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Richard Graham, David Little, Sarah Cade and Stewart Redman

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ABSTRACTS

British Nuclear Medicine Society Autumn Meeting 2022
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Richard Graham, David Little, Sarah Cade and Stewart Redman

This guideline must be read in conjunction with the British Nuclear Medicine Society (BNMS) Generic guidelines. The purpose of this guideline is to assist specialists in Nuclear Medicine and Radionuclide Radiology in recommending, performing, interpreting and reporting the results of bone scintigraphy studies. This guideline could also be used to help individual departments formulate their own local protocols. This does not aim to be prescriptive regarding technical aspects of individual camera acquisitions, which should be developed in conjunction with the local medical physics expert. Nucl Med Commun 43: 1109–1112

Background
Radionuclide bone scintigraphy or ‘bone scanning’ is a highly sensitive means of identifying regions of increased bone and joint metabolism. The radiopharmaceuticals used for bone imaging are $^{99m}$Tc-labelled phosphates. The mechanism of uptake of the radiopharmaceutical by a particular bony region is determined by the local level of blood flow to allow delivery of the tracer to the region and the degree of osteoblastic activity, which determines the concentration of the tracer. Sensitivity of bone scintigraphy for the demonstration of bone and joint pathology is high if the pathology involves increased osteoblastic activity, and bone scans are often able to detect bone and joint pathology earlier than other modalities. However, given that osteoblastic activity occurs in response to a very wide range of pathologies, the specificity of bone scintigraphy can be poor. The cause of osteoblastic activity often requires further clarification with consideration of the history, pattern of tracer uptake and correlation with imaging from other modalities, such as by hybrid single-photon emission computed tomography (SPECT)-computed tomography (CT) to establish the cause of abnormal tracer concentration.

Conditions that are commonly investigated using bone scintigraphy include:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Benign neoplastic</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td>b. Malignant neoplastic</td>
<td>Primary: osteosarcoma, secondary: metastases</td>
</tr>
<tr>
<td>c. Inflammatory</td>
<td>Inflammatory arthropathies</td>
</tr>
<tr>
<td>d. Infective</td>
<td>Osteomyelitis, discitis, septic arthritis</td>
</tr>
<tr>
<td>e. Neurovascular</td>
<td>Avascular necrosis, reflex sympathetic dystrophy</td>
</tr>
<tr>
<td>f. Metabolic</td>
<td>Osteomalacia, Paget’s disease</td>
</tr>
<tr>
<td>g. Trauma</td>
<td>Fracture, insufficiency fracture, Charcot’s joint, shin splints, NAI</td>
</tr>
<tr>
<td>h. Postsurgical</td>
<td>Postoperative periprosthetic or fixation device complication</td>
</tr>
<tr>
<td>i. Degenerative</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>j. Non-bony</td>
<td>Rhabdomyolysis, myositis ossificans</td>
</tr>
</tbody>
</table>

*Some maintain that bone scintigraphy is unhelpful in the context of nonaccidental injury (NAI) as it can be difficult to date an injury with confidence for legal purposes.

Contraindications
(1). Absolute: pregnancy.
(2). Relative: breastfeeding.
(3). Relative: pathology that has a predominantly osteoclastic process, resulting in lytic lesions such as multiple myeloma, which are unlikely to concentrate the tracer.
(4). Relative: trauma or surgery to the region of interest in the previous 6–12 months due to inability of osteoblastic activity relating to normal posttraumatic or postoperative resolution to be distinguished from that due to postoperative complications.

Radiopharmaceuticals and dose
$^{99m}$Tc-labelled hydroxymethylene diphosphonate (Oxidronate) or $^{99m}$Tc methylene diphosphonate ARSAC DRL for adults: 600 MBq for planar imaging and 800 MBq for SPECT.

Radiation exposure
The effective dose from bone scintigraphy is 2.9 mSv for planar imaging (600 MBq) and up to 3.9 mSv for SPECT (800 MBq).

Patient preparation
Patients should be very well hydrated to ensure background tissue clearance is optimized and to help minimize radiation exposure to the bladder and adjacent organs.

Imaging procedure
The study should be tailored to the individual patient and the differential diagnosis. Standardized protocols are required to ensure the highest quality images are acquired. The technical details of image acquisition need to be established by departments on individual cameras.

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Nuclear Medicine Communications 2022, 43:1109–1112

Keywords: bone, scintigraphy, SPECT/CT

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Received 1 September 2022
Accepted 2 September 2022

DOI: 10.1097/MNM.0000000000001615
following collaboration with the local medical physics expert; the parameters given here are for demonstrative purposes only.

**Angiographic and early blood pool phase imaging**

If a demonstration of vascular supply is required to aid clinical interpretation, a multiphase study should be performed with dynamic image acquisition during tracer injection. Image acquisition can be performed during the angiographic or perfusion phase and/or early blood pool phase to give (with the delayed bone phase study) a dual or triple-phase study.

Conditions that may benefit from consideration of a dynamic dual or triple phase study include:

1. Inflammatory/infective conditions such as osteomyelitis or septic arthritis.
2. Conditions that affect the blood supply to an area such as avascular necrosis and reflex sympathetic dystrophy.
3. Primary neoplastic conditions with increased vascularity: osteoid osteoma.

Examples of technical aspects of dynamic/early blood pool phase bone scans are shown in the following tables: Table 1: angiographic or perfusion phase acquisition, Table 2: early blood pool phase acquisition. SPECT-CT acquisition of early blood pool phase can be used instead of planar, and there is evidence this can be helpful in the imaging of bone infection [1].

**Delayed bone phase imaging**

Bone phase imaging is performed at 2–3 h following injection of tracer. This delay allows optimal concentration of tracer by active osteoblasts and allows time for background tissue tracer to be cleared and renally excreted. Image acquisitions are tailored to the patient and the differential diagnosis. The bladder should be emptied prior to imaging if this includes the pelvis. Any clothing, pocket contents or jewellery that may cause attenuation should be removed. The patient should be supported to ensure comfort and reduce movement during the scan acquisition.

‘Static’ or ‘spot’ images can be performed with a high-resolution collimator and stationary camera and couch to maximize linear resolution of a small region of interest. This is generally used for small joints and paediatric cases. Example of scanning parameters is shown in Table 3.

Whole body bone scans are acquired using a sliding acquisition, which images the whole skeleton in continuity. Anterior and posterior views are acquired simultaneously when using a dual-headed camera. This is commonly used in oncology staging studies. Examples of scanning parameters are shown in Table 4.

SPECT can be used to produce cross-sectional images in orthogonal planes and may also be used to separate and define the anatomy. SPECT is often used in scanning regions with complex overlying anatomy, which may be difficult to interpret from planar images such as the skull, spine, hands and feet. Examples of scanning parameters are shown in Table 5.

All delayed bone phase images need to be assessed immediately and repeated if images are suboptimal due to movement, suboptimal positioning and attenuation from jewellery or urinary contamination artefacts.

With the advent of 360° cadmium zinc telluride gamma cameras, whole body SPECT-CT acquisition has become a possibility for routine clinical practice. There is no agreement on how much of the body should be acquired in SPECT-CT, but it is anticipated that it will evolve like PET-CT with different amounts of acquisition depending on the clinical indication.
or CT images should be reviewed when available as this can significantly increase the accuracy of bone scintigraphy interpretation. SPECT-CT-fused hybrid imaging has been demonstrated to significantly improve the accuracy of bone scintigraphy interpretation when the CT component may be justified for indeterminate lesions and complex joint interpretation such as the spine, wrists and feet. The CT component is commonly used in attenuation correction of SPECT images. There is evidence of substantially increased interobserver agreement in bone scan interpretation with hybrid SPECT-CT as demonstrated by weighted kappa scores of 0.56 for SPECT alone and 0.87 for SPECT-CT [2] and improved receiver operating curves in bone scan interpretation of 0.771 (SPECT alone), 0.885 (SPECT correlated with separate CT) and 0.968 (fused hybrid SPECT-CT) [3].

Practitioners are being to use standardized uptake values in the reporting of bone SPECT-CT. There is no consensus yet on how best to use these but this is an area that is likely to progress to help the characterization of benign versus malignant and in malignant disease response assessment.

It is important to review the CT component of SPECT-CT studies and report any CT abnormalities and communicate any unexpected results as per the host institution’s standard operating procedures. Fused SPECT-CT images should be windowed appropriately and sent to picture archiving and communication system (PACS).

**Reporting**

Structured reports are recommended to include indication, technique, study description including both positive and negative findings, correlation with previous bone scans or alternative modalities if appropriate, conclusion and recommendations for further evaluation. It is good practice to produce a single image of relevant SPECT-CT images to send to PACS to illustrate text of report.

**Auditable aspects**

Bone scan studies are a good subject for departmental audits, which may include assessments of image quality (tissue doses, urinary contamination, patient positioning, use of supplementary views, etc.) and reporting quality.

**Review**

While every effort has been made to ensure the British Nuclear Medicine Society (BNMS) provides accurate and expert information and guidance, it is impossible to predict all the circumstances in which it may be used. Accordingly, the BNMS shall not be liable to any person or entity with respect to any loss or damage caused or alleged to be caused directly or indirectly by what is contained in or left out of this guidance.
References


Response to $[^{177}\text{Lu}]\text{Lu-PSMA}$ radioligand therapy in metastatic castration-resistant prostate cancer patients presenting with only lymph node metastases

Lucia Zisser$^a$, Josef Yu$^a$, André Oszwald$^b$, Tim Wollenweber$^a$, Elisabeth Kretschmer-Chotta$^a$, Bernhard Grubmüller$^c$, Gero Kramer$^c$, Shahrokh F. Shariat$^{c,d,e,f,g}$, Markus Mitterhauser$^{a,h}$, Chrysoula Vraka$^a$, Marcus Hacker$^a$, Alexander R. Haug$^{a,i}$ and Sazan Rasu$^a$

**Objective** $[^{177}\text{Lu}]\text{Lu-PSMA}$ radioligand therapy (PSMA-RLT) is a promising therapy for patients with metastatic castration-resistant prostate cancer (mCRPC) and offers a survival benefit particularly to patients with only lymph node metastases. We therefore sought to evaluate the clinical outcome of this therapy in such a cohort.

**Methods** Of all prostate cancer patients admitted to our department between September 2015 and March 2019 to receive 1–4 courses of PSMA-RLT (each course consisted of three cycles of highly standardized PSMA-RLT every 4 weeks), only 10 consecutive men were found to have nodal metastases only and were analyzed retrospectively.

**Results** Nine out of 10 patients responded to their first PSMA-RLT course with a mean prostate-specific antigen (PSA) decline of $71.8 \pm 25.2\%$, seven of them demonstrated a PSA decline of $\geq 50\%$. Collectively, seven of eight patients responded to further PSMA-RLT courses with a total PSA reduction of $59.8 \pm 30.0\%$, five of which showed a PSA reduction of $\geq 50\%$. One patient experienced complete remission. Median progression-free survival was 85 weeks (range 14–255 weeks) and median overall survival was not reached during the median observation time of 209 weeks (30–298 weeks). Univariate Cox-regression identified initial PSA decline as the only predictive parameter for progression-free survival ($P = 0.047$).

**Conclusion** mCRPC patients with only lymph node metastases showed favorable survival and excellent response to PSMA-RLT, leading to transient partial remission of the disease in most of them. Nucl Med Commun 43: 1113–1120 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: lymph node metastasis, mCRPC, prostate cancer, PSA, PSMA

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**Introduction**

Prostate cancer is the second most diagnosed type of cancer in men. While the 5-year survival rate of patients with localized or regional prostate cancer approaches 100%, it drops to 30% in case of distant metastases. Consequently, prostate cancer is the second leading cause of cancer deaths in males [1,2]. Currently, established therapies of metastatic castration-resistant prostate cancer (mCRPC) include chemotherapeutics of the taxane class and luteinizing hormone-releasing hormone analogs like abiraterone or enzalutamide. Nevertheless, the treatment success of these therapies is limited [3]. In recent years, $[^{177}\text{Lu}]\text{Lu-PSMA}$ radioligand therapy (PSMA-RLT) has emerged as a novel treatment modality for end-stage mCRPC. Prostate-specific membrane antigen (PSMA) is a membrane-bound glutamate-preferring carboxypeptidase that is markedly and strongly expressed in cancerous prostatic epithelium. Its inverse correlation with androgen levels promotes its attractiveness as a treatment target for castration-resistant prostate cancer [4]. The effectiveness and safety of PSMA-RLT in patients with mCRPC has already been demonstrated in several studies [5–11]. Moreover, it has been shown to improve patient outcome when added to standard care [12] and its capability to reduce PSA levels was evaluated to be superior to third-line therapies such as cabazitaxel [13,14]. Nevertheless, treatment response varies...
and predictive parameters for therapeutic benefit have yet to be fully elicited. Hitherto, prognostic factors for therapy response and longer overall survival (OS) with PSMA-RLT were observed to be chemotherapy naïveté, asymptomatic disease, small tumor volume, high PSMA-uptake of the lesions [10,15], low basal prostate-specific antigen (PSA) levels and normal basal hemoglobin levels [16]. Furthermore, previous studies [15,17–19], including our own most recent results [20], suggested a better survival of patients lacking bone or visceral metastases.

Considering these findings, the present study aimed to evaluate the effectiveness of an intensive, standard-ized PSMA-RLT treatment regime in a prostate cancer patient cohort with exclusively nodal metastasis. We therefore evaluated PSA-based treatment response, OS and progression-free survival (PFS) and its predictive parameters in mCRPC patients who received repeated treatment courses of highly standardized PSMA-RLT, every course consisting of three cycles of therapy at 4 weeks interval.

Subjects and methods
Patients
This retrospective study included all prostate cancer patients with lymph node-restricted metastases who received at least one full course consisting of three cycles PSMA-RLT every 4 weeks at the Department of Nuclear Medicine of the Medical University of Vienna, General Hospital of Vienna, between September 2015 and December 2020. Out of a total of 90 patients who received at least one full course of PSMA-RLT during the studied time frame, only 10 patients exhibited only lymph node metastases. This study cohort partially overlaps with our previously published cohorts that had mixed metastases [11,16,20,21]. There was no patient with lymph node-restricted metastasis who did not complete at least one course of PSMA-RLT. The diagnosis and localization of metastases was based on [18F]Ga-PSMA-11 PET/MR or PET/CT imaging conducted by two specialists in nuclear medicine and one radiologist (at least 5 years of experience) prior to the start of PSMA-RLT. The imaging protocols have previously been described [21] and patient follow-up was carried out until June 2021. The indication of each PSMA-RLT course was approved by an interdisciplinary tumor board. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Medical University of Vienna (EK: 1143/2019) and all patients gave written informed consent prior each therapy cycle.

[177Lu]Lu-PSMA-RLT regime
PSMA-RLT was conducted in line with §8 of the Austrian pharmaceutical law (AMG). The PSMA-RLT scheme was carried out in courses, each consisting of three cycles of 7450 (range 5760–7920) MBq intravenous [177Lu] Lu-PSMA administration at 4 weeks interval. From September 2015 to March 2019, patients were treated with [177Lu]Lu-PSMA-617 that was acquired from ABX GmbH (Radberg, Germany), and from April 2019 and thereafter with [177Lu]Lu-PSMA I&T, obtained from Scintomics Molecular Applied Theranostics Technologies GmbH (Fürstenfeldbruck, Germany). Patients further received 1L saline infusion (300 ml/h) 30 min before each [177Lu]Lu-PSMA administration. For clinical monitoring and radiation safety reasons, all patients were hospitalized for at least 48h during each cycle. All patients received at least one full course of the therapy.

During each admission, the general condition of the patients was evaluated by an experienced medical doctor and patient’s ECOG (Eastern Cooperative Oncology Group) Status and Karnofsky-Index were accordingly assessed. Furthermore, routine laboratory parameters including complete blood count, biochemistry, and PSA levels were measured. Therapy toxicity was evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Total tumor volume (TTV) before PSMA-RLT-start was calculated for each patient by PET-scan-based delineation of the tumor and metastases using the Hermes Hybrid 3D software (Hermes Medical Solutions, Stockholm, Sweden). In brief and as we published previously [21], significantly elevated PSMA expression was initially identified by using a threshold-based volume of interest (VOI) with 20% higher mean SUV than a cubic 10 × 10 × 10 voxel reference VOI of the liver. The resulting program generated VOIs were then edited manually. The remaining nonspecific and physiological PSMA uptake was cropped and PSMA expressing lymph nodes with SUVs below the specified threshold were added.

Continuation of PSMA-RLT was re-assessed before each course according to the previous response. The time between courses (minimum 3 months) depended on response to the previous PSMA-RLT, disease progression and the general clinical status of the patient.

Definitions of outcome parameters
Therapy response was evaluated by PSA reduction at the time of the nadir after PSMA-RLT relative to PSA before the start of the course. The term “initial PSA reduction” refers to PSA decrease in percentage after the first course of PSMA-RLT, whereas “total PSA reduction” is the PSA decrease in percentage after the last therapy course in relation to PSA levels before the first course. Response to PSMA-RLT was defined as any PSA decrease. Disease progression was noted in case of a PSA increase ≥25% relative to the previous nadir PSA-level. Progression-free survival (PFS) for each course spans from therapy start to following progression of disease. Total PFS refers to the time from the start of the first treatment course to progression after the last PSMA-RLT-related PSA decline during the entire time of follow-up.
Statistical analysis

Statistical analysis was carried out using the software IBM SPSS, version 26.0 (IBM Corp., Armonk, NY, USA). Data were tested for normal distribution by Shapiro-Wilk-test. Accordingly, normally distributed data are presented as mean ± SD and non-normally data are expressed in median and range (minimum-maximum). Univariate Cox-regression and Mantel-Cox test were used to identify predictive parameters for total PFS. Paired t-test was carried out for comparison of biochemical parameters before and after the entire PSMA-RLT and Wilcoxon signed-rank test was used to compare initial and total PSA reduction of patients who responded to consecutive PSMA-RLT. Kendall’s tau b was applied to test for an association between the number of conducted PSMA-RLT courses and total PFS. A two-sided P-value <0.05 was considered significant. Figures were plotted using R in RStudio (R Foundation for Statistical Computing, Vienna) using the packages ggplot [22], survminer [23] and swimplot [24].

