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ORIGINAL ARTICLE

Performance of FDG-PET/CT in the diagnosis of recurrent endometrial cancer

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Abstract
Objective To evaluate the accuracy of integrated positron emission tomography and computed tomography (PET/CT) using 18-F-fluorodeoxyglucose (FDG), compared with PET alone, in the diagnosis of suspected endometrial cancer recurrence.
Methods Thirty women who had undergone primary surgery for histopathologically proven endometrial cancer with suspected recurrence because of clinical, cytological, biochemical, and/or radiological findings were enrolled in this study. PET and integrated PET/CT images were evaluated by two different experienced radiologists by consensus for each modality. A final diagnosis of recurrence was confirmed by histopathology, other imaging and clinical follow-up for longer than 1 year. The statistical significance of differences between PET and PET/CT was determined by the McNemar test.
Results Patient-based analysis showed that the sensitivity, specificity, and accuracy of PET/CT were 93% (14/15), 93% (14/15), and 93% (28/30), respectively, whereas for PET, the corresponding data were 80% (12/15), 80% (12/15), and 80% (24/30), respectively (P = 0.479, 0.479, and 0.134, respectively). CT from PET/CT resolved the false-positive PET results because of hypermetabolic activity of benign inflammatory lesions and physiological variants and moreover detected lung metastasis and para-aortic lymph node metastasis that PET missed. However, tiny para-aortic lymph node metastasis could not be detected even with PET/CT.
Conclusions Integrated FDG-PET/CT is a useful complementary modality for providing good anatomic and functional localization of sites of recurrence during follow-up of patients with endometrial cancer.

Keywords Endometrial cancer · Recurrence · ^{18}F-FDG · PET/CT

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Introduction

Despite continuing advances in surgical and nonsurgical therapeutic strategies, cancer recurrence and distant metastasis following the initial treatment are often a major problem for women with gynecological cancers. Early and accurate detection of recurrence in patients with endometrial cancer has an important influence on therapy, and selection of appropriate treatment strategies can be expected to have a significant impact on overall survival [1–3]. The measurement of tumor markers has been used for screening and follow-up. However, benign gynecological as well as benign and malignant nongynecological conditions are known to be associated with elevated tumor markers, and the elevated tumor markers do not provide any information about the site of recurrence [4].

In gynecological malignancies, conventional morphological imaging modalities, including radiography, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are widely used to diagnose recurrent lesions. However, when used alone, these conventional imaging modalities are poor at visualizing small disseminated lesions, small lymph node metastases, and post-operative or post-radiation changes [5–9].

In the late 1990s, positron emission tomography (PET) with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG), which is based on the increased utilization of glucose by malignant cells and thereby high uptake of glucose, has opened a new field in clinical imaging. It is possible to diagnose cancer recurrence and distant metastasis by PET in the preclinical stage before it becomes evident on conventional diagnostic imaging modalities. However, PET lacks anatomic information, and precise localization of the suspicious lesions may be difficult. Early diagnosis of cancer recurrence by PET is also impaired by the presence of increased uptake of physiological, nonpathological, or inflammatory states [10, 11].

Integrated PET/CT, in which a full-ring-detector clinical PET scanner and multidetector row helical CT scanner are combined, makes it possible to acquire both metabolic and anatomic imaging data using a single device in a single diagnostic session and provides precise anatomic localization of suspicious areas of increased FDG uptake [12].

Several studies describing the usefulness of FDG-PET/CT for the diagnosis of recurrent uterine cervical and ovarian cancers have been published [13–15]. For endometrial cancers, however, few studies have described the usefulness of FDG-PET for post-treatment evaluation [16–18], and there have been no reports on PET/CT. The objective of the present study was to assess the diagnostic accuracy of FDG-PET/CT, as compared with PET alone, for the follow-up of patients previously treated for endometrial cancer.

