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ORIGINAL ARTICLE

^{18}F-FLT PET performs better than ^{18}F-FDG PET in differentiating malignant uterine corpus tumors from benign leiomyoma

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Abstract
Purpose The aim of this study is to test the hypothesis that positron emission tomography (PET) with 3′-deoxy-3′-[^{18}F]-fluorothymidine (^{18}F-FLT) can differentiate malignancy from benign leiomyoma better than PET with 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG), and to evaluate whether ^{18}F-FLT and ^{18}F-FDG uptake correlate with immunohistochemical index of cell proliferation.
Methods The protocol of this prospective study was approved by the institutional ethics committee, and all patients gave written informed consent. Fifteen patients (aged 26–65 years, median 44 years) with uterine corpus tumor which has the possibility of being leiomyosarcoma underwent ^{18}F-FLT and ^{18}F-FDG PET scans. Maximum standard uptake value (SUV_{max}) of PET scans and Ki-67 labeling index of surgical specimens were evaluated. Mann–Whitney's U test was used for comparing uptakes between benign and malignant, and linear regression analysis was used for evaluating the correlation between Ki-67 labeling index and SUV_{max}.
Results Five cases were diagnosed as malignant (leiomyosarcoma for 3 cases, and carcinoma for 2 cases), and the others were benign leiomyoma. Sensitivity and negative predictive value of both tracers for detecting malignancy was 100 %. Specificity, positive predictive value and accuracy of ^{18}F-FLT PET were higher than those of ^{18}F-FDG PET. Difference in SUV_{max} between malignant and benign was significant for ^{18}F-FLT PET ($P < 0.01$), but not for ^{18}F-FDG PET. While all the malignant cases showed positive uptake in both tracers, a case of leiomyosarcoma with huge necrosis showed relatively low uptake. Uptake of ^{18}F-FLT showed better correlation with Ki-67 labeling index compared with ^{18}F-FDG ($R^2 = 0.91$ vs. $R^2 = 0.26$).
Conclusion Negative findings on additional ^{18}F-FDG or ^{18}F-FLT PET may rule out the possibility of malignancy for the patients with suspected leiomyosarcoma diagnosed by conventional methods. ^{18}F-FLT PET is superior to ^{18}F-FDG PET in differentiating malignant from benign leiomyoma. Moreover, ^{18}F-FLT uptake correlated well with the immunohistochemical index of cell proliferation.

Keywords ^{18}F-FLT PET · ^{18}F-FDG PET · Uterine corpus tumor · Uterine leiomyosarcoma · Uterine leiomyoma

Registration identification number for the trial's registry: UMIN-CTR: UMIN000003338 (www.umin.ac.jp/ctr/index/htm).

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Introduction

Benign leiomyoma occasionally resembles malignant tumors such as leiomyosarcoma and endometrial carcinoma.

Although the incidence of uterine leiomyosarcoma is extremely low, accurate diagnosis is essential because of its aggressiveness and subsequent poor prognosis. Magnetic resonance imaging (MRI) is the representative imaging modality for diagnosing gynecological disorder. However, no acceptable consensus exists on differentiating malignancy from benign leiomyoma [1].

Positron emission tomography (PET) using 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) is effective for differentiating benign tumor from malignancy of various organs including lung [2], adrenal gland [3], and pancreas [4]. Although effectiveness has also been discussed in uterine corpus tumors by ^{18}F-FDG PET, discriminating malignancy from uterine leiomyoma is difficult because of high incidence of false-positive scans [5].

From the pathological approach, differential diagnosis between leiomyosarcoma and leiomyoma is basically based on the findings of high mitotic index, presence of coagulation necrosis, and the degree of nuclear pleomorphism [6]. However, the histopathological criteria have been controversial especially for the low grade leiomyosarcoma. Recent advances in immunohistochemical analysis are expected to improve the diagnosis. Several immunohistochemical studies on uterine leiomyosarcoma have been reported recently, and Ki-67 labeling index is considered to be one of the representative marker.

