Part 4  Oncology

Chapter 1  Overview of Musculoskeletal Tumors and Preoperative Evaluation  5

Chapter 2  Biopsy of Musculoskeletal Tumors  30

Chapter 3  Overview of Endoprosthetic Reconstruction  39

Chapter 4  Expandable Prostheses  51

Chapter 5  Surgical Management of Metastatic Bone Disease: General Considerations  60

Chapter 6  Cryosurgical Ablation of Bone Tumors  68

Chapter 7  Overview of Resections Around the Shoulder Girdle  77

Chapter 8  Total Scapular Resections with Endoprosthetic Reconstruction  87

Chapter 9  Proximal Humeral Resection with Allograft Prosthetic Composite  93
Chapter 10
Proximal Humerus Resection with Endoprosthetic Replacement: Intra-articular and Extra-articular Resections 100

Chapter 11
Distal Humeral Resection with Prosthetic Reconstruction 000

Chapter 12
Surgical Management of Metastatic Bone Disease: Humeral Lesions 000

Chapter 13
Axillary Space Exploration and Resections 000

Chapter 14
Forequarter Amputation 000

Chapter 15
Above-Elbow and Below-Elbow Amputations 000

Chapter 16
Primary and Metastatic Tumors of the Spine: Total En Bloc Spondylectomy 000

Chapter 17
Overview on Pelvic Resections: Surgical Considerations and Classifications 000

Chapter 18
Surgical Technique for Resection and Reconstruction of Supra-acetabular Metastatic Lesions 000

Chapter 19
Buttockectomy 000

Chapter 20
Surgical Management of Metastatic Bone Disease: Pelvic Lesions 000
Chapter 21
Posterior Flap Hemipelvectomy

Chapter 22
Anterior Flap Hemipelvectomy

Chapter 23
Hip Disarticulation

Chapter 24
Proximal and Total Femur Resection with Endoprosthetic Reconstruction

Chapter 25
Distal Femoral Resections with Endoprosthetic Replacement

Chapter 26
Proximal Tibia Resection with Endoprosthetic Reconstruction

Chapter 27
Fibular Resections

Chapter 28
The Use of Free Vascularized Fibular Grafts for Reconstruction of Segmental Bone Defects

Chapter 29
Use of Allografts and Segmental Prostheses for Reconstruction of Segmental Bone Defects

Chapter 30
Quadriceps Resections

Chapter 31
Adductor Muscle Group (Medial Thigh) Resection
Chapter 32
Hamstrings Muscle Group (Posterior Thigh) Resection

Chapter 33
Overview of Surgical Resection of Space Sarcomas

Chapter 34
Popliteal Resections

Chapter 35
Soleus Resection

Chapter 36
Surgical Approach and Management of Tumors of the Sartorial Canal

Chapter 37
Surgical Management of Metastatic Bone Disease: Femoral Lesions

Chapter 38
Foot and Ankle Amputations: Ray Resections

Chapter 39
Creating an Above-Knee Amputation Stump After Hip Disarticulation

Chapter 40
Above-Knee Amputation

Chapter 41
Below-Knee Amputation

Chapter 42
Foot and Ankle Amputations: Lisfranc/Chopart
OVERVIEW
- An understanding of the basic biology and pathology of bone and soft tissue tumors is essential for appropriate planning of their treatment.
- This chapter reviews the unique biologic behavior of soft tissue and bone sarcomas, which provides the basis for their staging and resection and the use of appropriate adjuvant treatment modalities.
- A detailed description of the clinical, radiographic, and pathological characteristics for the most common sarcomas is presented.

EPIDEMIOLOGY
- Soft tissue and bone sarcomas are a rare and heterogeneous group of tumors. These neoplasms represent less than 1% of all adult and 15% of pediatric malignancies.
- As of 2006, the annual incidence in the United States, which remains relatively constant, was approximately 6000 to 7000 soft tissue sarcomas and 2750 bone sarcomas.
- In 2006, the overall mortality rate was 30% for soft tissue sarcomas and 45% for bone sarcomas.
- In the U.S., the 5-year survival rates for osteosarcoma and Ewing sarcoma were comparable among 15- to 29-year-olds, about 60% for the most recent era. Survival rates for chondrosarcoma exceeded 90% in the most recent era. The U.S. bone cancer mortality was highest for males and females 15 to 19 years of age.

RISK FACTORS
- Risk factors for soft tissue and bone sarcomas include previous radiation therapy, exposure to chemicals (eg, vinyl chloride, arsenic), immunodeficiency, prior injury (scars, burns), chronic tissue irritation (foreign body implants, lymphedema, chronic infection), neurofibromatosis, Paget disease, bone infarcts, and genetic cancer syndromes (eg, hereditary retinoblastoma, Li-Fraumeni syndrome, Gardner syndrome, Rothmund–Thomson syndrome, Werner syndrome, Bloom syndrome), hereditary multiple exostoses. In most patients, however, no specific etiology can be identified.
- In the past two decades, both survival and quality of life of patients with soft tissue and bone sarcomas have improved dramatically as a result of the multimodality treatment approach. Limb-sparing surgery, used in combination with chemotherapy and radiation therapy, can achieve cure in the majority of patients with soft tissue and bone sarcomas, and resection is performed in lieu of amputation in more than 90% of all patients.
- The three most common soft tissue sarcomas are malignant fibrous histiocytoma (MFH), liposarcoma, and leiomyosarcoma. The most common bone sarcomas are osteosarcoma, chondrosarcoma, and Ewing sarcoma.

PATHOPHYSIOLOGY AND BIOLOGIC BEHAVIOR
- Sarcomas originate primarily from elements of the mesodermal embryonic layer.
- Soft tissue sarcomas are classified according to the adult tissue that they resemble.
- Similarly, bone sarcomas usually are classified according to the type of matrix production: osteoid-producing sarcomas are classified as osteosarcomas, and chondroid-producing sarcomas are classified as chondrosarcomas.
- Tumors arising in bone and soft tissues have characteristic patterns of biologic behavior because of their common mesenchymal origin and anatomic environment. Those unique patterns form the basis of the staging system and current treatment strategies.
- Histologically, sarcomas are graded as low, intermediate, or high grade. The grade is based on tumor morphology, extent of pleomorphism, atypia, mitosis, matrix production, and necrosis, with the two main factors being mitotic count and spontaneous tumor necrosis.
- Tumor grade represents the tumor's biologic aggressiveness and correlates with the likelihood of metastases. Low-grade lesions metastasize in fewer than 15% of patients. High-grade lesions metastasize in over 20% of patients.
- Sarcomas form a solid mass that grows centrifugally, with the periphery of the lesion being the least mature.
- In contradistinction to the true capsule that surrounds benign lesions, which is composed of compressed normal cells, sarcomas usually are enclosed by a reactive zone, or pseudocapsule. This pseudocapsule consists of compressed tumor cells and a fibrovascular zone of reactive tissue with a variable inflammatory component that interacts with the surrounding normal tissues.
- The thickness of the reactive zone varies according to the histogenic type and grade of malignancy. High-grade sarcomas have a poorly defined reactive zone that may be locally invaded by the tumor (FIG 1A).
- Tumor foci within the reactive zone are called satellite lesions.
- High-grade, and occasionally low-grade, may break through the pseudocapsule to form metastases, termed skip metastases, within the same anatomic compartment in which the lesion is located. By definition, these are locoregional micrometastases that have not passed through the circulation (FIG 1B).
- This phenomenon may be responsible for local recurrences that develop in spite of apparently negative margins after a resection.
- Although low-grade sarcomas regularly interdigitate into the reactive zone, they rarely form tumor skip nodules beyond that area (FIG 1C, D).
- Sarcomas respect anatomic borders. Local anatomy influences tumor growth by setting natural barriers to extension. In
Figure 1 • A. Gross specimen. A pseudocapsule of a high-grade soft tissue sarcoma (arrows) composed of compressed tumor cells and a fibrovascular zone of reactive inflammatory response. B. Pathology specimen. Multiple satellite nodules (arrows) associated with a high-grade malignant fibrous histiocytoma (MFH). Note the normal intervening tissue. C. Biologic behavior of bone and soft tissue sarcomas. Unique features are formation of reactive zone, intracompartmental growth, and, rarely, the presence of skip metastases. Skip nodules are tumor foci not in continuity with the main tumor mass that form outside the pseudocapsule. “Satellite” nodules, by contrast, form within the pseudocapsule. D. Gross specimen. Skip metastases (arrows) from an osteosarcoma of the distal femur. This finding is documented preoperatively in less than 5% of patients. E. Sagittal section of a high-grade osteosarcoma of the distal femur. The growth plate, although not invaded by the tumor in this case, is not considered an anatomic barrier to tumor extension, probably because of the numerous vascular channels that pass through the growth plate to the epiphysis. However, the articular cartilage is an anatomic barrier to tumor extension and very rarely is directly violated by a tumor. F. Coronal section of a high-grade osteosarcoma of the distal femur. Although gross involvement of the epiphysis and medial cortical breakthrough and soft tissue extension are evident, the articular cartilage is intact. This phenomenon allows intra-articular resection of high-grade sarcomas of the distal femur in most cases. Thick fascial planes are barriers to tumor extension. G. Axial MRI, showing a high-grade leiomyosarcoma of the vastus lateralis and vastus intermedius muscles. The tumor does not penetrate, looking in a clockwise direction, the lateral intermuscular septum, the adductor compartment, and the aponeuroses of the sartorius and rectus femoris muscles. (Courtesy of Martin M. Malawer.)
general, sarcomas take the path of least resistance and initially grow within the anatomic compartment in which they arose. It is only at a later stage that the walls of the compartment are violated (either the cortex of a bone or aponeurosis of a muscle), at which time the tumor breaks into a surrounding compartment.

