Evaluation of fluorodeoxyglucose positron emission tomography in the management of soft-tissue sarcomas


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We performed a retrospective analysis to evaluate the ability of whole-body $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET) to identify local recurrence and pulmonary metastases in patients with soft-tissue tumours after treatment. We compared the results of FDG PET with those of MRI for the detection of local recurrence, and with CT of the chest for pulmonary metastases.

We assessed 62 patients of mean age 51 years, who had 15 types of soft-tissue sarcoma, after a mean follow-up of 3 years 2 months. For the detection of local disease, 71 comparisons showed that the sensitivity and specificity of FDG PET were 73.7% and 94.3%, respectively; there were 14 true-positive and five false-negative results. MRI had a sensitivity and specificity of 88.2% and 96.0% respectively. For the identification of lung metastases, 70 comparisons showed that the sensitivity and specificity of FDG PET were 86.7% and 100%, with 13 true-positive results and two false-negative results. CT of the chest had a sensitivity and specificity of 100% and 96.4%.

Thirteen other sites of metastases were identified by FDG PET.

FDG PET can identify both local and distant recurrence of tumour as a one-step procedure and will detect other metastases. It seems that all three methods of imaging are needed to define accurately the extent of disease, both at initial staging and during follow-up.

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Adult soft-tissue sarcomas (STS) are a heterogeneous group of rare malignant tumours arising from soft tissues and account for approximately 1% of all cancers. The incidence in England and Wales is 1.7 per 100 000 men and 1.4 per 100 000 women giving approximately 1000 to 1500 new cases per year.¹ In the USA, there are approximately 7000 new cases per year.² When first seen, between 10% and 23% of patients will have metastases, the lung being the most common site with one-third of secondary tumours. Deposits in bone, liver, and brain comprise about 40%; the others are found in the regional lymph nodes, retroperitoneum and soft tissues.³,⁴

After treatment of the primary tumour between 30% and 35% of patients will develop recurrence either locally or at a distant site.⁵,⁶ Of these patients, between 15% and 47% will develop a local recurrence, depending on the margins achieved at surgical resection. Isolated metastases are seen in the lung in 38% to 64%, and from 28% to 34% will develop metastases at multiple sites.⁵-⁷

The optimal management of these tumours depends on the site, size and grade of the local growth and accurate staging of the disease when first seen. The site and size are best determined by MRI,⁸-¹⁰ but the accurate diagnosis of distant metastases is confounded by the wide distribution of potential sites. The detection of local recurrence is hampered by difficulty in differentiating between recurrence, the changes after operation, and the effect of any radiotherapy.

Local recurrence is best assessed using MRI with gadolinium contrast enhancement; regular clinical examination alone is insensitive. MRI has a sensitivity of 80% to 85% for the detection of local recurrence, better than CT which has a sensitivity of 57% to 70%.¹¹-¹⁴ Ultrasound has a similar sensitivity to MRI for the detection of local recurrence, but depends very much on the proficiency of the operator.¹⁰,¹² A variety of radionuclide methods has been tried with varying success.¹⁴,¹⁵

Lung metastases can be identified using CT, but other
potential sites of metastases need to be specifically examined. Whole-body gallium scanning has been used to identify sites of metastases to aid in staging at presentation and after treatment; it provides sensitivities of from 72% to 93%. There is concern about the ability to detect subclinical recurrences.

$^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET) can successfully identify primary, recurrent and metastatic cancer of the breast, colon, lung and the lymphomas. It can detect STS and give an indication of grade. There is limited information on its use in the early detection of local recurrence and metastases after primary surgical treatment of STS. FDG PET has the potential advantage of identifying both complications by a single procedure, and we have tried to evaluate this.

**Patients and Methods**

The 62 patients whom we studied had an STS treated between April 1988 and November 1995. The 34 men and 28 women had a mean age, at the time of diagnosis, of 50 years 11 months (2 years 11 months to 83 years 8 months). The mean follow-up from the time of accurate diagnosis, when operation had provided a definitive histological diagnosis, to the latest examination or death was 3 years 2 months (1 month to 9 years 1 month). The minimum follow-up was of a patient with a high-grade leiomyosarcoma with pulmonary metastases, who left the country to seek medical advice elsewhere.

