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Detection of Recurrence by ^{18}F-FDG PET in Patients with Endometrial Cancer Showing No Evidence of Disease

Sang-Young Ryu[1], Kidong Kim[1], Younha Kim[1], Sang-Il Park[1], Beob-Jong Kim[1], Moon-Hong Kim[1], Seok-Cheol Choi[1], Eui-Don Lee[1], Kyung-Hee Lee[1], and Byung Il Kim[2]

Departments of Obstetrics & Gynecology[1] and Nuclear Medicine[2], Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences (KIRAMS), Seoul, Korea

Address for Correspondence:
Sang-Young Ryu, M.D.
Department of Obstetrics & Gynecology, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences (KIRAMS), 75 Nowon-gil, Nowon-gu, Seoul 139-706, Korea
Tel: +82.2-970-1227, Fax: +82.2-970-1227
E-mail: ryu@kcch.re.kr

This study assessed the feasibility of F-18-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) in the post-therapy surveillance for patients with endometrial cancer showing no evidence of disease (NED). From April 1997 to June 2007, 127 patients with endometrial cancer showing NED were performed ^{18}F-FDG PET scan. The feasibility of ^{18}F-FDG PET for the early detection of recurrence in patients with endometrial cancer was evaluated retrospectively. Of the 127 patients, 32 patients showed positive lesions on ^{18}F-FDG PET scan. Nineteen (19/127 cases, 15%) of them were confirmed to have a recurrence clinically or histologically. The sensitivity, specificity and positive and negative predictive value of ^{18}F-FDG PET for detecting recurrences in patients with endometrial cancer were 100%, 88%, 59% and 100%, respectively. In conclusion, ^{18}F-FDG PET may be a useful method for the post-therapy surveillance in patients with endometrial cancer.

Key Words: Endometrial Neoplasms; Recurrence; Positron-Emission Tomography

INTRODUCTION

Endometrial cancer is one of the most common malignant tumors of women, and has a favorable prognosis if it is detected in the early stage (1). However, about one-fourth of patients with early endometrial cancer will eventually develop recurrences (2). The patients with a recurrence can be salvaged by radiotherapy or systemic chemotherapy; however, the prognosis of patients with recurrent endometrial cancer is known to be poor (2, 3).

The early detection of recurrence provides patients with an opportunity to receive more sophisticated treatment, which could impact on patient survival for many human cancers (4). However, there are few methods to detect early recurrences for patients with endometrial cancer at a point that improves survival by salvage therapy.

The conventional follow-up methods after the treatment of endometrial cancer include physical examination, Papanicolaou (PAP) smear, tumor markers such as CA-125 and imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) (5). However, the early detection of recurrences by conventional follow-up methods is known to be unsatisfactory. It has recently been reported that the detection rates in asymptomatic patients with recurrence of endometrial cancer were as low as 5% to 33% with physical examination, 0% to 4% with PAP smear, 0% to 14% with chest radiography, 4% to 13% with abdominal ultrasound, 5% to 21% with abdominal/pelvis CT and 15% with serum CA-125 level, which implicates the need for more sophisticated post-therapy surveillance methods (5).

F-18-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) is an up-to-date imaging technique that utilizes ^{18}F-FDG, which is preferentially trapped in tumor cells and so it reveals functional images of high glucose metabolism. The functional image of ^{18}F-FDG PET can differentiate recurrences from the lesions distorted by the fibrosis that happens after surgery or radiotherapy (6). ^{18}F-FDG PET also has high resolution power to detect lesions less than 1 cm, which are frequently missed by conventional imaging methods (7, 8).

In several human cancers, ^{18}F-FDG PET is widely used for detecting early recurrences and it is known to be more accurate than CT or MRI (9, 10). We previously reported that 11% of the patients (28/249 patients) with cervical cancer showing no evidence of disease (NED) were identified to have recurrent lesions on ^{18}F-FDG PET. The sensitivity and specificity of ^{18}F-FDG PET for detecting recurrence in patients with cervical cancer showing NED were 90% and 76%, respectively (11). For ovarian cancers, the sensitivity of ^{18}F-FDG PET for detecting early recurrenc-

es was reported to be almost 100% (12). However, there are currently few studies on the feasibility of ^{18}F-FDG PET as an effective tool of post-therapy surveillance in patients with endometrial cancer.

