Uterine Tumors: Pathophysiologic Imaging with $16\alpha$-$^{18}$Ffluoro-17$\beta$-estradiol and $^{18}$F Fluorodeoxyglucose PET—Initial Experience

**Purpose:**
To clarify prospectively the relationship between estrogen receptor (ER) expression and glucose metabolism by using $16\alpha$-$^{18}$Ffluoro-17$\beta$-estradiol (FES) and fluorine 18 ($^{18}$F) fluorodeoxyglucose (FDG) positron emission tomography (PET) in patients with benign and malignant uterine tumors.

**Materials and Methods:**
The institutional review board approved this study, and informed consent was obtained from all subjects. FES and FDG PET studies were performed in 38 patients (mean age, 54.1 years ± 14.0 [standard deviation]) with benign and malignant uterine tumors to compare differences in tracer accumulation. Regional values of tracer uptake were evaluated by using standardized uptake value (SUV), a normalized value corrected by using injection dose and body weight.

**Results:**
Patients with endometrial carcinoma showed significantly greater mean SUV for FDG (9.6 ± 3.3) than for FES (3.8 ± 1.8) ($P < .005$). Patients with endometrial hyperplasia showed significantly higher mean SUV for FES (7.0 ± 2.9) than for FDG (1.7 ± 0.3) ($P < .05$). Patients with leiomyoma showed significantly higher mean SUV for FES (4.2 ± 2.4) than for FDG (2.2 ± 1.1) ($P < .005$), and patients with sarcoma showed opposite tendencies for tracer accumulation. Tracer uptake in patients with endometrial carcinoma was significantly higher for FDG ($P < .001$) and significantly lower for FES ($P < .05$) when compared with values in patients with endometrial hyperplasia. On the other hand, patients with sarcoma showed a significantly higher uptake for FDG ($P < .005$) and a significantly lower uptake for FES ($P < .05$) compared with patients with leiomyoma.

**Conclusion:**
ER expression and glucose metabolism of uterine tumors measured by using PET showed opposite tendencies. PET studies with both FES and FDG could provide pathophysiologic information for the differential diagnosis of uterine tumors.

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Positron emission tomography (PET) with fluorine 18 ($^{18}$F) fluorodeoxyglucose (FDG) has been used for diagnosis of gynecologic malignant tumors and is considered to be superior to conventional imaging methods in diagnostic accuracy for detection of metastatic lesions and local recurrence (1–5). However, the diagnostic accuracy for primary tumors is inferior to that of magnetic resonance (MR) imaging (6–8). This is because the size of the tumor and inflammatory changes of the lesion may affect PET imaging and FDG accumulation. FDG uptake in the genital organs is affected by the menstrual cycle, as well (9,10). Additional physiologic information other than glucose metabolism may improve the diagnostic accuracy of PET.

$^{16a}$-$^{18}$Ffluoro-17β-estradiol (FES) is an $^{18}$F-labeled compound of estradiol, the most bioactive type of estrogen, and is used for the detection of estrogen receptor (ER)-positive organs and diseases (11,12). FES PET imaging is well established in patients with ER-positive breast cancer for diagnosis, staging, and posttherapeutic follow-up (13–18). Investigators in previous studies (13–15) reported that FES accumulation was well associated with the concentration of ER in vitro measurements, and it could therefore enable in vivo noninvasive measurement of ER density.

The purpose of our study was to clarify prospectively the relationship between ER expression and glucose metabolism by using FES and FDG PET in patients with benign and malignant uterine tumors.

**Materials and Methods**

Thirty-eight consecutive patients (mean age, 54.1 years ± 14.0 [standard deviation]), with uterine tumors that were suspected of being malignant at cytologic analysis, ultrasonography, or MR imaging, participated in this study. Nineteen women were premenopausal and 19 women were postmenopausal. None of them received any previous treatment or therapy before this study. Definitive diagnosis was determined by using postoperative histopathologic analysis ($n = 30$) or at least 6 months of follow-up by using cytologic analysis ($n = 3$) or clinical imaging ($n = 5$, all with fibroids). Final diagnoses were endometrioid adenocarcinoma ($n = 9$), endometrial hyperplasia ($n = 4$), leiomyoma ($n = 21$), and uterine sarcoma (leiomyosarcoma, $n = 1$; carcinosarcoma, $n = 3$). In five patients with leiomyoma who did not receive surgical treatment, a clinical decision was made by using results of follow-up studies with MR imaging and FDG PET. These results showed that there was no change in size and intensity, as well as no increase in FDG accumulation, in the lesions. Four of 21 patients with leiomyoma (including one woman with four lesions, one woman with three lesions, and two women with two lesions each) had multiple lesions assessed with MR imaging. Our study received institutional review board approval, and informed consent was obtained from all subjects.