Routine follow-up had been by traditional imaging techniques and, since 1992, also by whole-body FDG PET. We reviewed all FDG PET scans in a blinded manner with no reference to other imaging (MJO’D, JCHW). Two patients had whole-body FDG PET when first seen as part of the evaluation for staging, and were therefore only included in the assessment of the value of FDG PET in detecting distant metastases. We compared FDG PET findings with those of clinical examination, MRI and CT for local recurrence, and with histology when a biopsy had been performed. For the assessment of the detection of lung metastases, FDG PET was compared with CT of the chest, and with histological examination when available. Scans for other sites of metastases were evaluated against clinical examination, other imaging techniques as indicated, and the histology of biopsy material. Our absolute standard for the diagnosis of tumour recurrence both locally and at distant sites was histological examination. We tried to minimise the risk of false-negative results by maintaining a low threshold for biopsy material and by additional imaging.

**Histology.** The histological diagnosis and grading of the primary tumours were by two histopathologists (CDMF and PHM). Tumour differentiation, necrosis and the mitotic count were assessed to determine whether the tumour was grade 1, low; grade 2, intermediate; or grade 3, high.

**The FDG PET scan.** All patients had standard whole-body scanning after a six-hour fast. An emission whole-body scan was performed after the intravenous injection of 350 MBq FDG using an ECAT 951R Whole Body System (Siemens/CTI, Knoxville, Tennessee) with an image resolution of 8 mm and an axial field of view of 10.6 cm. The images were displayed as coronal, sagittal and transaxial sections. Areas with abnormally increased FDG uptake were noted and a decision made as to whether or not this represented potential malignant disease. Focal areas of uptake with activity equal to, or greater than, liver uptake were scored as metastatic. When the changes were at the site of recent surgery, a decision was made between reactive change and malignant disease.

**MRI of the local site.** Axial T1-weighted images with coronal STIR were followed by post-contrast axial T1 images with fat suppression. Gadolinium diethylenetriamine penta-acetic acid was given intravenously at a dose of 0.2 ml/kg of body-weight. The proximal and distal ends of the surgical scar were marked with oil capsules. All scans were reviewed blind and independently by an MR radiologist (JBB).

**CT of the chest.** Before May 1996 we used an 8 mm on 8 mm post-contrast scan using a Siemens CT scanner. Ultravist 370 (Schering Health Care Ltd, Burgess Hill, UK) was used as the contrast medium with 100 ml administered intravenously by hand; scanning started after 50 ml had been infused. From May 1996 a 10 mm on 10 mm volume spiral post-contrast scan was performed using a Philips Tomoscan AV/Spiral. Ultravist 370 was given intravenously with 75 ml injected at a rate of 3 ml/min, the scan starting ten seconds after infusion had commenced. Contrast administration and the scan start time were automated. All scans were reviewed blind and independently by one author (JBB).

**Results**

There were 15 types of sarcoma, liposarcoma being the most common (Table I). They were in 13 different sites, the

<table>
<thead>
<tr>
<th>Sarcoma type</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>Liposarcoma</td>
<td>18</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>12</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>9</td>
</tr>
<tr>
<td>Myxofibrosarcoma (myxoid MFH)*</td>
<td>5</td>
</tr>
<tr>
<td>Unclassifiable pleomorphic sarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Extraskeletal osteosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumour (MPNST)</td>
<td>2</td>
</tr>
<tr>
<td>Round-cell sarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Angiomatoid MFH</td>
<td>1</td>
</tr>
<tr>
<td>Epithelioid angiosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Clear-cell sarcoma (malignant melanoma of soft parts)</td>
<td>1</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Fibromyxoid sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Triton sarcoma (MPNST with rhabdomyo/lastic differentiation)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
</tr>
</tbody>
</table>

* malignant fibrous histiocytoma

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commonest being the thigh (Table II). The distribution of the grades of the tumours is shown in Table III.

Detection of local recurrence. In the group of 60 patients available for assessment, there were 72 comparisons of FDG PET with MRI in 67, CT in four and clinical examination alone in one patient who was subsequently shown to have a recurrence on histological examination. Biopsies were performed when changes on the scans suggested a recurrence. The median time between FDG PET and MRI or CT was one day (1 to 63).

FDG PET showed a sensitivity of 73.7% with a specificity of 94.3%. There were five false-negative results in each of which a recurrence was proven on histological examination. MRI had also been undertaken in four of these and had failed to identify the recurrence in two; in the fifth, false-negative CT had failed to diagnose the recurrence (Table IV). One false-negative result was for an intermediate-grade myxofibrosarcoma at the ankle, two were liposarcomas in the thigh (one high-grade round-cell and one an intermediate atypical dedifferentiated liposarcoma), one was an alveolar rhabdomyosarcoma in the thigh, and one was a synovial sarcoma at the knee. MRI failed to identify local recurrence of the high-grade liposarcoma and of the alveolar rhabdomyosarcoma, and CT did not show the recurrence of the synovial sarcoma.

