Malignant tumors arising from the skeletal system are rare, representing just 0.001% of all new cancers. Only 400 to 600 new primary bone sarcomas are diagnosed annually in the United States. Osteosarcoma and Ewing’s sarcoma, the two most common bone tumors, occur mainly during childhood and adolescence (Fig. 45.2.1). Other mesenchymal (spindle cell) neoplasms that characteristically arise after skeletal maturity—fibrosarcoma, chondrosarcoma, and malignant fibrous histiocytoma (MFH)—are less common. The vast majority of experience reported in the management of bone neoplasms has been obtained in patients with osteosarcomas. As a result, the surgical, chemotherapeutic, and radiotherapeutic principles developed for treatment of osteosarcomas form the basis of the management strategy for most of the spindle cell neoplasms.

Amputation had been the standard method of treatment for most bone sarcomas, but the 1980s witnessed the development of limb-sparing surgery for most malignant bone tumors. Today, limb-sparing surgery is considered safe and routine for approximately 90% of patients with extremity osteosarcomas. Advances in orthopedics, bioengineering, radiographic imaging, radiotherapy, and chemotherapy have contributed to safer, more reliable surgical procedures.

Paralleling these advances have been the demonstrated effectiveness of adjuvant chemotherapy in dramatically increasing overall survival: the bleak 15% to 20% survival rate associ-
Sarcomas of Bone

Ated with surgery alone before the 1970s rose to 55% to 80% with various adjuvant treatment regimens by the 1980s. Multiple-drug regimens are now considered essential treatment. The timing, mode of delivery, and different combinations of these agents are being investigated at many centers. Preoperative chemotherapy regimens (termed neoadjuvant or induction chemotherapy) and postoperative regimens are being evaluated to determine their effect on the tumor and

FIGURE 45.2.1. Osteosarcoma of the distal femur. **A:** Plain radiograph of a classic osteosarcoma. Marked sclerosis is present within the intramedullary canal, which represents new bone formation (malignant osteoid formation), in addition to a large posterior extraosseous component that shows osteoid formation. This is the typical appearance of a distal femoral osteosarcoma before treatment. New bone formation within the extraosseous tumor is highly suggestive of an osteosarcoma. The distal femur is the most common site of primary osteosarcoma. **B:** Gross specimen of a distal femoral osteosarcoma. The medullary canal is filled with tumor. Note that there is extraosseous extension (**arrows**) beyond the cortex. Approximately 95% of osteosarcomas have extraosseous components at the time of diagnosis. This finding necessitates accurate computed tomography, magnetic resonance imaging, and bone scan imaging before biopsy and induction chemotherapy. **C–E:** Plain radiographs demonstrate the classic variants of osteosarcoma. **Arrows (D)** delineate the approximate margins of the tumor.
their impact on the choice of operative procedure and on overall survival.

This chapter focuses only on malignant spindle cell tumors. Emphasis is placed on natural history, surgical staging, tumor imaging, criteria of patient selection for amputation versus limb-sparing surgery and technique of limb-sparing procedures. The development, role, timing, and mode of delivery of adjuvant chemotherapy and its relationship to stage of disease are discussed, along with the role of radiotherapy in specific clinical situations.

**CLASSIFICATION AND TYPES OF BONE TUMOR**

Bone consists of cartilaginous, osteoid, and fibrous tissue and bone marrow elements. Each tissue can give rise to benign or malignant spindle cell tumors. Bone tumors are classified on the basis of cell type and recognized products of proliferating cells. The classification system, described by Lichtenstein and modified by Dahlin, is presented in Table 45.2.1. Jaffe\(^1\) recommends that each tumor be considered a separate clinicopathologic entity. Radiographic, histologic, and clinical data are necessary to form an accurate diagnosis and to determine the degree of activity and malignancy of each lesion.

Cartilage tumors are lesions in which cartilage is produced. They are the most common bone tumors. Osteochondroma is the most common benign cartilage tumor; some 1% to 2% of solitary osteochondromas become malignant. Enchondroma is a benign cartilage tumor that occurs centrally; in adults, malignant transformation may occur. Chondrosarcoma, the most common malignant cartilage tumor, is either intramedullary or peripheral. Ten percent are secondary, arising from an underlying benign lesion. Most chondrosarcomas are low grade, although 10% dedifferentiate into high-grade spindle cell sarcomas or, rarely, a mesenchymal chondrosarcoma. Osteoid tumors are lesions in which the stroma produces osteoid. The benign forms are osteoid osteoma and osteoblastoma. Osteoid osteomas are never malignant. Osteoblastomas rarely metastasize; when they do, it is only after multiple local recurrences. Osteosarcomas are the most common primary malignant tumors of the bone. Histologically, they are composed of malignant spindle cells and osteoblasts that produce osteoid or immature bone. Several variants are now recognized. Parosteal, periosteal, and low-grade intraosseous osteosarcomas are histologically and radiographically distinct from the “classic” central medullary osteosarcomas and have a more favorable prognosis.

