Detection and Grading of Soft Tissue Sarcomas of the Extremities with ^{18}F-3′-Fluoro-3′-Deoxy-L-Thymidine

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ABSTRACT

Purpose: **The aim of the study was to investigate the feasibility of ^{18}F-3′-fluoro-3′-deoxy-L-thymidine positron emission tomography (FLT-PET) for the detection and grading of soft tissue sarcoma (STS).**

Experimental Design: **Nineteen patients with 20 STSs of the extremities were scanned, using attenuation corrected whole-body FLT-PET. Standardized uptake values (SUVs) and tumor:nontumor ratios (TNTs) were compared with histopathological parameters using French and Japanese grading systems.**

Results: **Mean SUV, maximal SUV, and TNT could differentiate between low- grade (grade 1; $n = 6$) STS and high-grade (grade 2 and 3; $n = 14$) STS according to the French grading system ($P = 0.001$). Mean SUV, max SUV, and TNT correlated with mitotic score, MIB-1 score, the French and Japanese grading system ($\bullet = 0.550–0.747$).**

Conclusions: **FLT-PET is able to visualize STS and differentiate between low-grade and high-grade STS. The uptake of FLT correlates with the proliferation of STS.**

INTRODUCTION

Soft-tissue sarcomas (STS) form a heterogeneous group of rare malignancies, which arise from mesenchymal soft tissues and account for ~1% of all cancers. In the United States, 8300 new cases are diagnosed each year and in the Netherlands, about 400 (1, 2). At first presentation, 13% of the patients with STS have metastases. The lung is the most common metastatic site, followed by bone, liver, and brain. Less common sites are regional lymph nodes, retroperitoneum, and soft tissues (3, 4). After treatment of the primary tumor, ~40% of the patients will develop recurrences either locally or distantly.

The presence or absence of metastases and the malignancy grade of the tumor will dictate the treatment. Grading is frequently performed according to the French grading system (5). In this grading system, points are scored for histological grade, tumor differentiation and amount of necrosis, and number of mitotic figures. Recently, a Japanese grading system, using the MIB-1 score instead of the mitotic score, has been introduced and correlates stronger with the prognosis than the French grading system (6, 7).

Optimal management of STS depends on the anatomical site, local growth pattern, tumor size and grade, and accurate staging of the disease, when first diagnosed. The site, growth pattern, and size of the primary tumor are best determined by magnetic resonance imaging or spiral computed tomography (CT). However, the clinical and radiological differentiation between benign soft tissue masses and STSs is difficult (8). Information regarding distant metastases is obtained primarily by chest radiography or a CT scan of the lungs, whereas bone-scintigraphy is of limited value (8, 9). Distant metastases to the lungs are ruled out by CT. Physical examination, CT, magnetic resonance imaging, or ultrasonography are best used for the detection of local recurrences. However, after surgery and radiation therapy, physical examination and interpretation of the diagnostic images remains difficult (8).

Therefore, the need for noninvasive detection, staging, and grading of a soft tissue tumor mass has increased. During the last decade, the value of positron emission tomography (PET) in STS with several tracers, especially [^{18}F]fluoro-2′-deoxy-D-glucose (FDG), has been investigated (10–16). However, the current potential of FDG-PET in the detection and/or grading is still unknown (10, 11, 15, 17–32).

Several years ago ^{18}F-3′-fluoro-3′-deoxy-L-thymidine (FLT) was introduced as PET tracer (33). This tracer has theoretical advantages over the currently used FDG, because no uptake in inflammatory cells is anticipated. The aim of this study was to investigate the feasibility of FLT-PET for the detection and grading of STS.

PATIENTS AND METHODS

This prospective study, approved by Medical Ethics Committee of the Groningen University Hospital, consisted of 19 consecutive patients with a STS of the extremity. All of the patients were treated at the Groningen University Hospital and gave written informed consent. For inclusion, the liver and kidney functions and hematological parameters (hemaglobin, hematocrit, erythrocytes, thrombocytes, leukocytes, and WBC count) should be within normal limits. Pregnant patients or patients with psychiatric disorders were excluded from the study.

