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ORIGINAL ARTICLE

The additional value of CT images interpretation in the differential diagnosis of benign vs. malignant primary bone lesions with 18F-FDG-PET/CT

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Abstract
Objective To evaluate the value of a dedicated interpretation of the CT images in the differential diagnosis of benign vs. malignant primary bone lesions with 18fluorodeoxyglucose-positron emission tomography/computed tomography (18F-FDG-PET/CT).
Materials and methods In 50 consecutive patients (21 women, 29 men, mean age 36.9, age range 11–72) with suspected primary bone neoplasm conventional radiographs and 18F-FDG-PET/CT were performed. Differentiation of benign and malignant lesions was separately performed on conventional radiographs, PET alone (PET), and PET/CT with specific evaluation of the CT part. Histology served as the standard of reference in 46 cases, clinical, and imaging follow-up in four cases.
Results According to the standard of reference, conventional 17 lesions were benign and 33 malignant. Sensitivity, specificity, and accuracy in assessment of malignancy was 85%, 65% and 78% for conventional radiographs, 85%, 35% and 68% for PET alone and 91%, 77% and 86% for combined PET/CT. Median SUV_{max} was 3.5 for benign lesions (range 1.6–8.0) and 5.7 (range 0.8–41.7) for malignant lesions.

In eight patients with bone lesions with high FDG-uptake ($SUV_{max} \geq 2.5$) dedicated CT interpretation led to the correct diagnosis of a benign lesion (three fibrous dysplasias, two osteomyelitis, one aneurysmatic bone cyst, one fibrous cortical defect, 1 phosphaturic mesenchymal tumor). In four patients with lesions with low FDG-uptake ($SUV_{max} < 2.5$) dedicated CT interpretation led to the correct diagnosis of a malignant lesion (three chondrosarcomas and one leiomyosarcoma). Combined PET/CT was significantly more accurate in the differentiation of benign and malignant lesions than PET alone (p=.039). There was no significant difference between PET/CT and conventional radiographs (p=.625).
Conclusion Dedicated interpretation of the CT part significantly improved the performance of FDG-PET/CT in differentiation of benign and malignant primary bone lesions compared to PET alone. PET/CT more commonly differentiated benign from malignant primary bone lesions compared with conventional radiographs, but this difference was not significant.

Keywords 18F-FDG-PET · Tumor imaging

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Introduction

Currently, the workup of primary bone neoplasms includes conventional radiographs and typically magnetic resonance imaging (MRI) for local staging as well as bone scintigra-

phy (BS) and computed tomography (CT) for general staging. If malignancy is suspected, bone biopsy has to be performed. Fluorodeoxyglucose (FDG)-PET and FDG-PET/CT are increasingly used for the differentiation of malignant and benign tumors in many organ systems [1–5]. However, the role of PET/(CT) in the evaluation of bone tumors is not well defined yet [6, 7]. Preliminary results showed that PET/(CT) may play an important role in biopsy guidance [8], grading [9, 10], staging [11], and therapy response assessment [12, 13]. Differentiation between benign and malignant primary bone lesions is crucial and has an important impact on therapy. FDG uptake measured by maximum standardized uptake value (SUV_{max}) is not reliable enough because of a considerable overlap between FDG uptake of benign and malignant bone lesions. It is known that especially histiocytic or giant cell containing benign lesions can have FDG uptake >2.5 SUV_{max} [14]. Conventional PET scanners are increasingly replaced by combined PET/CT. The CT part can be used for attenuation correction and anatomic correlation of FDG-positive lesions. In addition, a specific interpretation of the CT part of the PET/CT study may improve diagnostic performance [15]. The aim of this study was to evaluate the additional value of such an interpretation in the differential diagnosis of benign vs. malignant primary bone lesions.

Materials and methods

Patients

Fifty consecutive patients (21 women, 29 male, mean age 36.9, age range 11–72) were prospectively included in this study. In all patients, a primary bone tumor was suspected because of clinical symptoms (pain, fracture; n=42) and/or imaging findings (n=8). In all patients, conventional radiographs and an ^{18}F-FDG-PET/CT examination were performed. The time interval between the radiographs and PET/CT was <14 days in all cases. There was no therapeutic intervention between conventional and PET/CT imaging.

The study was conducted in accordance with the guidelines established by the local ethics committee.

