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Detection of Local Recurrence of Soft-Tissue Sarcoma with Positron Emission Tomography Using [^{18}F]Fluorodeoxyglucose

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Background: It is often difficult to detect a local recurrence of soft-tissue sarcomas due to disturbance of the normal anatomy by previous surgery and radiotherapy. The aim of this study was to assess the value of positron emission tomography (PET) with [^{18}F]fluoro-2-deoxy-D-glucose (FDG) for detecting local recurrences.

Methods: In the period 1992–1995, 17 patients with proven or suspected local recurrence of soft-tissue sarcoma were examined using FDG-PET. Fifteen of these patients were ultimately proven to have a recurrence.

Results: Recurrence was visualized in 14 patients (93%). Small tumors (maximum diameter 0.5 cm) were as easily visible as large lesions (maximum diameter 20 cm). In one patient the PET scan was positive, but the recurrence could not be proven histologically. Recurrence was proven 1 year later. A recurrent low-grade liposarcoma was not visualized. The two patients with benign lesions had a negative PET scan. The mean glucose metabolic rate was calculated to be 13.2 μmol/100 g/min (range 1.9–28.4). A correlation was found between the histological malignancy grade and the metabolic rate ($p < 0.05$; Kruskal-Wallis).

Conclusion: PET with FDG is a useful addition to the diagnostic armamentarium for detecting local recurrence of soft-tissue sarcomas and provides an indication of the malignancy grade of the recurrent lesion.

Key Words: Positron emission tomography—Sarcoma—Fluorodeoxyglucose—Detection—Recurrence.

Approximately 15% of patients with a soft-tissue sarcoma of the extremity develop a local recurrence, even after adequate therapy (1,2). Detection of a local recurrence is often difficult because of disturbance of the normal anatomy by previous surgery and radiotherapy. Scar tissue tends to impede detection by the palpating fingers of the physician. Distortion of the anatomy and fibrosis makes it more difficult to interpret images obtained by conventional imaging techniques. A technique that can detect local tumor recurrence would help to achieve local control.

With positron emission tomography (PET), metabolic processes can be studied in vivo. Other imaging techniques, such as magnetic resonance imaging (MRI) and conventional computed tomography (CT), are more suitable to visualize anatomy (3). [^{18}F]Fluoro-2-deoxy-D-glucose (FDG) is the most widely used radiopharmaceutical for oncological purposes. FDG acts as a glucose analog, and its

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uptake reflects glucose metabolism. Because glucose consumption is generally increased in tumor tissue, malignant neoplasms can be visualized using FDG-PET (4,5). In addition to primary tumors, metastases and local recurrences can be depicted (6–10). These features suggest that PET may be of particular value in the management of patients with soft-tissue sarcoma. It has been established that glucose metabolism in soft-tissue sarcomas is high and that these lesions can be visualized via PET (11,12). Glucose metabolism correlates with the malignancy grade (12).

The aim of the present study was to investigate FDG-PET for the detection of recurrent soft-tissue sarcomas.

PATIENTS AND METHODS

Patients

In the period 1992–1995, 17 patients (six men, 11 women) with proven or suspected local recurrence of soft-tissue sarcoma underwent PET scanning. Informed consent was obtained from each patient. The mean age was 54 years (range 32–83). In 13 patients, the location of the primary tumor was on the lower extremity, in one patient on the upper extremity, in two patients in the abdominal wall, and in one patient in the small intestine. In nine patients it was the first local recurrence, in five patients the second, in one patient the third, in one patient the fourth, and in one patient the fifth. Previous treatment had consisted of surgery, radiotherapy, chemotherapy, or a combination of the three. Relevant patient data are presented in Table 1. All lesions were subjected to biopsy for pathological evaluation. They were classified according to tumor type and were assigned a malignancy grade in a standard fashion (13,14). Tumor size was defined as the mean diameter of the tumor in the surgical specimen (13 patients), via MRI (three patients), or via CT (one patient). The size of the lesions at pathological examination ranged from 0.5 to 20 cm.

PET Studies

Fluor-18 was produced in a cyclotron using the $^{18}O(p,n)^{18}F$ reaction. FDG was synthesized using the technique described by Hamacher, with a radiochemical purity of >98% (15). A 951/31 ECAT positron camera (Siemens/CTI, Knoxville, TN, USA) was used for data acquisition. The camera acquires 31 contiguous tomographic slices simultaneously over a total axial length of 10.8 cm. The spatial resolution in a transaxial field of view in stationary mode is 6 mm.

