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Value of ^{18}F-FDG-PET in clinical management of patients with osteosarcoma

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Background. *The aim of this study was to define the value of ^{18}F-FDG-PET in clinical management of patients with osteosarcoma based on current treatment regimen.*

Patients and methods. *A total of 18 patients (4 female, 14 male) aged from 14 to 63 years with primary osteosarcoma (n=6) or suspect for relapse of osteosarcoma (n=12) were investigated retrospectively. First, all patients underwent conventional diagnostic work-up, i.e. X-ray and MRI of the primary bone lesion, CT scan of the chest as well as conventional bone scan. In addition, whole-body PET-images were acquired on an ECAT EXACT 47 (921) with an axial field-of-view of 16.2 cm (Siemens, CTI) after intravenous injection of 370 MBq ^{18}F-FDG. All tumor-suspicious PET-findings were evaluated histologically. Results of histology, PET findings and conventional imaging were correlated on a lesion-by-lesion basis.*

Results. *^{18}F-FDG-PET clearly depicted all primary osteosarcomas in 6 patients and a relapse of osteosarcoma in two patients. In the remaining 10 patients histology could not confirm a relapse of osteosarcoma. Eight out of 18 patients showed further lesions with an abnormal ^{18}F-FDG-uptake. These lesions were predominantly located in the lung (n=5), in the skeleton (n=3), and in the inguinal region (n=1). Three of 8 patients had primary diagnosis of osteosarcoma and 5 were suspected to have tumor relapse. All lesions but the lesion of the inguinal region turned out to be metastases of osteosarcoma. However, therapeutic management must be taken into consideration when interpreting these encouraging results. Since the vast majority of patients are known to have micro metastases at the time of diagnosis, combined treatment consisting of neoadjuvant chemotherapy and surgical resection of the tumor is the standard treatment. Thus, ^{18}F-FDG-PET has no significant impact in primary diagnosis of osteosarcoma. However, there are several clinical settings in which patients might benefit from ^{18}F-FDG-PET since their treatment regimen might be altered, i.e. differentiation of tumor relapse versus post-therapeutic changes, differential diagnosis of lung masses in post-therapeutic follow-up and detection of disseminated metastatic spread after initial therapy.*

Conclusions. *^{18}F-FDG-PET had no significant impact in initial staging. Nevertheless, it might be helpful in several clinical settings following neoadjuvant chemotherapy and surgical treatment of the primary tumor.*

Key words: osteosarcoma, diagnosis, pathology, tomography, emission-computed, treatment outcome

Introduction

Osteosarcoma is the second most common malignancy of the skeleton after multiple myeloma. Its incidence is estimated to be about 2-3/10^6 with a characteristic occurrence between 5-25 years of age and a second peak incidence in the fifth and sixth decades.[1,2] The disease may be divided into two categories: primary and secondary osteosarcoma. The primary osteosarcoma predominantly affects the metaphyseal portion of the extremity bones. However, its fundamental nature has yet been unknown. In contrast, the secondary osteosarcoma is often related to Paget's disease, fibrous dysplasia or is associated with retinolastoma.[1,3] The majority of secondary osteosarcomas are located in the truncus, craniofacial or even extraskeletal.[1]

According to the clinical stage of the UICC from 1997, the patients were divided into six groups based on TNM-stage and histological grading (Table 1).[1,4] At the time of primary diagnosis, as much as 75% of all patients were classified as clinical stage IIb that defines a histological grade three to four of osteosarcoma extended to the periost, but with no evidence of lymph node and distant metastases.[1] However, in 85-90% of these patients, occult metastases must be presumed which are predominantly located in the lungs (about 80%).[1] Moreover, osteosarcoma frequently metastasizes to secondary bone sites, which occurs in nearly 20% of all patients with occult metastases. The prognosis of osteosarcoma was poor prior to the development of effective chemotherapy.[3] The therapeutic management of osteosarcoma was improved by applying more potent and more aggressive chemotherapy. Therefore, accurate staging and re-staging procedures have become more and more important in the diagnosis of osteosarcoma. In this context, positron emission tomography (PET) using ^{18}F-fluorine-deoxyglucose (^{18}F-FDG) has become the focus of ongoing research, *i.e.* determining the metabolic rates of sarcoma[3,5-8], monitoring the neoadjuvant therapy response[9] and differentiating active sarcomas from post-treatment changes.[10-13] Since the management of osteosarcoma has been significantly improved by the introduction of a reliable staging system,[1,4] the diagnostic and therapeutic outcome might benefit from metabolic imaging using ^{18}F-FDG.[14]