According to the recent studies, the sensitivity, specificity and positive predictive value (PPV) and negative predictive value (NPV) of ^{18}F-FDG PET for post-therapy surveillance in patients with endometrial cancer were reported to be 93-96%, 78-100%, 89-100% and 91-92%, respectively (13, 14). However, the reports were limited by the small number of patients as there were only around 30 cases of patients with endometrial cancer at best (13-15). Therefore, the feasibility of ^{18}F-FDG PET for the post-therapy surveillance in patients with endometrial cancer remains to be clarified in larger series of patients.

In this study, we investigated the feasibility of ^{18}F-FDG PET for the post-therapy surveillance in 127 patients with endometrial cancer who showed NED after their initial treatment.

MATERIALS AND METHODS

Patients

One hundred twenty-seven patients with endometrial cancer showing NED after their initial treatment between April 1997 and June 2007 at Korea Cancer Center Hospital were enrolled in this study. The clinical characteristics such as age, stage and histologic grade were collected from the medical records, and were analyzed retrospectively. The institutional review board approved this study (K-0909-027-021).

All the patients were pathologically proven to have endometrial cancer, and were performed comprehensive surgical staging procedures including total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and intraperitoneal washing cytology. Adjuvant radiotherapy was applied when the postoperative pathological examination revealed risk factors for recurrence.

After treatment, the patients were observed every 3 months during the first 2 yr and every 6 months thereafter for 5 yr with physical examinations, PAP smears, serum CA-125 levels and annual imaging studies such as chest radiography, CT or MRI.

We defined NED as all normal follow-up tests, including the physical examinations, PAP smears, chest radiography, serum CA-125 levels and imaging studies.

^{18}F-FDG PET scan

^{18}F-FDG PET scan was performed for all patients who showed NED in conventional post-therapy surveillance. Conventional post-therapy surveillance included physical examination, PAP smears, serum CA-125 levels and annual imaging studies. ^{18}F-FDG PET scan was performed within 3 months after conventional surveillance. ^{18}F-FDG PET was performed on an ECAT HR+ (Siemens, Knoxville, TN, USA) or an Advance HR+ Scanner (General Electric, Waukesha, WI, USA). Their intrinsic spatial resolutions on the axial plane were 6 mm and 4.6 mm, respectively, and the thickness of the slice was 4.25 mm.

The patients fasted for at least 6 hours before ^{18}F-FDG injection to reduce the serum glucose and insulin levels to near basal concentrations. In order to decrease the misinterpretation caused by the accumulation of ^{18}F-FDG in the bladder and ureter, we inserted a Foley catheter and injected furosemide 40 mg intravenously 60 min before scanning.

After the intravenous injection of 370-555 Mbq of ^{18}F-FDG, the transmission images were obtained for 3 min with using Ge-68, and segmented attenuated correction was applied. The attenuated corrected images were reconstructed using a Hanning filter (cut-off 8.0 mm), and the ordered subset expectation maximization method was adopted as the reconstruction algorithm in both scanners.

The ^{18}F-FDG PET images were interpreted by consensus of two nuclear medicine doctors who were kept "blind" to the patients' clinical and radiological information. Any suspicious hot uptakes, except physiologic uptakes such as bowel activity with linear nature or mediastinal lymph node activity with calcification, were interpreted as positive.

Diagnosis of recurrence

The recurrence was diagnosed histologically as much as it is possible. In any suspicious hot uptake on ^{18}F-FDG PET, percutaneous fine needle aspiration cytology or biopsy was performed to confirm the recurrence.

For the deep lymph nodes, where cytology or biopsy was not applicable, 1) the lesions with a short axis >1 cm on imaging study such as CT or MRI were interpreted as metastasis, and 2) the lesions with a short axis <1 cm were followed-up by CT or MRI after 3 months. More than 20% change of size of the tumor on follow-up CT was determined to have a recurrence. If there was no change of size on the follow-up imaging study, then the patients were recommended for follow-up every 3 months for a year.