Patients fasted overnight before the PET study. In 12 patients, a 20-gauge needle was inserted into the radial artery under local anesthesia. In the contralateral arm, an intravenous cannula was inserted

TABLE 1. *Patient data*[a]

Patient	Histology	Grade	Size (cm)	Previous treatment	MRI/CT	Scan	MRGlc
1	Desmoid tumor	I	3.0	5 × S	–	+	5.3
2	Liposarcoma	I	9.5	4 × S	–	–	1.9
3	Myxoid liposarcoma	I	1.0–2.0[b]	2 × S	Not done	+	4.0
4	Myxoid liposarcoma	I	9.0	2 × S	+	+	5.0
5	Myxoid liposarcoma	II	20.0 (MRI)	1 × S and XRT	+	+	12.8
6	Fibrosarcoma	II	1.0	1 × S and XRT	+	+	21.3
7	Malignant fibrous histiocytoma	II	0.7	1 × S	+	+	14.0
8	Malignant schwannoma	III	0.5—0.8[b]	3 × S, 1 × CHT	Not done	+	–
9	Malignant schwannoma	III	4.0	1 × S and XRT	+	+	–
10	Malignant schwannoma	III	20.0 (MRI)	2 × S, XRT	–	+	5.9
11	Malignant schwannoma	III	12.0	1 × S	+	+	28.3
12	Leiomyosarcoma	III	9.0	2 × S	+	+	24.4
13	Malignant fibrous histiocytoma	III	15.0	1 × S	+	+	16.0
14	Synovial sarcoma	III	8.0	1 × S	+	+	19.8
15	Unspecified sarcoma[c]	III	9.0	2 × S, XRT	+	+	–
16	Ascaris[c]	[d]	[d](CT)	1 × S	+	–	–
17	Scar tissue[c]	–	2.0 (MRI)	1 × S	+	–	–

I, low grade; II, intermediate; III, high grade; S, surgery; XRT, radiotherapy; CHT, chemotherapy.

[a] Histopathological classification, malignancy grade, tumor size, previous treatment, imaging assessment, and mean rate of glucose consumption (MRglc in μmol/100 g/min) in each patient.

[b] Multiple nodules.

[c] Primary tumors of patients 15, 16, and 17 were a neurofibrosarcoma, a leiomyosarcoma, and a grade I liposarcoma, respectively.

[d] Inconclusive.

into the cephalic vein for the injection of FDG. The patients were positioned supine in the camera with the tumor in the field of view. A transmission scan was obtained to correct for attenuation of the signal by the body tissues in the imaging area followed by the intravenous administration of 370 MBq (10 mCi) FDG as a bolus. Dynamic scanning was performed at the level of the tumor by obtaining 16 frames from the time of injection through 50 min postinjection. These include ten 30-s frames, three 5-min frames, and three 10-min frames. For establishing the input function, 2-ml blood samples were taken simultaneously from the arterial canula (at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2.25, 2.75, 3.75, 4.75, 7.5, 12.5, 17.5, 25, 35, and 45 min after injection). Samples were centrifuged, and the plasma activity was assessed using a well counter.

Whole-body images were obtained after dynamic imaging. Five patients were scanned in whole-body mode only. For tumor detection, scanning in whole-body mode only is sufficient. This approach gives images that are easier to interpret than dynamic scanning and takes ~40 min. For calculation of the glucose metabolism, arterial cannulation and a more prolonged dynamic imaging time are required. A combined scanning procedure takes ~90 min.

Data Analysis

PET images were displayed in transaxial projections on a computer display using standard ECAT software. The glucose metabolic rate (MRglc) was calculated as described in detail previously (12). In short, above a visually chosen threshold, tumor tissue was outlined, and the tissue time-activity curves obtained from the voxels in these areas were averaged. By combining these time-activity data with the plasma input data, the average MRglc in μmol/100 g tumor tissue/min was calculated using the Patlak analysis (16,17). The MRglc in the contralateral normal tissue also was calculated using a region of interest technique. If the tumor could not be visualized clearly, a region of interest was drawn, based on the MRI.

Statistical analysis included the Kruskal-Wallis analysis to test for a relationship between the MRglc values and the different malignancy grades, whereas the Wilcoxon-test was used to compare the MRglc in tumor tissue with that in the corresponding contralateral normal tissue. A probability value of <0.05 was considered significant.

Whole-body images were interpreted by three physicians, who judged independently and were unaware of the histological outcome.

RESULTS

Local recurrence was proven histologically in 15 of the 17 patients (Table 1). In the other two patients, MRI and CT were suggestive of a local recurrent sarcoma. Biopsies in one of these two patients (patient 17 in Table 1) showed scar tissue and reactive changes. No evidence of tumor growth developed during follow-up for 6 months. The intraabdominal mass in the remaining patient (patient 16 in Table 1) proved on exploration to be caused by *Ascaris lumbricoides* 4 years after resection of a leiomyosarcoma of the small intestine.

