Prognostic Value of 16α-^{18}F-Fluoro-17β-Estradiol PET as a Predictor of Disease Outcome in Endometrial Cancer: A Prospective Study

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The purpose of this study was to evaluate the potential of 16α-^{18}F-fluoro-17β-estradiol (^{18}F-FES) PET to predict prognosis in patients with endometrial cancer (EC). **Methods:** In total, 67 patients with International Federation of Gynecology and Obstetrics (FIGO) stage I–IV EC underwent ^{18}F-FES and ^{18}F-FDG PET/CT before treatment. The SUV_{mean} of the primary tumor was compared with the clinical characteristics, and the relationships between SUV and progression-free survival (PFS) or overall survival were analyzed. **Results:** ^{18}F-FES SUV was significantly associated with stage, histology, lymphovascular space involvement (LVSI), and lymph node metastasis, and ^{18}F-FDG SUV was significantly associated with stage, myometrial invasion, tumor size, and lymph node metastasis. Receiver-operating characteristic curve analysis revealed that ^{18}F-FES SUV could significantly detect tumor progression and survival, with areas under the curve of 0.813 and 0.790, respectively, whereas ^{18}F-FDG SUV could detect them with areas under the curve of 0.557 and 0.635, respectively. The Kaplan–Meier survival curve showed that patients with a low ^{18}F-FES SUV had significantly poor PFS ($P < 0.001$) and overall survival ($P = 0.001$) compared with patients with a high SUV, whereas ^{18}F-FDG showed no significant differences. In a subanalysis of 27 patients with a low risk of recurrence (FIGO stage IA endometrioid carcinoma [grade 1 or 2] without LVSI), those with a low ^{18}F-FES SUV also had poorer PFS than those with a high SUV ($P = 0.002$). In multivariate analysis, an ^{18}F-FES SUV of less than 2.63 ($P = 0.037$; hazard ratio, 10.727; 95% CI, 1.16–99.35) and FIGO stages III and IV ($P = 0.042$; hazard ratio, 8.838; 95% CI, 1.09–71.84) were significantly associated with PFS. **Conclusion:** A low ^{18}F-FES for the primary tumor was strongly associated with prognostic factors of EC such as LVSI and lymph node metastasis, and a low ^{18}F-FES SUV was an independent prognostic factor for PFS in patients with EC. These data suggest that pretreatment ^{18}F-FES PET might be useful in determining the appropriate treatment for patients with EC.

Key Words: 16α-^{18}F-fluoro-17β-estradiol (^{18}F-FES); ^{18}F-FDG; PET/CT; endometrial cancer; prognostic marker

J Nucl Med 2021; 62:636–642
DOI: 10.2967/jnumed.120.244319

Received Mar. 2, 2020; revision accepted Sep. 2, 2020.
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Published online Oct. 2, 2020.

Endometrial cancer (EC) is the fourth most common cancer affecting women in developed countries (*1*), and the incidence of EC has continued to increase gradually (*2*). The 5-y survival rate for EC is around 80%, even for early-stage EC (*3*). Several risk factors are reported to be related to poor outcome in patients with EC, including surgical stage, lymph node metastasis, lymphovascular space involvement (LVSI), myometrial invasion, cervical involvement, and histology (*4*). However, these risk factors are insufficient to accurately estimate prognosis, and most can be identified only postoperatively. At present, there are no prognostic markers for patients who do not undergo surgery in order to preserve their fertility or because of a poor performance status. Thus, identifying new prognostic markers that can preoperatively and noninvasively predict the prognosis of patients with EC is critical.

Many studies have reported the prognostic value of estrogen receptor α (ERα) expression in EC. A higher level of ERα has been identified as a predictive factor for favorable survival (*5–7*). However, a tissue sample cannot be obtained without invasive biopsy or surgery. If a tissue sample is obtained, evaluation of ERα expression by immunohistochemistry can be performed in only a small part of the tumor. Therefore, a method for evaluating ERα expression in the whole tumor is required to evaluate the ERα status of the tumor. The radiopharmaceutical 16α-^{18}F-fluoro-17β-estradiol (^{18}F-FES) binds to ERα and is commonly used to confirm the presence of ERα-positive metastases throughout the tumor (*8*). Our previous study revealed that ^{18}F-FES uptake showed a significantly positive association with expression of ERα in EC (*9*). We have also reported that the mean ^{18}F-FES SUV combined with the mean ^{18}F-FDG SUV could indicate tumor aggressiveness in patients with EC (*10*). However, these studies had many limitations, including sample size and pathologic subtypes, and the association between ^{18}F-FES and EC patient outcomes, including recurrence or death, remains unclear.