- Typical anatomic barriers are articular cartilage, cortical bone, and fascial borders. The growth plate is not considered an anatomic barrier, because it has numerous vascular channels that run through it to the epiphysis (FIG 1E–G).
- Sarcomas are defined as **intracompartmental** if they are encased within an anatomic compartment.
- **Extracompartmental tumors** are those that grow out through the compartment barrier or tumors that have arisen in extracompartamental spaces (space tumors), ie, popliteal fossa, groin, sartorial canal, axilla, and antecubital fossa (FIG 2A,B).
- Most bone sarcomas are intracompartmental at the time of presentation; they destroy the overlying cortex and extend directly into the adjacent soft tissues.
- Carcinomas, which typically present in the extremities as metastatic disease, directly invade the surrounding tissues, irrespective of compartmental borders (FIG 2C–E).

- Joint involvement in sarcoma is uncommon, because direct tumor extension through the articular cartilage is rare. Mechanisms of joint involvement in sarcoma are as follows:
  - Pathological fracture with seeding of the joint cavity
  - Pericapsular extension
  - Structures that pass through the joint (eg, the cruciate ligaments) may act as a conduit for tumor growth (FIG 3)
  - Transcapsular skip nodules: demonstrated in 1% of all osteosarcomas
  - Direct articular extension.

**Metastatic Bone and Soft Tissue Sarcomas**

- Unlike carcinomas, bone and soft tissue sarcomas disseminate almost exclusively through the blood. Hematogenous spread of extremity sarcomas is manifested by pulmonary involvement in the early stages and by bony involvement in later stages. Abdominal and pelvic soft tissue sarcomas, on the other hand, typically metastasize to the liver and lungs.
- Low-grade soft tissue sarcomas have a low (under 15%) rate of subsequent metastasis, whereas high-grade lesions have a significantly higher (over 20%) rate of metastasis.
- Metastases from sarcomas to regional lymph nodes are uncommon; the condition is observed in only 13% of patients with soft tissue sarcomas and 7% of those with bone sarcomas.
at initial presentation. The prognosis is similar to that of distant metastasis (FIG 4).

- Most patients with high-grade primary bone sarcomas, unlike soft tissue sarcomas, have distant micrometastases at presentation; an estimated 80% of patients with osteosarcomas have micrometastatic lung disease at the time of diagnosis. For this reason, in most cases, cure of a high-grade primary bone sarcoma can be achieved only with systemic chemotherapy and surgery.
- As mentioned, high-grade soft tissue sarcomas have a lower metastatic potential. Because of that difference in metastatic capability, the role of chemotherapy in the treatment of soft tissue sarcomas and its impact on survival are still matters of some controversy.

**PROGNOSTIC FACTORS**

- Prognostic factors for bone sarcomas include grade, size, extension of tumor beyond the bone cortex, regional and metastatic disease, and response of the tumor to chemotherapy (necrosis rate).
- Prognostic factors for soft tissue sarcomas include grade, tumor size, depth, age, margin status, location (proximal vs. distal), histologic subtypes, and metastatic disease.

**Staging**

- **Staging** is the process of classifying a tumor, especially a malignant tumor, with respect to its degree of differentiation, as well its local and distant extent, to plan the treatment and estimate the prognosis. Staging of a musculoskeletal tumor is based on the findings of the physical examination and the results of imaging studies. Biopsy and histopathological evaluation are essential components of staging but should always be the final step. An important variable in any staging system for musculoskeletal tumors, unlike a staging system for carcinomas, is the grade of the tumor.
- The system most commonly used for the staging of soft tissue sarcomas is the one developed by the American Joint Committee on Cancer (Table 1). It is based primarily on the Memorial–Sloan Kettering staging system and does not apply to rhabdomyosarcoma. Critics of this system point out that it is based largely on single-institution studies that were not subjected to multi-institutional tests of validity. The Musculoskeletal Tumor Society adopted staging systems that
# OVERVIEW OF MUSCULOSKELETAL TUMORS AND PREOPERATIVE EVALUATION

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Primary Tumor</th>
<th>Metastasis in Regional Lymph Nodes</th>
<th>Distant Metastasis</th>
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<td>T1a or T1b</td>
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<td>M0</td>
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<tr>
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<td>N0</td>
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</tr>
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Table 2

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<td>G1 or G2</td>
<td>T1 or T2</td>
<td>M0</td>
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</table>

Table 3

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<th>Stage</th>
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<th>Distant Metastasis</th>
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<td>IVB</td>
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<td>Any T</td>
<td>N0</td>
<td>M1</td>
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*Groshen et al. 2001;39.2:1891–1935*

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originally were described by Enneking et al. 2–4 for malignant soft tissue and bone tumors (Table 2), and the American Joint Committee on Cancer developed, with a few changes, a staging system for malignant bone tumors (Tables 3 and 4).

- Enneking’s classical staging system is based on three factors: histologic grade (G), site (T), and the presence or absence of metastases (M). The anatomic site (T) may be either intracompartmental (A) or extracompartmental (B). This information is obtained preoperatively on the basis of the data gained from the various imaging modalities. A tumor is classified as intracompartmental if it is bounded by natural barriers to extension, such as bone, fascia, synovial tissue, peristeum, or cartilage. An extracompartmental tumor may be either a tumor that has violated the borders of the compartment from which it originated, or a tumor that has originated and remained in the extracompartmental space. A tumor is assigned to stage III (M1) if a metastasis is present at a distant site or in a regional lymph node.

- Enneking’s classification system is based on clinical data from an era in which chemotherapy was not given preoperatively and compartmental resections were much more common.
mon. Therefore, there was a clear correlation between the extent of the tumor at presentation, its relation to the boundaries of the compartment in which it is located, and the extent of surgery. A close correlation also was found between surgical stage of bone sarcoma and patient survival (FIG 5). Since that time, the use of neoadjuvant chemotherapy has been shown to decrease tumor size and facilitate limb-sparing surgery, as well as reduce the local recurrence rate. As a result, compartmental resections have become rare. Nonetheless, Enneking’s classification is based on the biological behavior of soft tissue and bone sarcomas, and its underlying concept is as relevant today as it was in the early 1980s (Tables 1–4).

Approximate survival rates by stage for extremity soft tissue sarcomas are 90% for stage I, 70% for stage II, and 50% for stage III.

### Staging Benign Bone Tumors

Enneking also described a staging system for benign bone tumors, which remains the one that is most commonly used (Table 4). That system is based on the biologic behavior of these tumors as suggested by their clinical manifestation and radiologic findings. Benign bone tumors grow in a centrifugal fashion, as do their malignant counterparts, and a rim of reactive bone typically is formed as a response of the host bone to the tumor. The extent of that reactive rim reflects the rate at which the tumor is growing: it usually is thick and well-defined around slowly growing tumors, and barely detectable around fast-growing, aggressive tumors.

- Latent benign bone tumors are classified as stage 1. Such tumors usually are asymptomatic and commonly are discovered as an incidental radiographic finding. Their natural history is of slow growth, and in most cases, they heal spontaneously. These lesions never become malignant and usually heal following simple curettage. Examples include fibrous cortical defects and nonossifying fibromas (FIG 6A).
- Active benign bone tumors are classified as stage 2 lesions. These tumors grow progressively but do not violate natural barriers. Associated symptoms may occur. Curettage and burr drilling are curative in most cases (FIG 6B–E).
- Aggressive benign bone tumors (stage 3) may cause destruction of surrounding bone and usually break through the cortex into the surrounding soft tissues. Local control can be achieved only by curettage and meticulous burr drilling with a local adjuvant such as liquid nitrogen, argon beam laser, or phenol. Wide resection of the lesion with a margin of normal tissue (FIG 6D,E) is another option.