Materials and methods

Patients

Thirty consecutive patients (age range 38–82 years, mean age 59 years) who had undergone surgery for histopathologically proven endometrial cancer with suspected recurrence underwent PET/CT examinations at our institution between April 2005 and June 2006, which was approved by the institutional review board. An informed consent was obtained from each patient after the nature of the procedures had been fully explained; 14 patients had undergone surgery and chemotherapy, 10 surgery alone, and 6 surgery and chemoradiotherapy. Further details of these patients and their demographic data are listed in Table 1. PET/CT examinations were performed

Table 1 Patient and tumor characteristics

Characteristics	Value	Percentage
Age (years)		
Median	59	
Range	38–82	
FIGO stage (no. of patients)		
I	7	23
II	10	33
III	12	40
IV	1	3
Original histology (no. of patients)		
Endometrioid adenocarcinoma	27	90
Serous papillary carcinoma	1	3
Adenosquamous cell carcinoma	2	7
Tumor nuclear grade (no. of patients)		
I	5	17
II	16	53
III	9	30
Treatment (no. of patients)		
Surgery	10	33
Surgery + chemotherapy	14	47
Surgery + chemoradiotherapy	6	20
Time from initial surgery to PET/CT study (months)		
Median	21	
Range	8–60	
Time from last treatment to PET/CT study (months)		
Median	14	
Range	6–72	

FIGO International Federation of Gynecology and Obstetrics, *PET/CT* integrated positron emission tomography and computed tomography

at the time of follow-up whereby no treatment was carried out for at least 6 months prior to PET/CT. Recurrence was suspected on the basis of elevated levels of tumor markers [carbohydrate antigen (CA) 125 and/or CA 19-9, $n = 12$ patients), physical examination ($n = 9$), abnormal findings on conventional morphological imaging modality studies including CT and/or MRI ($n = 5$), and both elevated tumor marker levels and conventional imaging findings ($n = 4$).

FDG-PET/CT study

Twenty-four patients underwent one PET/CT examination, and six underwent two. Whole-body imaging was performed using combined PET/CT scanners (Biograph, Sensation 16, Siemens Systems, Erlangen, Germany). Whole-body CT covered a region ranging from the meatus of the ear to the mid thigh. The technical parameters of the 16-detector row helical CT scanner were a gantry rotation speed of 0.5 s, a table speed of 24 mm per gantry rotation, 120 kVp, and 40 mA, 5 mm slice thickness, and no specific breath-holding instructions. No oral or intravenous contrast material was administered on CT scan. No bladder catheterization was performed. The PET component of the combined imaging system has an axial view of 16.2 cm (per bed position) with an interslice spacing of 3.75 mm in one bed position and provided an image from the meatus of the ear to the midthigh with six to seven bed positions. The transaxial field of view and pixel size of the PET images reconstructed for fusion were 58.5 cm and 4.57 mm, respectively, with a matrix size of 128×128. To avoid artifact by urinary tract, patients were asked to drink 1000 ml of water orally 1–2 h prior to the image acquisition and void just before starting the acquisition. No urinary bladder catheterization was used. After at least 4 h of fasting, patients received an intravenous injection of 4.0 MBq/kg body weight of FDG. The blood-glucose levels were checked in all the patients before FDG injection and no patients showed a blood-glucose level of more than 160 mg/dl. About 50 min later, CT images were acquired for 30 s. A whole-body emission PET scan for the same axial coverage was performed with 3-min acquisition per bed position using a three-dimensional acquisition mode. Attenuation-corrected PET images were reconstructed with an ordered-subset expectation maximization iterative reconstruction algorithm (eight subsets and three iterations). PET, CT, and fused PET/CT images were generated for review on a computer workstation (AZE Virtual Place Version 3.0035).

Data interpretation and image analysis

The PET/CT images were retrospectively interpreted by the consensus of two experienced radiologists (readers A and B with 3 years and 5 years of experience in PET/CT, respectively) who had no knowledge of the other imaging results or of the clinical data. Diagnostic ability was determined on a patient basis and also on a lesion location basis (local, various sites of metastasis such as lymph nodes, peritoneum, bone, liver, and lung). Semiquantitative analysis was not done in this study. Lymph nodes with increased FDG uptake were deemed positive for metastatic spread, even if they were less than 1 cm in short-axis diameter.