Therefore, the aim of this study was to define the impact of ^{18}F-FDG-PET on staging and re-staging of patients with osteosarcoma based on current treatment regimen.

Materials and methods

Patients

A total of 18 patients (4 female, 14 male) aged from 14 to 63 years with primary osteosarcoma (n=6) or suspect for relapse of osteosarcoma (n=12) were investigated retrospectively. The majority of the patients had tumor suspicious lesions on the lower extremities (n=7) or lumbar vertebras (n=8). The remaining three patients had tumor-suspicious lesions located on the upper extremities. First, all patients underwent conventional clinical work-up. Then, ^{18}F-FDG-PET was performed.

Clinical work-up

As part of the routine clinical work-up, all patients underwent morphological imaging, *i.e.* conventional X-ray and MRI of the primary lesion, CT scan of the chest as well as conventional bone scan. A biopsy of the tumor-suspicious bone lesion was performed in all patients.

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Table 1. Clinical stage and occurence of malignant bone tumors according to UICC from 1997

Clinical stage	TNM	Grading	Occurence
IA	T1, N0, M0	G1, 2	10 %
IB	T2, N0, M0	G1, 2	
IIA	T1, N0, M0	G3, 4	< 5 %
IIB	T2, N0, M0	G3, 4	75 %
III	Not defined	0	0
IVA	any T, N1, M0	G1-4	< 1 %
IVB	any T, any N, M1	G1-4	10 %

PET scanning

The patients fasted for at least 12 hours prior to PET scanning in order to minimize blood insulin levels and glucose utilization of normal tissue. Whole-body emission images were acquired without attenuation correction 60min after intravenous injection of 370 MBq ^{18}F-FDG using an ECAT EXACT 47 (921) scanner (Siemens/CTI, Knoxville, USA) with an axial field-of-view of 16.2 cm. Patients were placed in the PET gantry feet first with both arms folded over the abdomen. Images were acquired for 4 min per bed position covering the feet up to the middle of the femurs. Then, the patients were repositioned in the gantry head first, and the second set of images was acquired from the brain down to the waist. Prior to the third acquisition set from the waist down to the lower extremities, patients were asked to empty the bladder in order to decrease urine activity. Emission data were reconstructed by filtered back projection using a Hanning filter with a cut-off frequency of 0.4 of Nyquist frequency. Thus, transaxial spatial resolution was approximately 12 mm in reconstructed images. PET-images were printed on transparency film (Helios 810, Sterling) using a linear gray scale with the highest activity displayed in black. Images were displayed with an upper threshold of five times of the mean activity in the lung. Standardized documentation included both 20 transversal and 20 coronal slices with a slice thickness of 13.5 mm each, and maximum-intensity-projections (MIPs) in the anterior, left lateral, right-anterior-oblique, and left-anterior-oblique view as published previously.[15]

Evaluation

Two independent nuclear medicine physicians interpreted PET-images visually. All tumor-suspicious PET-findings were biopsized and evaluated histologically. The results of histology, PET-findings and conventional imaging were compared on a lesion-by-lesion basis.

Results

A total of 8 patients showed an increased uptake of ^{18}F-FDG in the area of the tumor-suspicious lesion. This included all patients (n=6) suspected for primary osteosarcoma and two patients suspected for local relapse of osteosarcoma.

In 3 out of 6 patients suspicious for primary osteosarcoma, an increased ^{18}F-FDG-uptake was the only pathologic activity seen within the PET-image. In contrast, 3 out of these 6 patients showed additional lesions with an abnormal ^{18}F-FDG-uptake. These lesions were located in the lungs or in the skeleton, each in one of the first two patients. Moreover, one patient showed up with pathological lung uptake as well as with an additional focus site in the left inguinal region.