### EVALUATION OF THE PATIENT WITH A MUSCULOSKELETAL LESION

#### Presenting Symptoms

- Bone sarcomas typically present with pain that starts out as intermittent and progresses to a constant pain. Night pain often is a component. Pain typically is deep-seated and dull and may resemble that of a toothache. Patients with high-grade tumors present with a history of several months of pain. Patients with low-grade tumors, by contrast, present with a history of mild pain, typically lasting more than half a year. Local soft tissue swelling is common.
- Soft tissue sarcomas can arise anywhere in the body, but the lower extremities are the most common site. The incidence is as follows:
  - Lower extremities: 46%
  - Trunk: 19%
  - Upper extremities: 13%
  - Retroperitoneum: 12%
  - Head and neck: 9%
  - Other locations: 1%.
- The presenting symptoms and signs of soft tissue sarcomas are nonspecific. These lesions commonly present as a painless, slow-growing mass, but in 20% of patients they present as a painful, rapidly growing mass.

#### Physical Examination

- Patients with suspected musculoskeletal tumors should be examined thoroughly. The affected site is inspected for soft tis-
sue mass or swelling, overlying skin changes, lymphadenopathy, neurologic deficit, and vascular deficiency.

Imaging and Other Staging Studies

Plain Radiography
- Plain radiographs remain key in imaging bone tumors. Based on medical history, physical examination, and plain radiographs, bone tumors can be diagnosed accurately in over 80% of cases.
- Because of the fine trabecular detail revealed by plain radiographs, bone lesions of the extremities can be detected at an earlier stage; lesions of the spine and pelvis, however, are not diagnosed until a large volume of bone has been destroyed.
- Plain radiographs can show the location of the tumor in the bone, cortical destruction and thickening, periosteal response to the tumor (e.g., Codman’s triangle, sunburst), type of matrix produced by the tumor (osteoid, chondroid, fibrous), and soft tissue calcifications.

Computed Tomography
- Computed tomography (CT) is the imaging modality of choice to evaluate the extent of bone destruction. CT should be performed on a helical scanner that enables improved two-dimensional images and three-dimensional (3D) reconstruction capability. The field of view should be small enough to allow adequate resolution, particularly of the lesion and the adjacent neurovascular bundle and muscle groups. A slice thickness of 1 mm or less through the tumor enables accurate 3D reconstructions. Intravenous contrast dye should be employed to demonstrate the anatomic relation between the tumor and arterial vessels and to enhance soft tissue tumors, unless there is a clear contraindication for its use.
- Three-dimensional CT reconstruction with intravenous contrast accurately demonstrates blood vessels that are likely to be distorted or, less commonly, incorporated directly into the tumor mass. This information helps the surgeon plan the anatomic approach and gauge the likelihood that a major blood vessel has to be resected en bloc with the tumor (FIG 7A).
- Chest CT is the modality of choice when evaluating the patient for metastatic lung disease for both preoperative staging and postoperative follow-up (FIG 7B).

Magnetic Resonance Imaging
- Magnetic resonance imaging (MRI) has been proven to be superior to CT in the evaluation of the intramedullary and extrasosseous soft tissue extent of bone tumors (FIG 7C-F) and soft tissue sarcomas.
- Anatomic location and relation of the tumor can be defined accurately, because the signal intensity of a tumor is assessed by comparing it with that of the adjacent soft tissues, specifically skeletal muscle and subcutaneous fat. MRI also make it possible to view a lesion in all three planes (i.e., axial, sagittal, and coronal).
Contrast-enhanced MRI is useful in evaluating the relation between a tumor and the adjacent blood vessels and in characterizing cystic lesions. The anatomic relation between the tumor and peripheral nerves may be assessed. The presence of orthopedic hardware or surgical clips is not a contraindication to the performance of MRI; however, if a lesion is immediately adjacent to the location of the hardware, the local field may be distorted.

MRI can accurately diagnose a variety of soft tissue tumors, including lipomas, liposarcomas, synovial cysts, pigmented villonodular synovitis, hemangiomas, and fibromatoses. Hematomas often have a characteristic appearance on MRI; however, high-grade sarcomas that have undergone significant intratumoral hemorrhage may resemble hematomas. For this reason, the diagnosis of a simple hematoma should be made cautiously, and, once it is made, close clinical monitoring must be made until the condition has been resolved. The general guidelines regarding narrowing of the field and recommended number of slices per tumor are similar to those for CT.

MRI allows accurate evaluation of the medullary extent of bone tumors to determine the level of bone resection with safe but narrow margins.

**Bone Scan**

Bone scan currently is used to determine the presence of metastatic and polyostotic bone disease and the involvement of a bone by an adjacent soft tissue sarcoma. This modality is more sensitive than plain radiographs for identifying bone lesions.

The appearance of a bone lesion in the flow and pool phases of a three-phase bone scan reflects its biologic activity and may be helpful in differentiating between benign and malignant lesions. This feature is known as **tumor blush**. Malignant tumors show uptake in the late flow phase. Response to
FIG 7 (continued) G. MRI of a large thigh high-grade (Stage IIb) soft tissue sarcoma. The thigh is the most common site for extremity soft tissue sarcomas. MRI evaluation is the most useful study in determining the extent of soft tissue sarcomas. H. Bone scan of a proximal humeral (RT) osteosarcoma. I. Limb-sparing surgery for a proximal humeral osteosarcoma. The defect was reconstructed by a modular segmental prosthesis. J. Extensive giant cell tumor of the proximal tibia. Angiography performed prior to a proximal tibia resection documented an absent peroneal artery. A successful effort was made to preserve the anterior tibial artery during the resection; otherwise, the leg would have been dependent on a single vessel. K. Angiogram of a distal femoral (diaphyseal) osteosarcoma following induction chemotherapy. Note that the tumor is avascular. The decrease of tumor vascularity is an extremely reliable finding in predicting tumor necrosis. L. Gross specimen of a diaphyseal osteosarcoma following resection and induction chemotherapy. There was 100% tumor necrosis. M. Axillary venogram showing venous occlusion. Venography is especially useful in evaluating tumors of the pelvis and shoulder girdle. (C–F, J: Courtesy of Martin M. Malawer.)
chemotherapy can be evaluated by comparing the tumor blush before and after neoadjuvant chemotherapy.

**Angiography and Other Studies**
- Angiography is useful in demonstrating arterial displacement and occlusion, which are common in tumors that have a large extraosseous component. It also can detect vascular anomalies (**FIG 7J**) and establish patency of collateral vessels. Proximal femur resection, for example, often necessitates ligation of the profundus femoral artery (PFA). A patent superficial femoral artery (SFA) must be documented by angiography prior to surgery, otherwise, the extremity will suffer severe ischemia following ligation of the PFA. CT angiography is an emerging modality that will likely replace angiography in preoperative tumor evaluation.
- Preoperative embolization may be useful in preparing for resection of metastatic vascular carcinomas if an intralesional procedure is anticipated. Metastatic hypernephroma is an extreme example of a vascular lesion that may bleed extensively and cause exsanguination without prior embolization.
- Serial angiographs may demonstrate reduced tumor vascularity as a result of chemotherapy treatment. Such a reduction has been shown to indicate a good response to preoperative chemotherapy (**FIG 7K–L**).

**Venography**
- Contrast venography demonstrates partial occlusion or complete obliteration of major veins as a result of direct tumor invasion or indirect compression by the tumor mass. Venography is used for direct assessment of deep vein thrombosis.
- Venography also can indirectly assess tumor invasion into major nerves that lie in close proximity. Axillary tumors often are found to have invaded the brachial plexus when venography shows axillary vein occlusion (**FIG 7M**).

**PET CT**
- Positron emission tomography (PET) is a functional diagnostic imaging technique that provides very different information from that obtainable with other imaging modalities. PET-CT scanners, which provide not only functional but also structural information leading to a detection of subcentimeter lesions, have made this technique useful in the early detection of the disease process and in decreasing false-positive lesions. The FDG uptake is measured in SUV units, quantifying uptake and thereby differentiating malignant disease from other possible causes such as inflammatory or infectious processes.

**FIGURE 8** summarizes the use of the various imaging modalities in the staging process of a primary bone sarcoma.

**Biopsy**
- The concept and practice of biopsy of musculoskeletal tumors are discussed in ON-2.

**Laboratory Studies**
- Laboratory studies often are nonspecific. For patients younger than 40 years of age, they include a complete blood count with differential, peripheral blood smear, and erythrocyte sedimentation rate. Patients older than 40 years also need blood calcium and phosphate levels, serum and urine electrophoresis, and urinalysis.
- Serum alkaline phosphatase levels in primary osteosarcomas correlate with disease prognosis; therefore, pretreatment levels should be recorded.

