8 PET in Sarcoma: Surgeons Point of View

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Sarcoma Diagnostic and Treatment Challenges

Sarcomas in adults and pediatric patients are a rare malignancy of mesenchymal, non-glandular, connective tissue. They carry an incidence of 15,000–20,000 new cases per year in the United States, if all subtypes and grades are included [1]. Diagnosing soft tissue tumors has historically proven challenging, and many patients present in a delayed fashion after many months of symptoms. Many benign, degenerative, and inflammatory processes serve as alternative diagnoses and distractions in the evaluation of patients with a possible soft tissue sarcoma, making the diagnostic process challenging.

Compared to carcinomas and other solid tumors, primary soft tissue sarcomas are the only soft tissue malignancy of any type that can occur in patients of any age and in any anatomic location (commonly found in the extremities, pelvis, head and neck, as well as spine). The early imaging of sarcomas is accurately defined with both MRI and PET scans, although often misinterpreted and the diagnostic histopathology remains challenging, even for the most experienced pathologists. Diagnostic errors in the assessment of the tumor grade and tumor subtype occur commonly, in spite of the promising development of sarcoma-specific molecular markers [2]. Given the challenges of assessing tumor malignancy and grade that exists for sarcomas, FDG-PET as a metabolic early diagnostic imaging modality for sarcomas appears to have significant accuracy in predicting initial tumor grade, response to neoadjuvant treatment (chemotherapy and/or radiation therapy), and local recurrence or metastasis [3, 4].

The value of PET imaging for most sarcomas is its capability to identify high-grade tumors by their metabolic activity, as reflected by the PET standard uptake value (SUV) before making decisions about systemic or local, primary treatment. Imaging with PET scans may be able to differentiate high-grade sarcomas from their intermediate and low-grade counterparts in the setting of equivocal or indeterminate microscopic pathology [5]. Additionally, PET provides the ability to identify an early response or lack of response to preoperative neoadjuvant chemotherapy with serial scans. Identifying early chemotherapy response, local recurrence, and/or the presence of metastatic disease with PET scanning allows more accurate and quicker decision-making in the treatment of many sarcomas. PET imaging is best initiated before or after the patient's initial biopsy as it can supplement, confirm, or challenge the biopsy determination in high- vs low-grade sarcomas (Fig. 8.1 Staging for musculoskeletal tumors). As new molecular

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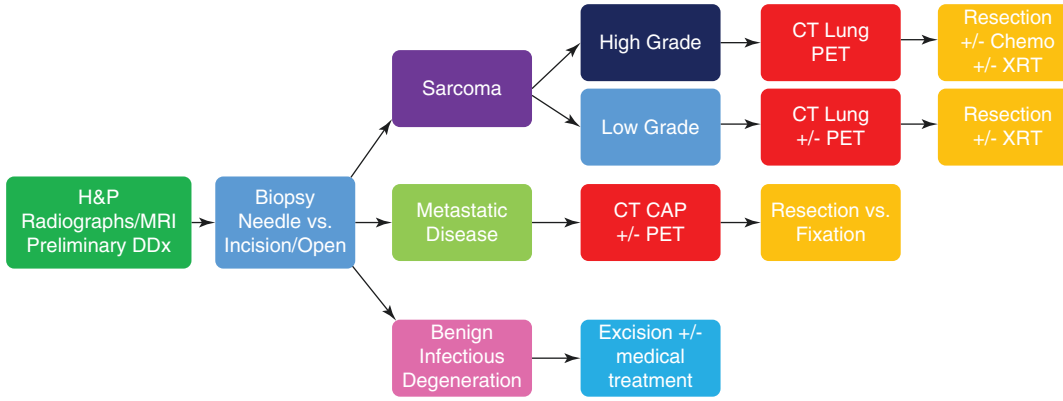

Fig. 8.1 "Staging" model for musculoskeletal tumors. Algorithm for the staging and work-up of bone and soft tissue sarcomas, metastatic disease, and other non-neoplastic lesions. (CAP Chest, abdomen, and pelvis)

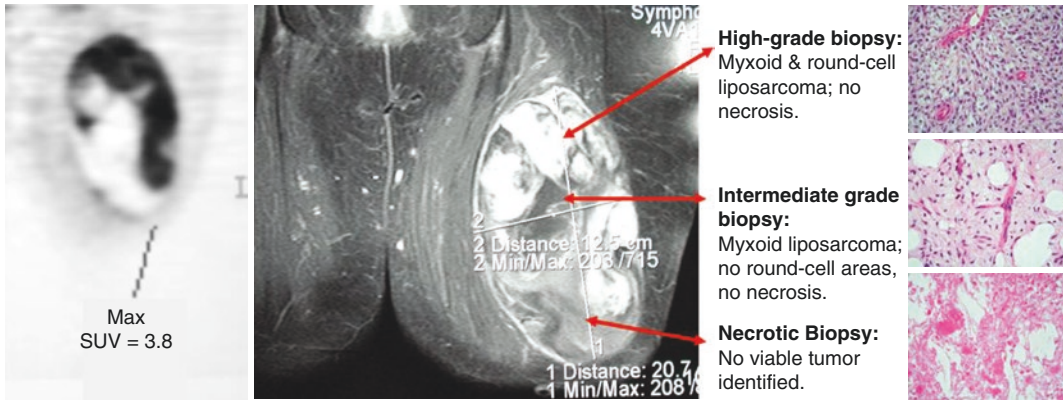

Fig. 8.2 Tumor heterogeneity and the challenges of sarcoma biopsy. Soft tissue sarcoma of the thigh in an adult patient. Sampling from three distinct areas of the tumor identified three distinct histopathologic subtypes. Due to the large size and heterogeneity of the tumor, errors in biopsy diagnosis, grade, and subtype may occur

targets develop with specificity to certain tumor subtypes, PET imaging should improve its accuracy and applications for monitoring the patient's response to adjuvant treatment.