In 2 out of 12 patients suspected for tumor

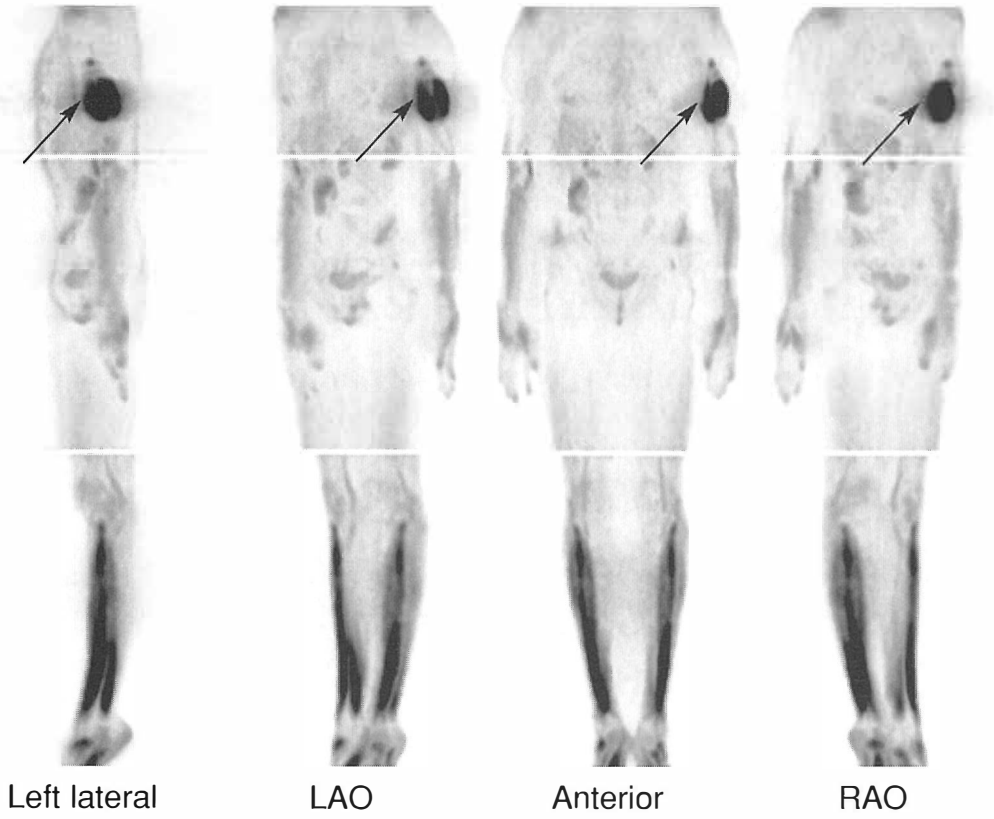

Figure 1. Maximum intensity projections of the truncus and the extremities of a patient with primary osteosarcoma of the left humerus. Note focal accumulation of ^{18}F-FDG at the primary tumour without any evidence of metastatic spread. However, the patient underwent adjuvant chemotherapy since microscopic metastatic foci must be presumed. Thus, ^{18}F-FDG-PET had no influence on treatment strategy.

relapse, ^{18}F-FDG-PET showed a focal increased uptake of ^{18}F-FDG at the tumor-suspected site of the bone. In 10 out of these 12 patients, PET was negative concerning the detection of a recurrent osteosarcoma. However, 5 out of 12 patients suspected for tumor relapse revealed further tumor-suspicious lesions with pathologic focally increased glucose metabolism. These lesions were located in the lungs (three patients) and in the skeleton (two patients). These 5 patients included one patient with positive ^{18}F-FDG-PET at the site suspected for tumor relapse, and also four patients with negative ^{18}F-FDG-PET concerning the detection of a tumor relapse.

