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Musculoskeletal System

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Diagnostic imaging has played a major role in the evaluation of patients with cancers of the bone and soft tissue. The imaging modalities have included radiography, computed tomography, magnetic resonance imaging, and bone scintigraphy. Current experience suggests that functional imaging with positron emission tomography (PET) and [F-18]fluorodeoxyglucose (FDG) may also have an important role in the imaging evaluation of patients with bone and soft tissue sarcoma, including guiding biopsy, detecting local recurrence in amputation stumps, detecting metastatic disease, predicting and monitoring response to therapy, and assessing for prognosis. Prospective studies with large patient groups will be essential to define the exact diagnostic role of FDG PET in this clinical setting, which should also include an evaluation of the cost-effectiveness and the short-term and long-term benefits in clinical decision making and management. In this article, we review the diagnostic utility of dedicated PET and PET combined with computed tomography imaging system in the evaluation of patients with bone and soft tissue malignancies.
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Cancers of bone and soft tissue accounted for a total of 10,700 new cases and a total of 5200 cancer deaths in 2003.[1] There is no clear sex predominance. Malignant tumors of the bone include osteosarcoma, Ewing's sarcoma, lymphoma, chondrosarcoma, and parosteal osteosarcoma. Sarcomas of the soft tissues comprise a wide range of solid neoplasms with varied anatomic and morphologic characteristics. Diagnostic imaging has played a major role in the evaluation of patients with the cancers of the bone and soft tissue. The imaging modalities have included radiography, computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy.[2-4] Functional imaging with positron emission tomography (PET) and [F-18]fluorodeoxyglucose (FDG) also has been shown to be useful in the imaging evaluation of these patients. In this article, we review the diagnostic utility of dedicated PET and combined positron emission tomography-computed tomography (PET-CT) imaging systems in the evaluation of patients with bone and soft tissue malignancies.

Bone Tumors

Malignant tumors of the bone include osteosarcoma, Ewing's sarcoma, lymphoma, chondrosarcoma, and parosteal osteosarcoma. In this section, we focus our attention to central osteosarcoma, which is the most common primary bone malignancy in childhood and of all ages if multiple myeloma is excluded. The lesion most frequently involves the distal femur and proximal tibia and is usually metaphyseal. The Paget's sarcoma in the elderly more commonly affects the humerus, pelvis, and proximal femur. The principal traditional imaging findings demonstrate a productive lesion with bone disruption and production, soft tissue component, and marked tumor accumulation of bone seeking radiotracers. The natural history of osteosarcoma involves a rapid enlargement of the primary tumor with propensity for metastatic disease in the lungs, other bones, and lymph nodes. Long-term survival has improved with the introduction of multidrug adjuvant and neoadjuvant chemotherapy.[5]

Magnetic resonance imaging (MRI) is used to define the local extent of osteosarcoma in bone and soft tissue. However, signal abnormalities caused by peritumoral edema can result in an overestimation of tumor extension.[6] Scintigraphy has been used primarily to detect osseous metastases of these tumors at diagnosis and during follow-up. With osteosarcoma, skeletal scintigraphy occasionally demonstrates extraosseous (eg, lung) metastases as the result of osteoid production by the metastatic deposits. Because of the nonspecific appearance of viable tumor on MRI, variable results have been reported for assessing chemotherapeutic response in planning for limb salvage surgery.[7,8] Scintigraphy with Tl-201 has been shown to be useful for assessing therapeutic response in osteosarcoma.[9-12] Marked decrease in Tl-201 uptake by the tumor indicates a favorable response to chemotherapy. A change in therapy may be needed when tumor Tl-201 uptake does not decrease within weeks of chemotherapy. Tc-99 month MIBI has also been reported to be useful in the imaging evaluation of osteosarcoma.[13,14]

The exact role of FDG PET in osteosarcoma is unclear. However, current experience suggests that in patients with bone sarcomas, FDG PET may play an important role in guiding biopsy, detecting