The successful treatment of high-grade sarcomas relies on an accurate initial diagnosis, tumor grade, and the identification of the histologic response to adjuvant treatment, as well as appropriate surgical resection. Initial tumor imaging and accurate biopsy are critical first assessments for all neoplasms and a very challenging first step for many sarcoma patients (Fig. 8.2 Tumor heterogeneity and the challenges of sarcoma biopsy). The accurate biopsy of sarcomas includes the issues of tumor heterogeneity, the quantification of mitotic activity, and the challenges of sampling error for many types of sarcomas. PET scans assist in both the diagnostic and treatment challenges of sarcomas with their initial assessment of tumor grade, response to treatment, and the identification of local recurrence and metastasis [2].

Preoperative Imaging of Soft Tissue Sarcomas: The Neoadjuvant PET Sarcoma Treatment Model

The adequate treatment of soft tissue sarcomas requires multiple factors, beginning with the diagnosis and preoperative evaluation. An initial and accurate high-grade diagnosis from a biopsy,

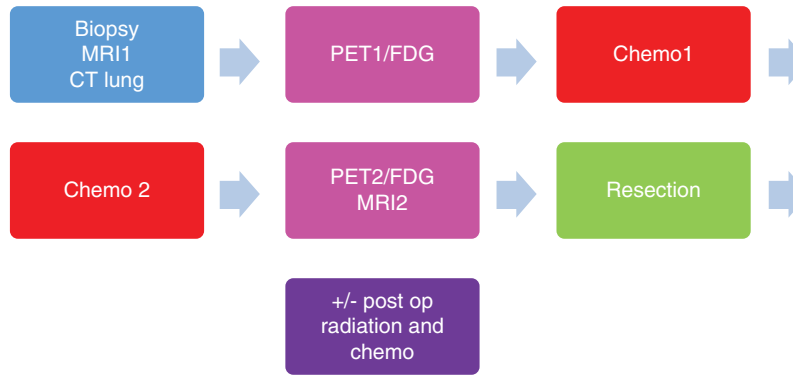

Fig. 8.3 Sarcoma PET neoadjuvant treatment model. Sequence of events following diagnosis of bone or soft tissue sarcoma. PET scans before and after neoadjuvant chemotherapy allow for monitoring and trending of SUVs

preoperative MRI, and PET imaging for all high-grade tumors is a crucial step in the patient's treatment algorithm (Fig. 8.3 Sarcoma PET "neo-adjuvant" treatment model for sarcoma). The prognosis and risk of local tumor recurrence or metastasis following resection is mostly related to tumor grade, size, and anatomic location. High-grade sarcomas have a higher risk of local recurrence and metastasis compared to low-grade sarcomas, as do larger or axial tumors, occurring in the spine and pelvis. Those higher-risk tumors have a greater need for more careful imaging with PET imaging in a neoadjuvant model. That model in its initial description included repeat PET imaging after two cycles and four cycles of neoadjuvant chemotherapy with an identification of the greatest tumor response after the first two cycles of chemotherapy [4]. Low-grade sarcomas, with one exception, typically have a low (approximately 10%) risk of local recurrence and are usually associated with a lower risk of regional or distant (pulmonary) metastasis. Desmoid tumor is considered a low-grade soft tissue sarcoma which has a relatively high risk of tumor recurrence (30–50% depending on the size and location). Its confirmation as a low-grade tumor and issues of possible local recurrence represent reasonable indications for PET imaging.

The primary surgical goal for patients with soft tissue and osseous sarcomas is an adequate surgical resection with negative margins to minimize the risk of local tumor recurrence. Contemporary sarcoma surgical resection margins were described initially by Enneking and described the surgical goal to obtain a "wide" margin of "normal tissue" surrounding the resected tumor [6]. In surgical practice today, the goal of a wide surgical margin of normal tissue of 5–10 mm is frequently compromised by several areas of "marginal" or "contaminated" surgical margins in at least one or two areas of the resected specimen. Those thinner margins may represent thinner margins secondary to an adjacent preserved anatomic structure (femur, artery, nerve) or an area lacking anatomic soft tissue coverage. The preoperative routine of planning surgical margins should consider tumor location, planned surgical margins or boundaries, grade, and the tumor response to neo-adjuvant chemotherapy or radiation therapy. Preoperative surgical planning for soft tissue or osseous sarcomas should carefully consider the identified surgical margins prior to resection and label those margins for subsequent postoperative pathological assessment. In the upper and lower extremity, preoperative planning includes identification of resection planes as well as anticipating the need for osseous and soft tissue reconstructions. Identifying tumor involvement of a major vessel (artery or vein) or a major peripheral nerve is critical to determining the resectability of the tumor as well as predicting functional outcomes and facilitating appropriate preoperative patient discussions.

A high-grade sarcoma typically deserves a wide rather than an intralesional or marginal margin. If, however, the patient has been treated with effective neoadjuvant chemotherapy (or radiation therapy), the resection may contain one to two areas of marginal margins (e.g., adjacent to a critical neurovascular structure) and have a suc-

cessful outcome without local recurrence. An example of a 65-year-old patient with a large, 20 cm soft tissue sarcoma of the posteromedial mid-thigh that presented with pulmonary metastases and preop MRI of a axial and coronal MRI (T2/STIR 5 B&C) demonstrated an initial PET SUV of 10.6 at presentation and a very close surgical margin at the superficial femoral artery on preoperative MRI. The preoperative surgical margin was predicted to be at least microscopically contaminated. Preoperative chemotherapy and radiation therapy were given with a close, marginal surgical margin and no evidence of local recurrence at 2 years despite progression of her lung metastases (Fig. 8.4: MRI and PET imaging for a high-grade soft tissue sarcoma – (A) Preop PET with high SUV = 10.6. (B) Preop MRI showing a probable, very close marginal surgical margin at the superficial femoral artery, (C) coronal preop MRI of a 25 cm high grade sarcoma treated with preop chemo, radiation, and resection without local recurrence, MRI and PET preoperative imaging for adult soft tissue sarcoma).

