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Initial experience with positron emission tomography/computed tomography in addition to computed tomography and magnetic resonance imaging in preoperative risk assessment of endometrial cancer patients

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ABSTRACT

Objective: Improved preoperative evaluation of lymph node status could potentially replace lymphadenectomy in women with endometrial cancer. PET/CT was routinely implemented in the preoperative workup of endometrial cancer at St Olav's University Hospital in 2016. Experience with PET/CT is limited, and there is no consensus about the use of PET/CT in the diagnostic workup of endometrial cancer. The aim of the study was to evaluate the diagnostic accuracy of PET/CT compared to standard CT/MRI in identifying lymph node metastases in endometrial cancer with histologically confirmed lymph node metastases as the standard of reference. We especially wanted to look at PET/CT as a supplement to the sentinel lymph node algorithm in the detection of paraaortic lymph nodes.

Study design: A retrospective study included all women undergoing surgery for endometrial cancer from January 2016 through July 2019 at St Olav's University Hospital. Clinical data, results of CT, MRI, and PET/CT, and histopathological results were analyzed.

Results: Among 185 patients included, 27 patients (15 %) had lymph node metastases. 17 (63 %) had pelvic lymph node metastases, one (4 %) had isolated paraaortic lymph node metastases, and 9 (33 %) had lymph node metastases in both the pelvis and the paraaortic region. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT for the detection of lymph node metastases were 63 %, 98 %, 85 %, 94 %, and 93 %, respectively. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CT/MRI were 41 %, 98 %, 73 %, 91 %, and 90 %, respectively ($p = 0.07$). For the 26 pelvic lymph node metastases, PET/CT had a sensitivity of 58 %, compared to 42 % for CT/MRI ($p = 0.22$). PET/CT detected all 10 paraaortic lymph node metastases, for a sensitivity of 100 %, compared to 50 % for CT/MRI ($p = 0.06$).

Conclusions: PET is superior to CT/MRI for detection of lymph node metastases in endometrial cancer, particularly in detecting paraaortic lymph node metastases. The ability of preoperative PET to exclude paraaortic lymph node metastases may strengthen the credibility of the sentinel lymph node algorithm.

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Introduction

Primary surgery for apparent early-stage endometrial cancer includes hysterectomy, bilateral salpingo-oophorectomy, and assessment of regional lymph node involvement. Lymph nodes are the most common site of extrauterine spread [1,2]. Detecting lymph node metastases in endometrial cancer is important for treatment and prognosis [3–6]. It is debated if paraaortic nodes should be removed, and whether comprehensive lymphadenectomy improves prognosis, at the cost of increased complications [3,4,7]. The sentinel lymph node (SLN) strategy has emerged as a compromise between comprehensive lymphadenectomy in high-risk patients and omittance of lymph node removal in low-risk patients, allowing sufficient lymph node assessment in patients of all risk categories [8].

Preoperative imaging provides important guidance in the choice of surgical procedure, especially as detection of suspicious paraaortic lymph nodes entails operation by laparotomy instead of minimally invasive surgery and SLN. Standard preoperative diagnostic tools in endometrial cancer are computed tomography (CT) and magnetic resonance imaging (MRI) [9–12]. The development of positron emission tomography (PET)/CT combines CT with radiolabeled ^{18}F-fluorodeoxyglucose (FDG), potentially allowing detection of small volume disease overlooked on CT and MRI. Since 2016, whole body FDG PET/CT has been included in the preoperative diagnostic workup of endometrial cancer in our hospital. However, experience and consensus about the use of PET/CT in the diagnostic workup of endometrial cancer are limited [9].

The aim of the present study was to evaluate the diagnostic accuracy of PET/CT compared to standard CT/MRI in identifying lymph node metastases in endometrial cancer, and particularly with regard to evaluation of the paraaortic region in candidates for SLN-mapping.

Materials and methods

Patient population

Patients with histologically confirmed endometrial cancer, operated in the period from 2016 through July 2019, were eligible to participate in a retrospective observational study. We compared the ability of preoperative PET/CT versus preoperative CT/MRI to detect lymph node metastases, with histologically confirmed lymph node metastases as the standard of reference. In our hospital, PET/CT was implemented as routine in 2016, and the sentinel lymph node (SLN) mapping algorithm has been used since 2012 [13].

