Quantitative evaluation of skeletal tumours with dynamic FDG PET: SUV in comparison to Patlak analysis

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Abstract. This study was carried out to evaluate bone lesions using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) and to explore whether dynamic and quantitative PET data may help to differentiate benign lesions from malignant masses. Forty patients with primary bone lesions were studied. The final diagnosis was confirmed by histopathology. A 60-min dynamic FDG PET acquisition was undertaken in all subjects. From the dynamic PET images, indices such as the average and maximal standardised uptake values (SUVs), the tumour SUV-to-muscle SUV ratio (T/M) and the SUV at 60 min-to-SUV at 30 min ratio (averSUV60/30 min and maxSUV60/30 min) were produced. Patlak graphical analysis was used to obtain the influx constant (K_i), and the metabolic rate of FDG (MRFDG) was calculated. Based on the receiver operator characteristic curve, the sensitivity and specificity for each parameter in differentiating between malignant and benign lesions were evaluated. The histological results revealed 21 malignant tumours and 19 benign lesions in this group. The MRFDG and SUV indices in malignant lesions were significantly higher than those in benign lesions. However, each index showed a considerable overlap between benign and malignant lesions. Average SUV correlated positively with MRFDG (r=0.67). When a cut-off of 1.8 average SUV was used, the sensitivity and specificity for discrimination of malignancy from benign disease were 85% and 82.4%, respectively. MRFDG showed a similar sensitivity (82.4%) and a better specificity (92.9%). A combination consisting of a cut-off of average SUV (1.8) and averSUV60/30 min (1.1) resulted in an improvement of specificity to 93.3%, with a small reduction in sensitivity (81.3%) as compared with exclusive use of SUV. The results of this study indicate that a detectable difference in glucose metabolism exists between malignant and benign skeletal lesions. The static FDG uptake indices alone may not enable adequate differentiation between benign and malignant lesions. Quantitative dynamic imaging may provide more helpful information, but will not permit a definite diagnosis. The use of uptake indices may represent an alternative and interesting approach to the evaluation of bone lesions.

Keywords: Bone neoplasms – Fluorine-18-fluordeoxyglucose – Positron emission tomography – Glucose metabolism

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Introduction

Over the past decade, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) has been extensively investigated in experimental and clinical oncology. It has been proved to be a valuable imaging modality for the evaluation of a variety of tumours, primarily on the basis of the observations that malignant tumours have increased glucose metabolism by comparison with normal tissues and that more aggressive malignant lesions have higher rates of glucose utilisation [1, 2, 3, 4]. However, there have been few publications about the use of FDG PET in patients with bone tumours, and the role of FDG PET for the assessment of such tumours has accordingly not yet been established [5].

Several studies have been reported in which FDG PET was used to evaluate skeletal tumours in a small

number of cases [6, 7, 8, 9]. Discrepant results were obtained regarding the discrimination of benign from malignant lesions on the basis of FDG uptake indices or glucose metabolic rates. One major problem in dealing with bone tumours is the wide variability in histology. However, early detection and precise classification are important to improve the prognosis of patients with such lesions. The purpose of this study was to evaluate bone lesions using FDG PET and to explore whether dynamic and quantitative PET data may help to differentiate benign lesions from malignant masses.

Materials and methods

Patients

Forty patients (11 women, 29 men; age range 12–70 years; mean age 35.8 years) who had clinical and radiographic bone lesion symptoms were studied. Conventional imaging for these patients consisted of radiography, magnetic resonance imaging (MRI) or computed tomography (CT) and bone scintigraphy. The final diagnosis was based on histological findings. Informed consent was obtained from all patients prior to the PET examination.

Data acquisition

^{18}F-FDG, with a radiochemical purity of more than 99%, was produced routinely according to the procedure described by Toorongian et al. [10]. An ECAT HR plus positron scanner (Siemens CTI Co., Knoxville, Tenn., USA) with 32 rings and an axial field of 15.5 cm was used for data acquisition.