Other hot uptake lesions on ^{18}F-FDG PET other than the lymph node were evaluated by biopsy, as much as it is possible. Any lesion for which biopsy was not applicable was examined by follow-up CT or MRI within 3 months and close observation for a year was recommended.

Two expert radiologists reviewed the CT or MRI image and came to a consensus without any ^{18}F-FDG PET data and clinical information.

RESULTS

The median age of the patients with endometrial cancer who showed NED was 52 yr (range, 27-71). The proportion of the FIGO stage was 79% in stage I, 4% in stage II, 15% in stage III and

2% in stage IV. The histologic type was mostly the endometrioid type (86%) and the histologic grade was I or II in 86% of the cases. The median interval from the initial diagnosis of endometrial cancer to ^{18}F-FDG PET was 30 months (Table 1).

Of the 127 patients, 32 patients showed positive lesions on ^{18}F-FDG PET. Among them, 19 patients were confirmed to have recurrence clinically and/or histologically (19/127 patients, 15%) (Fig. 1). Seven patients (37%) had only local recurrences, a patient (5%) had only distant recurrence, and 11 patients (58%) had a mix of distant and local recurrences (Table 2). Most of the recurrences were detected within 12 months after the initial diagnosis of endometrial cancer (11/19 patients, 58%) (Fig. 2).

The sensitivity, specificity, PPV and NPV of ^{18}F-FDG PET for detecting the recurrence in patients with endometrial cancer showing NED were 100%, 88%, 59%, and 100%, respectively (Table 3). The site-specific sensitivity and specificity of ^{18}F-FDG PET were generally high regardless of the site of recurrences, however, the false positive rate was high for the vaginal stump

(3/3 cases), spine (2/2 cases), and inguinal lymph node (1/1 cases) (Table 4). There was a site-specific false negative lesion in the lung parenchyma, which was not detected by ^{18}F-FDG PET, but was detected by additional chest CT scan.
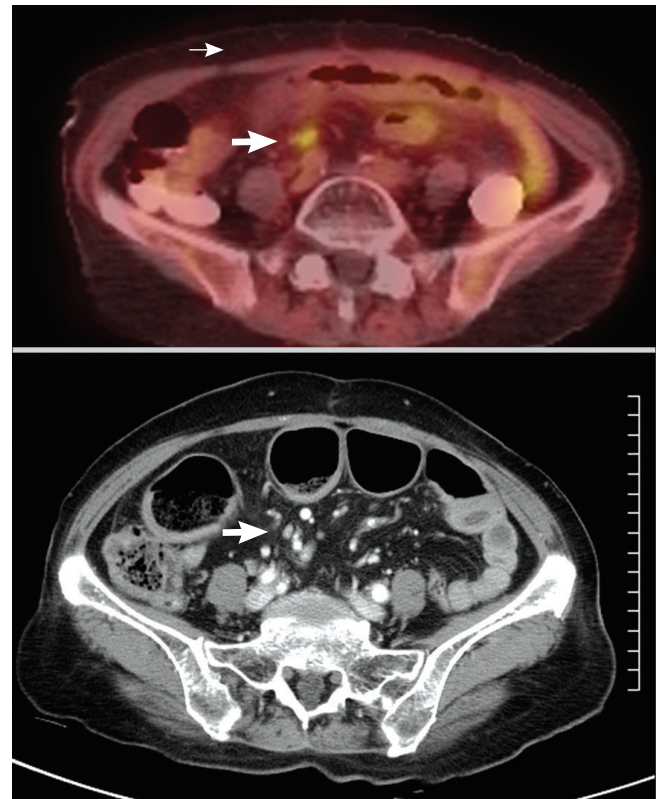

Fig. 1. A case where ^{18}F-FDG PET detected a recurrent lesion in a patient showing no evidence of disease at conventional studies. CT scan detected no lesion and the level of tumor marker was within normal range. However, PET scan detected a recurrent lesion (arrow) at small bowel mesentery. Retrospective review of CT scan revealed a lesion smaller than 1 cm (arrow) at small bowel mesentery. Bowel obstruction symptoms developed three weeks later and surgical exploration revealed a recurrent lesion at small bowel mesentery.