Fibrous tumors of bone are rare. Desmoplastic fibroma is a locally aggressive, nonmetastasizing tumor, analogous to fibromatosis of soft tissue. Fibrosarcoma of bone appears histologically as its soft tissue counterpart. Multiple sections must be obtained to demonstrate the lack of osteoid production. If osteoid is present, the lesion is classified as an osteosarcoma. MFH, a rare lesion and the counterpart of soft tissue MFH, has been described in bone. Giant cell tumors (GCTs) of unknown origin were originally described as benign but are now considered low-grade sarcomas. They have high rates of local recurrence and malignant transformation.

Tumors presumably arising from bone marrow elements are the round cell sarcomas. The two most common are Ewing’s sarcoma and non-Hodgkin’s lymphoma.

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**TABLE 45.2.1 General Classification of Bone Tumors**

<table>
<thead>
<tr>
<th>Histologic Type(^a)</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic (41.4%)</td>
<td>—</td>
<td>Myeloma</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>Reticulum cell sarcoma</td>
</tr>
<tr>
<td>Chondrogenic (20.9%)</td>
<td>Osteochondroma</td>
<td>Primary chondrosarcoma</td>
</tr>
<tr>
<td>—</td>
<td>Chondroma</td>
<td>Secondary chondrosarcoma</td>
</tr>
<tr>
<td>—</td>
<td>Chondroblastoma</td>
<td>Dedifferentiated chondrosarcoma</td>
</tr>
<tr>
<td>—</td>
<td>Chondromyxoid fibroma</td>
<td>Mesenchymal chondrosarcoma</td>
</tr>
<tr>
<td>Osteogenic (19.3%)</td>
<td>Osteoid osteoma</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>—</td>
<td>Benign osteoblastoma</td>
<td>Parosteal osteogenic sarcoma</td>
</tr>
<tr>
<td>—</td>
<td>Giant cell tumor</td>
<td>Ewing’s tumor</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>Malignant giant cell tumor</td>
</tr>
<tr>
<td>—</td>
<td>(Fibrous) histiocytoma</td>
<td>(Fibrous) histiocytoma</td>
</tr>
<tr>
<td>Fibrogenic (3.8%)</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>—</td>
<td>Desmoplastic fibroma</td>
<td>—</td>
</tr>
<tr>
<td>Notochordal (3.1%)</td>
<td>—</td>
<td>Chordoma</td>
</tr>
<tr>
<td>Vascular (1.6%)</td>
<td>Hemangioma</td>
<td>Hemangioendothelioma</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>Hemangiopericytoma</td>
</tr>
<tr>
<td>Lipogenic (&lt;0.5%)</td>
<td>Lipoma</td>
<td>—</td>
</tr>
<tr>
<td>Neurogenic (&lt;0.5%)</td>
<td>Neurilemoma</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)Distribution based on Mayo Clinic experience.

(Adapted from Dahlin DC. *Bone tumors: general aspects and data on 6,221 cases*, 3rd ed. Springfield: Charles C. Thomas Publisher, 1978, with permission.)
RADIOGRAPHIC EVALUATION AND DIAGNOSIS

Radiographic evaluation, combined with the clinical history and histologic examination, is necessary for accurate diagnosis. Bone scan, angiography, computed tomography (CT), and magnetic resonance imaging (MRI) are generally not helpful in determining a diagnosis but are important in delineating the extent of local involvement. A systematic approach to the radiographic evaluation of skeletal lesions has been described by Madewell et al.,2 who studied and correlated several hundred radiographic and pathologic specimens. They considered the radiograph as the gross specimen from which a detailed histologic interpretation could be made and biologic activity accurately diagnosed.

The radiographic parameters of benign and malignant tumors are quite different. Benign tumors have round, smooth, well-circumscribed borders. No cortical destruction and, generally, no periosteal reaction are found. Malignant lesions have irregular, poorly defined margins. Evidence of bone destruction and a wide area of transition with periosteal reaction are noted. Soft tissue extension is common.

NATURAL HISTORY

Tumors arising in bone have characteristic patterns of behavior and growth that distinguish them from other malignant lesions. These patterns form the basis of a staging system and current treatment strategies. These principles and their relationship to management, as formulated by Enneking et al.,3,4 are described.