Synthesis of FLT was performed according to the method of Machulla *et al.* (34) FLT was produced by fluorination with [^{18}F]fluoride of the 4,4′-dimethoxytrityl-protected anhydrothymidine, followed by a deprotection step and purification by

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Table 1 Patient characteristics, mean standardized uptake value (SUV), tumor:nontumor ratio (TNT), mitotic score, MIB-1 score, and grading

Patient	Sex	Age	Diagnosis	Max[a] diameter (cm)	Location	SUV tumor	SUV nontumor	TNT	Mitotic score[b]	French tumor grade[b]	MIB-1 score[c]	Japanese tumor grade[c]
1	M	55	Well-differentiated liposarcoma	17	Leg	0.2	0.1	2.4	1	1	1	1
2	M	55	Myxoid liposarcoma	10	Leg	1.1	0.5	2.1	1	1	1	1
3	M	62	Myxoid liposarcoma	11	Leg	1.5	0.6	2.4	1	1	1	1
4	M	71	Recurrent MFH	2	Leg	1.0	0.6	1.7	1	1	1	1
5	F	61	Well-differentiated liposarcoma	30	Leg	0.4	0.7	0.6	1	1	1	1
6	F	73	Well-differentiated liposarcoma	22	Leg	0.9	0.6	1.5	1	1	1	1
7	M	27	Epitheloid sarcoma	7	Leg	1.4	0.6	2.3	1	2	2	2
8	M	28	Synoviasarcoma	12	Leg	0.8	0.4	2.1	1	2	2	2
9	M	33	Myxofibrosarcoma	17	Leg	3.4	0.6	5.4	2	2	2	2
10	M	70	Pleiomorphic MFH	10	Leg	3.7	0.6	5.9	2	2	2	2
11	F	71	Leiomyosarcoma (recurrence)	7	Arm	2.1	0.6	3.4	2	2	2	2
12	F	75	Myxofibrosarcoma	14	Leg	3.5	0.6	6.4	1	2	1	1
13	M	52	Pleiomorphic MFH	20	Leg	2.8	0.4	7.0	2	3	2	3
			Pleiomorphic MFH (recurrence in opposite leg)	2	Leg	2.3	0.3	7.1	2	3	2	3
14	M	53	Pleiomorphic liposarcoma	28	Leg	2.2	0.6	3.4	3	3	3	3
15	M	70	Myxofibrosarcoma	10	Leg	2.3	0.5	4.7	2	3	3	3
16	M	71	Pleiomorphic leiomyosarcoma	20	Leg	4.9	0.7	6.6	2	3	3	3
17	F	47	Pleiomorphic leiomyosarcoma	11	Arm	4.8	0.9	5.3	3	3	3	3
18	F	56	Extraskeletal osteosarcoma	6	Leg	2.8	0.3	9.3	3	3	3	3
19	F	58	Pleiomorphic sarcoma NOS	5	Leg	3.7	1.5	2.5	3	3	3	3

[a] Max, maximum; NOS, not otherwise specified; MFH, malignant fibrous histocytoma.
[b] Ref. 5.
[c] Refs. 6 and 7.

high-performance liquid chromatography. FLT was produced with a radiochemical purity of >95% and specific activity of >10 TBq/mmol. The radiochemical yield was 5.6 ± 2.8% (decay corrected).

Nineteen patients were examined in the period of February 2002 until July 2003, using an ECAT EXACT HR+ (Siemens/CTI Inc., Knoxville, TN). Before PET imaging, patients were instructed to fast for at least 6 h to keep the study comparable with studies performed with FDG (35). They were also instructed to drink one liter of water before imaging to stimulate FLT excretion from the renal calyces and to stimulate subsequent voiding. For injection of FLT, a venous cannula was inserted in the forearm of the patient.

Patients received a median of 400 (115–430) MBq FLT. Sixty min after injection, the region of the tumor was imaged in emission-transmission-transmission-emission mode. After scanning the tumor region, a non-attenuation-corrected whole-body scan was performed from crown to femur for 5 min per bed position. Data from multiple bed positions were iteratively reconstructed (ordered subset expectation maximization; 36).