Positron emission tomography images were retrospectively assessed in consensus by two experienced radiologists (readers C and D with 2 years and 8 years of experience in PET, respectively) who had knowledge neither of the other imaging results nor of the clinical data. PET images were viewed in coronal, axial, and sagittal sections as is typically performed during clinical interpretation of these images. When focal ^{18}F-FDG uptake, with intensity higher than that of surrounding tissues, was seen in areas unrelated to physiological or benign processes, it was defined as recurrence.

Computed tomography and/or MRI was performed within 2 weeks of the PET/CT scan in 15 patients and interpreted by at least two board-certified radiologists. However, the parameter conditions such as target range, slice thickness, and the use of intravenous contrast material varied in individual studies as indicated.

The final diagnosis was obtained from the results of histopathological examination ($n = 13$), or clinical follow-up for periods longer than 1 year (range 12–25 months, mean 16 months) on the basis of tumor marker levels and contrast-enhanced CT and/or MRI findings ($n = 9$), tumor marker levels and PET/CT findings ($n = 6$), and tumor marker levels ($n = 2$).

Statistical analysis

We performed a patient-based and lesion-based analysis of the PET/CT and PET-alone interpretations on the consensus verdict in general. Patient-based sensitivity, specificity, and accuracy were calculated using standard statistical formulas, and 95% confidence interval (95% CI) and determined among PET/CT and PET-alone interpretations by the McNemar test. P values less than 0.05 were considered to be statistically significant.

Table 2 Patient-based results

TP	FN	TN	FP	Sensitivity (%), 95% CI	Specificity (%), 95% CI	Accuracy (%), 95% CI
PET						
12	3	12	3	80.0 59.8–100	80.0 59.8–100	80.0 67.2–92.8
PET/CT						
14	1	14	1	93.3 80.7–100	93.3 80.7–100	93.3 84.4–100

TP true positive, *FN* false negative, *TN* true negative, *FP* false positive

Results

In 15 (50%) of the 30 patients, recurrence and distant metastasis were confirmed by pathological examinations ($n = 12$) and clinical follow-up study ($n = 3$). On patient-based analysis, PET/CT interpretation was true positive in 14 of the 15 patients with recurrence and true negative in 14 of the 15 patients without recurrence, whereas PET interpretation was true positive in 12 of the 15 patients with recurrence and true-negative in 12 of the 15 patients without recurrence. Thus, on patient-based analysis, the sensitivity, specificity, and accuracy of PET/CT were 93.3% (95% CI, 80.7%–100%), 93.3% (95% CI, 80.7%–100%), and 93.3% (95% CI, 84.4%–100%), respectively, whereas those of PET were 80.0% (95% CI, 59.8%–100%), 80.0% (95% CI, 59.8%–100%), and 80.0% (95% CI, 67.2%–92.8%), respectively (Table 2). Although PET/CT interpretation yielded higher diagnostic results than PET-alone interpretation, the difference was not statistically significant ($P = 0.479$ in sensitivity or specificity, $P = 0.134$ in accuracy; McNemar test) because of the small sample size.