**Formulating an Initial Assessment**
- Age of the patient
- In younger patients (10–25 years), the common malignant bone tumors are osteosarcoma, Ewing sarcoma, and...
leukemia. The common benign bone tumors are enchondroma, fibrous dysplasia, and eosinophilic granuloma.

- In the older age groups (40–80 years), the common malignant bone tumors are metastatic bone disease, myeloma, and lymphoma.
- Anatomic location of the tumor within the bone. Certain lesions have a predilection for occurring at particular locations:
  - Adamantinoma: in the tibia
  - Chondroblastoma: in the epiphysis of long bones
  - Giant cell tumor: in the metaphysis and extending through the epiphysis to lie just below the cartilage, typically around the knee
  - Osteosarcoma: in the metaphysis of the distal femur or proximal tibia
  - Parosteal osteosarcoma: in the distal femur (posterior cortex)
  - Chondrosarcoma: in the pelvis
  - Chordoma: in the sacrum
  - Synovial sarcoma: in the foot and ankle
  - Enchondroma and metastatic lung carcinoma: in the fingers
- The effect of the lesion on the bone
  - High-grade lesions spread rapidly, causing early cortical bone destruction and expansion. The typical lytic appearance is permeative or moth-eaten.
  - Low-grade tumors spread at a slower pace, but may still destroy cortical bone and produce a soft tissue mass.
- The response of the bone to the lesion
  - High-grade lesions spread rapidly and give the bone little ability to contain the process. Cortical destruction, periosteal elevation (e.g., Codman’s triangle, onion skin appearance), and soft tissue spread (sunburst appearance) often are seen.
- Matrix production
  - Osteoid mineralization often is cloudlike and is typical of bone-forming tumors.
  - Cartilage calcification often appears stippled and is characteristic of cartilage-forming tumors.
  - Fibrous-forming tumors have a typical “ground glass” appearance

**SURGICAL MANAGEMENT**

**Classification of Surgical Procedures**

- Four basic types of excisions are used, each of which is based on the relation between the dissection plane and the tumor and its pseudocapsule: intralesional, marginal, wide, and radical excisions (FIG 9).
- An intralesional excision is performed within the tumor mass and results in removal of only a portion of the tumor; the pseudocapsule and macroscopic tumor are left behind.
- In a marginal excision, the dissection plane passes through the pseudocapsule of the tumor. Such a resection may leave microscopic disease.
- Wide (en bloc) excision entails removal of the tumor, its pseudocapsule, and a cuff of normal tissue surrounding the tumor in all directions. This is the desired resection margin for sarcoma; however, the adequate thickness of the normal tissue cuff is a matter of some controversy. For both soft tissue and bone sarcomas, it generally is believed to be between 0.5 and 2 cm.
- Radical excision involves removal of the tumor and the entire anatomic compartment within which it arises. Although traditionally mentioned as the fourth excision type, it does not define the component of the tumor that is left behind. In other words, a radical excision can achieve a marginal or a wide margin, depending on how close the tumor is to the border of the compartment. However, radical excision excludes the possibility of skip metastases.
- In general, benign bone tumors are adequately treated by either an intralesional procedure (e.g., curettage and burr drilling, cryosurgery) or by marginal excision. Primary bone sarcomas are treated with wide excision. Metastatic tumors are treated according to the general intent of the surgery. When a palliative surgery is performed, metastatic lesions are treated by an intralesional procedure. If a curative procedure is performed, as in the case of solitary breast metastasis, for example, the lesion is treated as if it was a primary bone sarcoma (i.e., wide excision).
Successful limb-sparing surgery consists of three phases:

- Resection of tumor. Resection follows the principles of oncologic surgery strictly. Avoiding local recurrence is the criterion of success and the main determinant of the amount of bone and soft tissue to be removed.
- Skeletal reconstruction. The average skeletal defect following adequate bone tumor resection measures 15 to 20 cm. Techniques of reconstruction (eg, prosthetic replacement [FIG 10], arthrodesis, allograft, or combination) vary and are independent of the resection, although the degree of resection may favor one technique over the other.
- Soft tissue and muscle transfers. Muscle transfers are performed to cover and close the resection site and to restore lost motor power. Adequate skin and muscle coverage is mandatory to decrease postoperative morbidity.

Guidelines for Surgical Resection

- The major neurovascular bundle must be free of tumor.
- Wide resection of the affected bone with a normal muscle cuff in all directions should be achieved.
- All previous biopsy sites and all potentially contaminated tissues should be removed en bloc.
- Bone should be resected 3 to 4 cm beyond abnormal uptake as determined by bone scan. (This is a safe margin to avoid intraosseous tumor extension.)
- The adjacent joint and joint capsule should be resected.
- Adequate motor reconstruction must be accomplished by regional muscle transfers.
- Adequate soft tissue coverage is needed to decrease the risk of skin flap necrosis and secondary infection.

MALIGNANT BONE TUMORS

- Primary malignancies of bone arise from mesenchymal cells (sarcoma) and bone marrow cells (myeloma and lymphoma). Bone also is a common site of metastasis from a variety of carcinomas. Osteosarcoma and Ewing sarcoma, the most common malignant mesenchymal bone tumors, usually occur during childhood and adolescence. Other mesenchymal tumors (eg, MFH, fibrosarcoma, chondrosarcoma), while occasionally seen in childhood, are more common in adults. Multiple myeloma and metastatic carcinoma typically increase in frequency with increasing patient age and usually are seen in patients over 40 years of age. This section describes the clinical, radiographic, and pathological characteristics and treatment of the primary bone sarcomas.
- Osteosarcoma provides the model on which treatment of all other sarcomas is based. The effectiveness of multiagent chemotherapy regimens has been proven with the increase in overall survival rates from the bleak statistic of 15% to 20% with surgery alone in the 1970s to 55% to 80% today. In par-
allele with improved survival, dramatic advances in reconstructive surgery have made it possible for limb salvage to supplant amputation as the standard method of treatment.

Osteosarcoma

- Osteosarcoma is the most common primary bone sarcoma. Osteosarcoma (OS) is a high-grade malignant spindle cell tumor arising within a bone. Its distinguishing characteristic is the production of "tumor" osteoid, or immature bone, directly from a malignant spindle cell stroma. OS typically occurs during childhood and adolescence. In patients over the age of 40, it usually is associated with a preexistent disease such as Paget disease, irradiated bones, multiple hereditary exostosis, or polyostotic fibrous dysplasia.
- The incidence of osteosarcoma peaks to 8 per million per year between the ages of 10 and 20 years. Survival of osteosarcoma patients has improved greatly over the past 30 years. The 5-year survival rate is 60%, except in patients over age 45, where it is 40%.
- The most common bone sites are the knee joint (50%) and the proximal humerus (25%). Between 80% and 90% of osteosarcomas occur in the long tubular bones; the axial skeleton rarely is affected (FIG 11).
- Pain, accompanied by a tender soft tissue swelling, is the most common complaint on presentation, with a firm, soft tissue mass fixed to the underlying bone found on physical examination. Systemic symptoms are rare. The incidence of pathologic fractures is less than 1%.

Radiographic Characteristics

- Typical radiographic findings include increased intramedullary sclerosis due to tumor bone or calcified cartilage; an area of radiolucency due to nonossified tumor; a pattern of permeative destruction with poorly defined borders; cortical destruction; periosteal elevation; and extrasosseous extension with soft tissue ossification. This combination of characteristics is not seen with any other lesion.
- Three broad categories are based on radiographic evaluation (FIG 12A–C): sclerotic osteosarcoma (32%), osteolytic osteosarcoma (22%), and mixed (46%). Although there is no statistically significant difference among overall survival rates of these types, it is important to recognize the patterns. The sclerotic and mixed types offer few diagnostic problems. Errors of diagnosis most often occur with pure osteolytic tumors. The differential diagnosis of osteolytic osteosarcoma includes giant cell tumor, aneurysmal bone cyst, fibrosarcoma, and MFH.

