX. There was no increase in peri-operative morbidity, but a significant tumor downstaging and a trend towards a lower 2-year failure rate.[26] The multicenter randomized controlled trial PRODIGE 22 study compared neoadjuvant FOLFOX 4 versus FOLFOX 4 plus cetuximab versus immediate surgery. While there was no difference in R0/complete mesocolic resection rate or overall morbidity and mortality, perioperative FOLFOX was tolerated well and was associated with a significant pathological regression and a trend to tumor downstaging.[27] While neither of these perioperative FOLFOX regimen demonstrated superiority over immediate surgical resection, they did allow for a safe postponement of colon resection by 10-12 weeks with no evidence of disease progression or increased post-operative complications. One potential limitation of neoadjuvant systemic therapy for clinically staged III colon cancer is the known CT-scan over-staging phenomenon which would result in the unnecessary overtreatment of a limited patient population with otherwise pathological stage I or II disease.

Total neoadjuvant therapy (preoperative systemic chemotherapy in combination with chemoradiation) has been accepted as a standard treatment approach for stage II/III rectal cancer and was shown to have pathologic complete response (pCR) rates of as high as 38%.[39] Follow up studies have confirmed this with improved complete response rates (pCR + cCR) of 36% versus 21% in chemoradiotherapy followed by adjuvant chemotherapy.[38] Multiple studies have evaluated the safety of the “watch-and-wait” approach to the management of patients with clinical complete response (cCR) after neoadjuvant chemoradiotherapy with good rectal preservation and pelvic tumor control, and despite increased local recurrence rates, similar 1, 2, 3, and 5 years OS.[69-72]

Statement: The role of neoadjuvant non-surgical modalities is uncertain for colon and for early rectal cancer (GRADE 1C: strong recommendation, weak quality of evidence).

There are no current indications for neoadjuvant chemotherapy or chemoradiation in patients with early stage colon (stage I-II) or rectal cancer (stage I). For patients with bulky nodal disease or colonic lesions which are clinically T4b, neoadjuvant chemotherapy should be considered.[24] The aforementioned FOxTROT provides further evidence of possible benefit of neoadjuvant chemotherapy for patients with T3 or T4 tumors.[26] At least part of the benefit of neoadjuvant chemotherapy in this group is the increased tolerance of the regimen. For many cancers, however, the nodal status will not be known preoperatively; therefore, it is less likely that a majority of clinical stage III cancers will be identifiable for neoadjuvant chemotherapy on a basis other than T stage.

COVID-19: In the setting of the pandemic when operating room capacity is diminished, there is enough reason to delay stage III colon cancer via the addition of neoadjuvant FOLFOX or CAPEOX. However, this

ANNALS OF SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

recommendation is based on a low level of evidence and assumes availability and ease of administering combination therapy in strained healthcare setting.

Legal aspects

Even if based on guidance and recommendations from the Centers for Disease Control and Prevention and other federal, state and local government directives, measures to prioritize medical care of some while sanctioning care to others raises the concern of legal liability. Federal and state agencies have taken action to implement liability protections for health care workers who provide services in the context of COVID-19 but this topic will likely evolve.[73]

Conclusion

The COVID-19 pandemic has stressed already limited health care resources and forced rationing, triage and prioritization of care in general and specifically of surgical interventions. Established guidelines require modifications for optimal timing and type of surgery for colorectal cancer during an unrelated pandemic. Until the medical community has the tools and capacity to cope with the pandemic, deferrable surgical cases should be postponed. Multidisciplinary and individualized treatment planning is recommended to determine the best course of action.

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ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

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ANNALS OF SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

Tables

Table 1: Impact of Phases of COVID-19 Escalation on Scheduling of Colorectal Cases (adapted from[15])

	Phase 1	Phase 2	Phase 3
I) Emergencies: • Acute obstruction • Acute perforation/acute sepsis • Transfusion-requiring active bleeding	Permitted	Permitted	Permitted if "reasonable" probability of success and high chance of death/morbidity without surgery
II) Urgent cases:	All permitted		To be rescheduled
II A) Urgent cases with looming emergency • Nearly obstructing tumors • Contained perforation, fistulization, smoldering sepsis		A: permitted	
II B) Oncologically urgent cases (non-emergency) • Stage I/II/III colon cancer • Stage I rectal cancer • Stage II/III rectal cancer after completed chemoradiation • Stage IV cancer with disease progression on chemotherapy • Diagnostic interventions that define the further management		B: To be rescheduled	
III) Elective cases: • Large benign polyps	To be rescheduled	To be rescheduled	To be rescheduled

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

- Stage 0/1 (polyposis, cancerous polyp after removal, dysplasia)
- Hereditary conditions without cancer
- Colitis with dysplasia
- Stoma reversal
- Surveillance
- Stage IV cancer cases with option of maintenance chemotherapy

ANNALS OF SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

Table 2. Clinical trials showing timing of disease progression on different chemotherapy regimens in metastatic colorectal cancer

Author	Study Acronym	Year	Chemotherapy	Progression Free Survival (months)	Grade 3 or 4 Adverse Events (%)
Hurwitz et al[44]	AVF2017: phase III	2004	Bevacizumab plus irinotecan, fluorouracil, and leucovorin	10.6	84.9
Falcone et al[43]	GONO: phase III	2007	Fluorouracil, leucovorin, oxaliplatin, and irinotecan	9.8	50
Venook et al[45]	CALGB/SWOG 80405: phase III (Abstract)	2017	Irinotecan/5-FU/leucovorin (FOLFIRI[a]) or oxaliplatin/5-FU/leucovorin (mFOLFOX6[b]) combined with bevacizumab (BV) or cetuximab (CET)	10.8	--
Douillard et al[46]	The PRIME study: phase III	2010	Panitumumab plus FOLFOX4 versus FOLFOX4 alone	9.6	84
Heinemann et al[47]	FIRE-3: phase III	2014	FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab	10.3	71
Parikh et al[48]	MAVERICC: phase II	2019	modified leucovorin/5-fluorouracil/oxaliplatin plus bevacizumab (mFOLFOX6-BV) with leucovorin/5-fluorouracil/irinotecan plus bevacizumab (FOLFIRI-BV)	13.8	81.4

[a]FOLFIRI: 5-fluorouracil, leucovorin, and irinotecan, [b]mFOLFOX: modified 5-fluorouracil, leucovorin, and oxaliplatin