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Differentiation of aggressive and indolent subtypes of uterine sarcoma using maximum standardized uptake value

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Objective **The aim of the study was to elucidate the differential metabolic activities in aggressive and indolent subtypes of uterine sarcomas, which may aid in managing these heterogeneous tumours.**

Methods **We retrospectively analysed the PET/computed tomography scans of consecutive patients ($N=18$) diagnosed with uterine sarcoma at our unit. The patients were divided into indolent ($N=4$) and aggressive ($N=14$) tumour groups, and the maximum standardized uptake values (SUV_{max}) of all lesions ($n=134$) were measured. The SUV_{max} of the lesions were compared between the two tumour groups using the Mann–Whitney *U*-test. We calculated the optimal cutoff value as determined by receiver operating characteristic analysis. A *P*-value less than 0.05 was considered statistically significant.**

Results **The mean SUV_{max} of aggressive ($n=104$) and indolent tumours ($n=30$) were significantly different (8.0±7.3 vs. 1.9±0.9 respectively; $P<0.001$). A cutoff of SUV_{max} greater than 4.0 was able to exclude indolent tumours, with 100% specificity and positive predictive value (sensitivity 72%, negative predictive value 50% and accuracy 78%; area under the curve 97%). By applying this same cutoff value on the most metabolic active lesion in each patient, we were able to correctly classify all but one patient into either the aggressive or indolent tumour group with 100% specificity and positive predictive value (sensitivity 93%, negative predictive value 80% and accuracy 94%).**

Conclusion **Aggressive and indolent uterine sarcoma subtypes have differential metabolic activities that can be used to classify them and this can aid in patient management for preoperative surgical planning and treatment stratification. *Nucl Med Commun* 34:1185–1189**

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Introduction

Uterine sarcoma is a rare disease, accounting for 3–8% of all uterine malignancies [1]. It comprises pure mesenchymal tumours – leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS) and undifferentiated endometrial stromal sarcoma (UES) – and mixed epithelial and mesenchymal tumours – adenosarcoma (AS) and adenosarcoma with sarcomatoid overgrowth (ASSO) [2]. We have also included carcinosarcoma (CS) and uterine smooth muscle tumours of uncertain malignant potential (STUMP) in our study given their related clinical and biological behaviours with uterine sarcoma [3]. CS is reclassified as the metaplastic form of endometrial cancer but the tumour aggressiveness closely resembles that of uterine sarcoma with a poor 5-year overall survival (OS) of 30%, significantly worse than that from endometrial cancer (5-year OS of 80%) and only marginally better than that from LMS (5-year OS of 15–25%) [3,4]. CS is managed more aggressively than endometrial cancer, and a wealth of literature has included CS in the discussion on uterine sarcoma [3,5,6]. In contrast, STUMP is treated as a borderline tumour with a favourable prognosis but in rare cases can recur as LMS years after hysterectomy [7,8]. The latter is characterized by a more aggressive biology because of the LMS component. Of these subtypes, STUMP, ESS and AS have more favourable outcomes with low incidences of late recurrence of 5–7% and improved 5-year OS of 50–98% [3,7,9,10]. In this study, we use the term uterine sarcoma to refer to all of these different pathological subtypes.

Total hysterectomy is the cornerstone of treatment for uterine sarcoma. In aggressive subtypes, that is, LMS, UES, ASSO and CS, this extends to include debulking of extrauterine tumour, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy and peritoneal cytology as part of the full surgical staging procedure. In the indolent subtypes, that is, ESS, AS and STUMP, routine lymphadenectomy and extensive surgical staging are not justifiable given the low incidence of nodal metastasis [3,11]. Adjuvant radiotherapy or chemotherapy can be added in aggressive subtypes, and hormonal therapy is considered

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for ESS [12]. Preoperatively, diagnosis can be difficult because of inadequate endometrial biopsy tissue, often confounded by sampling error and bias [13]. Unfortunately, morphological imaging findings overlap with each other and a definitive diagnosis is often not possible [5,6]. Therefore, a diagnostic tool that allows the evaluation of disease aggressiveness will be of clinical value to clinicians for surgical planning, treatment stratification and patient counselling.