Histological typing of the tumors of all patients was performed on H&E-stained sections according to the WHO classification (37). Immunophenotype was determined in poorly differentiated tumors. Tumors were graded using both the French and Japanese grading system (5–7).

The number of mitotic figures was counted per 2 mm^2 in H&E-stained slides, after selecting the most cellular areas with the highest mitotic rate. Proliferating cells were detected with immunohistochemistry, using monoclonal antibody MIB-1 and antigen retrieval, as described previously (12). Monoclonal antibody MIB-1 recognizes the protein Ki-67 in all phases of the cell cycle with the exception of G_0.

The MIB-1 score was estimated by counting the percentage

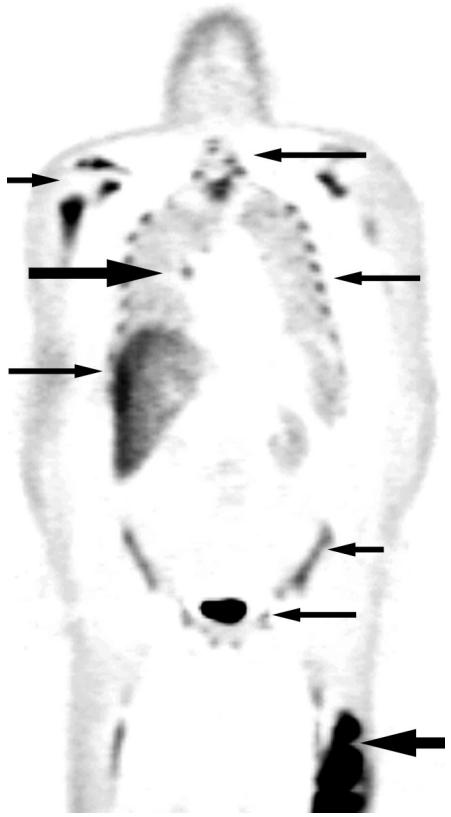

Fig. 1 The whole body ^{18}F-3′-fluoro-3′-deoxy-L-thymidine–positron emission tomography (FLT-PET) image of patient 16. *Small arrows*, physiological uptake of FLT can be seen in the bone marrow of the pelvis, ribs, and vertebrae; in the bones of the shoulder; in the liver; and in the bladder. *Large arrows*, the soft tissue sarcoma can be seen in the left upper leg and a lung metastasis in the mediastinum.

Table 2 Mean standardized uptake value (SUV), maximal SUV, and tumor:nontumor ratio (TNT) in the French or Japanese grading system

	French grading system[a]				Japanese grading system[b]			
	Grade 1[c] (n = 6)	Grade 2[c] (n = 6)	Grade 3[c] (n = 8)	Low grade[d] *vs.* high grade	Grade 1[c] (n = 7)	Grade 2[c] (n = 5)	Grade 3[c] (n = 8)	Low grade[d] *vs.* high grade
Mean SUV	0.9 (0.2–1.5)	2.8 (0.8–3.7)	2.8 (2.2–4.9)	0.001	1.0 (0.2–3.5)	2.1 (0.8–3.7)	2.8 (2.2–4.9)	0.011
Maximal SUV	1.2 (0.3–1.7)	3.4 (1.0–5.2)	3.3 (2.8–6.7)	0.001	1.3 (0.3–5.2)	2.8 (1.0–4.7)	3.3 (2.8–6.7)	0.014
TNT	1.9 (0.6–2.4)	4.4 (2.1–6.4)	6.0 (2.5–9.3)	0.001	2.1 (0.6–6.4)	3.4 (2.1–5.9)	6.0 (2.5–9.3)	0.008

[a] Ref. 5.
[b] Ref. 6 and 7.
[c] Values expressed as medians (range).
[d] Statistical difference between medians (*P*s). Low grade, grade 1; high grade, grade 2 + 3.

of MIB-1-positive cell nuclei per 1000 tumor cells in the region of the tumor with the greatest density of staining, which in most instances corresponds to areas with the highest mitotic activity.

Data Analysis

ROI. Qualitative and quantitative evaluation of the PET scans was performed by analyzing the hypermetabolic zones on transaxial sections. The slice with the highest uptake was selected for region of interest (ROI) analysis.