All patients were fasted for more than 4 h prior to the examination, and serum glucose levels were measured prior to tracer administration. The patients were placed in a supine position in the scanner with the bone lesion in the field of view. A 10-min transmission scan (with three rotating gallium-68/germanium-68 rod sources) was performed for attenuation correction. Then, 370–440 MBq ^{18}F-FDG was intravenously administered and dynamic images were acquired over 60 min: 10×60 s, 5×120 s, 8×300 s.

Data analysis

Volumes of interest (VOIs). PET cross-sections were reconstructed using an iterative reconstruction program (weighted least square method, ordered subsets, four subsets, six iterations) with an image matrix of 256×256 [11]. The PET cross-sections were compared with the corresponding MRI or CT slices. Volumes of interest (VOIs) were placed over the lesions, the aorta or other large vessels, and the contralateral normal muscle, and time-activity curves were generated for further data evaluation. A VOI consists of several regions of interest (ROIs) over the target area. Irregular ROIs were drawn manually. To compensate for patient motion during the acquisition time, the original ROIs were visually repositioned, but not redrawn. For the input function the mean value of the VOI data from a large arterial vessel was used. A vessel VOI consisted of at least ten ROIs in sequential PET images. The recovery coefficient is 0.85 for a diameter of 8 mm for the system described above. Partial volume correction was used for small vessels with a diameter <8 mm, but not for the descending aorta. Only data sets with a stable input function were used for final evaluation (Patlak analysis was performed in 31/40 patients).

Standardised uptake value. Standardised uptake values (SUVs) were calculated according to the following expression:

$$\mathrm{SUV} = \frac{\text{tissue concentration (MBq / g)}}{\text{injected dose (MBq) / body weight (g)}}.$$

The average SUV in a VOI, the maximum SUV in a VOI and the average tumour SUV/muscle SUV ratio (T/M) were calculated based on the last frame 55–60 min post injection. We calculated the ratios of average and maximal SUV (in a VOI) at 60 min to average and maximal SUV at 30 min, respectively, expressed as averSUV60/30 min and maxSUV60/30 min, respectively.

Patlak analysis. The dynamic quantitative data were analysed with the Patlak graphical model [12, 13]. The model equation is given by the expression:

$$\frac{Ci(t)}{Cp(t)} = Ki\frac{\int_0^t Cp(t')dt'}{Cp(t)} + (Vo + Vb)$$

where $C_i(t)$ is the tissue concentration of tracer at time t, $C_p(t)$ is the blood concentration of tracer at time t, V_o and V_b are the trace volume of distribution and the fractional volume of small capillaries in the tissue VOI, respectively, and K_i is the tracer blood-tissue transfer constant (influx constant). The input function used in this study was obtained from the time-activity curve, which was generated mostly from aorta or, in some cases, from a different large artery [14, 15]. K_i was obtained from the slope of the fit of $C_i(t)/C_p(t)$ versus $\int C_p(t')dt'/C_p(t)$. With the time-activity curves from the VOIs of arteries and tumours as input data, a PMOD software package (provided by cooperation with the University of Zürich, Switzerland) [16, 17] was used to fit the Patlak graphical model and calculate K_i. The tissue metabolic rate of glucose (MRGlu) could then be calculated using the following equation:

$$\mathrm{MRGlu} = K_i \times \text{Plasma glucose/LC}$$

where LC is a lumped constant which indicates the ratio of FDG uptake to glucose uptake and is used to account for the difference in uptake between normal glucose and FDG. Since the lumped constant of tumour tissue is unknown, we did not attempt to account for the differences in tissue handling of glucose and FDG. Therefore, the quantitative imaging result is expressed as the metabolic rate of FDG (MRFDG) according to [8]:

$$\mathrm{MRFDG} = K_i \times \text{Plasma glucose}$$

rather than as the inferred glucose metabolic rate based on an assumed lumped constant.