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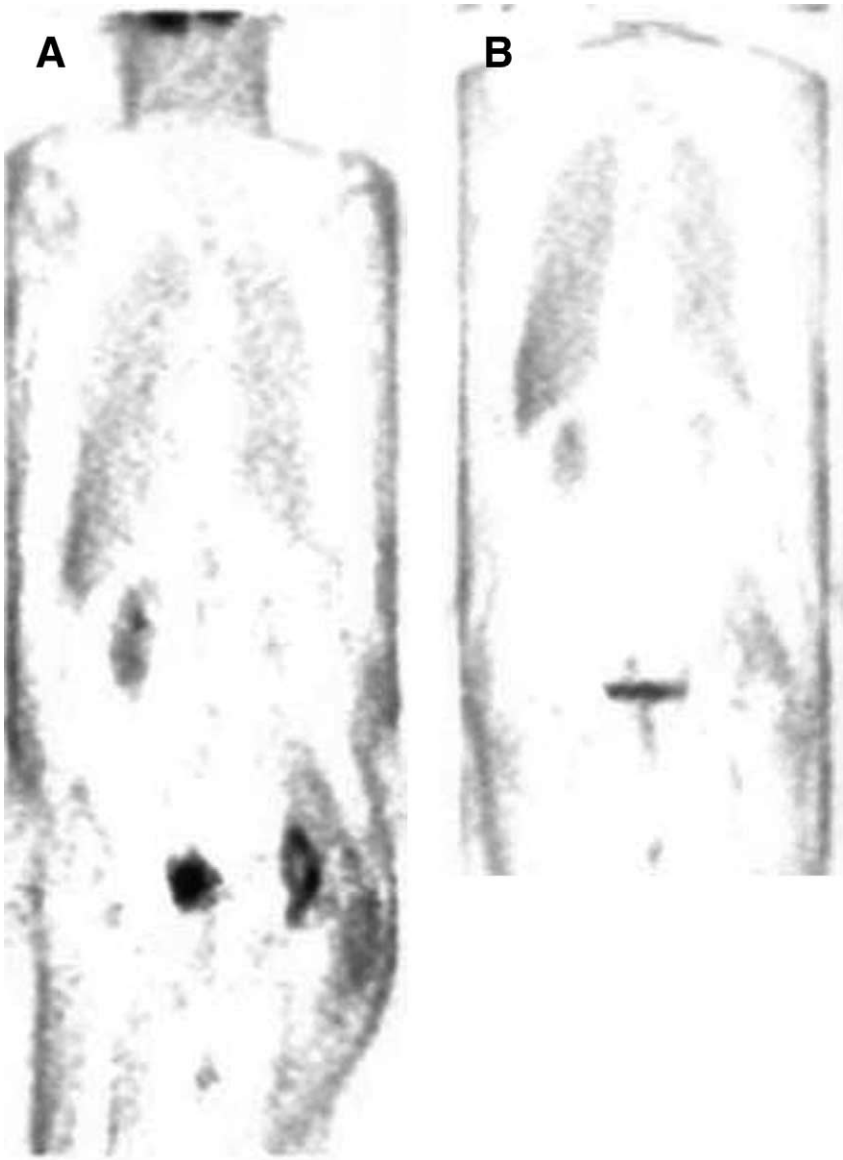

Figure 1 Shown is a 70-year-old male with left posteromedial ilial osteosarcoma. (A) Coronal FDG-PET before chemotherapy shows extensive hypermetabolism in the left ilial tumor and the adjacent soft tissue. (B) Coronal FDG-PET after chemotherapy shows marked decline in the extent and level of tumor metabolic activity compatible with favorable treatment response. The surgical specimen showed greater than 95% tumor necrosis.

local recurrence in amputation stumps, evaluating patients with suspected metastatic disease, monitoring response to therapy, and assessing for prognosis (Figs. 1 and 2).[15,16]

The potential utility of FDG-PET in the noninvasive differentiation of benign and malignant bone tumors has been studied.[17,18] Aoki and coworkers evaluated the standardized uptake value (SUV) of FDG in 19 malignant and 33 benign primary bone lesions.[18] There was a statistically significant difference in SUV between benign (2.18 ± 1.52) and malignant (4.34 ± 3.19) lesions. However, giant cell tumors (4.64 ± 1.05) showed significantly higher SUV than chondrosarcomas (2.23 ± 0.74) and had no statistically significant difference in SUV compared with osteosarcomas (3.07 ± 0.96). There was no statistically significant difference in SUV between fibrous dysplasias (2.05 ± 0.98) and osteosarcoma or chondrosarcomas. Therefore, FDG PET may be limited in distinguishing accurately malignant from benign bone tumors because of the high accumulation of FDG in some benign bone lesions. FDG-PET SUV analysis may, however, be useful in histologic grading and guiding biopsy toward the most metabolically active regions of large masses. The predictive value of SUV appears to be based on its correlation with such important underlying biological factors as cellularity, mitotic activity, K_i-67 proliferation index and p53 overexpression.[19]