BIOLOGY AND GROWTH

Spindle cell sarcomas form a solid lesion that grows centrifugally. The periphery is the least mature part of this lesion. In contradistinction to a true capsule, which surrounds a benign lesion and is composed of compressed normal cells, a malignant tumor is generally enclosed by a pseudocapsule and consists of compressed tumor cells and a fibrovascular zone of reactive tissue with an inflammatory component that interdigitates with the normal tissue adjacent to and beyond the lesion. The thickness of the reactive zone varies with the degree of malignancy and histogenic type. The histologic hallmark of sarcoma is their potential to break through the pseudocapsule to form satellite lesions of tumor cells. This characteristic distinguishes a nonmalignant mesenchymal tumor from a malignant one.

High-grade sarcomas have a poorly defined reactive zone that may be invaded and destroyed by the tumor. In addition, tumor nodules in tissue may appear to be normal and not continuous with the main tumor. These are termed skip metastases. Although low-grade sarcomas regularly demonstrate tumor interdigitation into the reactive zone, they rarely form tumor nodules beyond this area.

The three mechanisms of growth and extension of bone tumors are (1) compression of normal tissue, (2) resorption of bone by reactive osteoclasts, and (3) direct destruction of normal tissue. Benign tumors grow and expand by the first two mechanisms, whereas direct tissue destruction is characteristic of malignant bone tumors. Sarcomas respect anatomic borders and remain within one compartment. Local anatomy influences tumor growth by setting the natural barriers to extension. In general, bone sarcomas take the path of least resistance. Most benign bone tumors are unicompartmental; they remain confined and may expand the bone in which they arose. Malignant bone tumors are bicompartamental; they destroy the overlying cortex and go directly into the adjacent soft tissue. The determination of anatomic compartment involvement has become more important with the advent of limb-preservation surgery.

METASTASIS

Bone tumors, unlike carcinomas, disseminate almost exclusively through the blood; bones lack a lymphatic system. Early lymphatic spread to regional nodes has only rarely been reported. Lymphatic involvement, which has been noted in 10% of cases at autopsy, is a poor prognostic sign. McKenna et al.5 noted that six of 194 patients (3%) with osteosarcoma who underwent amputation demonstrated lymph node involvement. None of these patients survived 5 years. Hematogenous spread is manifested by pulmonary involvement in its early stage and secondarily by bone involvement. Kager et al.6 reported the findings of the Cooperative German-Austrian-Swiss Osteosarcoma Study Group (2003) that, of 1,765 previously untreated, newly diagnosed osteosarcoma patients, 202 (11.4%) had proven metastases at the time of diagnosis—pulmonary (9.3%) and secondary bony sites (3.9%). Bone metastasis is occasionally the first sign of dissemination (3.9%).

SKIP METASTASES

A skip metastasis is a tumor nodule that is located within the same bone as the main tumor but not in continuity with it. Transarticular skip metastases are located in the joint adjacent to the main tumor. Skip metastases are most often seen with high-grade sarcomas. They develop by the embolization of tumor cells within the marrow sinusoids; in effect, they are local micrometastases that have not passed through the circulation. Transarticular skips are believed to occur via the periarticular venous anastomosis. The clinical incidence of skip metastases is less than 1%. These lesions are a prognosticator of poor survival. Wuisman and Enneking7 reviewed 23 cases with histologically proven skip metastases. Eleven patients received adjuvant chemotherapy. In 22 of the 23 patients, either local recurrence or distant metastases developed within 16 months of surgery. The authors compared the clinical course of these patients with that of 224 individuals without skip lesions. The overall survival rate of patients with skips was comparable to that of those with metastatic (stage III) disease. The authors concluded that patients with skip metastases should be classified as stage III and should be excluded from ongoing therapy trials. Kager et al.7 reported their experience of 24 skip bony lesions in 1,765 patients (1.4%) at the time of initial presentation.

LOCAL RECURRENCE

Local recurrence of a malignant lesion is due to inadequate removal. Ninety-five percent of all local recurrences, regardless of histology, develop within 24 months of attempted removal. Local recurrence of a high-grade sarcoma was once thought to
Chapter 45.2 Sarcomas of the Soft Tissue and Bone

be independent of overall survival. Today, a local recurrence is believed to represent an inherent biologic aggressiveness and a tendency to metastasize; that is, tumors that tend to metastasize are those that are likely to recur locally. Local recurrence in patients who have undergone therapy is associated with an even poorer prognosis.

STAGING BONE TUMORS

MUSCULOSKELETAL TUMOR SOCIETY CLASSIFICATION

In 1980, the Musculoskeletal Tumor Society (MSTS) adopted a surgical staging system for bone sarcomas (Table 45.2.2). The system is based on the fact that mesenchymal sarcomas of bone behave similarly, regardless of histogenic type. The surgical staging system, as described by Enneking et al., is based on the GTM classification: grade (G), location (T), and lymph node involvement and metastases (M) (Fig. 45.2.2).