Statistical analysis

Statistical analysis included use of Student's t test to test the differences of the quantitative indices between benign and malignant lesions. For each quantitative index its cut-off value for discrimination of malignancy from benign disease was determined from the receiver operating characteristic (ROC) curve analysis. The correlations between MRFDG and the other indices such as average SUV, maximal SUV, T/M, averSUV60/30 min and blood glucose concentration were analysed. A P value of <0.05 was considered significant.

Results

The histological results are shown in Table 1. There were 21 malignant and 19 benign lesions. In the malignant group most cases were primary bone tumours, which included osteosarcoma (*n*=6), Ewing's sarcoma (*n*=6), plasmacytoma (*n*=2), malignant giant cell tumour (*n*=3), malignant fibrous histocytoma (*n*=1), malignant haemangioendothelioma (*n*=1) and two cases of metastasis.

An example of a malignant lesion, clearly visualised with FDG PET, is presented in Fig. 1a. Figure 1b demonstrates an example of enhanced FDG uptake in a patient with a giant cell tumour, which was considered semimalignant. Table 2 shows the mean values of quantitative indices for malignancy versus benign disease. The mean of the average SUV in malignant lesions was 3.06±1.78, which is significantly higher than that in benign lesions (1.23±0.80, *P*=0.0004). Patlak graphical analysis was successfully performed in 17 malignant and 14 benign cases. The MRFDG was also significantly higher for malignant than for benign lesions. However, the variance was large in both groups. The other quantitative indices were also higher in malignant than in benign lesions. Nevertheless, the plot distribution of each index overlapped considerably between the malignant and benign groups (Figs. 2, 3, 4). The MRFDG

Table 1. Histological diagnoses

Diagnosis	No.
Malignant	21
Osteosarcoma	6
Ewing's sarcoma	6
Plasmacytoma	2
Malignant giant cell tumour	3
Malignant fibrous histiocytoma	1
Malignant haemangioendothelioma	1
Metastatic thyroid carcinoma	1
Metastatic bronchiocarcinoma	1
Benign	19
Enchondroma	3
Osteochondroma	1
Giant cell tumour	1
Non-ossified fibroma	2
Bone cyst	4
Ganglion	2
Ossified myositis	1
Chronic osteomyelitis	2
Eosinophilic granuloma	1
Fibrous dysplasia	1
Infection	1

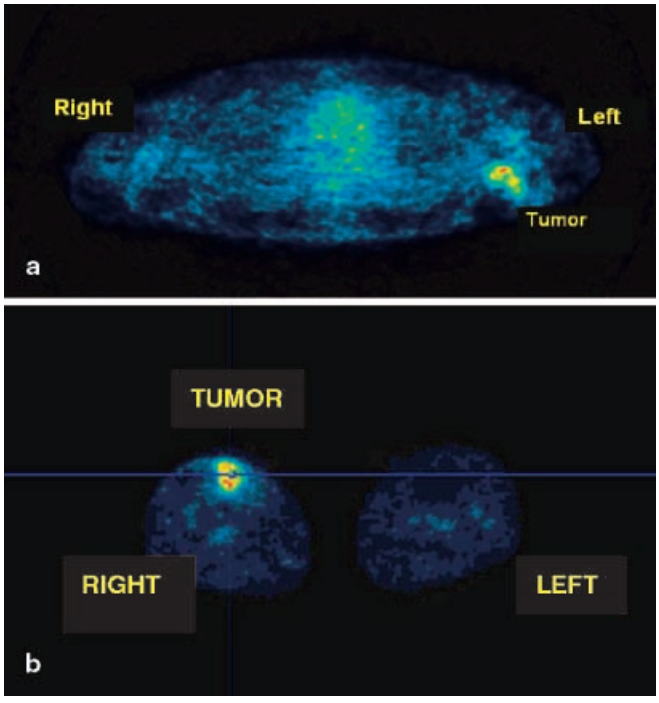

Fig. 1. a FDG PET image of the shoulder of a 22-year-old man with a Ewing's sarcoma in the left shoulder. **b** FDG PET image of the upper leg of a 35-year-old man with an giant cell tumour. Note the increased FDG uptake in the suspected semimalignant lesion