Therefore, the purpose of the present prospective study was to clarify the potential of preoperative ^{18}F-FES PET for predicting outcomes such as recurrence or death in patients with EC.

MATERIALS AND METHODS

Patients

This prospective study included 67 patients with untreated EC (International Federation of Gynecology and Obstetrics [FIGO] stage

IA–IVB) who were referred for pretreatment assessment to the University of Fukui Hospital between December 2004 and December 2015. The inclusion criteria were histologically confirmed primary EC diagnosed by endometrial biopsy, and surgical treatment, irrespective of age or menstrual status. Patients who had received hormone therapy, wished to preserve fertility, had participated in a clinical trial that was not a standard treatment, or had life-threatening complications were excluded.

All patients underwent ^{18}F-FES and ^{18}F-FDG PET/CT before initial treatment. All patients underwent surgery, and the surgical specimens from each patient were examined histologically. The World Health Organization classification was used for histopathologic diagnosis. Patients were followed up for at least 24 mo after the date of their first visit or until death. Of the present participants, 19 of 52 patients with G1–3 endometrioid carcinoma and 2 of 8 patients with carcinosarcoma were included in our previous studies (*10,11*).

The study was approved by the Institutional Review Board of the University of Fukui Hospital (approval 20108007), and all subjects signed an informed consent form before undergoing PET.

PET Procedure

^{18}F-FES was synthesized as previously reported (*8*). ^{18}F-FES PET was performed with a dedicated full-ring PET scanner (Advance; GE Healthcare) used for medical research, and ^{18}F-FDG PET was performed with a combined PET/CT scanner (Discovery LS; GE Healthcare) used mainly for clinical purposes. The patients underwent both ^{18}F-FES and ^{18}F-FDG PET scanning, as described in our previous studies (*10,11*). The 2 PET scans were performed on 2 separate days within 1 wk of each other, in random order. We previously reported that the ^{18}F-FES SUV of normal endometrium was significantly higher in the proliferative phase than in the secretory phase (6.03 ± 1.05 vs. 3.97 ± 1.29) (*12*). Therefore, to minimize the effects of normal endometrial uptake, the ^{18}F-FES PET scans of premenopausal patients were obtained in the luteal phase. Approximately 185 MBq of tracer were administered via the antecubital vein for each ^{18}F-FES or ^{18}F-FDG PET study. The patients fasted for at least 4 h before each study. Fifty minutes after tracer injection, each patient was placed supine on the PET or PET/CT scanner bed. For PET, a 16-min emission scan was obtained, with 3-min scans of the pelvic region (2 bed positions) and 2-min scans of each remaining region (5 bed positions) to provide total coverage from the head to the inguinal area. After the emission scans, postinjection transmission scans lasting 2 min for the pelvis and 1 min for other areas were acquired using a ^{68}Ge/^{68}Ga rod source for attenuation correction. For PET/CT, the following CT scanning parameters were used for attenuation correction: automatic amperage (upper limit, 40 mA; noise index, 20), 140 kV, section thickness of 5 mm, table feed of 15 mm, and pitch of 4. After the CT transmission scan, a whole-body emission scan was performed from the head to the inguinal region at 2 min per bed position (7–8 bed positions). The iterative method was used to reconstruct PET data by selecting 14 subsets and 2 iterations. The reconstructed images were then converted to SUVs.

Image Analysis

MRI was performed before the 2 PET examinations to obtain a diagnosis and anatomic information on the pelvic organs. T1- and T2-weighted images of the pelvis were acquired in the axial, sagittal, and coronal planes using a 1.5- or 3.0-T superconducting MRI system (Signa; GE Healthcare). After injection of gadolinium diethylenetriamine pentaacetic acid (0.1 mmol/kg), contrast-enhanced MRI was performed with and without fat saturation in the axial and sagittal planes. The method of image analysis has been reported previously (*9,13*). To obtain the regional SUV_{mean}, multiple circular regions of interest with a fixed diameter of 8 mm were drawn on primary tumor lesions irrespective of the presence of metastatic lesions. The SUV at the center of the lesion was obtained on 2 or 3 sagittal or transaxial slices 4 mm thick. For small lesions, a single section at the center of the lesion was used to avoid substantial partial-volume effects on the SUV_{mean}. To avoid the effect of uptake by normal uterine tissue, individual MR images were referenced for placement of regions of interest in the appropriate region after coregistration of the PET and MR images (Body Guide; Advance Biologic Co.). Because all 3 images have the same spatial coordinates, regions of interest were applied to resliced ^{18}F-FES and ^{18}F-FDG PET images in the same location. The SUVs for each patient were averaged for all regions of interest to obtain the SUV_{mean} of the tumor for ^{18}F-FES and for ^{18}F-FDG. The ^{18}F-FDG/FES SUV ratio for each lesion was also calculated.