FDG-PET may have some limitation in detecting local recurrence in the amputation stump. In one study, focal areas of uptake were associated with known pressure areas and skin breakdown for up to 18 months after surgery without any evidence of disease recurrence.[20] However, one should note that in the absence of localized clinical changes, stump hypermetabolism may represent local recurrence, and biopsy may be needed for definitive confirmation. For detecting lung metastases, FDG-PET may not be as sensitive as CT (50% versus 75%), although because of the high specificity of FDG-PET (98% versus 100%), a positive FDG-PET result can be used to confirm abnormalities seen on CT as metastatic disease.[21,22] In another study, FDG-PET and Tc-99m MDP bone scintigraphy were compared in detecting osseous metastases from osteosarcoma.[23] Diagnostic validation was by histopathological analysis, morphological imaging and clinical follow-up for 6 to 64 months (median, 20 months). Similar to the case with the limited sensitivity of FDG-PET in detecting pulmonary metastases, this study also reported that none of the five osseous metastases from osteosarcoma were detected by FDG-PET, but all of them were true-positive using bone scintigraphy. The use of the new combined PET-CT

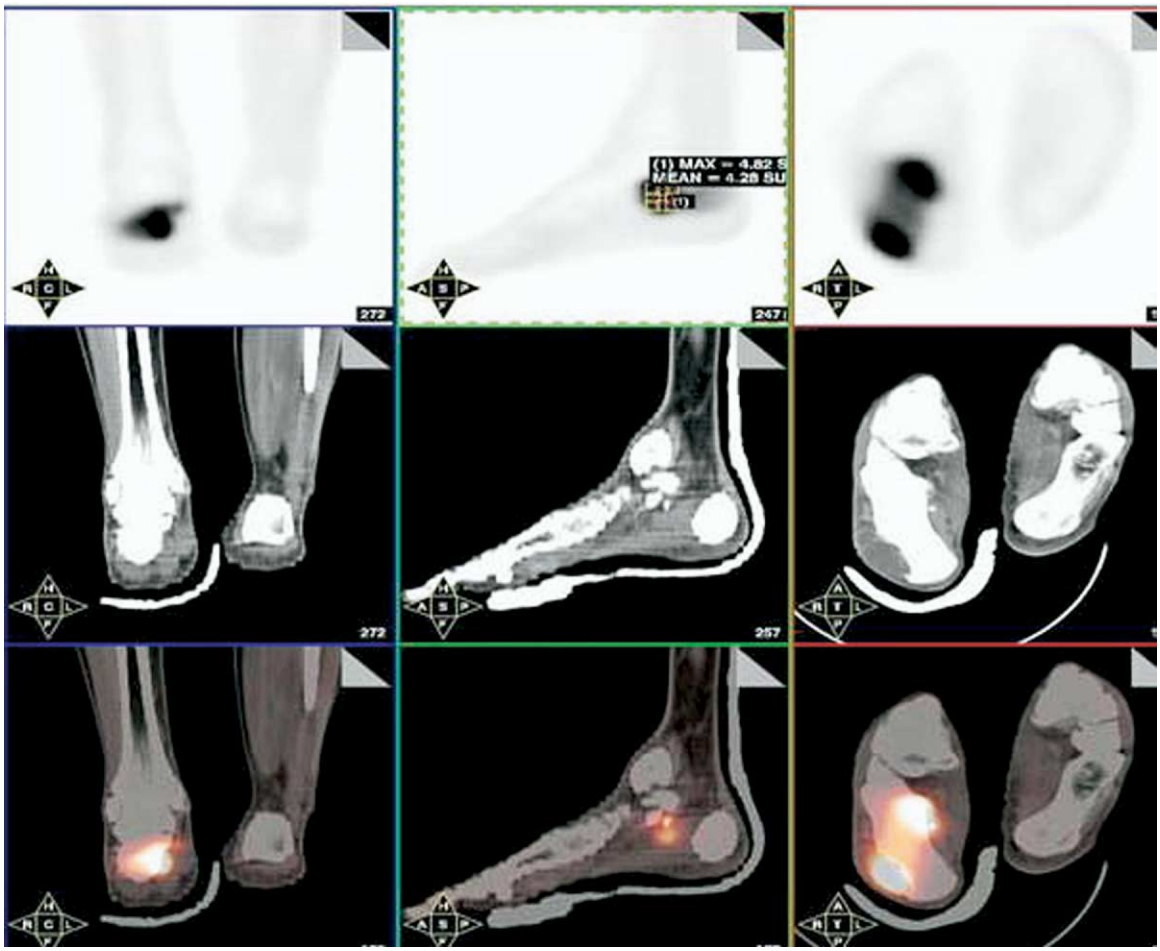

Figure 2 Shown is a 19-year-old male with left calcaneal osteosarcoma. PET-CT (upper panels: PET alone, middle panels: CT alone, lower panels: fused PET-CT) shows intense hypermetabolism (SUV = 3.5) in the tumor and the adjacent soft tissue. The patient was treated with below-the-knee amputation. (Coronal: left panel; sagittal, middle panel; axial: right panel.) (Color version of figure is available online.)

imaging systems will likely improve the accuracy of assessing for metastases by employing both the anatomic and metabolic diagnostic information.