The PET images were of a good technical quality. The three interpreting physicians reported unanimously on 15 of the 17 PET studies. Opinions diverted in patients 2 and 10. The final interpretation was based on the majority vote. Generally, recurrent sarcoma was clearly visible in the presence of surrounding scar tissue and fibrosis (Fig. 1). In two patients, even lesions smaller than 1 cm were depicted (Fig. 2). Soft-tissue sarcomas often have an inhomogeneous texture on pathological examination. Necrosis and hematoma may be interspersed

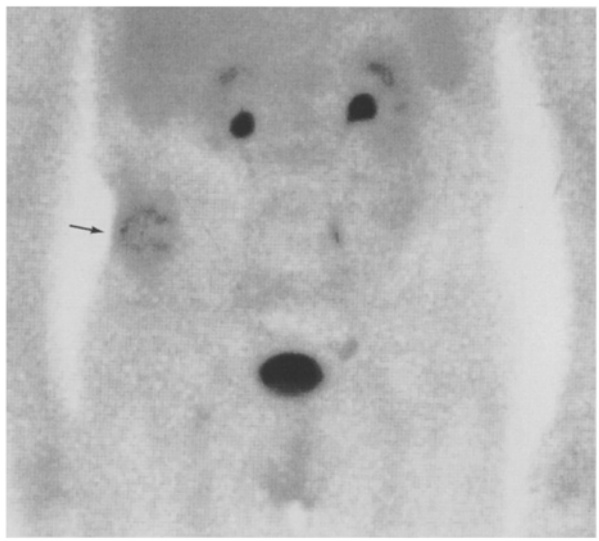

FIG. 1. Patient 15, a 75-year-old man with clinical recurrence of an unspecified sarcoma in the right abdominal wall. Fine needle aspiration could not confirm tumor recurrence. With PET, the recurrence was visualized as a large (diameter 8 cm) area of increased uptake, which was surgically resected.

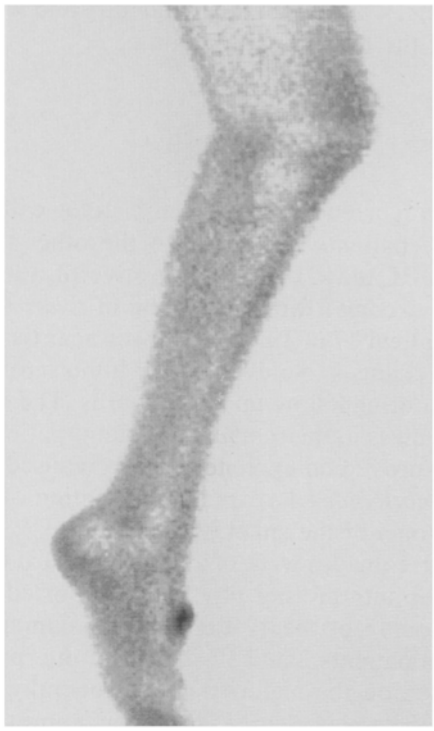

FIG. 2. Patient 1 with recurrent malignant fibrous histiocytoma in the left foot. The maximum diameter on pathological examination was 7 mm.

with areas of neoplastic cells. This variable texture of a sarcoma was also reflected by an inhomogeneous FDG uptake (Fig. 3).

Fourteen of the 15 recurrences were visualized on the PET images (93%). A false-negative result was obtained in a 57-year-old man (patient 2) with a 9.5-cm grade I liposarcoma in the right thigh. It was his fourth local recurrence after previous surgical excisions. Histological examination showed that the tumor was largely lipoma with some lipoblasts and scattered cells with polymorphic nuclei. This lesion was classified as a very well differentiated lipomalike liposarcoma. The two patients with benign lesions had negative PET scans.

MRI (10 patients), CT (one patient), or both MRI and CT (four patients) yielded false-negative results in three patients (patients 1, 2, and 10) and false-positive results in two (patients 16 and 17).

An interesting case involved patient 10, who had undergone multiple surgical procedures and radiotherapy for a malignant grade III schwannoma of the left thigh. Pain suggested the presence of a local recurrence, although physical examination, CT, and MRI yielded inconclusive results. The PET scan showed an area of higher glucose consumption, suggestive of the presence of a recurrence (Fig. 4). Extensive surgical exploration and multiple biopsies showed only reactive changes. It was not until a year later that a recurrence was proven after a wide excision of the fibrotic area.