Table 2. Quantitative analysis of malignant and benign bone lesions

	SUV		T/M	SUV60/30min		MRFDG (μmol min^{-1} 100 g^{-1})
	Average	Maximal		Average	Maximal	
Malignant	3.06±1.78 (*n*=20)	6.90±4.99 (*n*=18)	10.42±13.75 (*n*=19)	1.33±0.26 (*n*=16)	1.57±0.52 (*n*=16)	18.75±17.24 (*n*=17)
Benign	1.23±0.80 (*n*=17)	2.25±1.38 (*n*=15)	3.56±1.90 (*n*=16)	1.17±0.2 (*n*=15)	1.15±0.37 (*n*=15)	5.36±6.61 (*n*=14)
P value	0.0004	0.0014	0.0451	0.1136	0.0171	0.0108
Cut-off	1.80	3.0	3.50	1.10	1.14	9.0
Sensitivity (%)	85.0	84.2	73.7	93.8	87.5	82.4
Specificity (%)	82.4	80.0	75.0	60.0	60.0	92.9

T/M, Tumour-to-muscle average SUV ratio

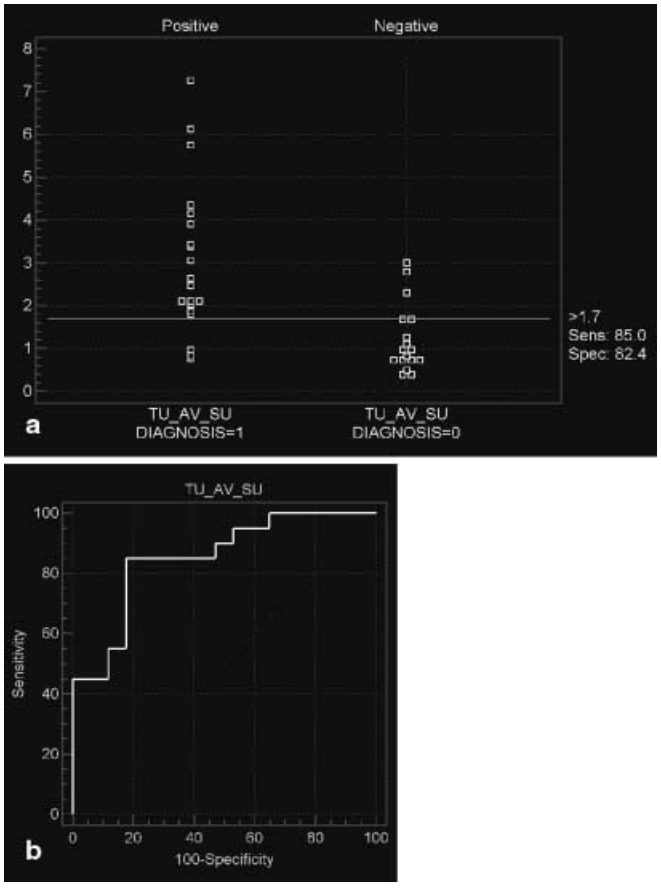

Fig. 2. a Plot of average SUV of malignant and benign bone lesions. Note: *DIAGNOSIS=1* includes the tumours and *DIAGNOSIS=0* includes all benign lesions. **b** ROC curve of the average SUV (*TU_AV_SU*) of malignant and benign bone lesions. For a cut-off value of 1.8 SUV the sensitivity is 85% and the specificity, 82.4%

