PET imaging of musculoskeletal tumours with fluorine-18 α-methyltyrosine: comparison with fluorine-18 fluorodeoxyglucose PET

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Abstract. Fluorine-18 labelled α-methyltyrosine (FMT) was developed for positron emission tomography (PET) imaging, and its potential for clinical application in patients with brain tumours has been demonstrated. This is the first trial to compare FMT with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) for the evaluation of musculoskeletal tumours. Seventy-five patients were examined with both FMT- and FDG-PET within a 2-week period. Imaging findings were visually inspected in conjunction with computed tomography and/or magnetic resonance imaging, and standardized uptake values (SUVs) for both FMT and FDG in lesions were also generated and compared with histological findings. A significant correlation between FMT and FDG SUVs was found for all lesions (r=0.769, P<0.0001), and mean values for malignant tumours were significantly higher than those for benign lesions in both FMT- and FDG-PET. The diagnostic sensitivities and specificities for malignancy were 72.7% and 84.9%, respectively, using FMT with a cut-off SUV of 1.2, and 72.7% and 66.0%, respectively, using FDG with a cut-off SUV of 1.9. The resultant accuracy with FMT was 81.3%, higher than that for FDG (68.0%), and the difference with respect to specificity was significant (χ^2cal=5.0625, P<0.05). On the other hand, while a significant correlation was found between malignant tumour grade and SUV with both FMT- (ρ=0.656) and FDG-PET (ρ=0.815), only the latter demonstrated significant differences among grades I, II and III. FMT and FDG for PET appear equally effective at detecting musculoskeletal tumours. In evaluating musculoskeletal tumours, FMT may be superior to FDG in the differentiation between benign and malignant tumours, while FDG may be the better choice for non-invasive malignancy grading.

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Introduction

The evaluation of many musculoskeletal masses remains a diagnostic dilemma in clinical practice. In general, computed tomography (CT) and magnetic resonance imaging (MRI) are excellent tools for visualizing anatomical detail including location, extent and inhomogeneity. These non-invasive modalities, however, are not sufficiently reliable indicators of the active tumour cell distribution, or of malignant potential [1, 2]. Such information is crucial for preoperative planning, including selection of the first operative procedure and identification of metabolically active areas of lesions to assist in biopsy guidance.

The glucose analogue fluorine-18 fluoro-2-deoxy-D-glucose (FDG) is widely used for positron emission tomography (PET) evaluation of various tumours [3], including musculoskeletal lesions, that demonstrate a relationship between FDG uptake and histopathological grade [4, 5, 6]. This approach has utility for detecting recurrent or residual sarcomas [7, 8, 9], and Griffeth et al. have suggested that FDG-PET may be a useful adjunct in the preoperative evaluation of soft tissue tumours [10]. Accumulated evidence indicates that the standardized uptake value (SUV), a quantitative index of tissue uptake of FDG, may provide information that is useful in differentiating malignant tumours from benign lesions in the musculoskeletal system [11, 12]. However, some benign lesions, such as schwannomas and giant cell tu-

mours of tendon sheath, exhibit high SUVs, resulting in a specificity of less than 80% for the diagnosis of malignancy [12]. There is controversy in the literature about the ability of FDG-PET to discriminate between malignant and benign osseous lesions [13]. Similarly, Nieweg et al. pointed out that FDG may be unsuitable for discriminating benign lesions from soft tissue sarcomas with low and intermediate malignancy grades [6]. To overcome this drawback, other markers allowing quantitative analysis are required for preoperative planning.

For protein metabolism imaging in tumours, L-[methyl-^{11}C]methionine (Met), an essential amino acid tracer, has been utilized [14]. However, methionine participates in too many metabolic pathways to obtain rate constants using kinetic models [15], and the half-life of ^{11}C (20 min) is short, so that only a limited number of PET studies have been performed. In fact Met-PET results were not found to be superior to those of FDG-PET for the detection of malignant tumours, including musculoskeletal neoplasms [16]. The potential clinical use of the iodine-123 labelled amino acid α-methyltyrosine (IMT) has been demonstrated for extracranial tumours [17]. Recently, we have developed L-[3-^{18}F]-α-methyltyrosine (FMT) as a tumour-detecting amino acid tracer for PET imaging [18], and confirmed its potential use for this purpose using experimental tumour models [19, 20]. In contrast to radiolabelled methionine and tyrosine, FMT, an amino acid analogue, is accumulated in tumour cells solely via an amino acid transport system [19]. This is unique to FMT; by contrast, FDG, a glucose analogue tracer, is utilized in glucose metabolism and metabolically trapped in the cells [21]. In a recent clinical trial, the clinical applicability of FMT-PET imaging for the detection of brain tumours was clearly demonstrated [22]. The purpose of the present study was to evaluate the potential of FMT-PET to distinguish malignant tumours from benign mass-producing lesions in the musculoskeletal system, in comparison with FDG-PET analysis.