Endpoints

The primary endpoints were progression-free survival (PFS) and overall survival (OS). The date on which endometrial biopsy was performed was used as the starting point for PFS and OS. Tumor progression was confirmed by either imaging or tissue biopsy showing evidence of progressive disease according to the World Health Organization RECIST guidelines. The secondary endpoint was the prediction of postoperative recurrence risk factors (surgical stage, lymph node metastasis, LVSI, myometrial invasion, and histology) by preoperative PET parameters.

TABLE 1
Patient and Tumor Characteristics

Characteristic	*n*	%
Total number of patients	67	100
Histology		
Endometrioid	52	77.6
G1	31	46.3
G2	18	26.9
G3	3	4.5
Nonendometrioid		
Mixed	4	6.0
Serous	2	3.0
Squamous	1	1.5
Carcinosarcoma	8	11.9
FIGO stage		
I	46	68.7
II	8	11.9
III	7	10.4
IV	6	9.0
Treatment		
Surgery	32	47.8
Surgery + chemotherapy	35	52.2
Lymphadenectomy	51	76.1
Myometrial invasion ≥ 1/2	20	29.9
Tumor size ≥ 2 cm	43	64.2
Presence of LVSI	26	38.8
Presence of lymph node metastasis	7	10.4
Tumor progression	14	20.9
Death	6	9.0

Statistical Analysis

Calculation of sample size was based on previous results for ER expression as a predictive marker for PFS (*14*). All data were collected in a structured database and analyzed using SPSS statistics, version 25 (IBM). The Mann–Whitney *U* test was used to analyze relationships between clinical characteristics and PET parameters. Receiver-operating-characteristic curve analysis was used to identify optimal cutoffs for each PET parameter. The Kaplan–Meier method was used to estimate PFS and OS, and these were compared using the log-rank test. Cox proportional hazards regression modeling was used for univariate and multivariate analyses. Significance was defined as a P level of less than 0.05 (2-sided testing).

RESULTS

Patient Characteristics

Table 1 lists the clinical information for the 67 patients included in the study. The median age at diagnosis was 59.1 y (range, 32–81 y). Histopathologic subtypes included endometrioid adenocarcinoma (n = 52), mixed adenocarcinoma (n = 4), serous adenocarcinoma (n = 2), squamous adenocarcinoma (n = 1), and carcinosarcoma (n = 8).

The patients underwent total-abdominal, modified-radical, or radical hysterectomy and bilateral salpingo-oophorectomy, and 51 patients (76.1%) underwent pelvic or paraaortic lymphadenectomy. Thirty-five patients (stage ≥ IB or stage IA with endometrioid G3 or other histologic type or positive LVSI) received adjuvant chemotherapy according to the clinical guidelines of the Japan Society of Gynecologic Oncology. The median follow-up period was 60 mo (range, 10.4–60 mo); 14 patients (20.9%) had tumor progression during the follow-up period, and 6 patients (9.0%) died.

The association between each PET parameter and the clinical factors is shown in Table 2. No association was seen between any PET parameter and the age of the patient at diagnosis. We found that advanced-stage (FIGO stage III–IV) patients had a significantly high ^{18}F-FDG SUV (P = 0.030) and ^{18}F-FDG/FES SUV ratio ($P < 0.001$) and a low ^{18}F-FES SUV (P = 0.015). Significant associations were identified between type II EC (grade 3 endometrioid and others) and both a low ^{18}F-FES SUV ($P < 0.001$) and a high ^{18}F-FDG/FES SUV ratio (P = 0.002). Myometrial invasion and tumor size were significantly associated with a high ^{18}F-FDG SUV (P = 0.023 and $P < 0.001$) and ^{18}F-FDG/FES SUV ratio (P = 0.010 and $P < 0.001$). Meanwhile, the presence of LVSI was significantly associated with a low ^{18}F-FES SUV ($P < 0.001$) and ^{18}F-FDG/FES SUV ratio ($P < 0.001$). Lymph node metastasis was significantly associated with all PET parameters; in particular, ^{18}F-FES SUV (P = 0.001) and ^{18}F-FDG/FES SUV ratio ($P < 0.001$) were more highly associated with lymph node metastasis than was ^{18}F-FDG SUV (P = 0.041). Tumor progression after adjuvant chemotherapy was also significantly associated with a low ^{18}F-FES SUV

TABLE 2
^{18}F-FDG SUV, ^{18}F-FES SUV, and ^{18}F-FDG/FES SUV Ratio of Primary Tumor According to Various Clinical Factors

