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An Overview about PET Imaging of primary bone tumors

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Abstract: Primary malignant bone tumors are fairly rare. The most common primary malignant bone tumors are osteosarcoma, chondrosarcoma, and Ewing's sarcoma. Staging of the disease is necessary for determination of the treatment plan as well as follow-up of the lesion and its response to therapy. This depends on complete imaging and histopathological confirmation of the suspected entity. Diagnostic imaging has a master role in evaluation and management of bone cancers. Standard imaging modalities as conventional radiography, computed tomography (CT) scanning, magnetic resonance imaging (MRI) and skeletal scintigraphy cannot reach the accurate staging of the tumor as they depend mainly on morphologic diagnostic criteria and cannot differentiate between post-treatment changes and recurrence or residual tumor due to distortion of the regional anatomy by surgery and/or radiation. Also, positron emission tomography (PET) is limited in this field as it depends only on functional imaging through localization of metabolic activity using various radiopharmaceutical agents with lack of anatomical localization. Viable malignant primary bone tumors are usually 18F-fluorodeoxyglucose (FDG) avid. Accumulation of FDG may reflect tumor characteristics based on its metabolic activity providing better characterization of indeterminate lesions and guidance of targeted biopsy of the most metabolically active area within larger tumors especially tumors of mixed grade and/or cell type.

Keywords: *PET Imaging, primary bone tumors*

Introduction

Primary malignant bone tumors are fairly rare. The most common primary malignant bone tumors are osteosarcoma, chondrosarcoma, and Ewing's sarcoma. Staging of the disease is necessary for determination of the treatment plan as well as follow-up of the lesion and its response to therapy. This depends on complete imaging and histopathological confirmation of the suspected entity **[1, 2]**.

Diagnostic imaging has a master role in evaluation and management of bone cancers. Standard imaging modalities as conventional radiography, computed tomography (CT) scanning, magnetic resonance imaging (MRI) and skeletal scintigraphy cannot reach the accurate staging of the tumor as they depend mainly on morphologic diagnostic criteria and cannot differentiate between post-treatment changes and recurrence or residual tumor due to distortion of the regional anatomy by surgery and/or radiation **[3, 4]**.

Also, positron emission tomography (PET) is limited in this field as it depends only on functional imaging through localization of metabolic activity using various radiopharmaceutical agents with lack of anatomical localization **[5]**.

The introduction of the hybrid 18F-fluorodeoxy-D-glucose positron emission tomography-computed tomography (18F-FDG PET/CT) technique has advanced the knowledge of the pathophysiology of cancers that significantly impacts the evaluation, staging and management of different tumors and thus providing more efficacious treatment, better quality of life, and increased survival **[6].**

Also, its unique advantages, as high sensitivity and an extremely long scan range provide an opportunity for wider clinical application, including low administered activity, total-body dynamic scanning, and long acquisition delay **[7]**.

The CT component of this imaging provides important morphologic information which is added to the functional information given by PET scans in the same session **[8]**.

Viable malignant primary bone tumors are usually 18F-fluorodeoxyglucose (FDG) avid. Accumulation of FDG may reflect tumor characteristics based on its metabolic activity providing better characterization of indeterminate lesions and guidance of targeted biopsy of the most metabolically active area within larger tumors especially tumors of mixed grade and/or cell type **[9, 10]**.

FDG-PET is used also for more accurate staging of histologically confirmed tumors, assessment of treatment response to detect disease course and find out any recurrent lesions. It also provides a non-invasive method in estimating tumors grade depending on the amount of FDG uptake; this is an important prognostic factor in most bone tumors and a reliable independent prognostic indicator **[11 12]**.