Materials and methods

Patients. A prospective comparison of FMT- and FDG-PET imaging was performed in patients with musculoskeletal tumour and tumorous conditions. Patients were recruited consecutively from those referred to undergo surgical treatment between February 1998 and June 1999, and had a follow-up period of more than 1 year. The patients' characteristics, including age, sex, size and localization of tumours, histopathological features, grade of malignancy and method of verification of FMT- and FDG-PET results, are listed in Table 1. The study group included 75 patients (37 males and 38 females) aged 12–83 years (mean 44.0 years) who had been referred for clinical evaluation of bone and soft tissue tumours and related conditions. Informed consent was obtained from each patient or child's guardian prior to the PET study. Seventy-five different lesions (27 of bone and 48 of soft tissue lesions) were evaluated. In one patient (patient TS), an extraskeletal osteogenic sarcoma developed in the foot, and was resected widely. Although no recurrent tumours were evident, pulmonary metastases arose which were then evaluated.

All patients had previously undergone routine evaluation with CT, MRI and/or angiography either at our institution or at the referring institution. PET imaging was performed as part of the preoperative evaluation of each patient for the general clinical purpose of elucidation of metabolically active areas of lesions for biopsy guidance. The final diagnosis was established with material taken at biopsy, surgical excision or autopsy for all patients. Malignant lesions were classified using the NCI grading system [23], with the exception of chondrosarcoma, for which determination of the histopathological grade was based on Evans' grading system [24]. The sizes of suspicious lesions were determined by gross sections of specimen, plain radiography, CT and/or MRI.

The local Ethics Committee (Gunma University) approved the study, and each individual participating in the study gave his or her informed consent.

PET studies. FMT was produced in our cyclotron facility using the method developed by Tomiyoshi et al. [18], and FDG was synthesized as described previously [12, 25]. In all cases, FDG-PET was performed within 2 weeks of FMT-PET. Prior to the PET studies, patients were fasted for at least 4 h, at which time normal glucose levels were confirmed by clinical laboratory tests [16]. PET studies were performed using a whole-body PET scanner, SET2400W (Shimazu Coop, Tokyo, Japan), with a 59.5-cm transaxial field of view and a 20-cm axial field of view which produced 63 image planes spaced 3.125 mm apart. Transaxial resolution at the centre of the field was 4.2 mm.

Using a simultaneous emission-transmission method with a rotating external source (370 MBq ^{68}Ge/^{68}Ga at installation) [26], acquisition of a static image was initiated 40 min after the injection of 185–350 MBq FMT or FDG. The software was set to provide an 8-min acquisition per bed position and 1–2 bed positions. Attenuation-corrected transaxial images with FMT and FDG were produced by an ordered subset expectation maximization (OSEM) iterative algorithm (an ordered subset of 16 with 1 iteration). Images were reconstructed into 128×128 matrices with a pixel dimension of 4.0 mm in-plane and 3.125 mm axially. Using transaxial images, coronal images with 9.8 mm slice thickness were produced for visual interpretation.

Data analysis. All PET images were prospectively interpreted in routine hard-copy consensus review by two experienced nuclear radiologists and an orthopedic surgeon. Based on comparison with the surrounding background radioactivity, lesion uptake was classified into one of four categories: no uptake, faint uptake, moderate uptake or intense uptake. Moderate uptake and intense uptake were defined as positive results of visual interpretation (+), and faint uptake and no uptake were defined as negative results (–). All PET findings were finally compared with CT and/or MR images, and results of pathological diagnosis.

For the semiquantitative analysis, functional images of the SUV were produced using attenuation-corrected transaxial images, injected doses of FMT and FDG, patient's body weight, and the cross-calibration factor between PET and dose calibration. SUV was defined as follows:

$$\mathrm{SUV} = \frac{\text{radioactive concentration in the tumour (MBq / g)}}{\text{injected dose (MBq) / patient's body weight (g).}}$$

Regions of interest (ROIs) 1 cm in diameter were drawn on the SUV images over the area corresponding to the tumour, which included the site of maximal FMT or FDG uptake. ROI analysis was