Results

Patient cohort

Collectively, only 10 prostate cancer patients (aged 71 ± 1 years), who received a median of 2 courses (range 1–4), median 6 cycles (range 3–12) of [177Lu]Lu-PSMA therapy, were found to exhibit only lymph node metastasis. Prior to therapy initiation, patients had a median PSA level of 13.6 μg/L (range 2.94–597) and a median TTV of 11.3 ml (range 0.35–361.6). The clinical and biochemical characteristics of the patients prior to PSMA-RLT are summarized in Table 1.

All patients except patient no. 7 had previously undergone radical prostatectomy, and six of them had additionally undergone radiotherapy. Eight patients were castration resistant, four of the patients had a history of chemotherapy (CHT) and new-generation hormone therapy (HT) (Table 1).

Despite a significant decrease of mean hemoglobin (Hb) and platelet count over the entire PSMA-RLT (Hb: 13.4 ± 0.6 vs. 12.7 ± 1.6 g/dl, P = 0.027; thrombocytes: 232 ± 27 vs. 180 ± 70 g/L, P = 0.004), we observed no emerging hematopoietic or renal toxicity as defined by CTCAE 5.0.

Response and outcome of the patient collective

Nine out of ten studied patients (90%) responded to their first PSMA-RLT course with a mean PSA decrease of 71.8 ± 25.2%, seven (70%) and five (50%) patients experienced a PSA decline of ≥50% and ≥80%, respectively. Two patients received only one course of the treatment, whereas the other eight patients received up to four consecutive PSMA-RLT courses. Of them, seven patients (88%) exhibited any PSA decline and demonstrated a total PSA reduction of 59.8 ± 30.0% at the end of all therapy courses, five patients (63%) revealed a PSA reduction of ≥50% and one patient (13%) had PSA reduction of ≥80% (Table 2 and Fig. 1). Among these patients, the difference between initial PSA reduction and total PSA reduction was NS (P = 0.176).

Nine patients (90%) of the entire studied cohort survived until the endpoint of the study with a median observation time of 209 weeks (range 30–298). The median total PFS of the entire patient cohort was 85 weeks. Table 3 depicts the survival outcome in detail and Fig. 2 summarizes the total PFS of the patient cohort. The trend toward shorter PFS with each consecutive course was statistically NS in Log Rank (Mantel-Cox) analysis (Chi-square = 7.08, df3, P = 0.06).

Response and outcome of the individual patients

For a better overview, the individual disease burden and outcome of each patient are listed in Table 2 and illustrated in Fig. 3.

Patient no. 1 and no. 2 both received one course of PSMA-RLT. The chemotherapy-naïve patient no. 1 experienced 98% PSA reduction with sustained metastatic remission in PSMA-PET imaging (Fig. 4), whereas patient no. 2 was the only nonresponder who was effectively treated with docetaxel after unsuccessful PSMA-RLT.

Patients no. 3 to no. 7 were treated with two courses of PSMA-RLT. Patient no. 3 and no. 4 both demonstrated continuous excellent therapy response, and the chemotherapeutically pretreated patient no. 3, who received

Table 1 Clinical and biochemical patient characteristics prior to prostate-specific membrane antigen-radioligand therapy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD) years</td>
<td>71 ± 1</td>
</tr>
<tr>
<td>Weight (mean ± SD) kilogram</td>
<td>86 ± 3</td>
</tr>
<tr>
<td>[177Lu]Lu-PSMA MBq</td>
<td>7450 (5760–7920)</td>
</tr>
<tr>
<td>ECOG index &lt; 2</td>
<td>10/10</td>
</tr>
<tr>
<td>Karnofsky score ≥ 80</td>
<td>10/10</td>
</tr>
<tr>
<td>Previous ADT</td>
<td>8/10</td>
</tr>
<tr>
<td>Previous enzalutamide</td>
<td>8/10</td>
</tr>
<tr>
<td>Previous CHT</td>
<td>8/10</td>
</tr>
<tr>
<td>TTV (mean ± SD) ml</td>
<td>11.3 (3.35–361.6)</td>
</tr>
<tr>
<td>PSAa μg/L</td>
<td>13.6 (2.94–597)</td>
</tr>
<tr>
<td>Hemoglobin (mean ± SD) g/dl</td>
<td>13.4 ± 0.6</td>
</tr>
<tr>
<td>Thrombocytes (mean ± SD) g/l</td>
<td>232.0 ± 26.7</td>
</tr>
<tr>
<td>Leucocytes a g/L</td>
<td>8.96 (2.94–22.73)</td>
</tr>
<tr>
<td>CRP a (g/dl)</td>
<td>0.15 (0.03–14.70)</td>
</tr>
<tr>
<td>Creatinine a mg/dl</td>
<td>0.92 (0.77–1.45)</td>
</tr>
<tr>
<td>AP (mean ± SD) U/L</td>
<td>73.8 ± 13.3</td>
</tr>
<tr>
<td>LDHa U/L</td>
<td>160 (136–396)</td>
</tr>
<tr>
<td>Lymph node metastases ± local recurrence</td>
<td>4/10</td>
</tr>
<tr>
<td>Cervical-axillary</td>
<td>4/10</td>
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<tr>
<td>Mediastinal-hilar</td>
<td>4/10</td>
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<tr>
<td>Abdominal</td>
<td>6/10</td>
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<tr>
<td>Regional</td>
<td>5/10</td>
</tr>
</tbody>
</table>

*ADT, androgen deprivation therapy; AP, alkaline phosphatase; CHT, chemotherapy; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MBq, megabecquerel; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy; TTV, total tumor volume.

Same four patients.
abiraterone in parallel to PSMA-RL T, reached persistent complete biochemical remission 59 weeks after the last therapy cycle. Furthermore, consecutive post-therapy PET scans of both patients did not reveal any PSMA-expressing metastases until the end of follow-up. Notably, their tumor burden at the start of therapy differed greatly (Table 2).

### Table 2  Tumor burden and outcome of the individual patients

<table>
<thead>
<tr>
<th>Pat.</th>
<th>C.</th>
<th>TTV (ml)</th>
<th>Initial PSA (μg/L)</th>
<th>Initial PSA decline (%)</th>
<th>Total PSA decline (%)</th>
<th>End PSA (μg/L)a</th>
<th>Total PFS (weeks)</th>
<th>OS (weeks)</th>
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<tr>
<td>1</td>
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<td>10</td>
<td>10</td>
<td>11.07</td>
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<td>91</td>
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<td>4.09</td>
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C., number of courses; <, less than; OS, overall survival; Pat., patient; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen; RLT, radioligand therapy; TTV, total tumor volume.

aNadir PSA value after last therapy course.

bNo progress after the last PSMA-RLT.

cDeath.

**Fig. 1**

Percentage of PSA decline in the studied patients after the first and all courses of PSMA-RLT, with each course consisting of three cycles at 4 weeks interval. PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.
contrast, patient no. 5 and no. 6 experienced PSA rebound after the first course, which was only partly repressed by the second course. Patient no. 7, the only patient who had not undergone prostatectomy, had been treated with trenantone, abiraterone, enzalutamide, docetaxel and cabazitaxel prior to PSMA-RLT and died shortly after not responding to his second treatment course. Another patient with history of new-generation hormone therapy and chemotherapy, patient no. 8, experienced successive moderate PSA decline over his three courses of PSMA-RLT, which was also reflected in PET imaging (Fig. 4). Remarkably, throughout the 11 months between his first and second course, he did not experience any PSA progression.

Patient no. 9 and no. 10 received 4 therapy courses. Both demonstrated intermittent PSA increases, patient no. 9 between his courses and patient no. 10 within his third and fourth course. Their last nadirs of PSA were above previous nadir values but still below PSA before treatment start.

Predictive parameters
The only predictive parameter for total PFS in our study was initial PSA reduction (univariate Cox-regression analysis; \( P = 0.047 \)). Total PSA reduction and following parameters were nonpredictive: age, weight, previous ADT, new-generation HT and CHT, TTV, nonregional lymph node metastases, basal PSA as well as basal hemoglobin, thrombocyte count, leucocyte count, C-reactive protein, creatinine, alkaline phosphatase, lactate dehydrogenase.

Furthermore, upon exclusion of the inaccurately high PFS of patient no. 6, even initial PSA reduction was no longer a significant prognosticator for total PFS.

To investigate whether the number of received courses is a mediating variable between initial PSA reduction and total PFS, Kendall’s tau b correlation analysis was performed. The number of PSMA-RLT courses was not associated with initial PSA reduction or total PFS.

Discussion
PSMA-RLT is an investigational treatment option for patients with mCRPC that has been available in Europe for less than 8 years. It has not yet been included in guidelines because promising study results have only been published very recently. The Vienna General Hospital in Vienna, Austria, offers this therapy since September 2015 as one of the few clinical centers in central Europe. We follow a highly standardized therapy protocol consisting

<table>
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<td>29</td>
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</table>

*M, median; PFS, progression-free survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

<sup>a</sup>No further PSA progression until the next course of PSMA-RLT.

<sup>b</sup>No PSA progression until the end of observation.
of three cycles of PSMA-RLT every 4 weeks per therapy course. Based on the evidence of numerous studies, PSMA-RLT is an effective and safe treatment option for patients with mCRPC [5–10,20]. Earlier results indicated that especially patients with exclusively nodal metastasis significantly benefit from PSMA-RLT [15,17–20]. Nevertheless, in most of these studies, this evidence was provided in the context of a large analysis with heterogeneous treatment protocols that included prostate cancer patients with all types of metastases treated with PSMA-RLT. To our knowledge, no study is published reporting results of standardized Lu-PSMA RL T in patients with lymph node metastases only. The present study assessed the PSMA-RLT response, PFS and OS of patients adhering to this criterion (n = 10) and found that 90% of the patients responded to their first course of PSMA-RLT (70% showed reduction ≥50%), resulting in a total progression-free survival of median 85 weeks (range 14–255) and the survival of 9 of the 10 (90%) patients during observation time. There were no severe adverse events related to PSMA-RLT. Moreover, even though this was not the main objective of this analysis, the results revealed no new-onset hematopoietic or renal toxicity according to CTCAE 5.0, despite a significant decrease in mean Hb and platelet count throughout PSMA-RLT.

Studies on the effect of PSMA-RLT in mCRPC patients with lymph node-restricted metastases are very limited. Previous meta-analyses such as one by Yadav et al. [9], including 17 studies with a total of 744 patients without stratification regarding the site of metastases, calculated a response to PSMA-RLT of approximately 75% of the patient collective. Another recent systematic review of 36 studies with a total of 2346 patients has further demonstrated a ≥50% PSA reduction for 50% of the mCRPC patients treated with PSMA-RLT [10]. In addition, the results of this review indicated a longer life for patients treated with an intensified PSMS-RLT regimen than for patients treated with a conventional regimen. The current study cohort has a higher response rate not only compared with these nonstratified patient collectives but also compared with the overlapping cohort of 54 patients.
that we previously analyzed (about 80% of any decline, 60% with ≥50%) [11]. PSA reduction ≥50% was associated with longer overall survival in previous other studies [10,25]. In our study, 70% of the patients surpassed this threshold, whereas in Eyben et al. [19], 90% of patients with only nodal metastasis surpassed it (n = 35, median therapy cycle n = 3). In this regard, it should be considered that in our study a higher proportion of included patients were pretreated with chemotherapy compared to Eyben et al. study (40% vs. 20%).

Importantly, the survival rate of 90% in patients studied over an observation time of 209 weeks (30–298) was strikingly longer than the median OS of 70 weeks calculated in the aforementioned recent meta-analysis [10]. Moreover, it exceeded the median OS of 108 weeks in the lymph node subcohort of Ahmadzadehfar et al. [15] and the OS of 89% of patients over approximately 130 weeks demonstrated by Eyben et al. [19]. Our latest analysis of 43 men with metastases in various organs reported a similarly long median overall survival of 188 weeks [20]. It has been shown that an intensive PSMA-RLT regimen, in terms of a higher applied activity and shorter intervals between the cycles, is associated with longer overall survival [10]. Our treatment strategy ranks among the most intensive PSMA-RLT protocols and might therefore contribute to the better OS of our patients. Nevertheless, the impact of visceral metastasis on OS was apparent in the homogenously treated patient cohort of our earlier study [20]. Factors previously identified as prognostic for OS in patients treated with PSMA-RLT, such as prior chemotherapy, concurrent enzalutamide treatment, total tumor volume, asymptomatic disease, basal levels of PSA, hemoglobin or alkaline phosphatase [10,15–17], were not associated with the total PFS in our current patient cohort. Interestingly, in this small cohort, lymph node metastasis site (regional or nonregional) was also irrelevant for total PFS during the given observation time. The only significant predictor was the magnitude of PSA reduction after the first course of PSMA-RLT.

Violet et al. [26] previously described a reduced time to progress after a re-challenge of PSMA-RLT, where a series of initially four cycles was followed by 1–5 cycles [26]. Although the results were not statistically significant, our current outcomes also point to a diminishing response to successive treatment courses, which is reflected by the lower total PSA response rate as compared to the initial response rate, and the tendency toward shorter PFS after each consecutive RLT course (Table 3). Nevertheless, the continuation of PSMA-RLT proved to be more beneficial than other systemic therapies, and the effectiveness and safety of two courses PSMA-RLT, each consisting of (median) 3 cycles, has further been demonstrated by two other independent studies [20,27].

This study primarily aimed to display the clinical impact of PSMA-RLT on the disease course of mCRPC patients presenting with lymph node-restricted metastasis, who received homogeneous PSMA-RLT treatment courses consisting of three cycles at 4 weeks interval. A main limitation is the small sample size that is easily influenced by outliers and provides low power for statistical analysis, especially regression analysis. A valuable aspect of this
subgroup of patients, however, is the opportunity to provide detailed data on each individual patient. Nevertheless, the retrospective character and heterogeneity in terms of therapies prior to PSMA-RLT as well as inconsistency in follow-up intervals might distort the results of the study.

**Conclusion**

Based on the clinical outcomes of this study, we conclude that mCRPC patients with exclusively nodal metastasis reveal a particularly favorable response to PSMA-RLT regarding PSA reduction and total PFS, especially in the magnitude and persistence of the initial therapy effect. Even though the overall response ultimately still remains variable, the outstanding OS of the patient cohort is consistent and evident. At the same time, significant severe hematopoietic or renal toxicity did not occur even following multiple cycles of treatment. We encourage future prospective studies to assess these results in a larger patient collective and to further investigate outcome predictors.

**Acknowledgements**

**Conflicts of interest**

There are no conflicts of interest.

**References**

Precise quantitative evaluation of pharmacokinetics of cisplatin using a radio-platinum tracer in tumor-bearing mice

Honoka Obata\textsuperscript{a,b,c}, Atsushi B. Tsuji\textsuperscript{b}, Hitomi Sudo\textsuperscript{b}, Aya Sugyo\textsuperscript{b}, Katsuyuki Minegishi\textsuperscript{a}, Kotaro Nagatsu\textsuperscript{a}, Mikako Ogawa\textsuperscript{c} and Ming-Rong Zhang\textsuperscript{a}

**Objective** The platinum-based antineoplastic drug cisplatin is commonly used for chemotherapy in clinics. This work aims to demonstrate a radio-platinum tracer is useful for precisely quantifying small amounts of platinum in pharmacokinetics studies.

**Methods** A cisplatin radiotracer (radio-cisplatin) was synthesized, and a comprehensive evaluation of cisplatin over 7 days after its intravenous injection into nude mice bearing a subcutaneous lung tumor (H460) was conducted.

**Results** A biphasic retention curve in the whole body and blood was observed \(T_{1/2}(\alpha) = 1.14\) h, \(T_{1/2}(\beta) = 5.33\) days for the whole body, and \(T_{1/2}(\alpha) = 23.9\) min, \(T_{1/2}(\beta) = 4.72\) days for blood. The blood concentration decreased within 1 day after injection. Most of the intact cisplatin was excreted via the kidneys in the early time points, and a small part was distributed in tissues including tumors. The plasma protein binding rate of cisplatin increased rapidly after injection, and the protein-bound cisplatin remained in the blood longer than intact cisplatin. The peak uptake in H460 tumors was 4.7% injected dose per gram at 15 min after injection, and the area under the curve (AUC\textsubscript{0–7 days}) was approximately one-half to one-third of the AUC\textsubscript{0–7 days} in the kidneys, liver, and bone, where some toxicity is observed in humans.

**Conclusion** The radio-platinum tracer revealed the highly quantitative biodistribution of cisplatin, providing insights into the properties of cisplatin, including its adverse effects. The tracer enables a precise evaluation of pharmacokinetics for platinum-based drugs with high sensitivity. *Nucl Med Commun* 43: 1121–1127 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: biodistribution, cisplatin, lung cancer, pharmacokinetics, radio-platinum

**Introduction**

Platinum (Pt) is a promising metal element in pharmaceuticals for cancer therapy, and numerous Pt-based antineoplastic drugs have been developed [1]. cis-diaminedichloroplatinum (cis-[PtCl\textsubscript{2}(NH\textsubscript{3})\textsubscript{2}]), commonly called cisplatin, is a widely used chemotherapeutic agent, and its value is supported by a large number of basic and clinical studies [2]. The generic drug cisplatin has been applied to almost all tumor types because it acts by simply forming various direct DNA-Pt adducts such as intra- and interstrand cross-links, leading to cell death [3–6]. However, it cannot specifically target tumor cells, causing adverse renal effects [7]. To decrease such unwanted side effects, next-generation tumor-targeting Pt drugs have been attracting interest in the chemotherapeutics field in recent years [1]. A method that enables the precise and practical quantitation of Pt has the potential to promote studies of the pharmacokinetics of Pt drugs.