FDG Uptake in Primary Bone Tumors

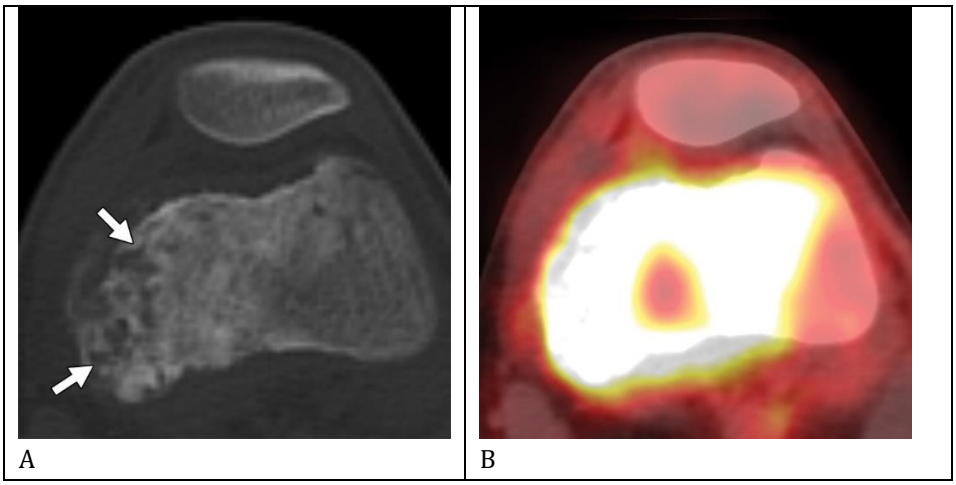
A spectrum of FDG uptake has been discovered in primary bone tumors, with more-aggressive lesions tending to be more FDG avid than nonaggressive lesions. Several studies have found malignancies to be significantly more avid than benign lesions overall **[13– 17]**.

The concept of the spectrum holds true particularly well when comparing tumors of the same histologic type, such as cartilage tumors. For example, it has been shown that FDG uptake of higher-grade chondrosarcomas is greater than that for lower-grade cartilage malignancies in general and that benign cartilage lesions typically have lower FDG uptake than do chondrosarcomas **[13, 16, 18, 19]**.

This orderly spectrum is less likely to apply when comparing tumors of differing histologic groups. FDG avidity of several benign tumors can be as high as or higher than some of the malignancies. For example, giant cell tumors of bone have been repeatedly reported to be more avid than grouped chondrosarcomas **[13, 14, 16]**. Schulte et al. **[13]** studied 202 lesions and found no significant difference between the FDG uptake of high-grade malignancies and benign aggressive lesions, and a different study found a trend toward higher uptake in the benign aggressive lesions than the malignancies **[84]**. Benign aggressive lesions, such as giant cell tumors of bone and giant cell reparative granuloma, can be locally destructive but do not typically metastasize with the resultant death of the patient. Additional examples of tumors that may exhibit deceptively high FDG avidity include chondroblastomas, osteoblastomas, osteoid osteomas, Langerhans cell histiocytosis, chondromyxoid fibromas, brown tumors, fibrous dysplasias, fibroxanthomas (non ossifying fibromas), desmoplastic fibromas, and aneurysmal bone cysts **[13–17, 20]**. Nevertheless, individual tumor types can have widely varying FDG uptake. For example, a study that included 15 aneurysmal bone cysts and six non ossifying fibromas (fibroxanthomas) found approximately half of each lesion type to be avid enough to be confused with malignancies **[13]**. Brown tumors have been found to lose their FDG avidity after treatment of hyperparathyroidism **[21]**. With the exception of some fibrous lesions, it has been observed that most highly avid benign bone tumors contain significant numbers of histiocytic or giant cells **[14]**.