Ki-67 antigen is a cell proliferation-associated protein that is expressed in all stages of the cell cycle except for G0 phase. The Ki-67 protein levels are comparatively low from G1 to early S phase, and gradually increase during mitosis. Ki-67 protein expression can be visualized by immunohistochemical staining, and it can be a useful marker of cell proliferation. Several studies have reported that expression of Ki-67 was useful for differentiating leiomyosarcoma from leiomyoma [7, 8].

Besides ^{18}F-FDG, 3′-deoxy-3′-[^{18}F]-fluorothymidine (^{18}F-FLT) was introduced as a PET tracer for tumor imaging. As an analog of thymidine, ^{18}F-FLT is phosphorylated by thymidine kinase 1 and accumulates within the cells with increased proliferation. Some papers showed that ^{18}F-FLT uptake was well correlated to Ki-67 immunohistochemical staining in various kinds of tumor [9–11]. Therefore, ^{18}F-FLT uptake has the possibility to reflect the malignant status of uterine corpus tumor directly.

The aim of this study is to test the hypothesis that ^{18}F-FLT PET can differentiate malignancy from benign leiomyoma better than ^{18}F-FDG, and to evaluate whether ^{18}F-FLT and ^{18}F-FDG uptake correlate with immunohistochemical index of cell proliferation.

Materials and methods

Patients population

The protocol of this prospective study was approved by the institutional ethics committee, and all patients gave written informed consent before entering the study.

Between March 2009 and March 2011, a total of 15 patients (median age 44 years; range 26–65 years) met the inclusion criteria (20 years or older, uterine corpus tumor with possibility of being leiomyosarcoma, surgical operation being considered without evidence of carcinoma cells detected by transvaginal cytology or biopsy prior to the PET scan) were enrolled in this study. Of these patients, 9 were premenopausal and 6 were postmenopausal. The subjects satisfied at least one of the detailed criteria for suspected leiomyosarcoma: tumor of 5 cm or larger and enlarging; resistance to hormonal therapy; heterogeneous high intensity lesions visualized in T2 weighted image of MRI; bleeding or necrosis suspected on MRI or ultrasound; and invasions to surrounding tissue or metastasis to other organs suspected. Even if the other differential diagnosis besides leiomyosarcoma was considered, cases completely filled the above-mentioned criteria without definitive diagnosis by the transvaginal histopathological approach were not excluded for this study.

PET protocol

The patients underwent ^{18}F-FLT and ^{18}F-FDG PET scans. Interval of the two scans was 1–34 days (median 4 days). PET scans were performed using a PET scanner (ECAT EXACT HR+, Siemens, Erlangen, Germany) except for 2 ^{18}F-FDG-PET scans performed using a PET/CT scanner (Discovery STEP, GE Healthcare, Milwaukee, WI, USA).

The patients fasted for 6 h or longer before the PET scans. For the ECAT PET scanner, images were obtained in 2-dimensional mode from 60 min post injection of ^{18}F-FLT (319-424 MBq) or ^{18}F-FDG (336–406 MBq), and reconstructed with ordered subsets-expectation maximization which provided image resolution of 8 mm full width at half maximum (FWHM). For the Discovery PET/CT scanner, images were obtained in 3-dimensional mode from 60 min post injection of ^{18}F-FDG (158 and 154 MBq), and reconstructed with VUE point plus (HD) which provided image resolution of 5.14 mm FWHM.

All the images were acquired to cover the entire tumor. MRI images were used to correlate PET with morphological structure using the image fusion software (VOX-BASE II, J-MAC SYSTEM, INC., Sapporo, Japan). Regions of interest (ROI) were placed over the PET images, and

maximum index of standardized uptake value (SUV_{max}) of the tumor was acquired for each tracer.