Numerous studies have evaluated the pharmacokinetics of Pt drugs using HPLC, atomic absorption analysis, or inductively coupled plasma-mass spectrometry [8–12]. Although these chemical analysis methods are common, they require at least nanogram quantities of Pt for precise quantification. Fluorescent imaging offers high sensitivity but is unsuitable for tracing Pt ideally because labeling Pt drugs with a fluorescent dye likely changes their behavior. Because of this experimental limitation in precisely quantifying small amounts of Pt, previous studies have mainly focused on blood or urine retention in the case of high injection doses for humans [9–12]; biodistribution data are rare, especially in the case of a low injection dose, long-term tracing, or low-uptake tissue retention. Efficient methods and detailed results of the biodistribution of Pt will contribute to the further development of Pt-based drugs.
Pt radionuclides (radio-Pt) can directly trace the distribution of Pt-based drugs without changing their structures; in this regard, a radiotracer of Pt can provide precise pharmacokinetics data for Pt drugs. Radio-Pt with a suitable half-life enables highly quantitative evaluations until late time points irrespective of small injection doses or low accumulation of Pt in organs. $^{191}$Pt ($T_{1/2} = 2.80$ days, EC = 100%) is a good candidate radionuclide that has a suitable half-life and emits easily detectable $\gamma$-rays \cite{13}, enabling the highly quantitative and practical analysis of Pt drugs. Recently, we established a novel method for producing high-quality $^{191}$Pt and radio-synthesized cisplatin (described as radio-cisplatin), as a model \cite{14,15}. The radio-cisplatin product was obtained with a high radiocchemical purity greater than 99%. Its lower detection limit at the femtomole scale (100 Bq of $^{191}$Pt = 0.06 fmol), and it can work as a radiotracer for investigating pharmacokinetics. Here, a comprehensive and quantitative biodistribution assay with radio-cisplatin in mice bearing subcutaneous lung cancer was conducted.

Materials and methods

General
Chemicals and reagents were purchased from FUJIFILM Wako Pure Chemical (Osaka, Japan), Tokyo Chemical Industry (Tokyo, Japan), Kanto Chemical (Tokyo, Japan), Otsuka Pharmaceutical Factory (Tokyo, Japan), Tanaka Metal (Tokyo, Japan), Hayashi Pure Chemical Industry (Osaka, Japan), or Merck (Darmstadt, Germany). Milli-Q ultrapure water or diluted water was used for dilution in all experiments.

High-purity germanium (HPGe) $\gamma$-ray spectrometry was performed to measure the radioactivity of $[^{189,191}\text{Pt}]$cisplatin in saline before all in-vitro experiments. The HPGe detector (EGC 15–185-R; Erisys Measures, Strasbourg, France) was coupled with a 4096 multichannel analyzer (RZMCA; Laboratory Equipment, Ibaraki, Japan) and calibrated using a mixed ($^{109}$Cd, $^{57}$Co, $^{137}$Ce, $^{51}$Cr, $^{85}$Sr, $^{54}$Mn, $^{88}$Y, and $^{90}$Co) standard source (Japan Radioisotope Association, Tokyo, Japan). A gamma counter (Wizard2 2-Detector Gamma Counter; PerkinElmer, Waltham, Massachusetts, USA) was used to measure radioactivity in biological samples. The X-rays and gamma-rays from both $^{189}$Pt and $^{189}$Pt were counted together under the energy window from 356 to 800 keV. Using an aliquot of the injection solution as a control for measurement, uptake was calculated from the radioactivity ratio of samples to the control.

Synthesis of $[^{189,191}\text{Pt}]$cisplatin

$^{189,191}$Pt was produced via the $^{nat}$Ir(p, xn)$^{189,191}$Ir reaction in a 30 MeV proton beam for 2–3 h at a beam current of 10 µA at the NIRS-QST AVF-930 isochronous cyclotron, as described previously \cite{14,15}. We used mixed $^{189,191}$Pt, described as radio-Pt because $^{189}$Pt ($T_{1/2} = 10.87$ h, EC) is coproduced along with $^{191}$Pt ($T_{1/2} = 2.83$ days, EC) from a natural Ir target. $[^{189,191}\text{Pt}]$cisplatin (referred to as radio-cisplatin) was radio-synthesized from $[^{189,191}\text{Pt}]$PdCl$_2$ and prepared in a saline solution \cite{14}; the radiocchemical purity at the end of synthesis (EOS) was 99+%. $[^{189,191}\text{Pt}]$cisplatin solution (500 kBq/ml, $^{189}$Pt: 350 kBq/ml, $^{191}$Pt at EOS) was used in all experiments.

Cell culture

The human lung cancer cell line NCI-H460 was obtained from ATCC (Manassas, Virginia, USA). The cells were cultured at 37 °C in a humidified atmosphere containing 5% CO$_2$ in RPMI-1640 (FUJIFILM Wako Pure Chemical) containing 10% fetal bovine serum (Thermo Fisher Scientific, Waltham, Massachusetts, USA).

Animal studies on the xenografted tumor model

The protocol for the animal experiments was approved by the Animal Care and Use Committee of the National Institutes for Quantum and Technology (13–1022, 26 May 2016), and all animal experiments were conducted following the institutional guidelines regarding animal care and handling. H460 cells were suspended in 1-ml PBS (2 × 10$^7$ cells/ml), and 2 × 10$^5$ cells in 100 µl were subcutaneously injected into the flank of male BALB/c-nu/nu mice (6 weeks old; CLEA Japan, Tokyo, Japan) under isoflurane anesthesia. Tumor volumes reached 100–400 mm$^3$ 2–3 weeks after inoculation. For the biodistribution study, 100 µl of saline solution containing radio-cisplatin (50 kBq/$^{189}$Pt + 35 kBq/$^{191}$Pt) and 50 µg of nonradioactive cisplatin (2 mg/kg BW) were intravenously injected into mice when tumor volumes reached 100–400 mm$^3$ ($\times = 4$ for each time-point). The mice were sacrificed by isoflurane inhalation at 2, 15, 60 min, 1, 3, 5, and 7 days after injection. Blood was obtained from the heart, and then tumor, lung, liver, pancreas, stomach, intestine, kidney, bone, and muscle were dissected. Uptake in tissues is represented as a percentage of the injected dose (%ID/g) (radioactivity) per gram of tissue and that for the whole body as a %ID. These values were corrected to those in the body weight of 20 g. Uptake in the whole body was calculated from the total radioactivity of dissected tissues and residual bodies.

Red blood cell partitioning and plasma protein binding of cisplatin

The red blood cell partitioning and the plasma protein binding of $^{191}$Pt were evaluated for the blood of mice. At 2 min, 60 min, and 1 day after the intravenous injection of cisplatin, blood was obtained from the heart and mixed with heparin (Mochida Pharmaceutical Factory, Tokyo, Japan). The whole blood was centrifuged and divided into blood cells and plasma. The red blood cell partitioning rate of $^{191}$Pt was calculated on the basis of the activity of blood and plasma, defined as $(A_{\text{blood}} - A_{\text{plasma}}) \times (1 – \text{Hct}) \times 100/A_{\text{blood}}$, where $A_{\text{blood}}$ is the radioactivity of 20 µl whole blood, $A_{\text{plasma}}$ is the radioactivity of a 20-µl plasma
fraction, and Hct is the hematocrit value (0.43). The plasma was ultrafiltered with Amicon Ultra (10 K, 0.5 ml Centrifugal Filters for DNA and Protein Purification and Concentration, Merck). The protein binding rate of $^{191}$Pt was calculated based on the activity of each separated fraction, defined as $(A_{\text{con}} - A_{\text{eni}})/A_{\text{con}} \times 100$, where $A_{\text{con}}$ is the radioactivity of a 50 µl concentrated fraction and $A_{\text{eni}}$ is the radioactivity of a 50 µl filtered fraction.

Results

Using a radiotracer of cisplatin and exploiting its advantages, the quantitative pharmacokinetics of cisplatin for 7 days after the intravenous injection in subcutaneous tumor-bearing mice was evaluated. A previous study showed that radio-cisplatin uptake was dose-dependent and proportional to the administered concentration of cisplatin [15]. To provide data under dose conditions of chemotherapy in clinical settings, a mixed solution of radio-cisplatin and nonradioactive carriers (2 mg/kg BW) was injected. A lung cancer cell line, H460, was used in this study because cisplatin is commonly used as a chemotherapy agent for lung cancer [16,17].

First, the retention of cisplatin in the whole body and blood was investigated, as shown in Fig. 1, where data are shown as %ID for the whole body (Fig. 1, upper panel) and %ID per gram for blood (Fig. 1, lower panel). These results show a rapid clearance of cisplatin from the whole body and blood, consistent with the biphasic exponential curve including the alpha and beta phases (alpha, white; beta, black in Fig. 1). Cisplatin in the whole body was excreted quickly to ~24% of the injected dose within 19 h after injection, corresponding to the alpha phase of the retention curve (Fig. 1, upper panel, white). Thereafter, cisplatin was eliminated slowly during the beta phase, and ~10% of the injected dose remained in the body 7 days after injection (Fig. 1, upper panel, black). The blood concentration also decreased mainly within 19 h after injection, which corresponds to the alpha phase of the retention curve (Fig. 1, lower panel, white). Although the blood concentration was ~1%ID/g in the beta phase of the retention curve, the radiotracer enabled a quantitative evaluation (Fig. 1, lower panel, black).

Second, the biodistribution of cisplatin is shown in Fig. 2, where the data are represented as %ID/g of tissues. From the data in Fig. 2, the uptake ratio of each tissue to blood was summarized in Table 1 to evaluate the effect of blood on the accumulation in tissues. The uptake of cisplatin was high in the lungs and kidneys in the early time points after injection (Fig. 2). The accumulation in the lungs was related to blood clearance (Table 1). Renal accumulation of cisplatin was observed in the early time points, and its excretion was observed thereafter (Fig. 2). Hepatic accumulation was also observed, and the cisplatin uptake in the liver was relatively higher than that in the kidneys in the late time points (Fig. 2). There is a slight increase in the accumulation of cisplatin in the bone 5 days after injection (Fig. 2).

Third, the area under the curve (AUC$_{0-7 \text{ days}}$) was calculated on the basis of the biodistribution data (Fig. 1 lower panel and Fig. 2); the ratios of the tumor to each tissue are shown in Table 2. The accumulation in H460 tumors was not high; the peak was 4.7%ID/g 15 min after the injection (Fig. 2). Compared with the AUC$_{0-7 \text{ days}}$ in the pancreas, stomach, intestine, and muscle, that in H460 tumors was approximately the same or greater (Table 2). The AUC$_{0-7 \text{ days}}$ in the kidneys and liver were almost three times higher and that in the bone was almost two times higher than that in H460 tumors (Table 2).

As separate experiments, radio-cisplatin uptake in blood, the red blood cell partitioning rate of radio-cisplatin in blood cells, and the plasma protein binding rate of cisplatin were also evaluated at 2 min, 1 h, and 19 h after the injection (Table 3). The uptake in blood was ~35%ID/g at 2 min after injection and quickly decreased thereafter (Table 3), consistent with the results in Fig. 2. The red blood cell partitioning rate of cisplatin increased gradually over the experimental period after injection and reached ~50% (Table 3). The plasma protein binding rate of cisplatin increased to ~80% within 1 h after injection (Table 3). From the end of the alpha phase to the beginning of the beta phase, the plasma protein binding rates remained high (Table 3).

Discussion

This study evaluated the quantitative pharmacokinetics of cisplatin in mice bearing lung cancer for 7 days after intravenous injection with radio-cisplatin. The radio-Pt tracer showed the clearance of cisplatin from the whole body and blood, and the results were in good agreement with the pharmacological and pharmacokinetic properties of cisplatin. In addition, we investigated the comprehensive biodistribution of cisplatin to tissues with different degrees of drug accumulation over 7 days. Our results are consistent with the known clinical side effects of cisplatin and could provide reference data for the development of the next generation of Pt-based anticancer drugs. Because $^{191}$Pt emits γ-rays and X-rays, which enable noninvasive imaging in humans, radio-Pt-based agents would provide comprehensive pharmacokinetics data not only in animals but also in humans.

The rapid clearance of cisplatin from the body and blood of mice intravenously injected with radio-cisplatin was observed. The blood concentration decreased immediately after injection and most of the injected cisplatin was excreted from the body by 1 day after injection. A biphasic retention curve in the whole body and blood was observed, and the biological half-life was calculated to be $T_1/2(\alpha) = 1.14$ h and $T_1/2(\beta) = 5.33$ days for the whole body and $T_1/2(\alpha) = 23.9$ min and $T_1/2(\beta) = 4.72$ days for blood (Fig. 1). This elimination of half-life in the blood is acceptably consistent with the results of previous studies [12,18,19].
Our biodistribution experiments with radio-cisplatin over 7 days provided comprehensive pharmacokinetics data showing high accumulation in the kidneys, liver, and bone. The renal uptake increased in the early time points rapidly after injection, and radio-cisplatin was excreted gradually in the late time points (Fig. 2). According to the literature, cisplatin is rapidly excreted via the kidneys although a part of it remains intact [12,19]. Most of the intact cisplatin would be excreted via the kidneys rapidly after injection before working in the body. Some intact cisplatin was uptaken into renal cells, inducing renal disorder as the main side effect of cisplatin [7]. This uptake into renal cells and their disorder could be caused by a rapid distribution of intact cisplatin in the early time points; this interpretation is supported.
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by our radio-cisplatin results. Uptake in the liver was relatively higher than in the kidneys in the late time points from 3 days after injection. This result might be related to the plasma protein binding of cisplatin. The plasma protein binding rate increased immediately after intravenous injection (Table 3), which is consistent with our understanding of the behavior of cisplatin [9–12,18,19]. Cisplatin easily reacts with sulfur-containing cysteine or methionine of proteins such as serum albumin [20–22], leading to an irreversible increase of protein-bound cisplatin. The protein-bound cisplatin is known to not be excreted predominately by the kidneys, to be retained longer in the blood, and to be accumulated in the liver [23,24]. This tendency might be responsible for the moderate retention in the liver in the late time points (Fig. 2), suggesting that the protein-bound cisplatin would be reaccumulated partly in the liver while remaining and circulating in the blood (Fig. 2). Numerous previous studies on cisplatin treatments have shown that high-dose administration of cisplatin causes hepatotoxicity [25–27], and the oxidative stress derived from the metal toxicity of Pt has been suggested to be the main cause [28–30]. Some authors have also reported a high accumulation of cisplatin in the liver [31–34]. The radio-Pt tracer could provide insights enabling the elucidation of the relationship between hepatotoxicity and cisplatin. Only the bone uptake of cisplatin increased slightly on day 5. Cisplatin remaining in blood or excreted from tissues appeared to be taken into bones. This effect is speculated to correspond to cisplatin side effects such as myelosuppression. Collectively, our comprehensive and quantitative biodistribution results provide insights into the cause of the adverse effects of cisplatin.

As a limitation of this study, the clearance rate was the result of a single and rapid administration of cisplatin in

Biodistribution of radio-cisplatin in mice bearing H460 tumors. Data are represented as the percentage of the injected dose per gram (%ID/g) of tissues (mean ± SD, n = 4). The data for blood are the same as in the lower panel of Fig. 1.

<table>
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<tr>
<th>Tissue</th>
<th>2 min</th>
<th>15 min</th>
<th>60 min</th>
<th>1 day</th>
<th>3 days</th>
<th>5 days</th>
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<td>0.83</td>
<td>0.44</td>
<td>0.39</td>
<td>0.38</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.74</td>
<td>2.79</td>
<td>3.95</td>
<td>3.07</td>
<td>2.98</td>
<td>2.72</td>
<td>2.35</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.17</td>
<td>0.25</td>
<td>0.31</td>
<td>0.50</td>
<td>0.70</td>
<td>0.72</td>
<td>0.82</td>
</tr>
<tr>
<td>Bone</td>
<td>0.20</td>
<td>0.89</td>
<td>1.38</td>
<td>1.51</td>
<td>2.13</td>
<td>2.74</td>
<td>3.20</td>
</tr>
<tr>
<td>Tumor</td>
<td>0.06</td>
<td>0.48</td>
<td>0.73</td>
<td>0.93</td>
<td>1.02</td>
<td>1.07</td>
<td>0.93</td>
</tr>
</tbody>
</table>

The ratios were calculated on the basis of the biodistribution data in Fig. 2.

<table>
<thead>
<tr>
<th>Tumor/tissue</th>
<th>AUCratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.91</td>
</tr>
<tr>
<td>Lung</td>
<td>0.76</td>
</tr>
<tr>
<td>Liver</td>
<td>0.35</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.17</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.24</td>
</tr>
<tr>
<td>Intestine</td>
<td>1.18</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.30</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.59</td>
</tr>
<tr>
<td>Bone</td>
<td>0.46</td>
</tr>
</tbody>
</table>

The ratios were calculated on the basis of the biodistribution data in Fig. 2. AUC, area under the curve.
mice (2 mg/kg body weight). According to previous studies [35–41], the administration protocol affects the clearance and the therapeutic efficacy of cisplatin. Numerous protocols are used in clinical settings, and maintaining a constant blood drug concentration at the optimal administration rate is important [35–41]. The radiotracer can enable such systematic investigations of the effect of the administration rate of cisplatin. Although our results are consistently discussed in relation to the clinical properties of cisplatin, further preclinical studies should be conducted for target regimens. In addition, our results are based on directly quantifying radio-Pt, which is a basic factor of the cytotoxic action of cisplatin. The biodistribution included both intact and protein-bound cisplatin, and metabolite analyses were not conducted.

Conclusion
This study clearly showed that a radio-Pt tracer is useful for acquiring comprehensive and quantitative biodistribution data because it can be detected quantitatively with high sensitivity. This work supports the current understanding of the pharmacological and pharmacokinetic properties of cisplatin and provides reference data for the further development of Pt-based drugs.

Acknowledgements
The authors would like to thank the cyclotron staff for operating the NIRS cyclotron AVF-930. We are grateful to Hisashi Suzuki, Akihito Abe, and Ayumi Kadoma for technical support.

This work was supported in part by JSPS KAKENHI Grant Number JP20J20518.

Conflicts of interest
There are no conflicts of interest.