Table 1. Patient characteristics and SUV values

Patient no.	Age (years)/ sex	Histopathological diagnosis	Grade[a]	Location	Lesion size[b] (cm)	FMT		FDG	
						Visual assessment[c]	SUV[d]	Visual assessment[c]	SUV[d]
Bone tumours									
1 (YA)	12/F	Ewing's sarcoma	III	Ilium	5×5×6	+	*3.63*	+	*8.1*
2 (KH)	77/F	Malignant lymphoma	III	Tibia	8×13×14	+	*2.52*	+	*9.1*
3 (CA)	75/F	Malignant lymphoma	III	Humerus	3×4x11	+	*2.09*	+	*13.68*
4 (KM)	61/M	Chondrosarcoma	III	Ilium	16×18×32	+	*1.88*	+	*3.3*
5 (TM)	67/F	Metastatic carcinoma	III	Rib	2×3×4	+	*1.6*	+	*2.0*
6 (FN)	83/F	Chondrosarcoma	II	Pharanx	3×3×4	+	*1.8*	+	*2.2*
7 (MO)	17/M	Osteogenic sarcoma	II	Tibia	5×6×7	+	*1.2*	+	*3.47*
8 (SY)	14/M	Osteogenic sarcoma	II	Femur	11×12×15	+	0.99	+	*2.0*
9 (HS)	47/F	Chondrosarcoma	II	Rib	3×4×8	+	0.95	+	1.27
10 (YN)	34/F	Osteogenic sarcoma	I	Femur	7×8×19	+	*1.37*	+	0.5
11 (YI)	56/F	Chondrosarcoma	I	Ilium	4×10×12	+	*1.26*	+	1.29
12 (YI)	41/M	GCT of bone		Femur	4×6×7	+	*1.87*	+	*5.8*
13 (SF)	18/F	Fibrous dysplasia		Metatarsus	2×2×5	+	*1.81*	+	*3.10*
14 (TO)	55/M	Fibrous dysplasia		Rib	5×6×6	+	*1.57*	+	*3.52*
15 (IN)	21/M	Eosinophilic granuloma		Rib	2×2×4	+	*1.47*	+	*3.3*
16 (KS)	50/M	GCT of bone		Femur	6×7×8	+	1.1	+	*4.6*
17 (TY)	15/M	Fibrous dysplasia		Femur	3×4×8	+	1.07	+	1.51
18 (NY)	25/M	Chondroblastoma		Femur	4×5×5	+	1.05	+	*2.1*
19 (RM)	13/M	Fibrous dysplasia		Radius	2×2×6	+	1.01	+	*2.2*
20 (TK)	16/M	Non-ossifying fibroma		Femur	3×3×4	+	0.96	+	1.71
21 (KY)	30/M	GCT of bone		Femur	6×6×7	+	0.94	+	*3.2*
22 (MS)	13/F	Fracture		Tibia	3×4×4	+	0.74	+	1.2
23 (SU)	48/M	Xanthofibroma of bone		Tibia	33×4×5	+	0.71	+	*2.2*
24 (HH)	22/F	Fibrous dysplasia		Rib	2×2×4	+	0.67	+	0.96
25 (YY)	57/F	Enchondroma		Femur	2×3×6	+	0.55	+	0.9
26 (MN)	34/F	Aneurysmal bone cyst		Patella	1×1×2	+	0.4	+	0.7
27(MT)	25/F	Sarcoidosis of bone		Ulna	1×1×3	–	0.31	+	*2.3*
Soft tissue tumour									
28 (MA)	81/F	Malignant lymphoma	III	Arm	3×5×6	+	*4.23*	+	*15.62*
29 (TS)	45/M	Osteogenic sarcoma	III	Lung	3×3×4	+	*2.1*	+	*11.5*
30 (YK)	81/M	MFH	III	Thigh	6×7×8	+	*1.7*	+	*6.74*
31 (HO)	38/M	MFH	III	Thigh	14×15×18	+	*1.4*	+	*6.5*
32 (YA)	51/M	MFH	III	Thigh	12×13×14	+	*1.39*	+	*6.2*
33 (KM)	71/F	Metastatic carcinoma	III	Buttock	3×6×6	+	0.51	+	*3.51*
34 (UK)	77/F	Liposarcoma	II	Thigh	12×17×23	+	*1.4*	+	*3.48*
35 (YK)	42/M	Liposarcoma	I	Thigh	13×14×16	+	*1.21*	+	*2.4*
36 (KM)	47/F	Haemangiopericytoma	I	Thigh	3×6×7×	+	0.88	+	1.65
37 (TK)	62/M	Liposarcoma	I	Shoulder	3×6×7	+	0.76	+	0.87
38 (HY)	77/M	Liposarcoma	I	Thigh	9×11×16	+	0.61	+	0.83
39 (MK)	51/M	Schwannoma		Poples	2×3×5	+	*1.47*	+	1.73
40 (HK)	57/F	Desmoid tumour		Back	4×6×8	+	*1.39*	+	*3.09*
41 (YS)	57/M	Schwannoma		Groin	3×3×4	+	*1.23*	+	1.67
42 (HO)	69/M	Desmoid tumour		Thigh	5×6×9	+	*1.2*	+	1.3
43 (MI)	24/F	Schwannoma		Subclavian	3×3×4	+	1.15	+	*2.5*
44 (KS)	27/F	Schwannoma		Neck	2×2×3	+	1.15	+	1.8
45 (TK)	67/M	Rheumatoid arthritis		Knee	2×3×5	+	1.1	+	*3.0*
46 (IT)	26/M	GCT of tendon sheath		Hand	2×2×3	+	1.09	+	*6.5*
47 (KT)	51/M	Abscess		Thigh	3×3×8	+	1.09	+	0.82
48 (GK)	69/M	Schwannoma		Poples	2×3×4	+	1.08	+	*2.84*
49 (MS)	53/M	Schwannoma		Forearm	1×1×3	+	1.07	+	1.0
50 (TI)	38/M	Desmoid tumour		Forearm	4×5×6	+	0.96	+	*5.0*
51 (SM)	58/F	Lipoma		Shoulder	10×9×5	–	0.83	+	0.9
52 (YF)	66/M	Lipoma		Forearm	4×4×6	–	0.81	–	0.9