The MRglc in the tumors is presented in Table 1. The MRglc in tumor tissue was higher than in the contralateral normal tissue ($p = 0.002$; Wilcoxon). The mean tumor MRglc was 13.2 μmol/100 g/min. Compared with tumors with a low malignancy

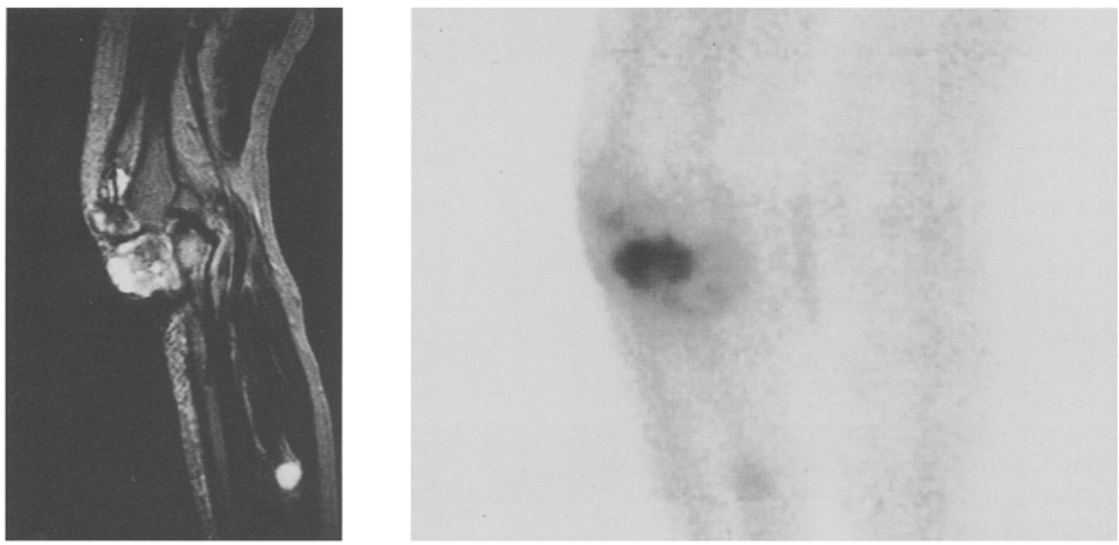

FIG. 3. MRI and PET of patient 4 with recurrence of a leiomyosarcoma in the left knee (maximum diameter 9 cm). Note the inhomogeneous FDG uptake in the tumor.

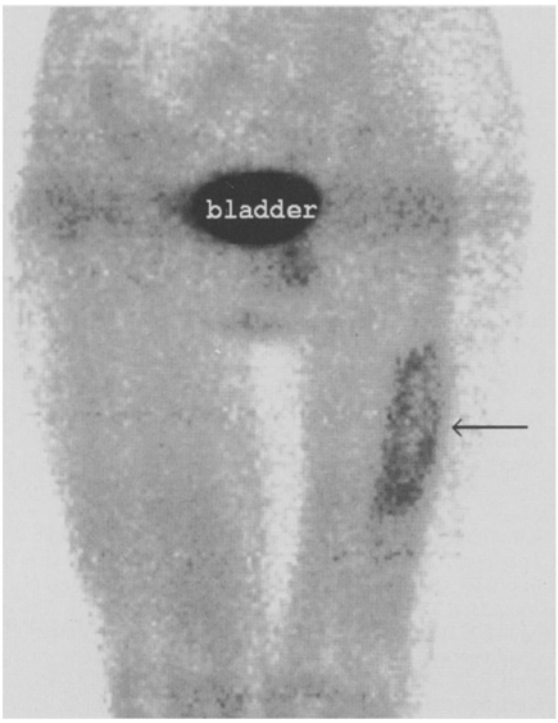

FIG. 4. PET of patient 10, a 65-year-old woman. The anterior view shows increased uptake of FDG over a large area. Biopsy samples did not contain viable tumor tissue. However, 1 year after this PET scan, pathological proof of recurrence was obtained.

grade, glucose turnover was significantly higher in intermediate-grade lesions and higher still in high-grade tumors when the three groups are assessed together for a trend ($p = 0.012$; Kruskal-Wallis) (Fig. 5).

DISCUSSION

The present study demonstrated that FDG-PET can visualize locally recurrent soft-tissue sarcomas. The majority of local recurrences could be depicted, regardless of tumor type and size. The finding that lesions as small as 5 and 7 mm were clearly outlined suggests that FDG-PET can be used for the early detection of local treatment failures, especially for high-grade sarcomas. To our knowledge this is the first report on PET for the detection of recurrent soft-tissue sarcomas.