A favorable histologic response to preoperative chemotherapy is more common in pediatric sarcomas (both osseous and soft tissue) relative to their adult counterparts. Because children, in general, have better histologic responses to high grade-sarcomas treated with preoperative chemotherapy, compared to adults, pediatric patients can be managed surgically with resections that have smaller, marginal margins, if those patients are followed carefully with serial MRI and PET scans to evaluate their response to preop chemotherapy [7] have PET imaging response has been best described by multiple studies in pediatric osteosarcoma, where a good response to preoperative chemo is defined as a 40–50% reduction in the PET SUV measurements following 8–10 weeks of preoperative chemotherapy [8]. Patients with a significant (>40%) reduction in SUV 2 compared to SUV 1 have a higher survival and a lower risk of local recurrence than those patients with a smaller (<40%) reduction in SUV [9].

Traditionally, response to neoadjuvant chemotherapy was determined by postoperative histologic analysis of tumor necrosis by a pathologist. PET tumor imaging in combination with MRI has the ability to identify histologic response after two to four cycles of neoadjuvant chemotherapy prior to surgery. Preoperative PET imaging after neoadjuvant chemotherapy may be a more accurate method of determining treatment response than the assessment of histologic response [10].

Routine preoperative sarcoma imaging should both MRI and PET imaging for all high grade tumors which can be obtained either before or after tumor biopsy but should be requested prior to the initiation of preoperative adjuvant chemotherapy or radiation therapy in order to assess treatment response and plan the details of surgical resection. The prediction of adequate surgical margins and the assessment of initial treatment response is a critical step in the successful treatment of high-grade and large (greater than 7–8 cm) sarcomas, in addition to the assessment of all recurrent sarcomas, regardless of tumor size [11–13].

For example, a 21-year-old female with thigh soft tissue sarcoma is treated with four cycles of neoadjuvant chemotherapy prior to resection in an initial neoadjuvant trial that was intended to compare the tumor response after two cycles (PET2) vs four cycles (PET3) of neoadjuvant chemotherapy (Fig. 8.5 – Neoadjuvant chemoresponse after two vs four cycles). This particular patient showed a greater SUV/PET response after the first 2 months of chemotherapy SUV (PET 2 vs PET1) compared to the PET SUV imaging after 4 cycles (PET 3 vs PET 1). That two- vs four-cycle chemotherapy comparison has been demonstrated in multiple patients, with serial preop PET scans after two vs four cycles. Comparing the initial chemotherapy response in PET 1-SUV1 (SUV = 14.3) with PET 2-SUV2 = 4.3 after two cycles vs PET 3-SUV3 (after 4 cycles), the first two cycles of chemotherapy in an adult soft tissue sarcoma population have demonstrated a greater tumor SUV response.