Table 1. (continued)

Patient no.	Age (years)/ sex	Histopathological diagnosis	Grade[a]	Location	Lesion size[b] (cm)	FMT		FDG	
						Visual assessment[c]	SUV[d]	Visual assessment[c]	SUV[d]
Soft tissue tumour									
53 (KS)	12/F	Haemangioma		Back	2×4×4	–	0.78	–	0.7
54 (SS)	17/F	GCT of tendon sheath		Ankle	3×3×4	+	0.78	+	*7.15*
55 (FI)	59/F	Schwannoma		Foot	1×2×2	+	0.78	+	0.7
56 (SS)	59/F	Schwannoma		Arm	3×4×4	+	0.72	+	0.95
57 (MK)	30/F	Haemangioma		Crus	3×3×5	+	0.71	+	1.04
58 (TY)	64/F	Schwannoma		Crus	3×4×6	+	0.7	+	1.0
59 (TH)	27/M	Schwannoma		Arm	1×1×15	–	0.7	+	1.58
60 (MS)	25/F	Haemangioma		Crus	3×4×6	+	0.62	+	1.4
61 (KM)	61/F	Haemangioma		Ankle	1×2×2	+	0.56	–	0.8
62 (ST)	20/F	Haemangioma		Crus	2×3×9	+	0.55	+	1.25
63 (YO)	40/F	Schwannoma		Subclavian	2×2×3	+	0.55	+	1.2
64 (SM)	45/M	Schwannoma		Arm	3×3×4	+	0.44	+	*2.8*
65 (YS)	26/F	Desmoid tumour		Thigh	2×3×5	+	0.42	+	0.72
66 (SN)	50/M	Lipoma		Thigh	2×4×12	–	0.4	+	0.97
67 (YM)	17/M	Haemangioma		Buttock	3×4×4	–	0.39	+	1.5
68 (CO)	20/F	Haemangioma		Arm	2×3×5	–	0.38	+	1.19
69 (NS)	32/F	Haemangioma		Foot	1×2×2	+	0.37	+	1.4
70 (HH)	77/M	Lipoma		Buttock	8×10×12	–	0.31	–	0.24
71 (MK)	36/F	Haemangioma		Hand	1×1×2	–	0.3	–	0.8
72 (TK)	49/M	Lipoma		Arm	3×5×6	–	0.26	–	0.68
73 (TA)	36/M	Ganglion		Ankle	1×1×2	–	0.19	–	0.70
74 (HM)	40/F	Haemangioma		Foot	1×2×2	–	0.14	+	1.15
75 (JS)	48/F	Ganglion		Poples	2×3×4	–	0.1	–	0.3

[a] Malignant lesions were classified according to the grading system described in Materials and methods
[b] Maximal extent in each of three orthogonal dimensions
[c] +, Visually assessed as positive; –, visually assessed as negative
[d] Italics indicate numbers in the high-value groups

conducted by a nuclear radiologist with the aid of corresponding CT scans and MR images. The average SUV in the ROI was defined as the tumour uptake of FMT and FDG.

Statistical analysis. The relationship between FMT and FDG SUVs for the lesions was assessed by linear regression analysis. Spearman's rho rank-order correlation coefficient, corrected for ties, was conducted to study the strength of the relationship between malignant tumour grade and the SUV [4]. The McNemar test was used for comparison of sensitivity and specificity since both FMT and FDG analyses were performed on the same patients [27]. Differences in mean SUV for both FMT and FDG between malignant and benign tumours, and among histological grades in malignant tumours, were evaluated for statistical significance using the unpaired Student's *t* test. A *P* value of less than 0.05 was considered significant.

Results

The results are summarized in Table 1. The sizes of suspicious lesions ranged from 1×1×2 to 16×18×32 cm, as determined by gross sections of specimen, plain radiography, CT and/or MRI images. On the basis of the histopathological results, there were 53 benign lesions and 22 malignant tumours, including six grade I, five grade II and 11 grade III lesions. All malignancies were easily visualized with both FMT- and FDG-PET analyses as areas of increased accumulation. Figures 1 and 2 show examples of high- and low-grade malignancies, respectively. Note that while there was a marked increase in tumour uptake of both FMT and FDG in the high-grade malignancy, a grade III Ewing's sarcoma (Fig. 1), the low-grade malignant tumour, a grade I chondrosarcoma, showed only mildly increased uptake at the margin of the lesion (Fig. 2). A metastatic lesion of osteogenic sarcoma to the lung (patient TS) showed high accumulation of FMT, although a higher SUV for FDG was obtained as compared with primary osteogenic sarcomas (MO, SY, YN). Thirty-nine (73.6%) and 45 (84.9%) out of 53 benign lesions were visually positive on FMT- and FDG-PET analyses, respectively. Tumour SUVs of FMT ranged from 0.1 to 4.23 with a mean of 1.05±0.70 (n=75), which was significantly lower than the tumour SUVs of FDG-PET (2.78±2.97, P<0.0001). However, a significant correlation (r=0.769, P<0.0001) was noted between FMT and FDG SUVs for all lesions (n=75) (Fig. 3).