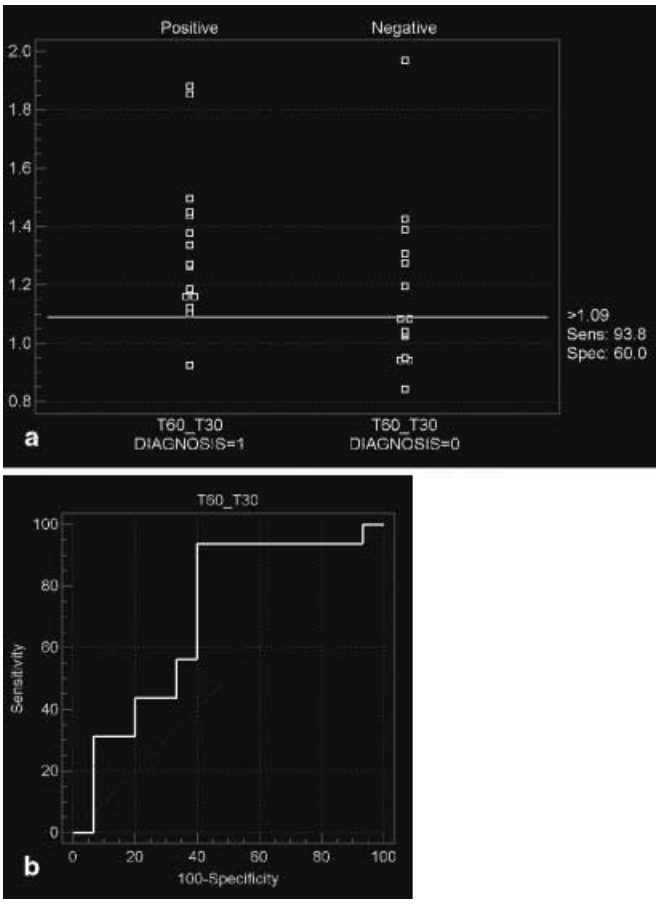

Fig. 3. a Plot of averSUV60/30 min of malignant and benign bone lesions. Note: *DIAGNOSIS=1* includes the tumours and *DIAGNOSIS=0* includes all benign lesions. **b** ROC curve of the averSUV60/30 min (*T60_T30*) of malignant and benign bone lesions. For a cut-off value of 1.1 SUV the sensitivity is 93.8% and the specificity, 60%

showed a sensitivity of 82.4% and a specificity of 92.9% for differentiation of malignancy from benign disease when the cut-off was defined as 9.0 µmol min^{-1} 100 g^{-1}. When cut-off for average SUV was defined as 1.8, the sensitivity and specificity were 85.0% and 82.4%, respectively (Fig. 2). When cut-off for averSUV60/30min was defined as 1.1, the sensitivity was 93.8% and the specificity, 60% (Fig. 3). The other parameters showed poorer specificity. When a combination of 1.8 for average SUV and 1.1 for averSUV60/30 min was used as the threshold value (that is, for malignancy both average SUV and averSUV60/30 min were equal to or greater than 1.8 and 1.1, respectively, while for benign disease either average SUV was less than 1.8 or averSUV60/30 min was less than 1.1), the specificity was improved to 93.3% and the sensitivity remained similar, at 81.3% (Fig. 5).

The shape of time-activity curves showed different characteristic between malignant and benign lesions. Visually assessed, most malignant lesions showed a persistent ascending curve, whereas most benign lesions had a low-flat or descending curve (Fig. 6).

Positive correlations were found between MRFDG and average SUV(r=0.67), maximal SUV (r=0.84), T/M (r=0.96, Fig. 7) and averSUV60/30min (r=0.75) (P<0.001).

Discussion

In the current study, which focussed on the differentiation of malignant and benign skeletal lesions, significantly higher MRFDG was found in malignant lesions than in benign lesions. Our results, in accordance with some other observations [7, 8, 9, 18], suggest that malignant bone tumours have a rate of glucose metabolism which is not only higher than that of normal tissues, but, more importantly, higher than that of benign lesions. One proposed explanation is that malignant cells have a higher concentration of hexokinase and higher rates of glycolysis than normal tissues and benign lesions [19, 20,

