Annals of Nuclear Medicine Vol. 19, No. 2, 137–145, 2005

Diagnostic accuracy of FDG PET imaging for the detection of recurrent or metastatic gynecologic cancer

Nasim KHAN,* Noboru ORIUCHI,* Akira YOSHIZAKI,** Tatsuya KANUMA,***
Tetsuya HIGUCHI* and Keigo ENDO*

*Department of Nuclear Medicine and Diagnostic Radiology, and **Department of Obstetrics and Gynecology, Gunma University Graduate School of Medicine
***Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine

Purpose: This study evaluated the diagnostic role and accuracy of positron emission tomography (PET) using 2-[F-18]fluoro-2-deoxy-D-glucose (FDG) for the detection of tumor foci in patients with suspected recurrent or metastatic lesions of gynecologic cancers. ***Materials and Methods:*** FDG PET imaging was performed on 51 patients with a previous history of gynecologic cancer who were referred for a clinical suspicion of recurrent disease. PET acquisition was started 50–60 min after the intravenous injection of 5–6 MBq/kg FDG in all patients. The PET images were interpreted visually, and tracer uptake was quantitated as the standardized uptake value adjusted to body weight (SUV) in the lesions showing FDG uptake. The accuracy of the PET results was assessed by a consensual verdict based on histology, cytology, other imaging and clinical follow-up. ***Results:*** FDG PET correctly diagnosed 33 of 36 patients with recurrent disease and 12 of 15 patients without recurrence. On patient-based analysis, the sensitivity, specificity and accuracy of FDG PET were 91.7%, 80.0% and 88.2%, respectively, depending on the selected scheme for visual scoring of the lesions. The area index in receiver-operating characteristic analysis was 0.95 for patient detection. Malignant lesions accumulated significantly more FDG than the benign ones (the mean SUVs were 3.7 ± 1.9 and 1.6 ± 1.1, respectively, $p = 0.004$). The sensitivity and specificity in correct identification of tumor recurrence or metastases using a threshold SUV 1.9 were 88.8% and 66.7% in contrast to the visual analysis (sensitivity 96.4%, specificity 50%) on a lesion-based analysis. The partial volume effect of SUV in a few small lesions and the presence of bone lesions in which FDG uptake was relatively low might be the reason for the lower sensitivity in SUV analysis. FDG PET was valuable when CT/MRI was negative or inconclusive, and in patients with elevated tumor marker levels as well as with normal tumor marker levels when recurrence was suspected clinically. However, PET failed to visualize some small metastatic lesions in lung and bone, and showed falsely high FDG uptake in some benign lesions. ***Conclusion:*** The results indicated that FDG PET is a reliable and accurate diagnostic method for detecting recurrent or metastatic gynecologic cancer particularly lymph node metastases. Although the sensitivity of PET for detecting small metastases was relatively limited, the overall sensitivity of FDG PET was significantly higher than morphologic imaging.

Key words: FDG PET, SUV, gynecologic cancer, recurrence, follow-up

INTRODUCTION

DESPITE CONTINUING ADVANCES in surgical and non-surgical therapeutic strategies, cancer recurrence after the initial treatment is often a major problem for women with gynecologic cancers. Early detection of recurrence has an important influence on therapy, and the proper selection

Received October 4, 2004, revision accepted December 7, 2004.

For reprint contact: Keigo Endo, M.D., Department of Nuclear Medicine and Diagnostic Radiology, Gunma University Graduate School of Medicine, Showamachi 3–39–22, Maebashi, Gunma 371–8511, JAPAN.

E-mail: endo@med.gunma-u.ac.jp

of treatment strategies can be expected to have a significant impact on overall survival.[1] Surgical treatment of locoregional recurrence significantly prolongs survival with or without adjuvant chemoradiotherapy, while patients with disseminated disease are good candidates for systemic chemotherapy.[2] As a consequence, careful patient selection and exact restaging is required to achieve in each individual situation the maximal benefit. This aim sometimes can not be achieved by routine clinical examination and clinical oriented investigations owing to their lack of sensitivity and specificity, invasiveness and limitations to distinct body locations. Often a series of diagnostic tools has to be combined for the diagnosis of recurrent cancer. This might be time consuming, expensive and troublesome for the patients. In this clinical setting, the application of a high technology imaging modality capable of detecting recurrences earlier and more accurately could potentially have a positive impact on patient management. Positron emission tomography using 2-[F-18]fluoro-2-deoxy-D-glucose (FDG PET) is such a tomographic imaging technique which has been increasingly used in clinical oncology.[3–5] The advantage of PET over conventional imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US) is that the deranged cellular biochemical activity detected by PET precedes the morphological changes (enlargement) detected by those methods.[6] Although PET has been successfully applied to the study of various human cancers,[3] there is still little clinical experience with FDG PET for gynecologic tumor imaging. So far, a few studies have dealt with its application in gynecologic cancers indicating a potential clinical benefit.[7–13] Although encouraging results have been reported in these studies, the efficiency of FDG PET for the detection of recurrent disease remains to be established in routine clinical practice. In addition, PET is not yet officially recommended by the International Federation of Gynecology and Obstetrics (FIGO) in the panel of imaging procedures. Therefore, more clinical PET studies in larger series of patients are necessary to establish the role of FDG PET in the evaluation of gynecologic malignancies.