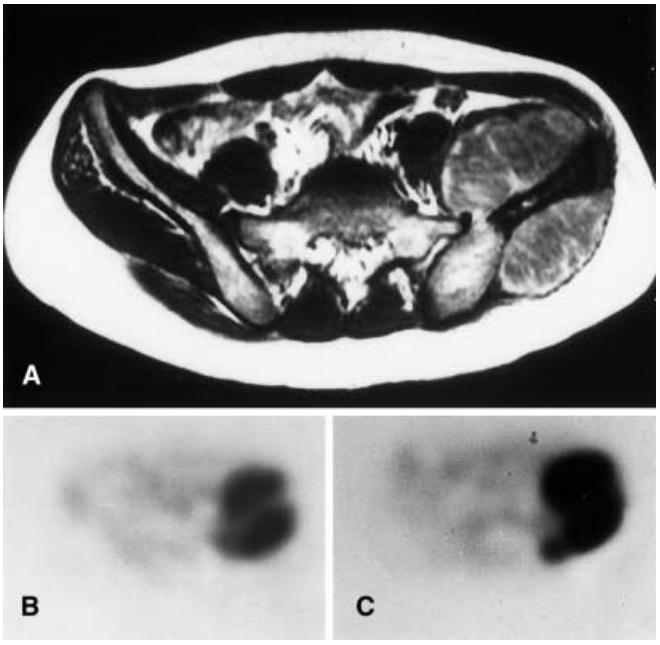

Fig. 1A–C. A 12-year-old female (YA) with a high-grade (grade III) Ewing's sarcoma of the left ilium. **A** T1-weighted MR images (TR/TE = 500/15) with gadolinium enhancement demonstrate destruction of the marrow space and of both anterior and posterior margins of the cortex with extension of huge masses on both sides. PET scan through approximately the same level shows markedly increased FMT (**B**) and FDG (**C**) accumulation with SUVs of 3.63 and 8.1, respectively, in a pattern corresponding to the extent of tumour involvement on MRI

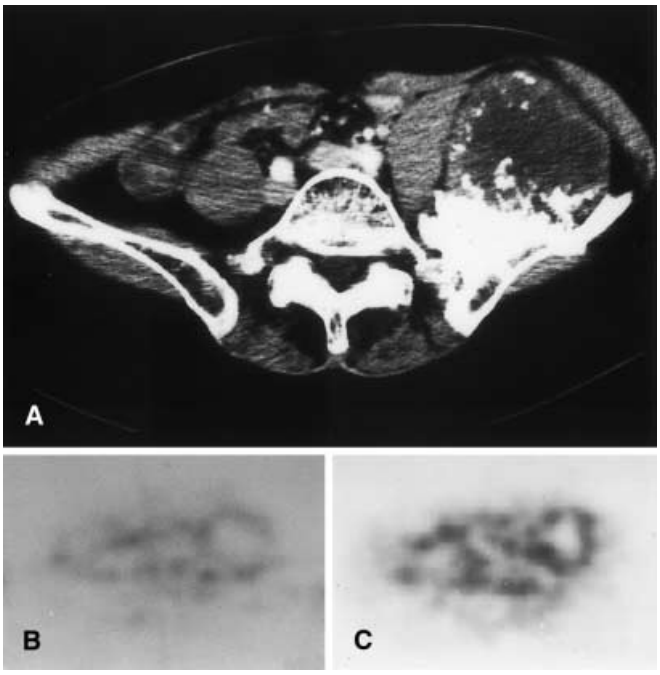

Fig. 2A–C. A low-grade (grade I) chondrosarcoma that developed at the ilium in a 56-year-old female (YI) with hereditary multiple exostosis. **A** The CT scan shows a large cartilaginous mass arising from the left ilium with marginal ossification. **B** FMT-PET scan reveals mildly increased uptake in the margin of the lesion. The SUV was 1.26, within the high-value group. **C** FDG-PET scan shows mildly increased accumulation, with a similar marginal pattern and an SUV of 1.29, in the low range

Table 2. SUV determination in patients with musculoskeletal tumours: FMT PET imaging analysis using a cut-off value of 1.2

Lesions	No. of patients		
	High-value group[a]	Low-value group[a]	Total
Malignant	16	6	22
Benign	8	45	53
Total	24	51	75

[a] Lesions were divided into high (≥1.2) and low (<1.2) SUV groups. The sensitivity of PET for correctly diagnosing malignancy was then calculated as 72.7%, with a specificity of 84.9% and an overall accuracy of 81.3%

Table 3. SUV determination in patients with musculoskeletal tumours: FDG PET imaging analysis using a cut-off value of 1.9

