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Prognostic value of 16α-^{18}F-fluoro-17β-estradiol positron emission tomography as a predictor of disease outcome in endometrial cancer: A prospective study

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Short running title: FES PET in endometrial cancer

ABSTRACT

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: A total of 67 patients with the International Federation of Gynecology and Obstetrics (FIGO) stage I–IV endometrial cancer underwent ^{18}F-FES and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) before treatment. The mean standardized uptake value (SUV) of the primary tumor was compared with the clinical characteristics, and the relationships between SUV and progression-free survival (PFS) or overall survival (OS) were analyzed.

Results: ^{18}F-FES SUV significantly associated with stage, histology, lymphovascular space involvement (LVSI), and lymph node metastasis; and ^{18}F-FDG SUV 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 area under the curve (AUC) of 0.813 and 0.790, respectively; whereas ^{18}F-FDG SUV could detect them with AUC of 0.557 and 0.635. The Kaplan–Meier survival curve showed that patients with low ^{18}F-FES SUV had significantly poor PFS (P <0.001) and OS (P = 0.001) compared with patients with high SUV, whereas ^{18}F-FDG showed no significant differences. In a sub-analysis of 27 patients with low risk of recurrence (FIGO stage IA endometrioid carcinoma [grade 1 or 2] without LVSI), those with low ^{18}F-FES SUV also had poorer PFS than those with high SUV (P = 0.002). In multivariate analysis, ^{18}F-FES SUV <2.63 (P = 0.037, hazard ratio (HR) 10.727, 95% confidence interval (CI) 1.16–99.35), and FIGO stages III and IV (P =

0.042, HR 8.838, 95%CI 1.09–71.84) were significantly associated with PFS.

Conclusion: Low ^{18}F-FES SUV of the primary tumor associated strongly with prognostic factors of EC such as LVSI and lymph node metastasis, and 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-fluorodeoxyglucose (^{18}F-FDG); positron emission tomography/computed tomography (PET/CT); endometrial cancer; prognostic marker

INTRODUCTION

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-year survival rate for EC is around 80%, even for early-stage EC (*3*). Several risk factors are reported to be related with 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 for the reasons of preservation of their fertility or 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 of 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

standardized uptake value (SUV) combined with the mean ^{18}F-fluorodeoxyglucose (^{18}F-FDG) SUV could indicate tumor aggressiveness in patients with EC (*10*). However, these studies had many limitations, including sample size and pathological 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 to 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 prior to initial treatment. All patients underwent surgery and histopathological examination was performed of the surgical specimens from each patient. The World Health Organization classification was

used for histopathological diagnosis. Patients were followed-up for at least 24 months after the date of their first visit or until death. Of the present participants, 19/52 patients with G1-3 endometrioid carcinoma and 2/8 patients with carcinosarcoma were included in our previous studies (*10,11*).

The study has been approved by the Institutional Review Board of the University of Fukui Hospital (IRB number: 20108007) and all subjects signed an informed consent form prior to PET.

PET Procedure

^{18}F-FES synthesis was performed as previously reported (*8*). ^{18}F-FES PET was performed with a dedicated full-ring PET scanner (Advance; GE Medical Systems, Milwaukee, WI) used for medical research, and ^{18}F-FDG PET was performed with a combined PET/CT scanner (Discovery LS; GE Medical Systems) used mainly for clinical purposes. Patients underwent both ^{18}F-FES and ^{18}F-FDG PET scanning, as described in our previous studies (*10,11*). The two PET scans were performed on two separate days within one week, in random order. We previously reported that ^{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 pre-menopausal 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 in the supine position 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 (two bed positions) and 2-min scans of each remaining region (five bed positions) to provide total coverage of the head-to-inguinal area. After the emission scans, post-injection transmission scans of 2 min of the pelvis and 1 min of 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: auto mA (upper limit, 40 mA; noise index, 20), 140 kV, section thickness 5 mm, table feed 15 mm, and pitch 4. Following the CT transmission scan, a whole-body emission scan was performed from the head to the inguinal region with 2 min per bed position (7–8 bed positions). The iterative reconstruction method was used to reconstruct PET data by selecting 14 subsets and 2 iterations. The reconstructed images were then converted to SUVs.