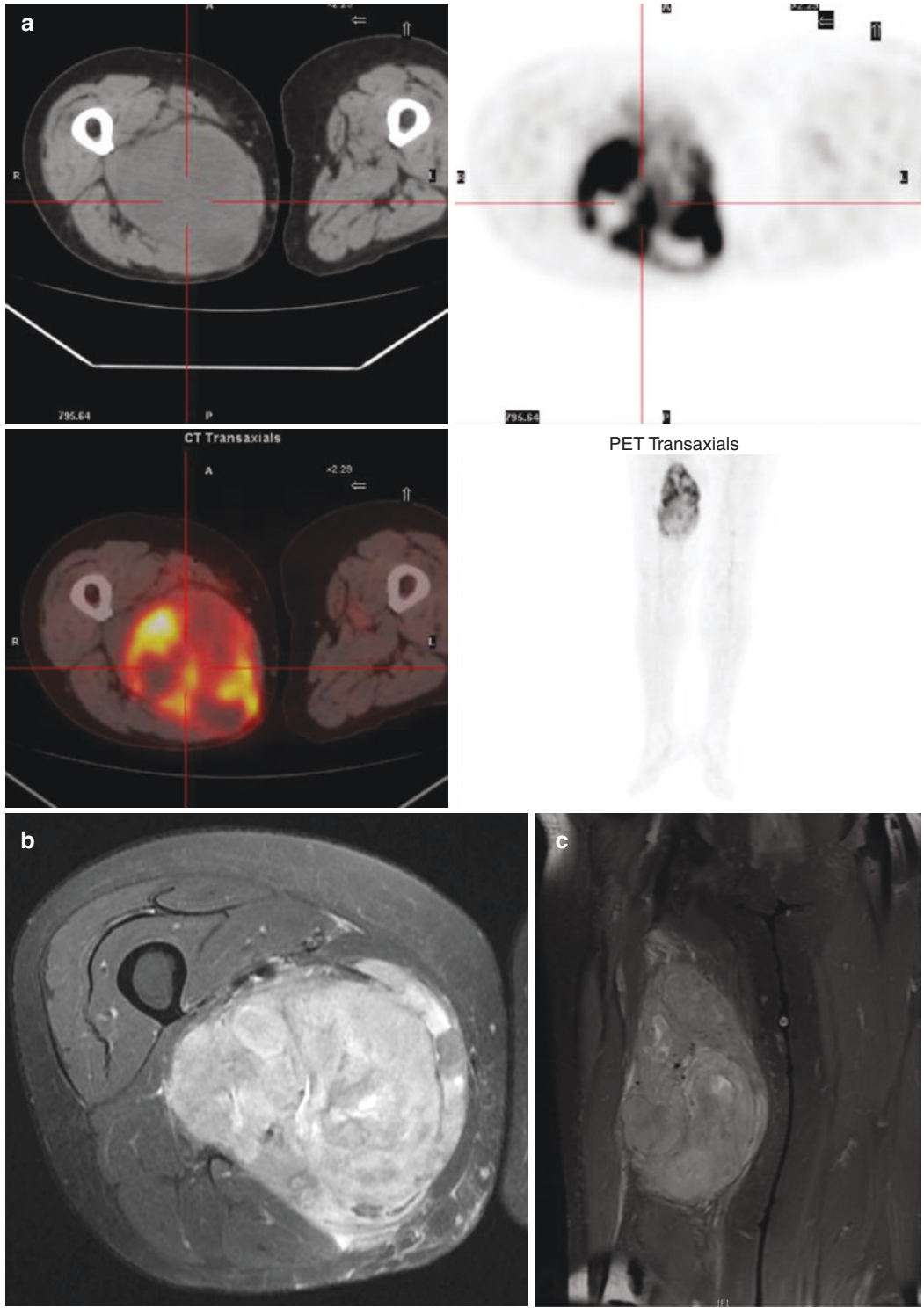

Fig. 8.4 MRI and PET imaging for high-grade soft tissue sarcoma. Imaging at initial presentation of a large, high-grade soft tissue sarcoma of the posteromedial thigh. Representative images of the lesion are (**a**) PET/CT with axial and coronal views, (**b**) axial, and (**c**) coronal fat-suppressed proton-density fast-spin-echo MRI. The maximum SUV of the mass was 10.6. This patient also had multiple pulmonary nodules found on PET/CT which were identified as metastases

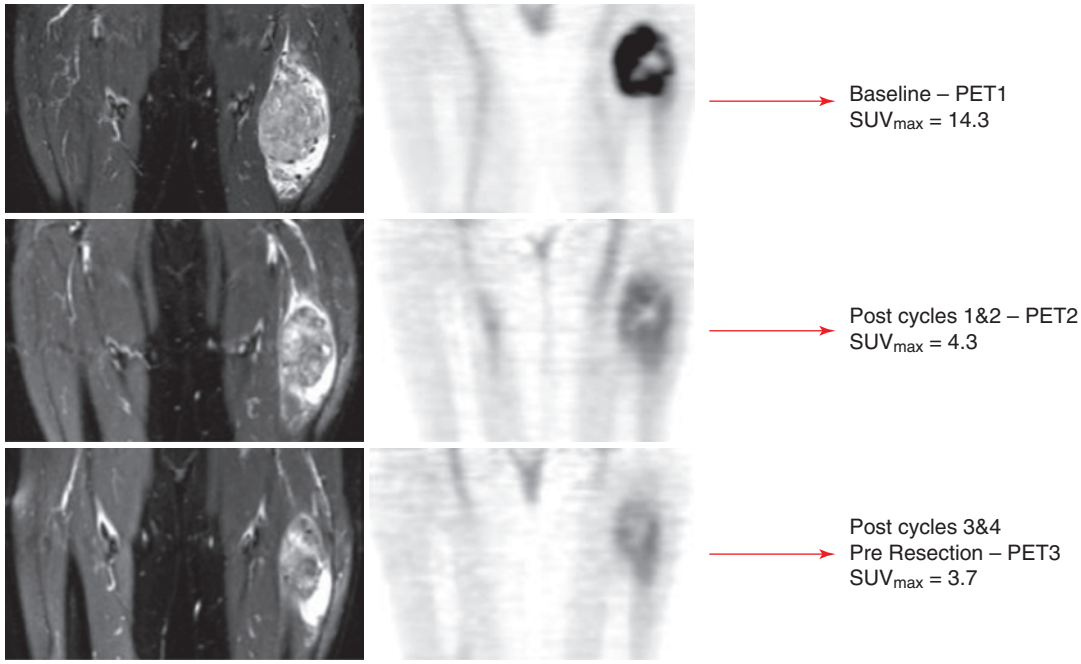

Fig. 8.5 Neoadjuvant chemotherapy response in a soft tissue sarcoma: Evaluating PET SUV after two vs four chemotherapy cycles. A 21-year-old female with a soft tissue sarcoma of the left thigh. Changes on MRI and PET scan in response to preoperative chemotherapy are seen sequentially. Decreasing SUVmax from prior to neoadjuvant chemotherapy (SUV1), following two cycles of neoadjuvant chemotherapy (SUV2) and following two additional cycles of neoadjuvant chemotherapy just prior to resection (SUV3). The biggest SUV changes occur between PET1 and PET2

Preoperative Assessment of Adult Osseous Sarcomas

Adult osseous tumors are comprised primarily of metastatic adenocarcinomas from primary tumors of the lung, breast, prostate, renal, or bone marrow (myeloma or lymphoma). A smaller number adult osseous sarcomas, including the diagnosis of chondrosarcoma or osteosarcomas. Metastatic adenocarcinomas to the skeleton comprise approximately 250,000 surgical orthopedic oncology patients per year in the United States [14]. These patients frequently require biopsy and skeletal stabilization or fixation, in addition to tumor staging and a diagnosis for what may be their presenting, initial diagnosis, requiring referral to medical oncology for systemic treatment of a new diagnosis.

