FDG–PET for detection of recurrences from malignant primary bone tumors: comparison with conventional imaging

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Background: The aim of this study was to assess the diagnostic ability of positron emission tomography using 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG–PET) in the detection of recurrences from malignant primary bone tumors compared with conventional imaging.

Patients and methods: In 27 patients (6 osteosarcomas, 21 Ewing’s sarcomas), 41 FDG–PET examinations performed for diagnosis or exclusion of recurrent disease were evaluated. Conventional imaging techniques consisted of magnetic resonance imaging of the primary tumor site, thoracic computed tomography, and Tc-99m methylene diphosphonate bone scintigraphy. The reference methods were the histopathological analysis and/or the clinical and imaging follow-up.

Results: In 25 examinations reference methods revealed 52 sites of recurrent disease (local n = 7; distant: osseous n = 22, pulmonary n = 13, soft tissue n = 10). On an examination-based analysis FDG–PET had a sensitivity of 0.96, a specificity of 0.81 and an accuracy of 0.90. Corresponding values for conventional imaging were 1.0, 0.56 and 0.82.

Conclusions: The sensitivity, specificity and accuracy of FDG–PET in the detection of recurrences from osseous sarcomas are high. On an examination-based analysis, FDG–PET had a not significantly lower sensitivity in comparison with conventional imaging. However, FDG–PET showed a small advantage in the detection of osseous and soft-tissue recurrences compared with conventional imaging.

Key words: bone scintigraphy, CT, FDG–PET, malignant primary bone tumors, MRI, recurrences

Introduction

The current diagnostic tools for the detection or exclusion of recurrences from primary osseous sarcomas are clinical examination, magnetic resonance imaging (MRI) [or computed tomography (CT) or X-ray] of the primary tumor site, chest X-ray (or thoracic CT) and bone scintigraphy [1, 2]. Positron emission tomography using 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG–PET) has been used for the grading and therapy monitoring of malignant primary osseous tumors [3–5]. However, a systematic evaluation of the ability of FDG–PET to detect local and distant recurrences from malignant primary bone tumors has not been published before now.

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Patient population

In this retrospective analysis, we included all 27 patients (aged between 8 and 35 years, median 17 years; nine female, 18 male; six osteosarcomas, 21 Ewing’s sarcomas) with a histologically proven malignant primary osseous tumor who underwent one (n = 19) or more (n = 8) FDG–PET examinations (total n = 41) within a 5.5-year period, and who had a documented complete remission of their disease before the examination(s). FDG–PET examinations and conventional imaging had been performed as routine follow-up (n = 33) or because of suspicious recurrence due to pain (n = 8).

Imaging techniques

FDG–PET. FDG–PET scans (15 emission, 26 emission/transmission scanning) were acquired as described previously [6]. Blood glucose levels at the time of injection were <6.66 mmol/l in all studies. All patients/parents gave their informed consent to all FDG–PET examinations.

Conventional imaging. The conventional imaging methods, performed within 1 month of the FDG–PET, either before or after, were Tc-99m...
methylene diphosphonate bone scintigraphy (n = 41), thoracic computed tomography (n = 38; thoracic X-ray in three examinations), and MRI of the primary tumor site (n = 39; CT in one examination and X-ray in one examination).

Planar bone scintigraphy and spiral thoracic CT examination were performed as described previously [6, 7]. MRI of the primary tumor site was performed using a 1.5 Tesla system (Magnetom SP or Magnetom Vision, Siemens, Erlangen, Germany) with the smallest available surface coil. Pulse sequences comprised pre-contrast T1- and T2-weighted spinecho (SE) images as well as post-contrast T1-weighted SE images with and without fat suppression after injection of gadolinium diethylentriamine penta-acid (0.1 mmol/kg body weight). Pulse sequence parameters and slice orientation varied with the examined anatomic site.

Imaging analysis

All images were evaluated qualitatively by two experienced observers (consensus readings) blinded to any results of other imaging studies and to pathological data. On FDG–PET scans (emission scans, and attenuation-corrected scans if available) any focal uptake above background level was considered to be recurrent disease, unless explained by other conditions, i.e. adequate trauma. FDG activity ratios between the visually detectable lesions and homologous normal tissue were calculated using regions of interest (maximum count rates).

Reference methods

Recurrent disease was confirmed by histological examination and/or by an obvious progression in the number and/or size of the lesions on follow-up examinations. A lesion was determined as being benign by a stable clinical and imaging follow-up for at least 5 months (5–34 months, median 15 months) and/or a histological examination.

Results

Reference methods

Reference methods (follow-up n = 24, histology n = 28) revealed 52 sites of recurrent disease [local n = 7 (13%)]; distant: osseous n = 22 (42%), pulmonary/pleural n = 13 (25%), soft tissue n = 10 (19%)] in 25 of 41 (61%) examinations (routine follow-up n = 7, symptoms n = 18; 16 patients). Follow-up and histological analyses (n = 4) revealed no recurrent disease in the remaining 16 examinations (11 patients).

Imaging

Results are shown in Tables 1 and 2. There were no significant differences between the tumor types, osteosarcoma and Ewing’s sarcoma.