References

Table 3 Uptake in whole blood (%ID/g), red blood cell partitioning rate (%), and plasma protein binding rate (%) (n = 2)

<table>
<thead>
<tr>
<th>Time</th>
<th>Whole blood uptake (%ID/g)</th>
<th>Red blood cell partitioning rate (%)</th>
<th>Plasma protein binding rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 min</td>
<td>33.7, 35.5</td>
<td>1.5, 8.8</td>
<td>35.5, 28.6</td>
</tr>
<tr>
<td>33.7</td>
<td>35.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>4.5, 5.0</td>
<td>27.3, 32.2</td>
<td>82.8, 79.5</td>
</tr>
<tr>
<td>19 h</td>
<td>1.9, 2.2</td>
<td>51.8, 55.7</td>
<td>91.6, 92.2</td>
</tr>
</tbody>
</table>

%ID, percentage of the injected dose.
of Lewis lung carcinoma-bearing mice: protective role of heme oxygenase. 
Is technetium-99m dimercaptosuccinic acid renal scintigraphy available for predicting vesicoureteral reflux in children with first febrile urinary tract infection under the age of 24 months?

Wei Yang, Qinghan Jiao, Haiyan Wang, Weizhen Chen, and Hongxiang Yao

Objective  Vesicoureteral reflux (VUR) is a common complication after urinary tract infection (UTI) and can lead to irreversible renal scar. Voiding cystourethrogram is the most reliable technology to detect VUR and its severity, but it is restricted in children’s examinations for various shortcomings. This study aimed to evaluate and compare the efficiency of Tc-99m DMSA renal scintigraphy and conventional ultrasonography (USG) in predicting VUR with the gold standard of cystourethrogram results.

Methods  This retrospective study consisted of 285 first febrile UTI children under the age of 24 months who completed inflammatory indicator examinations, USG, Tc-99m DMSA renal scintigraphy and underwent cystourethrogram after controlling infection with prophylactic antibiotics. The efficiency of Tc-99m DMSA renal scintigraphy and USG in predicting VUR was calculated and compared.

Results  Abnormal USG (40.23% vs. 21.72%, \(P = 0.001\)) and Tc-99m DMSA renal scintigraphy results (87.36% vs. 71.72%, \(P = 0.004\)) were more common in VUR children. The sensitivity of USG in predicting VUR was only 40.23%, whereas the sensitivity and negative predictive value of Tc-99m DMSA renal scintigraphy reached 87.63% and 83.58%, respectively. Tc-99m DMSA renal scintigraphy had a higher efficacy than USG in predicting high-grade reflux kidneys (73.87% vs. 33.33%; \(P < 0.001\)), but there was no significant difference in predicting low-grade reflux kidneys (\(P = 0.703\)).

Conclusion  Tc-99m DMSA renal scintigraphy had a significant higher efficiency in predicting VUR (a common cause of renal scarring, detected on DMSA) in first febrile urinary tract infection children under the age of 24 months as compared with USG, especially in high-grade reflux.

Nuclear Medicine Communications 2022; 43:1128–1135

Keywords: febrile urinary tract infection, Tc-99m dimercaptosuccinic acid renal scintigraphy, ultrasonography, vesicoureteral reflux

Introduction  Urinary tract infection (UTI) is one of the most common bacterial infections in childhood, of which Escherichia coli accounts for 80–90%. The symptoms and signs are nonspecific throughout infancy, and unexplained fever is the most common symptom of UTI during the first 2 years of life. Overall, the incidence of UTI in children within 2 years old reaches about 5% [1], and 10–15% of the children eventually developed irreversible renal scar [2] and faced a variety of complications such as hypertension, proteinuria, and end-stage kidney disease [3,4], whereas the proportion was greatly increased to 30–60% in the younger children [3,5,6]. Vesicoureteral reflux (VUR), as a retrograde flow of urine from the bladder to the kidneys, is also a common complication of UTI [7]. It has been stated that the first episode of febrile UTI could lead to the identification of VUR in 30% of the patients [8]. The presence of VUR and febrile UTI in infancy are significantly associated with the development of hypertension in adulthood and, in some cases, with late renal insufficiency [9]. Hence, accurately assessing the severity of febrile UTI and VUR is of great importance and conducive to the pediatricians so that effective intervention can be taken as early as possible to reduce the risk of renal scar formation and other complications.

Voiding cystourethrogram (VCUG) is recognized as the gold standard for detecting VUR and its severity [10,11], but it is limited in clinical practice because this procedure is invasive, painful, irradiating, and associated with an increased risk for catheter-related UTI or urethral injury. It is controversial whether to perform VCUG in children. The 2011 American Academy of Pediatrics Guidelines [1] pointed out that in infants and young children under the age of 24 months with febrile UTI, ultrasonography (USG) was preferred to determine the urogenital
system abnormalities. VCUG was recommended only for those having abnormal USG results such as hydronephrosis, renal scar, or other signs of high-grade VUR and obstructive uropathy. However, many studies had indicated that USG could not accurately predict VUR [12–14]. Technetium-99m (Tc-99m) dimercaptosuccinic acid (DMSA) renal scintigraphy is a noninvasive nuclear medicine imaging technique and can reflect renal parenchymal lesions. Many authors such as Piepsz et al. [15] and Bhatnagar et al. [16] believed that Tc-99m DMSA renal scintigraphy result was the gold standard of renal scar detection. This caught our attention that whether Tc-99m DMSA renal scintigraphy can help to pick out those at high risk of VUR to conduct cystourethrogram; hence, this study aimed to combine Tc-99m DMSA renal scintigraphy and conventional USG to evaluate the efficiency of Tc-99m DMSA renal scintigraphy in predicting VUR.

Materials and methods

Study population and protocol

The clinical records of 285 consecutive first febrile UTI children under the age of 24 months who were hospitalized in the Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University from August 2020 to November 2021 were reviewed. All children fulfilled the following criteria: (a) body temperature more than 38 °C (verified by a physician or as referred by parents); (b) abnormal urinalysis: white blood cell (WBC) count of more than 5 cells/high-power field, positive leukocyte esterase and/or nitrite test; and (c) positive pyuria on urinalysis with a monoculture with at least 100 000 organisms/ml in urine obtained by midstream clean-void samples. Children with body temperature less than 38 °C, prior UTI, ectopic ureter, ureterocele, posterior urethral valve, neurogenic bladder, solitary kidney, or other congenital urinary tract anomalies were excluded. All eligible children completed relevant inflammatory indicator examinations, USG, Tc-99m DMSA renal scintigraphy after admission and underwent retrograde cystourethrogram after controlling acute infection with prophylactic antibiotics. The data are anonymous, and the requirement for informed consent was therefore waived.

Laboratory examination

All the patients completed routine blood test, urinalysis, and C-reactive protein (CRP) examinations after admission. Children’s clinical information was recorded including sex, age, the highest temperature, and the delayed time (interval time from the first fever symptoms to admission). Inflammatory indicators including WBC count, neutrophil count, neutrophil ratio, lymphocyte count, lymphocyte ratio, and CRP were also recorded.

Ultrasonography examination

USG examination was performed within 3 days after admission to record the urinary abnormalities. It was operated by an experienced clinician blinded to the children’s clinical data. It was considered abnormal as the following appeared: hydronephrosis (grade I-IV), ureteral dilatation with a diameter of 7 mm, irregular contour, thinned parenchyma, renal scar formation, renal hypoplasia (such as small kidney), duplicated collecting system and so on.

Technetium-99m dimercaptosuccinic acid renal scintigraphy

Tc-99m DMSA renal scintigraphy was conducted within 1 week after admission. Tc-99m DMSA was injected intravenously. According to Clark’s rule, the dose was calculated based on the formula (weight/70 kg × standard adult dose of 5 mCi), with minimum dose of 1 mCi and maximum dose of 5 mCi [17]. The anterior and posterior images acquisition was carried out 1.5 h after injection, using single photon emission computer scanner (SPECT, vertex V60, ADAC, San Francisco, California, USA) equipped with a low-energy and high-resolution parallel hole collimator centered on the 140 keV photopeak with a 20% symmetric energy window. The matrix size was 128 × 128 or 256 × 256. The images were evaluated by consensus of two experienced observers, who were blinded to the children’s clinical data. Abnormal image referred to the sign of renal cortex damage with a radioactive distribution decrease or defect in one or more parts of the kidney.

Retrograde cystourethrogram

Retrograde cystourethrogram was performed according to the pediatric radiology standard after controlling acute infection with prophylactic antibiotics, and VUR was defined as grade I-V according to the five-level criteria proposed by the International Commission on reflux (Randomized Intervention for Children with Vesicoureteral Reflux) [18]. First, all eligible children were divided into two subgroups based on the cystourethrogram results, one of which was referred as the VUR group with unilateral or bilateral VUR and the other was non-VUR group. Furthermore, all kidneys were divided into nonreflux group, low-grade reflux group (grade I-II), and high-grade reflux group (grade III-V) by the analysis of the characteristic of each unilateral VUR.

Statistical analysis

All data were analyzed using SPSS 23.0 statistical software (IBM, Armonk, NY, USA). Measurements with normal distribution, including all the inflammatory indicators in VUR group and WBC count, lymphocyte count in non-VUR group, were expressed as mean ± SD. Measurements with nonnormal distribution, including age, delayed time, and the other inflammatory indicators of non-VUR group (such as neutrophil count, neutrophil ratio, lymphocyte ratio, and CRP), were presented as Median P50 (P25 and P75). Categorical variables (sex distribution and imaging findings) were described as percentage or number. t-test
was used in comparison of the data with normal distribution such as WBC count and lymphocyte count between VUR and non-VUR groups. The indicators such as age, delayed time, neutrophil count, neutrophil ratio, lymphocyte ratio, CRP between the two groups were compared using Mann–Whitney U test. The comparison of the sex distribution and imaging findings between the two groups was made with Fisher’s exact test or Chi-square analysis. According to results of retrograde cystourethrogram, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Tc-99m DMSA renal scintigraphy and USG in predicting VUR were calculated and compared. Furthermore, the association between Tc-99m DMSA renal scintigraphy results and VUR grades was analyzed. A two-sided $P$ value of 0.05 or lower was regarded as statistically significant.

Results
Patients and clinical characteristics
Of 828 consecutive UTI children who were hospitalized in the Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University from August 2020 to November 2021, 285 met inclusion criteria (Fig. 1), with a median age of 5.0 months (range, 10 days–24 months) and male-to-female ratio of 1.32:1. Of the 285 children, 246 were younger than 1 year, with 91.36% of the boys (148) and 79.67% of the girls (98). All of the boys in this study were uncircumcised.

Retrograde cystourethrogram findings
Among the 285 patients, there were 87 (30.53%) children diagnosed with VUR, including 53 boys and 34 girls. There was no statistically significant difference in age, sex, delayed time, WBC, neutrophil count, neutrophil ratio, lymphocyte count, lymphocyte ratio, and CRP between the VUR and non-VUR groups (all $P > 0.05$; Table 1). Based on the severity of unilateral VUR, all kidneys (570 in total) were divided into three groups (Table 2): nonreflux group (440), low-grade reflux group (eight in grade I, 11 in grade II), and high-grade reflux group (38, 49, and 24 in grades III, IV, and V, respectively).

Ultrasoundography findings
Abnormal USG results could be observed in 78 cases involving 102 kidneys, whereas normal USG results were observed in 52 VUR children and 89 reflux kidneys (Fig. 1 and Table 2). There were significant differences between children with and without VUR for the proportion of abnormal USG results (40.23% vs. 21.72%; $P = 0.001$) (Fig. 2). Among all the 130 unilateral reflux kidneys, only 41 (31.54%) kidneys were observed with abnormal USG results, of which 37 abnormal results were detected in the 111 high-grade unilateral reflux kidneys (Table 2). In addition, there were 15 normal USG results in the 19 low-grade unilateral reflux kidneys, and 74 normal USG results in the 111 high-grade reflux kidneys.

Technetium-99m dimercaptosuccinic acid renal scintigraphy findings
Abnormal Tc-99m DMSA renal scintigraphy results were detected in 218 children involving 282 kidneys. There were significant differences between children with and without VUR for the proportion of abnormal Tc-99m DMSA renal scintigraphy results (87.36% vs. 71.72%; $P = 0.004$) (Table 1). Among all the 130 unilateral reflux kidneys, 87 had abnormal Tc-99m DMSA renal scintigraphy results, of which 82 abnormal results were detected in the 111 high-grade unilateral reflux kidneys (Table 2). Furthermore, there were totally 43 unilateral reflux kidneys with normal Tc-99m DMSA renal scintigraphy results, of which low-grade reflux kidneys accounted for 73.68% (14/19), whereas high-grade reflux kidneys only accounted for 26.13% (29/111).

Assessment of efficiency in predicting vesicoureteral reflux
Based on the characteristic of unilateral VUR, both the proportion of abnormal USG and Tc-99m DMSA renal scintigraphy results in reflux kidneys were significantly higher than that in nonreflux kidneys (USG, 31.54% vs. 13.86%; Tc-99m DMSA renal scintigraphy, 66.92% vs. 44.32%; all $P < 0.05$). As Fig. 2 shows, the proportion of abnormal Tc-99m DMSA renal scintigraphy results in high-grade reflux group was significantly higher than that in low-grade and nonreflux groups. No significant difference was observed in both Tc-99m DMSA and USG results between low-grade and nonreflux groups. Furthermore, there was no significant difference between the high-grade and low-grade reflux groups in the proportion of abnormal USG results. However, high-grade reflux group had higher proportion of abnormal USG results as compared with the nonreflux group and the difference was statistically significant.

The sensitivity and specificity of USG in predicting VUR were 40.23 and 78.28%, respectively, whereas those of Tc-99m DMSA renal scintigraphy reached 87.36 and 28.28%, respectively (Table 3). There was no significant difference between the VUR and non-VUR groups in combined Tc-99m DMSA renal scintigraphy and USG results. As compared with Tc-99m DMSA renal scintigraphy, the sensitivity was slightly improved (89.66%) without statistical significance by combining the two methods, but the specificity, PPV, and NPV were not significantly improved or even slightly decreased. There was no significant difference between USG and Tc-99m DMSA renal scintigraphy in the prediction of low-grade reflux kidneys (21.05% vs. 26.32%; $P = 0.703$). However, Tc-99m DMSA renal scintigraphy (82/111) has higher predictive value than USG (37/111) in the high-grade reflux kidneys (73.87% vs. 33.33%; $P < 0.001$).
Discussion

Among the present study population, both abnormal USG and Tc-99m DMSA renal scintigraphy results were more common in VUR group as compared to non-VUR group, indicating that above two imaging techniques could predict VUR to some extent. In addition, Tc-99m DMSA renal scintigraphy had higher efficiency than USG in predicting high-grade reflux, whereas there was no significant difference between the two methods in predicting low-grade reflux.

UTI is one of the most common bacterial infections in febrile children within 2 years old, with an incidence of about 5% [1]. Recurrent UTI is an important risk factor of chronic renal damage and scar formation [19]. Van et al. [1131] found that Tc-99m DMSA renal scintigraphy had higher efficiency than USG in predicting high-grade reflux, whereas there was no significant difference between the two methods in predicting low-grade reflux.

Table 1 Comparison of clinical data, inflammatory indicators, and imaging results between vesicoureteral reflux and nonvesicoureteral reflux group

<table>
<thead>
<tr>
<th>Variable</th>
<th>VUR (n = 87)</th>
<th>Non-VUR (n = 198)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>5.0 (3.1–8.5)</td>
<td>5.5 (3.2–9.0)</td>
<td>0.543</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>53 (60.92)</td>
<td>109 (55.05)</td>
<td>0.357</td>
</tr>
<tr>
<td>Delayed time (days)</td>
<td>2 (1–3)</td>
<td>2 (1–4)</td>
<td>0.309</td>
</tr>
<tr>
<td>WBC (x10^9/l)</td>
<td>18.12 ± 7.85</td>
<td>18.10 ± 7.22</td>
<td>0.232</td>
</tr>
<tr>
<td>N (x10^9/l)</td>
<td>10.84 ± 7.1</td>
<td>9.33 (8.26–14.11)</td>
<td>0.945</td>
</tr>
<tr>
<td>N%</td>
<td>0.56 ± 0.17</td>
<td>0.58 (0.45–0.66)</td>
<td>0.869</td>
</tr>
<tr>
<td>L (x10^9/l)</td>
<td>5.34 ± 2.20</td>
<td>5.58 ± 2.01</td>
<td>0.555</td>
</tr>
<tr>
<td>L%</td>
<td>0.34 ± 0.15</td>
<td>0.31 (0.23–0.42)</td>
<td>0.893</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>92.31 (40.23)</td>
<td>72.10 (43.29–115.30)</td>
<td>0.327</td>
</tr>
<tr>
<td>Abnormal USG, n (%)</td>
<td>35 (40.23)</td>
<td>43 (21.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abnormal Tc-99m DMSA renal scintigraphy, n (%)</td>
<td>76 (87.36)</td>
<td>142 (71.72)</td>
<td>0.004</td>
</tr>
<tr>
<td>Combined abnormal USG and Tc-99m DMSA renal scintigraphy, n (%)</td>
<td>78 (90.66)</td>
<td>158 (78.78)</td>
<td>0.074</td>
</tr>
</tbody>
</table>

Both abnormal USG and Tc-99m DMSA renal scintigraphy results were more common in VUR group as compared to non-VUR group. No significant difference was observed between the two groups in clinical data (such as age, sex distribution, and delayed time) or inflammatory indicators.

CRP, C-reactive protein; DMSA, dimercaptosuccinic acid; L, lymphocyte; N, neutrophil; Tc-99m, technetium-99m; USG, ultrasonography; VUR, vesicoureteral reflux; WBC, white blood cell.

*P < 0.05.
al. [8,20] found that the incidence of high-grade (grade III-V) VUR in children with febrile UTI was about 17%. The severity of VUR was closely related to renal scar formation, and hidden high-grade VUR was the main risk factor of chronic renal damage [21]. Snodgrass et al. [22] also confirmed that VUR could increase the risk of renal cortical defect, which was more significant in high-grade VUR group. Therefore, early effective screening for VUR (especially in high-grade) in children with febrile UTI is of great significance to improve their long-term prognosis. VCUG is the gold standard of diagnosing VUR and evaluating its severity. However, it is restricted in children’s examinations for various shortcomings. The 2011 American Academy of Pediatrics no longer recommended the children with normal USG results for VCUG to determine VUR [1]. In the present study, both abnormal USG and Tc-99m DMSA renal scintigraphy results were more common in VUR group as compared with the non-VUR group, indicating that above two imaging techniques could predict VUR to some extent. Furthermore, the abnormality was more common in high-grade reflux group, whereas there was no significant difference between low-grade and nonreflux groups, suggesting that the above two techniques were more valuable for predicting high-grade reflux as compared with low-grade reflux, which is consistent with the previous study that high-grade VUR could be excluded with normal USG or Tc-99m DMSA results [21].