Lesions	No. of patients		
	High-value group[a]	Low-value group[a]	Total
Malignant	16	6	22
Benign	18	35	53
Total	34	41	75

[a] Lesions were divided into high (≥1.9) and low (<1.9) SUV groups. The sensitivity of PET for correctly diagnosing malignancy was then calculated as 72.7%, with a specificity of 66.0% and an overall accuracy of 68.0%

The mean SUVs for malignant tumours were significantly higher than those for benign lesions in both FMT- and FDG-PET analyses (1.61±0.907 vs 0.811±0.419, $P<0.0001$, 4.83±4.36 vs 1.93±1.55, $P<0.0001$, respectively). As shown in Table 2, using a cut-off value of 1.2 for the FMT SUVs, 16 of the 22 malignant lesions and 45 of the 53 benign lesions were characterized correctly, yielding a sensitivity and specificity of FMT-PET for the differentiation of benign from malignant musculoskeletal lesions of 72.7% and 84.9%, respectively, and an accuracy of 81.3%. On the other hand, a cut-off value of 1.9 was used for SUV in FDG-PET, as described previously [12]. With this value, 16 of the 22 malignant lesions and 35 of the 53 benign lesions were characterized correctly, and the sensitivity, specificity and accuracy of FDG-PET were 72.7%, 66.0% and 68.0%, respectively (Table 3). The specificity of FDG-PET was lower than that of FMT-PET, and the value of the McNemar statistic with

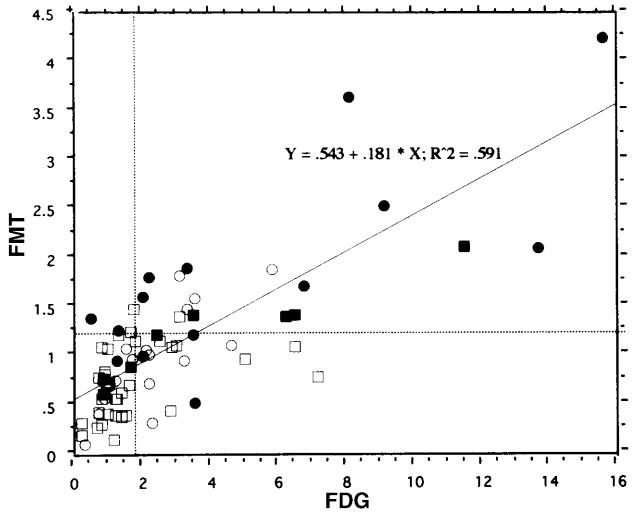

Fig. 3. Correlation between uptake of FMT and FDG measured as SUVs of malignant tumours (*closed symbols*) and benign lesions (*open symbols*) in bone (*squares*) and soft tissue (*circles*) mass lesions (n=75, r=0.769, P<0.0001). The cut-offs for FMT (1.2) and FDG (1.9) between benign and malignant lesions are shown by the *dotted lines*

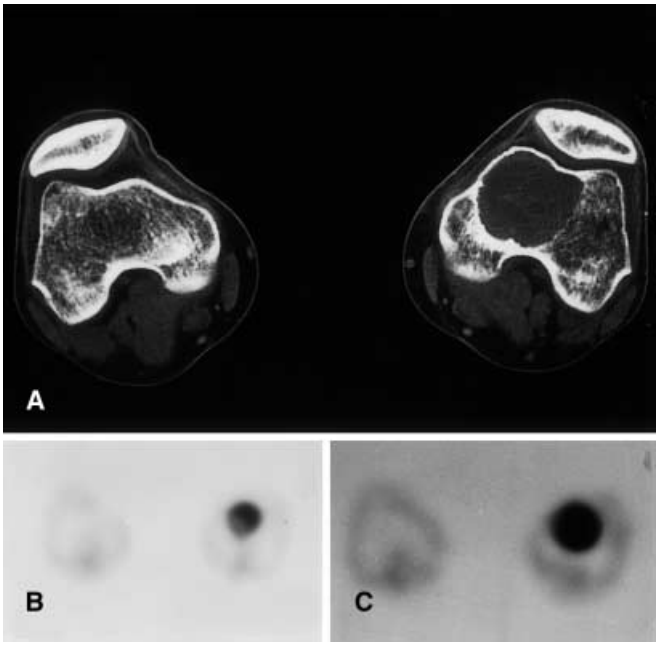

Fig. 4A–C. A 30-year-old male (KY) with a giant cell tumour of the medial condyle of the femur. **A** CT scan shows extensive destruction of the marrow space and expansion of the cortex with preservation of continuity. **B** FMT-PET scan demonstrates uniformly increased uptake through the lesion. The SUV was 0.94, indicative of a benign lesion. **C** An FDG-PET scan shows markedly increased accumulation in a similar uniform pattern with an SUV of 3.2, suggesting a malignancy