Histopathological finding

All histopathologic analysis was performed by a pathologist who was unaware of the PET results. Surgical specimens were fixed in 10 % buffered formalin and processed to create paraffin blocks in routine method. The sections (4 μm thick) were de-paraffinized in xylene and rehydrated thorough an ethanol series. The sections were treated with microwave in 0.1 mol/L citrate (pH 6.0) buffer for antigen retrieval before immunohistochemical staining. Then the sections were incubated with the primary antibodies, anti-Ki-67 antibody (Dako Japan, Tokyo, Japan), for 20 min. Immunostaining was performed with Dako Autostainer (Dako Japan, Tokyo, Japan) according to the instruction manual, and the slides were counterstained with hematoxylin. Ki-67 index was determined as percentage of the cells with Ki-67-positive nuclei per 500–1000 tumor cells in the regions of the tumor with the greatest density of staining.

Analyzed items and statistics

Final diagnosis was determined by the conventional histopathological method in 14 cases who had a surgical resection of the tumor. The 15th case was diagnosed as benign on the follow up of at least 6 month.

Based on the final diagnosis and SUV_{max} of each PET scan, receiver operating characteristic (ROC) analysis was performed to determine area under curve (AUC) and the cut-off SUV_{max} for differentiating between benign and malignant.

In addition, diagnostic capability such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were evaluated by the cut-off SUV_{max}. Also the difference in SUV_{max} between malignant and benign was statistically analyzed by Mann–Whitney's *U* test. In addition, correlation between PET tracers uptake and Ki-67 expression was evaluated by linear regression analysis on the cases whose surgical specimens were acquired. For the statistical analyses, *P* value of less than 0.05 was considered to be significant. Statistical analysis was implemented in JMP 7.0 (SAS Institute Japan, Tokyo, Japan).

Results

Final diagnosis was malignant in 5 cases (leiomyosarcoma for 3 cases, adenosquamous cell carcinoma for 1 case and endometrioid adenocarcinoma for 1 case), and benign in 10 cases (all cases were leiomyoma). Two cases of carcinoma were initially suspected of leiomyosarcoma, because endometrial biopsy preceded by the enrollment in this study could not prove carcinoma cells.

In the ROC analysis, AUC of ^{18}F-FLT was larger than ^{18}F-FDG, and the cut off SUV_{max} was 2.07 in ^{18}F-FLT, and 4.32 in ^{18}F-FDG (Fig. 1).

As the diagnostic capability, sensitivity for ^{18}F-FLT and ^{18}F-FDG was 100 % (5/5) each. NPV for ^{18}F-FLT (9/9) and ^{18}F-FDG (7/7) was also 100 % each. Specificity, PPV and accuracy of ^{18}F-FLT were 90.0 % (9/10), 83.9 % (5/6) and 93.3 % (14/15), respectively. Meanwhile, specificity, PPV and accuracy of ^{18}F-FDG were 70.0 % (7/10), 62.5 % (5/8) and 80.0 % (12/15), respectively.

Difference in SUV_{max} between malignant and benign was significant for ^{18}F-FLT, but not for ^{18}F-FDG (Fig. 2). A case of leiomyoma with extremely high ^{18}F-FDG uptake showed a low ^{18}F-FLT uptake (Fig. 3). All the malignant cases showed positive uptake in both tracers (Fig. 4). However, a case of leiomyosarcoma with huge necrotic