Further evaluation of PET findings revealed that ^{18}F-FDG-PET clearly depicted all primary osteosarcomas in 6 patients (Figure 1, Figure 2) and a relapse of osteosarcoma in 2 patients. Thus, sensitivity of ^{18}F-FDG-PET was as high as 100 % for the detection both, of the primary tumor site and of relapsed osteosarcoma. In the remaining 10 patients, histology could not confirm a relapse of osteosarcoma. Thus, specificity of ^{18}F-FDG-PET was also 100%.

As far as metastases are concerned, ^{18}F-FDG-PET was true-positive in 2 out of 6 patients with histologically proved primary osteosarcoma (Figure 2). Thus, lung metastases were proved by the subsequent CT of

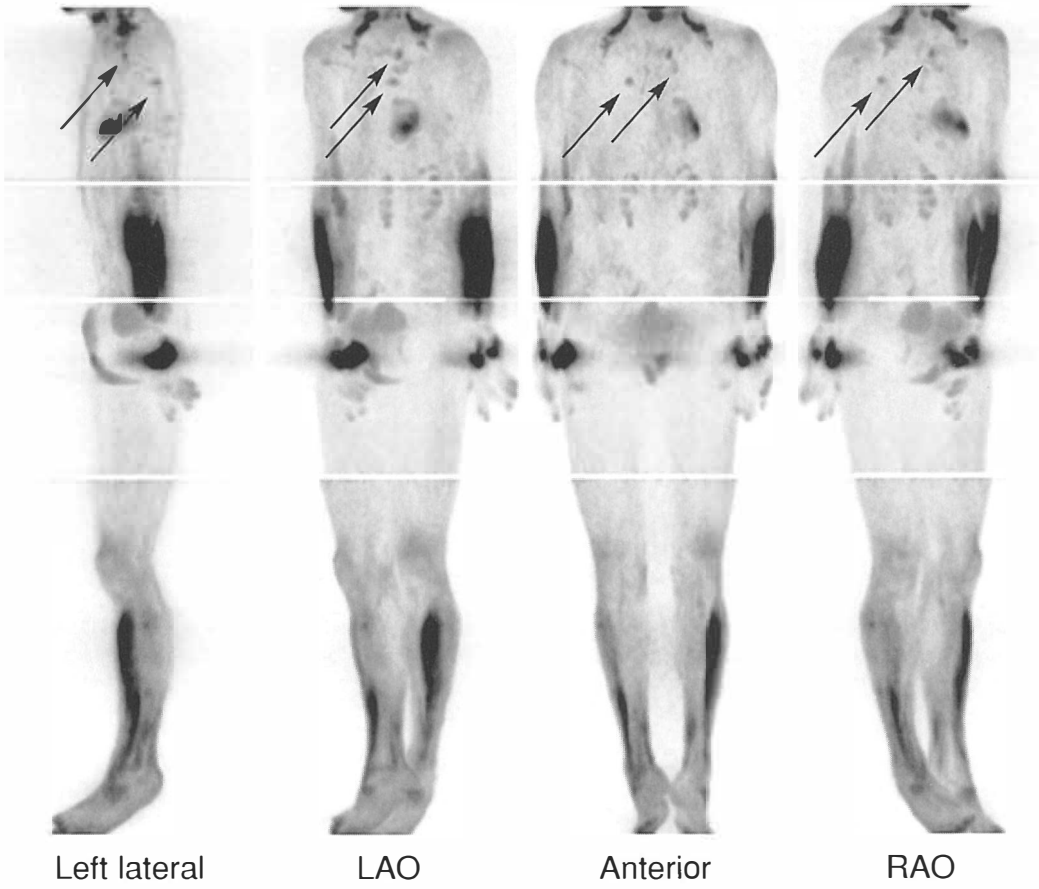

Figure 2. Maximum intensity projections of a patient with suspected relapse of osteosarcoma of the right tibia. Note focal accumulations of ^{18}F-FDG in both lobes of the lung without any evidence of local recurrence. This patient was staged as IVB. The patient underwent chemotherapy.

the chest and biopsy and a second site osteosarcoma was confirmed histologically, each in one of the two patients. Moreover, ^{18}F-FDG-PET was true-positive concerning the detection of lung metastases in one patient, but also false-positive in detecting inflammatory lymph nodes of the left inguinal region in the same patient. When comparing ^{18}F-FDG-PET to bone scintigraphy and CT of the chest, conventional imaging also proved all but one lesion each. Thus, based on PET findings, 3 out of 6 patients with primary osteosarcoma were classified being clinical stage IVB.