On lesion analysis, PET/CT revealed only one false-negative case and one false-positive case, whereas PET revealed three false-negative cases and five false-positive cases (Table 3; Figs. 1, 2, 3). One false-negative PET/CT case was a missed para-aortic lymph node metastasis measuring 6 mm, which was subsequently confirmed by follow-up PET/CT and surgery. One false-positive PET/CT case was an over-diagnosed Th6 vertebra bone metastasis owing to focal moderate FDG accumulation at PET and osteolytic degenerative change at CT, which were confirmed not to be a malignancy by bone biopsy and follow-up MRI. Three false-negative PET cases comprised two cases of para-aortic lymph node metastases measuring 6 mm and 11 mm and one case of tiny lung metastases, smaller than 1 cm (Fig. 3). Five false-positive PET cases were as follows: one case of physiological FDG uptake in the intestine that was misinterpreted as peritoneal dissemination, one case of physiological FDG uptake in the intrapelvic vessels that was misinterpreted as pelvic lymph node metastasis, one case of physiological and reactive FDG uptake in the mediastinal and hilar lymph nodes that was misinterpreted as lymph node metastasis, one case of pulmonary pneumonia that was misinterpreted as lung metastasis, and one case of degenerative vertebra bone change that was misinterpreted as bone metastasis. In short, of the three false negatives with PET, PET/CT correctly identified two lesions as true positive, and of the five false positives with PET, PET/CT correctly identified four lesions as true negative.

Table 3 Lesion-based results

Site	TP	FN	TN	FP
Lung				
PET	3	1	25	1
PET/CT	4	0	26	0
Liver				
PET	2	0	28	0
PET/CT	2	0	28	0
Bone				
PET	1	0	28	1
PET/CT	1	0	28	1
Pleura and peritoneum				
PET	3	0	26	1
PET/CT	3	0	27	0
Supraclavicular LN				
PET	2	0	28	0
PET/CT	2	0	28	0
Mediastinal and hilar LN				
PET	2	0	27	1
PET/CT	2	0	28	0
Para-aortic LN				
PET	2	2	26	0
PET/CT	3	1	26	0
Pelvic LN				
PET	4	0	25	1
PET/CT	4	0	26	0
Inguinal LN				
PET	1	0	29	0
PET/CT	1	0	29	0

LN lymph node

Discussion

To our knowledge this is the first study to investigate the added diagnostic value of PET/CT over PET for diag-