The present study was undertaken to further document the role of FDG PET and to evaluate its accuracy in the detection of recurrence or metastasis in patients with gynecologic cancer after primary treatment. Correlation and comparison of PET results were performed with other methods to determine the diagnostic accuracy of PET imaging.

MATERIALS AND METHODS

Patient population

Fifty-three post-treatment patients with histologically proven gynecological cancers (cervical, uterine corpus and ovarian cancer) and available information on primary treatment were included in this retrospective study. Approval from our institutional review board and written informed consent from the patients were obtained for this study. All patients underwent whole body PET examinations with FDG in the context of suspected recurrent cancer. Two patients were excluded because of detection of a second primary malignancy during follow-up: one patient had positive PET findings with a clinical history supporting recurrent ovarian cancer, but was finally diagnosed as a case of multiple myeloma; one had suspicious metastasis in lung on PET that was later diagnosed as a primary lung cancer. Hence, a total of 51 patients (median

Table 1 Patient and tumor characteristics

Characteristic	Value
Total patients	51
Age	
Median	52
Range	28–81
Site of primary cancer	
Uterine cervix	22
Endometrium	9
Ovary	20
Original histology	
Squamous cell carcinoma	12
Adenosquamous cell carcinoma	2
Adenocarcinoma	18
Serous adenocarcinoma	7
Serous cyst adenocarcinoma	2
Serous surface papillary carcinoma	2
Mucinous cyst adenocarcinoma	1
Clear cell carcinoma	2
Undifferentiated carcinoma	2
Choriocarcinoma	1
Carcinosarcoma	1
Yolk sac tumor	1
Primary treatment	
Surgery	15
Radiotherapy	5
Surgery + radiotherapy	7
Surgery + chemotherapy	18
Radiotherapy + chemotherapy	4
Surgery + radiotherapy + chemotherapy	2
Time since primary treatment to PET study (month)	
Median	14
Range	2–87
Tumor marker status at PET study	
Elevated	30
Normal	11
Unknown	10
Results based on consensual verdict (no. of patients)*	
Positive	36
Negative	15

* Positive and negative findings indicate the results of consensual verdict evaluation.

Table 2 Patient based results: Comparison of FDG PET, CT/MRI and tumor marker levels for detecting recurrent or metastatic gynecologic cancer

	TP	TN	FP	FN	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy % (95% CI)
FDG PET (n = 51)	33*	12	3	3	91.7 (77.5–98.2)	80.0 (51.9–95.7)	88.2 (76.1–95.6)
CT/MRI (n = 47)	21*	12	3	11	65.6 (46.8–81.4)	80.0 (51.9–95.7)	70.2 (55.1–82.7)
TM level (n = 41)	25	6	4	6	80.7 (62.5–92.5)	60.0 (26.2–87.8)	75.6 (59.7–87.6)

TP = true positive, TN = true negative, FP = false positive, FN = false negative, CI = confidence interval, TM = tumor marker.
* One patient in FDG PET and 2 patients in CT/MRI group had both true-positive and false-negative findings, which were included in the true-positive group for data analysis.

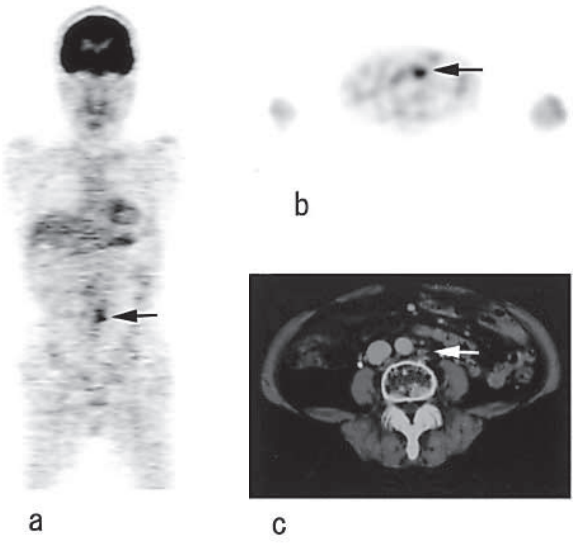

Fig. 1 A 67-year-old woman with a history of cervical cancer (stage 3C, squamous cell carcinoma) treated by chemoradiotherapy. Coronal and axial (a, b) FDG PET images show clearly increased focal FDG accumulation (SUV = 2.83) in the paraaortic lymph node (*arrow*) whereas contrast-enhanced CT image (c) shows normal-sized (9 × 8 mm in diameter) lymph node (false-negative diagnosis). Recurrence was confirmed by follow-up imaging.

age: 52 years; range 28–81 years) were evaluated in the current study. Further details of these patients and their demographic data are listed in Table 1. All patients were previously treated with a curative intent for gynecologic cancers according to FIGO stage. FDG PET scans were performed at the time of follow-up whereby no treatment was carried out for at least 2 months before PET scanning. The median interval from initial treatment and PET scanning was 14 months (range: 2–87 months). The primary clinical indications for the whole body PET examinations in this patient group were suspicious symptoms (n = 9), elevated serum tumor marker levels (n = 29), inconclusive conventional imaging findings (n = 12), and abnormal Pap smear (n = 1). Only one of the patients was known to have diabetes, which was being treated. The only diabetic patient in this series was under treatment control. Moreover, serum glucose concentration was monitored prior to PET study in all patients and ranged from 3.5 to 7.3 mmol/*l*.