Chondrosarcomas are the second most common primary malignant bone tumor, half of which are low grade or benign and are treated with marginal resection or intralesional surgical procedures [15]. The other half of adult chondrosarcomas are high grade and require careful wide resections. Chondrosarcoma carries a significant risk of local recurrence and pulmonary metastasis but has demonstrated only limited sensitivity to chemotherapy or radiation therapy. Consequently, there are currently limited indications for neoadjuvant treatment of high-grade chondrosarcomas. As a result, the surgical treatment for chondrosarcoma becomes more critical regarding control of both local recurrence and metastatic disease. As a general rule, chondrosarcomas do not occur in children unless they represent a variant of osteosarcoma (i.e., chondroblastic osteosarcoma), chondromyxoid fibroma (low-grade tumor), or "secondary" chondrosarcoma. Secondary pediatric chondrosarcomas occur following a transformation from a pre-existing pedi-

atric dysplasia associated with multiple hereditary exostosis (MHE) or enchondromatosis (i.e., Ollier disease) and other similar diagnoses [16]. Many of these secondary chondrosarcomas will occur in adolescents or young adults and will require local resection [17].

Adult osteosarcoma occurs with an incidence of 1000 cases per year in the United States [15] compared to osteosarcoma in children which has an incidence of approximately 15,000 cases per year in the United States. These adult patients, like their pediatric counterparts, are treated with neoadjuvant chemotherapy and surgical resection, but have 50% survival compared to their pediatric counterparts. Adult osteosarcoma patients deserve careful assessment of their preoperative chemotherapy response with PET scans. Adult osteosarcoma patients deserve careful assessment of their preoperative chemotherapy response with PET scans, because of their poor response to chemotherapy and high risk of metastasis. Adult patients with osteosarcoma, who have a poor response to neoadjuvant chemotherapy, are at higher risk of local recurrence and distant metastasis than pediatric patients and deserve careful assessment of their response to treatment. The higher risk of relapse in adult osteosarcoma also unfortunately includes adolescents and young adults with osteosarcoma whose prognosis worsens in patients over the age of 18 years [9].

Figure 8.6 demonstrates conventional imaging and PET imaging for a 19-year-old with a large 20 cm distal femoral osteosarcoma who presented with metastatic disease after diaphyseal allograft reconstruction (Fig. 8.6a–d). He presented with a delayed diagnosis, metastatic disease, and a high initial PET SUV = 15.8. He had a poor response to preoperative chemotherapy. He was reconstructed with a cadaveric femoral allograft fixed with a femoral rod and fixation plates. Alternative osseous sarcoma reconstructions following resection of the knee joint for osseous sarcomas include oncologic total knee reconstructions for distal femoral or proximal tibial sarcomas (see Fig. 8.7: Oncologic total knee replacement for osseous sarcomas).

Surgical resection and reconstruction for osteosarcoma or chondrosarcoma usually requires a resection and reconstruction with a complex, oncologic endoprosthesis (i.e., megaprostheses). These patients usually require 3–6 months of orthopedic rehabilitation and continued oncologic follow-up to determine local recurrence or lung metastasis. Imaging follow-up for local control usually requires an MRI at 3–6-month intervals, but those MRI images are challenging to interpret for local recurrence because of the adjacent metal implant. PET scan imaging can assist with the assessment of those patients for the possible local recurrence because of the limitations of MRI assessment adjacent to a large metallic implant [18].

Assessing Tumor Response, Local Recurrence, and Metastatic Disease with Pelvic and Sacral Sarcomas

Overall treatment goals for sarcoma patients include the treatment of the primary tumor, and prevention of distant (most commonly pulmonary) metastases after a confident diagnosis has been achieved. Evaluation of the resected primary tumor site includes monitoring of the surgical site with radiographic follow-up, typically at three-month intervals. Chest CTs at routine 3-month intervals are most useful for screening for metastatic disease to the lungs. When a recurrence or metastasis is suspected, PET scanning may be key to confirming that development [19].

Some of the most challenging sarcoma patients are those with pelvic or sacral sarcomas, as recurrences are frequently difficult to diagnosis with MRI or CT alone. Pelvic sarcomas, whether they occur as osseous or soft tissue sarcomas, represent high-risk tumors for both local recurrence and metastatic disease. PET presents an opportunity to confirm the occurrence of an early tumor recurrence and, when paired with CT, can assist in diagnosing distant pulmonary metastases [16].

Pelvic sarcomas frequently present challenges with surgical resection and have significantly higher risks of local recurrence or surgical complications such as neurovascular injuries, bladder, bowel and ureter, massive blood loss, and intra-operative death (Fig. 8.8). Pelvic and sacral tumors have a higher risk of local recurrence (30–