SUV. After selecting the plane with the maximum standardized uptake value (SUV), a ROI was drawn manually. ROIs were placed at the 70% contour of the maximal SUV in the tumor. The same ROI was applied in the contralateral leg or arm. The mean SUV of the tumor was divided by SUV of the background region to produce the tumor:nontumor ratio (TNT). In patients 3 and 13, it was not possible to let the ROI-tool calculate a mean SUV from 70% of the maximal SUV in the nontumor region, because the calculated ROI was below the background uptake of FLT (Table 1). Therefore, the highest mean of the manually drawn ROI with the highest SUV was used. TNTs and SUVs were compared with histopathological parameters.

The pathologist (A. J. H. S.) was unaware of the results of the PET-images. The images were analyzed independently by a clinical investigator (D. C. P. C.) unaware of histological typing and grading of the tumors. After calculating the SUVs and TNTs of the PET lesions, the PET data were correlated with the histopathological findings.

Whole Body Images. Whole body images were scored for presence/absence of lesions outside the location of the primary tumor, blinded for other clinical information. Lesions were interpreted visually as malignant, if the FLT uptake in the lesion was higher than the surrounding tissue.

Statistical Analysis

Kruskall-Wallis nonparametric testing was used to see whether the groups, as defined by the French or Japanese grading system, differed. Dunnett's T3 *post hoc* multiple comparisons test was performed for variance analysis between the different groups, as defined by the French or Japanese grading system, for mean SUV, maximal SUV, and TNT. Mann-Whitney testing was used to compare the mean SUV, maximal SUV, and TNT between the French or Japanese grading system. Spearman's correlation coefficient was used to correlate mean SUV, maximal SUV, and TNT, with mitotic score, MIB-1 score, and the French or Japanese grading system. Two-tailed *P*s <0.05 were considered significant.

RESULTS

Patients. Nineteen patients with a median age of 58 (range, 27–75) years, 7 women and 12 men, were included in this study (Table 1). Eighteen patients had one STS, and one patient had two STSs. Patient characteristics are presented in Table 1. Eighteen patients had a biopsy before the FLT-PET, and one patient had a FLT-PET before the biopsy. A total of 17 incision biopsies and 2 true-cut biopsies were performed.

Primary Tumors. Twenty tumors in a total of 19 patients were clearly visible with high contrast and were interpreted as malignant. Fig. 1 is an example of a FLT-PET whole body image (patient 16). The sensitivity for detecting malignant lesions was 100%. The Kruskal-Wallis variance analysis

Table 3 *P*s of Dunnett T3 comparisons for mean standardized uptake value (SUV), maximal SUV, and tumor:nontumor ratio (TNT) in the French or Japanese grading system

	French grading system[a]			Japanese grading system[b]		
	Grade 1 *vs.* grade 2	Grade 1 *vs.* grade 3	Grade 2 *vs.* grade 3	Grade 1 *vs.* grade 2	Grade 1 *vs.* grade 3	Grade 2 *vs.* grade 3
Mean SUV	0.056	0.001	0.594	0.385	0.011	0.473
Maximal SUV	0.066	0.002	0.660	0.536	0.032	0.409
TNT	0.063	0.003	0.468	0.503	0.022	0.286

[a] Ref. 5.
[b] Refs. 6 and 7.