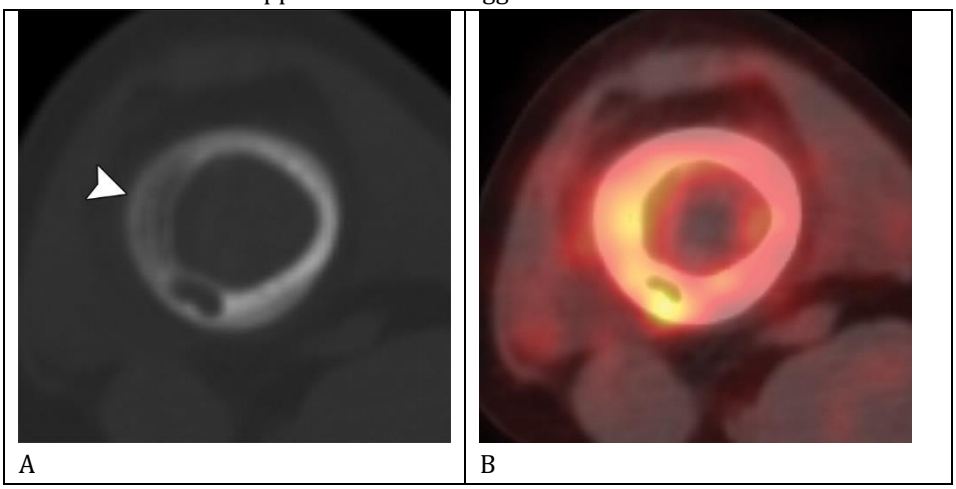
Some malignancies may exhibit a confusing paucity of FDG uptake. One study found that six low-grade chondrosarcomas had FDG avidity low enough to be confused with benign lesions **[90]**. Similar findings have

been reported for low-grade osteosarcoma and Ewing sarcoma **[14]**. Benign lesions with typically low FDG avidity included osteochondromas, enchondromas, hemangiomas, and intraosseous lipoma **[13–16, 20]**.



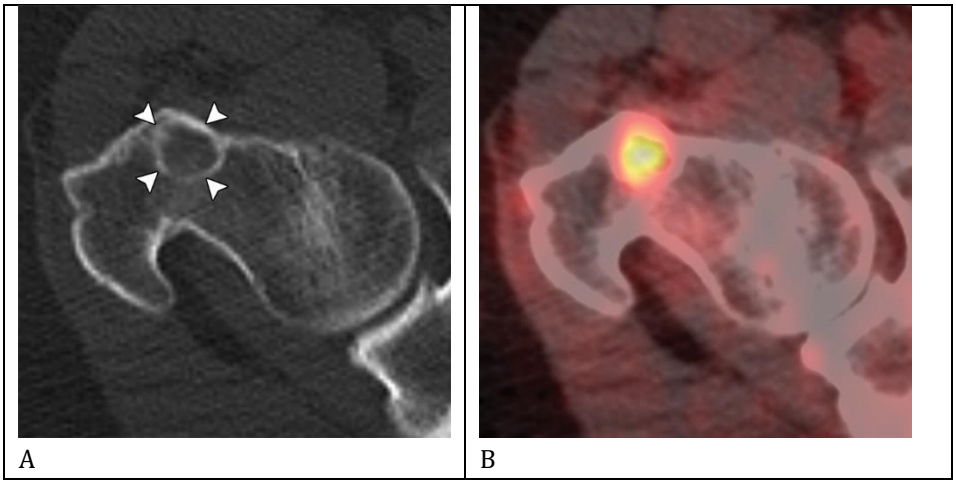
A B

Fig 1. 13 years old male with femur osteosarcoma. Image A shows moth eaten pattern of osteolysis, luccenies of various size are seen throughout affected bone, indicating aggressive lesion. Image B, in setting of moth eaten osteolysis, Max SUV = 10.7 SUV is supportive of lesion aggressive character.



A B

Fig. 2. 10 years old male with Ewing sarcoma of femur with onion skin periosteal reaction. Image A, in this type of periosteal reaction, layers are parallel to long axis of bone and cortex (arrow head). Image B, multiplicity of layers is consistent with aggressive process despite modest maximum standardized uptake = 5.2 SUV.



A B

Fig. 3. 36 years old man with incidental fibrous dysplasia of femur. Image A shows well defined sclerotic margin (arrowhead) that is indicated of. nonaggressive process. Image B fibrous dysplasia is benign lesion that can show deceptively high FDG uptake, maximum SUV = 4.3 SUV.