However, it was found that USG could not accurately predict VUR in clinical practice for its’ low sensitivity. Previous studies have already shown that USG could lead to missed diagnosis of VUR and renal scars. Juliano et al. [14] completed the follow-up of 95 pyelonephritis children with normal USG, and found that 14 (15%) faced recurrent pyelonephritis, whereas seven (7%) had undergone surgery and 23 were diagnosed as VUR later. Tse et al. [23] found that USG could result in missed diagnosis of 22 scarred kidneys in the study of 98 infants (196 kidneys) under the age of 6 months. Consistent with those studies, USG also had a low sensitivity of 40.23% in predicting VUR in the present study, and the sensitivity was further reduced to 31.54% with unilateral kidney as the research unit. Fifty-two children with VUR involving 89 kidneys in our study would be missed by USG. Moreover, forty-three children without VUR would undergo cystourethrography for their abnormal USG results, and their catheter-related UTI and radiation exposure would be increased. As Fig. 3 shows, the child in our study was diagnosed with VUR (grade III on the right and grade II on the left) according to retrograde cystourethrogram results, but no abnormality was observed in USG examination. However, obvious abnormality could be detected by Tc-99m DMSA renal scintigraphy.

In addition, Temiz et al. [24] thought that USG was not suitable for detecting renal scar as they found that 35% of the VUR children with renal scar in Tc-99m DMSA renal
Tc-99m DMSA renal scintigraphy in predicting VUR  Yang et al. 1133

scintigraphy were observed with normal USG results. We compared the efficiency of USG and Tc-99m DMSA renal scintigraphy in predicting high-grade reflux kidneys and found that 74 high-grade reflux kidneys were missed by USG, whereas only 29 by Tc-99m DMSA renal scintigraphy. These high-grade VUR children with normal USG would be treated as low-risk population, and the risk of progressive VUR, recurrent UTI, and renal scar formation would be further increased in their later growth. Moreover, our study found that Tc-99m DMSA renal scintigraphy had a higher sensitivity of 87.36% in predicting VUR. Rushton and Majd [25] had also reported that the sensitivity and specificity of Tc-99m DMSA renal scintigraphy in pyelonephritis could reach 87 and 100%, respectively. Meanwhile, Mohkam et al. [26] believed that Tc-99m DMSA renal scintigraphy was more accurate than other inflammatory markers and imaging methods in patients with clinical symptoms of pyelonephritis for predicting VUR, with a sensitivity of 84.1% and NPV of 80.6%. The consistent predictive value of Tc-99m DMSA renal scintigraphy for predicting VUR could be seen in the present study.

Since high-grade VUR was the main risk factor of chronic renal damage and could increase the risk of renal cortical defect [21,22], efficient identification of high-risk groups with high-grade VUR is of great importance to the pediatricians in clinical practice. Our study found that Tc-99m DMSA renal scintigraphy had higher efficiency than USG in predicting high-grade reflux, whereas there was no significant difference between the two methods in the predicting low-grade reflux, suggesting that Tc-99m DMSA renal scintigraphy was more available for predicting VUR, especially in high-grade VUR. The previous study [22] already found that the severity of VUR, recurrent febrile UTI, and age were independent risk factors for renal cortex radioactivity defect in Tc-99m DMSA; however, 43% of patients with grade IV-V VUR and 76% of patients with recurrent UTI may have normal Tc-99m DMSA results. We also found that there were 43 (12.64%) kidneys with VUR but normal Tc-99m DMSA results, of which low-grade reflux kidneys accounted for 73.68%, whereas high-grade reflux kidneys only accounted for 26.13%, suggesting that low-grade reflux kidneys were
There are no conflicts of interest.

Conflicts of interest

There are no conflicts of interest.

References


Simulated daily readout for maintaining nuclear medicine education in residency training amidst declining case volume: evidence from the COVID-19 pandemic

Vorapol Jaroonvanichkul\textsuperscript{a}, Surachai Leksuwankun\textsuperscript{b} and Sira Vachatimanont\textsuperscript{c}

\textbf{Background} Simulated daily readout (SDR) is a teaching initiative in radiology and nuclear medicine developed to simulate a resident's experience during periods of case volume reduction. SDR was employed by many training centers during the coronavirus disease 2019 (COVID-19) pandemic. This study aimed to evaluate the perception of radiology residents on the effectiveness of SDR.

\textbf{Method} The SDR was conducted in the nuclear medicine rotations from 2019 to 2020 during the shutdown of the radionuclide imaging facilities using a combination of strategies including case selection, assignment, reporting and feedback. A brief 8-item questionnaire with Likert scale values was completed by radiology residents who participated in the SDR-based nuclear medicine rotations.

\textbf{Results} Thirty-five of 54 residents returned the questionnaire. The majority of residents affirmed the negative impact of the reduction in case volume on their training experiences and perceived that SDR could alleviate the effects. The SDR strategies perceived as more effective were targeted case selection, in-advanced assignment, verbal interpretation and reporting, and verbal feedback.

\textbf{Conclusion} The radiology residents perceived the SDR as an effective tool to preserve their training experiences. The SDR has the potential to be a useful initiative when teaching centers face the threat of declining case volume.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused disruptions in nuclear medicine and radiology residency training on at least 3 dimensions. First, the postponement of non-urgent cases caused a decline in case volume and diversity. Secondly, some imaging procedures were required to be altered to conform with infection control measures \cite{1,2}. Third, physical distancing limited in-person mentoring and supervision. All of these impacts posed potential adverse effects on residency training \cite{3}.

The decreased case volume and diversity alone can cause severe challenges for the residency training process. Residents are not only required by the regulatory body to experience a predefined number of cases but sufficient case exposure also has been proven to be crucial for residents to develop their essential skills \cite{4,5}.

The simulated daily readout (SDR) is a teaching initiative for preserving training quality. The processes of SDR commences with the selection of cases from the picture archiving and communication system (PACS). The cases are used to create worklists of imaging studies for each trainee to interpret findings. The trainees are required to complete dictation of the reports. Revisions and feedback on each are then provided by the attending faculty.

The SDR aims to imitate the trainees’ experience in a radiology department during normal daily service. It had been employed in 2020 by Recht \textit{et al.} to maintain uninterrupted training activities across their radiology department during the lockdown in the USA. Their survey showed that both residents and teaching faculty perceived the negative impacts of the COVID-19 pandemic on education and training experiences. They found that residents and faculty felt SDR was effective in mimicking the daily-service learning experience and preserving training program quality \cite{6}.

Although the implementation of SDR across subspecialties of radiology has been initiated, the study of SDR specifically in nuclear medicine has been under-investigated. The current study aimed to describe the SDR we conducted and our residents’ experiences.
Methods

Implementation of SDR and context
From October 2019 to December 2020, an unexpected shutdown of the radionuclide imaging facilities of King Chulalongkorn Memorial Hospital and the Faculty of Medicine, Chulalongkorn University after a fire incident [7] and the COVID-19 pandemic left in-person mentoring and supervised daily readouts in clinical services, which are critical components of the traditional learning experience, non-existent. To preserve the training regimen for residents, the nuclear medicine unit employed SDR for residents who rotated into nuclear medicine rotation during the 15-month shutdown. SDR was conducted in combination with multiple strategies, summarized into four processes: case selection, worklist assignment, interpretation and reporting, and feedback. All SDR-based training was provided by the same teaching faculty comprised of eight board-certified nuclear medicine physicians.

Questionnaire
We developed an 8-item questionnaire to explore the resident’s experience during the SDR-implemented nuclear medicine rotation. Items included the effect of case absence on each resident’s experience in 4 domains: theoretical knowledge, patient management, interpretation, and reporting. (Table 1) The questionnaire also surveyed the perceived effectiveness of each method of SDR. A paper version of the questionnaire was given to residents at the end of the implementation of the SDR in January 2021 and collected anonymously. The retrieval and analysis of the questionnaire data were approved by the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Post-SDR-implemented nuclear medicine rotation feedback survey</th>
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<tbody>
<tr>
<td>Questions</td>
<td></td>
</tr>
<tr>
<td>Q1.1 Do you agree that ‘absence of radionuclide imaging case after fire incidence and COVID-19’ has negative effects on residency training?</td>
<td></td>
</tr>
<tr>
<td>1. Strongly disagree</td>
<td></td>
</tr>
<tr>
<td>2. Disagree</td>
<td></td>
</tr>
<tr>
<td>3. Neither agree nor disagree</td>
<td></td>
</tr>
<tr>
<td>4. Agree</td>
<td></td>
</tr>
<tr>
<td>5. Strongly agree</td>
<td></td>
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<tr>
<td>Q1.2 If your response was “agree” or “strongly agree”, please rate the severity of the negative effects on each of these domains.</td>
<td></td>
</tr>
<tr>
<td>a.) Theoretical knowledge.</td>
<td></td>
</tr>
<tr>
<td>1. Very mild</td>
<td></td>
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<tr>
<td>2. Mild</td>
<td></td>
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<tr>
<td>3. Moderate</td>
<td></td>
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<tr>
<td>4. Severe</td>
<td></td>
</tr>
<tr>
<td>5. Very severe</td>
<td></td>
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<tr>
<td>b.) Patient management.</td>
<td></td>
</tr>
<tr>
<td>c.) Radionuclide imaging interpretation.</td>
<td></td>
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<tr>
<td>d.) Radionuclide imaging report.</td>
<td></td>
</tr>
<tr>
<td>Q2.1 Do you agree that the SDR can alleviate the negative effects?</td>
<td></td>
</tr>
<tr>
<td>1. Strongly disagree</td>
<td></td>
</tr>
<tr>
<td>2. Disagree</td>
<td></td>
</tr>
<tr>
<td>3. Neither agree nor disagree</td>
<td></td>
</tr>
<tr>
<td>4. Agree</td>
<td></td>
</tr>
<tr>
<td>5. Strongly agree</td>
<td></td>
</tr>
<tr>
<td>Q2.2 If your response was ‘agree’ or ‘strongly agree’, how well did SDR alleviate the impact on each of these domains.</td>
<td></td>
</tr>
<tr>
<td>a.) Theoretical knowledge.</td>
<td></td>
</tr>
<tr>
<td>1. Very ineffective</td>
<td></td>
</tr>
<tr>
<td>2. Ineffective</td>
<td></td>
</tr>
<tr>
<td>3. Neither effective nor ineffective</td>
<td></td>
</tr>
<tr>
<td>4. Effective</td>
<td></td>
</tr>
<tr>
<td>5. Very Effective</td>
<td></td>
</tr>
<tr>
<td>b.) Patient management.</td>
<td></td>
</tr>
<tr>
<td>c.) Radionuclide imaging interpretation.</td>
<td></td>
</tr>
<tr>
<td>d.) Radionuclide imaging report.</td>
<td></td>
</tr>
<tr>
<td>Q3 Do you agree that the SDR can mimic the case volume of conventional daily readout?</td>
<td></td>
</tr>
<tr>
<td>1. Strongly disagree</td>
<td></td>
</tr>
<tr>
<td>2. Disagree</td>
<td></td>
</tr>
<tr>
<td>3. Neither agree nor disagree</td>
<td></td>
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<tr>
<td>4. Agree</td>
<td></td>
</tr>
<tr>
<td>5. Strongly agree</td>
<td></td>
</tr>
<tr>
<td>Q4 Do you agree that the SDR can mimic the case diversity of conventional daily readout?</td>
<td></td>
</tr>
<tr>
<td>1. Strongly disagree</td>
<td></td>
</tr>
<tr>
<td>2. Disagree</td>
<td></td>
</tr>
<tr>
<td>3. Neither agree nor disagree</td>
<td></td>
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<tr>
<td>4. Agree</td>
<td></td>
</tr>
<tr>
<td>5. Strongly agree</td>
<td></td>
</tr>
<tr>
<td>Q5 In your opinion, how would the SDR affect your confidence for practice after completing the training?</td>
<td></td>
</tr>
<tr>
<td>1. Far less confident.</td>
<td></td>
</tr>
<tr>
<td>2. Less confident.</td>
<td></td>
</tr>
<tr>
<td>3. Unaffected.</td>
<td></td>
</tr>
<tr>
<td>4. More confident</td>
<td></td>
</tr>
<tr>
<td>5. Far more confident</td>
<td></td>
</tr>
<tr>
<td>Q6 On a scale of 1 (very ineffective) to 5 (very effective), what were your perceived effectiveness of each following strategies employed during the SDR</td>
<td></td>
</tr>
<tr>
<td>a.) random case selection</td>
<td></td>
</tr>
<tr>
<td>b.) targeted case selection</td>
<td></td>
</tr>
<tr>
<td>c.) advanced worklist assignment</td>
<td></td>
</tr>
<tr>
<td>d.) immediate worklist assignment</td>
<td></td>
</tr>
<tr>
<td>e.) verbal interpretation and reporting (either on-site or remote)</td>
<td></td>
</tr>
<tr>
<td>f.) written interpretation and reporting</td>
<td></td>
</tr>
<tr>
<td>g.) verbal feedback (either on-site or remote)</td>
<td></td>
</tr>
<tr>
<td>h.) written feedback</td>
<td></td>
</tr>
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</table>
Institutional Review Board, Chulalongkorn University (IRB no.720/64).

Case selection
The simulated daily worklist for SDR typically comprised of at least 3–4 bone scintigraphy and at least 4–5 other radionuclide imaging studies. We employed two strategies of case selection to create the worklist. The first was a random selection strategy where cases were randomly selected to maximize the similarity to normal daily service. The second involved targeted selection where faculty selected the cases carefully based on salient teaching points and the requirements of the curriculum.

Worklist assignment
Worklists were assigned daily by teaching faculty to residents either in advance or immediately before daily supervised readouts. The advanced assignment enabled residents to review relevant clinical information and correlate the findings with prior or other medical images. The immediate assignment was designed to eliminate the potential bias due to the medical history of the patient.

Interpretation and reporting.
Two interpretation and reporting strategies were implemented. The first interpretation and reporting strategy were completed verbally during the supervised daily readouts. This method encouraged interactions between the residents and faculty. Due to the COVID-19 outbreak during the later phase of the SDR implementation, teleconferencing software was used in place of on-site supervision. The second strategy involved a written report typed in an electronic system. This allowed residents to revise and refine their scintigraphy reports before submission.

Feedback
Faculty provided verbal feedback to residents during supervised daily readouts. Written feedback is provided daily by teaching staff via the reporting system of the radiology department.

Statistical analysis
Survey questions used Likert scale values and were displayed in diverging stacked bar charts. Differences between Likert data distribution were assessed with the Kruskal–Wallis test and Mann–Whitney U test. P values of less than 0.05 were considered statistically significant. All statistical analyses were performed with R version 4.0 with Likert packages.

Results
A total of 54 residents were rotated into the nuclear medicine rotations during the 15 months when the SDR was implemented. Thirty-five residents returned the questionnaires (response rate = 64.8%). Twenty-seven respondents (79.4%) felt the absence of the radionuclide imaging cases had negative consequences (Fig. 1). The severity of the effects was not perceived as uniform across the domains ($X^2(3, N = 27) = 27.6, P < 0.001$). The numbers of respondents who felt their theoretical knowledge, patient management, interpretation, and reporting skills were severely or very severely affected were 3 (11.1%), 13 (48.1%), 17 (48.1%) and 22 (50.7%), respectively. Upon pairwise comparison of the Likert scale, the adverse effect on theoretical knowledge was less severe than on patient management ($U = 90, P < 0.001$), interpretation ($U = 72.5, P < 0.001$) and reporting skills ($U = 90, P < 0.001$) (Fig. 2).

Thirty-one respondents (88.6%) thought the SDR could mitigate the negative consequences of the lack of clinical service cases (Fig. 1). The effectiveness on each domain is, however, different ($X^2(3, N = 31) = 27.6, P < 0.001$). The number of respondents who ranked SDR as effective on preserving their theoretical knowledge, patient management, interpretation, and reporting skills was 26 (86.6%), 8 (26.6%), 22 (71.0%) and 19 (61.3%), respectively. The perceived effectiveness on patient management was significantly lower than on theoretical knowledge ($U = 759, P < 0.001$), interpretation ($U = 200, P < 0.001$) and reporting skills ($U = 265, P = 0.002$) (Fig. 3).

Nineteen respondents (55.9%) agreed that the SDR could simulate case volume and 21 respondents (61.7%) agreed that the SDR could simulate case diversity (Fig. 4). However, exposure to the SDR instead of regular service cases prompted 14 respondents (41.2%) to feel far less confident and 15 respondents (44.1%) to feel less confident about their future practice. Only 5 respondents (14.7%) felt unaffected, while no respondents felt more confident with the SDR.

Exploring our strategies of the SDR (Fig. 5), our results found that a higher proportion of students (75.5%) found targeted selection effective compared to random selection (31.4%) ($U = 267, P < 0.001$). Results on assignment showed a higher percentage responding that advanced assignment (69.6%) was more effective compared with immediate assignment (34.7%) ($U = 780, P = 0.001$).

Resident responses on reporting and feedback strategies, 28 respondents (82.3%) ranked verbal interpretation and reporting and 12 respondents (35.3%) ranked written interpretation and reporting as effective, concluding less effectiveness of the written strategy ($U = 913, P = 0.001$). There were 27 respondents (80.4%) who perceived verbal feedback and 13 respondents (38.1%) who perceived written feedback as an effective. In conclusion, based on the perception of our respondents, verbal feedback was more effective than written feedback ($U = 848, P = 0.001$).
Fig. 1

The negative effects of absence radionuclide imaging cases and the ability of the SDR in alleviating the consequences.

Fig. 2

The severity of negative effects to respondents’ experiences on each domain.