The ability of FDG-PET to detect small local recurrences is of clinical significance because sarcomas often develop deep beneath the fascia and tend to elude detection until sizable dimensions have been attained. The interpretation of images obtained by other imaging techniques may be hampered by previous surgery and radiotherapy. Ultrasonography, MRI, and CT are based on the visualization of tissue planes. Fibrosis and distortion of the normal anatomy may lead to confusing images using these conventional imaging techniques (18,19). Phosphorus-31 magnetic resonance spectroscopy does not have any value for the detection of recurrent sarcomas (20). The purpose of the present study was merely to investigate the potential of PET to visualize recurrent soft-tissue sarcoma. Although it was not our intention to compare FDG-PET with MRI and CT, FDG-PET had a sensitivity and accuracy of 93% and 94%, respectively, whereas MRI and (and/or CT) had a sensitivity and accuracy of 77% and 67%, respectively. However, these results should be interpreted with caution because we studied a selected patient population with a high pretest probability of disease. Other investigators have found sensitivities of 58% and 83% for serial CT and MRI (21).

Tumor differentiation may be more of a limiting factor in tumor detection than may tumor size. The ratio of uptake of a radiopharmaceutical in a lesion compared with the uptake in the surrounding normal tissue mainly determines the detectability of that lesion. FDG consumption tended to be lower in the well-differentiated recurrent tumors, as was reflected by the lower MRglc. The one tumor that was not visualized was a well-differentiated liposarcoma. The same problem was described by Adler et al. in three primary liposarcomas (22). In other tumor types, the MRglc has been shown to be a measure of not only the malignancy grade, but also of the proliferation rate and the prognosis (23–28).

Soft-tissue sarcomas are often inhomogeneous.

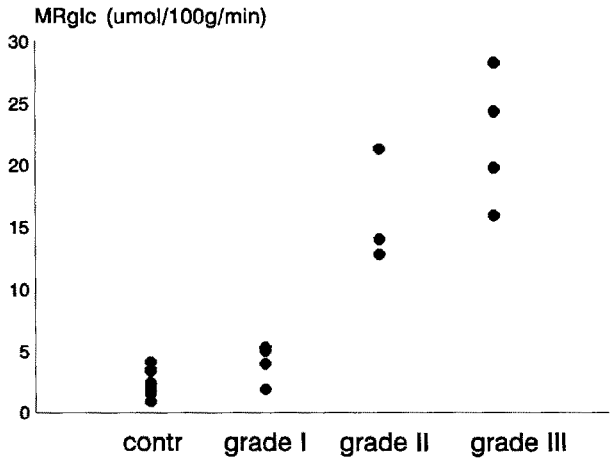

FIG. 5. Glucose metabolism in relation to tumor malignancy grade. Contr, contralateral normal tissue.

Different parts within a tumor may have different malignancy grades. Stroma, necrosis, hematoma, and edema may be found within a tumor. The PET study demonstrated in Fig. 2 shows that the FDG uptake can be variable within a tumor. Therefore, PET scanning may provide important information about metabolic activity and may be useful in combination with MRI/CT scanning for guiding a biopsy and avoiding sampling errors (29,30).

In The Netherlands, the costs of an FDG-PET study for detection of a recurrent neoplasm currently amount to the equivalent of approximately US$820, whereas MRI costs approximately $680 and CT $280. Now that it is clear that FDG-PET can visualize recurrent soft-tissue sarcomas, this technique needs to be compared with CT and MRI, both with respect to clinical value and cost effectiveness.

In conclusion, FDG-PET appears to be a sensitive and reliable method for detecting recurrent soft-tissue sarcomas. Still, these results should be interpreted with caution, because our patients had a high pretest probability of disease. The present findings reinforce the basis for performing subsequent clinical PET studies on malignant tumors in general and soft-tissue sarcomas in particular (31). An important subsequent question is: Can PET detect local recurrent lesions at an earlier stage than can CT and MRI? To learn more about the specificity of FDG in soft-tissue lesions, it would be interesting to examine whether PET can differentiate between benign and malignant lesions. Can whole-body scanning detect blood-borne metastases not visible with conventional imaging techniques? Evaluation of the results of radiotherapy and chemotherapy for soft-tissue sarcoma with FDG-PET is also an attractive topic for PET studies because a decrease in tissue viability results in a decrease in the glucose consumption (8,32,33). In an early treatment phase, PET may be able to indicate whether the ultimate outcome of that particular treatment will be good or poor so that treatment can be either continued or abandoned with confidence. Other PET tracers, such as amino acids and DNA substrates, also may be of value. The opportunities for further research are vast.

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