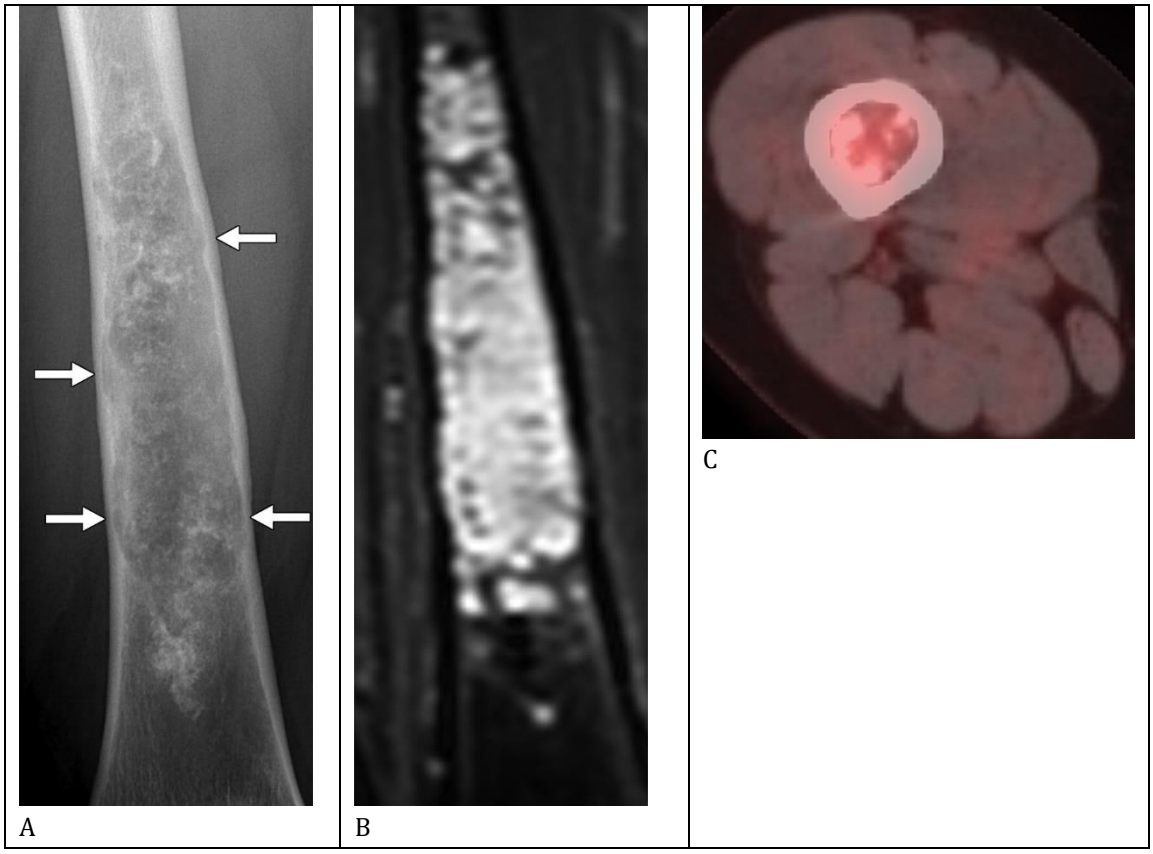
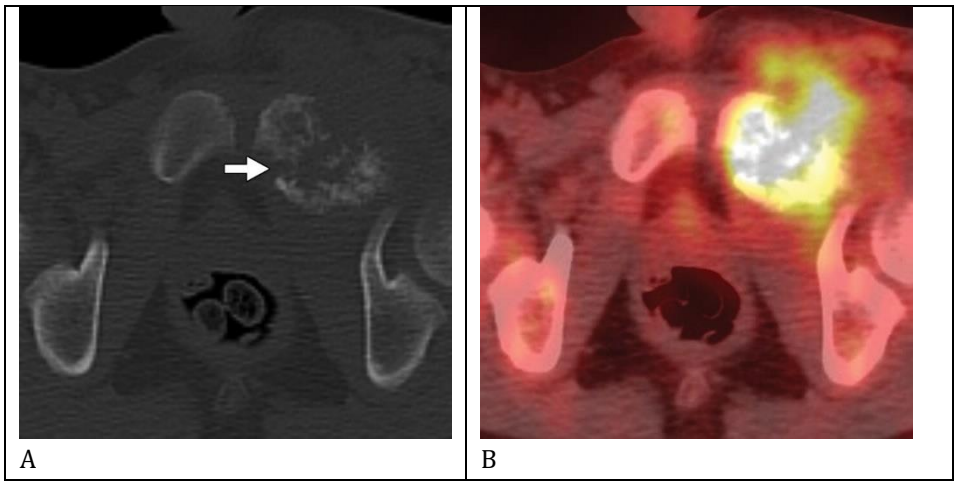