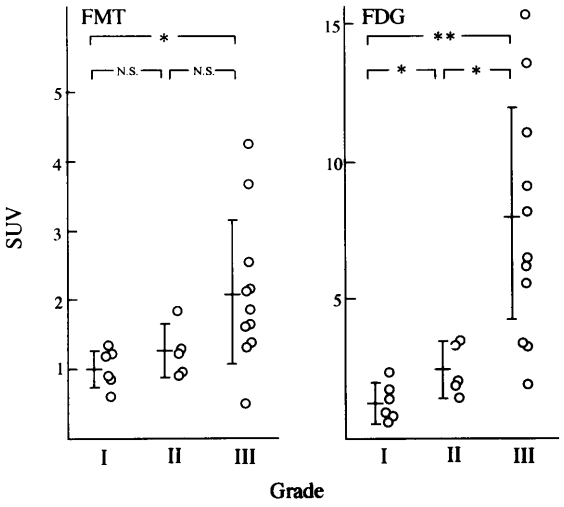

Fig. 5. Plot of tumour SUV versus tumour grade for all malignant tumours in FMT- and FDG-PET analyses

correction for continuity was 5.0625 at the P<0.05 level of significance. The benign bone lesions with an SUV of 1.9 or above on FDG-PET included all three giant cell tumours (GCTs) of bone (100%), three out of five fibrous dysplasias (60%), the eosinophilic granuloma (100%), the chondroblastoma (100%), the xanthofibroma (100%) and the sarcoidosis (100%). Of the benign soft tissue lesions, two GCTs of tendon sheath (100%), two out of four desmoid tumours (50%), 3 out of 12 schwannomas (25.0%), and the rheumatoid arthritis (100%) had high values of 1.9 or above. However, 13 out of 18 benign lesions in this high-SUV group on FDG-PET were evaluated correctly in the low-SUV group on FMT-PET, as shown in Fig. 4.

The SUVs for both FMT and FDG were significantly positively correlated with tumour grade in sarcomas (ρ=0.656 and 0.815, respectively). With FMT-PET, however, there was no significant difference between either grade I and II malignancies (P=0.2316) or grade II and III malignancies (P=0.1129), although grade III malignancies had significantly higher mean SUVs than the grade I tumours (P=0.0281) (Fig. 5A). On the other hand, there were significant differences in SUVs between grades I and II as well as between grades II and III on FDG-PET analysis (P=0.0363 and 0.0180, respectively) (Fig. 5B).

Discussion

Detection of musculoskeletal tumours

In a previous study, FMT-PET allowed all brain tumours investigated to be detected, demonstrating the clinical applicability of the technique [22]. Similarly, in this study, FMT-PET visualized all malignancies and a simi-

lar percentage of benign lesions to FDG-PET. There was a significant correlation between the uptake of the two markers (r=0.769), in line with that between the uptake of FDG and the ^{11}C-Met amino acid metabolic tracer [16]. FMT and FDG may thus be equally useful agents for the detection of bone and soft tissue tumours. It is also noteworthy that a pulmonary metastatic lesion (patient TS) showed strong accumulation of FMT, although the accumulation was more evident on FDG-PET. The patient is still alive without evidence of recurrence after surgical resection of the detected metastatic tumour. This suggests that the PET approach may be useful not only for preoperative detection of musculoskeletal tumour lesions but also for the postoperative monitoring of metastatic recurrence.

Differentiation of benign lesions from malignant tumours

The differentiation of benign from malignant lesions is crucial to preoperative planning for treatment of musculoskeletal tumours. Griffeth et al. demonstrated the average differential uptake ratio (DUR), a simple ratio of lesion-to-normal tissue FDG uptake, to be higher for malignant than for benign lesions [10]. SUV assessment of FDG accumulation also allowed discrimination of malignant from benign intraosseous lesions [11]. In our previous study a highly significant difference in SUVs between benign and malignant musculoskeletal lesions was demonstrated [12]. However, when the cut-off value was set at 1.9 the specificity for correct diagnosis of malignancy was relatively low (66%) in spite of a high sensitivity [12]. GCT of bone, fibrous dysplasia, eosinophilic granuloma, chondroblastoma, xanthofibroma and sarcoidosis in bone, as well as schwannoma, GCT of tendon sheath and desmoid tumour in soft tissue, presented problems in this respect. In particular, GCT of bone, chondroblastoma, xanthofibroma, sarcoidosis and GCT of tendon sheath were categorized into the high-SUV group in 100% of cases, and most showed strong accumulation. Thus, as has been suggested by Nieweg et al. [6], FDG appears to be unsuitable for discriminating benign lesions from sarcomas with relatively low malignancy. On the other hand, with a cut-off value of 1.2 for SUV of FMT, the sensitivity and specificity of FMT-PET for differentiation of benign from malignant musculoskeletal lesions were 72.7% and 84.9%, respectively, resulting in an accuracy of 81.3%. It is noteworthy that the specificity was clearly higher than that of FDG-PET. In particular, 13 out of 18 benign lesions that were false-positive on FDG-PET were evaluated correctly into the low-SUV group on FMT-PET. It is therefore suggested that FMT may be superior to FDG in PET analysis for the differentiation of benign from malignant tumours.