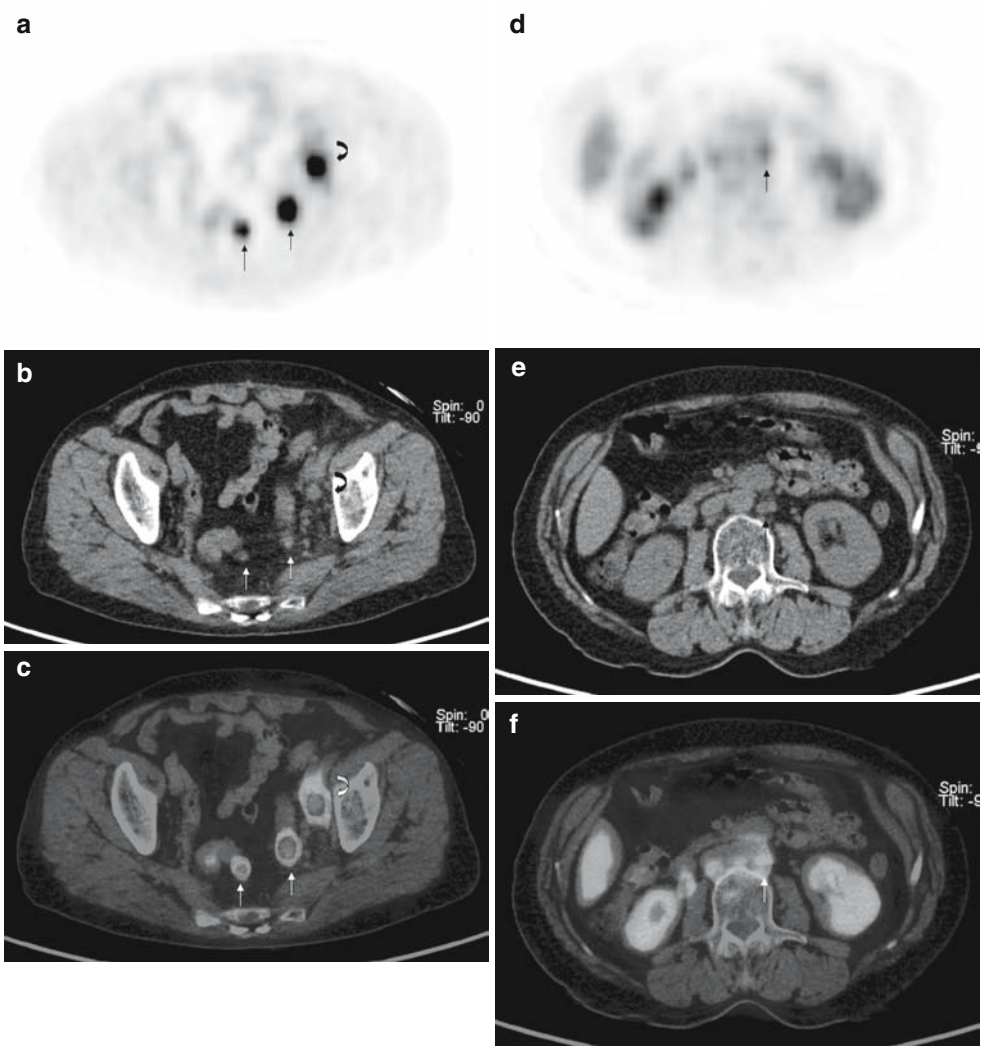

Fig. 1 A 73-year-old woman with initial International Federation of Gynecology and Obstetrics (FIGO) stage II b A with sigmoid colon mesenteric disseminations and para-aortic and pelvic lymph node metastases. Axial positron emission tomography (PET, **a**), computed tomography (CT, **b**), and PET/CT (**c**) showing two small sigmoid colon mesenteric disseminations (*arrows*) and a left internal iliac lymph node metastasis (*curved arrow*). Axial PET (**d**), CT (**e**), and PET/CT (**f**) showing para-aortic lymph node metastasis (*arrow*)

nosing recurrence of endometrial cancer. PET/CT tended to improve the restaging accuracy when compared with PET alone by slightly raising all of sensitivity, specificity, and accuracy. The difference, however, did not reach statistical significance, which might be attributed to the relatively small patient group.

Three groups have investigated the usefulness of FDG-PET for postoperative or post-therapy surveillance of patients with endometrial cancer. Belhocine et al. [16] performed 41 FDG-PET examinations in 34 women with previously treated endometrial cancer. They found the sensitivity, specificity, and accuracy to be 96%, 78%, and 90%, respectively. One false-negative result was microscopic lung metastases revealed by thoracic CT and three false-positive results were benign tumors, inflammatory post-therapy change, and physiological retention of the tracer in the urinary system or bowels. Saga et al. [17] performed 30 FDG-PET examinations in 21 postoperative patients with endometrial cancer and found that FDG-PET had a sensitivity of 100%, a specificity of 88%, and an accuracy of 93% with the help of anatomic information provided by CT and/or MRI. Four false-positive PET results comprised three cases of physiological uptake in the intestine that was misinterpreted as dissemination of lymph node metastases, and one case of heterogeneously increased uptake in the bone marrow following granulocyte-colony stimulating factor administration for chemotherapy-induced neutropenia that was misinterpreted as bone metastasis. Chao et al. [18] performed 60 FDG-PET examinations in 49 women with histologically confirmed endometrial cancer, among which 27 examinations were performed for primary staging and 33 for post-therapy surveillance or restaging on relapse. The sensitivity of FDG-PET alone or FDG-PET plus MRI/CT for detecting lesions overall was significantly higher than that of MRI/CT alone in the 60 scans. FDG-PET had a negative impact in three patients undergoing recurrence surveillance, or staging after