Fig. 4. 55 years old woman with low grade chondrosarcoma of femur. A) radiographically lesion is elongated measuring approximately 15 cm and occupies entire marrow cavity of majority of its length, characteristic arc and ring cartilage martrix mineralization indicate cartilage tumor, lesion shows thickened cortex with numerous areas of deep endosteal scalloping (arrows), thick cortex indicates choronicity with can be deceptive unless other factors are considerded. B) fat saturated T2WI shows finely lobulated margin composed of cartilage lobules. C) FDG PET CT of lesion show low maximum SUV 1.3 SUV. Morphologic feature of lesion and presence of pain are more helpful indicator of malignancy than degree of FDG uptake in this particular tumor.



A B

Fig. 5. 15 years old boy with Ewing sarcoma. A & B aggressive lesions (arrow A) with moth eaten osteolysis and pathologic fracture of left pubic body is seen with high activity on pre therapeutic pet CT (B) And maximum SUV 10.7 SUV.

Morphologic Features of Primary Bone Tumors on CT

Because of the lack of predictable FDG up-take in a sizeable minority of primary bone tumors, morphologic assessment remains necessary to evaluate their biologic potential and form a plausible differential diagnosis. Radiography is the preferred method of analysis [16], but important information is immediately available from the CT that is simultaneously acquired with the PET dataset. An aggressive biologic potential indicates that the tumors are capable of metastasizing and/ or producing excessive local destruction and/ or local recurrence. A nonaggressive biologic potential indicates that the lesions are indolent or quiescent and not worrisome, unless they predispose to pathologic fracture or produce deleterious mass effect on adjacent structures.

Aggressive Features

The margin of a primary bone tumor is one of the most sensitive indicators of biologic potential that can be evaluated on imaging studies **[22]**. The edge of most aggressive tumors will appear unsharp or indistinct, reflective of active osteolysis. The lack of a sclerotic margin is worrisome and may indicate that the reparative mechanisms of the bone are unable to equal or exceed the rate of osteolysis caused by the tumor. Nevertheless, aggressive tumors may have partial sclerotic margins, and non-aggressive lesions may produce small areas of severe cortical thinning or absence. The lesser the degree of marginal sclerosis, the more likely the lesion is to be aggressive. Aggressive lesions may be geographic (round or oval) but often show a wide zone of transition between the tumor and host bone. Highly aggressive lesions may present as a large field of osteolysis, rather than a discrete round or oval lesion. The osteolysis may resemble numerous holes of varying size or may be associated with fine “fuzzy-appearing” areas of bone destruction. Aggressive tumors often extend through the cortex directly into the adjacent soft tissues. Less-aggressive malignancies and benign lesions may expand the cortex. These lesions grow slowly enough to allow the cortex to remodel around the periphery of the tumor. Nevertheless, even relatively indolent malignancies will often produce cortical breakthrough of the expanded cortex.

Some forms of periosteal reaction are seen more typically with aggressive than with nonaggressive primary bone tumors. Before skeletal maturity, a major function of the periosteum is to enlarge the circumference of the bone. Throughout life, the periosteum also produces callous that aids in the stabilization of fractures when motion occurs at the fracture site **[23]**. When irritated by a primary bone tumor, the periosteum can produce new bone in various forms. Bony spicules that form perpendicular to the cortex are found in a “sunburst” or “hair-on-end” periosteal reaction. Layers that form parallel to the long axis of the bone describe an “onionskin” periosteal reaction. Typically, the larger the number of spicules or layers, the more aggressive the underlying process, though aggressive malignancies may produce only mild or no periosteal reaction. Interruption of

periosteal reaction by the tumor is also an aggressive feature. Periosteal reaction at the interface between the bone and tumor extending into adjacent soft tissues is termed a "Codman triangle" **[22]**.