Imaging protocol

FDG PET examinations were performed on overnight fasted patients (at least 6 h) after 50–60 min of intravenous administration of 5–6 MBq/kg FDG using a dedicated PET scanner (SET 2400W, Shimadzu, Japan). By performing 5–6 bed positions, PET scanning included the entire field of view from the upper thigh to the head. To minimize the tracer accumulation into the urinary bladder, patients were asked to void just before the start of the emission scan or the urinary bladder was continuously drained with a Foley catheter during image acquisition in some patients. Attenuation correction and image reconstruction were performed using the previously reported methods.[14] The reconstructed images were assessed on a computer monitor at all three levels (axial, coronal and sagittal views).

Besides FDG PET examination, the patients underwent conventional imaging such as CT/MRI (only CT 32 patients, only MRI 7 patients and both CT & MRI 8 patients) with standard protocols as required during their follow-up assessment in the referral hospitals or in our institute.

Data evaluation

All PET images were analyzed visually by two nuclear medicine physicians experienced in PET (consensus readings) with information on initial clinical history but without knowledge about the current CT/MRI findings. The visual analysis of PET images was scored using a 4-point scale (0 = no uptake of FDG, 1 = faint uptake, 2 = moderate uptake, 3 = clearly abnormal intense uptake) compared with the surrounding normal tissue radioactivity while the physiological areas of tracer uptake were not taken in account. The visual scores 0 and/or 1 were classified as negative for recurrence, while scores 2 and 3 were defined as positive for the depiction of recurrence or metastatses on the basis of a dichotomous grouping. Any discrepancies were resolved by a third observer who was aware that a discrepancy existed but was not informed of the specifics of the discrepancy. The semiquantitative evaluation of tumor uptake of FDG was performed as the standardized

uptake value adjusted to body weight (SUV) on the attenuation-corrected transverse images. SUVs were calculated only on visually positive lesions and some of the morphological imaging findings placing a circular region of interest (ROI) 5 mm diameter manually over the lesions which included the site of maximal FDG uptake. The location of the ROI in the lesions corresponded to the CT and/or MR images when available. The average SUV within an ROI was used to represent the tissue uptake of FDG.

Recurrence or metastases detected by FDG PET were reported as regional recurrence, organ metastases (lung, liver, spleen), bone, peritoneal and lymph node metastases. The lymph node metastases included pelvic, para-aortic, mediastinal, and supraclavicular lymph node involvement. The hepatic, renal and splenic hilar lymph nodes were included in the para-aortic group for data analysis.

The CT/MR images were evaluated by two board certified radiologists who were blinded to the PET results. Any abnormal mass lesion with enhancement or interval soft tissue increases compared with previous imaging were considered positive whereas edema and soft tissue swelling were interpreted as inconclusive for malignancy. Lymph nodes of >1 cm in short diameter, detected by CT/MRI, were considered pathological.

Because not all lesions could be histologically validated, we used a consensual verdict achieved by a committee consisting of two radiologists and two nuclear physicians for each patient with respect to the presence or absence of disease and the number and localization of tumor lesions. This consensus verdict based on the results of available histology, cytology, tumor marker levels, CT/MRI and clinical follow-up of at least 8 months served to

Table 3 Lesion-based results: FDG PET versus CT/MRI

Lesion sites	FDG PET positive	CT/MRI positive	P value
Regional recurrence	9 (10)	7 (10)	NS
Organ metastases			
Lung	1 (5)	4 (5)	NS
Liver	7 (7)	5 (7)	NS
Spleen	2 (2)	2 (2)	NS
Bone	11 (12)	12 (12)	NS
Lymph node	34* (36)	23* (36)	$p < 0.05$
Peritoneal	19 (19)	15 (19)	NS
Total	83 (91)	68 (91)	$p < 0.05$

Data are expressed as number of true-positive lesions (Total lesions of recurrence or metastases).
NS = not significant.
*For 3 PET positive lymph nodes, CT/MRI data were not available during PET scanning; therefore, these were not included in this comparison.