PET/CT imaging protocol

All data were acquired on a combined PET/CT in-line system (Discovery LS or Discovery STE, GE Healthcare, Milwaukee, WI, USA).

Patients fasted for at least 4 h prior to scanning, which started approximately 60 min (median 58 min; range 52–77 min) after the injection of 350–400 MBq of ^{18}F-FDG. All patients were tested for a normal glucose level before scanning. Patients with elevated glucose levels were rescheduled and scanned with normal glucose levels. No intravenous contrast agent was given. Initially, the CT scan was acquired starting from the level of the head using the following parameters: 40 mAs, 140 kV, 0.5 s/tube rotation, slice thickness 4.25 mm, scan length 867 mm, data-acquisition time 22.5 s. Breathhold CT in non-forced expiration position was performed. In the patients with primary tumors in the lower extremities, scanning of the lower legs was added.

Immediately following CT acquisition, a PET emission scan was acquired with an acquisition time of 3 min per bed position with a one-slice overlap in 2D mode (matrix 128× 128). The eight to nine bed positions starting from the head to the knees resulted in an acquisition time of approximately 24–27 min. CT data were used for the attenuation correction, and the images were reconstructed using a conventional iterative algorithm (OSEM). The acquired images were viewed with a software providing multiplanar reformatted images of PET alone, CT alone and fused PET/CT with linked cursors (Advantage Windows workstation, GE Healthcare, Milwaukee, WI, USA). PET/CT imaging was performed according to the published "procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0" [16].

Standard of reference

Histology, obtained by image-guided (ultrasound or CT) or open biopsy or tumor resection served as the standard of reference in 46 cases. The histopathological examination were performed by a board certified pathologist (B.B). The tumor diagnoses were done according to the criteria of the World Health Organization and, if indicated, were confirmed by the appropriate molecular methods [fluorescence in situ hybridization (FISH) and/or polymerase chain reaction (PCR)]. Imaging and clinical follow-up for at least 12 months (mean 24 months, range 12–36) was used as the standard of reference in the remaining four cases.

Interpretation of conventional radiographs

Conventional radiographs were analyzed by a radiologist (J.H.). The reader was blinded to the results of other imaging modalities and to the clinical history but aware about the suspicion of a bone tumor. Differentiation of benign and malignant lesions were based on the established criteria described by Lodwick and several other authors [17–19]. Signs of benignity were, for example, well-defined lesions, rim sclerosis, ground glass appearance. Signs of malignancy were, for example, ill-defined lesions, cortical destruction, malignant periosteal reactions.

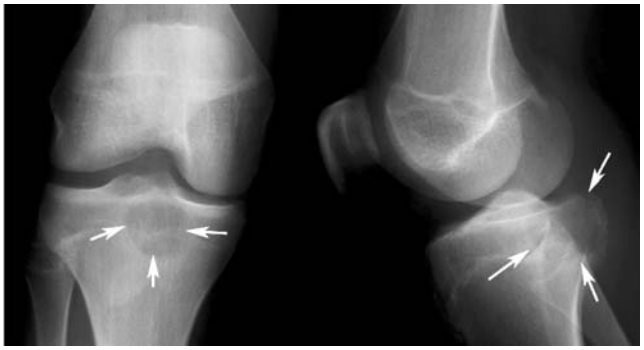


Fig. 1 Conventional X-ray images of the right knee of a 15-year-old boy showing an osteolysis (*arrows*) in the epiphysis of the right proximal tibia

PET/CT interpretation and measurement of SUV_{max}

Semiquantitative analysis of FDG uptake was performed by measuring the SUV_{max}. In our institution, SUV is corrected for lean body mass. A personal scale (Tanita, model 2001; Tanita, Tokyo, Japan) with an integrated foot-to-foot bioelectric impedance analyser was used to determine the lean body mass (LBM) of the patients. The manufacturer supplied a model including gender, weight, height, and a measured impedance value for determination of the percentage of body fat and for calculation of LBM. By using attenuation-corrected PET data, SUV_{max} was calculated with the following equation based on a freehand region of interest including the entire lesion on the fused PET/CT image: $SUV_{max(lbm)}=(LBM-C_{FDG})/Dose$ where LBM is measured in grams, C_{FDG} is the concentration of ^{18}F-FDG in Becquerels per milliliter, and Dose is the injected dose measured in Becquerels.