FDG PET gave three false-positive results. These were for a high-grade clear-cell sarcoma (malignant melanoma of soft parts) in the foot, and two low-grade myxoid liposarcomas in the thigh. MRI gave false-positive results for the clear-cell sarcoma and one of the liposarcomas. All three patients had incisional biopsies under general anaesthesia to provide multiple tissue samples which showed no recurrence of tumour.

MRI had a sensitivity of 88.2% with a specificity of 96.0% (Table IV). Of the 15 incidences of local recurrence detected (Fig. 1), all were confirmed histologically; only two of them had been identified on clinical examination.

Patients with negative FDG PET were followed subse-
quently with further imaging using either FDG PET or MRI, in combination with clinical examination to determine that no recurrence had occurred.

**Detection of lung metastases.** In the 62 patients, there were 70 comparisons of FDG PET with CT of the chest and, when available, tissue diagnosis. FDG PET had a sensitivity of 86.7% and a specificity of 100%. CT of the chest had a sensitivity of 100% and a specificity of 96.4% (Table V).

There were two false-negative FDG PET scans in patients with multiple lung metastases, one from a high-grade extraskeletal osteosarcoma and the other from a high-grade leiomyosarcoma. Tissue diagnosis was not obtained in either case because the CT findings were considered to be conclusive (Fig. 2).

![FDG PET and CT images](Fig. 2a)

A high-grade leiomyosarcoma in the thigh which was false-negative for lung metastases. Figure 2a – FDG PET showing no abnormal uptake in either lung. There is delayed excretion from the left kidney (arrow) and accumulation of FDG in the bladder. Figure 2b – CT of the chest showing a large parenchymal lung metastasis (large arrow) and bilateral changes due to lung atelectasis (small arrows).
There were two false-positive CT scans; the FDG PET was negative in both. The first was in a patient with a low-grade fibromyxoid sarcoma in the thigh in whom CT of the chest showed hilar lymphadenopathy and some nodules within the lung parenchyma. Two subsequent CT scans over a period of a year demonstrated resolution of the hilar lymphadenopathy, but the parenchymal nodules were unchanged and the patient remains well. The initial diagnosis of metastases was therefore considered to be incorrect. In the second patient, CT showed two distinct masses, one in the left lower lobe and the other in the right apex, both of which were thought to be metastases. FDG PET at the same time showed minor uptake in the left lower zone only, which was not considered to be significant. Biopsy of one of the lesions showed it to be a lung infarct.

**Detection of sites of metastases other than the lungs.** In nine patients, FDG PET identified 13 sites of metastases other than in the lungs; seven of them had concurrent lung metastases (Fig. 3). In eight patients, the sites of the metastases were not clinically evident, and were confirmed by histological examination (Table VI). At five sites the nature of the lesion was not confirmed histologically. Three were in one patient who died from the sarcoma, one was in a patient who had an obvious retroperitoneal metastasis confirmed on CT, and in the other there was an obvious metastasis in the anterior chest wall which was also seen on CT.

One false-positive FDG PET scan was in a patient who had had an above-elbow amputation for a high-grade leiomyosarcoma. FDG PET identified a region of intense uptake in the ipsilateral acromioclavicular joint and in the subacromial space, which was thought to be a metastasis. MRI using gadolinium contrast medium showed degenerative changes within the acromioclavicular joint and rotator cuff, but no evidence of a mass. In another patient with a synovial sarcoma of the leg, FDG PET identified significant, symmetrical upper hilar lymphadenopathy which was confirmed by CT. This was not typical of a metastatic synovial sarcoma and a biopsy was therefore performed which revealed a grade-two nodular sclerosing Hodgkin’s lymphoma. This has been classified as a true-negative result.

**Discussion**

The behaviour of the lesions in this group of patients is representative of the natural history of STS. Of the 60
patients who were assessed after treatment of the primary tumour, 23 (38.3%) developed a recurrence locally or at a distant site. There were nine (39.1%) isolated local recurrences and five (21.7%) isolated lung metastases. Eight patients (34.7%) had lung metastases combined with other sites of recurrence and one (4.3%) had isolated distant metastases at sites other than the lung. Not all these patients had FDG PET to identify these metastases.