G represents the histologic grade of a tumor and other clinical data. Grade is further divided into two categories: G1 is low grade, and G2 is high grade. T represents the site of the lesion, which may be intracompartmental (T1) or extracompartmental (T2). Compartment is defined as an anatomic structure or space bounded by natural barriers or tumor extension. The significance of T1 lesions is easier to define clinically, surgically, and radiographically than that of T2 lesions, and the chance is better for adequate removal of the former without amputation. In general, low-grade bone sarcomas are intracompartmental (T1), whereas high-grade sarcomas are extracompartmental (T2).

Lymphatic spread is a sign of widespread dissemination. Regional lymphatic involvement is equated with distal metastases (M1). Absence of any metastasis is designated as M0.

The surgical staging system developed by Enneking et al. for surgical planning and assessment of bone sarcomas is summarized as follows:

Stage IA (G1, T1, M0): Low-grade intracompartmental lesion, without metastasis
Stage IB (G1, T2, M0): Low-grade extracompartmental lesion, without metastasis
Stage IIA (G2, T1, M0): High-grade intracompartmental lesion, without metastasis
Stage IIB (G2, T2, M0): High-grade extracompartmental lesion, without metastasis
Stage IIIA (G1 or G2, T1, M1): Intracompartmental lesion, any grade, with metastasis
Stage IIIB (G1 or G2, T2, M1): Extracompartmental lesion, any grade, with metastasis

AMERICAN JOINT COMMITTEE ON CANCER BONE TUMOR CLASSIFICATION AND INTERNATIONAL UNION AGAINST CANCER

In 1983 the American Joint Committee on Cancer (AJCC) Bone Tumor Classification recommended a staging system for the malignant tumors of bone. This system has undergone several changes and is now in its sixth edition (2002). This classification is identical to that used by the International Union Against Cancer (Union Internationale Contre le Cancer [UICC]). Cases are categorized by histologic type and grade. This system is based on the four-part TNMG designation: extent of the tumor (T), nodal status (N), distant metastases (M), and grade (G). The system is similar to the MSTS classification; however, the AJCC uses four stages instead of three. In the most recent version of the TNM system, it is noted that different grading systems are used in different centers and jurisdictions. Therefore, a translation of three- and four-tiered grading systems into a two-tiered system is required for TNM. In the most commonly used three-tiered classification, grade 1 is considered low grade and grades 2 and 3 high grade. In the less common four-tiered systems, grades 1 and 2 are considered low grade and grades 3 and 4 are high grade. The 2002 TNM classification contains substantial modifications from previous editions (Table 45.2.3). It considers maximum lesion size (with a breakpoint at 8 cm) in the differentiation of T1 versus T2 and the presence of discontinuous tumors in the same bone without other distant metastasis as T3 disease. Metastases to nonpulmonary sites are distinguished from M1.
Disease on the basis of lung involvement alone. One potential problem is that the existing stages need adjustment for the impact of grade in the stage-grouping algorithm. Thus, discontinuous tumor in the same bone that is low grade would likely have a better prognosis than if high grade, even though both tumor types are considered stage III in the new classification.

A similar problem exists when considering lung versus nonpulmonary metastases. The UICC and AJCC staging systems are applicable to all primary malignant tumors of bone except multiple myeloma, malignant lymphoma (both having different natural history), and juxtacortical osteosarcoma and chondrosarcoma (both with much more favorable prognosis). Although cancer registries will likely use the TNM system, at the present time most orthopedic oncologists tend to use the MSTS classification.

**International Union Against Cancer and American Joint Committee on Cancer TNM Classification (6th Edition) of Bone Sarcomas**

<table>
<thead>
<tr>
<th>PRIMARY TUMOR (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
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<tr>
<td>T0</td>
</tr>
<tr>
<td>T1</td>
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<td>T2</td>
</tr>
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<td>T3</td>
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<table>
<thead>
<tr>
<th>REGIONAL LYMPH NODES (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
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<table>
<thead>
<tr>
<th>DISTANT METASTASIS (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
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<td>M0</td>
</tr>
<tr>
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<tr>
<td>M1b</td>
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<table>
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<tr>
<th>STAGE GROUPING</th>
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</thead>
<tbody>
<tr>
<td>IA G1, 2 T1 N0 M0</td>
</tr>
<tr>
<td>IB G1, 2 T2 N0 M0</td>
</tr>
<tr>
<td>IIA G3, 4 T1 N0 M0</td>
</tr>
<tr>
<td>IIB G3, 4 T2 N0 M0</td>
</tr>
<tr>
<td>III Any G T3 N0 M0</td>
</tr>
<tr>
<td>IVA Any G Any T N0 M1a</td>
</tr>
<tr>
<td>IVB Any G Any T N0/N1 M1b</td>
</tr>
</tbody>
</table>

*G, grade.*

*Because of the rarity of lymph node involvement in sarcomas, the designation NX may not be appropriate and could be considered N0 if no clinical involvement is evident.