Inclusion criteria were histologically confirmed endometrial cancer, preoperative CT of the thorax, abdomen, and pelvis, MRI of the pelvis, preoperative ^{18}F-FDG PET/CT, pelvic lymph node removal, and histologically confirmed presence of lymph nodes (Fig. 1).

In addition, patients operated between November 2012 through 2015 were included as a reference group, to determine if the addition of PET/CT had any influence on the performance and interpretation of CT/MRI. Patients in the reference group who had a PET/CT scan performed in the preoperative workup of endometrial cancer were excluded.

The patients were preoperatively classified into traditional risk categories, based on histopathological type and grade, and depth of myometrial infiltration assessed by preoperative imaging.

Preoperative imaging

The PET/CT procedure was performed according to the institutional standard with ^{18}F-FDG (4 M Bq/kg) injection following 6 h fasting. Blood glucose was controlled to be <10 nmol/l. PET/CT from the vertex to the middle femur was obtained 60 min after FDG injection. 3D image reconstruction was made using 256 × 256 matrix, 4 mm FWHM, Time Of Flight and Point Spread Function. All studies were performed on Siemens Biograph mCT. The images were assessed by experienced nuclear medicine physicians.

The classification of lymph nodes on PET/CT as imaging-suspicious was based on the presence of focally increased FDG uptake compared to the background uptake in blood and in the liver, and on the size, shape, symmetry and location of the lymph node. The classification of lymph nodes as imaging-suspicious on CT and MRI was based on size, shape and location. According to the clinical pathway for endometrial cancer, the preoperative assessment is completed within 36 days from the time of referral.

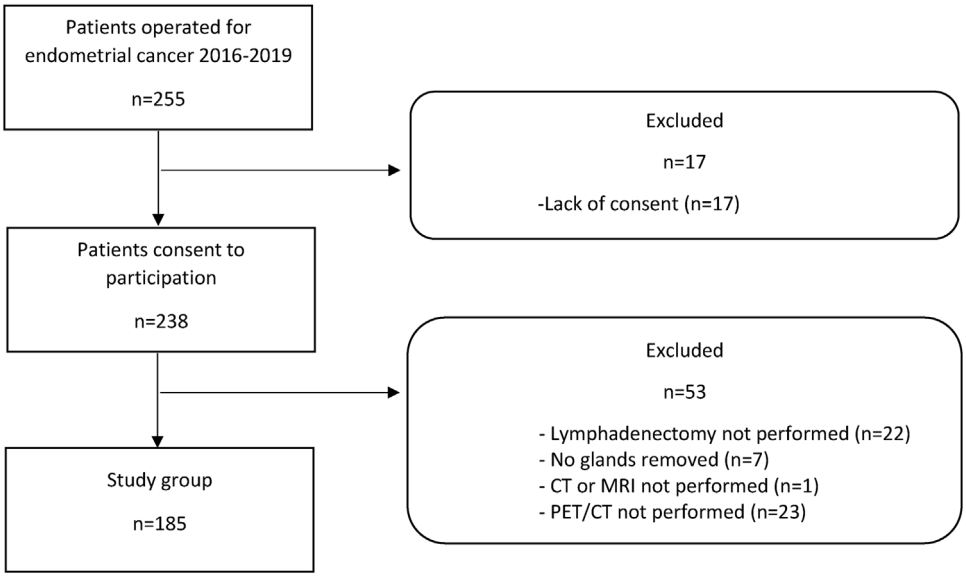

Fig. 1. Study population.

Surgical treatment

All patients underwent hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node removal. Patients with apparent early stage disease underwent robot-assisted laparoscopic operation with pelvic SLN mapping using indocyanine green fluorescence following the Memorial Sloan Kettering surgical algorithm [13,14]. Patients with uterine size >8 cm or imaging-suspicious lymph nodes cranial to the level of the inferior mesenteric artery had hysterectomy, bilateral salpingo-oophorectomy, and conventional lymph node removal (pelvic and eventually paraaortic) without SLN mapping by laparotomy.