Variable	Patients (*n*)	^{18}F-FDG SUV		^{18}F-FES SUV		^{18}F-FDG/FES SUV ratio	
		Mean ± SE	*P*	Mean ± SE	*P*	Mean ± SE	*P*
Age (y)							
<50	15	9.21 ± 1.06	0.447	4.82 ± 0.55	0.272	2.59 ± 0.54	0.895
≥50	52	8.76 ± 0.80		4.05 ± 0.28		3.11 ± 0.27	
FIGO stage							
I–II	54	8.02 ± 0.66	0.030*	4.54 ± 0.25	0.015*	2.23 ± 0.27	<0.001*
III–IV	13	12.42 ± 1.73		2.92 ± 0.63		6.27 ± 1.32	
Histology							
Endometrioid G1 and G2	49	8.81 ± 0.80	0.658	4.81 ± 0.26	<0.001*	2.20 ± 0.30	0.002*
G3 and others	18	9.02 ± 1.13		2.63 ± 0.40		5.32 ± 1.05	
Myometrial invasion							
<1/2	47	7.94 ± 0.77	0.023*	4.47 ± 0.29	0.166	2.55 ± 0.46	0.010*
≥1/2	20	11.00 ± 1.17		3.66 ± 0.46		4.03 ± 0.65	
Tumor size							
<2 cm	24	5.50 ± 0.91	<0.001*	4.70 ± 0.38	0.133	1.26 ± 0.19	<0.001*
≥2 cm	43	10.67 ± 0.76		3.96 ± 0.32		3.93 ± 0.52	
LVSI							
Absent	41	7.91 ± 0.73	0.116	4.90 ± 0.27	<0.001*	1.88 ± 0.25	<0.001*
Present	26	10.40 ± 1.23		3.15 ± 0.40		4.81 ± 0.80	
Lymph node metastasis							
Absent	60	8.33 ± 0.64	0.041*	4.52 ± 0.25	0.001*	2.52 ± 0.35	<0.001*
Present	7	13.92 ± 2.69		1.72 ± 0.19		7.53 ± 1.19	

*$P < 0.05$.

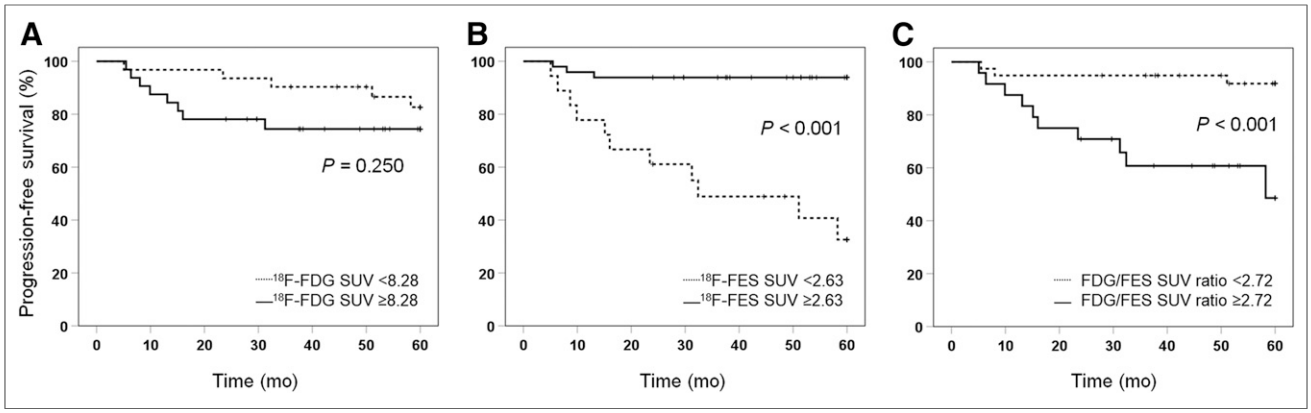

FIGURE 1. Kaplan–Meier survival curves for PFS rates among patients with EC according to ^{18}F-FDG SUV (A), ^{18}F-FES SUV (B), and ^{18}F-FDG/FES SUV ratio (C).