Table 1. Clinical characteristics

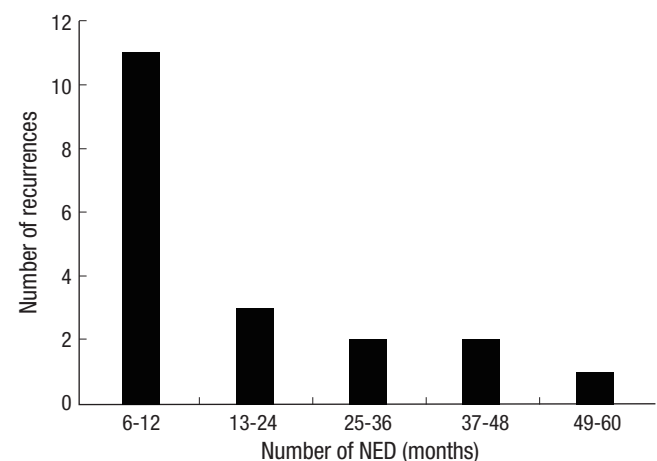| Clinical characteristics	Values (n=127)
Median age (range)	52 (27–71 yr)
Stage (%)	
I	101 (79)
II	5 (4)
III	19 (15)
IV	2 (2)
Histologic type (%)	
Endometrioid	109 (86)
Adenosquamous	5 (4)
Others*	13 (10)
Grade (%)	
1	52 (41)
2	57 (45)
3	18 (14)
Interval from initial diagnosis to ^{18}F-FDG PET, median (range), month	30 (6-279)

*Six papillary serous, 5 clear cell, 2 undifferentiated.

Table 2. Clinical characteristics of the patients with recurrence

Clinical characteristics	Values (n=19)
Stage (%)	
I	9 (47)
II	0 (0)
III	9 (47)
IV	1 (5)
Histologic type (%)	
Endometrioid	16 (84)
Adenosquamous	2 (11)
Others	1 (5)
Grade (%)	
1	4 (21)
2	9 (47)
3	6 (32)
Recurrence pattern (%)	
Local	7 (37)
Distant+local	11 (58)
Distant	1 (5)

Fig. 2. Interval from the initial diagnosis to ^{18}F-FDG PET for the patients with endometrial cancer who had recurrent disease.

Table 3. Detection of recurrence with ^{18}F-FDG PET in endometrial cancer patients showing NED (n=127)

^{18}F-FDG PET	No. of patients (%)
^{18}F-FDG PET (−)	95 (75)
True negative	95 (75)
False negative	0 (0)
^{18}F-FDG PET (+)	32 (25)
True positive	19 (15)
False positive	13 (10)

Table 4. Accuracy of ^{18}F-FDG PET according to the site of recurrences

Site of recurrences	^{18}F-FDG PET (+)		^{18}F-FDG PET (−)		Sn (%)	Sp (%)
	TP	FP	TN	FN		
Local recurrences	16	11	100	0	100	90
Vaginal stump	0	3	124	0	–	98
Pelvis	10	7	110	0	100	94
Paraaortic LN	6	0	121	0	100	100
Inguinal LN	0	1	126	0	–	99
Distant recurrences	19	3	104	1	95	97
Pulmonary hilar LN	2	0	125	0	100	100
Scalene LN	3	1	123	0	100	99
Mediastinal LN	1	0	126	0	100	100
Lung	7	0	119	1	88	100
Liver	5	0	122	0	100	100
Spine	0	2	125	0	–	98
Small bowel	1	0	126	0	100	100

Pulmonary hilar LN: the proximal lobar nodes, distal to the mediastinal pleural ref–lection and the nodes adjacent to the bronchus intermedius on the right; Mediastinal LN, from highest mediastinal lymph node to pulmonary ligament nodes except hilar lymph node.
LN, lymph node; TP, true positive; FP, false positive; TN, true negative; FN, false nega–tive; Sn, sensitivity; Sp, specificity.