Image Analysis

Magnetic resonance imaging (MRI) was performed before the two PET examinations for diagnosis and to obtain anatomic information of 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 Medical Systems). Following 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 regional SUVmean values, multiple circular regions of interest (ROIs) with a fixed diameter of 8 mm were drawn on primary tumor lesions, and placed to avoid metastatic lesions. The SUV at the center of the

lesion was obtained on two or three sagittal or transaxial slices of thickness 4 mm. In the case of small lesions, a single section at the center of the lesion was used to avoid substantial partial-volume effects on the mean SUV. To avoid the effect of normal uterine tissue uptake, individual MR images were referenced for placement of ROIs in the appropriate region following co-registration of the PET and MR images (Body Guide, Advance Biologic Co., Toronto, Canada). As all three images have the same spatial coordinates, ROIs were applied to re-sliced ^{18}F-FES and ^{18}F-FDG PET images in the same location. The SUVs for each patient were averaged for all ROI values to obtain the SUVmean of the tumor for ^{18}F-FES and for ^{18}F-FDG. The 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 at 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 Response Evaluation Criteria in Solid Tumors (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.

Statistical Analysis

Sample size calculation was performed based on previous results of ER expression as

predictive markers for PFS (*14*). All data were collected in a structured database and analyzed using SPSS statistics version 25 (IBM, Armonk, NY). The Mann–Whitney U test was used to analyze relationships between clinical characteristics and PET parameters. Receiver-operating characteristic (ROC) curve analysis was used to identify optimal cut-off values 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 $P < 0.05$ (2-sided testing).

RESULTS

Patient Characteristics

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

The patients received total abdominal, modified radical, or radical hysterectomy and bilateral salpingo-oophorectomy, and 51/67 patients (76.1%) received pelvic and/or para-aortic lymphadenectomy. Thirty-five patients (stage ≥ IB or stage IA with endometrioid G3 or other histological 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 months (range, 10.4–60 months); 14/67

patients (20.9%) had tumor progression during the follow-up period, and 6/67 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 significantly high ^{18}F-FDG SUV ($P = 0.030$) and FDG/FES SUV ratio ($P < 0.001$), and low ^{18}F-FES SUV ($P = 0.015$). Significant associations were identified between Type II EC (grade 3 endometrioid and others) and both low ^{18}F-FES SUV ($P < 0.001$) and high FDG/FES SUV ratio ($P = 0.002$). Myometrial invasion and tumor size were significantly associated with high ^{18}F-FDG SUV ($P = 0.023$ and $P < 0.001$) and FDG/FES SUV ratio ($P = 0.010$ and $P < 0.001$). Meanwhile, presence of LVSI was significantly associated with low ^{18}F-FES SUV ($P < 0.001$) and 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 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 low ^{18}F-FES SUV ($P = 0.038$) (Supplemental Table 1).

Cut-off Values for PET Parameters

ROC curve analysis identified an ^{18}F-FDG SUV cut-off of 8.28 for tumor progression and survival (area under the curve (AUC) 0.557, 61.5% sensitivity, 54.0% specificity for tumor progression; AUC 0.635, 83.3% sensitivity, 54.4% specificity for survival), an ^{18}F-FES SUV cut-off of 2.63 for tumor progression and survival (AUC, 0.813, 78.6% sensitivity,

86.8% specificity for tumor progression; AUC 0.790, 83.3% sensitivity, 78.7% specificity for survival), and FDG/FES SUV ratio cut-offs of 2.72 for tumor progression (AUC 0.788, 76.9% sensitivity, 72.0% specificity) and 4.23 for survival (AUC 0.830, 83.3% sensitivity, 87.7% specificity) (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 low ^{18}F-FES SUV showed significantly poor PFS (P <0.001) and OS (P = 0.001) compared with patients with high ^{18}F-FES SUV; in addition, patients with a high FDG/FES SUV ratio showed significantly poor PFS (P <0.001) and OS (P <0.001) compared with patients with a low ratio (Figs 1, 2). Moreover, in 27 patients with low risk of recurrence (FIGO stage IA endometrioid carcinoma, [grade 1 or 2] without LVSI), Kaplan–Meier analysis revealed that those with low ^{18}F-FES SUV had significantly poor PFS (P = 0.002) (Fig. 3).