Pelvic lymph node removal in addition to SLNs included removal of all imaging-suspicious lymph nodes, perioperative enlarged or fixed lymph nodes, or sampling of lymph nodes from the external iliac and obturator fossa. Some patients underwent additional paraaortic lymph node dissection, performed at the discretion of the surgeon, including imaging-suspicious lymph nodes, or sampling of lymph nodes below the inferior mesenteric artery.

Histopathological evaluation of lymph nodes

The surgical specimens underwent standard histopathological examination after formalin fixation and hematoxylin-eosin staining. For the patients undergoing SLN mapping, routine histology negative SLNs were further examined with ultrastaging, including additional sectioning and immunohistochemistry for cytokeratin. Lymph node metastases were categorized into macro-metastases (>2 mm) and micro-metastases (0.2–2 mm). Isolated tumor cells (<0.2 mm) were not defined as lymph node metastases and the isolated tumor cells category was diagnosed only when the tumor focus was visible in both the hematoxylin-eosin and the adjacent immunohistochemistry sections. The histopathological evaluation was performed by experienced gynecologic oncology pathologists.

Statistics

Patients characteristics were summarized using the median (range) for continuous variables and percentages for categorical variables. The result of the histological evaluation was set as standard of reference for statistical analyses of lymph node metastases. Differences in sensitivity and specificity between PET/CT and CT/MRI were examined using the McNemar exact test. Comparison of lymph node detection with CT/MRI between the study group and the reference group was performed with the Chi square test. For all analyses, p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using International Business Machines Corporation (IBM) Statistical Package for the Social Science (SPSS), version 27.

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK midt 7193/2019).

Results

Patient population

A total of 255 patients underwent primary surgery due to endometrial cancer in the study period. Of the 238 patients who consented to participate, 185 fulfilled the inclusion criteria, constituting the study population (Fig. 1). Demographic and clinical characteristics are given in Table 1.

Table 1
Demographic and clinical characteristics (N = 185).

	Median	Range
Age (years)	69.0	39–88
Body mass index (kg/m^2)	28.1 *	16.6–53.7
Operation time (minutes)	109	65–312
Blood loss (milliliters)	50	0–1920
	N	**Percentage**
Histologic type		
Endometrioid	134	72.4
Serous	20	10.8
Clear cell	9	4.9
Carcinosarcoma	5	2.7
Mixed	8	4.3
Others	9	4.9
FIGO stage		
IA	96	51.9
IB	47	25.4
II	5	2.7
IIIA	8	4.3
IIIB		
IIIC	26	14.1
IV	3	1.6
Blood- or lymph vascular space invasion		
No	142	76.8
Yes	43	23.2
Postoperative chemotherapy		
No	115	62.2
Yes	70	37.8
Operation method		
Robotic with SLN	130	70.3
Robotic without SLN	2	1.1
Laparotomy	53	28.6

* Three missing body mass indexes.

In the study group, 132/185 (71 %) underwent robot-assisted laparoscopic surgery, and 53/185 (29 %) laparotomy. Pelvic lymph node removal with SLN mapping was performed in 130/132 (98 %) of the robot-assisted cases.

Of the 185 patients in the study group, 168 (91 %) had a PET positive uterine tumor. Of the 17 patients with PET negative uterine tumors, 14 had stage 1A, one stage 1B. Two patients had stage 3C due to lymph node spread, both had uterine stage 1A disease, one had PET negative while one had PET positive lymph node metastases.

Prevalence of metastatic disease

The overall metastatic rate was 19 % (35/185).

Prevalence of lymph node metastases

The lymph node metastatic rate was 15 % (27/185). Seventeen (63 %) had pelvic lymph node metastases, 1 (4%) had isolated paraaortic lymph node metastases, and 9 (33 %) had metastases in both regions.

Size of lymph node metastases

The median size of the lymph node metastases was 4.5 mm (0.20–80.0 mm). Fourteen out of 27 (52 %) were macro-metastases and 13/27 (48 %) micro-metastases. Additionally, isolated tumor cells (<0.2 mm) were detected in 12 patients (6%). The characteristics of the patients with lymph node metastases are given in Table 2.