The FDG activity ratios of foci ranged from 1.3 to 4.0. A differentiation between malignant and benign lesions was not possible using this semi-quantitative analysis.

Discussion

In the present analysis, FDG–PET demonstrated a high accuracy in the detection of recurrent disease of osseous sarcomas in both local and distant sites.

Local recurrences

All local recurrences (n = 7) were identified by FDG–PET and conventional imaging in our patient group. This is in agreement with previous investigations performed in patients with soft-tissue sarcomas [8–10]. In the present study, the number of false-positive results showed a superiority of FDG–PET. Despite advances in MRI, differentiating viable tumors from scarring after treatment can be difficult [2, 10]. Furthermore, scar tissue may co-exist with tumor tissue. In addition, tracer enhancement in skeletal scintigraphy could also be a result of trauma or infection [11]. By characterizing metabolic behavior, FDG–PET has potential in distinguishing recurrent lesions from metabolically inactive tissue and in providing unique information about the distribution of active

Table 1. Patient- and examination-based analysis

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>n</th>
<th>SN</th>
<th>SP</th>
<th>ACC</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
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<tr>
<td>FDG–PET</td>
<td></td>
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<td></td>
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<tr>
<td>Patients</td>
<td>27</td>
<td>0.93 (15/16)</td>
<td>0.73 (8/11)</td>
<td>0.85 (23/27)</td>
<td>0.83 (15/18)</td>
<td>0.88 (8/9)</td>
</tr>
<tr>
<td>Examinations</td>
<td>41</td>
<td>0.96 (24/25)</td>
<td>0.81 (13/16)</td>
<td>0.90 (37/41)</td>
<td>0.89 (24/27)</td>
<td>0.93 (13/14)</td>
</tr>
<tr>
<td>Conventional imaging</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Patients</td>
<td>27</td>
<td>1.0 (16/16)</td>
<td>0.36 (4/11)</td>
<td>0.74 (20/27)</td>
<td>0.70 (16/23)</td>
<td>1.0 (4/4)</td>
</tr>
<tr>
<td>Examinations</td>
<td>41</td>
<td>1.0 (25/25)</td>
<td>0.56 (9/16)</td>
<td>0.82 (34/41)</td>
<td>0.78 (25/32)</td>
<td>1.0 (9/9)</td>
</tr>
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</table>

Abbreviations: 95% CI, 95% confidence interval; SN, sensitivity; SP, specificity; ACC, accuracy; PPV, positive predictive value; NPV, negative predictive value.
tumor. This may help in finding appropriate regions for biopsy [9].

Pulmonary/pleural recurrences

The inferiority of FDG–PET in the detection of pulmonary recurrences is in agreement with data from soft-tissue sarcoma patients [10]. Furthermore, the superiority of thoracic CT in the diagnosis of pulmonary/pleural metastases from osseous sarcomas has been shown [6]. Reasons for the poor FDG–PET results might be the small size of pulmonary lesions resulting in partial volume effects and the blurring of the lesions in the FDG–PET images caused by breathing [6]. However, sensitivity of FDG–PET in the detection of pulmonary recurrences in this study (0.85) is higher compared with the overall detection of pulmonary involvement, either at the time of the first tumor manifestation or of the recurrent disease (0.50) [6]. Data from grading studies suggest that the higher sensitivity may indicate a more aggressive biological behavior [3].

Osseous recurrences

Pathological tracer uptake in skeletal scintigraphy is unspecific, resulting in a high number of false-positive findings [1]. In the present analysis, there is a superiority of FDG–PET in sensitivity and specificity (false-positive findings), although the number of false-positive lesions seems to be a problem with FDG–PET as well. In a previous study, the few skeletal metastases deriving from osteosarcoma (five metastases in two patients) were false negative using FDG–PET [7]. In the present study, all sites of osseous recurrent disease (n = 6)
deriving from osteosarcoma were true positive by FDG–PET, possibly because of a higher metabolic activity compared with primary metastases.

**Soft-tissue recurrences**

Using conventional imaging, asymptomatic soft-tissue recurrences could only be detected in cases where they were located in the field of view of local MRI or thoracic CT, or if they produced osseous matrix (osteosarcoma) resulting in phosphonate uptake in skeletal scintigraphy. The advantage of FDG–PET is that all organ systems, including soft tissue, can be visualized in a single whole-body examination [4–7, 10].

**Conclusion**

In the detection of recurrences of osseous sarcoma, sensitivity, specificity and accuracy of FDG–PET are high. Compared with conventional imaging, FDG–PET shows only a small advantage in the detection of osseous and soft-tissue recurrences. The results of the present study warrant a systematic, prospective and multi-centric evaluation of the clinical value of FDG–PET in the diagnosis of bone sarcoma recurrences, including assessment of the convenience for the patients, the influence on outcome and cost–benefit analysis. In particular, the detection of bone and soft-tissue recurrences in comparison with bone scintigraphy and, furthermore, with whole-body MRI [12] should be addressed. In future, FDG–PET might replace bone scintigraphy within the imaging follow-up.

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