FDG-PET has been reported to be useful as a noninvasive surrogate to predict treatment response in patients with bone tumors.[24-27] Hawkins and coworkers determined the correlation between FDG-PET imaging and chemotherapy response in 33 pediatric patients with osteosarcoma or Ewing's sarcoma.[27] All patients received standard neoadjuvant chemotherapy. FDG-PET standard uptake values before (SUV1) and after (SUV2) chemotherapy were analyzed and correlated with chemotherapy response assessed by histopathology in surgically excised tumors. The ratio of SUV2 to SUV1 (SUV2:SUV1) less than 30% to 40% predicted a favorable histologic response to chemotherapy (defined as ≥90% necrosis). FDG-PET also has been evaluated as an objective imaging method, in association with the current treatment protocols of the Cooperative Osteosarcoma Study (COSS), to monitor preoperative chemotherapy response in patients with osteosarcoma.[24] The tumor-to-background ratios of FDG uptake with PET before and after neoadjuvant chemotherapy were compared. With a tumor-to-background ratio cutoff level of 0.6, all responders and 8 of 10 nonresponders could be identified by FDG-PET.

The prognostic utility of FDG-PET in osteosarcoma has also been investigated. In 29 patients, Franzius and coworkers measured semiquantitatively the levels of FDG and Tc-99m MDP accumulation in the primary osteosarcoma at the time of diagnosis.[28] After chemotherapy, the patients underwent surgery for their primary tumor, and the response was determined histologically. Cumulative overall survival and event-free survival were determined by clinical and imaging follow-up. Both overall and event-free survivals were significantly better in patients with low FDG uptake in the tumor than in patients with high FDG accumulation in the tumor. FDG uptake values correlated moderately and positively with Tc99m MDP uptake values. Therefore, FDG uptake appears to be complementary to the other well-known factors in judging the prognosis in patients with osteosarcoma.

PET imaging with tracer other than FDG has also been reported. In one canine study, PET was performed after intravenous injection of the 18F-labeled Fab fragment of TP-3, a monoclonal antibody specific for human and canine osteosarcomas.[29] PET images demonstrated increased accumulation of the radiotracer at the primary tumor site relative to normal contralateral bone in as early as 15 minute after injection. F-18-fluoride ion PET, which provides quantitative high quality images of the skeleton, has also been investigated for the evaluation of the skeletal abnormalities including osteosarcoma.[16,30]

Soft Tissue Tumors

Soft tissue sarcomas are relatively rare. They comprise a wide variety of solid malignancies with diverse morphologic and anatomic character-