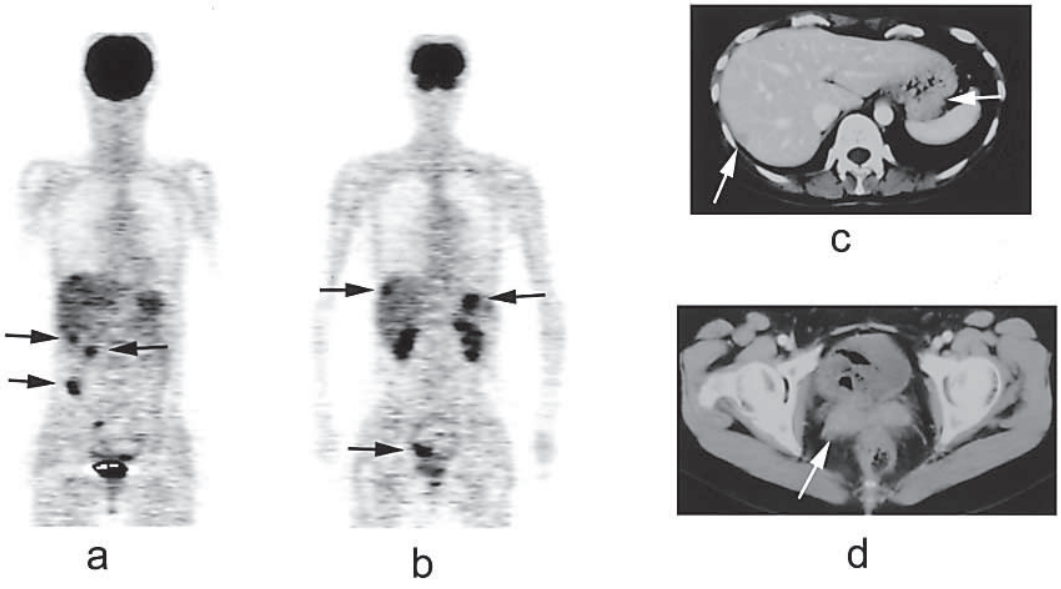

Fig. 2 A case of ovarian cancer (stage 3C, serous adenocarcinoma) initially treated by radical surgery and adjuvant chemotherapy presented with elevated CA125 level. Whole body FDG PET demonstrated multiple lesions (*arrows*) on coronal images in the peritoneal cavity (a), and liver, splenic hilum and pelvis (b). SUVs of the lesions ranged from 2.3 to 4.2. Abdominopelvic CT scan showed lesions in the liver, splenic hilum (c), and an inconclusive mass lesion (postoperative fibrotic change/recurrence) in the pelvic cavity (d). CT did not show the peritoneal small lesions detected by FDG PET. Corresponding high level of serum tumor marker (CA125 = 555 units) strongly indicated recurrence, and after multi-agent chemotherapy tumor marker level was reduced and the patient showed improvement during follow-up.

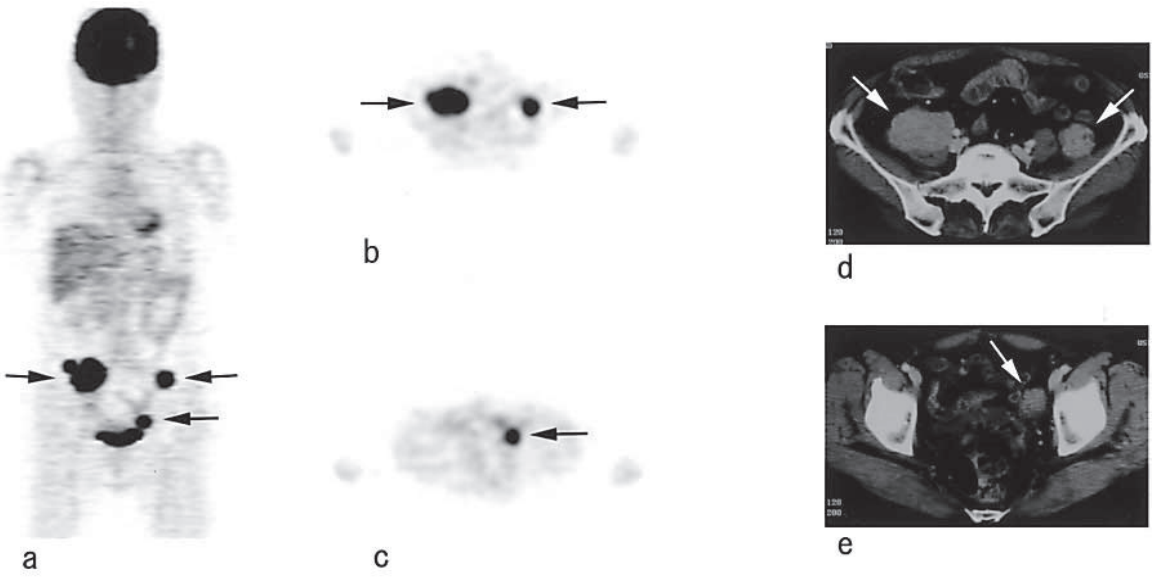

Fig. 3 A patient with stage 1 endometrial cancer (adenocarcinoma) who underwent total hysterectomy previously presented with lower abdominal pain and a mass on deep palpation but normal tumor marker (CA125, CA19-9) levels. FDG PET demonstrated three foci (*arrows*) on coronal (a) and axial (b, c) images in the abdominopelvic cavity. SUVs of the lesions were 8.1, 6.4, 5.5. Corresponding enhanced CT also showed 3 tumors (*arrows*) consistent with high FDG uptake. Recurrent tumors of endometrial adenocarcinoma were histologically proven by operation.

define the cases as true-positive, true-negative, false-positive or false-negative. Absolute validation of abnormal PET findings is one of the difficulties of whole body imaging; therefore, the requirement of at least 8 mo of careful clinical follow-up was included in the study so that indeterminate lesions or a negative scan at the study period could be better characterized by the absence or presence of disease progression.

