However, a comeback of nuclear medicine procedures in the study of soft tissue tumors has been observed. This is mainly due to the introduction of positron emission tomography (PET) into clinical diagnosis, resulting in a sensitivity and a specificity that are unattained by other imaging modalities.

There are two main reasons to perform scintigraphic procedures in the management of soft tissue tumors:

1. If the tumor takes up the radiopharmaceutical, metastases and recurrences will generally also do so. This, combined with the possibility of performing total body imaging and as many additional spot views as may appear necessary without increasing the radiation burden leads naturally to the use of radiotracer techniques in staging procedures and in follow-up.

2. Some radiopharmaceuticals appear to be taken up only by viable tumor cells, which makes it possible to distinguish between scar tissue and residual tumor in post-therapeutic follow-up.

### 4.2 Radiopharmaceuticals

Some radiopharmaceuticals have been used extensively in the workup of soft tissue tumors ([67Ga]gallium citrate, 99mTc-labeled sestamibi, 99mTc-MIBI, skeletal imaging agents).

More specific radiopharmaceuticals are increasingly being used: [123I]iobenguane (MIBG), 111In-labeled octreotide, and in particular [18F]fluorodeoxyglucose ([18F]FDG).

#### 4.2.1 Radiopharmaceuticals for General Use

Lesser-used radiopharmaceuticals in the diagnosis of soft tissue tumors include 99mTc-labeled red blood cells (RBC; restricted to the diagnosis of hemangiomas) [3, 8, 20, 52, 73, 77], 99mTc-labeled diethyltriamine pentaacetic acid (DTPA) [29], 99mTc-labeled pentavalent dimercaptosuccinic acid (DMSA(V)) [11, 48, 49, 69], and 111In-labeled antimony monoclonal antibodies or fragments.
which have been used especially in muscle tumors [17, 36, 37, 38, 45, 75]. None of these have become widely used, owing to the introduction of other imaging techniques with better sensitivity and/or specificity, in particular MRI and PET.

### 4.2.1.2 $^{67}$Ga Gallium Citrate

The mechanism of $^{67}$Ga uptake by tumors is still not completely understood. Larson et al. have suggested that $^{67}$Ga uptake in tumors is mediated by a cell-surface transferrin receptor [57].

However, soft tissue sarcomas have been reported to show a high avidity for $^{67}$Ga: sensitivities as high as 96% have been reported [80, 86]. Specificity (i.e., detecting only tumorous processes) is generally very good, except in patients with inflammation.

For a few weeks after radiotherapy or chemotherapy, $^{67}$Ga uptake in the tumor may be artificially decreased, perhaps through increased binding of iron to transferrin, displacing $^{67}$Ga [68]. Iron therapy, as well as scandum and gadolinium contrast agents, have been reported to decrease $^{67}$Ga uptake [33, 42, 97].

In a prospective study on 55 patients to evaluate the efficacy of gallium scintigraphy in detecting malignancy in any soft tissue mass, Schwartz et al. have reported a sensitivity of 96% and a specificity of 87%. Large and small sarcomas, irrespective of their fascial location, are identifiable by gallium imaging [80].

In a series of 56 patients with metastatic or recurrent soft tissue sarcoma, Southee et al. have reported $^{67}$Ga avidity to be closely associated with tumor grade, with the exception of mesothelioma. No relationship has been found between $^{67}$Ga avidity and cell type, lesion size, or disease site. The sensitivity for detection of metastases and recurrences is similar to that for the primary tumor (93% versus 91%). Tumor size is not a determining factor: high-grade lesions as small as 3\times3 mm have been detected, while low-grade lesions of more than 1 cm remain undetected. Due to liver and bowel activity, however, sensitivity in these areas is substantially lower (e.g., 56% for intrahepatic lesions) [86].

Kaposi sarcoma, which biologically behaves differently from other sarcomas, generally does not show $^{67}$Ga uptake. This feature may be used to distinguish Kaposi sarcoma from infection [76].

Imaeda et al. have conducted a study on 90 patients with soft tissue tumors of the extremities (19 malignant, 55 benign, 16 tumor-like lesions). Increased uptake of $^{67}$Ga was found in 78% of patients with malignant tumors, 25% of patients with benign tumors, and 31% of patients with other disorders. High uptakes were observed in liposarcoma, leiomyosarcoma, malignant lymphoma, neurinoma, extraabdominal desmoid, and sarcoidosis [41].

In 1994, Cogswell et al. published a 10-year review of bone and gallium scintigraphy in children with rhabdomyosarcoma. With respect to detection of metastatic disease in all tissues, gallium scans had a sensitivity of 84% (specificity 95%) and bone scans a sensitivity of 70% (specificity also 95%). When only patients with gallium-avid primary tumors were considered, gallium scan sensitivity for detecting metastases was 94% [16].

Lin et al. studied the value of bone and gallium imaging in 34 patients with malignant fibrous histiocytoma. Gallium scintigraphy sensitivity was 93% with respect to primary tumors and 100% for metastases [60].

From these studies, we can conclude that $^{67}$Ga imaging can have an adjunctive role in the staging of patients with soft tissue sarcomas and in identifying foci unsuspected clinically or radiographically, which are reported to be present in 9% [86] to 13% [80] of the patients. In particular, foci of active tumor within residual, post-treatment masses can be detected. Moreover a $^{67}$Ga-positive site that reverts to negative is indicative of a favorable response to therapy [86].

### 4.2.1.3 $^{201}$Tl Chloride

$^{201}$Tl is a monovalent cationic radionuclide with biological properties similar to those of potassium [26]. The mechanism of intracellular uptake is one of active transport, which makes thallium chloride a more accurate indicator of the viability of the tumor cells and of metabolic activity than radiotracers that are more flow dependent [66].