Physiological ^{18}F-FDG uptake and uptake caused by benign abnormalities for instance in muscles, brown fat, or pulmonary infiltrates were excluded from the analysis.

For the evaluation with PET alone, a SUV_{max} cutoff of 2.5 was used for the differentiation of low FDG uptake (<2.5 max) versus high FDG-uptake (≥2.5 SUV_{max}). Lesions with low FDG uptake were interpreted as benign and lesions with high FDG uptake as malignant The SUV_{max} measurements were performed by a nuclear physician (K.D.M.S.), again, blinded to the results of the other imaging modalities and the clinical history but aware about the suspicion of a bone tumor. For the combined PET/CT evaluation, the CT part of the PET/CT study was separately analyzed by a reader with double board certification as a radiologist and a nuclear medicine

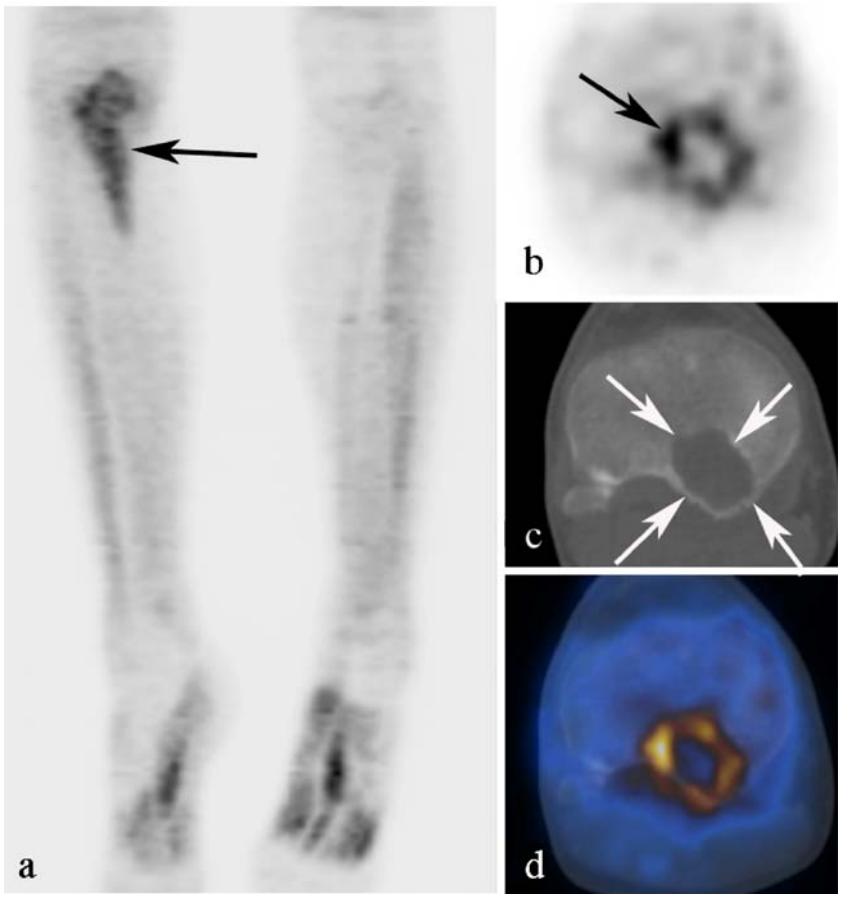


Fig. 2 (same patient as Fig. 1) Moderate FDG-uptake (SUV_{max} 4.0) of the lesion on PET images (**a**, MIP). Axial PET (**b**) and fused PET/CT (**d**) images demonstrating that the tumor takes up FDG in the periphery with a FDG-negative centre. CT (**c**) shows a well-defined eccentric osteolysis without clear sclerotic rim. No calcifications are seen inside the lesion. So also in CT, this lesion was difficult to assess because clear signs of benignity like a sclerotic rim are missing. Biopsy and histological work-up confirmed the diagnosis of a chondroblastoma

physician (K.S.). He was also blinded to the results of the other imaging modalities and the clinical history. He was only aware that a bone tumor was suspected [20–22]. Signs of benignity were, for example, well-defined lesions, rim sclerosis, ground glass appearance. Signs of malignancy were, for example, ill-defined lesions, cortical destruction, malignant periosteal reactions. Bone and soft tissue window settings were used for the evaluation. In lesions with low uptake but aggressive CT appearance, including aggressive periosteal reactions and cortical destruction, the final PET/CT interpretation was that of malignant lesion. In cases of PET-positive lesions, indicating malignancy with benign CT patterns such as a well-defined osteolysis with rim sclerosis, the final interpretation was that of a benign lesion.