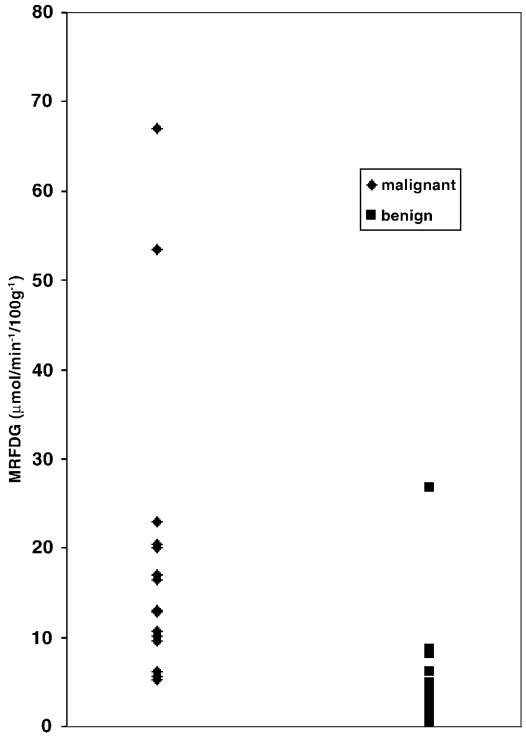

Fig. 4. Plot of MRFDG of malignant and benign lesions. Note: one case of malignancy with MRFDG of 166.26 is not demonstrated

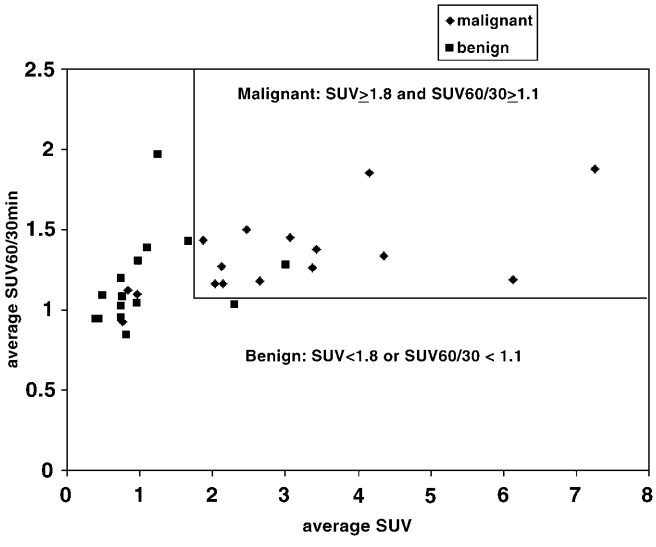

Fig. 5. Plots of average SUV and averSUV60/30 min of all lesions. When a combination of 1.8 for SUV and 1.1 for averSUV60/30 min was used as the cut-off for malignancy (that is, for malignancy both average SUV and averSUV60/30 min were equal to or greater than 1.8 and 1.1, while for benign disease, either average SUV was less than 1.8 or averSUV60/30 min was less than 1.1), the sensitivity was 81.3% and the specificity, 93.3%

21]. It has been also reported [8, 22, 23] that the glucose metabolic rate correlates with the histopathological malignancy grade in sarcoma. It is believed that in the assessment of cancer patients with FDG PET, the parameter of choice for the classification of a particular neoplasm and/or to monitor its response to treatment is the glucose metabolic rate [24]. However, determination of this parameter is complex and time-consuming and it is therefore not routinely performed.