(From ref. 8, with permission.)

**PREOPERATIVE RADIOGRAPHIC EVALUATION**

If the plain radiographs suggest an aggressive or malignant tumor, staging studies should be performed before biopsy. All radiographic studies are influenced by surgical manipulation of the lesion, making interpretation more difficult. More importantly, the biopsy site may be in a location that is not optimal for subsequent en bloc removal or radiotherapy. Bone scintigraphy, MRI, CT, angiography, or a combination of these is required to delineate local tumor extent, vascular displacement, and compartmental localization (Fig. 45.2.3). More recently, positron emission tomography (PET) imaging has been used. Its exact role has not yet been determined. Systemic staging includes a three-phase bone scan (looking for bony metastases) and chest CT (to determine the absence or presence of pulmonary metastases). Evaluation of regional lymph nodes, the abdomen, or the pelvis is not necessary.
BONE SCANS

Bone scintigraphy helps determine polyostotic involvement, metastatic disease, and intraosseous extension of tumor. Malignant bone tumors, although solitary, may in rare cases present with skeletal metastasis. Skip metastases are rarely detected by bone scan because they are small and localized to the fatty marrow and do not excite cortical response.

Appreciation of the intraosseous extension of a bone tumor is important in surgical planning. Removal of bone 3 to 4 cm beyond the area of scintigraphic abnormality has been accepted as a safe margin for limb-sparing procedures after induction chemotherapy. Three-phase bone scans (flow, pool, and late-phase) are necessary to completely evaluate a bony tumor. Pre- and postchemotherapy bone scans can be compared only when identical areas of the scan are evaluated. To eliminate uncontrolled variations in technique, the method of determining the tumor-to-nontumor ratio of uptake is important. This ratio is obtained for each of the three phases. The flow and pool phases indicate tumor vascularity, whereas the late phase is a sign of bone formation (osteoblastic activity).

COMPUTED TOMOGRAPHY

CT allows accurate determination of intra- and extraosseous extension of skeletal neoplasms. It accurately depicts the transverse relationship of a tumor. By varying window settings, one can study cortical bone, intramedullary space, adjacent muscles, and extraosseous soft tissue extension. CT should include the entire bone and the adjacent joint. Infusion of intravenous contrast material permits identification of the adjacent large vascular structures. CT evaluation must be individualized. To obtain the maximum benefits from image reconstruction, the surgeon should discuss with the radiologist what information is desired. Three-dimensional reconstruction may be useful. Today, CT and MRI are considered complementary studies for bone sarcomas. Both studies are recommended for most patients. Pulmonary CT is routinely performed to determine the presence of pulmonary disease; approximately 11% of all newly diagnosed patients with osteosarcoma have pulmonary metastases.

MAGNETIC RESONANCE IMAGING AND STAGING

MRI has several advantages in the diagnoses of bone sarcomas. It has better contrast discrimination than any other modality; furthermore, imaging can be performed in any plane. MRI is ideal for imaging the medullary marrow and thus for detection of tumor as well as the extraosseous component. It has proven especially helpful in several heretofore difficult clinical situations, such as detecting small lesions, evaluating a positive bone scan when the corresponding plain radiograph is negative, determining the extent of infiltrative tumors, and detecting skip metastases.

ANGIOGRAPHY

The technique of angiography for bone lesions differs from that used for arterial disease. At least two views (biplane) are necessary to determine the relation of the major vessels to the tumor. Because experience with limb-sparing procedures has increased, it has become essential to determine individual vascular patterns before resection. This is especially crucial for tumors of the proximal tibia, where vascular anomalies are common. Angiography is the most reliable means of determining vascular anatomy and displacement, whereas MRI and CT better demonstrate extraosseous extension. The major advantage of angiography is its ability to determine residual tumor vascularity, which correlates well with chemotherapy-induced necrosis. Presently, magnetic resonance angiography (MRA) is being evaluated in the treatment of bone sarcomas (Fig. 45.2.4).

Figure 45.2.4. Computerized three-dimensional computed tomography-angiogram (3D CT-angio) reconstruction showing the relationship of a surface sarcoma of the proximal tibia to the political artery and the trifurcation. This technique combines bony anatomy and the vascular anatomy in order to determine the exact relationship of the major vessels. 3D CT-angio is increasingly replacing interventional angiography.

POSITRON EMISSION TOMOGRAPHY

\[^{18}\text{F}\]fluorodeoxy-glucose (FDG)-PET (for bony and pulmonary evaluation) is one of the newer techniques to evaluate the local and distal extents of cancers. Today, only preliminary data are available on the role of PET with respect to diagnosis, imaging, staging, therapy, monitoring, and follow-up for osteosarcomas. These early studies show that PET imaging is not accurate in determining pulmonary metastases. Investigations of the effectiveness of PET imaging in determining tumor response to chemotherapy are under way in several institutions. Brenner et al.\(^9\) have imaging for osteosarcoma. They concluded that too few patients have been evaluated and that further research needs to be done in a larger, perspective series.