Indeterminate margins also exist and can be seen with malignant or benign geographic primary bone tumors. These margins are well defined with no sclerotic rims. They may result from tumors that destroy the bone incrementally faster than the rate at which it can repair itself, or they may be seen in tumors that either do not induce or suppress the reparative response (multiple myeloma). Biopsy is recommended when encountering tumors with indeterminate margins, and to confirm the diagnosis of any potentially aggressive primary bone process.

Benign (Nonaggressive) Features

Nonaggressive lesions are typically benign. Their margins often show a rim that is predominantly or completely sclerotic. The spicules associated with periosteal reactions incited by benign lesions are often few, unilaminar, and thick. Solid cortical thickening is often indicative of a healed prior periosteal reaction. The cortical expansion of non-aggressive lesions is typically not interrupted by lysis, and the expanded cortex may be relatively thick. The simple lack of aggressive features in a primary bone tumor can be reassuring. This discussion does not apply to metastases. Although they are malignant by definition, sclerotic metastases may have sharply defined margins and lytic metastases may have sclerotic rims.

Cartilage Lesions

Enchondromas represent a common exception to the concept that the rim of a benign bone tumor should be predominantly sclerotic. On radiographs and CT, the intramedullary margin of enchondromas is often poorly discerned, and cartilaginous matrix mineralization (arc-and-ring or stippled) and/or small areas of endosteal scalloping (cortical thinning) are the most readily visible features. The tumor can be distinguished from marrow on MRI, which typically depicts a finely lobulated margin. Some enchondromas show a predominantly sclerotic rim, which can be confused with bone infarct. A painless lesion that is found incidentally and shows no aggressive features can be followed with radiographs.

Low-grade chondrosarcomas may appear deceptively nonaggressive unless one is familiar with their appearance. Particularly when they involve the diaphysis of the long bones of the appendicular skeleton, they are often large (> 5 cm) and thin, more than two thirds the thickness of the cortex over a length of more than two thirds of the lesion **[24]**. They often produce circumferential expansion of the bone and are typically associated with pain. All suspicious lesions that are not immediately biopsied must be followed regularly with imaging studies, such as radiography, CT, or MRI, until biologic potential is established.

Therapeutic Response

FDG PET/CT scans have been successfully shown to predict therapeutic response in primary bone malignancies, such as osteosarcoma and Ewing sarcoma. Changes in FDG avidity and morphologic features can be indicators of the efficacy of the regimen.

Morphologic Analysis

Morphologic changes on the CT portion of the PET/CT scan can be a valuable adjunct to the metabolic analysis. A positive response is typically accompanied by partial or complete reconstitution of cortex that was previously interrupted by tumor lysis, maturation of periosteal reactions, and an increase in central mineralization. Nevertheless, morphologic analysis is limited for assessing tumor response. For example, osteosarcomas may not diminish sufficiently in size to satisfy response criteria for therapeutic protocols, such as the Response Evaluation Criteria in Solid Tumors version 1.1, which require a minimum 30% decrease **[25, 26]**. Investigations of the impact of change in tumor size and volume on therapeutic response in Ewing and osteosarcoma have been mixed **[27–31]**. When a poor response is morphologically apparent, the aggressive features previously discussed can develop or progress.

Metabolic Analysis

Because of the limitations of morphologic analysis, tumor metabolism has been investigated as a prognostic indicator. Osteosarcoma and Ewing sarcoma are the two most common primary nonhematologic bone