DISCUSSION

This study showed that ^{18}F-FDG PET could effectively detect early recurrences in patients with endometrial cancer showing NED after primary treatment. Nineteen patients who were confirmed to have recurrence in this study did not have any sign of recurrence by conventional follow-up methods including physical examination, PAP smear, serum CA-125 level and imaging study such as CT or MRI. Thus, the 19 patients (15%, 19/127 patients) who were identified to have recurrence were detected solely by ^{18}F-FDG PET.

The feasibility of ^{18}F-FDG PET for detecting early recurrence in patients with endometrial cancer was already suggested by several studies that had the limitation of a small number of cases. A study on ^{18}F-FDG PET for the post-therapy surveillance in 34 patients with endometrial cancer showed that early recurrence was detected by ^{18}F-FDG PET in 12% of patients who were not suspected to have recurrence at the control visits (7). However, because the population of the previous studies is small and limited, the role of ^{18}F-FDG PET as a post-therapy surveillance method has been remained unclear.

Our study confirmed that 15% of patients with endometrial cancer who showed NED by conventional follow-up methods had a recurrence, showing that ^{18}F-FDG PET was a useful post-therapy surveillance method in patients with endometrial cancer. The number of enrolled patients in this study is the largest series up-to-date, and it well represents the general characteristics of patients with endometrial cancer (Table 1).

The higher detection rate of ^{18}F-FDG PET over conventional imaging methods such as CT or MRI can be explained in several ways. First, ^{18}F-FDG PET detects the metabolic change that precedes the anatomical change (8). This characteristic of ^{18}F-FDG PET is particularly useful for lesions where the anatomical structure is deformed by fibrosis due to previous surgery or radiotherapy (6, 9). Second, ^{18}F-FDG PET is convenient for obtaining a whole-body image at once. It is known that distant metastases frequently occur in patients with endometrial cancers; however, the conventional follow-up methods are usually limited to the abdomen and pelvis (16). This suggests that ^{18}F-FDG PET can be useful as a post-therapy surveillance tool in patients with endometrial cancer because ^{18}F-FDG PET can obtain a whole-body image at once.

Most recurrences in patients with endometrial cancer are known to develop within two years (2). In this study, 58% of the recurrences were detected within 12 months, suggesting that ^{18}F-FDG PET could detect recurrences earlier than the conventional methods. The early detection of recurrence is important because it provides an earlier opportunity for salvage treatment, which might improves the prognosis (17). It was recently reported that the early detection of recurrence by ^{18}F-FDG PET significantly altered the treatment plan in patients with endometrial cancer, which supports the importance of early detection of recurrence (7). In this study, even though most of the recurrence was detected at 6-12 months after treatment, the optimal time of ^{18}F-FDG PET should be investigated by prospective studies.

Although ^{18}F-FDG PET showed a high sensitivity and specificity for detecting recurrent lesions, a high false positivity was reported as well (7, 11, 18). In this study, the high false positivity of ^{18}F-FDG PET was observed in the vaginal stump, spine and inguinal lymph nodes, where the physiologic uptake by the bladder, ureter and intestine is common. The relative low PPV of ^{18}F-FDG PET in this study also arose from the high false positivity in these areas. Therefore, hot uptake lesions on ^{18}F-FDG PET in the vaginal stump, spine and inguinal lymph nodes should be interpreted more carefully to exclude the possibility of false positivity. However, we thought that the false positive lesions on PET could be correctly interpreted as physiologic uptake if the PET/CT had been performed. Considering the PET/CT is gaining popularity in Korea, further studies on the role of PET/CT in post-therapy surveillance of endometrial cancer is necessary.

There was a pulmonary metastasis smaller than 1 cm that was not detected by ^{18}F-FDG PET, but it was detected by additional chest CT scan. The false negativity of ^{18}F-FDG PET for lung lesion was also reported in other studies, and this can be explained by

the small size of the lesion, which was below the resolution power of ^{18}F-FDG PET, or the respiratory movement of the lung parenchyma, which may obscure the accuracy of ^{18}F-FDG PET (7).

In conclusion, our study showed that ^{18}F-FDG PET could detect recurrences in 15% of the patients with endometrial cancer who showed NED by the conventional follow-up methods. ^{18}F-FDG PET may be a useful method for post-therapy surveillance and provide the opportunity for a more sophisticated treatment in patients with endometrial cancer.

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