The further evaluation of metastatic lesions suspected by ^{18}F-FDG-PET revealed a clinical stage IVB in 5 patients suspected for relapse of osteosarcoma (Figure 3).

Discussion

Despite the fact that osteosarcoma represents only 0.1% of all tumor diseases, it is the second most common primary bone malignancy[1,2] after multiple myeloma. The pretherapeutic diagnostic work-up usually starts with a conventional X-ray of the tumor-suspi-

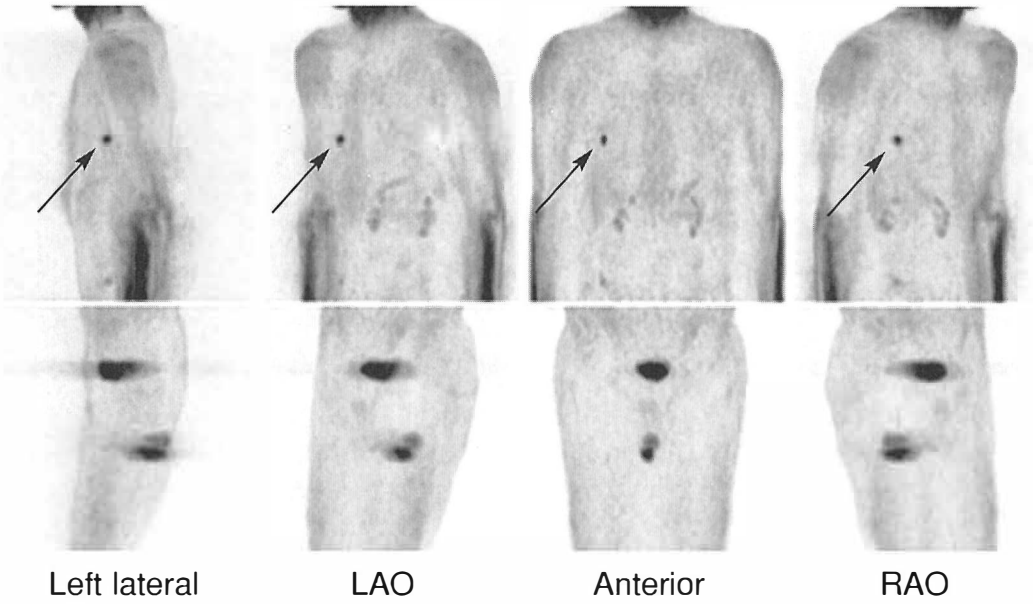

Figure 3. Maximum intensity projections of the truncus of a patient after therapy of an osteosarcoma of the right tibia and a newly diagnosed lung mass visualized by conventional X-ray in follow-up study. Note focal accumulation of ^{18}F-FDG in the right apical lobe confirming viable tumor tissue. Due to PET-findings the patient underwent surgery of the metastases and subsequent chemotherapy.

cious bone and subsequent biopsy.[16,17] MRI is performed in order to define the degree of penetration of the tumor into surrounding soft tissue as well as to estimate the local tumor infiltration into bone marrow.[14,17,18] Usually, CT of the chest and conventional bone scan are performed[19] since the metastases of osteosarcoma are known for their hematogenous route with predilection sites in the lungs and in the skeleton.

The standardized therapeutic management of osteosarcoma includes neoadjuvant chemotherapy followed by wide resection of the primary tumor.[20,21] Nowadays, limb-sparing procedures are more frequently performed than amputations.[22-24] However, as compared to ablative surgery procedures, limb sparing surgery has a 3-5 fold increased risk of local recurrence, which significantly worsens the prognosis.[25,26] Since both, the disease free survival rate and overall survival rate were shown to be higher, aggressive neoadjuvant chemotherapy was included into the routine therapeutic management of osteosarcoma.