($P = 0.038$) (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

Cutoffs for PET Parameters

Receiver-operating-characteristic curve analysis identified an ^{18}F-FDG SUV cutoff of 8.28 for tumor progression and survival (for an area under the curve [AUC] of 0.557 for tumor progression, sensitivity was 61.5% and specificity 54.0%; for an AUC of 0.635 for survival, sensitivity was 83.3% sensitivity and specificity 54.4%). An ^{18}F-FES SUV cutoff of 2.63 was identified for tumor progression and survival (for an AUC of 0.813 for tumor progression, sensitivity was 78.6% and specificity 86.8%; for an AUC of 0.790 for survival, sensitivity was 83.3% and specificity 78.7%). An ^{18}F-FDG/FES SUV ratio cutoff of 2.72 was identified for tumor progression (for an AUC of 0.788, sensitivity was 76.9% and specificity 72.0%), and the cutoff was 4.23 for survival (for an AUC of 0.830, sensitivity was 83.3% and specificity 87.7%) (Supplemental Fig. 1).

PET Parameters and Prediction of Prognosis

Kaplan–Meier survival curves showed no significant differences in PFS or OS according to ^{18}F-FDG SUV. However, patients with a low ^{18}F-FES SUV showed a significantly poor PFS ($P < 0.001$) and OS ($P = 0.001$) compared with patients with a high ^{18}F-FES SUV; in addition, patients with a high ^{18}F-FDG/FES SUV ratio showed a significantly poor PFS ($P < 0.001$) and OS ($P < 0.001$) compared with patients with a low ratio (Figs. 1 and 2). Moreover, in 27 patients with a low risk of recurrence (FIGO stage IA endometrioid carcinoma [grade 1 or 2] without LVSI), Kaplan–Meier analysis revealed that those with a low ^{18}F-FES SUV had a significantly poor PFS ($P = 0.002$) (Fig. 3).

Univariate analysis showed a significant association of ^{18}F-FES SUV ($P < 0.001$), ^{18}F-FDG/FES SUV ratio ($P = 0.002$), low ^{18}F-FES SUV combined with high ^{18}F-FDG SUV ($P < 0.001$), FIGO stage ($P < 0.001$), histopathologic type ($P = 0.001$), myometrial invasion ($P = 0.017$), LVSI ($P = 0.002$), and lymph node metastasis ($P < 0.001$) with PFS and that ^{18}F-FES SUV ($P = 0.013$), ^{18}F-FDG/FES SUV ratio ($P = 0.002$), FIGO stage ($P = 0.003$), and lymph node metastasis ($P = 0.002$) were significantly associated with OS (Tables 3 and 4; Supplemental Table 2). Patient age and ^{18}F-FDG SUV were not significantly associated with PFS or OS. In multivariate analysis, we used 2 different models that included ^{18}F-FES SUV and ^{18}F-FDG/FES SUV ratio separately because these are related variables. An ^{18}F-FES SUV of less than 2.63 ($P = 0.037$) and a FIGO stage of III–IV ($P = 0.042$) were significantly associated with a poor PFS, whereas an ^{18}F-FDG/FES SUV ratio of at least 2.72 was not an independent prognostic factor for PFS ($P = 0.368$) (Table 3). No independent prognostic factor for OS was identified other than FIGO stage III–IV ($P = 0.043$) (Table 4). Representative cases are shown in Figure 4 and Supplemental Figure 2.

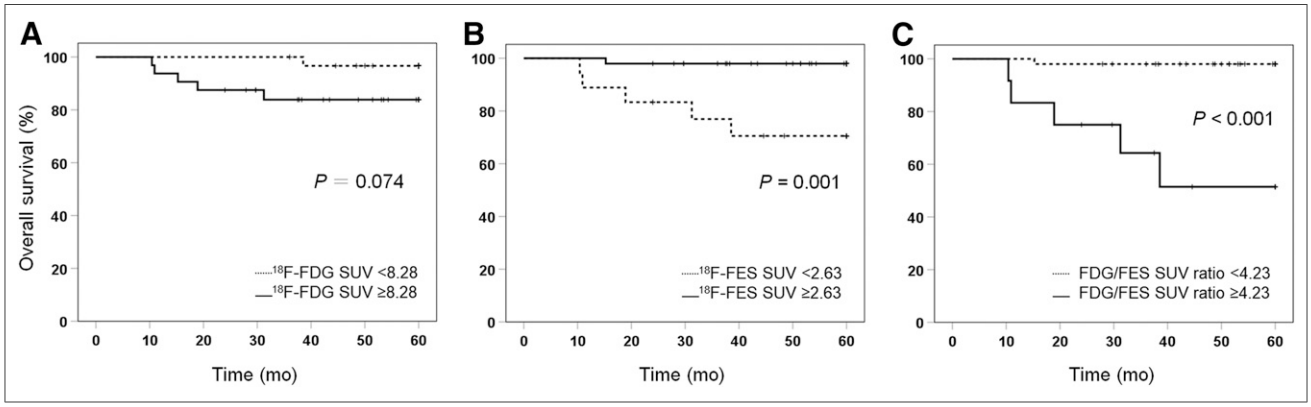

FIGURE 2. Kaplan–Meier survival curves for OS rates among patients with EC according to ^{18}F-FDG SUV (A), ^{18}F-FES SUV (B), and ^{18}F-FDG/FES SUV ratio (C).