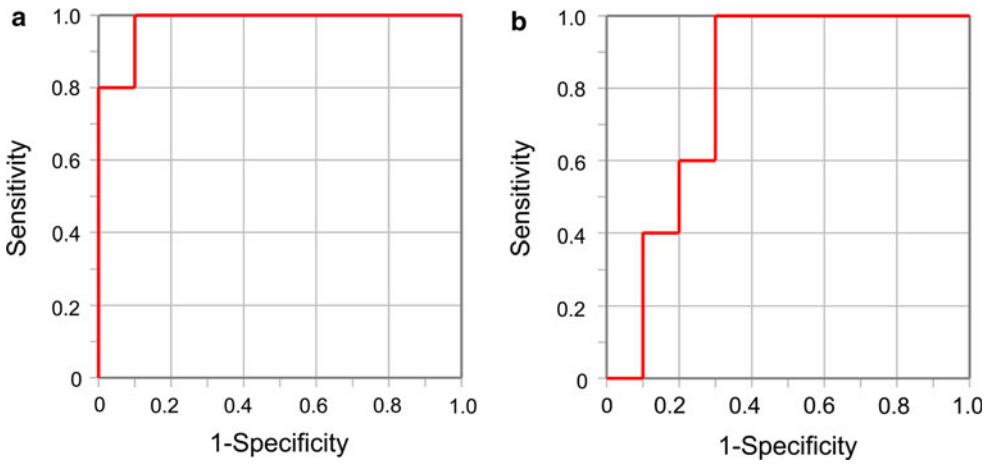

Fig. 1 Receiver operating characteristic analysis of **a** ^{18}F-FLT and **b** ^{18}F-FDG PET for detecting malignant disease. Area under curve for ^{18}F-FLT was larger than that for ^{18}F-FDG (0.98 vs. 0.80). Cut off SUV_{max} for ^{18}F-FLT was determined at a lower level than ^{18}F-FDG (2.07 vs. 4.32)

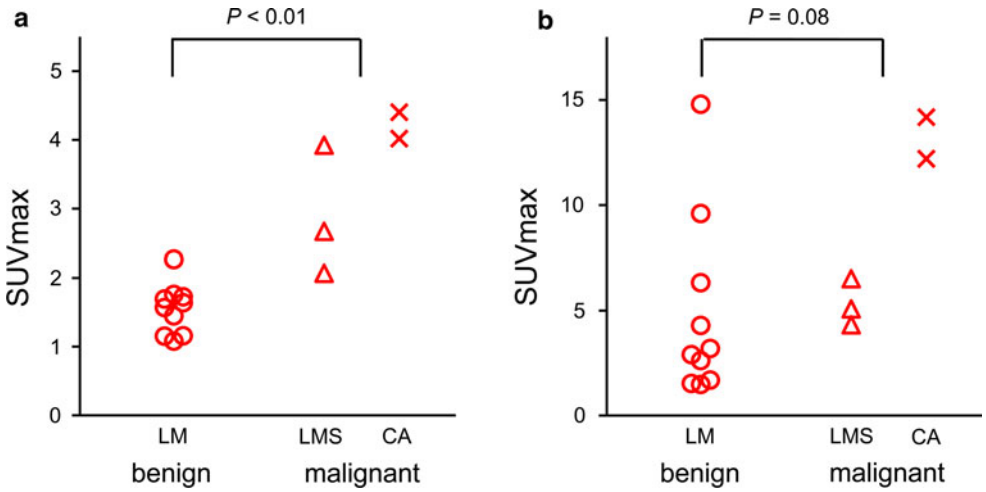

Fig. 2 SUV_{max} of **a** ^{18}F-FLT and **b** ^{18}F-FDG PET. Difference in SUV_{max} between malignant (leiomyosarcoma and carcinoma) and benign (leiomyoma) was significant in for ^{18}F-FLT ($P < 0.01$, Mann–Whitney's U test), but not for ^{18}F-FDG. (*Open circles* LM, leiomyoma; *open triangles* LMS, leiomyosarcoma; *multisymbols* CA, carcinoma)