Statistical analysis

We performed a patient-based analysis comparing FDG PET to the results based on the consensus verdict in general, and compared to CT/MRI and TM profiles. Sensitivity, specificity and accuracy were calculated using standard statistical formulas, and 95% confidence interval (95% CI) was determined for each parameter. Fisher's exact test was used to determine statistical significance for the comparison of FDG PET and CT/MRI and TM levels. The receiver-operating characteristic (ROC) analysis was performed using the Medcale software on a patient-by-patient basis and for SUV analysis. The mean SUVs were compared for malignant and benign lesions by using two tailed Student's t test. A p value <0.05 was considered as statistically significant.

RESULTS

Of the 51 patients examined, 36 were confirmed to have recurrent or metastatic disease and 15 were without evidence of recurrence based on the consensual verdict taken as the gold standard. FDG PET correctly diagnosed 33 of 36 patients with disease and 12 of 15 patients without disease, resulting in sensitivity, specificity and accuracy of 91.7% (95% CI = 77.5%–98.2%), 80% (95% CI = 51.9%–95.7%), and 88.2% (95% CI = 76.1%–95.6%), respectively on a patient-based analysis (Table 2). The corresponding area index in ROC analysis was 0.95 for patient detection. PET accurately demonstrated 86 (91.5%) of 94 recurrent sites in 36 patients, while 8 sites were not detected by PET on lesion-based analysis. A representative case of positive FDG PET scan is shown in Figure 1. Three false-positive and three false-negative PET diagnoses were observed in this study. Falsely high FDG uptake was observed in a uterine myoma, in the colonic mucosa and in the supraclavicular lymph node which were confirmed by histology (n = 1), other imaging modality and clinical follow-up (n = 2). FDG PET was false-negative in two patients (3 lesions) who underwent PET imaging after 3–4 months of radiation therapy and in one patient, PET failed to visualize 4 foci of lung metastases (5–10 mm) which were detected by CT scan. In addition, PET missed a small (<7 mm) bone metastasis in another patient in whom it detected multiple lesions in the liver, pelvis and bone also.

Comparing with CT/MRI results based on the number of patients undergoing both procedures, it was clear that FDG PET showed higher sensitivity although there was no difference in the specificity in our study. If the results

are subdivided into regional recurrence, organ metastases, bone and lymph node metastases; it is seen that FDG PET has a significantly higher sensitivity in the diagnosis of total lesions and lymph node metastases (Table 3). Although PET showed a relatively low sensitivity for the detection of lung and bone metastases, the whole body PET imaging clearly demonstrated more lesions in other locations than CT/MRI. An example is shown in Figure 2. There were 41 patients with available tumor marker levels (29 with elevated and 12 with normal levels) during PET examination. Among the 25 patients with true-positive tumor marker results, FDG PET correctly detected recurrence or metastases in 23 patients (92%, 23/25) while CT/MRI showed recurrent disease in only 14 patients (70%,14/20). In three patients, CT/MRI results were not available during PET scanning. In two patients, FDG PET was false-negative whereas CT/MRI were true-positive. On the other hand, PET successfully excluded recurrence in 3 of 4 patients with falsely elevated tumor marker levels, but in one patient PET was also false-positive whereas CT/MRI was true-negative in 2 patients and false-positive in 2 patients. In 12 patients with normal tumor marker levels, 6 were without recurrence and 6 patients presented with recurrent disease. FDG PET correctly detected recurrence in 5 of 6 patients and excluded recurrent disease in 5 of 6 patients with false-negative tumor marker levels. A representative case of a true-positive FDG PET scan and false-negative tumor marker level is shown in Figure 3. PET was false-negative in one patient and also false-positive in one patient with normal tumor marker levels. In this patient group, CT/MRI was true-positive in 5 patients, true-negative in 6 patients, and false-negative in one patient.

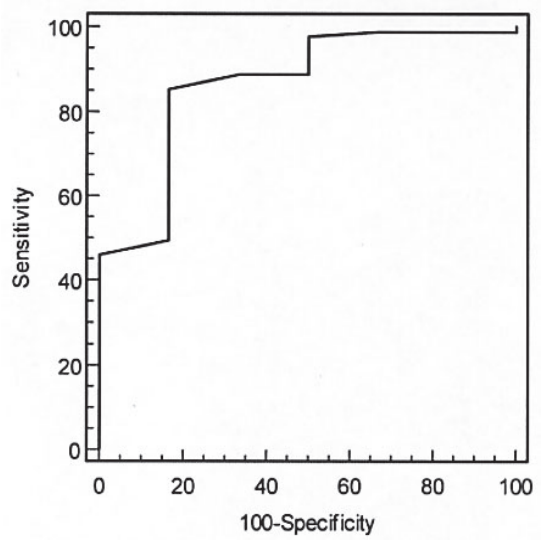

Fig. 4 Receiver-operating characteristics (ROC) curve of SUVs of malignant and benign lesions. The area under the curve = 0.866, SE = 0.055. For a threshold value of 1.9 SUV, the sensitivity is 85.4% and the specificity, 83.3%.