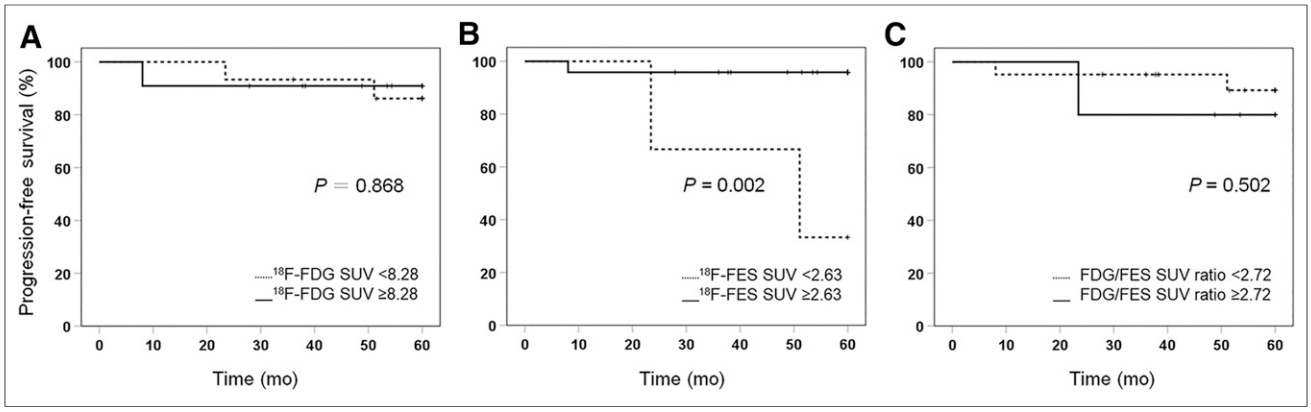

FIGURE 3. Kaplan–Meier survival curves for PFS rates among patients with low risk of recurrence (FIGO stage IA endometrioid carcinoma [grade 1 or 2] without LVSI) according to ^{18}F-FDG SUV (A), ^{18}F-FES SUV (B), and ^{18}F-FDG/FES SUV ratio (C).

DISCUSSION

The ^{18}F-FES SUV of the primary tumor was an independent prognostic factor for PFS in patients with EC. Moreover, ^{18}F-FES SUV was significantly associated with predictors of recurrence (such as LVSI and lymph node metastasis) that are difficult to predict before surgery. These data suggest that pretreatment ^{18}F-FES PET might be useful in determining therapeutic strategies and might improve the prognosis for patients with EC.

Standard treatment for early-stage EC is surgical resection, including hysterectomy and bilateral salpingo-oophorectomy. In a systematic review of the Cochrane database, lymphadenectomy did not decrease the risk of death or recurrence and appeared to increase the risk of surgery-related complications in women with a low risk of recurrence; however, in patients at intermediate or high risk of recurrence, combined pelvic and paraaortic lymphadenectomy may improve OS (*15*). Thus, accurate assessment of the risk of recurrence may be necessary to determine the optimal treatment strategy.

The ER status of EC is routinely assessed by immunohistochemistry to make the histopathologic diagnosis (*16*) or to determine tumor origin (*17*). ERα expression has also been reported to be associated with the presence of LVSI in patients with EC (*6*). Moreover, ERα loss predicted lymph node metastasis and poor outcome, because various steps of metastasis such as angiogenesis are modulated by sex steroid hormones (*7,18*). This finding suggests that assessment of ERα status can be important in predicting lymphatic metastasis. ^{18}F-FES PET has been reported to be useful for determining ERα expression and predicting hormone therapy response in patients with endometrial stromal sarcoma (*19*) or with atypical endometrial hyperplasia and low-grade EC (*20*). ^{18}F-FES PET enables noninvasive assessment of in vivo ERα status across the whole tumor, suggesting that ^{18}F-FES SUV might be a biomarker for predicting these poor-prognosis factors of EC before surgery; accordingly, accurate patient selection for additional lymphadenectomy would lead to improved outcomes.