Microscopic Characteristics

- The diagnosis of osteosarcoma is based on the following findings:
  - Identification of a malignant stroma that produces unequivocal osteoid matrix. The stroma consists of a haphazard arrangement of highly atypical cells.
  - Pleomorphic cells that contain hyperchromatic, irregular nuclei. Mitotic figures, often atypical, usually are easy to identify. Between these cells is a delicate, lacelike eosinophilic matrix, assumed to be malignant osteoid (FIG 12D).
  - The predominance of one tissue type in many osteosarcomas has led to a histologic subclassification of this neoplasm.
  - The term osteoblastic osteosarcoma is used for those tumors in which the production of malignant osteoid prevails. Calcification of the matrix is variable.
  - Some tumors reveal a predominance of malignant cartilage production; hence, they are referred to as chondroblastic osteosarcoma. Even though the malignant cartilaginous elements may be overwhelming, the presence of a malignant osteoid matrix warrants the diagnosis of osteosarcoma.
  - Yet another variant is characterized by large areas of proliferating fibroblasts, arranged in intersecting fascicles. Such areas are indistinguishable from fibrosarcoma, and thorough sampling may be necessary to identify the malignant osteoid component.
  - As the neoplasm permeates the cortex, the periosteum may be elevated. This stimulates reactive bone formation and accounts for a distinctive radiologic feature called "Codman's triangle." Longitudinal sectioning of the involved bone often reveals wide extension within the marrow cavity. Rarely, skip areas within the medullary canal can be demonstrated. There may be necrotic and hemorrhagic foci. At the time of diagnosis, most tumors already have caused substantial cortical destruction. Continued tumor growth results in involvement of the adjacent soft tissues (FIG 12E).

Natural History and Chemotherapy

- Prior to the development of adjuvant chemotherapy, effective treatment was limited to radical margin amputation. Metastasis to the lungs and other bones generally occurred within 24 months. Overall survival rates 2 years after surgery ranged from 5% to 20%.8 No significant correlation between overall survival and histologic subtypes, tumor size, patient age, or degree of malignancy was seen. The most significant clinical variable
FIG 12 • The three radiographic matrix types of osteosarcoma: osteolytic (A; arrows indicate tumor); mixed (B); and sclerosing (C). There is no prognostic difference in survival based on the radiographic type of matrix formation. 

D. Classical high-grade osteosarcoma reveals a population of pleomorphic spindle cells intimately associated with a mesh of immature lacy osteoid. The amount of osteoid can be minimal, or it may be a predominant element forming wide intersecting trabeculae lined by the malignant osteoblasts. Giant cells also can be present. E, Pathologic specimen. High-grade osteosarcoma of the proximal humerus with cortical breakthrough and tumor extension into the soft tissues. F, CT scan demonstrating a large pelvic osteosarcoma. (A-E: Courtesy of Martin M. Malawer.)
was anatomic site: pelvic and axial lesions had a lower survival rate compared with extremity tumors, and tibial lesions had a better survival rate than femoral lesions (FIG 12F).

- The dismal outcome associated with osteosarcoma has been altered dramatically by adjuvant chemotherapy and also by aggressive thoracotomy for pulmonary disease. No difference in local recurrence or overall survival was seen between patients undergoing amputation and those undergoing limb-sparing surgery.

**Overall Treatment Strategy**

- The patient with a primary tumor of the extremity without evidence of metastases requires surgery to control the primary tumor and chemotherapy to control micrometastatic disease. From 80% to 90% of all patients with osteosarcoma fall into this category.

- Chemotherapy protocols typically have included various combinations and dosage schedules of high-dose methotrexate (HD-MTX), doxorubicin hydrochloride (Adriamycin), and cisplatin. Ifosfamide, which is as effective as Adriamycin in single-agent studies, recently has supplanted methotrexate in many ongoing protocols. Multagent chemotherapy, using various dosing schedules, now is considered standard treatment for osteosarcoma. Success with adjuvant chemotherapy led to investigation of treatment in the neoadjuvant (preoperative) setting. When used in that setting, tumor response results in shrinkage of the soft tissue components, facilitating surgical excision and subsequent limb salvage. Tumor response is measured by tumor necrosis rate on microscopic pathology and is a significant prognostic factor.

- Limb-salvage surgery is a safe surgical procedure for approximately 85% to 90% of patients. This technique may be used for all spindle cell sarcomas, regardless of histogenesis. The majority of OSs can be treated safely by a limb-sparing resection combined with effective adjuvant treatments. The successful management of localized OS and other sarcomas requires careful coordination and timing of staging studies, biopsy, surgery, and preoperative and postoperative chemotherapy, radiation therapy, or both. The site of the lesion is evaluated as previously described. Preoperative studies allow the surgeon to understand the local anatomy and the volume of tissue to be resected and reconstructed.

- Surgery alone results in a cure rate of 15% to 20% at best. The choice between amputation and limb-sparing resection must be made by an experienced orthopaedic oncologist, taking into account tumor location, size, or extramedullary extent; the presence or absence of distant metastatic disease; and patient factors such as age, skeletal development, and lifestyle preference that might dictate the suitability of limb salvage or amputation. Routine amputations are no longer performed; all patients should be evaluated for limb-sparing options. Intensive, multagent chemotherapeutic regimens have provided the best results to date. Patients who are judged unsuitable for limb-sparing options may be candidates for presurgical chemotherapy; those with a good response may then become suitable candidates for limb-sparing operations. The management of these patients mandates close cooperation between chemotherapist and surgeon.

**Variants of Osteosarcoma**

- There are 11 recognizable variants of the classic OS. OS arising in the jaw bones is the most common of these. Parosteal and periosteal OS are the most common variants of the classic OS occurring in the extremities. In contrast to classic OS, which arises within a bone (intramedullary), parosteal and periosteal OS arises on the surface (juxtapartical) of the bone. Parosteal osteosarcoma is the most common of the unusual variants, representing about 4% of all osteosarcomas.

**PAROSTEAL OSTEOSARCOMA**

- Parosteal osteosarcoma is a distinct variant of osteosarcoma. Its prevalence is estimated to be 4%. It arises from the cortical bone and generally occurs in an older age group and has a better overall prognosis than osteosarcoma. As in osteosarcoma, the distal femur is the most common location; characteristically, the tumor attaches to its posterior aspect (FIG 13A–C). The proximal humerus and the proximal tibia are the next most common sites. Parosteal osteosarcomas usually present as a mass, occasionally associated with pain. The natural history is slow growth and late metastasis. The long-term survival rate is 75% to 85%. The tumor arises from the cortical surface and presents as a protuberant multinodular mass. The surface of the lesion may be covered in part by a cartilaginous cap resembling an osteochondroma; other areas may infiltrate into the adjacent soft tissues. The tumor usually encircles, partially or completely, the shaft of the underlying bone. In contrast to osteochondromas, the medullary canal of the bone is not contiguous with that of the neoplasm. Radiologically, parosteal osteosarcoma presents as a large, dense, tubulated mass that is broadly attached to the underlying bone without involvement of the medullary canal (FIG 13D,E). If present long enough, the tumor may encircle the entire bone. The periphery of the lesion typically is less mature than the base. Despite careful evaluation, intramedullary extension is difficult to determine from plain radiographs. It is more accurately detected with CT scan.

- Diagnosis of parosteal osteosarcoma, more than that of other bone tumors, must be based on the clinical, radiologic, and pathologic findings (FIG 13F–H). Most parosteal osteosarcomas are low grade; they do not require neoadjuvant and adjuvant chemotherapy, and are best treated with wide excision. This tumor commonly is mislabeled by inexperienced clinicians and pathologists as osteochondroma, myositis ossificans, or conventional osteosarcoma. In the classic low-grade lesion, irregularly formed osteoid trabeculae, usually of woven bone, are surrounded by a spindle cell stroma containing widely spaced, bland-appearing fibroblastic spindle cells (FIG 13I). There may be foci of atypical chondroid differentiation. With the higher grades the likelihood of intramedullary involvement is increased. This, in turn, correlates well with the presence of distant metastases.