Statistical analysis

Data were analysed using SPSS 15 for Windows (SPSS). Statistical significance was assessed with the sign test. $p<0.05$ was considered to indicate a significant difference.

Results

Seventeen lesions were benign and 33 malignant. In the benign group, there were seven benign bone tumors (Figs. 1, 2, 3 and 4), three fibrous dysplasias (Figs. 5 and 6), two osteomyelitis, one insertion tendinopathy, one stress fracture, one postoperative defect, one fibrous cortical defect, and one bone infarction. Of the 33 malignant lesions, there were 18 sarcomas (Fig. 7), six lymphomas, three metastases, one melanoma, one chordoma, one hemangioendothelioma, one eosinophilic granuloma, one malignant peripheral nerve sheath tumor, and one neuroendocrine tumor. Patient characteristics are summarized in Table 1. Median SUV_{max} of benign lesions was 3.5 (range 1.6–8.0) and 5.7 (range 0.8–41.7) for malignant lesions (Table 2). Sensitivity, specificity, accuracy, PPV, and NPV regarding the diagnosis of a malignant lesions was 85%, 65%, 78%, 82%, and 67% for CI, 85%, 35%, 68%, 72%, and 55% for PET alone and 91%, 77%, 86%, 88%, and 81% for combined PET/CT (Table 3).

In eight patients with a $SUV_{max}>2.5$, the dedicated CT interpretation led to the correct diagnosis of a benign lesion (three fibrous dysplasias, two osteomyelitis, one aneurysmal bone cyst, one fibrous cortical defect, one phosphaturic mesenchymal tumor). In four patients with a $SUV_{max}<2.5$, CT interpretation led to the correct diagnosis of a malignant lesion (three chondrosarcoma, one leiomyosarcoma). Combined PET/CT interpretation was significantly more accurate compared to PET alone ($p=0.039$). The diagnostic performance of PET/CT was not significantly different from conventional radiographs ($p=0.63$). Furthermore, no statistically significant difference was found between PET alone and conventional radiographs ($p=0.18$).

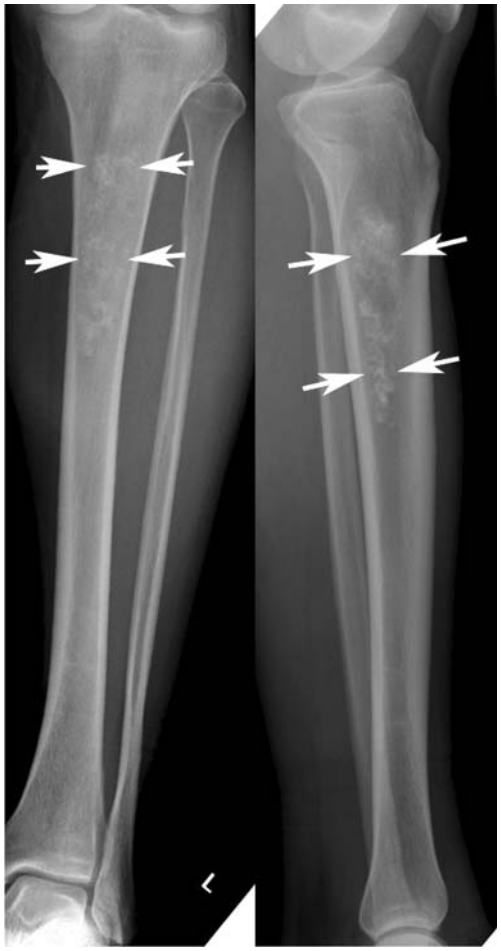


Fig. 3 Conventional X-ray images of the left thigh in a 21-year-old male patient with a calcified lesion in the upper third of the diaphysis of the left tibia (*arrows*)

Discussion

Although malignant bone lesions have generally higher FDG uptake than benign bone tumors, there is a considerable overlap regarding the amount of FDG uptake. Our results confirm the findings of previously published studies that many benign lesions can have moderate to high FDG-uptake [14, 23]. This fact can lead to misinterpretation because incidentally detected benign FDG-positive bone lesions may mimic metastases if FDG-PET/CT is performed for staging of extra-skeletal malignancies [23, 24]. Fibrous dysplasia is a good example where separate interpretation of CT images with the pathognomonic "ground glass" pattern and absence of bone destruction overrules the positive PET result and leads to the correct diagnosis of a "no-touch" benign lesion [25]. We found