There were 15 examples of local recurrence in 14 patients, one of whom developed a second recurrence. Of the primary tumours 12 were high grade and two were intermediate. Only three had a maximum diameter of less than 5 cm. All local recurrences had had a marginal excision of the primary tumour, and 12 of these had been performed at other hospitals. There were three recurrences in two patients who were treated primarily in our centre. Both had high-grade tumours; one was in the groin and the other around the knee and they had had marginal excision and postoperative radiotherapy.

Surgery for recurrence of STS, both locally and at distant sites, is known to improve survival and decrease morbidity. The early detection of recurrence is therefore advantageous and the use of a technique for whole-body single scanning which is able to identify both local and distant sites of recurrence is attractive.

There were five false-negative results, and three of these patients subsequently developed positive MRI and FDG PET scans within six months. A tumour was probably present at the time of the initial FDG PET scan but in such a small volume as to be undetectable. There is a limit to the sensitivity of current techniques in detecting small volumes of viable tumour and that of FDG PET may depend on the grade of the tumour, reflecting the increased rate of glucose metabolism in high-grade malignancies. FDG PET identified subclinical recurrences in four patients who had previously had excision of high-grade sarcomas.

The three false-positive FDG PET scans can be explained by the presence of inflammatory changes which were confirmed on histological examination. Such a reactive response may continue for some time after operation and must be taken into account when assessing individual FDG PET scans. It is possible that the addition of local transmission/emission scans of the area resected may give quantitative data which will allow a tumour to be distinguished from an inflammatory change with more confidence. Our study considered only whole-body emission scans since this allowed a standard throughput of patients at a reasonable speed of scanning.

FDG PET was inferior to CT of the chest in detecting lung metastases, failing to identify multiple deposits in two cases. Both were high-grade tumours, one an extraskeletal osteosarcoma and the other a leiomyosarcoma. In one, four pulmonary metastases were present ranging from 16 to 43 mm in diameter and in the other there were seven lesions ranging from 5 to 9 mm. FDG PET satisfactorily identified the presence of lung metastases in four other leiomyosarcomas and one extraskeletal osteosarcoma, the size and location of the parenchymal metastases being comparable.

One explanation for the failure of the FDG PET to identify these lung metastases is that it may have been taken too soon after injection of FDG. Scanning of the chest was at between 45 and 90 minutes after injection, but there is increasing evidence that maximum accumulation of FDG in tumours is at about two hours after the injection; the time which we allowed for the accumulation of FDG in the metastases may have been insufficient to allow their proper differentiation. Detection of lung metastases was based on the evaluation of whole-body FDG PET, and lesions may be missed because of soft-tissue photon attenuation by the chest. The addition of a localised transmission/emission scan may improve the contrast and detectability of the metastases. Another reason for failure may be that lung metastases do not have as good a vascular supply as the original tumour until they reach a specific size and this may restrict the uptake of FDG. This seems unlikely in a richly vascular area such as the lung, but could be investigated further using flow tracers.

FDG PET identified 13 other sites of metastases, only five of which were clinically evident. One of these patients had an epithelioid angiosarcoma located just above the ankle. A below-knee amputation was performed for residual tumour after an incomplete primary excision at another hospital. At the same time, a small lymph node in the ipsilateral groin which had been identified as the site of a metastasis on FDG PET, was removed; histological examination confirmed the diagnosis. The patient subsequently developed two subclinical deposits in the thigh above the amputation. Both were 0.5 cm in diameter and were identified by FDG PET. After excision of the latest metastasis, the patient is free from disease 4 years and 5 months after the original diagnosis.

MRI is the investigation of choice for recurrent and/or residual local disease after operation for STS. CT is the preferred investigation for pulmonary metastases. The differentiation between a recurrence and postoperative inflammatory change is difficult, and FDG PET can be useful in helping to identify tumours, particularly those of high grade, and is important in detecting metastatic spread at other sites.

We found that FDG PET is not as satisfactory as conventional imaging for the identification of local recurrence (MRI is better) and lung metastases (CT is better) in patients with surgically-excised STS. It is, however, of considerable value in detecting extrapulmonary visceral spread. We believe that whole-body FDG PET has a major role in the staging of STS both initially and at follow-up. Whole-body scanning with specific views of the primary tumour will allow quantitative measurement of the rate of FDG metabolism. This, combined with the optimal timing of scanning after injection of FDG, may greatly enhance the sensitivity of this technique for the identification of
both local and distant recurrence as a one-step procedure. A combined approach utilising FDG PET with MRI and CT will allow accurate assessment before treatment and aid the monitoring of the effectiveness of subsequent treatment.

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References