Fig. 3

The effectiveness of the SDR in mitigating negative consequences on each domain.
Discussion

Our paper found that radiology residents felt the absence of radionuclide imaging cases had adversely affected their training experience in nuclear medicine. Their concerns were likely legitimate because there have been several studies that showed adequate case exposure can improve the accuracy of scintigraphy interpretation. Nishiyama et al. found that the accuracy of radioiodine liver scintigraphy interpreted by experienced nuclear medicine physicians was 88%, higher than the 77–78% interpreted by those with fewer experiences [4]. Slart et al. also found increases in both sensitivity and specificity of myocardial perfusion scintigraphy interpretation after one year of extensive training [5].

Residents did perceive that the SDR could improve their experience not only in interpretation and reporting but also in the theoretical knowledge domain. This phenomenon might be explained by the enhancing effect of case-based learning, which had been extensively studied in medical students. The case-based approach had been demonstrated by Lee et al. to be more effective than conventional approaches in teaching nuclear medicine in clinical clerkships [8]. The head-to-head comparison between case-based and conventional teaching approaches during the residency training in nuclear medicine has not been studied.

The residents felt that SDR could mimic the case volume and diversity of normal daily service. We believed this was achieved by recruiting a sufficient number of patients into the simulated worklists. Moreover, the SDR could surpass normal daily readouts in terms of case diversity through careful case selection. Some authors have proposed using SDR as an adjunctive tool to ensure sufficient exposure of residents to certain rare pathologies [5,6]. This idea was concordant with the more favorable resident attitude towards targeted over random case selection.

Our worklist assignment strategies were also different from those conducted by Recht et al. The advanced assignment method we imposed could lessen Recht’s concern over disconnection between SDR, clinical context and prior imaging [6]. Our strategies, however, could provoke privacy concerns, because the judgment on which clinical information was relevant was decided subjectively by the teaching faculty.

The residents’ perception that verbal feedback was more effective than written feedback is supported by several previous studies. Porte et al. demonstrated that verbal feedback was superior to written feedback on surgical skill teaching of medical students [9]. Verbal and ‘on-the-fly’ feedback was also recommended in the gynecology department by Bienstock et al. [10]. We suspected that the residents preferred the verbal feedback rather than written because it facilitates two-way communications with prompt discussions and clarifications [11]. The increase in residents’ workload that was unrelated to nuclear medicine during the COVID-19 crisis could be another culprit impacting the responses of the residents because the heavy workload reduced the time that residents could have used to review and comprehend the written feedback provided by the teaching faculty.

Despite evidence supporting verbal interpretation, reporting and feedback, implementation in nuclear medicine poses unique challenges. Since the primary mode of communication in medical imaging is in written formats, residents are required to develop sufficient skills in dictating these written reports [12]. Therefore, we strongly believe that the strategy of written interpretation and reports remains quite necessary. Teaching faculty can be encouraged to engage more in verbal feedback with their trainees. Although ‘on-the-fly’ feedback is generally not feasible for radiology reporting, teaching faculty still can provide feedback to trainees in person after report revisions are completed [13,14].

We speculate that SDR can be a crucial adjunctive tool for nuclear medicine education and residency training, especially during periods of low case volume. While the situation of low case volume due to the COVID-19...
crisis was unanticipated, the trend of a declining population has been seen in many countries and can lead to an unavoidably low case volume. The complex referral and reimbursement systems can also divert cases from some teaching hospitals and further reduce practice cases for residents [15].

Our results emphasize that while SDR is very useful, it is not meant to completely replace the traditional daily readouts. Certain essential skills for residents, such as skills in patient management, cannot be replicated with SDR. Other initiatives such as the utilization of standardized patients may be needed for those skills when case-loads are low [16].

There are a few limitations to consider from our report. First, our data could not infer whether the perception of residents reflected their true skills [17]. To access the real effectiveness of the SDR requires data from standardized evaluation and assessment, which can be a subject for further study. Secondly, we did not provide information on whether teleconferencing implementation during the later phase affected residents’ experiences. Thirdly, although the questionnaires were collected anonymously, the possibility of courtesy bias and response bias remained. Lastly, our survey was conducted during the extremely unique and difficult situation of the COVID-19 crisis. The sudden onset of restrictions did not allow us to conduct a baseline survey on residents’ perceptions and attitudes towards SDR before implementation. The COVID situation also could have negatively altered residents’ physical and psychological well-being, learning capabilities, enthusiasm, and perceptions, and subsequently impacted questionnaire responses.

In conclusion, the SDR may be effective in preserving training quality in nuclear medicine during a period of reduced case volume. From the perspective of our residents, it could mimic case volume and diversity well and could likely mitigate any negative consequences from low case volume on theoretical knowledge, interpretation, and reporting. Targeted case selection, advanced assignment, verbal interpretation, reporting and verbal feedback were perceived as more effective than random case selection, immediate assignment and written interpretation, reporting and written feedback, respectively.

Acknowledgements
The authors would like to thank Stephen J Kerr (https://orcid.org/0000-0002-1919-4525) for statistical consultation in this study. The manuscript also received English editing by the English editing service, Research Affairs, Faculty of Medicine, Chulalongkorn University.

Conflicts of interest
There are no conflicts of interest.

References


Comparing the diagnostic accuracy of PET and CMR for the measurement of left ventricular volumes and ejection fraction: a system review and meta-analysis

Yong Ye\textsuperscript{a}, Ying Yang\textsuperscript{b,*} Jie Gong\textsuperscript{a}, Wen-wen Shao\textsuperscript{a} and Cheng-xin Yu\textsuperscript{a}

\textbf{Background} Cardiac magnetic resonance (CMR) has been recognized as the gold standard for the evaluation of left ventricular (LV) function. Cardiac gated PET allows the simultaneous assessment of LV function with the evaluation of myocardial perfusion and metabolism. But the correlations between PET and CMR remain controversial.

\textbf{Methods} We conducted a systematic electronic search of PubMed, Embase and the Cochrane Library. Forest plot, spearman correlation analysis and Bland-Altman analysis were used to evaluate the correlations between PET and CMR.

\textbf{Results} Pooled analysis of 13 studies showed that PET underestimated left ventricular end-diastolic volumes (LVEDV) [mean difference (MD), $-$15.30; 95% confidence interval (CI), $-$23.10 to $-$7.50; $P<0.001$] and left ventricular end-systolic volumes (LVESV) (MD, $-$6.20; 95% CI, $-$12.58 to 0.17; $P=0.06$) but not left ventricular ejection fraction (LVEF) (MD, $-$0.35; 95% CI, $-$1.75 to 1.06; $P=0.63$). Overall, there were very good correlations between PET and CMR measurements for LVEDV (r, 0.897), LVESV (r, 0.924) and LVEF (r, 0.898). Subgroup analysis indicated that LVEDV $\geq$180 ml and LVEF $<40\%$ reduced the accuracy of PET, especially the measurement of LVEF ($r_{\text{LVEDV} \geq 180} vs. r_{\text{LVEDV} < 180}: 0.821 \text{ vs. } 0.944$; $r_{\text{LVEF} \geq 40\%} \text{ vs. } r_{\text{LVEF} < 40\%}: 0.784 \text{ vs. } 0.901$).

\textbf{Conclusions} Correlations between PET and CMR measurements of LVEDV, LVESV and LVEF were excellent, but these two methods could not be used interchangeably for accurate measurements of LV volume and LVEF in patients with significantly increased LV volume and decreased LVEF. Nucl Med Commun 43: 1143–1154

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\textbf{Introduction} Left ventricular (LV) volume and LV ejection fraction (LVEF) are the most meaningful index of LV function, which is the major predictor of mortality in patients with coronary artery disease (CAD), myocardial infarction (MI) and heart failure [1–3]. So, an accurate assessment of LV functions, and early prevention of LV function dysfunction, is indispensable for the management and risk stratification in patients with cardiovascular diseases [4].

Cardiac magnetic resonance (CMR), providing an accurate evaluation of cardiac structure and function, has been recognized as the gold standard for the evaluation of LV volume and LVEF because of its high spatial and temporal resolution [4,5]. However, this approach is restricted in patients with implanted metal devices, claustrophobic or poor breath-hold. An alternative method for the assessment of LV volume and LVEF are particularly important. Cardiac gated PET with different tracers has been recognized as the most reliable noninvasive tool for the evaluation of myocardial viability, perfusion and metabolism, which allows the simultaneous assessment of LV function [4–6]. But the accuracy and correlations between PET and CMR in the assessment of LV volume and LVEF remain controversial [7–19].

Therefore, we performed a systematic review and meta-analysis of currently available medical literature to assess the accuracy of PET in the evaluation of LV volume and LVEF. In addition, we performed subgroup analysis for different levels of LV volume and LVEF to identify the effect on the accuracy of PET measurements.

\textbf{Materials and methods} 
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2021 without the restriction of language. The keywords applied for computerized searching were positron emission tomography or PET, and cardiac magnetic resonance imaging, cardiac MRI or CMR. The reference lists of trials, systematic reviews and meta-analyses were also manually screened for additional studies that fit our inclusion criteria.

**Inclusion criteria and exclusion criteria**
The inclusion criteria were: (1) LV volume and LVEF had been measured by PET and CMR in the same individuals; (2) data of LV end-diastolic volumes (LVEDV), LV end-systolic volumes (LVESV) and LVEF were available and (3) intervals between PET and CMR were less than 1 month. The exclusion criteria were as follows: (1) conference abstracts were excluded; (2) studies enrolled less than five patients and (3) studies included only PET or CMR.

**Data extraction**
After the removal of duplicates, two authors (Y.Ye and Y.Y.) independently screened the title and abstract, and the candidate list of articles were confirmed by reviewing the full text of the remaining studies based on predefined inclusion criteria. We used a predefined standard data-extraction form to collect information by one author (Y.Ye) and verified by another author (Y.Y.). The information for each trial included: author, disease category, sample size, percentage of prior MI, sex, age, intervals between PET and CMR measurements and the technical characteristics of each imaging procedure. Data of each patient were extracted from scatter plots shown in the articles by GetData Graph Digitizer software. Quality Assessment Tool for Case Series Studies was used to assess study quality [22].

**Statistical analysis**
Review Manager 5.3 was used for all data analyses. We used the fixed-effects model to pool data. Heterogeneity across each meta-analysis was evaluated by $I^2$, values around 25–50%, 50–75% and >75% represented mild, moderate and severe heterogeneity, respectively. Mean and SD of extracted data was calculated, and paired t-test with data provided in the original article was performed to verify the accuracy of extracted data. The strength of agreement between PET and CMR was analyzed using spearman correlation [23,24] by SPSS 25.0 software. Bland-Altman analysis was used to evaluate the degree of agreement between PET and CMR [23,24] by MedCalc software. The limits of agreement (LoA) were calculated from the mean difference ± 1.96 SD of differences [23,24]. $P < 0.05$ was considered statistically significant.

**Results**

**Study characteristics**
Two authors independently screened titles and abstracts of 2701 citations yielded from the electronic search, after removing the duplicate and irrelevant articles, 13 studies met the predefined inclusion criteria and were included in our meta-analysis (Fig. 1). The characteristics of included studies and technical characteristics of each imaging procedure were summarized in Tables 1 and 2. Among these studies, at least five studies [7,8,12,16,17] included only patients with CAD or prior MI. Intervals between PET and CMR ranged from 0 day to 1 month. Seven studies used tracers with [F-18] fluoro-D-glucose (18F-FDG) [7,10–12,14,15,18], two used 15O-CO [13,19], and only one used 13N-ammonia [8], [11C]-acetate [9], 15O-water [16] and 11C-hydroxyephedrine (HED) [17], respectively. Finally, a total of 545 patients simultaneously evaluated LV volume and LVEF and then included...

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**Fig. 1**
Flowchart of literature search and reports selection.
Table 1 Characteristics and quality analysis of thirteen included studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Disease category</th>
<th>Sample size, n</th>
<th>Prior MI n (%)</th>
<th>Male n (%)</th>
<th>Age, year</th>
<th>Interval between two methods, days</th>
<th>Mean LVEF (%)</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yao, et al., 2021 [7]</td>
<td>China</td>
<td>Post MI</td>
<td>76</td>
<td>76 (100.0)</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt;14</td>
<td>28</td>
<td>Good</td>
</tr>
<tr>
<td>Kiko, et al., 2020 [8]</td>
<td>Japan</td>
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<td>51</td>
<td>13 (25.4)</td>
<td>38 (75.4)</td>
<td>61.4±15.6</td>
<td>35–81</td>
<td>Same day</td>
<td>64</td>
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<tr>
<td>Nordström, et al., 2017 [9]</td>
<td>Sweden</td>
<td>Mitral or aortic regurgitation</td>
<td>16*</td>
<td>0 (0.0)</td>
<td>12 (75.0)</td>
<td>35–81</td>
<td>Same day</td>
<td>49</td>
<td>Good</td>
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<tr>
<td>Lücke, et al., 2017 [10]</td>
<td>Germany</td>
<td>Mixed</td>
<td>29</td>
<td>N/A</td>
<td>23</td>
<td>58±17</td>
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<td>8</td>
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<tr>
<td>Hansson, et al., 2016 [11]</td>
<td>Denmark</td>
<td>Moderate-severe aortic valve stenosis</td>
<td>35</td>
<td>N/A</td>
<td>25 (71.4)</td>
<td>68±9</td>
<td>N/A</td>
<td>6</td>
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<tr>
<td>Wei, et al., 2014 [12]</td>
<td>China</td>
<td>Left ventricular aneurysm</td>
<td>96</td>
<td>96 (100.0)</td>
<td>88 (91.7)</td>
<td>35–81</td>
<td>N/A</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>Li, et al., 2014 [13]</td>
<td>China</td>
<td>HF</td>
<td>89</td>
<td>N/A</td>
<td>69 (77.5)</td>
<td>54.7±13.1</td>
<td>Same day</td>
<td>31</td>
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<tr>
<td>Nordström, et al., 2017 [9]</td>
<td>Sweden</td>
<td>Mitral or aortic regurgitation</td>
<td>16a</td>
<td>0 (0.0)</td>
<td>12 (75.0)</td>
<td>35–81</td>
<td>Same day</td>
<td>49</td>
<td>Good</td>
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<td>Lücke, et al., 2017 [10]</td>
<td>Germany</td>
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<td>29</td>
<td>N/A</td>
<td>23</td>
<td>58±17</td>
<td>N/A</td>
<td>8</td>
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<td>Hansson, et al., 2016 [11]</td>
<td>Denmark</td>
<td>Moderate-severe aortic valve stenosis</td>
<td>35</td>
<td>N/A</td>
<td>25 (71.4)</td>
<td>68±9</td>
<td>N/A</td>
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<td>Wei, et al., 2014 [12]</td>
<td>China</td>
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<td>96</td>
<td>96 (100.0)</td>
<td>88 (91.7)</td>
<td>35–81</td>
<td>N/A</td>
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<td>Li, et al., 2014 [13]</td>
<td>China</td>
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<td>89</td>
<td>N/A</td>
<td>69 (77.5)</td>
<td>54.7±13.1</td>
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<td>Nordström, et al., 2017 [9]</td>
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<td>0 (0.0)</td>
<td>12 (75.0)</td>
<td>35–81</td>
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<td>Lücke, et al., 2017 [10]</td>
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<td>29</td>
<td>N/A</td>
<td>23</td>
<td>58±17</td>
<td>N/A</td>
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<td>Hansson, et al., 2016 [11]</td>
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<td>Wei, et al., 2014 [12]</td>
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<td>35–81</td>
<td>N/A</td>
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<td>Li, et al., 2014 [13]</td>
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<td>Nordström, et al., 2017 [9]</td>
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<td>12 (75.0)</td>
<td>35–81</td>
<td>Same day</td>
<td>49</td>
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<td>Lücke, et al., 2017 [10]</td>
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<td>58±17</td>
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<td>Hansson, et al., 2016 [11]</td>
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<td>35</td>
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<td>25 (71.4)</td>
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<td>N/A</td>
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<td>Wei, et al., 2014 [12]</td>
<td>China</td>
<td>Left ventricular aneurysm</td>
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<td>Li, et al., 2014 [13]</td>
<td>China</td>
<td>HF</td>
<td>89</td>
<td>N/A</td>
<td>69 (77.5)</td>
<td>54.7±13.1</td>
<td>Same day</td>
<td>31</td>
<td>Good</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; DCM, dilated cardiomyopathy; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable.

*Two outliers were removed in the scatter plots, so 14 patients' data available.