FDG uptake was quantitated in all PET positive lesions (malignant/benign) and abnormalities shown by CT/MRI if there was uptake of FDG. The mean SUV of all lesions (n = 95) was 3.6 ± 1.9 (range: 0.4 to 10.3). The SUVs of the malignant lesions (n = 89) ranged from 0.4 to 10.3 (mean: 3.7 ± 1.9) and that of the benign lesions (n = 6) from 0.5 to 3.2 (mean: 1.6 ± 1.1). The difference of mean SUV between malignant and benign lesions was statistically significant (p = 0.004). The mean SUVs in the regional lesions (pelvic) were 3.9 ± 2.6 (n = 13), in organ metastases (lung, liver, spleen) 3.3 ± 0.9 (n = 10), in bone metastases 3.6 ± 3.2 (n = 11), peritoneal metastases 4.2 ± 1.9 (n = 19) and in lymph nodes 3.2 ± 1.4 (n = 42). There were no significant differences among these groups. The calculated SUV values in all lesions were analyzed with ROC curve to obtain an optimal threshold to differentiate malignant and benign lesions (Fig. 4). A cut-off SUV of 1.9 selected from ROC analysis provided the optimal diagnostic accuracy (sensitivity 88.8%, specificity 66.7% and accuracy 87.4%) (Table 4).

DISCUSSION

In this study, we examined the diagnostic accuracy of FDG PET imaging using both visual and SUV analysis, and found that it was an effective method for the detection of recurrent or metastatic lesions in post treatment gynecologic cancer patients. Particularly in the involved lymph nodes with metastatic disease of gynecologic cancer,

Table 4 Results of SUV analysis of FDG PET studies for the differentiation of recurrent or metastatic tumors from benign lesions

SUV threshold	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy % (95% CI)
1.8	88.8 (80.3–94.5)	50.0 (12.4–87.6)	86.3 (77.6–92.5)
1.9	88.8 (80.3–94.5)	66.7 (22.7–94.7)	87.4 (78.9–93.3)
2.2	85.4 (76.3–92.0)	83.3 (36.1–97.2)	85.3 (76.5–91.7)
2.3	78.7 (68.7–86.6)	83.3 (36.1–97.2)	78.9 (69.3–86.6)
2.4	74.2 (63.8–82.9)	83.3 (36.1–97.2)	74.7 (64.7–83.1)
Visual analysis	96.6 (90.5–99.3)	50.0 (11.8–88.2)	93.6 (86.7–97.4)

SUV = standardized uptake value, CI = confidence interval.

FDG PET was more sensitive than morphologic imaging. Our results agree with data published in the literature,[15,16] using FDG PET in gynecologic cancer in smaller numbers of patients. It has been speculated that early detection of metastatic lymphadenopathy can offer improved chances of cure and better 5-year survival rate. Thus, improved accuracy of detecting early cancer spread in lymph nodes should improve patient outcome following surgical resection. FDG PET is more sensitive than CT in detecting early metastatic disease in lymph nodes because of its ability to show increased tumor metabolism even in normal-sized lymph nodes.[17] Morphologic imaging procedures are known to have low specificity, particularly in cases with post treatment anatomic changes (e.g. after surgery or radiotherapy). This frequently causes difficulties in the discrimination of scar tissue or fibrosis from local recurrence and of nonspecific lymph node enlargement from lymph node metastases. In addition, morphological imaging techniques lack sensitivity owing to their limited field of view.[18]

In many cases visual image interpretation is sufficient for differentiation of malignant and benign tumors. However, we think that SUV estimation may complement visual image interpretation because it provides objective criteria for differentiation of malignant and benign lesions, thus minimizing interobserver variability in image interpretation. Moreover, SUV analysis may support the diagnosis of borderline cases at visual interpretation. In the present study, we found that SUV analysis helped to differentiate two lesions as benign which were considered as malignant at visual interpretation resulting in improved specificity of the technique. The heterogeneity of lesions in the whole body PET imaging creates difficulty for an optimal threshold value determination. However, the ROC analysis demonstrated an acceptable accuracy of the quantitative approach and indicated a good likelihood for finding a clinically feasible optimal cut-off value 1.9 for FDG uptake index if SUV was adapted. When this cut-off SUV was used, the diagnostic accuracy obtained was 87.4% in the present study. It is acknowledged that SUV analysis has to be performed with caution in lesions that are small in comparison with the spatial resolution of the PET scanner. Compared with the visual assessment, SUV analysis demonstrated lower sensitivity (96.6% vs. 88.8%) but higher specificity (50% vs. 66.7%) in our study. The relatively low sensitivity might be due to a partial volume effect in some of the small lesions particularly in the bone and peritoneum. Moreover, the threshold value for discriminating benign and malignant bone lesions is relatively low.[19] Therefore, SUV evaluation seems to be a helpful measure for differentiating malignant and benign lesions in patients with gynecologic cancer in addition to visual assessment.