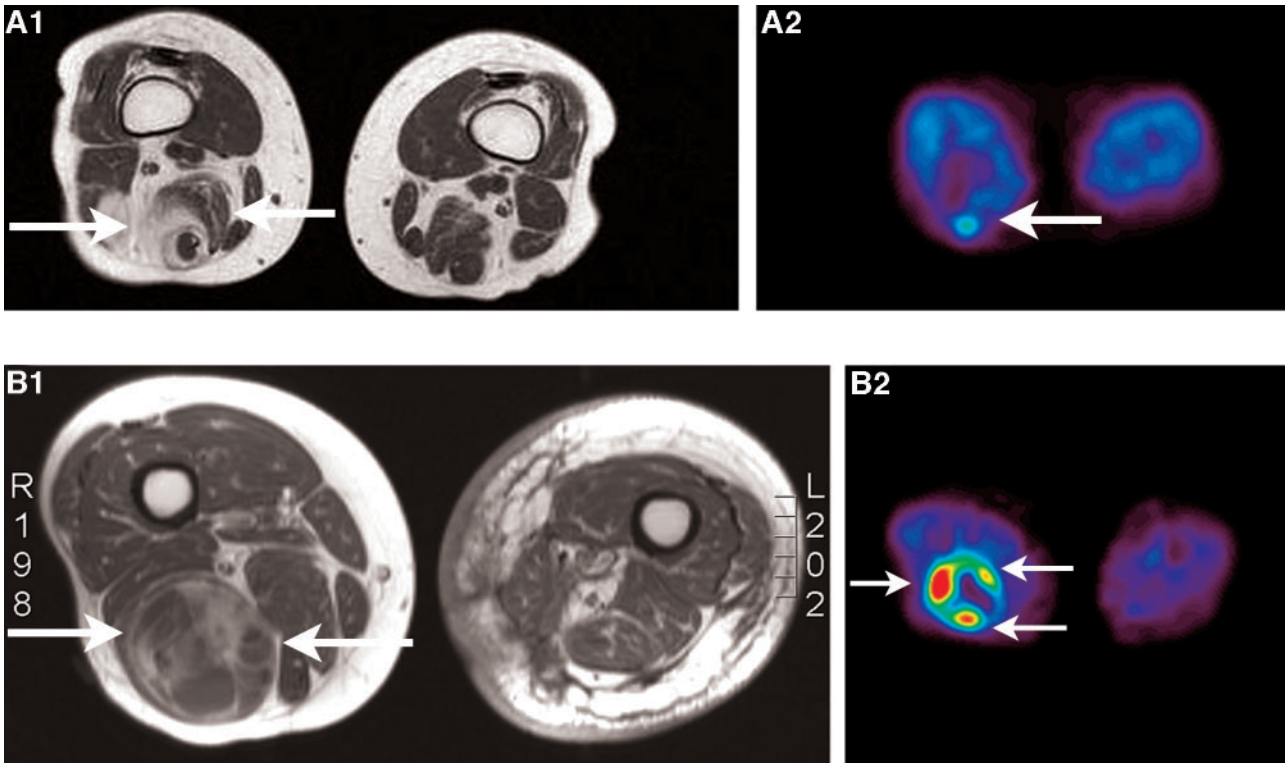

Fig. 2 *A*, the magnetic resonance imaging (MRI; *A1*) and 3′-[^{18}F]fluoro-3′-deoxy-L-thymidine–positron emission tomography (FLT-PET; *A2*) images of a low-grade soft tissue sarcoma (STS; patient 6); *B*, the MRI (*B1*) and FLT-PET (*B2*) images of a high-grade STS (patient 13). The MRI images of both patients demonstrate a heterogeneous tumor. However, the FLT uptake in the high-grade STS is higher than in the low-grade STS.

showed significant different variance in mean SUV, maximal SUV, and TNT between the groups, defined by the French or Japanese grading system.

The French and Japanese grading systems were compared with mean SUV, maximal SUV, and TNT. Mean SUV, maximal SUV, and TNT could differentiate between grade 1 STS and grade 3 STS and between low-grade and high-grade STS (Tables 2 and 3).

Mean SUV, maximal SUV, and TNT were able to differentiate between low-grade STS and high-grade STS according to the French and Japanese grading system. Fig. 2*A* is an example of a FLT-PET of a low-grade STS (patient 6) and Fig. 2*B* of a high-grade STS (patient 13).

All of the correlations between mean SUV, maximal SUV, TNT, mitotic score, MIB-1 score, and the French and Japanese grading systems were significant (Table 4). The correlation coefficients varied from 0.550 to 0.747 with all *P*s < 0.05. The strongest correlation was found between TNT and the French grading system.

Additional Findings with Whole Body FLT-PET. In four patients, single or multiple lesions were seen or missed on the whole body FLT-PET. In two patients, the lesions detected on FLT-PET were malignant. In patient 13, FLT-PET detected, besides a new primary STS in the right thigh, a 1.5-cm small local recurrence of a sarcoma in the left thigh, which was previously treated with surgery and radiation therapy. In patient 16, FLT-PET detected lung metastases, which were confirmed on CT as well (Fig. 1).