From a surgical point of view, this superiority of FMT-PET may be especially helpful in the management of patients with schwannoma. Schwannoma necessitates a special approach whereby resection is performed carefully as an enucleation. Wide resection and even biopsy, which are usually selected for malignant tumours as a first operation, may induce important neurological damage. Previously we performed wide resection in a patient since FDG uptake was high, with an SUV of 3.3. Fortunately, only a minor sensory defect was left in that case [12]. In the present study, again, 3 out of 12 schwannomas (25.0%) showed high SUVs for FDG. However, all of these three lesions showed FMT-SUVs lower than 1.2, indicating benignancy. Enucleation was then correctly applied for these three lesions on the basis of a diagnosis of schwannoma

Grading of malignancy

Since the staging system of the Musculoskeletal Tumor Society was proposed for the surgical treatment of both bone and soft tissue tumours by Enneking et al. [28], new developments in staging have given greater importance to the imaging of such tumours [29]. Histological grading has an important role in the staging and is evaluated non-invasively with various modalities [29]. In the present study, a significant correlation was found between malignant tumour grade and SUV in both FMT- and FDG-PET (ρ=0.656, and 0.815, respectively), despite the inclusion of malignancies originating from many different types of tissue. FDG-PET has been reported to provide useful information about sarcoma grade, non-invasively, even when the cell type is unknown [4, 5, 6]. This was confirmed by the present study, which showed a significant difference for FDG-SUV between grades I and II as well as between grades II and III. In contrast, there was no significant difference for FMT-SUV either between grades I and II malignancies or between grades II and III, though grade III malignancies did have significantly higher mean SUVs than grade I tumours. Probably the observed difference in capacity for distinction between grades with the two tracers is due in part to lower tumour SUVs with FMT- as compared with FDG-PET (1.05±0.70 vs 2.78±2.97) in a narrower range (0.1–4.23 vs 0.22–15.62). It is therefore conceivable that FDG may be more useful than FMT for malignancy grading of musculoskeletal neoplasms. For example, a grade III metastatic soft tissue lesion of colon cancer (patient KM) showed a high FDG SUV of 3.51, whereas FMT-PET revealed a weak accumulation (SUV, 0.51). FDG-PET may thus be a useful modality for non-invasive grading in the management of surgical staging, as speculated by Smith and O'Doherty [30].

Limitations of the PET study

Three malignancies that fell into the low-SUV group with both FMT- and FDG-PET were two liposarcomas,

both of which were grade I, and a chondrosarcoma (grade II). It has been reported in the literature that some liposarcomas show low uptake of FDG [4], presumably as a function of the cell type as well as their low grade of malignancy. Although FDG-PET could be a quantitative adjunct for differentiating chondrosarcomas from enchondromas and osteochondromas and in assessing their grade, an SUV of 1.3 was suggested to be borderline in a previous study [31]. Thus malignancies, such as liposarcomas and enchondromas, cannot be precluded even when low tracer accumulation is observed on both FMT- and FDG-PET.

It has been suggested that for patients with small tumours the SUV may be lower theoretically, and that partial volume averaging of SUVs in a lesion with a diameter less than 3 cm might be considered [32]. Among the patients investigated in this study there were 20 such lesions, one malignant and 19 benign. To exclude such an influence, we re-analysed our data using the other 55 cases with a diameter of more than 3 cm. This reanalysis revealed a similar significant correlation between FMT and FDG SUVs (r=0.783, P<0.0001), and mean values for malignant tumours were significantly higher than for benign lesions in both FMT- (1.61±0.930 vs 0.860±0.384, P=0.0001) and FDG-PET (4.96±4.42 vs 2.04±1.60, P=0.0009). The diagnostic sensitivities and specificities for malignancy were 71.4% and 82.4%, respectively, using FMT, and 71.4% and 64.7%, respectively, using FDG. The resultant accuracy with FMT was 78.2%, which was higher than that for FDG (67.3%). The difference in specificity between FMT-PET and FDG-PET reached statistical significance (χ^2cal=4.90, P<0.05), as was the case when all 75 cases were considered. Also, a significant correlation was shown between malignant tumour grade and SUV with both FMT- (ρ=0.647) and FDG-PET (ρ=0.866), and only the latter demonstrated significant differences among grades I, II and III. These results were similar to those obtained from all 75 patients investigated in the present study, suggesting that small tumour size had little influence on the statistical analyses.

Conclusion

Our results indicate that FMT may be a useful agent for the evaluation of bone and soft tissue tumours. In particular, FMT may be superior to FDG for differentiation of benign from malignant tumours, and thus be important for preoperative planning. However, FMT appeared to be inferior to FDG with regard to malignancy grading, and the latter tracer consequently may be more useful for non-invasive grading in the surgical staging of musculoskeletal sarcoma. Use of FMT-PET in combination with FDG-PET might be a useful approach for preoperative planning in patients with musculoskeletal tumours.

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