TABLE 3
Prognostic Factors for PFS Selected by Cox Uni- and Multivariate Analysis

	Univariate analysis		Multivariate analysis			
			Model 1		Model 2	
Variable	Hazard ratio	*P*	Hazard ratio	*P*	Hazard ratio	*P*
Age at diagnosis (y)	1.008 (0.96–1.05)	0.742				
^{18}F-FDG SUV (≥8.28)	1.913 (0.62–5.89)	0.258				
^{18}F-FES SUV (<2.63)	13.459 (3.73–48.61)	<0.001*	10.727 (1.16–99.35)	0.037*		
^{18}F-FDG/FES SUV ratio (≥2.72)	7.553 (2.04–27.98)	0.002*			2.215 (0.39–12.53)	0.368
FIGO stage (stage III–IV)	12.374 (4.05–37.78)	<0.001*	8.838 (1.09–71.84)	0.042*	3.588 (0.50–25.77)	0.204
Histopathologic type (G3 and other)	6.104 (2.04–18.28)	0.001*	0.433 (0.05–3.49)	0.432	1.615 (0.38–6.91)	0.518
Myometrial invasion (≥1/2)	3.641 (1.26–10.53)	0.017*	3.331 (0.50–22.33)	0.215	1.279 (0.26–6.22)	0.760
LVSI (present)	7.797 (2.16–28.11)	0.002*	0.972 (0.13–7.02)	0.977	1.655 (0.24–11.24)	0.606
Tumor size (≥2 cm)	4.393 (0.98–19.77)	0.054				
Lymph node metastasis (present)	12.502 (4.12–37.99)	<0.001*	0.443 (0.05–3.76)	0.456	1.270 (0.20–8.30)	0.803

*$P < 0.05$.
Data in parentheses are 95% CIs.

TABLE 4
Prognostic Factors for OS According to Cox Uni- and Multivariate Analysis

	Univariate analysis		Multivariate analysis			
			Model 1		Model 2	
Variable	Hazard ratio	*P*	Hazard ratio	*P*	Hazard ratio	*P*
Age at diagnosis (y)	1.001 (0.94–1.08)	0.752				
^{18}F-FDG SUV (≥8.28)	5.693 (0.66–48.92)	0.113				
^{18}F-FES SUV (<2.63)	15.306 (1.79–131.12)	0.013*	4.982 (0.42–59.05)	0.203		
^{18}F-FDG/FES SUV ratio (≥4.23)	28.661 (3.31–248.10)	0.002*			8.998 (0.78–104.44)	0.079
FIGO stage (stage III–IV)	26.942 (3.13–231.90)	0.003*	12.866 (1.09–152.35)	0.043*	7.535 (0.56–100.69)	0.127
Histopathologic type (G3 and other)	531.672 (0.02–16,142,371.35)	0.233				
Myometrial invasion (≥1/2)	5.252 (0.96–28.71)	0.056				
LVSI (present)	155.323 (0.11–226,818.17)	0.175				
Tumor size (≥2 cm)	45.064 (0.05–41,088.27)	0.273				
Lymph node metastasis (present)	14.187 (2.75–73.11)	0.002*	1.005 (0.15–6.98)	0.996	1.432 (0.22–9.27)	0.706

*$P < 0.05$.
Data in parentheses are 95% CIs.

In the present analysis of patients with a low risk of recurrence (FIGO stage IA endometrioid carcinoma [grade 1 or 2] without LVSI), the PFS of patients with a low ^{18}F-FES SUV (<2.63) was significantly shorter than that of patients with a high ^{18}F-FES SUV. A possible reason is that ^{18}F-FES PET might predict lymphatic metastasis by detecting ERα loss earlier than is possible pathologically, by showing lymph node metastasis or LVSI. Although further study with a larger number of patients is needed, ^{18}F-FES PET may be useful for identifying those patients who should receive adjuvant therapy to prevent recurrence.

In 2009, we reported that the ^{18}F-FDG/FES SUV ratio reflected tumor aggressiveness in patients with EC (*10*). In the present study, ^{18}F-FDG/FES SUV ratio was significantly associated with all predictors of recurrence except for age; however, only the ^{18}F-FES SUV of the primary tumor was an independent prognostic factor for PFS. A possible reason for the difference between the 2 studies is that uptake of ^{18}F-FDG is affected by numerous physiologic and complicating factors, such as inflammation and menstruation (*21,22*). Another important reason is the many limitations of the previous study (*10*), which included only 22 patients and specific pathologic subtypes of endometrioid carcinoma. Moreover, patients with grade 2 endometrioid carcinoma were classified as a high-risk group, although they should be classified as a low-risk group. Because more cases were included and all pathologic subtypes were included in the