**Advances in Knowledge**

- Estrogen receptor expression and glucose metabolism of uterine tumors measured by using PET with $^{16a}$-$^{18}$Ffluoro-17β-estradiol (FES) and $^{18}$F fluorodeoxyglucose (FDG) showed opposite patterns between benign and malignant lesions, providing pathophysiologic information for differential diagnosis.
- Patients with endometrial carcinoma showed a significantly higher accumulation of FDG than of FES in the primary tumors (mean standardized uptake value [SUV], $9.6 \pm 3.3$ vs $3.8 \pm 1.8$; $P < .005$), whereas those with endometrial hyperplasia showed a significantly higher uptake for FES than for FDG (mean SUV, $7.0 \pm 2.9$ vs $1.7 \pm 0.3$; $P < .05$).
- In patients with smooth-muscle tumors of the uterus, leiomyoma showed a significantly higher uptake for FES than for FDG (mean SUV, $4.2 \pm 2.4$ vs $2.2 \pm 1.1$; $P < .005$), whereas leiomyosarcoma showed higher accumulation of FDG and lower accumulation of FES (mean SUV, $6.4 \pm 4.3$ vs $1.6 \pm 0.6$; $P = .11$).
- FDG uptake for endometrial carcinoma was significantly higher than it was for endometrial hyperplasia ($P < .001$), and FES uptake was significantly lower for endometrial carcinoma than it was for endometrial hyperplasia ($P < .05$).
- FDG uptake was significantly higher ($P < .005$) and FES uptake was significantly lower ($P < .05$) for leiomyosarcoma than it was for leiomyoma.

**Implications for Patient Care**

- PET studies with both FES and FDG could provide information for the differential diagnosis of uterine tumors, which could help clinicians avoid inappropriate surgical operations and invasive whole endometrial curettage.
- FES PET could be used to evaluate the response of ER-positive endometrial carcinoma, as well as that of large uterine leiomyoma, to hormonal therapy.
PET Procedures
All patients underwent whole-body PET with FES and FDG to compare differences in tracer accumulation. Two scans were obtained on two separate days within 1 week in random sequence. In premenopausal patients, one patient underwent FES PET at the menstrual phase, eight patients underwent it at the proliferative phase, and five patients underwent it at the secretory phase. Six patients underwent FDG PET at the proliferative phase, and eight patients underwent it at the secretory phase. The other five patients had irregular menstruation, and, therefore, it was unclear in what phase of the menstrual cycle the studies were performed. We used a whole-body tomographic scanner (Advance; GE Medical Systems, Milwaukee, Wis), which permits simultaneous acquisition of 35 image sections in a two-dimensional acquisition mode with intersection spacing of 4.25 mm. Performance tests showed the intrinsic resolution of the scanner to be 4.0–5.3 mm in the axial direction (z axis) and 4.6–5.7 mm in the transaxial direction (xy plane).

\(^{18}\)F FES was synthesized by using the method reported elsewhere (11,19). The specific activity was 100–200 GBq/μmol, and radiochemical purity was greater than 99%. For each study with FES and FDG PET, approximately 185 MBq of tracer was administered into the antecubital vein. Before tracer administration, patients fasted at least 4 hours for each study. Fifty minutes after the tracer injection, the patient was positioned supine in the PET scanner, and a 16-minute emission scan was obtained, with 3-minute scans obtained at the pelvic region (two bed positions) and 2-minute scans obtained in each remaining region (five bed positions) to completely cover the region from the head to the inguinal areas. Postinjection transmission scans of 2 minutes at the pelvis and 1 minute in other areas were obtained after the emission scans by using a germanium 68/gallium 68 rod source for attenuation correction. The PET data were reconstructed by the iterative reconstruction method, with selection of 14 subsets and two iterations. The reconstructed images were then converted to a semiquantitative image corrected by the injection dose and the subject’s body weight (standardized uptake value [SUV]) for data analysis.

Data Analysis
All subjects underwent MR imaging during the time between the two PET examinations, or within 1 week from them, for diagnosis and to obtain anatomic information about the pelvic organs. T1- and T2-weighted images in the sagittal and coronal planes were acquired with a 1.5-T superconducting MR imaging system (Signa; GE Medical Systems). For T1-weighted MR images, the repetition time msec/echo time msec was 533/8, and that for T2-weighted images was 4700/90.