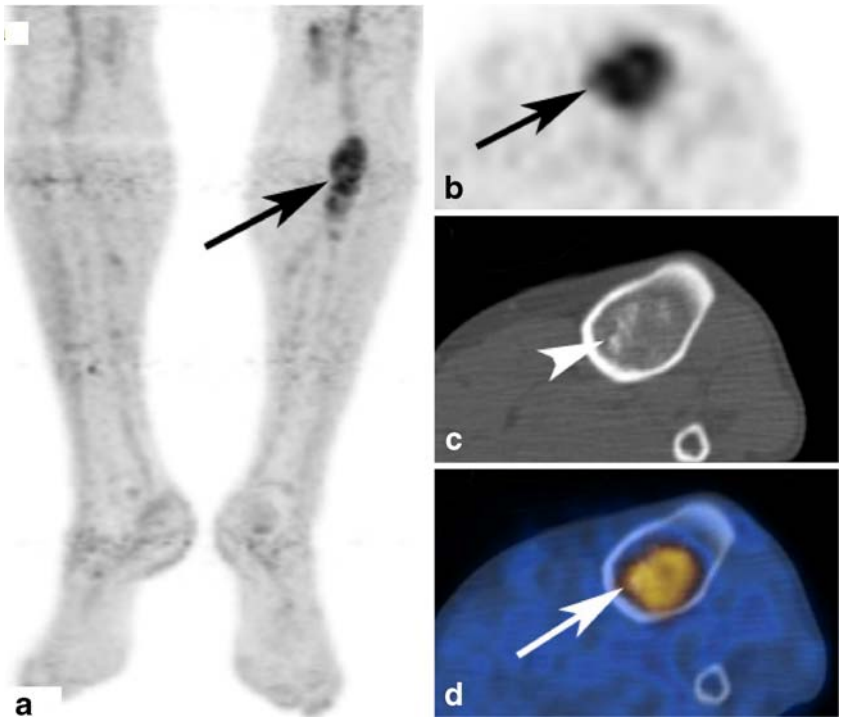


Fig. 4 (same patient as Fig. 3) PET (MIP (**a**); axial PET (**b**); fused PET/CT images (**d**) with increased FDG-uptake (SUV_{max}.3.5) of the lesion (*arrows*) indicating malignancy. CT (**c**) images demonstrating calcifications (*arrowheads*) without cortical destructions typical for an enchondroma, which was confirmed with biopsy

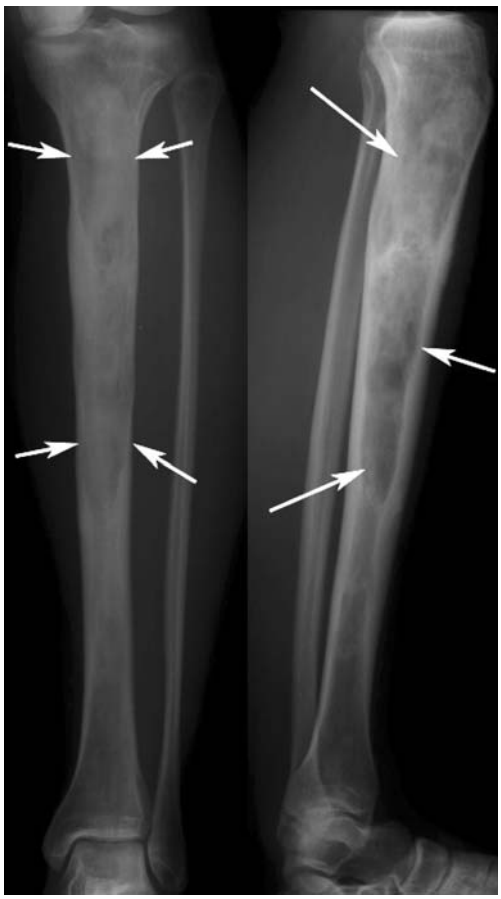


Fig. 5 Conventional X-ray images (Fig. 5) of a 33-year-old female patient with an inhomogeneous ground-glass like lesion (*arrows*) in the left tibia

SUV_{max} values>2.5 (range 2.9–8.0) in all four patients with fibrous dysplasia. Aoki et al. published six cases with fibrous dysplasia, of which only two presented with a SUV_{max}>2.5 [14].