$^{201}$Tl in particular appears to reflect tumor activity more accurately than $^{67}$Ga, because of the larger nonspecific uptake of the latter, due to uptake by inflammatory lesions [40]. $^{201}$Tl can play a role in differentiating post-therapy changes from residual viable tumor tissue, local recurrence, or necrosis [95].

$^{201}$Tl chloride has been shown to have an affinity for a variety of soft tissue sarcomas [40, 51]. Terui et al. have reported a sensitivity of 81.2% for $^{201}$Tl and 68.8% for $^{67}$Ga in a group of 78 patients with soft tissue sarcomas and 22 patients with benign soft tissue tumors [90]. In a series of 29 patients previously treated for musculoskeletal sarcomas, Kostakoglu et al. found no correlation between different tumor types and $^{201}$Tl uptake [51]. However, a relationship was found between the tumor grade, the number of viable cells, and the vascular supply. The presence of necrosis decreased $^{201}$Tl uptake. The highest tumor-to-background ratio (TBR) was found in a patient with rhabdomyosarcoma and the lowest in one with low-grade osteosarcoma. The authors suggest that $^{201}$Tl is particularly valuable in distinguishing benign from malignant tissue. In their series, $^{201}$Tl scintigraphy performed better than other imaging modalities (CT, MRI, or angiography): sensitivity of
100% versus 95%, specificity of 87.5% versus 50%, and accuracy of 96.5% versus 82.7%.

In a series of 62 patients with bone and soft tissue tumors, Goto et al. evaluated sequential \(^{201}\text{Tl}\) scans on both early images and delayed images. Sensitivity, specificity, and accuracy in detecting malignant tumors was 94%, 65%, and 82% for early imaging and 94%, 85%, and 90%, respectively, for delayed imaging. They concluded that \(^{201}\text{Tl}\) scintigraphy, although showing some false-positive and false-negative findings, is a useful tool in differentiating malignant tumors from benign lesions [30].

4.2.1.4 \(^{99m}\text{Tc}\)-Labeled Sestamibi

Because of its similarity to \(^{201}\text{Tl}\), and also because of its better imaging characteristics, \(^{99m}\text{Tc}\)-MIBI has been proposed as a suitable radiotracer for use in imaging malignant tumors. In the specific area of soft tissue sarcomas, a few reports are available that explore these possibilities.

Taki et al. have compared the ability of \(^{201}\text{Tl}\) and \(^{99m}\text{Tc}\)-MIBI to detect and assess tumor response to chemotherapy in malignant and benign bone and soft tissue lesions. They studied 42 patients with various bone and soft tissue pathologies (29 malignant and 13 benign lesions). In quantitative analysis, the uptake ratios obtained with \(^{201}\text{Tl}\) and \(^{99m}\text{Tc}\)-MIBI were similar. In 11 patients with malignant tumors, \(^{201}\text{Tl}\) and \(^{99m}\text{Tc}\)-MIBI scintigraphy was repeated after chemotherapy, and the uptake of both tracers was significantly suppressed in patients with complete response confirmed by histological evaluation. The ability of \(^{99m}\text{Tc}\)-MIBI to detect malignant and benign bone and soft tissue lesions and to assess tumor response to chemotherapy was comparable with that of \(^{201}\text{Tl}\). In addition blood flow was assessed by means of radionuclide angiography with \(^{99m}\text{Tc}\)-MIBI [88].

Nagaraj et al. studied the usefulness of serial \(^{99m}\text{Tc}\)-MIBI scans in evaluating the tumor response to preoperative chemotherapy in 28 patients with bone (\(n=10\)) and soft tissue sarcomas (\(n=18\)). They concluded that \(^{99m}\text{Tc}\)-MIBI is an excellent indicator of tumor viability. Serial scans provide an accurate correlation between MIBI uptake and histological response to treatment, which allows optimization of chemotherapy prior to limb salvage [67].

Garcia et al. compared the diagnostic accuracy of FDG-PET and \(^{99m}\text{Tc}\)-MIBI single-photon emission CT (SPECT) in 48 patients with clinically suspected recurrent or residual musculoskeletal sarcomas. The diagnostic sensitivities and specificities were 98% and 90% using \(^{18}\text{F}\)FDG, and 82% and 80% using \(^{99m}\text{Tc}\)-MIBI, respectively. Four of nine patients with positive FDG but negative MIBI scans failed to respond to multidrug therapy (see also Comparison with Other Radiotracers, Sect. 4.2.4.1) [25].

\(^{99m}\text{Tc}\)-MIBI has also been proposed as an indicator for multidrug resistance, both in vitro [6] and in vivo [13]. Multidrug resistance, which is a major limitation in chemotherapy, has been associated with amplification or increased expression of the \(ABCB1\) [ATP-binding cassette, sub-family B (MDR/TAP), member 1] multidrug gene and overproduction of its product, the transporter glycoprotein Pgp (P-glycoprotein), which causes washout of intracellular cytostatic drugs [46]. Several reports suggest that intracellular MIBI is also eliminated by Pgp, so that MIBI could be used for multidrug resistance scintigraphy in vivo.

Taki et al. studied \(^{99m}\text{Tc}\)-MIBI as a functional imaging agent that reflected Pgp expression in malignant bone and soft-tissue tumors in 30 patients. The washout ratio of \(^{99m}\text{Tc}\)-MIBI was higher in patients with a high Pgp expression than in patients without. They concluded that \(^{99m}\text{Tc}\)-MIBI scintigraphy with washout analysis may be a useful method for evaluating Pgp overexpression and its function (washout of intracellular cytostatic drugs) [89].