**Chondrosarcomas (Central and Peripheral)**

**Clinical Characteristics and Physical Examination**

- Half of all chondrosarcomas occur in persons over the age of 40. The most common sites are the pelvis, femur, and shoulder girdle. The clinical presentation varies. Peripheral chondrosarcomas may become quite large without causing pain, and local symptoms develop only because of mechanical irritation. Pelvic chondrosarcomas often are large and present with referred pain to the back or thigh, sciatica secondary to sacral plexus irritation, urinary symptoms from bladder neck involvement, unilateral edema due to iliac vein obstruction, or as a painless abdominal mass. Conversely, central chondrosar-
FIG 13  •  A. Gross specimen of a resection of a distal femoral osteosarcoma. The average bony defect is 15 to 20 cm. Note how the biopsy site is removed en bloc with the tumor. The proximal tibia routinely is removed en bloc. The length of bone resected is determined by preoperative CT and MRI evaluation. B. CT scan of a typical parosteal osteosarcoma. C. Gross specimen of a distal femoral parosteal osteosarcoma. There is minimal intraosseous extension. D,E. Plain radiographs of the distal femur, anteroposterior (D) and lateral (E) views, show a dense, irregular, sclerotic lesion, attached to the posterior femoral cortex. The posterior aspect of the distal femur is a classic location for parosteal osteosarcomas, and that diagnosis should be considered for any sclerotic lesion in that location. F. The relation of the parosteal osteosarcoma to the medullary canal is better viewed on this CT scan, which shows no tumor extension to the canal. In contrast to osteochondromas, the medullary canal of the bone is not contiguous with that of the tumor. G. Gross pathological specimen. H. Specimen shown illuminated with tetracycline fluorescence, which demonstrates minimal medullary tumor extension through the posterior cortex. I. Parosteal osteosarcoma. There are parallel or intersecting osseous trabeculae (arrows) that may be either lamellar or woven-type bone matrix. The intervening fibrocollagenous tissue is composed of bland, widely-spaced fibroblastic cells. (D-I: Courtesy of Martin M. Malawer.)
comas present with dull pain. A mass is rarely present. Pain, which indicates active growth, is an ominous sign of a central cartilage lesion. This cannot be overemphasized. An adult with a plain radiograph suggestive of a “benign” cartilage tumor but who is experiencing pain most likely has a chondrosarcoma (FIG 14A).

Radiographic Findings
- Central chondrosarcomas have two distinct radiological patterns. One is a small, well-defined lytic lesion with a narrow zone of transition and surrounding sclerosis with faint calcification. This is the most common malignant bone tumor that may appear radiographically benign (FIG 14B). The second type has a sclerotic border and is difficult to localize. The key sign of malignancy is endosteal scalloping. This type is difficult to diagnose on plain radiographs and may go undetected for a long period of time.
- Peripheral chondrosarcoma is easily recognized as a large mass of characteristic calcification protruding from a bone. Correlation of the clinical, radiographic, and histologic data is essential for accurate diagnosis and evaluation of the aggressiveness of cartilage tumor. In general, proximal or axial location, skeletal maturity, and pain point toward malignancy, even though the cartilage may appear benign.

Grading and Prognosis
- Chondrosarcomas are graded 1, 2, and 3; most are either grade 1 or grade 2. The metastatic rate of moderate-grade versus high-grade is 15% to 40% versus 75%.
- Grade 3 lesions have the same metastatic potential as osteosarcomas.
- In general, peripheral chondrosarcomas are a lower grade than central lesions. Ten-year survival rates among those with peripheral lesions are 77% with 32% among those with central lesions.
- Secondary chondrosarcomas arising from osteochondromas (FIG 14D,E) also have a low malignant potential; 85% are grade 1. The multiple forms of benign osteochondromas or enchondromes have a higher rate of malignant transformation than the corresponding solitary lesions. The pelvis, shoulder girdle, and ribs are the most common sites of malignant transformation of osteochondromes. The risk of malignant transformation is approximately 20% to 25%.

Microscopic Characteristics
- The histologic spectrum of chondrosarcomas varies tremendously. High-grade examples are easy to identify, whereas certain low-grade tumors are exceedingly difficult to distinguish from chondromes. Correlation between the histologic features (FIG 14F) and both the clinical setting and the radiographic changes is, therefore, of utmost importance in avoiding serious diagnostic error. The grade of malignant cartilaginous tumors correlates with clinical behavior. Grade 1 tumors are characterized by an increased number of chondrocytes set in a matrix that is chondroid to focally myxoid.
- Areas of increased cellularity with more marked variation in cell size, significant nuclear atypia, and frequent pleomorphic forms define a grade 2 lesion. Binuclear forms are more common in this group.
- Grade 3 chondrosarcomas, which are relatively uncommon, show even greater cellularity, often with spindle cell areas, and reveal prominent mitotic activity. Chondrocytes may contain large, bizarre nuclei. Areas of myxoid change are common.

Treatment
- The treatment of chondrosarcoma is surgical removal. Guidelines for resection for high-grade chondrosarcomas are similar to those for OSs. The sites of origin and the fact that chondrosarcomas tend to be low-grade often make them amenable to limb-sparing procedures. The four most common sites are the pelvis, proximal femur, shoulder girdle, and diaphyseal portions of the long bones.

Variants of Chondrosarcoma
- There are three less-common variants of classic chondrosarcoma. Each is briefly described below (FIG 15).
- Clear cell chondrosarcoma, the rarest form of chondrosarcoma, is a slow-growing, locally recurrent tumor resembling a chondroblastoma but with some malignant potential that typically occurs in adults. The most difficult clinical problem is early recognition; it often is confused with chondroblastoma. Metastases occur only after multiple local recurrences. Primary treatment is wide excision. Systemic therapy is not required.
- Mesenchymal chondrosarcoma is a rare, aggressive variant of chondrosarcoma characterized by a biphasic histologic pattern, ie, small, compact cells intermixed with islands of cartilaginous matrix. This tumor has a predilection for flat bones; long tubular bones rarely are affected. It tends to occur in the younger age group and has a high metastatic potential. The 10-year survival rate is 28%. This type responds favorably to radiation therapy.
- Dedifferentiated chondrosarcoma. About 10% of chondrosarcomas may dedifferentiate into either a fibrosarcoma or an OS,1,7 They occur in older individuals and are often fatal. Surgical treatment is similar to that described for other high-grade sarcomas. Adjuvant therapy is warranted.

Ewing Sarcoma
- Ewing sarcoma is the second most common bone sarcoma of childhood; it is approximately one half as common as osteosarcoma. The lesion is characterized by poorly differentiated, small, round cells with marked homogeneity. The exact cell of origin is unknown. These mesenchymal cells are rich in glycolgen and typically manifest a unique reciprocal chromosomal translocation, t(11;22)(q24;q12) that results in a chimeric protein, EWS/FLI-1. This translocation occurs in approximately 90% of these tumors. The clinical and biologic behavior is significantly different from that of spindle cell sarcomas. Within the past 2 decades, the prognosis of patients with Ewing sarcoma has been improved dramatically thanks to a combination of adjuvant chemotherapy, improved radiation therapy techniques, and the select use of limited surgical resection.

Clinical Characteristics and Physical Examination
- Ewing sarcomas tend to occur in young children, although rarely in those younger than 5 years. The flat and axial bones are involved in 50% to 60% of cases. When a long (tubular) bone is involved, it most often is the proximal or diaphyseal area that is affected (FIG 16). In contrast, OSs occur in adolescence (average age 15), most often around the knees, and involve the metaphysis of long bones.
- Another unique finding with Ewing sarcomas is systemic signs, ie, fever, anorexia, weight loss, leukocytosis, and anemia.1 All may be a presenting sign of the disease and are seen in 20% to 30% of patients; this is in contrast to the distinct
absence of systemic signs with OS until late in the disease process. The most common complaint is pain or a mass. Localized tenderness often is present with associated erythema and induration. These findings, in combination with systemic signs of fever and leukocytosis, closely mimic those of osteomyelitis.

**Radiographic Findings**

- Ewing sarcoma is a highly destructive radiolucent lesion without evidence of bone formation. The typical pattern consists of a permeative or moth-eaten destruction associated with periosteal elevation. Multilaminated periosteal elevation (onion skin appearance) or a sunburst appearance is
FIG 15 • A,B. Plain radiographs of the proximal tibia: anteroposterior and lateral views show a central chondrosarcoma (arrows). Macrophase sections of central chondrosarcomas of the proximal tibia (C) and proximal femur (D). E. Plain radiograph of the femoral shaft shows a central chondrosarcoma, presenting as a well-defined lytic lesion with a sharp transition zone, calcifications, and endosteal scalloping. Immunohistochemical stains, differentiation among these tumors has become simpler. F. Cross-section of an intramedullary chondrosarcoma discloses its lobular architecture and translucent, hyaline-like matrix. Note the characteristic endosteal erosions (arrows). G. Low-grade chondrosarcoma maintains a lobular architecture. There is slightly increased cellularity, occasional binucleate cells, and nuclear atypia. These cells typically are found in lacunae. The tumor tends to permeate between the normal osseous trabeculae. H. The juxtaposition of high-grade spindle sarcoma with lobules of low-grade chondrosarcoma is the hallmark of dedifferentiated chondrosarcoma. The spindle cell component usually reveals features of malignant fibrous histiocytoma, osteosarcoma, or it may be unclassifiable. This neoplasm pursues an aggressive clinical course with very low long-term survival. (Courtesy of Martin M. Malawer.)
characteristic. When Ewing sarcoma occurs in flat bones, however, these findings usually are absent. Tumors of flat bones appear as a destructive lesion with a large soft tissue component. The ribs and pelvis are involved most often. Pathologic fractures occur secondary to extensive bony destruction and the absence of tumor matrix.