The role of imaging in the assessment of uterine sarcoma has not been well described given the rarity of the disease, and hence the lack of methodical large cohort studies in the literature. Generally, ultrasound and MRI are used for diagnosis and pretreatment assessment of local uterine spread. The use of computed tomography (CT) is generally confined to disease that has high risks of extrauterine involvement, to delineate the extent of metastatic disease and for disease surveillance [6].

Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET or combined with CT (PET/CT) has increasingly been used for disease detection of uterine sarcoma [14–18]. Murakami *et al.* [14] reported that PET had 100% sensitivity in detecting recurrence in the aggressive subtypes and has been reproduced by others in the range of 87.5–100% by using a combination of PET and PET/CT [16,18]. PET and PET/CT had been shown to positively impact the clinical management by initiating unplanned treatment or avoiding unnecessary intervention in correctly identifying inoperable disease and nonmalignant lesion, changing management in up to 67% of cases [15,16]. Aggressive tumours were shown to be ^{18}F-FDG avid, with reported standardized uptake values (SUV) of 2.0–16.0 [18,19]. The increase in *GLUT-1* expression may account for the findings on PET/CT; *GLUT-1* correlates to increased metabolic uptake based on SUV and is a measure of tumour aggressiveness [20–22]. Given this unique property of PET/CT, we hypothesize that the metabolic uptake determined by SUV is able to distinguish between aggressive and indolent subtypes of uterine sarcoma and is thus potentially useful in surgical planning and treatment stratification.

Methods

Patients

All consecutive patients histologically confirmed to have uterine sarcoma who underwent PET/CT over a period of 6 years (2007–2013) at a single PET/CT unit formed the study cohort. Inclusion criteria included PET/CT examinations that were performed for pretreatment assessment or for recurrence detection in patients treated at our institution who had available radiological and clinical follow-up data. In addition, we included only positive scans, as the study was performed with the aim of quantifying tumour metabolic uptake for comparison. Patients had to be chemotherapy or radiotherapy naive in the preceding 6 months to be eligible for inclusion. A total of 29 patients were identified from the database, from among whom 11 were excluded for the following reasons: two were lost to follow-up, three had PET/CT for postchemoradiatherapy response assessment and six had negative PET/CT results. Finally, 18 patients were included in the study. This retrospective study was approved with waiver of informed consent by the local institutional research and ethics review board.

To test our hypothesis, the patients were divided into two groups. They were classified as indolent if they had either ESS, AS or pure STUMP, and as aggressive if they had LMS, UES, ASSO or CS. If there was a mixture of cell types, the higher histological grade was taken as the final pathology.

PET/CT acquisition and analysis

All PET/CT examinations were conducted using a combined PET/CT scanner (Discovery VCT, 64-multislice CT; GE Healthcare Bio-Sciences Corp., Piscataway, New Jersey, USA). All patients fasted for 6 h before the examination and serum glucose levels had to be within 180 mg/dl before injection of 10 mCi (370 MBq) ^{18}F-FDG. Scanning was performed 60 min after ^{18}F-FDG injection. The CT imaging parameters were as follows: field of view, 50 cm; pixel size, 3.91 mm; 120 kVp; 80–200 and 200–400 mA for noncontrast-enhanced and contrast-enhanced protocol, respectively; 0.5 s/CT rotation; and pitch 0.984 : 1; 2.5 mm intervals. Intravenous contrast medium (1.5 ml/kg) was injected at a rate of 2.0 ml/s for contrast-enhanced CT. The scan coverage included the skull base to the upper thighs. PET images were reconstructed using an ordered-subset expectation maximization iterative algorithm (14 subsets and two iterations), and CT was used for attenuation correction of the PET emission data. The background liver metabolic uptake was taken as the internal reference from each examination with a mean liver uptake of maximum SUV (SUV_{max}) of 2.1 ± 0.3.