De Moerloose et al. evaluated the usefulness of \(^{99m}\text{Tc}\)-MIBI scintigraphy in the screening of neural crest tumors for the presence of Pgp. They studied ten children suffering from proto-oncogene \(MYCN\)-negative neuroblastoma, ganglioneuroblastoma or ganglioneuroma. In nine of ten patients they found that the intratumoral \(^{99m}\text{Tc}\)-MIBI activity was comparable with the background activity, suggesting the presence of Pgp. In one patient \(^{99m}\text{Tc}\)-MIBI enhancement was seen in the primary tumor and the bone marrow metastases, and this result was concordant with a negative Pgp status [19].

4.2.1.5 Skeletal Imaging Agents

\(^{99m}\text{Tc}\)-labeled phosphate compounds, which were originally intended for skeletal imaging, are also known to be taken up by a wide variety of soft tissue abnormalities, including various soft tissue tumors [14]. Several authors have suggested radiophosphate uptake to correlate with blood flow, hypervascularity, and microscopic calcification in the tumor [7, 71].

In a series of 113 patients with soft tissue masses, Chew et al. found that all but one of the patients with normal scans (28 of 29) had benign processes or no identifiable lesion at all. However, many other benign lesions did demonstrate radionuclide uptake (e.g., some angiolipomas, hematomas, lipomas, neurofibromas, myxomas; Figs. 4.1, 4.2) [12]. Moreover, soft tissue trauma, including surgical incisions, can produce focal uptake on the scan. Therefore confusion can arise if the patient has recently undergone biopsy.

Bone metastases from primary soft tissue sarcomas are unusual. Felix et al. [24] detected no metastases on
the radionuclide bone scans of 59 patients with sarcomas, and Chew et al. [12] found metastases on the bone scans of only 5 of 80 sarcoma patients (Fig. 4.3). The value of the radionuclide bone scan in the preoperative workup of soft tissue tumors lies therefore in the evaluation of the relationship of the primary tumor to adjacent bone rather than in the detection of metastases.

**Fig. 4.1.** Intramuscular myxoma of the left musculus vastus lateralis in a 38-year-old woman. Anterior view (planar scintigraphy). Scintigraphy with the skeletal imaging agent $^{99m}$Tc-labeled methylene diphosphonate shows a large oval zone of slightly increased tracer uptake, lateral from the left femur, at about mid-shaft. The tumor shows a relatively less pronounced uptake in the center of the distal half, corresponding to a glazy substance found at biopsy.

**Fig. 4.2.** Low-grade hemangiopericytoma within the greater pelvis of a 53-year-old woman. Anterior view (from total body scintigraphy). This very large soft tissue tumor invaded the bone structures of the left iliac wing. Scintigraphy with $^{99m}$Tc-labeled methylene diphosphonate revealed a very intense, but inhomogeneous uptake in the tumor itself.

**Fig. 4.3a–c.** Soft tissue metastasis of an osteosarcoma in a 21-year-old man. **a** Anterior view (planar scintigraphy). **b** Three-dimensional reconstruction viewed from four different angles: anterior, left lateral, right posterior oblique, and right lateral (single-photon emission computed tomography, SPECT). **c** Transverse slice (SPECT) showing the large central uptake defect. An enormous abdominal soft tissue metastasis of a resected osteosarcoma of the left knee was found on follow-up bone scintigraphy images with $^{99m}$Tc-labeled methylene diphosphonate (**a, b**). The uptake is very intense but also very inhomogeneous, with a large central uptake defect (necrosis) (**c**).
Enneking has shown that increased uptake in bone adjacent to a soft tissue sarcoma indicates bone involvement [22]. Such involvement may also be present when the bone tracer accumulation in the soft tissue lesion itself is contiguous with the bone and cannot be separated even on appropriate multiple scan views. Because adequate surgical resection of aggressive tumors requires complete removal of all involved structures, the bone scan may be useful when knowledge of the tumor’s relationship to bone is critical for planning the appropriate operative treatment.

4.2.2 Specific Radiopharmaceuticals

4.2.2.1 Iobenguane

Iobenguane (MIBG), a norepinephrine analog, radio-labeled with either $^{123}$I or $^{131}$I, accumulates in neural crest-derived tumors [96]. Since MIBG uptake depends on the active transport of the radiopharmaceutical into viable tumor cells, it is a highly specific test to assess tumor activity. Normal uptake sites of MIBG are salivary glands, myocardium, liver, gut, and bladder. Normal adrenal glands are frequently seen when $^{123}$I-MIBG is used, but seldom visualized with $^{131}$I-MIBG.

The high sensitivity and specificity of this tracer have been well established for the detection of primary and metastatic neuroblastoma sites [34, 64, 70]. In a series of 745 scintigraphic studies on 150 patients with neuroblastoma (of whom 143 were children), Hoefnagel et al. found a sensitivity of 96%, detecting multiple tumor sites regardless of the location [35]. When analyzing the results of the major series of $^{131}$I-MIBG scanning reported in the world literature involving 776 patients, they found a cumulative sensitivity of 91.5% (range 76.6–96.3%) with very high specificity (range 88–100%). In four studies, totaling 300 patients, the specificity was found to be 100%.

A report by Rufini showed that SPECT imaging may identify additional sites of disease and allow better anatomical localization in patients with neuroblastoma [78].