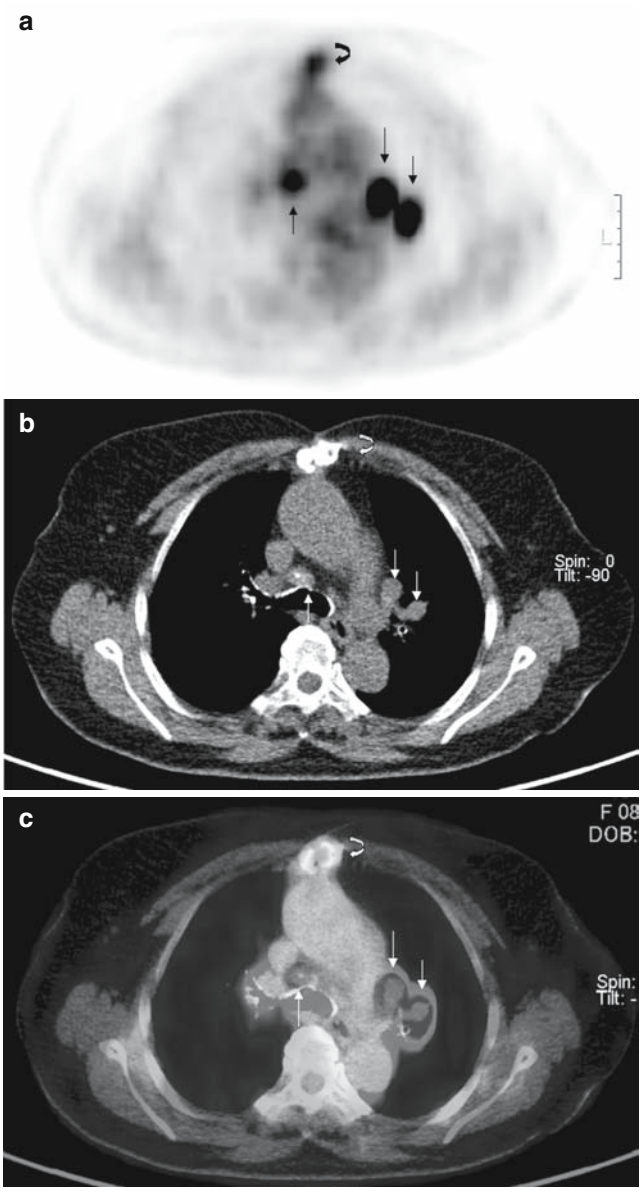

Fig. 2 An 82-year-old woman with initial FIGO stage III c with mediastinal and hilar lymph node metastases. Axial PET (**a**), CT (**b**), and PET/CT (**c**) showing mediastinal and hilar lymph node metastases (*arrows*)