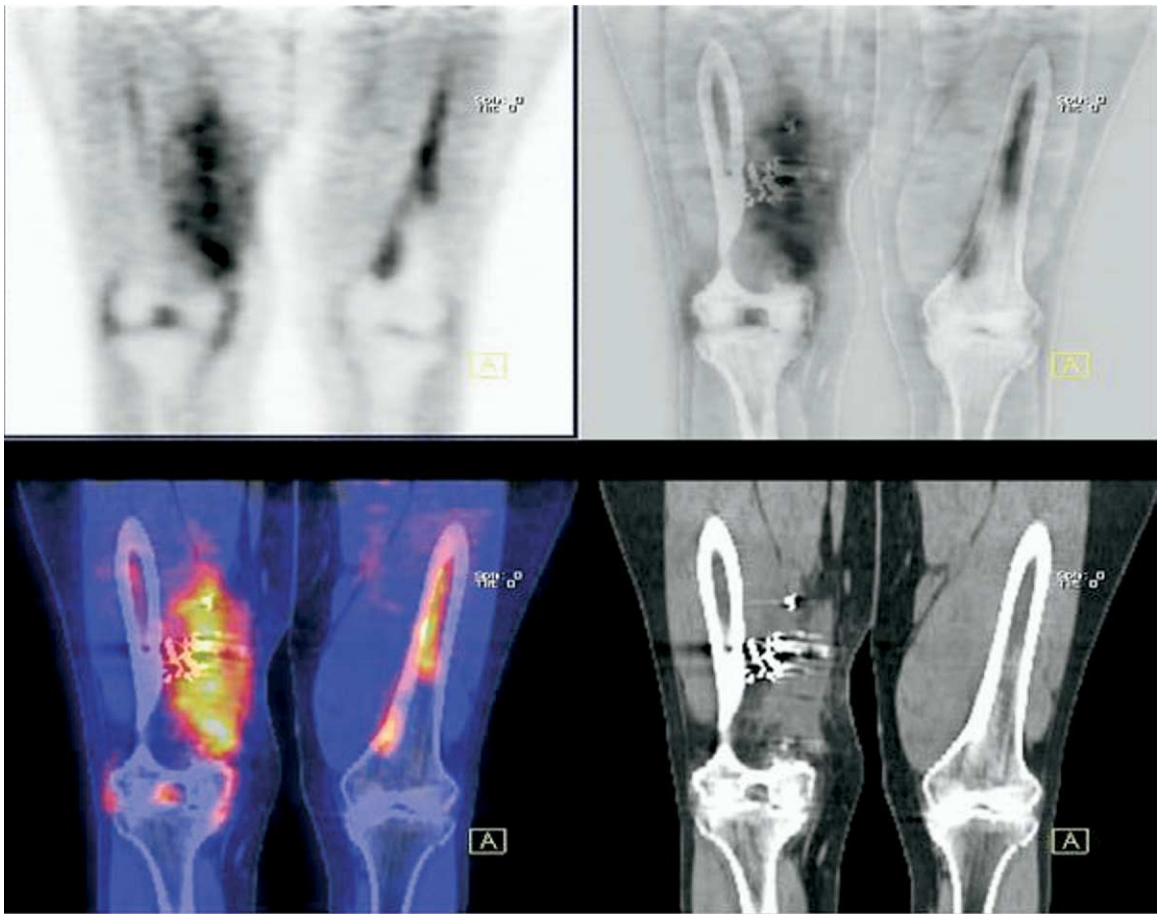

Figure 3 Shown is a 40-year-old male with right medial thigh angiosarcoma previously treated with resection. PET-CT shows hypermetabolic recurrent tumor in the surgical bed confirmed by biopsy. (Color version of figure is available online.)

istics.[31] The most common sites of initial presentation are the extremities followed in decreasing order of frequency by retroperitoneum/intraabdominal, trunk, genitourinary, visceral, and head and neck. Retroperitoneal and visceral sarcomas are more likely to metastasize than the extremity tumors. Similarly high-grade lesions and tumors larger than 5 cm are more likely to be associated with metastases. The predominant tumor subtypes include liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma, and fibrosarcoma.[31] Management of soft tissue sarcomas have evolved considerably. Aggressive tumor resection is the primary method of local control. For extremity sarcomas, limb-sparing surgery, which involves resection of tumor with a cuff of surrounding normal tissue at all margins and skeletal reconstruction, currently is the goal of therapy. Limb-sparing procedures can be appropriately performed in most patients by using the current chemotherapeutic regimens pre- and postoperatively and imaging to define tumor extent and viability.

Functional imaging with FDG-PET has been shown to be useful in directing biopsy, differentiating benign from malignant soft tissue masses, and predicting tumor grade, staging, restaging, and prognosis (Figs. 3 and 4).[32-38] Sarcomas in general tend to be highly FDG avid, although significant heterogeneity in glucose metabolism may be evident. Several single case reports and small case series have shown relatively high glucose metabolism in tumors such as angiosarcoma, liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma, chondrosarcoma, rhabdomyosarcoma, and gastrointestinal stromal tumors.[39-50] In view of significant intralesional morphologic variation of sarcoma, FDG-PET has been used to direct biopsy to the most metabolically active area of the lesion to improve the diagnostic yield.[51] The new combined PET-CT imaging will facilitate this application by providing the precise CT anatomic localization of the PET-directed metabolic abnormality.

Lucas and coworkers performed a prospective evaluation of the diagnostic utility of FDG PET in staging 30 patients with a soft tissue mass suspected to be malignant.[52] FDG-PET was 95% sensitive and 75% specific in diagnosing soft tissue sarcomas. Three patients had metastases at presentation and FDG-PET identified two of these patients correctly. Similar results in staging 62 patients with soft-tissue sarcomas were also reported by the same group of investigators in another study.[53] For detection of local disease, the sensitivity and specificity of FDG-PET were 73.7% and 94.3%, respectively, and those for MRI were 88.2% and 96.0%, respectively. For the identification of lung metastases, the sensitivity and specificity of FDG-PET were 86.7% and 100%, respectively, and those of chest CT were 100% and 96.4%, respectively. However, FDG-PET also identified other unexpected sites of metastases.[53]

Bastiaannet and coworkers conducted a systematic review and meta-analysis of 29 clinical studies on diagnostic value of FDG-PET in the detection, grading, and therapy response of soft tissue and bone sarcomas.[54] Pooled sensitivity, specificity, and accuracy of PET for the detection of sarcomas were 91%, 85%, and 88%, respectively. The differences between the mean SUV in malignant and benign tumors and that between low- and high-grade mixed sarcomas were statistically significant. Another similar meta-analysis reviewed the diagnostic performance of FDG-PET in grading of soft-