Franzius et al.\(^10\) evaluated the use of FDG-PET for the detection of osseous metastases from malignant primary tumors,
specifically osteosarcoma and Ewing’s sarcoma, and compared these findings with bone scintigraphy. PET scans were analyzed with regard to osseous metastasis with comparison to bone scintigraphy. They reported that for osteosarcomas, FDG-PET scans were less reliable than bone scintigraphy; in fact, none of the five metastases from osteosarcomas were detected by FDG-PET although all were true positive on bone scan. In comparison, Ewing’s sarcomas were more accurately identified.

FED-PET scans have also been evaluated for the detection of pulmonary metastases from primary bony sarcomas. Studies have compared FDG-PET to the gold standard of spiral CT. Franzius et al.11 evaluated 71 patients (32 osteosarcomas and 39 Ewing’s sarcomas). FDG-PET had a false negative CT scan. No patient had a pulmonary metastasis detected earlier by FDG-PET in the detection of pulmonary metastasis from malignant primary bone tumors. In addition, they concluded that a negative FDG-PET cannot be recommended to exclude lung metastases. However, the specificity of FDG-PET is high, and it can be used to confirm abnormalities seen on spiral or thoracic CT scans with suspected metastases. Therefore, spiral CT scans are the most useful in following patients with primary bone tumors, but if a CT finding is questionable, a PET scan will show tumors with high specificity.

BIOPSY TECHNIQUE AND TIMING

The biopsy of a suspected bone tumor must be performed with great care and skill. This principle cannot be overemphasized. The consequences of a poorly executed biopsy are often the deciding factor in the choice between a limb-salvage procedure and amputation. Ayala et al.12 from the M. D. Anderson Cancer Center judged that only 19% of patients referred to that institution for treatment of primary bone sarcomas had properly placed biopsies. All of these patients had open (incisional) biopsies, whereas 92% of such procedures performed at the M. D. Anderson Cancer Center over the same period were needle biopsies. It is recommended that the biopsy be performed by the surgeon who will make the ultimate decision about the operative procedure. This entails referring some patients who are strongly suspected of having primary bone malignancies to a regional cancer center for biopsy.

RESTAGING AFTER INDUCTION (PREOPERATIVE) CHEMOTHERAPY

With the advent of preoperative chemotherapy for osteosarcoma, a need has developed for serial evaluation of the clinical and radiographic response of the tumor before surgery. The staging and preoperative clinical studies previously described are used to evaluate tumor response. These studies have been summarized. Complete restaging studies should be obtained after the completion of induction chemotherapy. MRI, CT, three-dimensional CT-angiogram, bone scan, and angiography should be evaluated before a final surgical decision is made.

CLINICAL EVALUATION

Pain often decreases after induction chemotherapy. Alkaline phosphatase (AP) levels also decrease. The tumor shrinks, especially if significant matrix is not present. Conversely, increase of pain, elevated AP values, and increasing tumor size are signs of tumor progression.

PLAIN RADIOGRAPHY

A good correlation is found between radiographic response and the amount of necrosis. Smith et al.13 described the radiographic responses seen on serial radiographs: increased ossification of tumor osteoid, marked thickening and new bone formation of the periosteum and tumor border (giving the tumor a more “benign” appearance), and decreased soft tissue mass. The healing ossification is usually solid, homogeneous, and regular and is easily differentiated from tumor osteoid. Less significant changes take place within the intramedullary component, which may include increased sclerosis and lysis, presumably caused by necrosis and hemorrhage.

ANGIOGRAPHY

After chemotherapy, vascularity decreases markedly. Chuang et al.14 evaluated 53 patients and reported that those with a complete angiographic response had more than 90% necrosis; among those with a partial response, necrosis ranged from 40% to 78%. They concluded that angiographic evaluation was as reliable as pathologic evaluation, and that the angiographic features were the best clinical criteria for the evaluation of tumor response.

Carrasco et al.15 from the M. D. Anderson Cancer Center reported on their extensive experience with intraarterial chemotherapy for osteosarcoma (81 patients) and evaluated the angiographic appearance and changes after two and four cycles of preoperative chemotherapy. They developed a simple radiographic system for angiographic changes. These authors evaluated the midarterial (tumor vascularity) and parenchymal (capillary) phases and described three types of responses: (1) angiographic response: complete disappearance of tumor vascularity and stain; (2) total disappearance of tumor vascularity, with slight persistence of tumor stain (capillary phase); and (3) no response: persistence of tumor vascularity and capillary stain. They reported that 40% of the histologic responders (more than 90% tumor necrosis) and 91% of nonresponders were identified after two cycles. The number of courses was no different between the responders and nonresponders. These authors concluded that the disappearance of tumor vascularity after two courses of chemotherapy was highly suggestive of a good histologic response and was unlikely to occur in the histologic nonresponders.