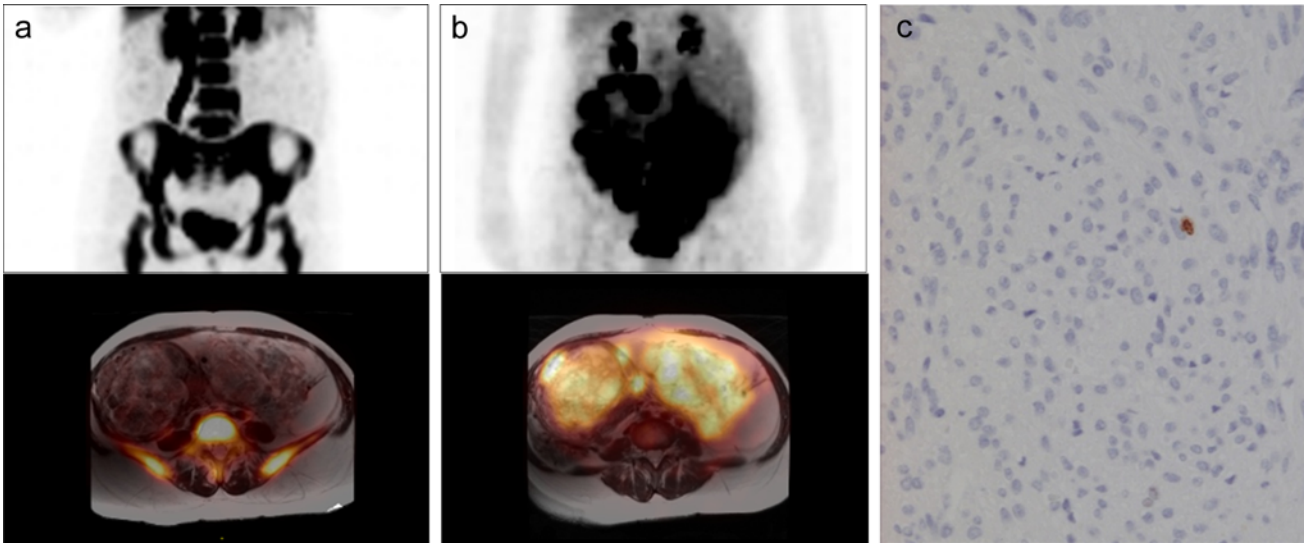

Fig. 3 A representative case of leiomyoma. Maximum intensity projection PET images and transaxial PET images fused with MRI acquired with **a** ^{18}F-FLT and **b** ^{18}F-FDG PET, and **c** Ki-67 immunohistochemical staining. Although ^{18}F-FLT uptake was not apparent (SUV_{max} 1.8), ^{18}F-FDG accumulated in the tumor strongly (SUV_{max} 14.8). Ki-67 labeling index was low (1.7 %)

tissue showed a lower uptake than the other malignant cases (Fig. 5).

^{18}F-FLT showed better correlation with the expression of Ki-67 compared with ^{18}F-FDG by the linear regression analysis of the cases for which operation was performed (Fig. 6).

Discussion

Uterine leiomyoma, the most common gynecological tumor, is usually asymptomatic and needs no treatment, except in some cases presenting serious symptoms such as atypical genital bleeding, abdominal pain and infertility. While hysterectomy is one of the radical treatment methods, patients who wish to preserve the uterus have other options recently. In addition to the conventional myomectomy, intervention radiological methods such as uterine artery embolization and high-intensity focused ultrasound are notable for less-invasive treatment [12, 13]. However, according to recent reports, some patients who underwent uterine artery embolization based on the diagnosis of leiomyoma were later diagnosed as leiomyosarcoma [14, 15]. There is a great benefit especially for the patients who wish to preserve their fertility if malignancy is correctly ruled out and unnecessary operation is avoided. Unfortunately ^{18}F-FDG PET is not perfect because it sometimes presents a false positive scan. In the present