Non-lymphatic metastases

Fifteen patients (8%) had non-lymphatic spread of disease. Eleven had spread of tumor to the ovary or the fallopian tube, the

Table 2
Characteristics of patients with lymph node metastases.

Case	Histology	Grade	Risk category*	Diameter of largest lymph node metastasis (mm)	Location	Metastatic lymph node(s) on PET/CT	Metastatic lymph node(s) on CT/MR	Metastatic lymph node in SLN or non-SLN
1	Endometrioid	1	Low	20	Pelvic	Pelvic	Pelvic	SLN
2	Endometrioid	1	Intermediate	0.3	Pelvic	Negative	Negative	SLN
3	Endometrioid	1	Intermediate	1.5	Pelvic	Negative	Negative	SLN
4	Endometrioid	1	Intermediate	4.5	Pelvic	Negative	Negative	SLN
5	Endometrioid	2	Low	0.6	Pelvic	Negative	Pelvic	SLN
6	Endometrioid	2	Intermediate	0.2	Pelvic	Negative	Negative	SLN
7	Endometrioid	2	Intermediate	0.5	Pelvic	Pelvic	Negative	SLN
8	Endometrioid	2	Intermediate	0.7	Paraaortic	Paraaortic	Negative	Non-SLN***
9	Endometrioid	2	Intermediate	9	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***
10	Endometrioid	3	Intermediate	0.2	Pelvic	Negative	Negative	SLN
11	Endometrioid	3	Intermediate	0.3	Pelvic	Negative**	Negative	SLN
12	Endometrioid	3	Intermediate	12	Pelvic + paraaortic	Pelvic + paraaortic	Negative	Non-SLN***
13	Endometrioid	3	High	6	Pelvic + paraaortic	Pelvic + paraaortic	Negative	Non-SLN***
14	Endometrioid + serous	2	High	5	Pelvic	Pelvic	Pelvic	SLN
15	Endometrioid + serous	3	High	1.5	Pelvic	Pelvic	Pelvic	Non-SLN***
16	Serous		High	1	Pelvic	Pelvic	Pelvic	Non-SLN***
17	Serous		High	17	Pelvic + paraaortic	Paraaortic**	Negative	Non-SLN****
18	Serous		High	18	Pelvic + paraaortic	Pelvic + paraaortic	Negative	Non-SLN***
19	Serous		High	24	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***
20	Serous		High	25	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***
21	Clear cell		High	0.4	Pelvic	Negative	Negative	SLN
22	Clear cell		Inconclusive	42	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***
23	Carcinosarcoma		High	0.9	Pelvic	Negative	Negative	SLN
24	Carcinosarcoma		High	2	Pelvic	Negative	Negative	SLN
25	Carcinosarcoma		High	18	Pelvic	Pelvic	Negative	Non-SLN***
26	Carcinosarcoma		High	29	Pelvic	Pelvic	Pelvic	Non-SLN***
27	Neuroendocrine		High	80	Pelvic + paraaortic	Pelvic + paraaortic	Pelvic + paraaortic	Non-SLN***

* Risk category: Based on histopathological type and grade, and depth of myometrial infiltration (assessed by preoperative imaging).
** Tumor PET negative.
*** Operated by laparotomy.
**** Converted to laparotomy.

remaining four patients to the omentum, lung/skeleton, small bowel serosa, or the pouch of Douglas. Preoperative detection of non-lymphatic metastases was 5/15 (33 %) with PET/CT compared to 4/15 (27 %) with CT/MRI.

Lymph node findings on pre-operative imaging

The sensitivity to detect metastatic nodes was higher for PET/CT than for CT/MRI. Lymph node metastases were detected in 17/27 (63 %) patients on PET/CT, compared to 11/27 (41 %) on CT/MRI (p = 0.07). The sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratios for PET/CT and CT/MRI are presented in Table 3. Of the 26 patients with pelvic lymph node metastases, these metastases were detected in 15 (58 %) on PET/CT, and in 11 (42 %) on CT/MRI (p = 0.22). Of the 10 patients with paraaortic lymph node metastases, these metastases were detected in 10 (100 %) on PET/CT, and 5 (50 %) on CT/MRI (p = 0.06) (Fig. 2). One patient had isolated paraaortic lymph node metastases which was detected on PET/CT, but not on CT/MRI.