COMPUTED TOMOGRAPHY

The most consistent finding in patients who respond to therapy is a decrease in soft tissue mass and the development of a rim-like calcification similar to that seen on plain radiographs. Changes in marrow are not helpful in evaluating response.

BONE SCINTIGRAPHY

Bone scan changes are difficult to evaluate. A decrease in activity generally indicates a favorable response; however,
reparative bone formation, signaled by increased activity, may be misleading. Dynamic (quantitative) bone scans, which are based on tumor blood flow and regional plasma clearance by bone and soft tissue, may allow more valid evaluations. Regions that show a greater than 20% decrease in technetium-99m-methylene diphosphonate plasma clearance are reported to be associated with necrotic tumor. To quantify bone scans, a tumor-to-nontumor ratio is obtained after bone scintigraphy. This ratio is then determined preoperatively and after induction chemotherapy on serial scans. A decrease in this ratio (usually less than 4) is an indication of a good response to chemotherapy.

MAGNETIC RESONANCE IMAGING

Monitoring of neoadjuvant chemotherapy by MRI has become the focus of many studies. Holscher et al.16 evaluated 57 patients at the University Hospital of Leiden. T1- and T2-weighted images were obtained in longitudinal, coronal or sagittal, and axial planes. Factors evaluated were margins, homogeneity, hematoma, fibrosis, calcification liquefaction, edema, joint effusion, and fracture. The authors concluded that increased tumor volume or increased or unchanged peritumoral edema and inflammation indicated a poor response. Subjective criteria, such as improved tumor demarcation or an increase in size of area of low signal intensity (presumably necrotic tumor), were independent of tumor response. The authors concluded that subjective criteria could not predict the good responders.

POSITRON EMISSION TOMOGRAPHY

As previously stated, PET scans are nuclear medicine scintigraphy techniques that use 2-FDG as the radiopharmaceutical. This technique is under investigation. It is hoped that it will be able to dynamically evaluate the tumor and the percentage of tumor necrosis after chemotherapy. Hawkins et al.17 evaluated 33 patients with osteosarcoma and Ewing’s-related bone tumors before and after chemotherapy and compared the FDG-PET standard uptake values (SUV1 and SUV2; 1 refers to the average value and 2 to the peak value), respectively, to the tumor response of the resected specimens. The SUV2 and SUV2:SUV1 ratio correlated with histologic response. Franzius et al.18 reported that good responders could be distinguished from poor responders in all cases in which there was a decrease in the tumor-to-nontumor ratio of greater than 30%.

SURGICAL MANAGEMENT OF SKELETAL TUMORS

Limb-sparing techniques were developed during the early 1970s. Marcove et al.20-21 have described cryosurgery for some bony tumors. Enneking et al.8 have formulated a means of classifying surgical procedures on the basis of the surgical plane of dissection in relationship to the tumor and the method of accomplishing the removal. The scheme, summarized below, affords meaningful comparisons of various operative procedures and gives surgeons a common language.

Intralesional: An intralesional procedure passes through the pseudocapsule of the neoplasm directly into the lesion. Macroscopic tumor remains, and the entire operative field is potentially contaminated. Curettage is an intralesional procedure.

Marginal: A marginal procedure is one in which the entire lesion is removed in a single piece. The plane of dissection passes through the pseudocapsule or reactive zone around the lesion. When performed for a sarcoma, it leaves macroscopic disease.

Wide (intracompartmental): A wide excision, commonly termed en bloc resection, includes the entire tumor, the reactive zone, and a cuff of normal tissue. The entire structure of origin of the tumor is not removed. In patients with high-grade sarcomas, this procedure may leave skip nodules.

Radical (extracompartmental): A radical procedure involves removal of the entire tumor and the structure of origin of the lesion. The plane of dissection is beyond the limiting fascial or bony borders.

It is important to note that any of these procedures can be accomplished by either a limb-sparing procedure or by amputation. The local anatomy determines how such a margin can be obtained. Therefore, the aim of preoperative staging is to assess local tumor extent and important local anatomy to enable the surgeon to decide how to achieve a desired margin (i.e., to evaluate the feasibility of one surgical procedure over another). This system allows meaningful comparisons of surgical procedures, end-result reporting, and analysis of combined data.

PRINCIPLES AND TECHNIQUES OF LIMB-SPARING SURGERY

Limb-salvage surgery is a safe operation for selected cases. This technique can be used for all spindle cell sarcomas, regardless of histogenesis. Approximately 95% of osteosarcomas can be treated successfully with this technique. Successful management of localized osteosarcomas and other sarcomas requires careful coordination and timing of staging studies, biopsy, surgery, and preoperative and postoperative chemotherapy.