Low-grade chondrosarcomas are good examples in which interpretation of the CT part with the typical calcifications overrules a negative PET result and leads to the correct diagnosis of a malignant lesion. Three of our four chondrosarcomas had SUV_{max} values<2.5 which confirms the results of other authors that especially low-grade chondrosarcomas can be almost FDG-negative [26].

FDG uptake is not specific for the diagnosis of a malignant neoplasm. Traumatic, inflammatory, and infectious lesions like osteomyelitis can show significant FDG uptake as shown in experimental and clinical studies [27, 28]. We observed SUV_{max} of 5.2 and 6.9 in both of our patients with biopsy-proven osteomyelitis.

F-18 FDG PET/CT has been employed for differentiation between malignant and benign fractures based on the SUV_{max} and based on medullary uptake, which is characteristic for malignant fractures [29, 30]. Fractures in two of our patients were caused by benign lesions, one was PET positive (SUV_{max} 3.9 in a patient with fibrous dysplasia) and one PET negative (SUV_{max} 1.6 in a patient with a stress fracture).

Our results underline that the CT part of the PET/CT study can add important information. Those evaluating PET/CT studies should be familiar with both the metabolic and morphologic features of bone tumors and tumor-like lesions.

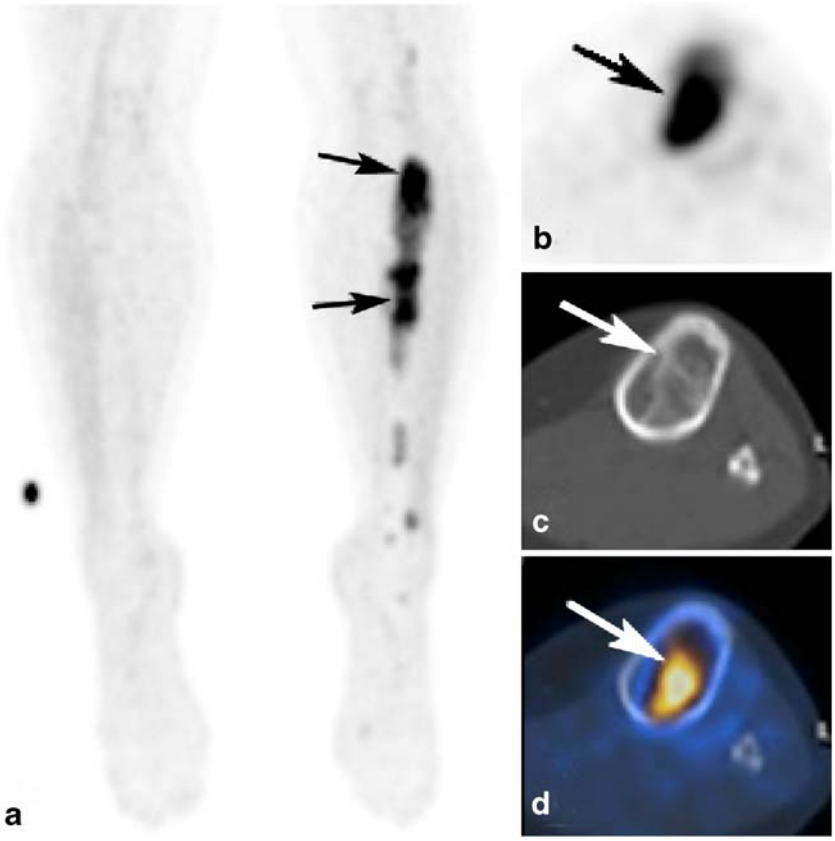


Fig. 6 (same patient as Fig. 5) FDG-PET (MIP (**a**); axial PET (**b**), fused PET/CT images (**d**) showing intense FDG-uptake (SUV_{max}.7.7) of the lesion indicating malignancy. CT (**c**) demonstrating well-defined ground glass lesions without cortical destruction typical for fibrous dysplasia. Biopsy confirmed the diagnosis of fibrous dysplasia