The outcome of osteosarcoma has also been improved by the introduction of reliable staging systems.[27,28] Therefore, apart from conventional, well-standardized imaging procedures, radionuclide imaging using ^{18}F-FDG-PET became the focus of ongoing research by assessing its potential utility in sarcoma patients.[29] Nieweg and coworkers[8] examined 22 patients with malignant soft-tissue sarcomas. They found a sensitivity of 100% for the detection of the tumor. However, ^{18}F-FDG-PET seemed to be inappropriate in differentiating benign lesions from soft-tissue sarcomas of low or intermediate malignancy grades. Jones and coworkers[9] investigated the impact of ^{18}F-FDG-PET in treatment monitoring of soft-tissue and musculoskeletal sarcoma in nine patients. Their results suggested that ^{18}F-FDG-PET might be beneficial in this

special clinical setting. Garcia and coworkers[10] who found ^{18}F-FDG-PET helpful in differentiating active musculoskeletal sarcomas from post-treatment changes reported corresponding results. Moreover, ^{18}F-FDG-PET was investigated for differentiating various types of bone lesions by calculating the metabolic rate of glucose consumption.[30] However, a correlation between the metabolic rate and the biologic aggressiveness of bone tumors could not be shown.

In this study, the impact of ^{18}F-FDG-PET was defined in staging and re-staging of patients with osteosarcoma. It was shown that all primary osteosarcomas were detected by ^{18}F-FDG-PET revealing a sensitivity of 100%. Moreover, ^{18}F-FDG-PET was helpful in differentiating post-therapeutic changes from tumor relapse. As far as metastases were concerned ^{18}F-FDG-PET detected a hematogenous spread of the osteosarcoma in more than 50% of all patients investigated. However, the therapeutic management of patients with osteosarcoma must be taken into consideration when interpreting these encouraging results. The great majority of patients were classified as clinical stage IIB according to UICC at the time of initial diagnosis. However, only 10-15% of these patients can be reliably presumed to be free of distant metastases. In contrast, in 85-90% of these patients, hematogenous metastatic spread must be presumed, especially to the lungs. Thus, standardized treatment of osteosarcoma includes surgery of the primary bone tumor as well as the treatment of potential metastatic spread, *i.e.* neoadjuvant chemotherapy according to the Cooperative Osteosarcoma Study Group. Performing this treatment protocol, disease-free and overall survival rates after 4 to 5 years in patients with no detectable metastases increased from 20% in case of ablative surgery alone to 80% in case of additional neoadjuvant chemotherapy.[1,3,31] Since the detection of hematogenous spread has no clinical impact on influencing therapeutic management of patients with primary diagnosis of osteosarcoma at all, no clinical impact in incorporating ^{18}F-FDG-PET in this clinical setting can be expected.

However, there are some clinical settings in which ^{18}F-FDG-PET might be helpful to delineate further treatment regimen. First, ^{18}F-FDG-PET might be helpful in differentiating postoperative changes from tumor tissue in case of surgically treated osteosarcoma with prosthetic devices, since MRI is hampered due to technical reasons. Second, post-treatment follow-up consists of X-ray of the chest in half-year-intervals for the duration of about eight years post surgery. In case of newly diagnosed lung masses, ^{18}F-FDG-PET might be helpful to differentiate benign from malignant lesions.[32] This is especially important since the treatment of lung metastases is still potentially curative. Third, ^{18}F-FDG-PET might be helpful in the detection of hematogenous spread after the therapy of osteosarcoma. It was reported that patients with disseminated metastatic spread benefited from chemotherapy.[33] One third of all investigated patients showed a partial remission or a stable disease after combined chemotherapy. Thus, the detection of distant metastases significantly influences further therapeutic regimen.

Conclusions

In our series, ^{18}F-FDG-PET has no significant impact in initial staging of osteosarcoma. However, it may be helpful in several clinical settings following neoadjuvant chemotherapy and surgical treatment of the primary tumor, e.g. differentiation of tumor relapse versus posttherapeutic changes especially at the site of prosthesis, differential diagnosis of lung masses in posttherapeutic follow-up, and detection of disseminated metastatic spread after therapy.

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