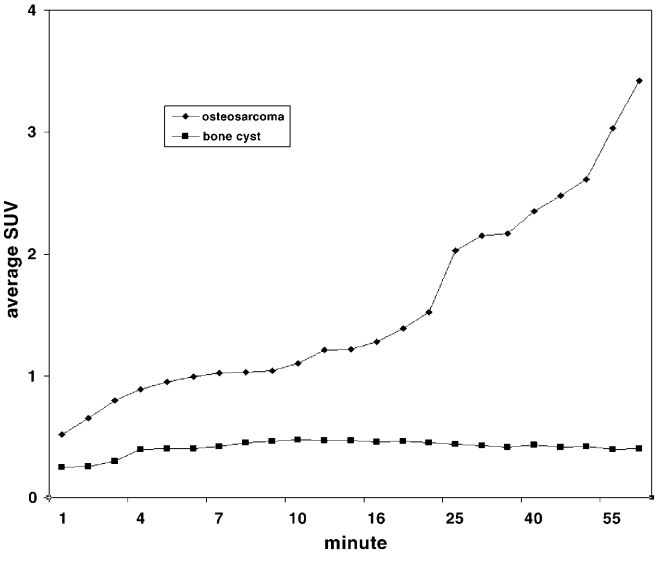

Fig. 6. Comparison of time-activity curves of a case of osteosarcoma and a case of bone cyst

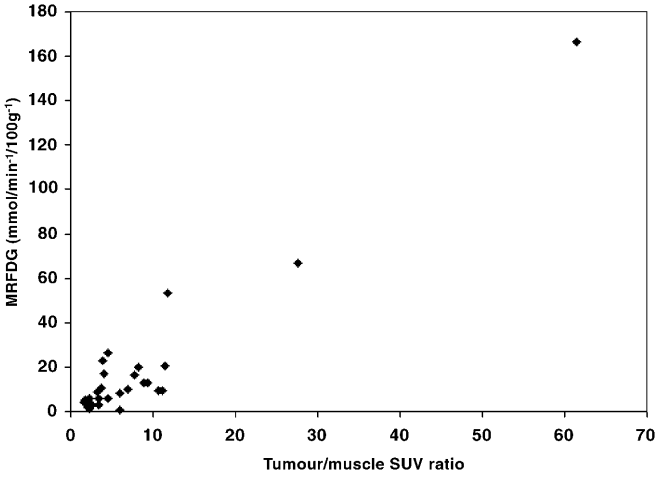

Fig. 7. Correlation between tumour/muscle average SUV ratio (T/M) and MRFDG (r=0.96, P<0.001)

As an alternative to calculation of glucose consumption, many clinicians use the SUV. This is a relative measure of activity uptake in a tissue of interest in comparison to the whole-body distribution. In our series of patients, we found that there were statistically significant differences in the SUV between malignant and benign lesions and that there was a positive correlation between SUV and MRFDG. Nevertheless, the correlation coefficients of 0.67 (average SUV–MRFDG) and 0.84 (maximal SUV–MRFDG) obtained in this study, which are in

agreement with some other reports [24, 25], are not as high as one would wish. It is known that the variability of SUV may be affected by such factors as habitus and body weight, uptake period, plasma glucose concentration and partial volume effect [24, 25, 26]. Interestingly, the ratio of tumour SUV to muscle SUV (T/M) showed a high correlation (r=0.96) with MRFDG. However, Fig. 7 demonstrates that the high correlation may be attributable to the two extreme cases with very high T/M and MRFDG. Despite the above-mentioned reservations, the correlations between maximal SUV and MRFDG (r=0.84) or averSUV60/30min and MRFDG (r=0.75) suggest that indices based on the SUV may still be helpful clinically to evaluate the metabolic state of tumours when quantitative dynamic data are not available. Eary and Mankoff [23] reported similar results in which plasma glucose-corrected SUV correlated with MRFDG with a correlation coefficient of 0.94. They believed that this correlation could be used clinically to infer the tumour metabolic rate from a static FDG PET image. Considering the advantage of the use of the SUV, it seems interesting to investigate its possible limitations for clinical application.