Table 3
Preoperative detection of lymph node metastases on PET/CT and CT/MRI by histopathology in removed lymph nodes in the study group.

		Histopathology		Total
		Positive	Negative	
PET/CT	Positive	17	3	20
	Negative	10	155	165
CT/MRI	Positive	11	4	15
	Negative	16	154	170
	Total # (%)	**27 (15)**	**158 (85)**	**185**

PET/CT: Sensitivity 63.0 %. Positive predictive value 85.0 %. Specificity 98.1 %. Negative predictive value 93.9 %. Accuracy 93.0 %. Positive likelihood ratio 32.5, negative likelihood ratio 0.38.
CT/MRI: Sensitivity 40.7 %. Positive predictive value 73.3 %. Specificity 97.5 %. Negative predictive value 90.6 %. Accuracy 89.2 %. Positive likelihood ratio 16.1, negative likelihood ratio 0.61.

Size of lymph node metastases

The median size of metastases detected on PET/CT was 17.0 mm (0.5–80.0 mm) and on CT/MRI 20.0 mm (0.6–80.0 mm). Macro-metastases were more often detected on PET/CT: 13/14 (93 %), compared to CT/MRI: 8/14 (57 %), (p = 0.06). There was no difference in the detection of micro-metastases, 4/13 (31 %) on PET/CT versus 3/13 (23 %) on CT/MRI (p = 1.0).

The median size of lymph node metastases *not* detected was 0.5 mm (0.2–4.5 mm) for PET/CT and 1.2 mm (0.2–18.0 mm) for CT/MRI.

Among the 12 cases of isolated tumor cells in lymph nodes, all were CT/MRI negative, while one (8%) was PET positive.

Detection of lymph node metastases in different risk categories

The distribution of preoperative uterine risk categories was 39 % low-risk, 30 % intermediate-risk and 28 % high-risk. Six patients could not be categorized into a preoperative risk group due to insufficient preoperative histology. The presence of lymph node metastases in the different risk groups, and the detection rates for PET/CT and CT/MRI are shown in Table 4.

Detection in the SLN group

In the patients treated with the SLN algorithm, the sensitivity, specificity and accuracy for PET/CT was 29 %, 98 %, and 91 %, compared to 21 %, 98 %, and 90 % for CT/MRI.