PET was analysed qualitatively and semiquantitatively on a dedicated PET/CT ADW4.3 workstation (GE Healthcare, Milwaukee, Wisconsin, USA) by E. Y. P. L. (a radiologist with 5 years of postfellowship experience and working as the radiology lead in the gynaecological oncology group at a tertiary referral unit). Lesions detected by PET and/or CT were identified; these were lesions with ^{18}F-FDG uptake above the mediastinal blood pool or in an area unrelated to physiological uptake on PET, including all measureable lesions on CT with a minimum short axis of 1.0 cm. A region of interest was placed over the primary tumour or metastasis, encompassing the entire lesion to derive the SUV_{max}. SUV_{max} quantified the pixel with the highest metabolic uptake by calculating the injected dose of ^{18}F-FDG normalized by lean body mass. Fused PET/CT was used for anatomical correlation.

Follow-up

Histology was taken as the gold standard and histological subtypes were based on the WHO classification and uterine neoplasm classification of the International Society of Gynecologic Pathologists. All pathological specimens were reviewed by an experienced gynaecological pathologist and discussed at the gynaecological oncology tumour board review in a multidisciplinary manner.

For suspected lesions that had no histological confirmation, diagnoses were based on follow-up CT or PET/CT and clinical progression. Lesions were considered sarcomatous if there was evidence of treatment response, either partial or complete, or if there was evidence of disease progression. Patients who had subsequent rapid clinical deterioration with clinical diagnosis in keeping with terminal malignancy were assumed to have had lesions that were sarcomatous on PET/CT.

Statistical analysis

Descriptive statistics were used. Mean values were expressed with SD (mean ± SD). The follow-up period was expressed in median and range. Nonparametric comparisons between aggressive and indolent tumours were performed using the Mann–Whitney *U*-test. The extreme outliers were values beyond three interquartile ranges away from either the 25th or 75th percentile and the mild outlier was a value of 1.5 interquartile ranges away from the 25th or 75th percentile. Receiver operating characteristic (ROC) curve analysis was used to determine the discrimination threshold value of SUV_{max} for the indolent and aggressive subtypes. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the statistical package SPSS for Windows (version 20; SPSS Inc., Chicago, Illinois, USA).

Results

Patient demographics

Distribution of the tumour histology subtypes is tabulated in Table 1. There were 18 patients with a mean age of 55.9 ± 15.9 years. Ten scans were performed for pretreatment evaluation and eight for recurrence detection. The time between PET/CT and surgery was 14 days (6–49 days). The median duration of clinical follow-up was 10 months (0.4–39 months) and that of radiological follow-up was 6.7 months (4.1–14.9 months). There were six patients with less than 6 months of clinical and radiological follow-up: five patients succumbed to disseminated disease following PET/CT, and in one patient a solitary lung metastasis from STUMP/LMS was confirmed by histological analysis. By the conclusion of the study, 10 patients had died, six were in clinical remission and two patients experienced progressive disease.

Table 1 Tumour histology subtype distribution

Histology	Number of patients
Indolent group	
ESS	2
AS	1
STUMP	1
Aggressive group	
LMS	4
UES	1
CS	9

AS, adenosarcoma; CS, carcinosarcoma; ESS, endometrial stromal sarcoma; LMS, leiomyosarcoma; STUMP, uterine smooth muscle tumours of uncertain malignant potential; UES, undifferentiated endometrial stromal sarcoma.

Data on histological diagnosis was available for 13 patients: for all 10 patients with new disease for pretreatment assessment, based on endometrial aspirate, surgical dissection and full surgical staging procedures, and for three patients with recurrent disease, based on debulking surgery. In the remaining five patients with recurrent disease, no further histological data were obtained and diagnosis was based on histological information obtained at initial diagnosis; among them, lesions were verified by follow-up CT or PET/CT in the case of four patients and on the basis of rapid clinical deterioration in one patient who succumbed to the disease a month later following PET/CT.