malignancies for which standard chemotherapy regimens exist. Researchers who investigate these tumors have found that one or a combination of pretherapeutic FDG avidity **[32– 34]**, posttherapeutic FDG avidity **[30, 33, 35– 40]**, or change in FDG uptake between the two scans **[107, 110, 112–120]** correlate with outcome in osteosarcoma **[30, 32–33, 40, 41- 43]** and Ewing sarcoma **[116, 119]**. The two most robust reference standards for the outcome of patients with osteosarcoma or Ewing sarcoma are the histologic response of the resected tumor and short-term patient prognosis. Most of the studies investigating the role of FDG PET/CT in this context have used histologic response as their reference standard **[30,32, 35–40, 42]**. Histologic response is determined by post-chemotherapeutic tumor necrosis. Although tumor necrosis is only a surrogate for actual prognosis, it is considered a strong indicator of patient outcome, and treatment decisions are commonly based on this result. Patients with tumors that undergo 90% or more tumor necrosis have been shown to experience a better prognosis than patients with more viable tumors **[43]**. Patients with suboptimal tumor necrosis will often undergo postoperative (adjuvant) chemotherapy in addition to the standard pre-operative (neoadjuvant) chemotherapy. FDG avidity has been successfully correlated with tumor necrosis in osteosarcoma **[33]** and Ewing sarcoma **[42]**. One of the greatest potential advantages of FDG PET/CT in determining therapeutic response is through the early identification of poor responders. This can allow preoperative chemotherapy to be modified or extended while eliminating the delay associated with surgery and histopathologic analysis of the resected specimen. The relationship between FDG uptake and prognosis may be different in osteosarcoma than Ewing sarcoma. Denecke et al. **[30]** found significant relationships between FDG up-take and tumor necrosis in osteosarcoma but not in Ewing sarcoma. Gaston et al. **[37]** found a posttherapeutic maximum standardized uptake value of less than 2.5 to be predictive of tumor necrosis in osteosarcoma but not in Ewing sarcoma. They also discovered that a 50% decrease in metabolic tumor volume was predictive of tumor necrosis in osteosarcoma, whereas a 90% reduction in metabolic tumor volume was necessary for statistical significance in Ewing sarcoma.

Clinical therapeutic indicators, such as progression-free survival and/or overall survival, have also been used as the reference standard for outcome in patients with osteosarcoma **[33, 34, 38, 40]** and Ewing sarcoma **[39]**. Progression-free survival is defined as the time from treatment until tumor recurrence, progression, or stability at the study endpoint. Overall survival is defined by whether the patient is alive or has died of their disease by the end of the observation period. Short-term prognosis is considered a robust reference standard, provided that an adequate number of years are allowed for follow-up. The median follow-up periods of studies that have used this reference standard was 2.3–5.8 years **[22, 24, 29, 40]** with a preferred interval of 3 or more years. Pre-therapeutic FDG uptake, posttherapeutic FDG uptake **[33, 40]**, and change in FDG uptake **[33, 40]** have been found to correlate with progression-free and overall survival in osteosarcoma. Posttherapeutic avidity was found to correlate with progression-free survival in Ewing sarcoma **[39]**. Irrespective of the reference standard, FDG PET/CT has been found to be beneficial for the assessment of therapeutic response.

Staging

FDG PET/CT is a whole-body imaging modality that has been found to be successful in the staging of malignancies. In a study that compared FDG PET, bone scan, and bone marrow biopsy or aspirate in 91 patients with Ewing sarcoma, Newman et al. **[44]** found that FDG PET detected bone metastases in all patients who had lesions detected by biopsy or bone marrow aspirate. PET found a metastasis in one patient with a negative bone scan. Overall, bone scan found more metastases in the skull, likely because of the close proximity of the highly metabolic gray matter on the PET scans. PET-only scans have been found to be comparable to conventional imaging for detecting local and distant metastases from Ewing and osteosarcoma **[45]**, but the PET-only scans were inferior to diagnostic CT for detecting lung nodules **[46, 47]**. London et al. **[48]** compared PET/CT with conventional imaging (CT, MRI, ultrasound, and bone scan) in a study that included 314 lesions on 86 scans in children with metastatic osteosarcoma and Ewing sarcoma. They showed that PET/CT had a higher sensitivity (98% vs 83%) and specificity (97% vs 78%) than did conventional imaging for detecting distant metastases, with the exception of pulmonary nodules. Regarding pulmonary nodules, PET/CT was found to have a higher specificity (96% vs 87%) but lower sensitivity (80% vs 93%) than did conventional

imaging **[48]**. The acquisition of PET data requires several sets of images to cover the chest and upper abdomen, each.

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