Univariate analysis showed a significant association of ^{18}F-FES SUV (P <0.001), 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), 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 two different models that included

^{18}F-FES SUV and the FDG/FES SUV ratio separately because ^{18}F-FES SUV and the FDG/FES SUV ratio are related variables. An ^{18}F-FES SUV <2.63 (P = 0.037) and FIGO stage III–IV (P = 0.042) were significantly associated with poor PFS, whereas an FDG/FES SUV ratio ≥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 Fig. 4 and Supplemental Fig. 2.

DISCUSSION

^{18}F-FES SUV of the primary tumor was an independent prognostic factor for PFS in patients with EC. Moreover, ^{18}F-FES SUV 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 could 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 low risk of recurrence; however, in patients at intermediate or high risk of recurrence, combined pelvic and para-aortic lymphadenectomy may improve overall survival (*15*). Thus, accurate assessment of the risk of recurrence may be necessary to determine the optimal treatment strategy.

Assessing ER status of EC by immunohistochemistry is routinely performed for histopathological diagnosis (*16*) or to determine tumor origin (*17*). It has been reported that ERα expression is also associated with presence of LVSI in patients with EC (*6*). Moreover, ERα loss predicted lymph node metastasis and poor outcome, for the reason that 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. It has been reported that ^{18}F-FES PET is useful for determining ERα expression and predicting hormone therapy response in patients with endometrial stromal sarcoma (*19*), and in those 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, which suggests that ^{18}F-FES SUV might be a biomarker for predicting these poor prognostic factors of EC before surgery; accordingly, accurate patient selection for additional lymphadenectomy would lead to improved outcomes.

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 low ^{18}F-FES SUV (<2.63) was significantly shorter than those of patients with high ^{18}F-FES SUV. The possible reason for this finding 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 FDG/FES SUV ratio reflected tumor aggressiveness in

patients with EC (*10*). In the present study, FDG/FES SUV ratio was significantly associated with all predictors of recurrence except for age; however, only ^{18}F-FES SUV of the primary tumor was an independent prognostic factor for PFS. A possible reason for the difference in results between the two studies is that uptake of ^{18}F-FDG is affected by numerous physiological 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 pathological subtypes of endometrioid carcinoma. Moreover, grade 2 endometrioid carcinoma was classified as high-risk group although it should be classified as low-risk group. Because more cases were included and all pathological subtypes were included in the present study, these findings reflect the prognosis of the patients much more accurately than do those of previous studies, and may therefore be used to determine the treatment strategy in EC.

There are some limitations of 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 and above. Pre-menopausal 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*), which suggests that menstrual phase would have had little effect on the results. Third, no PET parameter was identified as an independent prognostic factor for OS, for the reason that there were

few deaths, and because 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 SUVmean of the primary tumor was an independent prognostic factor for PFS in patients with EC. Moreover, there was a significant association of ^{18}F-FES SUV with 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 for scientific research from the Japan Society for the Promotion of Science (Nos. 16K10345 and 18K16763). No conflicts of interest exist.

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KEY POINTS

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

PERTINENT FINDINGS: This prospective study included 67 patients with endometrial cancer, all of whom underwent ^{18}F-FES PET before treatment. The primary endpoints were progression-free survival (PFS) and overall survival. ^{18}F-FES SUV 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: These findings suggest that ^{18}F-FES PET could be used to determine therapeutic strategies such as adjuvant chemotherapy and lymphadenectomy, and thus potentially improve the prognosis of patients with endometrial cancer.

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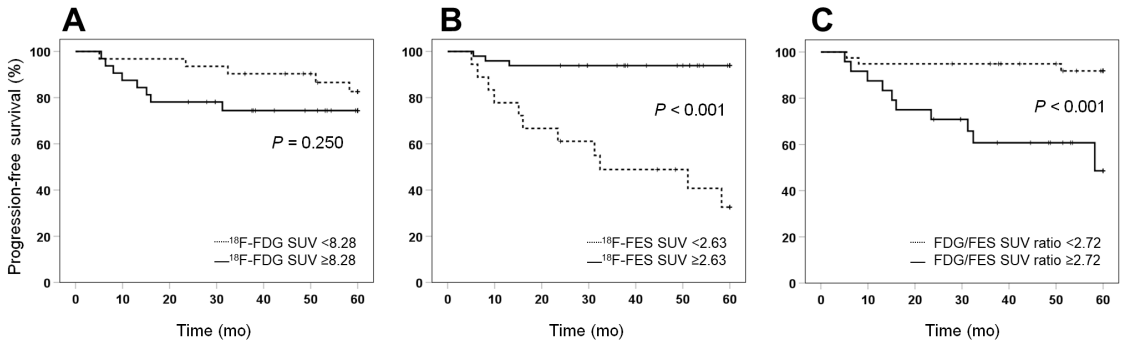