The differential diagnosis is osteomyelitis, osteolytic osteosarcoma, metastatic neuroblastoma, and eosinophilic granuloma.

**Natural History**

- Ewing sarcoma is highly lethal and disseminates rapidly. Historically, fewer than 10% to 15% of patients remain disease free at 2 years.1

  Many patients present with metastatic disease. The most common sites for metastases are other bones and the lungs. Ewing sarcoma once was thought to be a multicentric disease because of the high incidence of multiple bone involvement. Unlike other bone sarcomas, Ewing sarcoma is associated with visceral, lymphatic, and meningeal involvement, and all of these areas must be investigated.

**Radiographic Evaluation and Staging**

- No general staging system for Ewing sarcoma exists. The musculoskeletal staging system does not apply to the round cell sarcomas of the bone.

  Because these lesions have a propensity to spread to other bones, bone marrow, the lymphatic system, and the viscera, evaluation is more extensive than that for spindle cell sarcomas. It must include a careful clinical examination of regional and distal lymph nodes and radiographic evaluation for visceral involvement. Liver–spleen scans and bone marrow aspirations are required, in addition to CT of the lungs and the primary site. Angiography is required only if a primary resection is planned.

**Microscopic Characteristics**

- Because accurate pathological interpretation often is difficult, and bone heating is subject to several potential problems, the following guidelines have been established for the biopsy of suspected round cell tumors:
  - Adequate material must be obtained for histologic evaluation and electron microscopy.
  - Routine cultures should be made to aid in the differentiation from osteomyelitis.
  - Biopsy of the bony component is not necessary. The soft tissue component usually provides adequate material. Bone biopsy should be through a small hole on the compressive side of the bone. Pathologic fracture through an irradiated bone often does not heal.
  - Large nests and sheets of relatively uniform round cells are typical. The sheets often are compartmentalized by intersecting collagenous trabeculae. The cells contain round nuclei with a distinct nuclear envelope. Nucleoli are uncommon, and mitotic activity is minimal. Occasional rosette-like structures may be found, although neuroectodermal origin has never been confirmed. In the vicinity of necrotic tumor, small pyknotic cells may be observed. Vessels in these necrotic regions often are encircled by viable tumor cells. The cells often contain cytoplasmic glycogen. This neoplasm belongs to the category of small blue round cell tumors, a designation that also includes neuroblastoma, lymphoma, metastatic OS, and, occasionally, osteomyelitis and histiocytosis. When confronted with this differential diagnosis, the pathologist may turn to electron microscopy or immunohistochemistry for additional information.

**Combined Multimodality Treatment**

- Ewing sarcomas generally are considered radiosensitive. Radiation therapy to the primary site has been the traditional mode of local control. Within the past decade, surgical resec-
Natural History and Potential Malignancy

Although GCTs rarely are malignant de novo (2%–8%), they may undergo transformation and demonstrate malignant histology after multiple local recurrences. Between 8% and 22% of known GCTs become malignant following local recurrence.1 This rate decreases to less than 10% if patients who have undergone radiation therapy are excluded. Approximately 40% of malignant GCTs become malignant at the first recurrence. The remainder typically become malignant by the second or third recurrence; thus, each recurrence increases the risk of malignant transformation. A recurrence after 5 years is extremely suspicious for a malignancy. Primary malignant GCT generally has a better prognosis than does secondary malignant transformation of typical GCT, especially if the transformation occurs after radiation therapy. Local recurrence of a GCT is determined by the adequacy of surgical removal rather than by histologic grade.

Radiographic and Clinical Evaluation

- GCTs are eccentric lytic lesions without matrix production occurring at the end of long bones. About 10% are axial. They have poorly defined borders with a wide area of transition. They are juxtapaphyseal with a metaphyseal component. Although the cortex is expanded and appears destroyed, at surgery it usually is found to be attenuated but intact. Periosteal elevation is rare; soft tissue extension is common. In the skeletally immature patient, GCT must be differentiated from aneurysmal bone cyst, although both lesions are closely related. GCTs are classified as type I, II, or III using the Enneking staging system.

Microscopic Characteristics

- Two basic cell types constitute the typical GCT.
- The stroma is characterized by polygonal to somewhat spindled cells containing central round nuclei.
- Benign, multinucleated giant cells are scattered diffusely throughout the stroma. Small foci of osteoid matrix, produced by the benign stroma cells, can be observed; however, chondroid matrix never occurs.

Treatment

- Treatment of GCT of bone is surgical removal. In general, curettage of the bony cavity with “cleaning” of the walls with a high-speed burr drill and the use of a physical adjuvant will kill any cells remaining within the cavity wall. Where we prefer the combined use of cryosurgery (either liquid nitrogen or a closed system of argon and helium) to obtain temperatures of −40°C. The cavity is then reconstructed with bone graft, polymethylmethacrylate, and internal fixation devices, which permit early mobilization.
- Cryosurgery has been used with more success for GCTs than for any other type of bone tumor. Cryosurgery is effective in eradicating the tumor while preserving joint motion and avoiding the need for resection or amputation. Liquid nitrogen is a very effective physical adjuvant and is recommended following curettage resection. Curettage alone is not recommended because of the associated high rate of local recurrence.

COMMON SOFT TISSUE SARCOMAS

Treatment

- The treatment of high-grade soft tissue sarcomas (STS) has undergone fundamental changes within the past decade. Treatment of these patients requires a multimodality approach, and successful management requires cooperation among the surgeon, medical oncologist, and radiation oncologist. The appropriate role of each modality is continuously changing, but general descriptions are provided in the following sections.

Chemotherapy

- The impact of chemotherapy for high-grade STS on survival remains controversial. Combination chemotherapy has been shown to be more effective than single-agent therapy in...
preventing pulmonary dissemination from high-grade sarcomas. The most effective drugs in use today are doxorubicin hydrochloride (Adriamycin) and ifosfamide. Dacarbazine, methotrexate, and cisplatin also have activity against these tumors and are included in many current protocols. The various combinations traditionally are given in an adjuvant (postoperative) setting and are presumed effective against clinically undetectable micrometastases. Neoadjuvant (preoperative) chemotherapy is being evaluated in several institutions. Early results have indicated that significant reduction in tumor size can occur, thereby facilitating attempts at limb salvage. In patients with tumors deemed unresectable who are therefore destined for limb amputation, the tumors may shrink drastically in response to preoperative chemotherapy, thereby making them candidates for wide resection and limb-sparing surgery.

**Radiation Therapy**

- Radiation typically is administered in a dose of 5000 to 6500 cGy over many fractions. This modality is effective in an adjuvant setting in decreasing local recurrence following nonablative resection. The degree to which the initial surgical volume should be decreased in these circumstances is controversial, although the rate of local recurrence following a wide excision and postoperative radiation therapy is 5% to 10%. Radiation therapy includes irradiating all the tissues at risk, shrinking fields, preserving a strip of unirradiated skin, and using filters and radiosensitizers. Local morbidity has been greatly decreased within the past decade. Preoperative radiation is effective in reducing tumor volume but is associated with increased morbidity resulting from significant wound-healing complications and, therefore, is not recommended as often as postoperative radiation.

**Surgery**

- Removal of the tumor is necessary to achieve local control, by either a nonablative resection (limb salvage) or an amputation. The procedure chosen depends on results of the preoperative staging studies. A prospective randomized National Cancer Institute (NCI) trial established that a multimodality approach employing limb-salvage surgery combined with adjuvant radiation and chemotherapy offered local control and survival rates comparable to those of amputation plus chemotherapy, while simultaneously preserving a functional extremity.

- The use of adjuvant therapy (chemotherapy or radiation) permits limb-sparing procedures for most extremity soft tissue sarcomas. Enneking et al have shown that a radical resection for an STS has a local recurrence rate of about 5% with surgery alone. Wide excision (without adjuvant radiation or chemotherapy) has a 50% rate of local failure. Results from the NCI showed that the rate of local recurrence decreased to 5% following local excision (either a marginal or wide excision) when combined with postoperative radiation therapy and chemotherapy. Others have reported similar good results from preoperative radiation, with or without preoperative chemotherapy. Contraindications to limb-sparing surgery are similar to those for the bony sarcomas. In general, nerve or major vascular involvement is a contraindication.

- Studies of referred patients show that approximately half of all patients with soft tissue sarcomas treated with attempted excisional biopsy by the referring surgeon will have microscopic or gross tumor remaining. As a result, referred patients undergo routine re-resection of the surgical site to ensure adequate local control prior to institution of adjuvant treatment.