MIBG has also been used in the detection of paragangliomas. Maurea et al. compared MIBG, CT, and MRI in the preoperative and postoperative evaluation of paragangliomas in 36 patients [65]. Preoperatively, CT and MRI were more sensitive (100% for both) than MIBG (82%), but MIBG was more specific (100% versus 50% for both CT and MRI). Postoperatively, MIBG and MRI were more sensitive (83% for both) than CT (75%), but again MIBG was more specific (100% versus 67% for both CT and MRI).

MIBG scintigraphy provides an additional method of locating paragangliomas, which can be effective even when anatomy has been distorted by tumor growth or previous surgery [84]. MIBG is also useful for assessing extra-adrenal or unexpected disease [65].

As well as in tumor detection, MIBG also has an important role to play in therapy: when a tumor accumulates MIBG, it may be treated with therapeutic doses of $^{131}$I-MIBG, with encouraging results [92].

4.2.2.2 Somatostatin-Receptor Scanning

Somatostatin membrane receptors have been identified on many cells and tumors of neuroendocrine origin, including neuroblastomas and paragangliomas [56]. The somatostatin analog octreotide has been shown to bind to somatostatin receptors on both tumorous and nontumorous tissues.

As a result, $^{111}$In-labeled octreotide (Octreoscan) scintigraphy is a simple and specific technique with which to demonstrate somatostatin receptor-positive localizations.

Using $^{111}$In-labeled octreotide scintigraphy, Kwekkeboom et al. reported a sensitivity of 94% in 25 patients with 53 known paraganglioma lesions [55]. Moreover, in 9 of these 25 patients (36%), unexpected additional paraganglioma sites undetected by conventional imaging techniques were found. This finding is of special interest, since multicentricity and distant metastases have each been reported to occur in only 10% of patients based on information from conventional imaging techniques [31]. The true frequency of multifocality may therefore have been underestimated previously. In this respect, one of the major advantages of octreotide scintigraphy is in identifying multiple tumor sites in one whole body examination. Krenning therefore advocates the use of octreotide scanning as a screening test, to be followed by CT, MRI, or ultrasonography at the sites at which abnormalities are found (Fig. 4.4) [53].

Apart from its merit in tumor localization, in vivo somatostatin receptor imaging, as a result of its ability to demonstrate somatostatin receptor-positive tumors, can be used to select those patients who are likely to respond favorably to octreotide treatment. In addition, octreotide scintigraphy may be used to monitor the efficacy of therapy.

In 2002, Lebtahi et al. compared the sensitivity of $^{111}$In-labeled octreotide and $^{99m}$Tc-P829, a new $^{99m}$Tc-labeled somatostatin analog, in 43 patients with neuroendocrine tumors. They concluded that, for the detection of neuroendocrine tumors, $^{111}$In-labeled octreotide clearly remained the most sensitive tracer [58].
4.2.3 Positron-Emitting Radiopharmaceuticals

The use of PET in oncology is increasing at a very rapid rate, primarily thanks to the increased use and widespread availability of [18F]FDG. FDG-PET does not replace other imaging modalities such as CT or MRI, but appears to be very helpful in specific situations in which CT or MRI have known limitations, such as differentiation of benign from malignant lesions, differentiation of posttreatment changes from residual or recurrent tumor, differentiation of benign from malignant lymph nodes, monitoring of therapy, and detection of unsuspected distant metastases [18]. The unique capability of PET to perform an easy whole-body survey adds significant value to this technique. Besides [18F]FDG, other radiopharmaceuticals are being used, albeit mainly in research settings so far.

4.2.3.1 [18F]Fluorodeoxyglucose

Detection of Soft Tissue Neoplasms and Differentiation of Benign from Malignant Lesions. The substantial elevation of glucose uptake and retention by tumors compared with most nonneoplastic tissue is fundamental to FDG-PET imaging in oncology [94]. In 2003 Aoki et al. studied 114 soft tissue masses (80 benign and 34 malignant) with FDG-PET. They evaluated the standardized uptake value (SUV) of [18F]FDG for preoperative differentiation between benign and malignant soft tissue masses. There was a statistically significant difference in SUV between benign and malignant soft tissue masses in total, although a considerable overlap in SUV was observed. Liposarcomas and synovial sarcomas did not show significantly higher SUV than any benign lesions, while some benign lesions such as sarcoidosis and giant cell tumors of the tendon sheath, showed an SUV as high as that of high-grade soft tissue sarcomas [2].

Feldman et al. studied the usefulness of FDG-PET in detection, analysis, and management of musculoskeletal lesions. From the 45 lesions studied, 19 cases were soft tissue tumors. Overall sensitivity, specificity, and accuracy for differentiating malignant from benign osseous and nonosseous lesions were 91.7%, 100%, and 91.7% (Fig. 4.5) [23].

Schwarzbach et al. investigated the use of FDG-PET in 42 patients with suspected liposarcomas. Pathology investigations revealed 11 primary liposarcomas, 14 locally recurrent liposarcomas, 5 other sarcomas, 1 lymphoma, and 11 benign lesions. [18F]FDG uptake was increased in higher-grade liposarcomas, while most low-grade liposarcomas presented a low [18F]FDG uptake. Pleomorphic, mixed, and myxoid liposarcomas showed an increased [18F]FDG uptake [83].

Cardona et al. investigated the use of FDG-PET to assess the nature of neurogenic soft tissue tumors in 25 patients (13 malignant peripheral nerve sheath tumors and 12 benign lesions). [18F]FDG uptake was significantly higher in malignant peripheral nerve sheath tumors than in benign lesions. They concluded that FDG-PET allows discrimination of benign from malignant neurogenic tumors (Fig. 4.6) [10].
but low-grade soft tissue sarcomas ($n$=7) could not be differentiated from benign lesions. Using a quantitative assessment, there was 95% sensitivity and 75% specificity in diagnosis of soft tissue sarcoma [63].