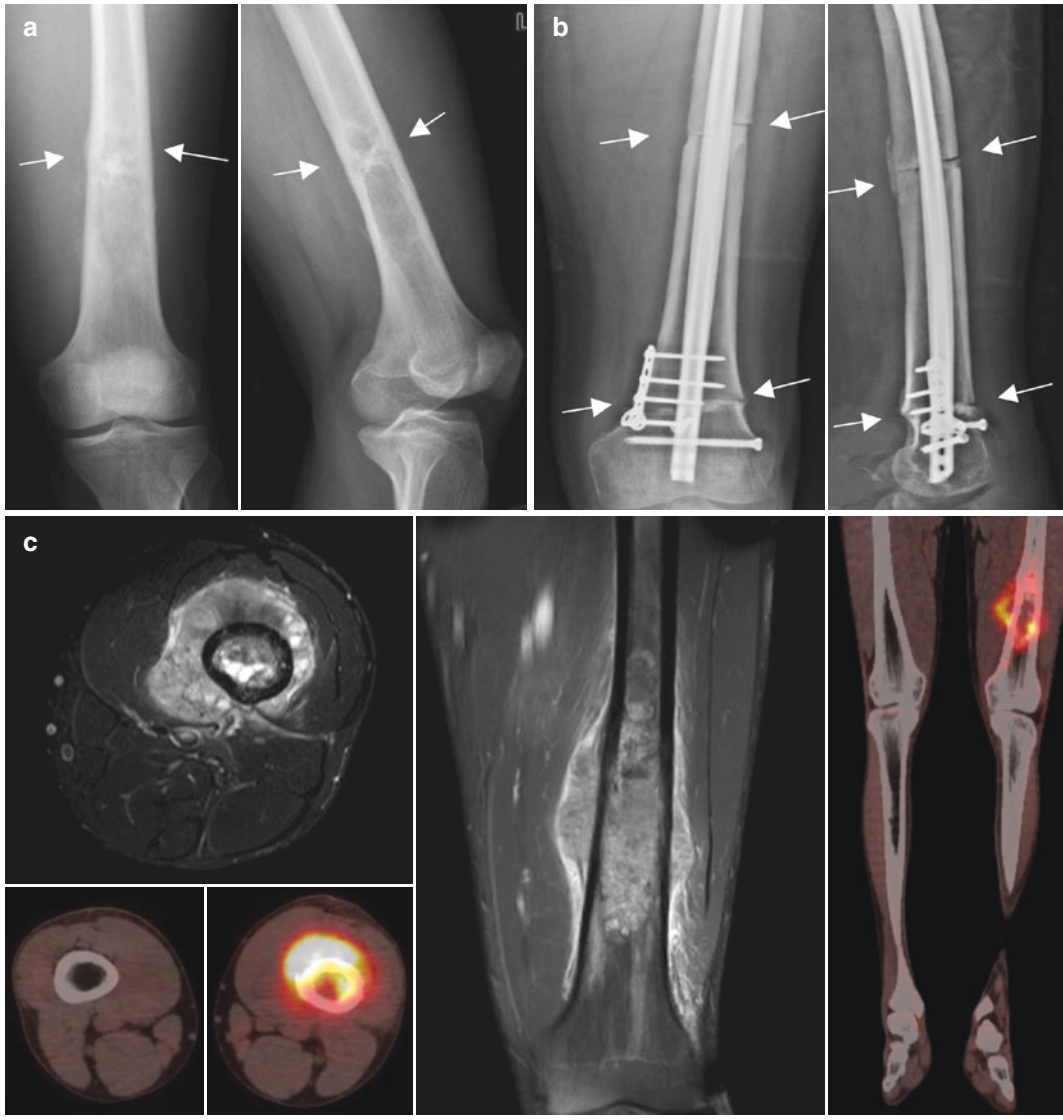

Fig. 8.6 Preop MRI and PET Imaging for a 19-year-old with femoral osteosarcoma. (**a**) Preop X-rays of femur, (**b**) postop cadaver femoral allograft reconstruction. (**c**) Pre-resection MRI. (**d**) Pre-resection PET. A 20-year-old male with a diaphyseal osteosarcoma. Preoperative (**a**) and postoperative (**b**) radiographs following a wide resection and reconstruction with an intercalary allograft fixed with an intramedullary rod as well as a unicortical plate and screws. (**b**) MRI and PET/CT scan of the same patient preoperatively. There is large, initial preoperative FDG uptake in his primary tumor site with SUV of 15.8. This patient also had multiple bilateral pulmonary metastases at presentation

50%), metastasis (30–50%), and death from their disease (10–20%) for high-grade sarcomas. Pelvic tumors also require careful preoperative imaging and surgical planning which includes both CT and MRI of the pelvis and abdomen as well as CT of the chest. Large, high-risk pelvic tumors can also be treated with neoadjuvant radiation therapy in addition to 2–3 months of neoadjuvant preop chemotherapy. In this situation, of both preop chemo and preop radiation, the surgical tumor resection will be delayed at least 12–18 weeks. Lastly, hemipelvic amputation is