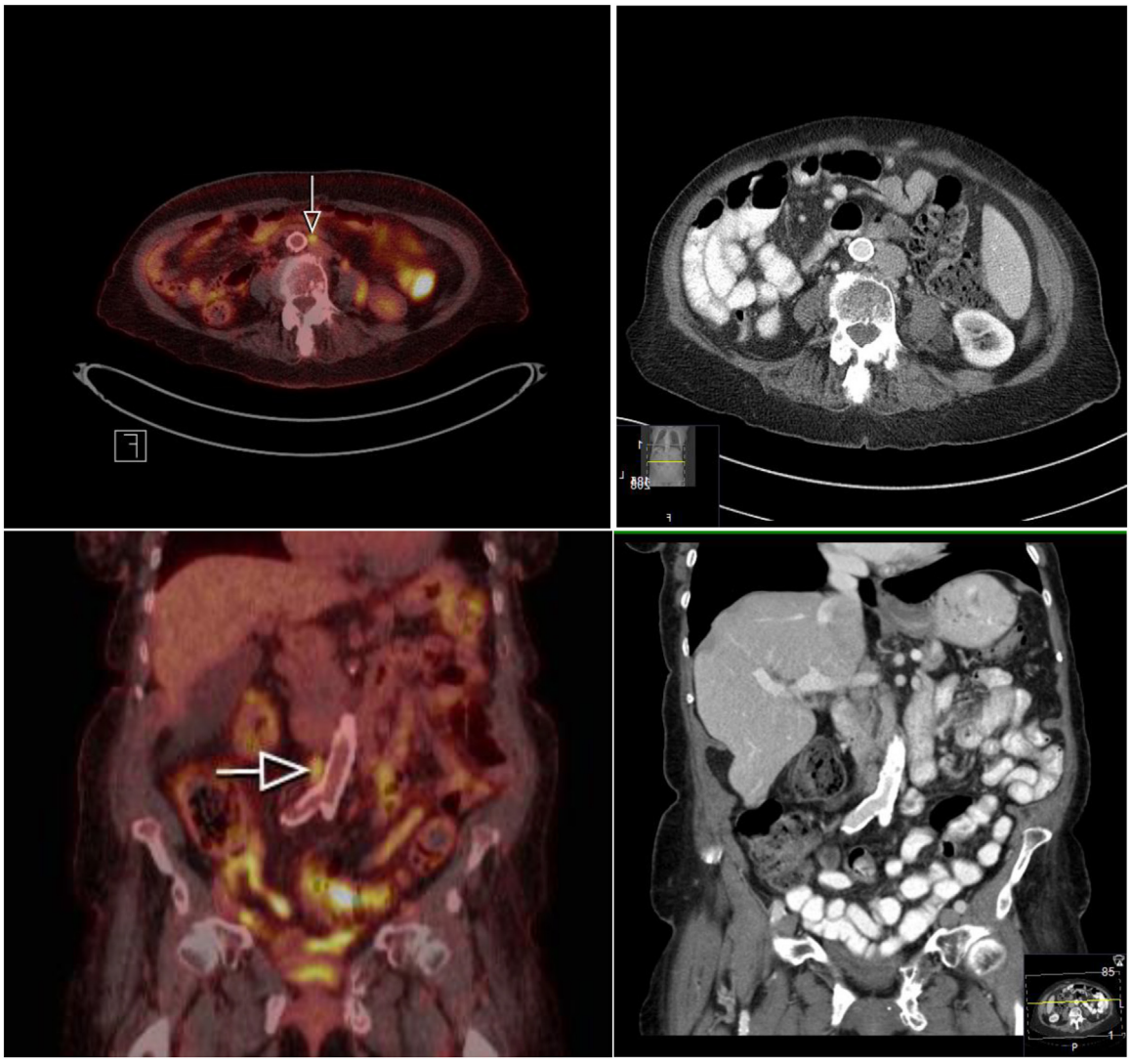

Fig. 2. PET/CT images (left) showing metastatic paraaortic lymph node overseen on CT (right). The pictures are published with the patient's consent.

Table 4
The distribution of risk categories, corresponding rates of lymph node (LN) metastases and detection by CT/MRI vs PET/CT.

Preoperative risk category	Number of patients (%)	Number with LN metastases (%)	Number of LN metastases detected on PET/CT (%)	Number of LN metastases detected on CT/MRI (%)
Low	73 (39)	2 (3)	1 (50)	2 (100)
Intermediate	55 (30)	10 (18)	4 (40)	1 (10)
High	51 (28)	14 (27)	11 (79)	7 (50)
Missing	6 (3)	1 (17)	1 (100)	1 (100)
Total	185	27		

Detection rate in the reference group

Lymph node metastases were detected in 36 of those 173 patients (21 %) operated before 2016 (reference group). There was no statistically significant difference in the detection of lymph node metastases on preoperative CT/MRI between the reference group and the study group; 20/36 (56 %) versus 11/27 (41 %), respectively (p = 0.244).

Discussion

The present study indicates a diagnostic value of PET/CT in the preoperative work-up of endometrial cancer patients, especially in detecting paraaortic lymph node metastases. Several studies have suggested a prognostic benefit of surgical removal of metastatic paraaortic lymph nodes [15–17]. In our study, all paraaortic

metastases were detected on PET/CT, but only half of them on CT/MRI. Most of the patients with paraaortic lymph node metastases also had pelvic lymph node metastases, but one patient had isolated paraaortic lymph node metastases, only detected on PET/CT.

We found a sensitivity of 63 % and a specificity of 98 % to detect lymph node metastases with PET/CT. Chang et al. found a similar sensitivity of 63 % and a specificity of 95 % in a meta-analysis of 243 endometrial cancer patients [18]. In a meta-analysis including 861 patients, Bollineni et al. found a sensitivity of 72 % and a specificity of 94 % [19].