The role of the tumor markers has been well recognized in the follow-up of patients with gynecologic cancers.[20–22] An elevated tumor marker level is usually a strong indication of the presence of recurrent disease.[22] In the present study, FDG PET showed a high sensitivity (92%, 23/25) in the group of patients with elevated tumor marker levels. Therefore, it can be concluded that, particularly in cases with elevated tumor marker levels, FDG PET has a high sensitivity for the detection of tumor sites and is a useful method for this purpose. On the other hand, PET was also able to diagnose recurrence in patients with clinical suspicion but in whom the tumor marker levels were normal. In our study, PET correctly detected recurrent disease in 5 of 6 patients with normal tumor marker levels. Figure 3 shows a representative case of this group.

There were three false-positive patients: 1 uterine myoma, 1 chronic inflammation in the lymph node and 1 case of physiological tracer uptake in intestine (colon). It is well known that the tissue uptake of FDG is dependent on several factors including tissue perfusion, oxygenation and the presence of inflammatory conditions. In addition, some organs normally take up increased FDG such as brain, heart, liver, kidney and gastrointestinal tract.[23] FDG may be accumulated in normal uterine muscle and uterine myoma.[24,25] Chronic inflammation was the cause of false-positive diagnosis in a lymph node. In the third patient, the false-positive result was related to the physiological uptake of FDG in the mucosa of the colon. The false-negative findings of FDG PET in a patient with lung metastases and in a bone metastasis were due to the small size of the lesions, and in two other patients (2 lymph nodes and 1 cervical carcinoma) because of radiation effect following radiotherapy. A study on esophageal squamous cell carcinoma reported that tumors responding well to radiotherapy may relapse as early as 3–4 months after the end of treatment.[26] Greven et al.,[27] found that radiation can decrease the FDG uptake in tumor cells rapidly even if some tumor cells remain active resulting in tumor regrowth.

The ideal gold standard for any investigative analysis is the histological confirmation of the findings. In our study, the lesions in 11 patients could be confirmed by histology, the diagnosis in the remaining 28 was validated by consensus based on other imaging procedures and clinical follow-up. This is a limitation of this study, but clinical follow-up is a valid way to evaluate diagnostic accuracy and response to therapy. In certain cases it would have been unethical to investigate all PET-detected lesions by invasive procedures, and radiotherapy or chemoradiotherapy was usually started based on criteria which are routinely used at our institution. Another limitation is related to the retrospective nature of this study and producing a referral bias such that only more difficult cases (not resolved by conventional methods) were referred for PET examination. Further prospective FDG PET studies in larger numbers of patients are warranted in order to more precisely define its clinical role and accuracy in the detection of gynecologic malignancies.

In conclusion, our results suggested that FDG PET

imaging is a highly sensitive noninvasive diagnostic test for the detection of recurrent or metastatic gynecologic cancer. Although sensitivity for lung and bone metastasis was relatively low, it was higher for other tissues particularly for the lymph node metastases. Thus FDG PET appears to be valuable if CT/MRI is negative or inconclusive, and positive PET scans can be used to guide diagnostic biopsies and/or surgery to confirm the recurrence. FDG PET also seems to be a reliable imaging method for identification of tumor recurrence or metastases in patients with elevated tumor marker levels as well as in patients with clinically suspected recurrence without elevation of tumor marker levels.

ACKNOWLEDGMENTS

We thank Professor Kunihiko Hayashi, Department of Epidemiology and Biostatistics, Gunma University School of Health Sciences, Gunma, Japan for his kind assistance with the statistical analysis. We also thank Dr. Mitsuyuki Miyakubo, Dr. Paudyal Bishnuhari, Department of Nuclear Medicine, Gunma University Graduate School of Medicine, Gunma, Japan, and Dr. Yasuhiko Iida and Dr. Hirofumi Hanaoka, Department of Bioimaging Information Analysis, for their help with the manuscript preparation.