FIGURE 1 Kaplan–Meier survival curves for progression-free survival rates among patients with endometrial cancer according to ^{18}F-FDG SUV (A), ^{18}F-FES SUV (B), and FDG/FES SUV ratio (C).

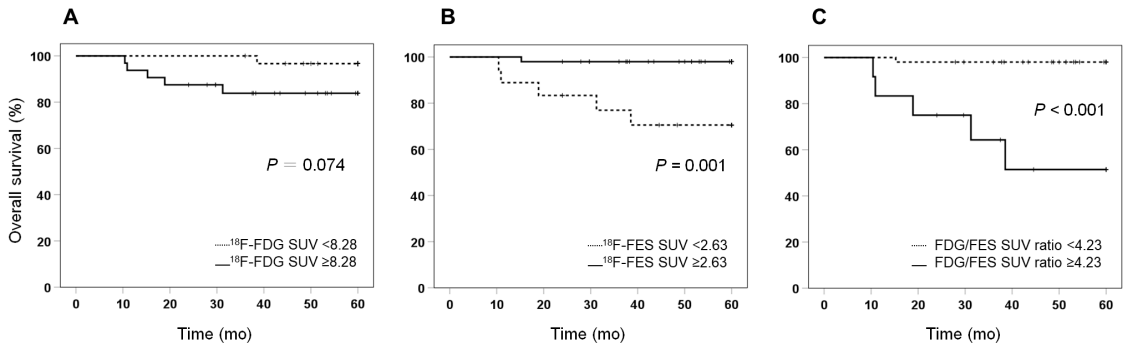


FIGURE 2 Kaplan–Meier survival curves for overall survival rates among patients with endometrial cancer according to ^{18}F-FDG SUV (A), ^{18}F-FES SUV (B), and FDG/FES SUV ratio (C).

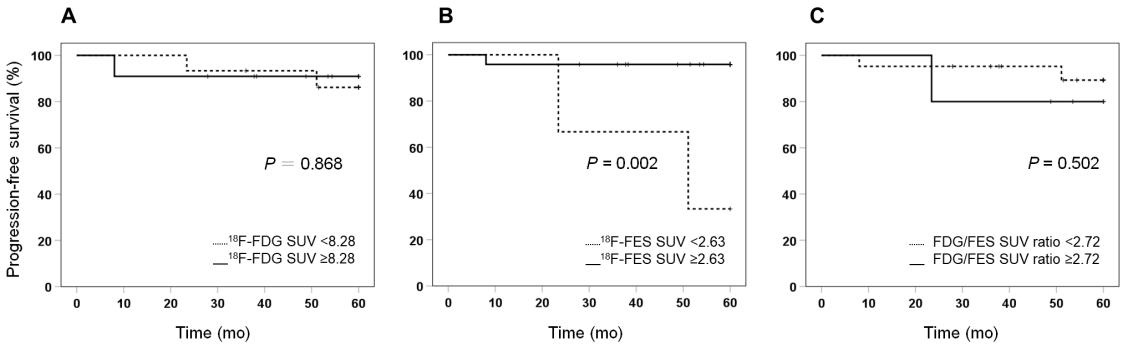


FIGURE 3 Kaplan–Meier survival curves for progression-free survival rates among patients with low risk of recurrence (FIGO stage IA endometrioid carcinoma [grade 1 or 2] without LVSI) according to ^{18}F-FDG SUV (A), ^{18}F-FES SUV (B), and FDG/FES SUV ratio (C).