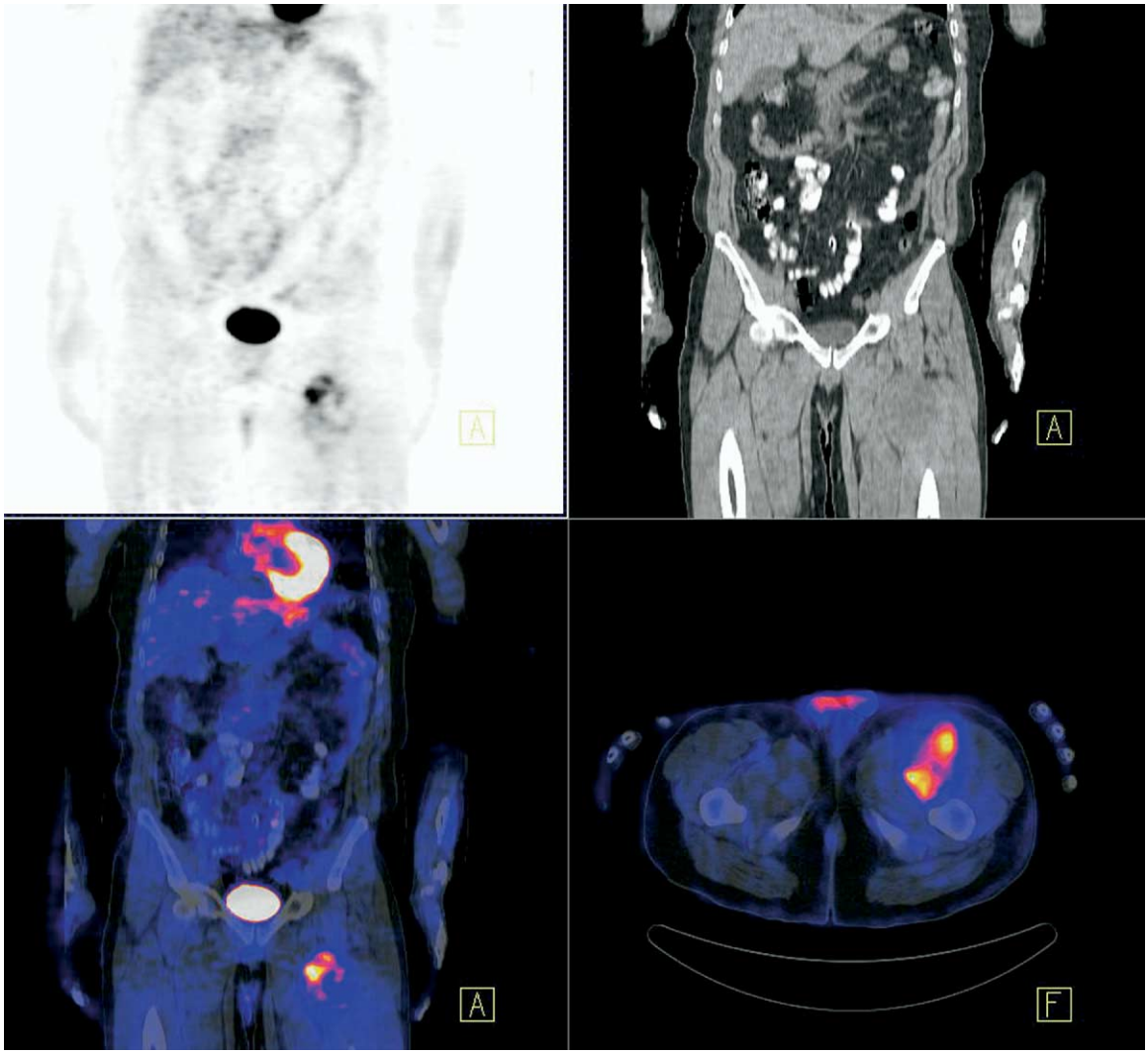

Figure 4 Shown is a 50-year-old male with a left anteromedial thigh liposarcoma. PET-CT shows intense hypermetabolism corresponding to the hypoattenuated tumor mass with a maximum SUV of 6.13. (Color version of figure is available online.)

tissue sarcomas in 15 clinical studies encompassing 441 soft-tissue lesions (227 malignant, 214 benign).[55] For diagnosis of malignant versus benign lesions, typical pairs of sensitivity and specificity estimates from the summary receiver operating characteristic curves were 92% and 73% for qualitative visualization, 87% and 79% for SUV of 2.0, and 70% and 87% for SUV of 3.0. Diagnostic performance was similar for both primary and recurrent lesions. Schwarzbach and coworkers reached a similar conclusion that SUV analysis correlates with tumor grade in soft tissue sarcomas and that FDG-PET can complement preoperative radiologic assessment for soft tissue sarcomas.[56] Although FDG-PET may be helpful in tumor grading but low-grade tumors and benign lesions may not be adequately discriminated.[57]