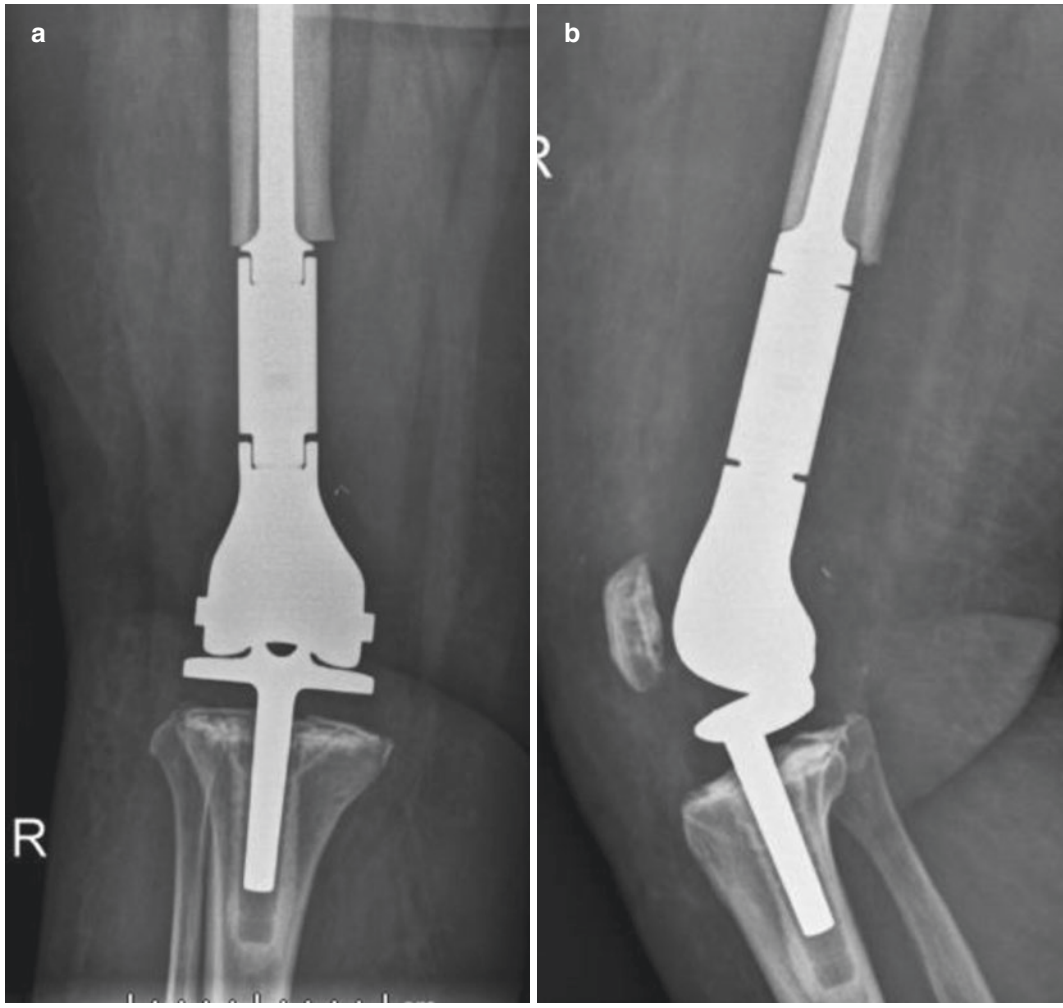

Fig. 8.7 Oncologic total knee – post 15 cm femoral resection. (**a**) Postop: Anterior view. (**b**) Postop: Lateral view

sometimes the best patient choice for resection but is also surgically challenging in obtaining adequate surgical margins at the pelvic and or sacral midline. Surgical resection for osseous pelvic tumors may also include intraoperative navigation to assist in resection accuracy which is more challenging in the pelvis than the extremities. Soft tissue sarcomas of the pelvis may present great challenges in histologic tumor response, especially as large pelvic or sacral sarcomas. Decisions regarding neoadjuvant chemotherapy and radiation therapy should be carefully planned for high-grade pelvic soft tissue sarcomas [20].

Osseous pelvic and sacral sarcomas, including osteosarcoma and osteosarcoma variants, are good candidates for preoperative chemotherapy, though they have a higher incidence of poor response to their preoperative treatment and much greater challenges with adequate surgical margins and local control after their resections. Large sacral tumors can present sarcoma imaging challenges because of PET "overlap" imaging with the bladder anteriorly, which will need resolution with both CT and MRI comparisons (Fig. 8.8: Sacral sarcoma preop imaging). Both preoperative and radiation therapy should be considered for pelvic sarcomas because of a greater challenge with local control and achieving a good response to chemo as seen with this 30-year-old male with a 14 cm syno-

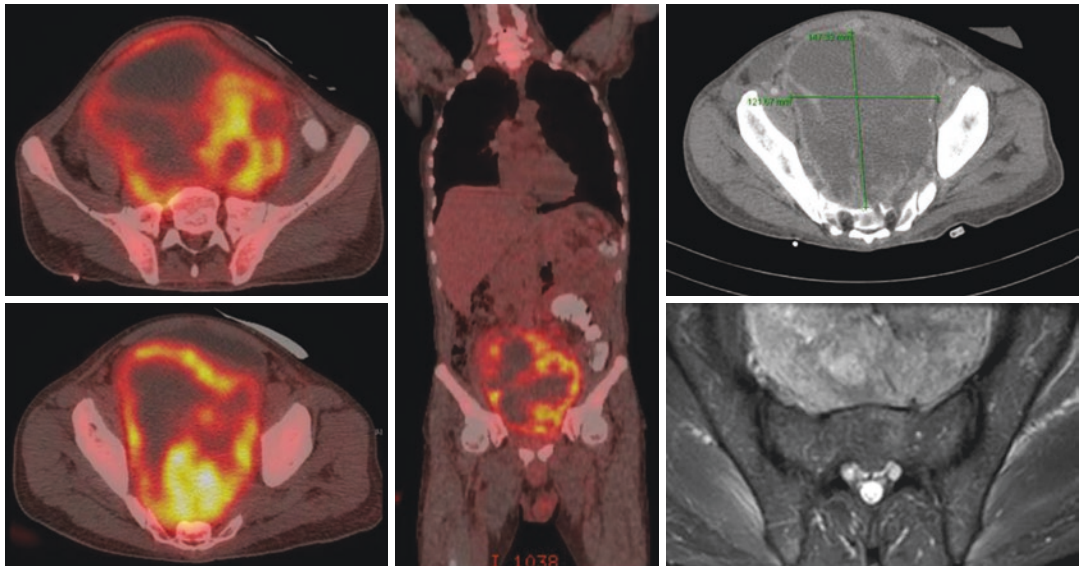

Fig. 8.8 MRI and PET Imaging for a large sacral sarcoma. Preoperative PET, CT, and MRI of a patient with a 17 cm sacral sarcoma. PET images demonstrated intense FDG activity peripherally (SUVmax = 12), with a central necrotic area. Needle biopsy demonstrated undifferentiated pleomorphic sarcoma