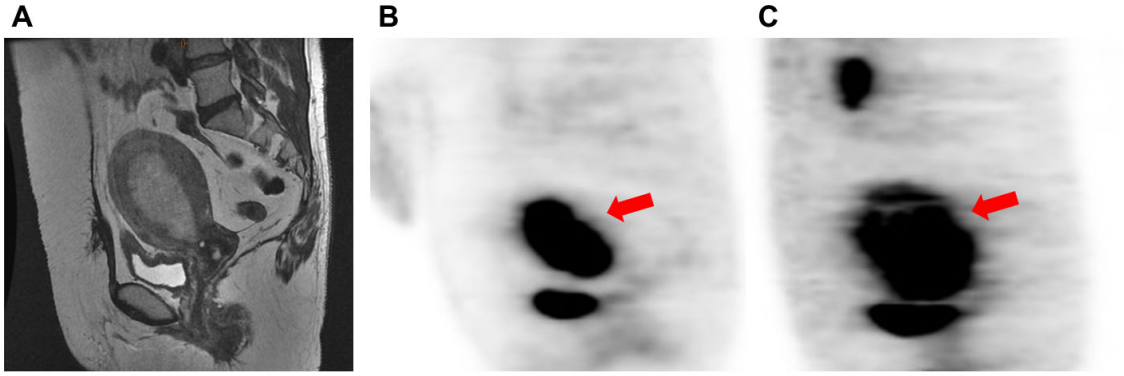


FIGURE 4 Representative case of grade 2 endometrioid adenocarcinoma in a 50-year-old patient, FIGO stage IVB (metastasis to supraclavicular lymph node). T2-weighted MR image (A), and ^{18}F-FDG (B) and ^{18}F-FES (C) PET images are shown. ^{18}F-FDG SUV, ^{18}F-FES SUV, and FDG/FES SUV ratio of the primary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

TABLE 1 Patient and tumor characteristics

Characteristic	n	%
Total number of patients	67	
Histology		
Endometrioid	52	77.6
G1	31	46.3
G2	18	26.9
G3	3	4.5
Non-endometrioid		
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 lymphovascular space involvement	26	38.8
Presence of lymph node metastasis	7	10.4
Tumor progression	14	20.9
Death	6	9.0

TABLE 2 ^{18}F-FDG SUV, ^{18}F-FES SUV, and FDG/FES SUV ratio of the primary tumor according to various clinical factors

Variable	Number of patients	^{18}F-FDG SUV		^{18}F-FES SUV		FDG/FES SUV ratio	
		mean±SE	*P*	mean±SE	*P*	mean±SE	*P*
Age (years)							
<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 2	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	
Lymphovascular space involvement							
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	

* $P < 0.05$

TABLE 3 Prognostic factors for progression-free survival selected by Cox's uni- and multivariate analysis