In three patients, the lesions seen on FLT-PET were not malignant according to pathological examination or follow-up. In patient 10, the lesions on FLT-PET in the groin and supraclavicular region were negative on physical examination and follow-up. In patient 13, the lesion on FLT-PET in the groin was histologically negative after lymph node dissection. In patient 14, the lesions on FLT-PET in the groin were indicated as lymph nodes with follicular hyperplasia after lymph node dissection.

In one patient, a metastatic lymph node was missed on FLT-PET. In patient 7, an axillary lymph node dissection was performed. In the lymph node dissection, one lymph node contained two metastases, both with a diameter of 5 mm, with 11 mitotic figures per 2 mm^2. This metastatic lymph node was not detected on whole-body FLT-PET.

Table 4 Spearman's correlations (ρ) between grade, mean standardized uptake value (SUV), tumor:nontumor ratio (TNT), mitotic score and MIB-1 score

	Mitotic score[a]	MIB-1 score[b]	French grading system[a]	Japanese grading system[b]
Mean SUV	0.721[c]	0.652[c]	0.724[c]	0.647[c]
Maximal SUV	0.668[c]	0.610[c]	0.723[c]	0.627[c]
TNT	0.646[c]	0.550[d]	0.747[c]	0.668[c]

[a] Ref. 5.
[b] Refs. 6 and 7.
[c] $P < 0.005$.
[d] $P < 0.05$.

DISCUSSION

The results of this study revealed that FLT-PET is able to visualize STS and recurrent STS and has the clinical potential to distinguish between low- (grade 1) and high-grade (grade 2 and 3) STS.

FLT uptake appeared to be related to proliferation and tumor grade. Mean SUV, maximal SUV, and TNT correlated with mitotic score, MIB-1 score, and the French and Japanese grading of STS. No difference between the French and Japanese grading systems was found, based on the correlations.

In the French grading system of STS, all three parameters (level of histological differentiation, amount of necrosis, and mitotic index) are independent predictors of metastasis (38). It has been demonstrated that, when using the MIB-1 score instead of the mitotic score in the French grading system, the grading of STS improved. This modified Japanese grading system proved to be the most significant predictor of overall survival (6, 7). Therefore, a PET-tracer that would reflect proliferation, could have the potential to visualize the grading of STS. For this purpose, ^{18}F-fluoro-3′-deoxy-3′-L-fluorothymidine (FLT) was developed (33, 39). This pyrimidine analog is phosphorylated by the enzyme thymidine kinase 1, which leads to intracellular trapping (33). During DNA synthesis, thymidine kinase 1 concentration increases almost 10-fold and is, therefore, an accurate reflection of cellular proliferation (40).

Most previous studies for detecting sarcomas have been performed with ^{18}F-fluoro-2′-deoxy-D-glucose-PET (FDG-PET) and have recently been critically reviewed in two meta-analyses (31, 32). The sensitivity of FDG-PET for detecting primary and recurrent sarcomas varies from 88 to 92%, and specificity varies form 73 to 87% (31, 32). FDG-PET can be useful in tumor grading but is, with the exception of a study of Eary *et al.,* (17) not able to differentiate between benign lesions and low-grade sarcoma (16, 17, 31, 32). The accuracy for the differentiation is influenced by technical limitations, time between injection and scanning, and false negative and false positive findings (18, 21, 22, 26, 29). The SUV for FDG-PET for low-grade (grade 1) STS varied between 1.6 and 2.6, as compared with 0.2 and 1.5 for FLT-PET; the SUV for FDG-PET for high-grade STS (grade 2 and 3) varied between 8.0 and 9.4 as compared with 0.8 and 4.9 for FLT-PET (23, 29). Despite the lower sensitivity of FDG-PET than FLT-PET, the uptake of FDG was higher than of FLT. In a comparative study with FLT-PET, the correlation between FDG SUV and the proliferation of the STS should be investigated.

In conclusion, FLT-PET is able to visualize and differentiate high-grade from low-grade STS. The uptake of FLT correlates with the proliferation of STSs.

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