Quantitative dynamic PET with FDG kinetic analysis and determination of tumor metabolic rates have also been found to be useful in tumor characterization.[58-60] In one study using dynamic FDG-PET kinetic analysis, 84% of grade III tumors, 37.5% of grade II tumors, 80% of grade I tumors, 50% of lipomas, and 14.3% of scars could be classified correctly.[59] The authors concluded that evaluation of the full FDG kinetics can accurately discriminate grade I and grade III tumors at a positive predictive value of >80%.[59] In another study, quantitative FDG PET was employed to evaluate 29 patients with soft tissue masses.[60] Imaging was performed using a 6-h scanning protocol and various indices of glucose metabolism were compared with histological grade. Significant differences were observed in the time-activity responses of benign and high-grade tumors. High-grade sarcomas were found to reach a peak activity concentration at about 4 h after injection whereas benign lesions reached a maximum within 30 minute. An SUV measured 4 h after injection was found to be a useful index for discriminating high-grade sarcomas from benign tumors with a sensitivity of 100% and a specificity of 76%.[60]

An important diagnostic utility of FDG-PET has been in the early prediction and evaluation of therapy response in soft-tissue sarcoma (Figs. 5 and 6).[61-63] In one example, FDG-PET has been shown to be a sensitive method for evaluating an early response to imatinib mesylate (Gleevec/Glivec) treatment in gastrointestinal stromal tumors, which are soft tissue sarcomas of the gastrointestinal tract originating from mesenchymal cells. Successful treatment results in a sharp decline in tumor glucose metabolism in comparison with the high level of glucose metabolism in the tumor before therapy.[49,64-66] In another study, the diagnostic potential of FDG-PET was investigated in distinguishing viable tumor from changes caused by therapy in areas with equivocal MRI findings.[67] FDG-PET and gadopentetate dimeglumine-enhanced

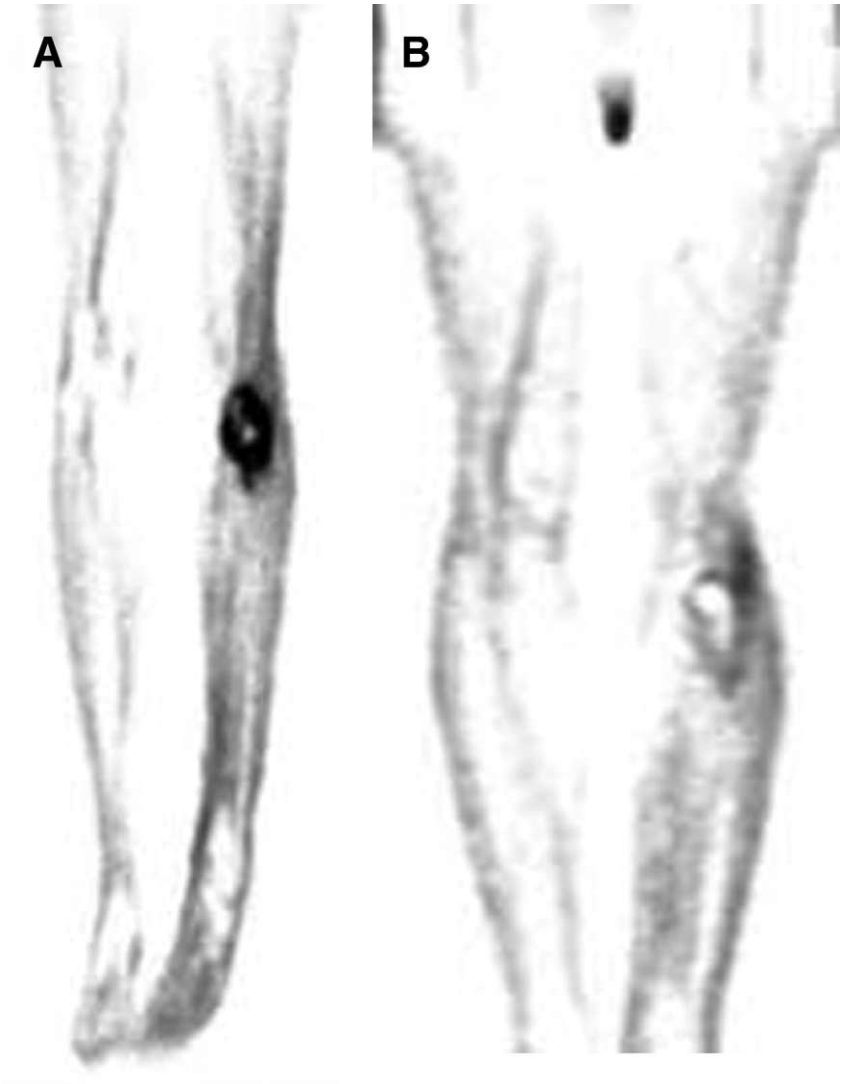

Figure 5 Shown is a 47-year-old male with a left upper posterior calf malignant Schwanoma. (A) Pretreatment coronal FDG-PET shows focal hypermetabolism with central photophenia in the tumor. (B) Coronal FDG-PET after cryosurgery shows marked decline in the metabolic activity with a larger photopenic region. Surgical specimen showed residual tumor with 75% necrosis.