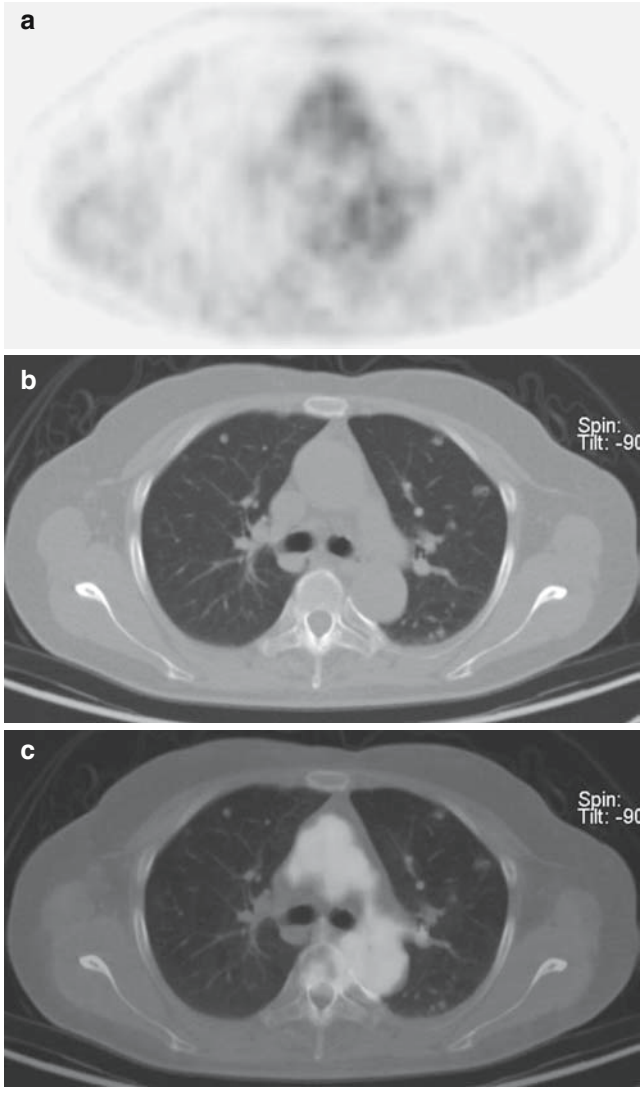

Fig. 3 A 67-year-old woman with initial FIGO stage III a with tiny lung metastases. Although axial PET (**a**) showing no abnormal FDG uptake in the lung, CT (**b**), and PET/CT (**c**) clearly showing many tiny lung metastases

recurrence: one false-positive result was a liver lesion and two false-negative results were peritoneal dissemination and liver metastasis.

Like these previous PET reports, PET interpretation in our series overdiagnosed benign inflammatory/infectious tissue and physiological uptake as recurrence and distant metastasis. This limited specificity of PET could partially be resolved by PET/CT acquiring both metabolic and anatomic imaging information in our series. Moreover, CT from PET/CT could detect tiny lung metastasis and para-aortic lymph node measuring 11 mm that PET missed. But a tiny para-aortic lymph node metastasis could not be detected not only by PET but also by PET/CT. PET or PET/CT can only detect the lymph nodes that have a certain volume of malignant cells sufficient to change the glucose metabolism, and neither of these modalities can detect micrometastasis. The spatial resolution of PET scans is insufficient for the detection of microscopic metastases to lymph nodes [19]. With a given spatial resolution of 4–6 mm with currently available PET and PET/CT systems, the detection of microscopic lesions remains challenging. Improving the spatial resolution and sensitivity of PET and PET/CT scanners and developing new, more specific radioactive tracers may help overcome this limitation in the future.

In this study, the CT component of PET/CT was low dose and did not use oral or intravenous contrast mate-

rial. Because the low-dose unenhanced CT from PET/CT is certainly not optimal for diagnostic interpretation and comparing PET/CT with the CT from PET/CT would have had little clinical relevance, CT alone from PET/CT was not interpreted in our study. Adding an oral contrast agent would possibly help to better delineate normal bowel activity and demonstrate pathological intra-abdominal activity (peritoneal implants). Use of an intravenous contrast agent can differentiate small lymph nodes from vessels, intestine, or the ureter, and correctly detect small liver metastasis, small peritoneal dissemination, and local recurrence at the vagina. A further PET/CT study with oral and intravenous contrast material is warranted to more precisely define its clinical role and accuracy for the detection of recurrent lesions.

This study had certain limitations. First, the number of patients with suspected endometrial cancer recurrence in our series was small. More studies are needed with a larger sample size to help verify the sensitivity and specificity of PET/CT. Second, the ideal gold standard for any analysis is the histological confirmation of the findings. However clinical follow-up is a valid way to evaluate diagnostic accuracy and response to therapy, and it would have been unethical to investigate all PET/CT-detected lesions by invasive procedures. Positive findings are easy to confirm, but negative findings only mean that we were unable to acquire positive findings during the follow-up period, making it uncertain as to whether the findings were truly negative. Third, conventional morphological imaging modalities including CT and MRI, which were used to detect recurrent lesions before PET/CT scan were not performed in all patients and we could not accurately compare the results of conventional imaging interpretation and PET/CT interpretation.

In conclusion, integrated FDG-PET/CT is a useful complementary modality for providing good anatomic and functional localization of sites of recurrence during follow-up of patients with endometrial cancer.

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