Adler et al. studied 25 patients with mass lesions involving the musculoskeletal system. There were 6 benign lesions and 19 malignant lesions of various grades. The high-grade malignancies had significantly greater uptake of $^{18}$F-FDG than the benign lesions and low-grade malignancies combined [1]. Because soft-tissue sarcomas are often heterogeneous, with large areas of necrosis and hemorrhage, FDG-PET can guide the biopsy to a region with the highest-grade tumor [18, 32].

Detection of Residual or Recurrent Soft Tissue Tumors and Differentiation of Posttreatment Changes.

Johnson et al. studied the role of FDG-PET in the detection of local recurrent and distant metastatic sarcoma in 28 patients. FDG-PET detected all 25 cases of local and distant recurrences with 100% sensitivity, while CT was able to detect 18 of the 22 cases of recurrent disease and MRI detected 5 of 7 cases of recurrence. FDG-PET was particularly useful in patients with extensive histories of surgery and radiation therapy, precisely the setting in which CT and MRI have the lowest specificity and sensitivity (Fig. 4.8) [43].

Beaulieu et al. studied the use of FDG-PET in nine patients with schwannomas. They concluded that schwannomas often have a high level of $^{18}$F-FDG uptake and distinguishing schwannomas from malignant peripheral nerve sheath tumors before biopsy or surgery is not possible (Fig. 4.7) [4].

In a report by Schulte et al., an evaluation is given of the usefulness of FDG-PET in patients with suspected soft tissue neoplasms. In 102 patients the uptake of $^{18}$F-FDG was evaluated semiquantitatively by determining the TBR. All patients underwent biopsy, resulting in the histological detection of 39 high-grade sarcomas, 16 intermediate-grade sarcomas, 11 low-grade sarcomas, 25 benign tumors, 10 tumor-like lesions such as spontaneous myositis ossificans (in 6 patients), and 1 non-Hodgkin lymphoma. All lesions except 2 lipomas showed an increased $^{18}$F-FDG uptake. Using a TBR cutoff level of 3.0 for malignancy, the sensitivity of FDG-PET was 97.0%, the specificity 65.7%, and its accuracy 86.3%. Except for patients with pseudotumoral myositis ossificans, lesions with a TBR of more than 3 were sarcomas (91.7%) or aggressive benign tumors (8.3%). Tumors with a TBR of less than 1.5 were latent or active benign lesions exclusively. The group with intermediate TBR values (less than 3 and more than 1.5) had primarily latent or active benign lesions, but also 4 aggressive benign tumors and 2 low-grade sarcomas [79].

Lucas et al. studied the value of FDG-PET in patients presenting with soft tissue masses. Thirty-one masses were removed from 30 patients: 12 were benign and 19 were malignant soft tissue sarcomas. Using qualitative assessment of the FDG-PET images, all the high-grade soft tissue sarcomas ($n$=12) were correctly identified, but low-grade soft tissue sarcomas ($n$=7) could not be differentiated from benign lesions. Using a quantitative assessment, there was 95% sensitivity and 75% specificity in diagnosis of soft tissue sarcoma [63].

Schwarzbach et al. reported 50 patients with 59 masses that were potentially either suspicious primary or locally recurrent soft tissue sarcomas. FDG-PET was performed and SUV was calculated in tumor and normal muscle. Local recurrence was detected with a sensitivity of 88% and a specificity of 92%. All intermediate-grade and high-grade soft tissue sarcomas were clearly visual-
ized, while 50% of low-grade sarcomas showed a $[^{18}F]$FDG uptake equivalent to muscle. Benign soft tissue tumors did not accumulate $[^{18}F]$FDG [82].

Bredella et al. studied the potential of FDG-PET to distinguish viable tumor from changes caused by therapy in areas with equivocal MRI findings in patients with musculoskeletal sarcomas. They evaluated 12 patients with a history of bone or soft tissue sarcoma who had undergone various treatments and who presented with clinically suspected recurrent or residual tumor. In 9 patients MRI was equivocal and in 5 of these patients PET images showed increased $[^{18}F]$FDG uptake, suggestive of recurrent tumor, which was confirmed by biopsy. In 4 patients FDG-PET showed no increased uptake and no tumor recurrence was found [9].

Lucas et al. compared the results of FDG-PET with those of MRI for the detection of local recurrence, and with CT of the chest for the detection of pulmonary metastases. They studied 62 patients who had 15 types of soft tissue sarcoma. For the detection of local disease, the sensitivities for FDG-PET and MRI were 74% and 88%, respectively, while the specificities for both techniques were 94% and 96%, respectively. For the identification of lung metastases, the sensitivities for FDG-PET and CT were 87% and 100%, respectively, while the specificities for both techniques were 100% and 96%, respectively [62].

Kim et al. reported on a prospective study in 43 patients with previously treated musculoskeletal sarcoma, in which they tried to distinguish between residual or recurrent tumors and posttreatment nonmalignant changes [47]. FDG-PET appeared to be useful in detecting metabolically active musculoskeletal sarcomas (sensitivity 98%, specificity 89%, positive predictive value 98%, negative predictive value 89%).

In a large group of 81 patients with proven musculoskeletal sarcomas, Korkmaz et al. compared the value of FDG-PET, $[^{11}C]$methionine PET, and MRI and CT in differentiating recurrent or residual tumor from posttherapy changes [50]. FDG-PET showed a better overall performance than MRI and CT, which in turn both performed better than $[^{11}C]$methionine (Table 4.1).