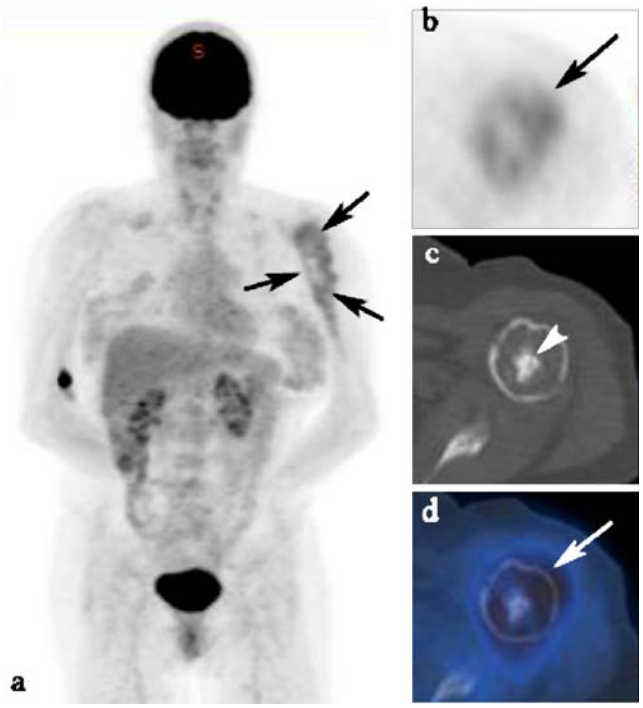


Fig. 7 A 50 year-old female patient with a calcified lesion in the bone marrow of the left proximal humerus. PET (Fig. 7 a, b, d) images demonstrating low FDG-uptake (SUV_{max} 2.3) in the lesion (arrows) indicating benignity. CT (arrow, Fig. 7c) shows calcifications inside the lesion with cortical destructions (*arrow*, **d**) suspicious for chondrosarcoma. Histology showed a grade I–II chondrosarcoma

Similarly to previously published studies, our data indicate the difficulty to define a reliable cutoff value for the differentiation between benign and malignant lesions. Beside the previously described cutoff value of SUV_{max}=2.5, also values of 2.0 or 3.0 do not provide sufficient accuracy [14, 31, 32]. Since the SUV is a semiquantitative measurement, there are various calculation variants, and reproducibility suffers from influences such as blood glucose level, uptake time, and several others. Therefore, the use of additional criteria for diagnosing bone neoplasms is important [33]. Nevertheless, Dehdashti et al. have demonstrated that SUV measurements were more effective than subjective interpretation of FDG uptake in bone lesions [34]. We believe that a combined interpretation of metabolic information and morphologic information, both provided by a PET/CT examination should be implemented.

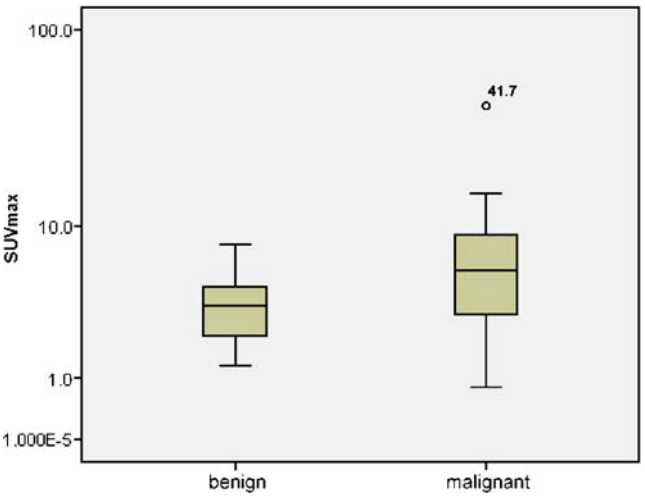
Conventional radiographs remain the first imaging modality in the evaluation of suspected bone neoplasms. A final diagnosis can often be made based on radiographs, obviating additional imaging and biopsy. This is the case for fibrous dysplasia, Paget's disease, and nonossifying fibroma. In equivocal cases and in aggressive tumors such as osteosarcoma, MR imaging is typically employed as the second imaging tool for grading and staging [35]. The importance of bone scintigraphy for the evaluation of bone tumors has decreased over the last years. However, this