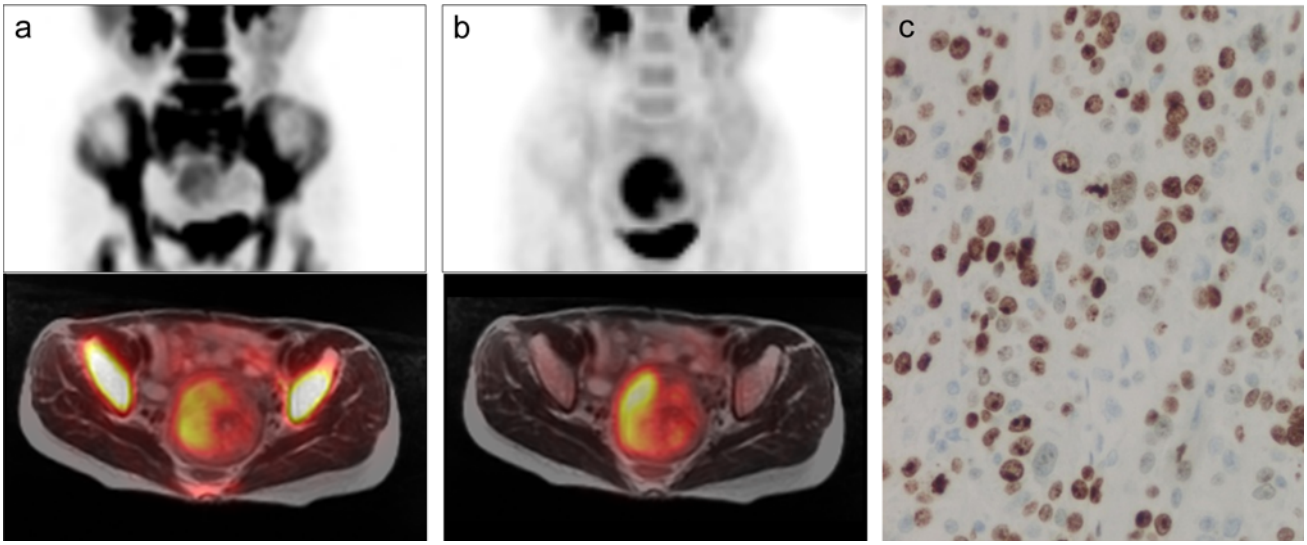

Fig. 4 A case of leiomyosarcoma. Maximum intensity projection PET images and transaxial PET images fused with MRI acquired with **a** ^{18}F-FLT and **b** ^{18}F-FDG PET, and **c** Ki-67 immunohistochemical staining. Both ^{18}F-FLT and ^{18}F-FDG uptake were positive (SUV_{max} 3.9 and 6.5, respectively). Ki-67 labeling index was high (53.4 %)