**GENERAL SURGICAL TECHNIQUE AND CONSIDERATIONS**

- All tissue at risk should be removed with a wide, en bloc excision that includes the tumor, a cuff of normal muscle, and all potentially contaminated tissues. It is not necessary to remove the entire muscle group. The biopsy site should be removed with 3 cm of normal skin and subcutaneous tissue en bloc with the tumor.

- The tumor or pseudocapsule should never be visualized during the procedure (FIG 17). Contamination of the wound with tumor greatly increases the risk of local recurrence.

- Distant flaps should not be developed at the time of resection. This may contaminate a noninvolved area.

- The margin surrounding the surgical wound should be marked with metallic staples to help the radiotherapist determine the high-risk area if radiation treatment is needed later.

- Reconstruction of the defect should include local muscle transfers to protect exposed neurovascular bundles and bone cortex.

- All dead space should be closed, and there should be adequate drainage to prevent hematoma.

- Perioperative antibiotics should be given. These procedures have a low but significant rate of postoperative infection. The risk of infection following preoperative adjuvant therapy is particularly high.

**Malignant Fibrous Histiocytoma**

- Malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma in adults. High-grade pleomorphic MFHs are a heterogeneous collection of poorly differentiated sarcomas, many of which can be specifically classified with the application of DNA and protein analysis. It most commonly affects the lower extremity and has a predilection for originating in deep-seated skeletal muscles.

- The tumor usually presents as a multinodular mass with well-circumscribed or ill-defined infiltrative borders. The size and location at the time of diagnosis often correlate with the ease of clinical detection: superficial variants, presenting as dermal or subcutaneous masses, may be only a few centimeters in diameter, whereas those arising in the retroperitoneum often attain a diameter of 15 cm or more. Color and consistency vary considerably and reflect, in part, the cellular composition. Red-brown areas of hemorrhage and necrosis are not uncommon. The myxoid variant of MFH contains a predomi-

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**FIG 17** Gross specimen of a soft tissue sarcoma arising within the anterior compartment of the leg treated by an amputation. Note the relation to the adjacent bone and related vessels of the popliteal (arrows) trifurcation. The reactive zone and pseudocapsule are shown.
nance of grayish white, soft, mucoid tumor lobules, created by the high content of myxoid ground substance.

About 5% of MFHs undergo extensive hemorrhagic cystification termed telangiectatic transformation, leading to a clinical and radiologic misdiagnosis of hematoma. A needle biopsy can result in a benign diagnosis if only the hemorrhagic center of the tumor is sampled. For these reasons, until proven otherwise, one should assume that an underlying soft tissue sarcoma is present in any adult patient with a deep-seated hematoma that does not resolve after a few weeks, even when there is a history of trauma to that site.

The currently accepted broad histologic spectrum of MFH encompasses many variants that formerly were considered distinct clinicopathologic entities. These lesions, which had been named according to the predominant cell type, include fibroxanthoma, malignant fibroxanthoma, inflammatory fibrous histiocytoma, and giant cell tumor of soft parts. Immunohistochemical studies and electron microscopy can assist in the accurate diagnosis of a significant percentage of these tumors. The basic neoplastic cellular constituents of all fibrohistiocytic tumors include fibroblasts, histiocyte-like cells, and primitive mesenchymal cells (FIG 18). Both an acute and a chronic inflammatory cell component usually are present as well. The proportion of these malignant and reactive cell elements, the degree of pleomorphism of the neoplastic cells, and the predominant pattern account for the wide histologic variances.

The histologic pattern most commonly associated with MFH is a storiform arrangement of the tumor cells, which is characterized by fascicles of spindle cells that intersect to form a “pinwheel” or “cartwheel” pattern (FIG 18). Atypical and bizarre giant cells, often containing abnormal mitotic figures, may be present. The histologic grade (almost always intermediate to high) is a good prognosticator of metastatic disease. In the myxoid variant, the second most common histologic type, the tumor cells are dispersed in a richly myxoid matrix. The less common giant cell type (malignant giant cell of soft parts) is characterized by abundant osteoclast-like giant cells that are diffusely distributed among the malignant fibrohistiocytic elements. Myxoid MFH has a more favorable prognosis than other subtypes.

We recently analyzed our data of 150 MFH lesions. Our 5-year survival rates were 74%; the distant recurrence rate was 28%; and the local recurrence rate was 19%. A local recurrence, large tumor size, deep tumors, close margins, and proximal location in the extremity were found to have a significant negative prognostic influence on survival.

Liposarcoma

Liposarcoma is the second most common soft tissue sarcoma in adults. It has a wide range of malignant potential that correlates well with the histologic classification of the individual tumor. The lower extremity is the most common site and accounts for over 40% of all cases. These tumors, particularly those arising in the retroperitoneum, can attain enormous size; specimens measuring 10 to 15 cm and weighing more than 5 kg are not uncommon (FIG 19A). Liposarcomas tend to be well circumscribed and multilobulated. Gross features usually correlate with the histologic composition. Well-differentiated liposarcomas contain variable proportions of relatively mature fat and fibrocollagenous tissues, vary from yellow to grayish white, and can be soft, firm, or rubbery. A tumor that is soft, is pinkish tan, and has a mucinous surface probably is a myxoid liposarcoma, and has a mucinous surface probably is a myxoid liposarcoma, the most common histologic type. The high-grade liposarcomas (ie, round cell and pleomorphic) vary from pinkish tan to brown and may disclose extensive hemorrhage and necrosis.

Identification of typical lipoblasts is mandatory to establish the diagnosis of liposarcoma. This diagnostic cell contains one or more round, cytoplasmic fat droplets that form sharp, scalloped indentations on the central or peripheral nucleus. Well-differentiated liposarcomas often contain a predominance of mature fat cells and only a few, widely scattered lipoblasts. Inadequate sam-

FIG 18 • Malignant fibrous histiocytoma, a high-grade sarcoma, is characterized by pleomorphic spindle cells forming fascicular or typical storiform patterns. Bizarre tumor giant cells are interspersed. (Courtesy of Martin M. Malawer.)

FIG 19 • A. Large, low-grade liposarcoma of the posterior thigh. B. The diagnosis of a well-differentiated liposarcoma depends on the identification of characteristic lipoblasts. These cells can be mono- or multivacuolated with hyperchromatic, scalloped nuclei. This variant can closely mimic ordinary lipoma. (Courtesy of Martin M. Malawer.)
plung can, therefore, lead to a misdiagnosis of a benign lipoma (FIG 19B). Well-differentiated liposarcomas that arise in the superficial soft tissues have been called “atypical lipomas.” In the sclerosing variant of a well-differentiated liposarcoma, delicate collagen fibrils that encircle fat cells and lipoblasts make up a prominent part of the matrix. Treatment with wide excision and adjuvant radiation therapy is recommended only if marginal margins were achieved. We treat high-grade liposarcomas like any other high-grade soft tissue sarcoma, with neoadjuvant chemotherapy, wide excision, and adjuvant chemotherapy. Radiation therapy is indicated if wide margins were not achieved.

- Sixty-five percent of liposarcomas arise in the extremities; the remaining 35% arise in the retroperitoneum. Negative prognostic factors for survival are retroperitoneal location, tumor size greater than 10 cm, and locally recurrent disease at initial presentation.

Synovial Sarcoma

- Synovial sarcoma is the fourth most common soft tissue sarcoma. In spite of its name, this tumor rarely arises directly from a joint but, rather, arises in proximity to it, with a propensity for the distal portion of the extremities. Synovial sarcomas occur in a younger age group than do most other sarcomas: most patients are below the age of 40. Typical findings of synovial sarcoma include a painful mass, soft tissue calcifications on radiography, and a malignant tumor of the foot. The tumor typically presents as a deep-seated, well-circumscribed, multinodular, firm mass. Contiguity with a synovium-lined space is a joint but, rather, arises in proximity to it, with a propensity for the distal portion of the extremities. Synovial sarcomas occur in a younger age group than do most other sarcomas: most patients are below the age of 40. Typical findings of synovial sarcoma include a painful mass, soft tissue calcifications on radiography, and a malignant tumor of the foot. The tumor typically presents as a deep-seated, well-circumscribed, multinodular, firm mass. Contiguity with a synovium-lined space is

Synovial sarcoma is characterized by a distinctive biphasic pattern that implies an admixture of spindle cell areas along with epithelioid cells forming gland-like structures. The proportions of these two components are variable. When only one of the elements of synovial sarcoma is present—almost invariably the spindle cell component—it is termed monophasic synovial sarcoma. (Courtesy of Martin M. Malawer.)

REFERENCES