Table 1 Characteristics of 50 patients with benign and malignant bone lesions

Patient no.	SUV_{max}	Final diagnosis
1	5.2	Brodie abscess
2	2.5	Lymphoma
3	11.3	Osteosarcoma
4	7.4	Leiomyosarcoma
5	3.6	Neuroendocrine tumor
6	5.1	Ewing sarcoma
7	6.2	Lymphoma
8	1.6	Stress fracture
9	2.9	Fibrous dysplasia
10	6.9	Osteomyelitis
11	3.5	Phosphaturic mesenchymal tumor
12	1.4	Chondrosarcoma
13	8.0	Fibrous dysplasia
14	3.9	fibrous dysplasia with Pathologic fracture
15	9.0	Leiomyosarcoma
16	4.6	Fibrous cortical defect
17	9.0	Lymphoma
18	8.8	Malignant peripheral nerve sheath tumor
19	0.8	Eosinophilic granuloma
20	2.0	Osteochondroma
21	3.0	Hemangioendothelioma
22	4.0	Chondroblastoma
23	41.7	Lymphoma
24	14.9	Osteosarcoma
25	5.9	Lymphoma
26	3.7	Aneurysmatic bone cyst
27	3.1	Chondrosarcoma
28	1.4	leiomyosarcoma
29	4.7	Clear cell renal carcinoma metastasis
30	7.7	Fibrous dysplasia
31	2.2	Bone infarction
32	2.1	Insertion tendinopathy
33	2.2	Hemangioma
34	3.5	Enchondroma
35	1.3	Postoperative defect
36	2.2	Chondrosarcoma
37	8.7	Osteosarcoma
38	5.3	Osteosarcoma
39	5.7	Osteosarcoma
40	11.3	Lymphoma
41	3.5	Ewing sarcoma
42	10.9	NSCLC metastasis
43	3.0	Chordoma
44	10.7	NSCLC metastasis
45	12.0	Melanoma
46	5.0	Ewing sarcoma
47	7.8	Osteosarcoma
48	5.4	Ewing sarcoma
49	2.3	Chondrosarcoma
50	13.2	Osteosarcoma

NSCLC Nonsmall cell lung cancer, *SUV* conventionalized uptake value

Table 2 Polar plots showing the SUV_{max} of benign and malignant bone lesions in 50 patients



method still is valuable in staging of osteosarcoma. The accuracy of a bone scan can be increased by using SPECT and SPECT/CT [36, 37].

Because combined FDG-PET/CT did not improve differentiation of bone lesions compared to conventional radiographs, it cannot be recommended for this indication. Another problem in clinical routine in most countries is the fact that PET/CT is only reimbursed for staging of confirmed malignant tumors but not for assessment of malignancy in equivocal cases. PET/CT has a potential role for the detection of transformation of a benign into a malignant bone tumor and of development into more aggressive patterns as observed in malignant lymphoma [38]. We observed no proven transformation in our patients, and studies with high numbers of patients with transformation are missing because such malignant transformations are infrequent [39].

Our study has limitations. For the CT evaluation, only a low-dose CT part of the combined PET/CT study was available. Another approach would be to perform a thin-slice conventional "high-dose" CT centered on the primary bone lesions. This better CT quality may improve the

Table 3 Performance of conventional X-rays (CI), PET alone (PET), and combined PET/CT (PET/CT) in the differentiation of benign vs. malignant primary bone lesions in 50 patients

Parameter	CI (%)	PET (%)	PET/CT (%)
Sensitivity	85	85	91
Specificity	65	35	77
Accuracy	78	68	86
PPV	82	72	88
NPV	67	55	81

CI Conventional imaging, *PPV* positive predictive value, *NPV* negative predictive value

performance of the combined PET/CT. This study is intentionally limited to the assessment of the dignity of the primary lesion but does not assess additional information provided by the PET/CT such as grading and staging of a proven malignant tumor, or detection of multifocality, second primaries, or metastases. These aspects have been investigated before in other publications [7, 36, 40, 41]. Delayed images might help in the differentiation between benign and malignant bone lesions like those observed in soft tissue sarcomas [42]. Because of our busy schedule with approximately 20 PET/CT scans per day, we were not able to evaluate the additional value of delayed images.

In conclusion, dedicated interpretation of the CT part significantly improved the performance of FDG-PET/CT in differentiation of benign vs. malignant primary bone lesions compared to PET alone. PET/CT more commonly differentiated benign from malignant primary bone lesions compared with conventional radiographs, but this difference was not significant.

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