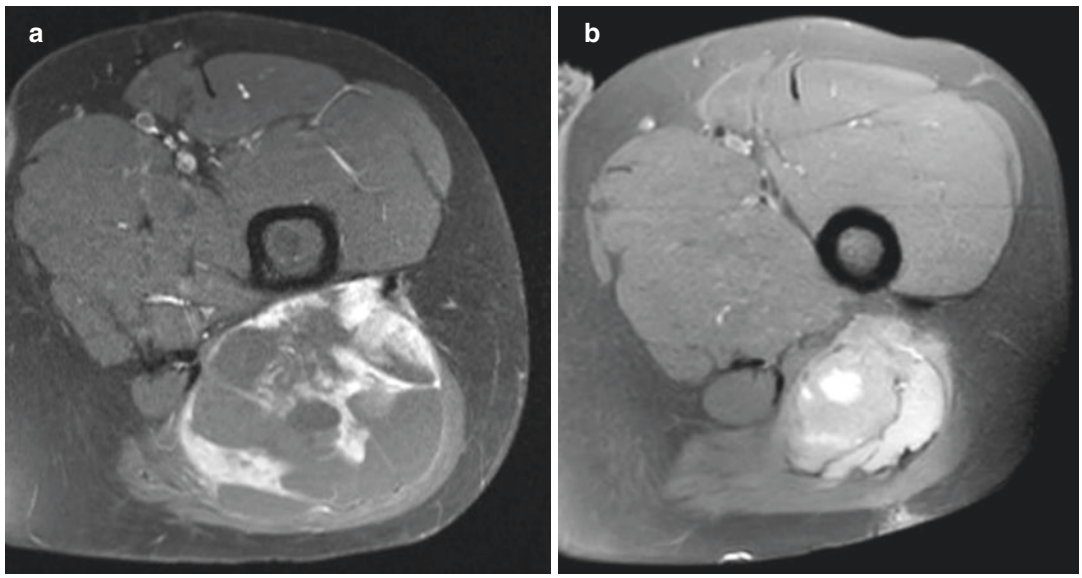

Fig. 8.9 A 30-year-old male with 15 cm posterior synovial sarcoma in the gluteus maximus – treated with preop chemotherapy and radiation therapy showing a decrease in size on pre-resection axial MRI (A pre-chemo vs B post-chemo) and a decrease in PET SUV1 (10.0) vs PET SUV2 (5.0). (**a**) Pre-chemo MRI. (**b**) Post-chemo MRI

vial sarcoma located in his gluteus maximus with a very close margin at the sciatic nerve. Figure 8.9 demonstrates a 30-year-old with a gluteal synovial sarcoma (A preop coronal FS T2 MRI) and Fig. 8.9b post-chemotherapy coronal MRI showing a decrease in tumor diameter following preop chemo therapy and radiation therapy. Preop-chemotherapy and radiation therapy allowed an uncontaminated marginal resection at the sciatic nerve after a good response to preoperative chemotherapy (preop SUV = 9.0 vs post SUV = 5.0).

After surgical resection, and after chemotherapy and radiation therapy, pelvic sarcoma patients should be followed with alternating pelvic CT and MRI at 3-month intervals for 2 years with consideration for PET scans at 6- or 12-month intervals postoperatively. As with all sarcoma patients, post-treatment follow-up should occur more frequently for the first 2 years followed by less frequent imaging for local recurrence and distant (lung) metastasis in years 3–5 [21].

Pediatric Sarcomas: The Best Indications for PET Imaging

The overall survival for pediatric patients following chemotherapy and resection is relatively high (60–70% 5-years survival) compared to their adult counterparts (40–50% 5-years survival) with a similar diagnosis. Pediatric patients with sarcomas are the optimal patients for PET imaging to assess response of neoadjuvant chemotherapy [22, 23]. Usually these patients have a better response to chemotherapy than their adult counterparts, which is usually predicted accurately by serial pre- and post-chemotherapy FDG-PET imaging. Multiple studies have corroborated the accuracy of PET in predicting chemotherapy response to pediatric osteosarcoma, Ewing sarcoma, and soft tissue sarcoma and the effectiveness of PET with pediatric staging [19, 24].

Predicting treatment response is particularly important for pediatric patients for several reasons. First, pediatric patients with a poor response to initial therapy, as measured by repeat PET/SUVs typically after 10–12 weeks of initial therapy, may receive a better and safer surgical resection or earlier modification in their systemic therapy if a poor response is appreciated on PET imaging. Second, surgical decisions and better surgical margins can be affected by the recognition of an initial positive or negative tumor response to chemotherapy is assessed. Patients with a good response are candidates for a smaller, more narrow surgical margins, potentially allowing the surgeon to spare an adjacent growth plate, knee joint, or leg with a more limited resection. Lastly, both MRI and PET SUV have been demonstrated to have good accuracy in predicting surgical margins [7]. This approach for pediatric patients has been associated with good results with regard to local tumor control (90%) and may facilitate a more functional limb salvage procedure [25].

Osseous resections in pediatric sarcomas have the surgical options of amputation, rotation plasty (modified amputation, with transfer of the ankle to the knee), an oncologic total knee, or a joint sparing diaphyseal resection of the femur or tibia with a cadaveric allograft or fibular autograft reconstruction. Sparing the patients native, adjacent physis or growth plate is a major issue for surgical decisions, and osseous reconstructions sparing the physis are greatly facilitated by serial MRI and PET/SUV imaging. The prognosis for pediatric osteosarcoma or Ewings sarcoma worsens with patient age, tumor size, or the presence of metastatic disease at presentation, and higher-risk patients require careful observation at 3–6-month intervals for 3–5 years to exclude the risk local recurrence or pulmonary metastases. Surgical treatment for children under the age of 10–12 years is associated with a better response to initial chemotherapy, but surgical resections are more challenging decisions because of the desire to spare the adjacent growth plate (physis) and/or articular joint. As a result of growth issues and a better response to preoperative chemotherapy, surgery for younger pediatric patients involves more surgical options and more challenging surgical decisions.

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