Table 2 Technical characteristics of each imaging procedure included in studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>PET Tracer</th>
<th>Dose, MBq</th>
<th>Frames/RR</th>
<th>Algorithms</th>
<th>CMR Tracer</th>
<th>Dose, MBq</th>
<th>Frames/RR</th>
<th>Papillary muscles in LV volume</th>
<th>Sequence</th>
<th>Data analysis software</th>
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<tr>
<td>Yao, et al., 2021 [7]</td>
<td>18F-FDG</td>
<td>148–185</td>
<td>8</td>
<td>QGS, ECTB, 4DM</td>
<td>18F-FDG</td>
<td>185</td>
<td>8</td>
<td>N/A</td>
<td>4DM</td>
<td>MASS software</td>
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<tr>
<td>Lücke, et al., 2017 [10]</td>
<td>18F-FDG</td>
<td>330±61</td>
<td>N/A</td>
<td>Corridor 4DM</td>
<td>18F-FDG</td>
<td>330±61</td>
<td>N/A</td>
<td>20</td>
<td>4DM</td>
<td>MASS software</td>
</tr>
<tr>
<td>Hansson, et al., 2016 [11]</td>
<td>18F-FDG</td>
<td>185</td>
<td>8</td>
<td>QGS</td>
<td>18F-FDG</td>
<td>185</td>
<td>8</td>
<td>N/A</td>
<td>N/A</td>
<td>MASS software</td>
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<tr>
<td>Wei, et al., 2014 [12]</td>
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<td>3 MBq/kg</td>
<td>8</td>
<td>QGS, 4DM</td>
<td>18F-FDG</td>
<td>3 MBq/kg</td>
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<td>4DM</td>
<td>MASS software</td>
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<td>Magota, et al., 2013 [14]</td>
<td>18F-FDG</td>
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<td>N/A</td>
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<td>Software package provided by Philips</td>
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<td>N/A</td>
<td>N/A</td>
<td>Gradient echo Simpson’s method</td>
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<tr>
<td>Khorsand, et al., 2003 [18]</td>
<td>18F-FDG</td>
<td>370</td>
<td>8</td>
<td>Simpson’s rule</td>
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<td>370</td>
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<td>N/A</td>
<td>N/A</td>
<td>Gradient echo Simpson’s method</td>
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<tr>
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<td>8</td>
<td>Simpson’s rule</td>
<td>11C-hydroxyephedrine</td>
<td>370</td>
<td>8</td>
<td>N/A</td>
<td>N/A</td>
<td>Gradient echo Simpson’s method</td>
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<tr>
<td>Rajappan, et al., 2002 [19]</td>
<td>11C-hydroxyephedrine</td>
<td>370</td>
<td>8</td>
<td>Threshold-based edge detection</td>
<td>11C-hydroxyephedrine</td>
<td>370</td>
<td>8</td>
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<td>N/A</td>
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<tr>
<td>Slart, et al., 2004 [17]</td>
<td>11C-hydroxyephedrine</td>
<td>370</td>
<td>8</td>
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<td>8</td>
<td>N/A</td>
<td>N/A</td>
<td>Gradient echo Simpson’s method</td>
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<tr>
<td>Schaefer, et al., 2004 [16]</td>
<td>11C-hydroxyephedrine</td>
<td>370</td>
<td>8</td>
<td>Threshold-based edge detection</td>
<td>11C-hydroxyephedrine</td>
<td>370</td>
<td>8</td>
<td>N/A</td>
<td>N/A</td>
<td>Gradient echo Simpson’s method</td>
</tr>
</tbody>
</table>

4D, 4D-MSPECT; BPGS, blood-pool gated SPECT; CMR, cardiac magnetic resonance; ECTB, emory cardiac toolbox; FDG, fluor-D-glucose; HED, 11C-hydroxyephedrine; QGS, quantitative gated SPECT; SSFP, steady-state free precession.
in our meta-analysis. Results of paired t-test between extracted data and data provided in the original article verified the accuracy of the extracted data ($P > 0.05$).

**The correlations between PET and cardiac magnetic resonance measurements of left ventricle volume and left ventricular ejection fraction**

To investigate the correlations between PET and CMR measurements of LV volume and LVEF, we pooled all data from 13 studies including 545 patients to perform an analysis. Compared with CMR, PET underestimated LVEDV by 15 ml (mean difference [MD], −15.30; 95% CI, −23.10 to −7.50; $P < 0.001$), as shown in Fig. 2a. LVESV was underestimated by 6 ml, but with borderline statistical difference (MD, −6.20; 95% CI, −12.58 to 0.17; $P = 0.06$), as shown in Fig. 2b. LVEF measured by PET and CMR had no significant difference (MD, −0.35; 95% CI, −1.75 to 1.06; $P = 0.63$), as shown in Fig. 2c.

Overall, there were very good correlations between PET and CMR measurements of LVEDV ($r = 0.897; P = 0.000$), LVEF ($r = 0.924; P = 0.000$) and LVEF ($r = 0.898; P = 0.000$) in all included 545 patients, as shown in Fig. 3a,c,e. Bland-Altman plots showed that the deviations of PET and CMR measurements of LVEDV, LVESV and LVEF were 20.9 ± 72.9 ml, 12.7 ± 60.7 ml and 0.7% ± 15.4%, respectively, shown in Fig. 3b,d,f.

**The influence of left ventricular ejection fraction (LVEF) on accurate measurements of left ventricle volume and LVEF**

To further determine the influence of LVEF on accurate measurements of LV volume and LVEF, an advanced subgroup analysis was performed. Patients were divided into two groups, including LVEF ≥40% ($n = 204$) and LVEF <40% ($n = 341$). In the mean LVEF ≥40% group, LVEDV, LVESV and LVEF measured by PET and CMR had no significant difference ($P > 0.05$). While in LVEF <40% group, LVEDV (MD, −19.75; 95% CI, −30.19 to −9.32; $P < 0.05$) and LVEF measured by PET and CMR had no significant difference (MD, 0.99%; 95% CI, −0.78 to 2.76%; $P > 0.05$). LVEF measured by PET and CMR had no significant difference (MD, 0.99%; 95% CI, −0.78 to 2.76%; $P > 0.05$). While in LVEDV <180 ml group, LVEF measured by PET and CMR had no significant difference ($P > 0.05$). LVEDV (MD, −10.73; 95% CI, −21.16 to −0.29; $P < 0.05$) and LVEF (MD, −2.64%; 95% CI, −4.96 to −0.32%; $P < 0.05$) were both underestimated. Shown in Fig. 6a-c.

Spearman correlation analysis showed that the correlation between PET and CMR measurements of LVEDV ($r = 0.933$ vs. 0.872), LVEF ($r = 0.955$ vs. 0.903) and LVEF ($r = 0.944$ vs. 0.821) were better in LVEDV <180 ml group than LVEDV ≥180 ml group, especially LVEF, as shown in Fig. 7a,c,e,g,i,k. Bland-Altman plots showed that the deviations of PET and CMR measurements of LVEDV (11.5 ± 44.0 vs. 27.1 ± 84.9) and LVEF (3.5 ± 35.3 vs. 18.9 ± 70.3) were lower in LVEDV <180 ml group than LVEDV ≥180 ml group, shown in Fig. 7b,d,h,j. Deviations of PET and CMR measurements of LVEF (1.7% ± 12.2% vs. 0.1% ± 17.2%) were comparable in LVEDV <180 ml group and LVEDV ≥180 ml group, shown in Fig. 7f,l.

**Discussion**

Our meta-analysis is the first attempt to determine the correlations between PET and CMR measurements of LV volume and LVEF. In the present study, we found: (1) the correlations were excellent between PET and CMR measurements of LV volume and LVEF; (2) LVEF measured by PET and CMR had no significant difference, whereas LVEDV and LVEF were underestimated by 6–15 ml and (3) high LV volume (mean LVEDV ≥180 ml) and low LVEF (mean LVEF <40%) reduced the correlation, and increased deviations between PET and CMR, especially the measurements of LVEF. Hence, PET and CMR could not be used interchangeably for accurate measurements of LV volume and LVEF, especially in patients with significantly increased LV volume and decreased LVEF.

Compared with single photon emission computed tomography (SPECT), the PET imaging system has some unique advantages. First, it has a higher temporal and spatial resolution, and gated acquisition is routinely performed for the assessment of myocardial viability, and thus can simultaneously assess LV function; also, dysfunctional but viable myocardium often shows preserved uptake of 18F-FDG in perfusion defect area, PET may provide more accurate
Fig. 2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
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<td>54</td>
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<td>154</td>
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<td>35</td>
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<td>220.3</td>
<td>90.7</td>
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<tr>
<td>Wei, 2014</td>
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<td>60</td>
<td>96</td>
<td>193</td>
<td>63</td>
<td>96</td>
<td>20.1%</td>
<td>-16.00 [-33.40, 1.40]</td>
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<tr>
<td>Yao 2021</td>
<td>191</td>
<td>90.2</td>
<td>76</td>
<td>254.6</td>
<td>99.8</td>
<td>76</td>
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<td><strong>Total (95% CI)</strong></td>
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<td>100.0%</td>
<td>-15.30 [-23.10, -7.50]</td>
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<td>P</td>
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<td>P</td>
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<td>1.91</td>
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<td>(P = 0.06)</td>
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</table>

Forest plot showing the differences between PET and CMR measurements of LV volume and LVEF. CMR, Cardiac magnetic resonance; LVEF, left ventricular ejection fraction.
LV volume and LVEF parameters than SPECT [12,25,26]. All above, PET measurements for LV functional parameters theoretically had a better correlation with CMR than SPECT. A previous meta-analysis enrolled 164 subjects from nine studies showed a good correlation between ECG-gated SPECT and CMR for LVEDV ($r$, 0.89), LVESV ($r$, 0.92) and LVEF ($r$, 0.87), but substantial errors may occur in individual patients [23]. Another meta-analysis reached
### PET and CMR for the measurement of left ventricular function

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**Fig. 4**

#### Subgroup analysis between LVEF ≥40% and LVEF <40%

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV</td>
<td>Fixed</td>
<td>95% CI</td>
</tr>
<tr>
<td>LVEDV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- LVEDV: LV end-diastolic volume
- LVESV: LV end-systolic volume
- LVEF: left ventricular ejection fraction

**Test for overall effect:**
- Z: 1.82, df = 7 (P = 0.11), F = 66%

**Test for subgroup differences:**
- CHF: 1.58, df = 1 (P = 0.21), F = 36%

---

**Table 1**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PET-EDV</th>
<th>CMR-EDV</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40%</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Legend:**
- CHF: congestive heart failure
a similar result [24]. Our analysis also indicated a good correlation between PET and CMR for LVEDV \( (r, 0.897) \), LVESV \( (r, 0.924) \) and LVEF \( (r, 0.898) \), which is similar to SPECT vs. CMR [23,24]. Besides, a forest plot of 13 studies showed that PET measurements slightly underestimated LVEDV (by 15 ml) and LVESV (by 6 ml), but with wider deviations in both LVEDV (up to 90 ml), LVESV (up to 70 ml) and LVEF (up to 16%).

Several possible reasons may affect the consistency between PET and CMR measurements for LV volume and LVEF. First, in terms of CMR, several studies included papillary muscles as part of LV volume [9,11,15,16], whereas other studies excluded [7,10,12,14,17,19], indicating inconsistent LV border by the gold standard (CMR) between studies, which may contribute part of the difference. Second, compared
Subgroup analysis between LVEDV≥180 ml and LVEDV <180 ml. (a) LVEDV; (b) LVESV; (c) LVEF. LVEF, left ventricular ejection fraction; LVEDV, LV end-diastolic volumes; LVESV, LV end-systolic volumes.
with CMR, the lower temporal and spatial resolution of PET made endocardium and epicardium unclear, which directly affect LV volume measurements. Third, algorithms (QGS, ECTB and 4DM) now used for LV function parameters in PET were developed primarily for SPECT, which may not be fully suitable for PET. More importantly, patients with different statuses may affect the correlation between PET and CMR, such as abnormal cardiac structure (left ventricular aneurysm [12], aortic valve stenosis [11], mitral or aortic regurgitation [9]), abnormal heart size (too large [7,9] or too small [24]), decreased LVEF [7,12,13] and acute stage of myocardial ischemia [24]. Although, PET had good correlations with CMR measurements of LV volume and LVEF, there are still many practical problems for PET use, such as, who chose PET, how to reduce the deviations and
in further studies. Patients with high LV volume or low LVEF usually have different extents of total perfusion defect, viable myocardium and scar, which may be associated with the differences in LV functional measurements between PET and CMR [7,12]. Besides, LVEF in patients with obviously cardiac dysfunction is changeable over time, intervals between PET and CMR ranged from 0 day to 1 month, which may be the reason for the lower correlation of LVEF between PET and CMR. So in patients with high LV volume (mean LVEDV ≥180 ml) and low LVEF (mean LVEF <40%), hybrid PET/MRI is the best choice [10,27,28].

Limitation

Given the nature of our study as a systematic review and meta-analysis, our analyses are limited by the reported data in the original reports. The limitations of our meta-analysis are as follows. First, CMR, as a gold standard for measurements of LV volumes, had inconsistent border delineation between studies, which may affect the correction between PET and CMR. Second, tracers ([18]F-FDG, [15]O-CO, [13]N-ammonia, [15]O-water and HED) for PET used in studies have different myocardial uptake and half-time, which partly affected image quality and volumetric accuracy [29–31]. Third, tracer, software and quality of image employed in the various studies were different, which increased the heterogeneity of enrolled studies. Fourth, LV volumes and LVEF estimation are radiotracer [32], algorithms and software-dependent [33] with radionuclide imaging, but in our meta-analysis, we were unable to extract enough data for subgroup analysis. Finally, the correlation between PET and CMR measurements of LV function in patients with different disease categories should be determined in further studies.

Conclusion

Although excellent correlations for PET and CMR measurements of LV volume and LVEF, PET and CMR could not be used interchangeably for accurate measurements of LV volume and LVEF, especially in patients with significantly increased LV volume and decreased LVEF.

Acknowledgements

C-X.Y. and Y.Ye are responsible for initial study conception and design. Material preparation, data collection and analysis were performed by Y.Ye, Y.Y, J.G. and W-W.S. The first draft of the article was written by Y.Ye, C-X.Y. and Y.Y. All authors revised and implemented the article critically for important intellectual content and approved the final article.

Conflicts of interest

There are no conflicts of interest.

References

The value of the SUV ratio between lymph node and bone marrow in predicting pelvic lymphatic metastasis of patients with locally advanced cervical cancer: an integrated PET/CT study

Ying Liu, Jun Hua, Lisheng Liu, Wei Zhang, Shufan Xu and Xiaoliang Chen

Purpose  This study aimed to evaluate the value of the standardized uptake value (SUV) ratio between lymph nodes and bone marrow (BM) measured by Fluorine-18-fluorodeoxyglucose PET and computed tomography (18F-FDG PET/CT) for predicting pelvic lymph node (PLN) metastasis in patients with locally advanced cervical cancer (LACC).

Materials and methods  A total of 62 patients with pathological stage Ib-Iva cervical cancer who underwent 18F-FDG PET/CT before treatment were reviewed retrospectively. We measured the metabolic and morphological parameters of lymph nodes and primary tumors, bone marrow SUV (SUVBM) and calculated the ratio of lymph nodes maximum SUV (SUVmax) to bone marrow SUV (SUVLN/BM) and the ratio of short-axis diameter to long-axis diameter (Ds/l) of lymph nodes. A receiver operating characteristic (ROC) curve was performed to evaluate the diagnostic efficacy of each parameter.

Results  There were 180 lymph nodes with pathological evidence included in the study. Our results indicated that Ds/l, SUVmax of lymph nodes (SUVLN) and SUVLN/BM were independent risk factors for PLN metastasis in LACC (P<0.05), and SUVLN/BM showed the best diagnostic performance by ROC curve analysis. The SUVBM in the anemia group was significantly higher than that in the nonanemia group (3.05 vs. 2.40, P<0.05); furthermore, false-positive cases decreased when the SUVLN/BM was used as the diagnostic criterion instead of SUVLN, especially in the anemia group. ROC curve analysis showed that the area under the curve value of the combination of SUVLN/BM and Ds/l was 0.884 (P<0.05), which was higher than Ds/l or SUVLN/BM alone.

Conclusions  SUVLN/BM could improve the ability to predicting PLN metastasis in patients with LACC, and the diagnostic efficacy of the combination of SUVLN/BM and Ds/l might be better than that of a single parameter. Nucl Med Commun 43: 1155–1160 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: 18F-FDG PET/CT, locally advanced cervical cancer, metastasis, pelvic lymph node

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Received 8 June 2022 Accepted 16 August 2022

Introduction  Cervical cancer is the fourth most common malignant tumor in women worldwide [1], and more than 60% of the newly diagnosed patients were diagnosed with locally advanced cervical cancer (LACC) [2]. Extra-cervical invasion of cervical cancer is mainly through the lymph node pathway, and the pelvic lymph node (PLN) is the most common metastatic site. The assessment of lymph node by imaging or pathological examination is integrated into the latest International Federation of Gynecology and Obstetrics (FIGO) staging system [3]. Therefore, it is extremely important to predict PLN metastasis accurately for the treatment strategy and prognosis in patients with LACC.

Preoperative evaluation of PLN of cervical cancer mainly depends on imaging examination. Traditional imaging examinations, such as computed tomography (CT) and MRI, usually base the identification of metastatic nodes on node size measurements, a short-axis diameter greater than 10 mm is the most accepted criterion [4]. However, the size of lymph node does not always correlate with their tumor involvement [5,6]. Fluorine-18-fluorodeoxyglucose PET and computed tomography (18F-FDG PET/CT), with the dual advantages of anatomical positioning and functional imaging, has been widely used in the diagnosis, staging and prognosis evaluation of various tumors; recently, it tends to be the best imaging method to detect lymph node metastasis [7]. Some semiquantitative metabolic parameters of 18F-FDG PET/CT, especially the maximum standard uptake value (SUVmax), have proved to be valuable in the diagnosis of lymph node metastasis [8,9]. However, high uptake...
of $^{18}$F-FDG can be also seen in benign or inflammatory lymph node, which has resulted in false-positive results [10–14]. Thus, many researchers turned their attention to other metabolic parameters. For example, some investigators used the SUV ratio of lymph node to the primary tumor, mediastinum or liver to predict mediastinal lymph node metastasis to eliminate the influence of blood glucose, weight, reconstruction technology, noise, as also as background hypermetabolism caused by systemic inflammation or other [15–17]. Similar methods have been used in cervical cancer. For example, a study had shown that the SUV ratio of lymph node to the primary tumor is an independent predictor of cervical cancer recurrence [18]. Another study showed that the SUV ratio of the lymph node to pelvic blood pool was related to extractive recurrence free-survival [19]. There were some studies indicated that increased bone marrow $^{18}$F-FDG uptake was caused by systemic inflammation [20,21] and anemia [22,23]. To our knowledge, vaginal bleeding is the most common symptom in patients with cervical cancer that could result in anemia. But so far, there have been no studies showing that anemia leads to the high uptake of FDG in the lymph node. If we assume that anemia will lead to high FDG uptake in the lymph node, will the SUVLN/bone marrow (BM) have better diagnostic efficacy than the SUV lymph node (SUVLN)?

In addition, some researchers have proposed a ‘combined diagnosis’ method based on $^{18}$F-FDG PET/CT to improve the diagnostic efficiency of lymph node metastasis, and these results proved that the combination of metabolic parameters and morphological parameters can better predict lymph node metastasis for patients with lung cancer [24,25] and cervical cancer [26].

The purpose of this study was to assess the predictive ability of the SUVLN/MV for PLN metastasis in patients with locally advanced cervical cancer, and to explore whether it can reduce false-positive cases; and further evaluate the diagnostic value of the combination of morphological parameters (lymph node diameter based on CT) and metabolic parameters (SUVLN/BM-derived from SUV based on PET); moreover, this study is the first time to apply the ratio of the lymph node SUV max to bone marrow SUV to predict PLN metastasis of cervical cancer.