Circular regions of interest with a fixed size of 8 mm in diameter were drawn on the lesions to obtain the local SUV. Individual MR images were referenced for placement of regions of interest in the appropriate region after PET and MR images were coregistered (Body Guide; Advance Biologic, Toronto, Canada). Two or three sagittal or coronal planes with 6-mm thickness were used to obtain SUV at the center of the lesion. A single section at the center of the lesion was used when the lesion was small and substantial partial volume effects on the mean SUV value were expected. The same numbers of regions of interest were drawn on the FES and FDG PET images in each patient by using similarly placed uterine sections. The regions of interest were placed by two radiologists (T.T. and H.O., with 8 and 19 years of experience, respectively). SUVs of three patients with carcinosarcoma were obtained from the sarcoma-rich region of each tumor, which was diagnosed as leiomyosarcoma from MR imaging findings.

In patients with multiple lesions, SUVs for each patient were averaged. The FDG/FES ratio of the mean SUV for each lesion was also calculated.

Statistical Analysis
The mean SUVs of the lesions were compared between diseases by using analysis of variance with a post hoc Fisher protected least-significant difference test. Differences in tracer accumulation also were compared between the two tracers by using a paired t test. The FDG/FES ratios of mean SUV were compared among the four groups by using analysis of variance and the post hoc test. A probability value of less than .05 was considered to indicate a significant difference. Statistical analysis was performed by using a software package (StatView, version 5.0 for Windows; SAS Institute, Cary, NC).

Results
The mean SUVs for each disease are given in the Table. Patients with endometrial carcinoma showed a significantly higher accumulation of FDG than of FES in the primary tumors (P < .005). In contrast, patients with endometrial hyperplasia showed a significantly higher uptake for FES than for FDG (P < .05). In patients with smooth-muscle tumors of the uterus, those with leiomyomas showed a significantly higher uptake for FES than for FDG (P < .005), whereas leiomyo-

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Note.—Values are the mean ± standard deviation. Numbers in parentheses are ranges.
sarcomas and carcinosarcomas showed a higher concentration for FDG and a lower accumulation for FES. The tracer accumulation pattern was different between benign and malignant tumors for both endometrial and myometrial diseases.

Group analysis by using analysis of variance featured a pattern of each tracer accumulation. Figure 1 summarizes the difference in tracer accumulation of the two tracers for four diseases. In the comparison of uterine endometrial neoplasms, FDG uptake in patients with endometrial carcinoma was significantly higher than it was in those with hyperplasia ($P < .001$), whereas FES uptake was significantly lower in patients with endometrial carcinoma than it was in patients with endometrial hyperplasia ($P < .05$). When sarcoma and leiomyoma of the uterus were compared, FDG uptake was significantly greater ($P < .005$), whereas FES uptake was significantly lower ($P < .05$), in patients with sarcoma than it was in those with leiomyoma.

Representative images of each disease are shown in Figures 2–5. Patients with endometrial carcinoma of the uterus showed high FDG accumulation and moderate FES accumulation (Fig 2). All patients with endometrial carcinoma had high FDG accumulation with SUV of 3 or higher, and each patient showed a lower uptake for FES than for FDG. Patients with endometrial hyperplasia had a high level of FES accumulation; however, at FDG PET, patients did not show a higher uptake in endometrial tissue compared with the muscle layer of the uterus (Fig 3). Figure 4 shows images of multiple leiomyomas of the uterus. FDG PET showed a relatively diffuse uptake pattern in all of the leiomyomas with SUV of less than 2, whereas FES accumulation was different for each tumor. Although the histologic findings in all these tumors revealed benign leiomyoma, the ER density varied among them. Four of 21 patients with leiomyoma, including the patient in Figure 4 who had four lesions, had multiple lesions. Another patient had three lesions and the remaining two patients had two lesions each with values within the range of 3.5–7.6 for FES and 1.5–2.9 for FDG.

Most patients with leiomyoma had a higher uptake of FES than of FDG (Fig 1). Leiomyosarcoma of the uterus also showed a different accumulation pattern between FDG and FES (Fig 1). Figure 5 shows a case of carcinosarcoma with a sarcoma-rich area and carcinomarich area. The sarcoma-rich area displays substantially lower FES accumulation compared with leiomyomas. The SUV ratios of FDG/FES for each lesion showed a significant difference among four diseases ($P < .001$). The mean ratios were $3.2 \pm 2.2$ versus $0.26 \pm 0.08$ for endometrial carcinoma and hyperplasia, respectively ($P < .01$), and $4.7 \pm$
4.4 versus 0.63 ± 0.38 for leiomyosarcoma and leiomyoma, respectively (P < 0.001). A cutoff value of 1.0 for this ratio provided complete detection of benign and malignant tumors among the endometrial tumors (sensitivity, 100%; specificity, 100%), and only one false-positive leiomyoma among the myometrial tumors (sensitivity, 100%; specificity, 95.2%).