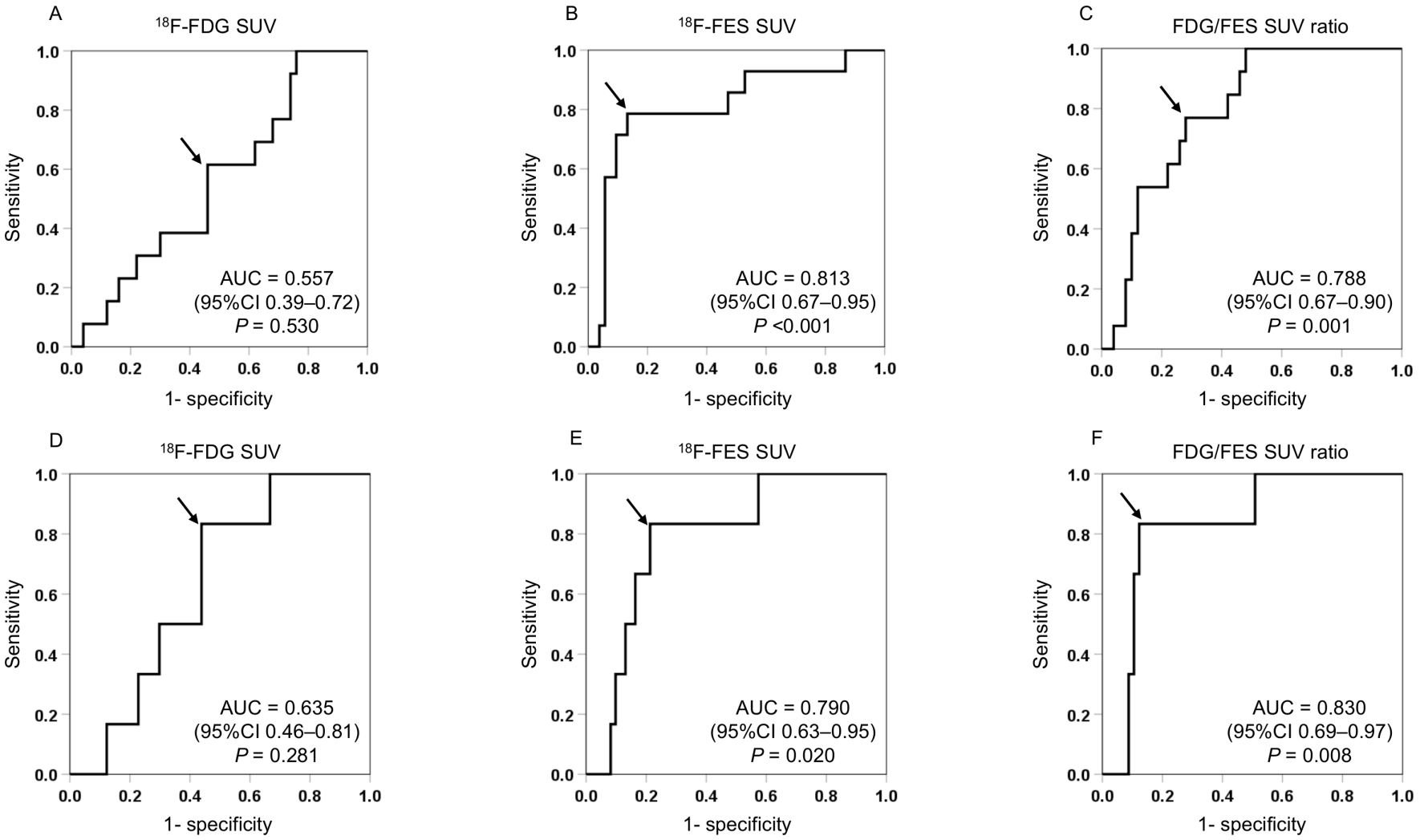
Variable	Univariate analysis		Multivariate analysis			
			Model 1		Model 2	
	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*
Age at diagnosis (years)	1.008 (0.96–1.05)	0.742				
^{18}F-FDG SUV (≥8.28)	1.913 (0.62–5.89)	0.258				
^{18}F-FES SUV (<2.63)	13.459 (3.73–48.61)	<0.001*	10.727 (1.16–99.35)	0.037*		
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

* $P < 0.05$

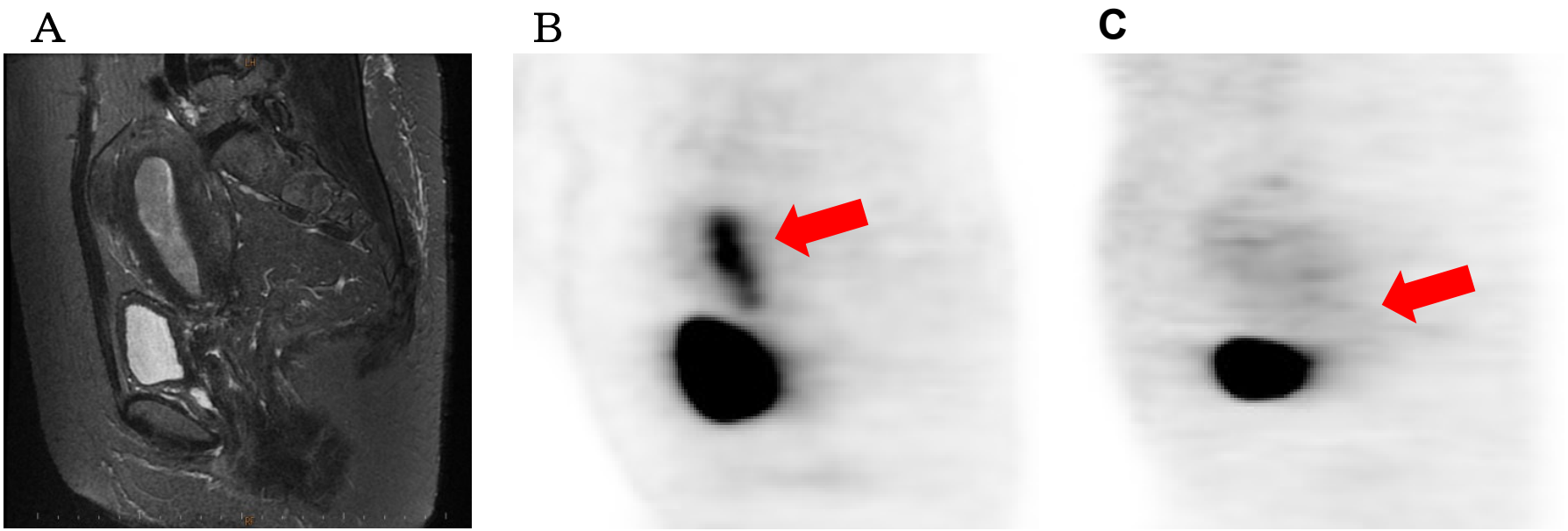
TABLE 4 Prognostic factors for overall survival according to Cox's uni- and multivariate analysis