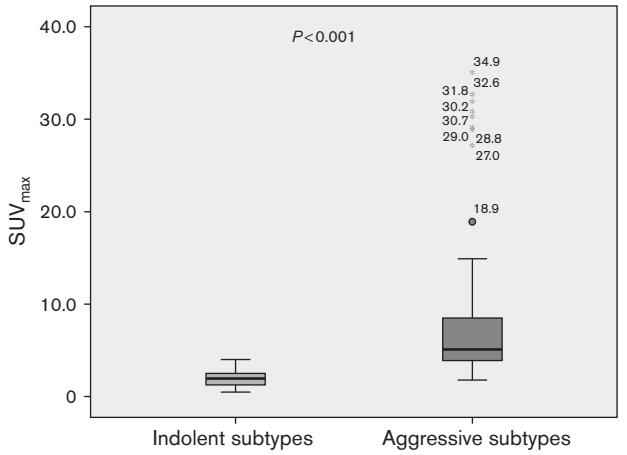
PET/CT assessment and tumour metabolism

Eighteen PET/CT examinations were analysed in 18 patients. A total of 134 primary and metastatic lesions were identified, with an SUV_{max} of 6.7 ± 7.0 (mean ± SD). These were confirmed by histological analysis in 41% of patients (55 lesions) and verified by follow-up CT or PET/CT in 35% of patients (47 lesions). The remaining 32 lesions were assumed to be metastases by rapid clinical progression in the context of prior histological diagnosis of uterine sarcoma.

There were 30 lesions in the indolent group with an SUV_{max} of 1.9 ± 0.9 (range 0.5–4.0) and 104 lesions in the aggressive group with an SUV_{max} of 8.0 ± 7.3 (range 1.8–34.9). The difference in metabolic activities between the two groups was statistically significant (Mann–Whitney *U*-test, $P < 0.001$), as illustrated in Fig. 1. After excluding the outliers from analysis, the result remained statistically significant (Mann–Whitney *U*-test, $P < 0.001$). When the most-avid lesion was selected from each patient from the two subgroups and compared, the difference remained statistically significant: SUV_{max} 3.0 ± 0.9 (range 1.9–4.0) versus 10.6 ± 7.9 (range 1.8–34.9) for indolent and aggressive tumours, respectively (Mann–Whitney *U*-test, $P = 0.008$).

We used the ROC curve to investigate whether SUV_{max} could separate aggressive tumours from indolent ones. The ROC curve demonstrated that SUV_{max} was reliable at distinguishing the two with an area under the ROC curve of 97%. A cutoff value of SUV_{max} 4.0 would yield a sensitivity of 72%, a specificity of 100%, a positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 50% in separating the indolent from the

Fig. 1



The box plot shows the SUV_{max} of lesions in the indolent and aggressive groups of uterine sarcoma; the difference was statistically significant. The grey boxes represent the 25th–75th percentiles of the SUV_{max}, and the crossbars denote the minimum and maximum values that were not outliers. The asterisks are the extreme outliers and the circle represents the mild outlier. Values adjacent to the asterisks and circle are the absolute SUV_{max} of the outliers. SUV_{max}, maximum standardized uptake value.

aggressive subtypes. Diagnostic accuracy was 78%. Using SUV_{max} greater than 4.0, all the lesions in the indolent subtype were correctly classified, with a trade-off of lower NPV with 30 lesions in the aggressive subtype having SUV_{max} of up to 4.0 (Table 2).

When the most ^{18}F-FDG-avid lesion was selected in each patient and this same cutoff value was applied, 17 patients were correctly grouped into the aggressive and indolent subtypes, with 100% specificity and PPV (sensitivity of 93%, NPV of 80% and accuracy of 94%). The only patient who was classified incorrectly using this cutoff SUV_{max} had a previous history of STUMP and a recurrence as LMS in a solitary lung metastasis with an SUV_{max} of 1.8.

Both the aggressive and indolent subtypes had similar disease distribution (Table 3), with the peritoneum being the most affected site of metastasis.

Discussion

Treatments options can be varied in uterine sarcoma depending on the disease subtype – namely, whether it is aggressive or indolent. Establishing a pathological diagnosis preoperatively with endometrial aspirate can be challenging because of sampling error and tumour heterogeneity. The ability of a noninvasive method to separate the indolent from the aggressive subtypes can assist clinical management in terms of the merit of surgery, surgical planning and types of adjuvant therapy. To the best of our knowledge, the clinical value of quantifying the metabolic activity using the SUV_{max} of uterine sarcomatous lesions derived from PET/CT has not been described. Our study is the first to report that the

Table 2 The number of lesions in the aggressive (grey rows) and indolent groups (white rows) categorized according to the cutoff value of SUV_{max} 4.0

Histology	$SUV_{max} > 4.0$ (number of lesions)	$SUV_{max} \leq 4.0$ (number of lesions)
LMS	18	0
LMS	2	1
LMS	5	2
STUMP/LMS	0	1
UES	1	1
CS	2	3
CS	7	0
CS	1	0
CS	21	6
CS	1	0
CS	1	0
CS	1	0
CS	12	7
CS	2	9
ESS	0	14
ESS	0	4
AS	0	4
STUMP	0	8

AS, adenosarcoma; CS, carcinosarcoma; ESS, endometrial stromal sarcoma; LMS, leiomyosarcoma; STUMP, uterine smooth muscle tumours of uncertain malignant potential; SUV_{max}, maximum standardized uptake value; UES, undifferentiated endometrial stromal sarcoma.