Despite major advances in recent years in different imaging modalities, histological analysis remains the most reliable means for establishing a diagnosis and differentiating benign from malignant skeletal lesions [8, 27, 28]. Therefore development of non-invasive methods of evaluation and differentiation for intraosseous lesions is clinically interesting and necessary. Limited studies have evaluated the application of FDG PET in skeletal lesions and assessed its quantitative analysis [6, 7, 8, 9]. Dehdashti et al. [7] reported that with use of a cut-off of 2.0 for the SUV, 14 of 15 malignant lesions and four of five benign lesions were characterised correctly, and the sensitivity and specificity were 93% and 80% respectively. However, in their malignant group 12 of the 15 lesions were metastatic. We found that metastatic skeletal lesions usually had a higher SUV (mean 6.29). Furthermore, the number of benign lesions in Dehdashti et al.'s group was small. Therefore, the sensitivity may not be representative for primary bone tumours. In the study of Adler et al. [9], with a cut-off of 1.6 for the SUV, the sensitivity for diagnosing malignancy was 81% and the specificity was 100%. However, the number of subjects with benign lesions was only six. The results of a similar study by Kole et al. [6] were quite different. They found that the maximum and average metabolic rate of glucose consumption and SUV were not significantly different for malignant and benign lesions. An acceptable cut-off point for discrimination could not be provided.

In our series of patients, most of whom had primary bone lesions, only moderate sensitivity (84.2%–85%) and specificity (80%–82.4%) were obtained when average or maximum SUV was used to discriminate malignant from benign lesions. Overlap existed between malignancy and benign disease, which was in agreement with other reports [5, 6, 30]. It seems that exclusive use of FDG uptake indices from the static image may not achieve adequate differentiation between benign and malignant lesions. The results from MRFDG evaluation appeared a little more promising. The sensitivity of MRFDG in differentiating malignancy from benign disease was similar to that of SUV, and the specificity was much higher (92.9%). Our study indicates that quantitative analysis of glucose metabolic rate from dynamic imaging may be more helpful than uptake indices from static imaging in discriminating between malignant and benign bone lesions.

Considering the complexity of the analysis and calculation using kinetic models and quantitative glucose metabolism, we used SUV60 min-to-SUV30 min ratios as an alternative index with the goal of evaluating the dynamic data in an easier way. These indices only reflect the relative changes in activity responses to time without reflecting the absolute activity concentrations. The use of SUV60/30 min as a quantitative index was based on the observation that the time-activity curves for malignant and benign lesions showed different characteristics. For most benign lesions the time-activity curves showed a low slope, whereas a persistent, ascending curve was seen for the majority of the malignant lesions. It was also observed that in untreated, malignant tumours the FDG uptake may not achieve the peak value within 60 min. This observation is in accordance with the study of Lodge et al. [30], who performed a 6-h FDG PET protocol and found that high-grade sarcomas reached a peak activity concentration approximately 4 h after injection, whereas benign lesions reached a maximum within 30 min. The results in this study showed that averSUV60/30 min had a sensitivity of 93.8% for diagnosing malignancy, which is higher than that with SUV or MRFDG. However, its specificity was disappointing.

It appears that false-positive results represent a major problem for the evaluation of bone lesions with FDG PET [30, 31, 32]. The specificity for SUV was reported by Choi et al. [19] to be only 50%, while for tumour-to-background ratios it was 74.5% based on the data reported by Schulte et al. [32]. It is generally accepted that the enhanced FDG accumulation in acute inflammatory lesions is associated with local hyperperfusion, hyperaemia and increased metabolic activity in leucocytes and other cells [33]. Furthermore, other benign lesions may contribute to false-positive PET results [5, 6, 32, 34]. The three false-positive cases (which had higher SUVs) in our series of patients were due to myositis ossificans progressiva, chronic osteomyelitis and eosinophilic granuloma. Actually, a low specificity or a high false-positive rate is a common problem faced by FDG PET in oncological applications [34]. To enhance the accuracy of PET with FDG, a way to reduce the false-positive rate is being sought [30, 31, 34].

In this study, taking the combination of average SUV (cut-off=1.8) and averSUV60/30 min (cutoff=1.10) as

the threshold increased the specificity to 93.3% while the sensitivity remained essentially unchanged. Since the number of subjects and types of lesion were limited, further investigations are required to establish whether combined evaluation of SUV and uptake indices retrieved from dynamic data will provide a simpler and more feasible means of differential diagnostic assessment in patients with bone lesions.

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