The identification of metastatic lymph nodes on both CT and MRI is based on measurements of node size. A common threshold for considering a lymph node metastatic is 8−10 mm [11,20–25]. However, it is a challenge to differentiate metastatic lymph nodes from benign reactive nodes of similar size, and metastatic lymph nodes of normal size and enlarged reactive lymph nodes can be misclassified [23,25]. PET/CT provides functional data due to increased glucose metabolism in malignant cells, and therefore PET/CT is potentially able to detect smaller lymph node metastases than CT and MRI.

We found a relatively high rate of false negative lymph node metastases on PET/CT. Current PET/CT technology has low spatial resolution and can only detect lesions with a sufficient number of metabolically active malignant cells [9,18,26,27]. The mean value of spatial resolution in PET is 5 mm [21,23,28]. This limited spatial resolution makes the presence of metastases in small lymph nodes hardly detectable.

In our study, PET/CT detected 93 % of the macro-metastases and 31 % of the micro-metastases. In comparison, CT/MRI detected 57 % of the macro-metastases and 23 % of the micro-metastases. The median size of the lymph node metastases *not* detected on PET/CT was 0.5 mm, whereas the median size of the lymph node metastases not detected on CT/MRI was 0.9 mm. Kitajima et al. found a detection rate on PET/CT of only 12.5 % in metastatic lymph nodes measuring 4 mm or less, but 100 % when the lymph nodes were 10 mm or larger [21]. Budak et al. found a 0% detection rate for lymph node metastases 4 mm or less, but a 100 % detection rate for lymph node metastases 10 mm or larger [20].

The relatively high rate of false negative PET/CT results may partly be related to the SLN ultra-staging technique, which allows detection of micro-metastatic deposits too small for detection on PET/CT [29]. Most patients in our study underwent robot-assisted laparoscopic surgery with sentinel lymph node removal and ultra-staging. Tanaka et al. compared the combined diagnostic accuracy of FDG-PET/CT and sentinel lymph node biopsy in the prediction of pelvic lymph node metastases in endometrial cancer. They found that PET/CT had lower sensitivity for lymph node metastases compared to sentinel node biopsy (36.8 % versus 57.9 %), especially in patients with small metastatic lymph nodes [30]. However, the sensitivity was higher for PET/CT than for sentinel node biopsy in lymph node metastases $\geq$5 mm (62.5 % versus 37.5 %). The limited sensitivity of PET/CT in detection of metastatic lymph nodes in low-/intermediate-risk patients in our study emphasizes the importance of SLN in endometrial cancer patients.

The omittance of paraaortic nodes in SLN algorithms is a potential limitation. Taskin et al. recently evaluated the complementary role of PET/CT in the sentinel lymph node algorithm in high-risk patients. In their study of 38 patients, two out of 10 patients with lymph node metastases had isolated paraaortic metastases diagnosed only on PET/CT [31].

Limitations of our study include the retrospective study design and few patients with lymph node metastases. Further, evaluation of PET/CT and CT/MRI was performed unblinded by the radiologists. To address this, we investigated the detection of lymph node metastases by CT/MRI before and after PET/CT was introduced, and did not find improved CT/MRI detection after the introduction of PET/CT.

In our study we have performed PET only in combination with CT (PET/CT) and used ^{18}F-FDG as tracer. Studies on PET/MRI and use of other tracers have shown various results and should be further explored [10,32–39].

Conclusion

In conclusion, PET/CT was superior to CT and MRI in the detection of lymph node metastases in endometrial cancer. PET/CT has a diagnostic value, in particular in detecting paraaortic lymph node spread in endometrial cancer patients that are candidates for minimal access surgery with SLN mapping. It is reasonable to continue performing PET/CT in the preoperative evaluation of patients with endometrial cancer.

Declaration of Competing Interest

The authors report no declarations of interest.

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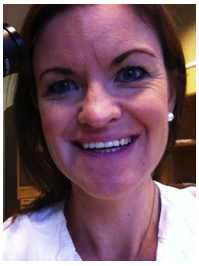

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