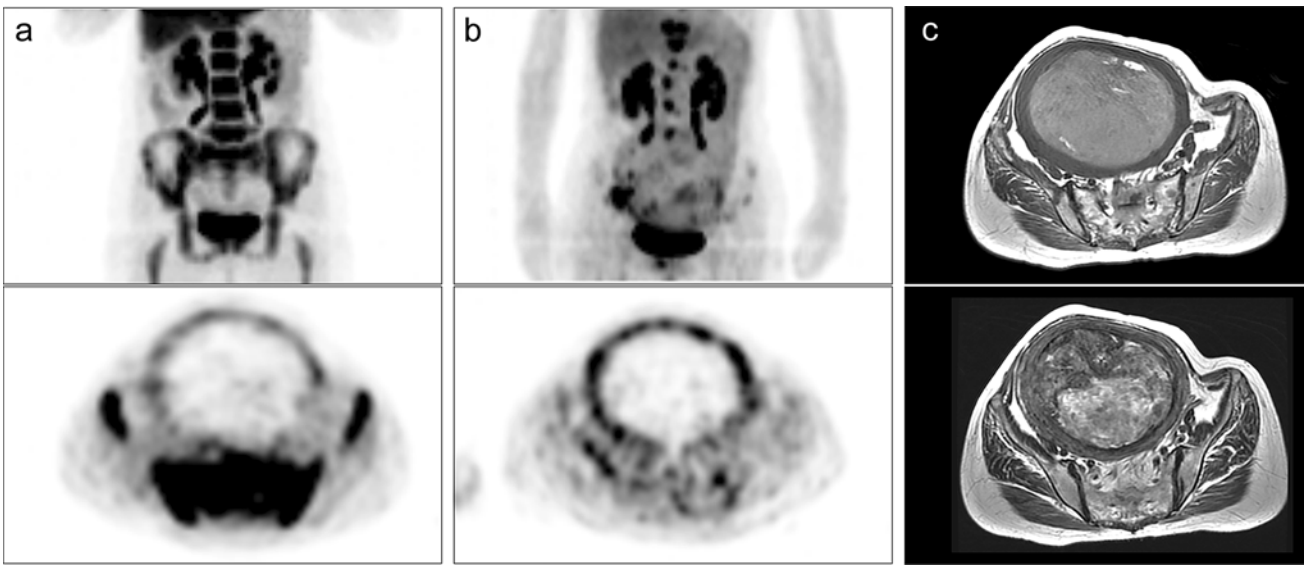

Fig. 5 A case of leiomyosarcoma with a huge necrotic area. Maximum intensity projection and transaxial images of **a** ^{18}F-FLT and **b** ^{18}F-FDG PET, and **c** MRI images (*upper* T1 weighted image, lower: T2 weighted image) of the same slice. Most of the tumor was occupied by non-active necrotic tissue, and leiomyosarcoma cells existed only on the edge of the tumor. Compared with Ki-67 labeling index (19.1 %), ^{18}F-FLT uptake was low. While metastatic lesions in vertebrae are visualized in ^{18}F-FDG PET images, they cannot be confirmed in ^{18}F-FLT PET images because of physiological ^{18}F-FLT uptake of the bone marrow

study, ^{18}F-FLT proved to be potentially useful for the differential diagnosis and it may contribute to select an optimal treatment method.

Incidence of positive ^{18}F-FDG uptake in uterine leiomyoma has been reported as 10.4 % in premenopausal women, and 1.2 % in postmenopausal women [16]. However, most of the leiomyoma cases in the present study showed positive ^{18}F-FDG uptake. One of the reasons for the differences may be explained by the differences in the subjects. All subjects in the present study were suspected leiomyosarcoma, while most of the subjects in the former study were asymptomatic women.

In some case of benign leiomyoma, ^{18}F-FDG was positive and showed higher uptake than ^{18}F-FLT. Therefore, ^{18}F-FLT was superior to ^{18}F-FDG in specificity and PPV. While ^{18}F-FDG PET is widely used for various kinds of tumors, physicians are occasionally bothered by the unexpected ^{18}F-FDG-avid finding in the uterus in