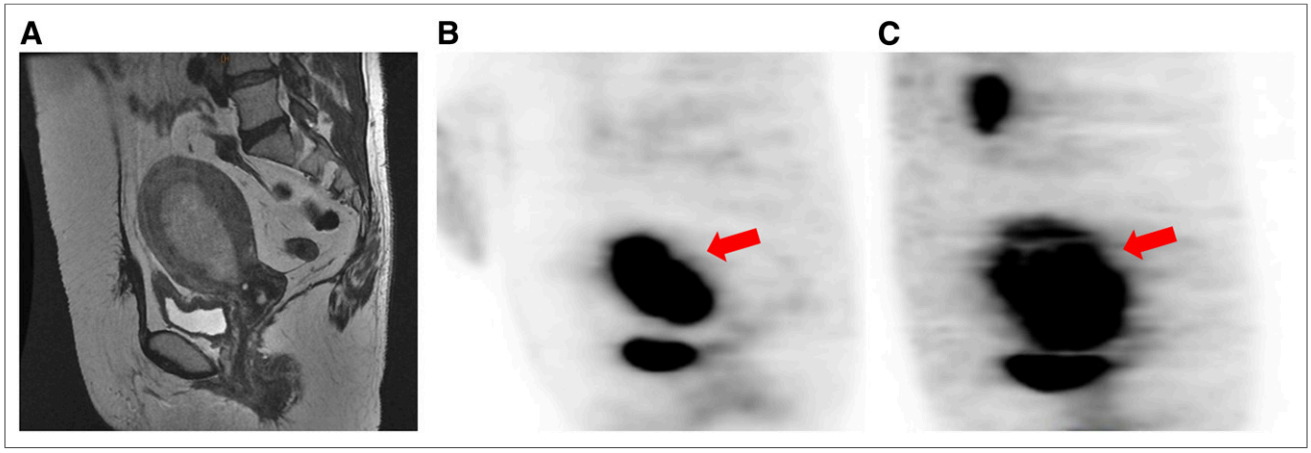

FIGURE 4. Representative case of grade 2 endometrioid adenocarcinoma, FIGO stage IVB (metastasis to supraclavicular lymph node), in 50-y-old patient. (A–C) T2-weighted MR image (A), ^{18}F-FDG PET image (B), and ^{18}F-FES PET image (C). ^{18}F-FDG SUV, ^{18}F-FES SUV, and ^{18}F-FDG/FES SUV ratios of primary tumor were 8.5, 16.6, and 2.0, respectively. Arrows indicate primary tumor. Patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and chemotherapy and was free from recurrence or metastasis for 60 mo.

present study, these findings reflect the prognosis of the patients much more accurately than do the previous findings and may therefore be used to determine the treatment strategy in EC.

There are some limitations to the present study. First, the investigation was performed at a single institution and the patient cohort was small. Second, both pre- and postmenopausal patients were included. EC is most commonly detected after menopause (*23*), and most of our patients were aged 50 y and above. Premenopausal patients had PET scans in the luteal phase to minimize the effects of normal endometrial uptake. Moreover, a previous study by our group showed that the plasma level of endogenous estrogen was not associated with ^{18}F-FES accumulation in the uterine endometrium, and the SUV in the myometrium is relatively constant in most healthy premenopausal control subjects (*12*), suggesting that menstrual phase would have had little effect on the results. Third, no PET parameter was identified as an independent prognostic factor for OS, because there were few deaths and OS can be affected by treatment after recurrence. Further larger studies and analyses considering menopausal status and treatment after recurrence should be conducted to evaluate the predictive value and role of ^{18}F-FES PET.

CONCLUSION

^{18}F-FES uptake measured as the SUV_{mean} of the primary tumor was an independent prognostic factor for PFS in patients with EC. Moreover, there was a significant association between ^{18}F-FES SUV and predictors of recurrence such as LVSI and lymph node metastasis. These data suggest that pretreatment ^{18}F-FES PET might be useful for determining the appropriate treatment for patients with EC.

DISCLOSURE

This study was supported in part by grants-in-aid 16K10345 and 18K16763 for scientific research from the Japan Society for the Promotion of Science. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We thank Prof. Ryousuke Fujita of the Department of Biostatistics, Faculty of Medical Sciences, University of Fukui, for his invaluable statistical advice.

KEY POINTS

QUESTION: Can uptake of ^{18}F-FES PET preoperatively predict patient outcomes such as recurrence or death in patients with EC?

PERTINENT FINDINGS: ^{18}F-FES SUV was significantly associated with predictors of recurrence such as LVSI and lymph node metastasis and was an independent prognostic factor for PFS.

IMPLICATIONS FOR PATIENT CARE: ^{18}F-FES PET might be used to determine therapeutic strategies such as adjuvant chemotherapy and lymphadenectomy and thus potentially improve the prognosis of patients with EC.

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