MRI were performed in 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 nine patients, MRI was equivocal in differentiating between post-therapeutic changes and tumor recurrence whereas FDG-PET showed evidence for recurrent tumor, as confirmed by biopsy, in five of these patients. In the remaining four patients with equivocal MRI, no hypermetabolism suggestive of recurrent tumor was seen on FDG-PET and those patients remained free of evident disease during the follow-up period.[67] Therefore, FDG-PET was useful in distinguishing viable tumor from post-therapy morphologic alterations in patients with sarcoma and equivocal MRI. However, occasionally prominent FDG accumulation may be observed in benign therapy-related fibrous tissue both within and adjacent to the treated tumor, presumably due to local inflammation and healing.[68] Despite this potential limitation, the ability to differentiate postoperative changes from local recurrence may lead to an impact on the clinical management of patients with sarcoma.[69,70]

In a retrospective analysis of 209 patients with sarcoma, the ability of pretherapy FDG-PET was determined in predicting patient survival and disease-free interval.[71] A multivariate analysis showed that SUV(max) was a statistically significant independent predictor of patient survival such that tumors with larger SUV(max) had a significantly poorer prognosis.

Other tracers also have been investigated. In one study that compared FDG-PET with C-11 choline PET, the latter was considered advantageous as the result of its shorter examination time and little bladder activity, which was particularly helpful for evaluating lesions in the pelvis and around the hip joints.[72] The receiver operating characteristic curves of two analyses showed that the mean area under the curve for choline PET (0.9577 ± 0.041) was significantly greater than that for FDG-PET (0.8192 ± 0.0806). However, there was no significant difference in sensitivity and specificity between choline PET and FDG-PET in characterizing soft tissue masses.[72] Oxygen-15-labeled water has also been shown to accumulate in primary and recurrent soft tissue sarcomas of different histologic types but its exact role as a potential diagnostic agent remains to be established.[73]

Conclusion

In conclusion, the published literature suggests that FDG-PET may have an important role in the imaging evaluation of patients with bone and soft tissue sarcoma. Prospective studies with large patient groups are essential to further evaluate the cost-effectiveness and the short-term and long-term benefits of FDG-PET in these patients. Recent consensus conferences are important in defining the exact diagnostic and prognostic roles of FDG-PET in this clinical setting.[74]

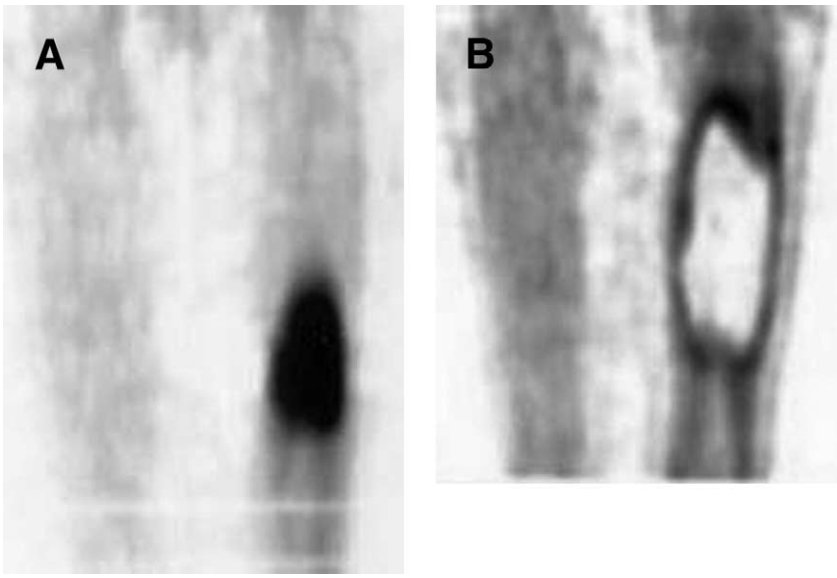

Figure 6 Shown is a 35-year-old female with a left mid thigh malignant fibrous histiocytoma. (A) Coronal FDG-PET before surgery shows intense hypermetabolic activity in the tumor. (B) Coronal FDG-PET after cryosurgery shows large internal area of photopenia surrounded by a hypermetabolic rim. Surgical specimen showed 95% tumor necrosis.

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