Discussion

Our study aimed to clarify the relationship between ER expression and glucose metabolism by using FES and FDG PET in patients with uterine tumors and to evaluate whether the addition of ER density information for various uterine lesions could contribute to accurate diagnosis. The major finding of our study was that ER expression and glucose metabolism of uterine tumors measured by using PET show opposite patterns between benign and malignant lesions. 

Our study showed that benign lesions had low FDG uptake compared with malignant lesions, indicating that FDG PET is a useful tool for the detection of malignancy in uterine tumors. However, the differentiation of leiomyosarcoma from leiomyoma remains challenging, and further studies are needed to improve the diagnostic accuracy of PET in the differential diagnosis of uterine tumors.

Figure 3: (a) Sagittal T2-weighted MR image, (b) FES PET scan, and (c) FDG PET scan in 30-year-old woman with endometrial hyperplasia (arrow). MR image showed high accumulation in the endometrial lesion of hyperplasia (SUV, 5.6). FDG PET scan did not show a higher uptake compared with the muscle layer of the uterus (SUV, 1.9).

Figure 4: (a) T2-weighted MR image, (b) FES PET scan, and (c) FDG PET scan in 39-year-old woman with multiple uterine leiomyoma (arrowheads). FES accumulation varied among four leiomyomas (SUV, 4.7, 3.1, 2.6, 2.0), whereas FDG PET showed relatively diffuse uptake in all tumors (mean SUV, 1.7; range, 1.5–1.8).
conventional imaging methods such as MR imaging (21, 22). Combined PET examinations with the use of FES and FDG may solve this problem because the tracer accumulation pattern is different between these tumor types (Fig 1). Previous investigations showed that estrogens affect the genesis and development of leiomyoma and that each tumor grows monoclonally from a single cell (23–25). Estrogens promote the progression of leiomyomas of the uterus. These findings are consistent with the results of the present study, which showed variability in FES accumulation for each tumor despite the diffuse moderate FDG accumulation in cases of multiple leiomyomas (Fig 4). It is difficult to exclude malignancy in cases of degenerative uterine leiomyoma with strong FDG accumulation. However, intense FES uptake by the lesion at additional FES PET scanning would suggest that the lesion is a benign leiomyoma (Fig 1).

Although nearly 100% of uterine leiomyomas show expression of ER, ER expression in leiomyosarcoma is reported to be significantly lower than it is in leiomyoma (26–29). Together, these reports and our data suggest that FES PET can be used to distinguish malignant smooth-muscle tumors from benign leiomyomas.

The FDG/FES SUV ratio showed significant differences between benign and malignant tumors of the endometrium and the myometrium. This index enhances the tendency of FDG and FES accumulation for each lesion shown in Figure 1, and, thus, a high SUV ratio indicates a malignant lesion. Although a cutoff value of 1.0 for this ratio gave high diagnostic accuracy for benign and malignant tumors, further investigation is needed to evaluate the reliability of this new index because only a small number of patients for two of the tumor groups (hyperplasia and sarcoma) underwent scanning in our study.

FES PET also is used for prediction of the response of ER-positive advanced breast cancers to hormonal therapies, such as tamoxifen (16, 17). Linden et al (18) revealed that quantitative FES PET can be used to predict the response to hormonal therapy, predominantly with aromatase inhibitors. On the basis of the findings in our study, a similar application of FES PET can be expected for evaluation of the responses of ER-positive endometrial carcinomas, as well as large uterine leiomyomas, to hormonal therapy.

Accumulation of FES in the endometrium may vary according to the menstrual cycle of the subject. However, a previous study by our group (30) showed that the plasma level of endogenous estrogen was not correlated with FES accumulation in the endometrium of the uterus, and SUV in the myometrium of the uterus was relatively constant in most healthy premenopausal control subjects. Although most of our patients with endometrial tumors were older women, and the influence of menstrual cycle on the PET scans was assumed to be small, further evaluation is still needed.

Our study had some limitations. The direct comparison of SUVs for FDG and FES may not be appropriate because FES and FDG reflect quite different tracer kinetics and biodistribution. However, the different tendencies of tracer accumulation seen in the same window range for SUV indicated the possibility to use either SUV or a ratio of the two SUVs for distinction between benign and malignant lesions.

Another limitation was the parametric statistical analysis used to compare groups with relatively small sample sizes (n = 4) for two groups. We applied the parametric statistical procedures because a normal distribution of SUVs in the uterus was observed in our previous study with FES PET in 16 healthy volunteers (30). Although the statistical analysis used in the present study may not be robust because of the small sample sizes, our findings warrant further study with a larger sample size of patients.

In conclusion, ER expression and glucose metabolism of uterine tumors measured by PET showed opposite patterns between benign and malignant lesions. PET studies with both FES and FDG could provide considerable noninvasive information for the differential diagnosis of uterine tumors.
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