Variable	Univariate analysis		Multivariate analysis			
			Model 1		Model 2	
	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*
Age at diagnosis (years)	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		
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 (0.02–16142371.35)	0.233				
Myometrial invasion (≥1/2)	5.252 (0.96–28.71)	0.056				
LVSI (present)	155.323 (0.11–226818.17)	0.175				
Tumor size (≥2 cm)	45.064 (0.05–41088.27)	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

* $P < 0.05$



Supplemental Fig. 1 Receiver-operating characteristic curve analysis for predicting progression-free survival (A–C) and overall survival (D–F) for the three PET parameters ^{18}F-FDG SUV, ^{18}F-FES SUV, and FDG/FES SUV ratio. AUC = area under the curve



Supplemental Fig. 2 A representative case of grade 1 endometrioid adenocarcinoma in a 48-year-old patient, FIGO stage IA. T2-weighted MR image (A), 18F-FDG (B), and 18F-FES (C) PET images are shown. 18F-FDG SUV, 18F-FES SUV, and FDG/FES SUV ratio of primary tumor were 5.2, 1.9, and 2.7, respectively. The red arrows indicate the primary tumor. This patient underwent abdominal total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy, but developed local recurrence 21 months after surgery.

Supplemental Table 1 ^{18}F-FDG SUV, ^{18}F-FES SUV, and FDG/FES SUV ratio of the primary tumor according to tumor progression in 35 patients who received adjuvant chemotherapy

Variable	Number of patients	^{18}F-FDG SUV		^{18}F-FES SUV		FDG/FES SUV ratio	
		mean±SE	*P*	mean±SE	*P*	mean±SE	*P*
Tumor progression							
Positive	9	11.54±1.64	0.401	2.52±0.63	0.038	5.38±0.98	0.053
Negative	26	9.99±1.19		4.24±0.41		3.76±0.79	

* P <0.05

Supplemental Table 2 Prognostic factors for progression-free survival according to Cox's uni- and multivariate analysis, including high ^{18}F-FDG SUV (≥8.28) and low ^{18}F-FES SUV (<2.63)

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*
Age at diagnosis (years)	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*		
Low ^{18}F-FES SUV (<2.63) and high ^{18}F-FDG SUV (≥8.28)	8.624 (2.70–27.56)	<0.001*	2.947 (0.56–15.43)	0.201
FIGO stage (stage III–IV)	12.374 (4.05–37.78)	<0.001*	6.698 (1.03-43.43)	0.046*
Histopathologic type (G3 and other)	6.104 (2.04–18.28)	0.001*	1.623 (0.36–7.34)	0.530
Myometrial invasion (≥1/2)	3.641 (1.26–10.53)	0.017*	1.355 (0.27–6.86)	0.714
LVSI (present)	7.797 (2.16–28.11)	0.002*	1.601 (0.25–10.21)	0.618
Tumor size (≥2 cm)	4.393 (0.98–19.77)	0.054		
Lymph node metastasis (present)	12.502 (4.12–37.99)	<0.001*	0.679 (0.08–5.53)	0.178

* *P* <0.05