REFERENCES

1. Benedet JL, Bender H, Jones H 3rd, Ngan HY, Pecorelli S. FIGO classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. *Int J Gynecol Obstet* 2000; 70: 209–262.
2. Pazdur R, Coia LR, Hoskins WJ, Wagman LD. *Cancer management: a multidisciplinary approach, 5th edn*. New York; PRR, 2001.
3. Scott AM. Current status of positron emission tomography in oncology. *Int Med* 2001; 31: 27–36.
4. Tempero M, Brand R, Holdeman K, Matamoros A. New imaging techniques in colorectal cancer. *Semin Oncol* 1995; 22: 448–471.
5. Gallowitsch HJ, Kresnik E, Gasser J, Kumnig G, Ignerc I, Mikosch P, et al. F-18 fluorodeoxyglucose positron emission tomography in the diagnosis of tumor recurrence and metastases in the follow-up of patients with breast carcinoma: a comparison to conventional imaging. *Invest Radiol* 2003; 38: 250–256.
6. Wahl RL, Hutchins GD, Buchsbaum DJ, Liebert M, Grossman HB, Fisher S. ^{18}F-2-deoxy-D-glucose uptake into human tumor xenografts: feasibility studies for cancer imaging with positron emission tomography. *Cancer* 1991; 67: 1544–1550.
7. Koyama K, Okamura T, Kawabe J, Ozawa N, Torii K, Umesaki N, et al. Evaluation of ^{18}F-FDG PET with bladder irrigation in patients with uterine and ovarian tumors. *J Nucl Med* 2003; 44: 353–358.
8. Havrilesky LJ, Wong TZ, Secord AA, Berchuck A, Clarke-Pearson DL, Jones EL. The role of PET scanning in the detection of recurrent cervical cancer. *Gynecol Oncol* 2003; 90: 186–190.
9. Ryu SY, Kim MH, Choi SC, Choi CW, Lee KH. Detection of early recurrence with ^{18}F-FDG PET in patients with cervical cancer. *J Nucl Med* 2003; 44: 347–352.
10. Saga T, Higashi T, Ishimori T, Mamede M, Nakamoto Y, Mukai T, et al. Clinical value of FDG -PET in the follow-up of post-operative patients with endometrial cancer. *Ann Nucl Med* 2003; 17: 197–203.
11. Belhocine T, De Barsy C, Hustinx R, Willems-Foidart J. Usefulness of ^{18}F-FDG PET in the posttherapy surveillance of endometrial carcinoma. *Eur J Nucl Med* 2002; 29: 1132–1139.
12. Torizuka T, Nobezawa S, Kanno T, Futatsubashi M, Yoshikawa E, Okada H, et al. Ovarian cancer recurrence: role of whole body positron emission tomography using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med* 2002; 29: 797–803.
13. Nakamoto Y, Saga T, Ishimori T, Mamede M, Togashi K, Higuchi T, et al. Clinical value of positron emission tomography with FDG for recurrent ovarian cancer. *AJR* 2001; 176: 1449–1454.
14. Khan N, Oriuchi N, Ninomiya H, Higuchi T, Kamada H, Endo K. Positron emission tomographic imaging with ^{11}C-choline in differential diagnosis of head and neck tumors: comparison with ^{18}F-FDG PET. *Ann Nucl Med* 2004; 18: 409–417.
15. Sugawara Y, Eisbruch A, Kosuda S, Recker BE, Kison PV, Wahl RL. Evaluation of FDG PET in patients with cervical cancer. *J Nucl Med* 1999; 40: 1125–1131.
16. Umesaki N, Tanaka T, Miyama M, Kawanabe J, Okamura T, Koyama K, et al. The role of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET) in the diagnosis of recurrence and lymph node metastasis of cervical cancer. *Oncol Rep* 2000; 7: 1261–1264.
17. Gupta NC, Graeber GM, Bishop HA. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small (<1 cm), intermediate (1 to 3 cm), and large (>3 cm) lymph node lesions. *Chest* 2000; 117: 773–778.
18. Grunwald F, Kaliche T, Fiene U, Lietzenmayer R. Fluorine-18 fluorodeoxyglucose positron emission tomography in thyroid cancer: results of a multicenter study. *Eur J Nucl Med* 1999; 26: 1547–1552.
19. Dimitrakopoulou-Strauss A, Strauss LG, Heichel T, Wu H, Burger C, Bernd L, et al. The role of quantitative ^{18}F-FDG PET studies for the differentiation of malignant and benign bone lesions. *J Nucl Med* 2002; 43: 510–518.
20. Fujii S, Konishi I, Nanbu Y, Nonogaki H, Kobayashi F, Sagawa N, et al. Analysis of the levels of CA125, carcinoembryonic antigen, and CA 19-9 in the cervical mucus for a detection of cervical adenocarcinoma. *Cancer* 1988; 62: 541–547.
21. Niloff JM, Bast RC Jr, Schaetzl EM, Knapp RC. Predictive value of CA 125 antigen levels in second-look procedures for ovarian cancer. *Am J Obstet Gynecol* 1985; 151: 981–986.
22. Kurihara T, Mizunuma H, Obara M, Andoh K, Ibuki Y, Nishimura T. Determination of a normal level of serum CA125 in postmenopausal women as a tool for preoperative evaluation and postoperative surveillance of endometrial carcinoma. *Gynecol Oncol* 1998; 69: 192–196.

23. Shreve PD, Anzai Y, Wahl RL. Pitfalls in oncologic diagnosis with FDG PET imaging: physiologic and benign variants. *Radiographics* 1999; 19: 61–77.
24. Goldberg E, Rosenblum I. Uptake and phosphorylation of 2-deoxy-D-glucose by normal uterine muscles and uterine myomata. *Experientia* 1968; 24: 700.
25. Kao CH. FDG uptake in a huge uterine myoma. *Clin Nucl Med* 2003; 28: 249.
26. Nakamura R, Obara T, Katsuragawa S, Tamakawa Y, Koeda K, Ikeda K, et al. Failure in presumption of residual disease by quantification of FDG uptake in esophageal squamous cell carcinoma immediately after radiotherapy. *Radiat Med* 2002; 20: 181–186.
27. Greven KM, Williams DW 3rd, Keyes JW Jr, McGuirt WF, Watson NE Jr, et al. Positron emission tomography of patients with head and neck carcinoma before and after high dose irradiation. *Cancer* 1994; 74: 1355–1359.