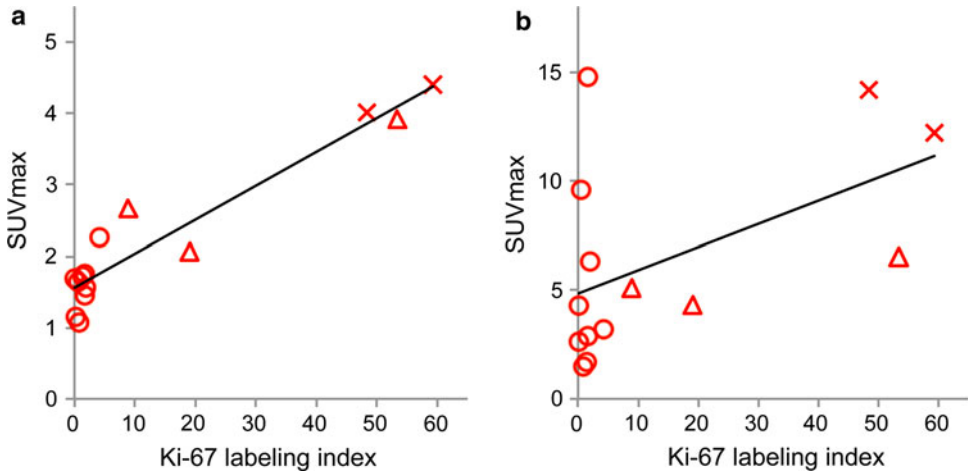

Fig. 6 Correlation between Ki-67 labeling index and SUV_{max} for **a** ^{18}F-FLT and **b** ^{18}F-FDG PET in uterine corpus tumors (*Open circles* leiomyoma, *open triangles* leiomyosarcoma, *multisymbols* carcinoma). ^{18}F-FLT showed better and significant linear correlation ($R^2 = 0.91$, $P < 0.001$) compared with ^{18}F-FDG ($R^2 = 0.26$, $P = 0.06$)

managing the original tumor. Therefore, additional ^{18}F-FLT PET may facilitate the process of differential diagnosis for the possible uterine tumor. Although AUC of ^{18}F-FLT was larger than that of ^{18}F-FDG in the ROC analysis in the present study, SUV_{max} of ^{18}F-FLT were relatively lower than ^{18}F-FDG, suggesting lower contrast. Furthermore as SUV should be measured properly, standard way of ROI definition and SUV measurement such as SUV_{peak} [17] may be considered for the sake of further multi-institutional studies.

In this study, NPVs for both tracers were 100 %. Therefore, negative result in ^{18}F-FLT or ^{18}F-FDG PET may rule out the possibility of malignancy. Previous papers on ^{18}F-FDG PET of leiomyosarcoma also showed positive finding for primary lesion in most of the cases [18–20]. However, we need to pay attention to the existence of necrotic area in leiomyosarcoma. In a case of leiomyosarcoma shown in Fig. 5, majority of the tumor was occupied by central necrosis. Although the Ki-67 labeling index was not low, ^{18}F-FLT and ^{18}F-FDG uptake was not significantly increased due to partial volume effect. Therefore, leiomyosarcoma with huge necrosis have a possibility to be underestimated in interpretation of PET results.

^{18}F-FLT uptake was better correlated with the expression of Ki-67 than ^{18}F-FDG, which may be an evidence of the correlation between ^{18}F-FLT uptake and malignancy in uterine corpus tumor. In addition, some recent studies indicate that the high Ki-67 labeling index is correlated with poor prognosis [21, 22]. Therefore, ^{18}F-FLT may be a possible biomarker for predicting prognosis of uterine tumor.

Two cases of carcinoma in the present study showed higher uptake than leiomyoma in both tracers. High Ki-67 labeling index was confirmed in these cases. As there are few previous studies concerning ^{18}F-FLT uptake or Ki-67 labeling index, carcinoma cases must be re-evaluated with a large number of patients.

The limitation of this study is the small number of patients, because there is wide variation and heterogeneity both in leiomyosarcoma and leiomyoma. Low-proliferating malignant tumors may not show up at ^{18}F-FLT PET, leading to an increased false negative rate. Actually, uterine leiomyomas often shows various histopathological changes such as coagulation necrosis, hemorrhage, calcification, hyalinization, myxoid change and hydropic degeneration [23]. In addition, we could not evaluate the other types of intramuscular malignancies such as endometrial stromal sarcoma. With various types of tumors, further examination is required to evaluate the relationship between ^{18}F-FLT uptake and malignancy of uterine corpus tumor.

Conclusion

Negative findings on additional ^{18}F-FDG or ^{18}F-FLT PET may rule out the possibility of malignancy for the patients with suspected leiomyosarcoma diagnosed by conventional methods. However, leiomyosarcoma with extensive necrosis has a possibility of false negative diagnosis. ^{18}F-FLT PET is superior to ^{18}F-FDG PET in efficiently selecting benign leiomyoma out of possible malignant tumors. Moreover, ^{18}F-FLT uptake correlated well with the histopathological index of cell proliferation.

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