**Materials and methods**

**Patients**

This retrospective analysis included 62 patients diagnosed with LACC between July 2017 and June 2021, who underwent $^{18}$F-FDG PET/CT examination before receiving any therapy. The inclusion criteria were as follows: (1) LACC confirmed in all patients by cytology or histopathology; (2) radical resection of cervical cancer and pelvic lymph node dissection were performed within 1 month after PET/CT examination; (3) staged IB-IVA according to FIGO stage system (2018) [3] and (4) no systemic inflammation and other tumors. Patients who conducted blood routine examination within 1 week before PET/CT examination were divided into the anemia group and the nonanemia group. Anemia is defined as hemoglobin level <120 g/L in females according to the WHO criteria [27].

**$^{18}$F-FDG PET imaging protocol**

All patients underwent PET/CT scan (Discovery PET-CT 710, GE Healthcare, USA). $^{18}$F-FDG is produced by our medical cyclotron, radiochemical purity >95%. The patients fasted for at least 6h, and the glucose levels in the peripheral blood were <120 mg/dl before $^{18}$FDG injections. The CT and PET data were acquired for the proximal thigh towards the base of the skull, 60 min after the injection of a weight-adjusted dose of 3.70–5.55 MBq/kg. After the initial low-dose CT (120 kV, 100 mA, noise index 18, thickness 3.75 mm), conventional PET imaging with an acquisition time of 2.5 min/bed position in a 3-dimensional (3D) mode was conducted. The images were reconstructed using iterative methods.

**$^{18}$F-FDG PET image analysis**

All PET and CT images were analyzed by volume viewer 4.6 in an AW workstation (GE Healthcare). The morphological and metabolic parameters of the primary lesion and lymph node were measured by two experienced nuclear medicine physicians, such as primary tumor maximum SUV (SUVT), primary tumor metabolic volume (MTVT), primary tumor total glycolysis (TLGT), SUVBM, SUVLN, the maximum diameter of the primary tumor (DT), short-axis diameter of lymph node (Ds) and long-axis diameter of lymph node (Di). To measure FDG uptake of the BM, a volume of interest (VOI) was drawn over the vertebral body of each of five vertebrae (L3-5 and S1-2 spine), unless a pathologic condition such as compression fracture or severe osteoarthritic changes was present. The mean SUV of each VOI was measured using an automatic contour set at 75% of the maximum SUV because the 75% cutoff value of the maximum SUV showed good reproducibility between subjects for measuring the most representative of the lesions. The mean SUV of the four selected vertebrae was calculated and defined as SUVBM [28–30]. SUVLN/T and SUVLN/BM are the SUV max ratios of lymph node to primary lesion and the ratio of lymph node SUV max to SUVBM; Ds/Di is the ratio of short-axis diameter to long-axis diameter of lymph node.

**Statistical analysis**

The semiquantitative parameters of primary tumor and lymph node were quantitative data; The data of normal distribution were expressed as mean ± SD ($\bar{x}$ ± s), and the data of abnormal distribution is expressed as the medians (P25, p75). To compare the statistical difference of
quantitative parameters between the group with lymphonodus metastasis and without lymphonodus metastasis, the t-test was used for normal distribution data, while the Mann-Whitney U test was used for abnormal distribution data. Binary logistic regression analysis was applied to select predictive factors of lymph node metastasis. The receiver operating characteristic (ROC) curve was used to analyze the diagnostic efficacy of PET/CT parameters in lymph node metastasis. All statistical tests were performed using IBM SPSS software, version 22.0, and differences were presumed to be significant when the P value was <0.05.

Results

General characteristics of patients
Among the 62 patients with LACC, the median age was 51.0 (range, 23–68) years. There were 59 cases of squamous cell carcinoma (95.2%) and three adenocarcinomas (4.8%). According to the FIGO stage system, 13 (21.0%) were reported as stage I, 14 (22.6%) stage II, 30 (48.4%) stage III and 5 (8.0%) stage IV. In total 28 patients (45.2%) were confirmed to have metastasis in lymph node through postoperative pathology and 34 (54.8%) have no metastasis in lymph node. The patients’ characteristics were summarized in Table 1.

Lesion-based comparison between metastatic and nonmetastatic lymph node
A total of 180 lymph nodes were identified by pathology in the study, including 80 metastatic lymph nodes and 100 nonmetastatic lymph nodes. The median of Ds, Ds/l, SUVLN, SUVLN/T and SUVLN/BM in metastatic lymph node were significantly higher than those in nonmetastatic lymph node (all P < 0.05). The median of the Ds/l in metastatic lymph node and in nonmetastatic lymph node were 0.80 and 0.70, SUVLN were 3.90 and 2.40 and SUVLN/BM were 1.80 and 0.90, respectively (Table 2).

Diagnostic performance of PET/CT quantitative parameters and combined parameters
The ROC curves analysis (Table 3) revealed that the area under the curve (AUC) value of Ds, Ds/l, SUVLN, SUVLN/T and SUVLN/BM were 0.685 (95% CI, 0.602–0.767), 0.725 (95% CI, 0.646–0.805), 0.787 (95% CI, 0.714–0.853), 0.784 (95% CI, 0.718–0.857) and 0.852 (95% CI, 0.793–0.910), respectively, all P < 0.05, and the cutoff values were 1.05, 0.75, 3.35, 0.25 and 1.45, respectively. The AUC value of the combination of SUVLN/BM and Ds/l was 0.884 (95% CI, 0.832–0.935; P < 0.05), which was higher than Ds/l or SUVLN/BM alone (Fig. 1). The diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the combination of SUVLN/BM and Ds/l were 68.8, 87.5, 78.1, 84.6 and 73.7%, respectively. The AUC value of the combination of SUVLN/BM and Ds/l was greater than Ds or SUVLN/BM alone (Fig. 1). The diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the combination of SUVLN/BM and Ds/l were 75.0, 87.5, 81.3, 85.7 and 77.8%, respectively.

Univariate and multivariate logistic regression model for predicting pelvic lymph node metastasis
The results of the logistic regression model for predicting PLN metastasis are shown in Table 4. Univariate analysis revealed that Ds, Ds/l, SUVLN, SUVLN/T and SUVLN/BM were significantly associated with PLN metastasis, whereas in multivariate analysis, only Ds/l ( odds ratio [OR] = 2.302; 95% CI, 1.205–5.697; P = 0.001), SUVLN (OR = 2.974; 95% CI, 1.386–4.933; P = 0.026), SUVLN/BM (OR, 3.280; 95% CI, 1.696–5.280; P = 0.001) were statistically significant predictors for PLN metastasis.

Patient-based comparison of SUVBM in anemia group and nonanemia group
The average value of SUVBM in the anemia group (n = 20) and nonanemia group (n = 38) were 3.05 and 2.40 (P = 0.01), respectively. When SUVLN/BM and SUVLN were used as diagnostic criteria for PLN metastasis, the number of false-positive diseases was 10 and 22, respectively, of which the number of false-positive diseases in the anemia group was 4 and 13, respectively, and the number of false-positive diseases in the nonanemia group was 6 and 9 respectively (P = 0.26).

Discussion
This study showed that the SUVLN/BM, derived from SUV on PET, is a useful predictor for PLN metastasis in patients with LACC, and may result in the reduction of false-positive cases; the combination of SUVLN/BM and Ds/l derived from lymph node size on CT could improve the diagnostic efficiency of PLN metastasis in patients with LACC.

In our study, SUVLN/BM, the SUV ratio of the lymph node to bone marrow, showed the best diagnostic performance
was to be better than SUVLN in this study, which may both increased the risk of metastasis (HR = 2.974, 3.280; [9]). Our study showed higher SUVLN and SUVLN/BM to distinguish between benign and malignant lymph node metastasis better than the SUV max of lymph node. In another study, Kuo et al. [16] found that lymph node/mediastinal SUV ratio of lymph node to primary tumors, mediastinum or liver was among all parameters. In previous studies, the SUV ratio of lymph node to primary tumors, mediastinum or liver was considered to be more valuable in predicting lymph node metastasis of lung cancer and breast cancer [16,17,31]. For example, in a study involving 136 breast cancer patients, Park et al. [31] found that the SUVmax ratio of lymph node to primary tumor could predict axillary lymph node metastasis better than the SUVmax of lymph node. In another study, Kuo et al. [16] found that lymph node/mediastinal blood pool and lymph node/liver SUV ratios improved the detection of N2 metastases in patients with nonsmall cell lung cancer compared with SUVLN. There are a few similar studies on patients with cervical cancer. Brunette et al. [19] used the normalization of lymph node SUVmax (SUV ratio of lymph node to pelvic blood pool) to predict lymph node metastasis of cervical cancer, and the results showed that the standardized SUV did not increase the diagnostic accuracy, but was related to extractive recurrence free-survival. In addition, a study has shown that SUVLN/T is an independent predictor of cervical cancer recurrence [18]; however, our study showed that SUVLN/T is not an independent predictor of PLN metastasis of cervical cancer. SUVLN (the SUVmax of lymph node) was commonly used to distinguish between benign and malignant lymph node [9]. Our study showed higher SUVLN and SUVLN/BM both increased the risk of metastasis (HR = 2.974, 3.280; P < 0.05), and the diagnostic efficiency of SUVLN/BM was to be better than SUVLN in this study, which may be related to a large proportion of anemia patients in this study. The SUVLN/BM, as a diagnostic index was applied to predict PLN metastasis of cervical cancer for the first time in our study, and more research are needed to confirm the role of SUVLN/BM.

Previous studies have suggested that anemia could cause the FDG uptake of BM [22,23], and this study also confirmed that SUVBM in the anemia group was significantly higher than that in the nonanemia group (P < 0.05). Moreover, false-positive cases decreased when the SUVLN/BM was used as the diagnostic criterion instead of SUVLN for PLN metastasis, and the decreasing degree of false-positive cases in the anemia group was higher than that in the nonanemia group, Unfortunately, there is no statistical difference in the false-positive rate between the anemia group and the nonanemia group with different diagnostic criteria (SUVLN and SUVLN/BM) (P = 0.267) (P = 0.267), whose reason may be attributed to the small sample size of the anemia subgroup. Therefore, more data are needed to affirm this in the future.

Ds/l as a morphological parameter on CT is also a potential parameter to predict lymph node metastasis in this study. Short-axis diameter greater than 10 mm is the most accepted criterion in traditional imaging examination [32,33]. Li et al. [26] hold that although the overall diagnostic efficacy of Ds/l alone is limited it provides a certain contribution to reduce false-negative cases. Ds/l is better

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Table 2: Comparison of parameters on 18F-FDG PET/CT between metastatic and nonmetastatic lymph nodes

<table>
<thead>
<tr>
<th>Variables</th>
<th>LNM (−) (n=100)</th>
<th>LNM (+) (n=80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DT(cm)</td>
<td>4.26 ± 1.39</td>
<td>4.30 ± 1.65</td>
<td>0.915</td>
</tr>
<tr>
<td>SUVmax</td>
<td>15.25</td>
<td>17.00</td>
<td>0.692</td>
</tr>
<tr>
<td>MTVT(cm³)</td>
<td>11.60</td>
<td>131.20</td>
<td>0.052</td>
</tr>
<tr>
<td>TLGT</td>
<td>89.70</td>
<td>1.00</td>
<td>0.121</td>
</tr>
<tr>
<td>SUVBM</td>
<td>2.75</td>
<td>2.45</td>
<td>0.232</td>
</tr>
<tr>
<td>Lymph node</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ds(cm)</td>
<td>0.60 (0.50, 0.80)</td>
<td>0.80 (0.60, 1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ds/l</td>
<td>1.00 (0.90, 1.28)</td>
<td>1.00 (0.80, 1.45)</td>
<td>0.053</td>
</tr>
<tr>
<td>SUVLN</td>
<td>2.40 (1.90, 3.40)</td>
<td>3.90 (2.90, 6.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUVLN/T</td>
<td>0.20 (0.10, 0.20)</td>
<td>0.30 (0.20, 0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUVLN/BM</td>
<td>0.90 (0.70, 1.20)</td>
<td>1.80 (1.20, 2.30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BM, bone marrow; DT, the maximum diameter of the primary tumor; Ds, short-axis diameter of LN; D1, long-axis diameter of LN; LN, lymph node; LNM, lymph node metastasis; MTVT, primary tumor metabolic volume; SUV, standardized uptake value; SUVT, primary tumor maximum SUV; TLGT, primary tumor total glycolysis.

Table 3: Diagnostic performance of 18F-PET/CT quantitative parameters and combined parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>AUC</th>
<th>95% CI</th>
<th>P-value</th>
<th>Cutoff Value</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Accuracy%</th>
<th>NPV%</th>
<th>PPV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ds</td>
<td>0.685</td>
<td>0.602–0.767</td>
<td>&lt;0.001</td>
<td>1.05</td>
<td>30.00</td>
<td>97.50</td>
<td>63.75</td>
<td>92.31</td>
<td>58.21</td>
</tr>
<tr>
<td>D1</td>
<td>0.529</td>
<td>0.437–0.620</td>
<td>0.0553</td>
<td>1.45</td>
<td>25.00</td>
<td>92.50</td>
<td>58.75</td>
<td>76.92</td>
<td>55.22</td>
</tr>
<tr>
<td>Ds/l</td>
<td>0.725</td>
<td>0.648–0.805</td>
<td>&lt;0.001</td>
<td>0.75</td>
<td>68.75</td>
<td>67.85</td>
<td>68.75</td>
<td>68.75</td>
<td>68.75</td>
</tr>
<tr>
<td>SUVLN</td>
<td>0.787</td>
<td>0.714–0.853</td>
<td>0.001</td>
<td>3.35</td>
<td>70.00</td>
<td>72.50</td>
<td>71.25</td>
<td>71.79</td>
<td>70.73</td>
</tr>
<tr>
<td>SUVLN/T</td>
<td>0.784</td>
<td>0.718–0.857</td>
<td>&lt;0.001</td>
<td>0.25</td>
<td>63.75</td>
<td>78.75</td>
<td>71.25</td>
<td>75.00</td>
<td>68.48</td>
</tr>
<tr>
<td>SUVLN/BM</td>
<td>0.852</td>
<td>0.793–0.910</td>
<td>&lt;0.001</td>
<td>1.45</td>
<td>68.75</td>
<td>87.50</td>
<td>76.13</td>
<td>84.62</td>
<td>73.68</td>
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<tr>
<td>Combination</td>
<td>0.884</td>
<td>0.832–0.935</td>
<td>&lt;0.001</td>
<td>1.80</td>
<td>75.00</td>
<td>87.50</td>
<td>81.25</td>
<td>85.71</td>
<td>77.79</td>
</tr>
</tbody>
</table>

AUC, area under the curve; BM, bone marrow; CI, confidence interval; Ds, short-axis diameter of LN; D1, long-axis diameter of LN; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value; SUV, standardized uptake value.
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than DS and becomes the best morphological parameter to predict PLN metastasis of cervical cancer in our study. In our study, the diagnostic efficacy of the combination of SUVLN/BM and Ds/l was better than that of any single parameter. Li et al. [26] revealed the combination diagnosis method that can better predict PLN metastasis for patients with early-stage cervical cancer, and the results coincide with our research. However, their study showed that the combination of primary tumor metabolic parameter and the morphological parameter is helpful to evaluate lymph node metastasis, whereas our study showed the combination of lymph node metabolic parameters and morphological parameters is helpful to evaluate lymph node metastasis. Our study showed that the metabolic parameters of the primary tumor are not related to lymph node metastasis, these differences may be related to different constituent samples, such as tumor stage, pathological type, and so on.

However, this study had several limitations. First, this study is a retrospective study, and it was conducted at a single institution with a limited number of cases and a small proportion of anemia, therefore, prospective, multicenter and large sample studies are essential to further confirm these results. Second, the measurements of metabolic parameters and nodal size were made in every case also including traditional normal-sized nodes, implying a large workload requires a large amount of time.

Conclusion
This study suggested SUVLN/BM, a metabolic parameter derived from SUV on ¹⁸F-FDG PET, could improve the ability to predict PLN metastasis in patients with LACC and might reduce the false-positive cases; the diagnostic efficacy of the combination of the metabolic parameter derived from SUV based on ¹⁸F-FDG PET and the morphological parameter based on CT could better than that of a single parameter.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.
References


Abstracts

British Nuclear Medicine Society Autumn Meeting 2022

Nuclear Medicine Communications 2022, 43: 1161–1162

P01. Use of summed stress score to select patients for stress-only myocardial perfusion imaging

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P02. Left ventricular ejection fraction on IQ-SPECT versus parallel hole collimator

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P03. Comparison of left ventricular ejection fraction (LVEF) from re-projected planar radionuclide ventriculography (RNVG) and a native planar RNVG obtained from solid state cameras

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P04. Nuclear Medicine aiding Paraganglioma diagnosis: Case report.

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P05. Sublingual ectopic thyroid

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P06. The use of F-Choline PET-CT compared to [99mTc]Tc-MIBI Scintigraphy in hyperparathyroidism

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P07. Development of a 3D printed PET-CT anthropomorphic phantom model to mimic human total knee replacement

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P08. Artefacts and pitfalls using novel tracer [18F] PSMA-1007 during PET-CT imaging of prostate cancer patients

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P09. The clinical utility of [18F]-FDG PET-CT in thymic lesions – a single centre retrospective review.

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P10. Optimisation of Clinical [68Ga] PSMA PET Image Quality on a GE Discovery 710 PET-CT Scanner

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P11. Needle stick injury dose estimation from experimental measurements and VarSkin+ software

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P13. Phantom Validation of SPECT-CT Quantification

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P14. Cooking with radiation – Calculation of leaching rates for various foods for Gastric Emptying Studies in Nuclear Medicine

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Robert Leigh, Sarah Cade, Martyn Evans
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P16. Production of patient-based 3D printed phantoms using tissue mimicking solutions

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P17. Modelling aspects of Targeted Auger Therapy using Geant4

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P18. The Role of the Radionuclide Nurse Case Manager

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P20. Modelling Post-Administration Contact Restrictions for [177Lu] PSMA Therapy

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