Table 3 Disease spread according to different subtypes

Site	Aggressive subtypes [*n* (%)]	Indolent subtypes [*n* (%)]
Primary tumour and pelvis	16 (15)	7 (23)
Lymph nodes	12 (12)	3 (10)
Peritoneal metastases	60 (57)	15 (50)
Lung	7 (7)	3 (10)
Solid organ	7 (7)	0 (0)
Osseous/soft tissue	2 (2)	2 (7)
Total lesions	104	30

metabolic uptakes of aggressive and indolent tumours are different, and to utilize SUV_{max} to separate the two disease groups in uterine sarcoma. Although our cohort was small because of the rarity of this disease, our results show that SUV_{max} is a good discriminator that can differentiate between the two disease groups. Using a cutoff value of SUV_{max} 4.0, we could separate the indolent from the aggressive subtypes with high specificity and PPV (both 100%). On a per-patient basis, all but one patient were correctly classified (specificity and PPV of 100%). This patient had an aggressive tumour subtype (LMS) with a small lung nodule of SUV_{max} 1.8 and was incorrectly classified. Correctly identifying indolent tumours could be beneficial in sparing the patient from unnecessary extensive surgery, who may later benefit from hormonal therapy, as in ESS. The difference in metabolic activities between the aggressive and indolent subtypes of uterine sarcoma is likely related to the differential expression of biological markers such as *GLUT-1*, Ki-67 and p53 [21,23]. Furthermore, the lower mitotic index in indolent tumours and the presence of a cystic component may both explain the low ^{18}F-FDG activity in this group [24]. It is unsurprising that the aggressive subtypes have higher ^{18}F-FDG avidity, given that

SUV_{max} is a surrogate marker of disease aggressiveness as shown in other types of tumour [25,26]. It is, however, remarkable that in our study the differentiation had 100% specificity and PPV, higher than that of other studies. For examples, SUV_{max} greater than 10 was suggested to differentiate aggressive from the indolent form of non-Hodgkin's lymphoma with a sensitivity of 71% and a specificity of 81%, and recently in a study on 24 cardiac tumours a cutoff value of SUV_{max} 3.5 yielded a sensitivity of 100%, a specificity of 86%, a PPV of 94% and an NPV of 100% in separating malignant from benign cardiac tumours [25,26].

In our study, the disease distribution was very similar in both groups. The peritoneum was the most affected site, whereas lymph node metastases were not uncommon in either group. Therefore, the pattern of disease spread in uterine sarcomas may not be useful in differentiating the aggressive from the indolent subtypes in a patient with metastatic disease. Our results show that characterization of metabolic activity using SUV_{max} provides useful adjunct information that may better describe the underlying tumour behaviours and thus increase the clinical value of PET/CT.

There are several limitations in the current study. This is a retrospective study with a relatively small number of patients, given the rarity of uterine sarcoma. The heterogeneity of the disease makes the analysis challenging and less homogeneous. There was inherent selection bias as more advanced-staged and more aggressive subtypes of disease were more likely to be referred for PET/CT. This would explain the small number of patients with indolent subtypes. We acknowledge that by defining histology as the gold standard our study would be biased by sampling errors, especially in specimens collected from biopsies rather than surgical resections.

Conclusion

The preliminary finding suggests that SUV is a promising noninvasive biomarker for differentiating the aggressive from the indolent subtypes of uterine sarcoma, with an optimal cutoff value of SUV_{max} 4.0, providing a clinically relevant quantitative index and thus adding value to preoperative surgical planning and streamlining treatment strategies. PET/CT should be performed for pretreatment assessment.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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