**Table 4.1.** Performance of $[^{18}F]$fluorodeoxyglucose (FDG) PET, $[^{11}C]$methionine (MET) PET, and magnetic resonance imaging (MRI) or computed tomography (CT) in musculoskeletal sarcomas [50].

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<thead>
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<th>$[^{18}F]$FDG PET (%)</th>
<th>MRI/CT (%)</th>
<th>$[^{11}C]$MET PET (%)</th>
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<tr>
<td>Sensitivity</td>
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<td>93</td>
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<td>Negative predicted value</td>
<td>87</td>
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**Monitoring of Therapy.** Stroobants et al. evaluated whether FDG-PET can be used for the early evaluation of response to imatinib mesylate treatment in soft tissue sarcomas. They performed FDG-PET in 21 patients (17 gastrointestinal stromal tumors, 4 other soft tissue sarcomas) prior to and 8 days after the start of treatment. PET response was observed in 13 gastrointestinal stromal tumors (11 complete responders, 2 partial responders), followed by CT response in 10 of these patients af-
Loskeletal sarcomas. The changes depended on the type of neoadjuvant therapy administered (chemotherapy or combined radiotherapy and hyperthermia): in the tumors treated with combined radiotherapy and hyperthermia, well-defined regions of absent [18F]FDG uptake developed within responsive tumors. Pathological examination showed that this was due to necrosis. In tumors treated with chemotherapy, [18F]FDG accumulation decreased more homogeneously throughout the tumor in responsive cases. Despite 100% tumor-cell kill in some patients, persistent tumor [18F]FDG uptake was observed which correlated with uptake within benign therapy-related fibrous tissue at pathological examination [44].

Similar findings have been reported by another group of investigators, who performed FDG-PET to evaluate the response to hyperthermic isolated limb perfusion for locally advanced soft tissue sarcomas. On the basis of the pretreatment glucose consumption in soft tissue sarcomas, they could predict the probability of a patient’s achieving complete response confirmed at pathological examination after hyperthermic isolated limb perfusion. FDG-PET findings gave an indication of the tumor response to hyperthermic isolated limb perfusion, although the lack of specificity of [18F]FDG, in terms of differentiation between an inflammatory response and viable tumor tissue, hampered the discrimination between complete response and partial response at pathological examination [27].

Assessment of Prognosis. Eary et al. studied tumor maximum [18F]FDG uptake (SUVmax) for its ability to predict patient survival and disease-free interval. They imaged 209 patients with sarcoma prior to treatment with neoadjuvant chemotherapy or resection. The multivariate analyses showed that SUVmax information is a statistically significant independent predictor of patient survival and disease progression. In general, tumors that are more metabolically active (with high SUVmax) are more aggressive, as this increased metabolism reflects cell proliferation, vascularity increase, and cell activity [21].

Methodological Factors Affecting the Ability of FDG-PET to Assess Tumor Malignancy. Lodge et al. studied 29 patients with soft tissue masses, using a 6-h scanning protocol, and various indices of glucose metabolism were compared with histological grade. High-grade sarcomas were found to reach a peak activity concentration approximately 4 h after injection, whereas benign lesions reached a maximum within 30 min. This translated to improved differentiation between these two tumor types using a standardized uptake value derived from images acquired at later times. A standardized uptake value measured 4 h after injection was...
found to be as useful an index of tumor malignancy as the metabolic rate of \([1^{18}F]FDG\) determined by means of either Patlak or nonlinear regression techniques. These indices each had a sensitivity and specificity of 100% and 76%, respectively, for the discrimination of high-grade sarcomas from benign tumors [61].

**Comparison with Other Radiotracers.** Kushner et al. studied the utility of FDG-PET in 51 patients with high-risk neuroblastoma. FDG-PET was equal or superior to MIBG for identifying neuroblastoma in soft tissue and extracranial skeletal structures, for revealing small lesions, for delineating the extent of disease and for localizing disease sites. FDG-PET and MIBG scans showed more skeletal lesions than bone scans, but the normally high physiological brain uptake of \([1^{18}F]FDG\) blocked PET visualization of cranial vault lesions [54].

Shulkin et al. reported on a study on seven patients with neuroblastoma, using \([1^{11}C]\)-hydroxyephedrine (HED) PET. They showed that HED uptake in neuroblastomas was rapid: tumors were evident on images within 5 min following i.v. injection. Such imaging is limited, however, by the short half-life of the \(^{11}C\) label (20.3 min). In addition, these tumors were also visualized using \([^{123}I]\)MIBG. The advantage of HED over MIBG is the possibility of very early imaging after administration (5 min versus 18–24 h) [85].

Garcia et al. compared the diagnostic accuracy of FDG-PET and \(^{99m}\)Tc-MIBI SPECT in 48 patients with clinically suspected recurrent or residual musculoskeletal sarcomas. The diagnostic sensitivities and specificities were 98% and 90% with \([^{18}F]FDG\), and 82% and 80% using MIBI, respectively. The tumors were demonstrated better in \([^{18}F]FDG\) studies, which produced higher visual grades (2.1 versus 1.6), and the tumors showed increasing standardized uptake values with time (from 6.3 to 7.3). Four of nine patients with tumors evident on FDG-PET images but not visible on \(^{99m}\)Tc-MIBI SPECT images failed to respond to multidrug therapy [25].

Schwarzbach et al. evaluated three different PET radiotracers \([^{18}F]FDG,\ [^{11}C]\)aminoisobutyric acid, AIB, and \(^{15}O\)-labeled water) for imaging and detection of local recurrence of soft tissue sarcomas. They studied 21 patients, who had: 9 primary soft tissue sarcomas, 5 recurrent soft tissue sarcomas, and 10 lesions suspicious for local recurrence. All tracers accumulated in soft tissue sarcomas with no difference between primary and locally recurrent tumors. Of 10 patients with suspected recurrence, 6 presented neither PET criteria for recurrence nor confirmation of recurrence in the specimens or during follow-up, while 4 patients with positive PET scans were ultimately diagnosed with local failure [81].

### 4.2.3.2 \(^{18}F\)-Labeled Dihydroxyphenylalanine

Becherer et al. studied the use of \(^{18}F\)-labeled dihydroxyphenylalanine \((^{18}F\)-DOPA) as PET tracer in 21 patients with histologically verified neuroendocrine tumors in advanced stages. FDOPA-PET was most accurate in detecting skeletal lesions (sensitivity 100%, specificity 91%) but was insufficient in the lung (sensitivity 20%, specificity 94%). Somatostatin-receptor scintigraphy was less accurate than \([^{18}F]\)-DOPA-PET in all organs. In about 40% of patients, initial CT failed to detect bone metastases shown by PET that were later verified by radiological follow-up [5].

Hoeğerle et al. reported on a patient with metastasizing carcinoid in whom various imaging procedures were not successful in detecting the primary tumor. PET with \([^{18}F]\)-DOPA enabled localization of a potential primary tumor in the ileum. Moreover it detected an unknown mediastinal lymph node metastasis and a pulmonary metastasis [39].

### 4.2.3.3 \(^{18}F\)Fluorodeoxythymidine

Cobben et al. studied the feasibility of \([^{18}F]\)-3'-fluoro-3'-deoxy-L-thymidine PET (FLT-PET) for the detection and grading of soft tissue sarcomas of the extremities in 19 patients. FLT uptake resulted in visualization of the tumors and facilitated differentiation between low-grade and high-grade soft tissue sarcomas. The uptake of FLT correlated with the proliferation of soft tissue sarcoma [15].

### 4.2.3.4 \(^{11}C\)Choline

The use of short-lived PET tracers such as \([^{11}C]\)choline depends on the availability of a cyclotron near to a PET center (the half-life of \(^{11}C\) is 20 min). Zhang et al. compared the usefulness of \([^{11}C]\)choline PET with FDG-PET for the differentiation between benign and malignant bone and soft tissue tumors. They studied 43 patients with 45 lesions. The sensitivity, specificity, and accuracy of \([^{11}C]\)choline-PET were 100%, 64.5%, and 75.6%, respectively. The sensitivity, specificity, and accuracy of FDG-PET were 85.7%, 41.9%, and 55.6%, respectively. The \([^{11}C]\)choline uptake in the lesions correlated with \(^{18}F\)FDG uptake [98].

### 4.2.3.5 \(L\)-[\(1\)-\(11\)C]Tyrosine

Protein synthesis rate (PSR) can be assessed in vivo using PET with \(L\)-[\(1\)-\(11\)C]tyrosine (TYR-PET) [72]. Pruim et al. reported on a study in 13 patients with soft tissue tumors (9 sarcomas, 4 benign lesions) using dynamic
PET with L-[1-11C]tyrosine for visualization of the tumors and quantification of the PSR before and after therapy [74]. All malignant lesions were correctly identified. After therapy the PSR appeared to distinguish the patients with large tumor necrosis from patients with lesser tumor necrosis, suggesting a possible use as an indicator of therapeutic success.

Van Ginkel et al. investigated the use of TYR-PET in 17 patients undergoing hyperthermic isolated limb perfusion (HILP) with recombinant tumor necrosis factor alpha (rTNFα) and melphalan for locally advanced soft tissue sarcoma and skin cancer of the lower limb. TYR-PET studies were performed before HILP and 2 and 8 weeks afterwards, and the PSRs were calculated. All tumors were depicted as hot spots on PET studies before HILP. In the complete response group, the PSR was significantly lower at 2 and 8 weeks after perfusion than before HILP. With a threshold PSR of 0.91, the sensitivity and specificity of TYR-PET were 82% and 100%, respectively. The predictive value of a PSR of more than 0.91 for having viable tumor after HILP was 100%, whereas the predictive value of a PSR of 0.91 or less for having nonviable tumor tissue after HILP was 75% [28].

4.2.3.6 Practical Use of PET Tracers

FDG-PET is a useful tool for the detection of soft tissue neoplasms and the differentiation of benign from malignant lesions. High-grade malignancies have significantly greater uptake of [18F]FDG than the combination of benign lesions and low-grade malignancies. Rarely, certain benign lesions can show a high level of [18F]FDG uptake, for example as in schwannomas. FDG-PET presents the metabolic activity of the entire tumor and can be used to prevent sampling error by guiding a biopsy to a region with the highest grade tumor.

For the detection of residual or recurrent soft tissue tumors, the reported results of FDG-PET range from slightly inferior to superior compared with MRI and CT. FDG-PET is particularly useful in patients with extensive histories of surgery and radiation therapy, precisely the setting in which CT and MRI have the lowest specificity and sensitivity. Additional value is added to the technique of FDG-PET by its capabilities of therapy-monitoring and the performance of an easy whole-body survey with the possibility of detection of unsuspected distant metastases.

The clinical role of other PET tracers in the initial staging and follow-up of soft tissue neoplasms remains to be determined and will be partially dependent on the availability of a cyclotron nearby a PET-center, in order to be able to use short-lived PET-tracers such as [11C]choline and [11C]tyrosine.

4.3 Clinical Applications

To summarize the preceding data, nuclear medicine procedures may have an important role in the clinical workup of soft tissue tumors. This role, however, has been greatly underestimated, owing to the rather disappointing results of previous nuclear medicine techniques.

The introduction of FDG-PET in clinical use has been a major step forward in nuclear medicine, and there is enough evidence for FDG-PET to be the nuclear medicine imaging modality of choice for detection, staging, and follow-up of soft tissue neoplasms. In addition, bone scintigraphy, MIBG scintigraphy, and somatostatin-receptor scanning maintain a specific role in clinical practice. The use of other tracers such as gallium, thallium chloride, and sestamibi will be restricted mostly to hospitals without a PET scanner or in more specific clinical situations, as with sestamibi for the evaluation of multidrug resistance.

4.3.1 Diagnosis

If PET is available, FDG-PET is the first choice for diagnosis, although [18F]FDG does not seem to be able to differentiate between low-grade malignancies and benign lesions. Furthermore, certain benign lesions can show a high level of [18F]FDG uptake, for example in certain inflammatory conditions and in schwannomas. FDG-PET presents the metabolic activity of the entire tumor and can prevent sampling error by guiding a biopsy to a region with the highest-grade tumor. If PET is not available, gallium, thallium chloride, or sestamibi can be used, preferably in the absence of inflammatory lesions. Histological diagnosis can be attempted, e.g., in tumors accumulating MIBG or somatostatin-receptor labels (neuroendocrine tumors), antimyosin (muscular tumors), or RBC (hemangiomas).

4.3.2 Staging

A generally very high sensitivity, combined with the possibility of total body scanning, makes nuclear medicine very helpful in the staging of tumors (evaluation of locoregional extension or search for unsuspected additional tumor sites not seen with other imaging modalities). Most radiopharmaceuticals ([18F]FDG, 67Ga, 201Tl, MIBI, MIBG, octreotide, antimyosin) are suited for this purpose, provided they accumulate at the primary tumor site.
An advantage of PET over traditional SPECT and planar whole body scintigraphy is the improved image quality with higher resolution, three-dimensional whole body imaging, facilitating the detection of smaller tumoral lesions. The role of bone scintigraphy in the preoperative workup is to evaluate involvement of bone structures adjacent to soft tissue tumors and, hence, to assess whether a broader resection is necessary.

### 4.3.3 Prognosis

Some nuclear medicine procedures provide prognostic information:

- The uptake of $^{[18F]}$FDG is reported to be an independent predictor of patient survival and disease progression. In general, tumors that are more metabolically active (with high $^{[18F]}$FDG uptake) are more aggressive.
- The uptake of $^{201}$Tl and $^{[18F]}$FDG is reported to correlate well with tumor grade.
- Accumulation of $^{111}$In-octreotide is proof of the presence of somatostatin receptors, and hence a favorable prognostic factor for somatostatin treatment; conversely, absence of $^{111}$In-octreotide uptake is associated with a poor prognosis for somatostatin treatment.
- Accumulation of MIBG enables the use of $^{131}$I-MIBG as a form of treatment.
- Fast tracer wash-out on sequential MIBI scans may be indicative of future multidrug resistance.

### 4.3.4 Therapy

As stated before, MIBG-accumulating tumors may be treated with $^{131}$I-MIBG and somatostatin receptor-positive tumors may be treated with radiolabeled octreotide.

### 4.3.5 Follow-up

Because they concentrate in viable cells only, some radiopharmaceuticals may be used to monitor the effect of the treatment. Moreover, they can be used to distinguish residual tumor masses and recurrence from nonmalignant posttreatment changes, such as fibrotic masses. This is reported to be the case with $^{[18F]}$FDG, $^{67}$Ga, $^{201}$Tl, MIBI, MIBG and octreotide. The increasing access to clinical PET facilities is resulting in a rapidly rising use of FDG-PET for this specific purpose.

### 4.4 Conclusion

After a rather long period of underutilization in the field of soft tissue tumors, nuclear medicine procedures have made a remarkable comeback. This is due to technical improvements, the introduction of newer, more specific radiopharmaceuticals, and the introduction of FDG-PET. As a result, nuclear medicine methods are now not only used in the more classic context of staging and follow-up, but also in diagnosis, therapy, and even prognosis of soft tissue tumors. The future availability of other specific radiopharmaceuticals (e.g., labeled monoclonal antibodies and more specific PET tracers) is likely to confirm and enhance the current evolution.

**Things to remember:**

1. If a primary tumor takes up a radiopharmaceutical, metastases and recurrences will generally also do so. This, combined with the possibility of performing easy total body imaging, forms the strength of nuclear medicine techniques in primary staging and in follow-up of soft tissue tumors.
2. The fact that some radiopharmaceuticals appear to be taken up only by viable tumor cells makes it possible to distinguish between scar tissue and residual tumor or tumor recurrence in post-therapeutic follow-up.
3. The introduction of FDG-PET in clinical use has been a major step forward in nuclear medicine, and there is enough evidence for FDG-PET to be the first-choice nuclear medicine imaging modality for detection, staging, and follow-up of soft tissue neoplasms.
4. FDG-PET does not replace other imaging modalities such as CT or MRI, but appears to be very helpful in specific situations in which CT or MRI have known limitations.
5. FDG-PET reveals the metabolic activity of the entire tumor and can prevent sampling error by guiding a biopsy to a region with the highest-grade tumor.
6. The uptake of FDG is reported to be an independent predictor of patient survival and disease progression.
7. Due to technical improvements and the introduction of newer, more specific radiopharmaceuticals, the role of nuclear medicine in the management of soft tissue tumors is likely to become more important in the future.
References