PHASES OF OPERATION

Successful limb-sparing procedures consist of three surgical phases:

1. Resection of tumor: Tumor resection strictly follows the principles of oncologic surgery. Avoiding local recurrence is the criterion of success and the main determinant of how much bone and soft tissue are to be removed.

2. Skeletal reconstruction: The average skeletal defect after adequate bone tumor resection measures 15 to 20 cm. Techniques of reconstruction vary and are independent of the resection, although the degree of resection may favor one technique over another.

3. Soft tissue and muscle transfers: Muscle transfers are performed to cover and close the resection site and to restore motor power. Adequate skin and muscle coverage is mandatory. Distal tissue transfers are not used because of the possibility of contamination.
GUIDELINES FOR LIMB-SPARING RESECTION

The surgical guidelines and technique of limb-sparing surgery used by the surgical author (MMM) are as follows:

1. No major neurovascular tumor involvement;
2. Wide resection of the affected bone, with a normal muscle cuff in all directions;
3. En bloc removal of all previous biopsy sites and potentially contaminated tissue;
4. Resection of bone 3 to 4 cm beyond abnormal uptake, as determined by CT or MRI and bone scan;
5. Resection of the adjacent joint and capsule;
6. Adequate motor reconstruction, accomplished by regional muscle transfers. Soft tissue coverage should be adequate.

TYPES OF SKELETAL RECONSTRUCTION

Large skeletal defects are reconstructed after tumor resection by several different modalities. Osteoarticular defects are most often reconstructed by segmental, modular prostheses that are fixed to the remaining intramedullary bone by polymethylmethacrylate (PMMA) or press fixation. The newer knee prostheses allow rotation as well as flexion and extension. This mobility decreases the forces on the bone-cement interface and thus reduces the risk of loosening.

Increasing interest has been shown in applying a porous coating to the prosthesis in the hope of obtaining long-term, perhaps even permanent, fixation. In addition, titanium, an alloy with superior metallurgical properties, has been introduced. Modular endoprosthetic replacement systems that can be assembled in the operating room are now available and avoid the problem of long delays for custom manufacturing. Alternative methods of segmental replacement include large allografts or osteoarticular allografts that may replace the affected joint. Composite allograft (i.e., allograft placed over a prosthesis) has been used. In general, allografts have been used successfully for low-grade sarcomas and for GCTs of bone that do not require chemotherapy or radiotherapy. Most large cancer centers in the United States now favor the use of endoprosthetic implants for high-grade bone sarcomas. Long-term results of allograft survival in this group of patients have been extremely disappointing.

CONTRAINDICATIONS TO LIMB-SPARING SURGERY

Major Neurovascular Involvement

Although vascular grafts can be used, the adjacent nerves are usually at risk, making successful resection less likely. In addition, the magnitude of resection in combination with vascular reconstruction is often prohibitive.

Pathologic Fractures

A fracture through a bone affected by a tumor spreads tumor cells via the hematoma beyond accurately determined limits. The risk of local recurrence increases under such circumstances. If a pathologic fracture heals after neoadjuvant chemotherapy, a limb-salvage procedure can be performed successfully.

Inappropriate Biopsy Sites

An inappropriate or poorly planned biopsy jeopardizes local tumor control by contaminating normal tissue planes and compartments.

INFECTION. The risk of infection after implantation of a metallic device or an allograft in an infected area is prohibitive.

SKELETAL IMMATURE. The predicted leg-length discrepancy should not be greater than 6 to 8 cm, although expandable prostheses have been used with success in this situation. Upper extremity reconstruction is independent of skeletal maturity.

EXTENSIVE MUSCLE INVOLVEMENT. Enough muscle must remain to reconstruct a functional extremity.

MANAGEMENT FOLLOWING INAPPROPRIATE SURGERY AS A BENIGN TUMOR

A common problem often seen in major oncology centers is the patient with a sarcoma treated as a benign tumor with an inappropriate surgical procedure. In general, these patients have been treated by an amputation. It has been the assumption that an amputation offered the highest survival and local control rate.

Jeon et al. reported their results of 25 patients (22 osteosarcoma) with high-grade primary bone sarcomas who underwent unplanned intralesional procedures and then were treated with adjuvant chemotherapy and limb-sparing surgery. Surprisingly, they showed a 5-year continuous disease-free survival rate of 65% for the 22 osteosarcoma patients. Their indications for limb-sparing procedures included a good response to the induction chemotherapy with attainable negative surgical margins. The relevant contraindications to limb-sparing surgery were cases of pathological fracture and extensive operative procedures. It has been the senior author’s (M. M. M.) experience that most lesions inadvertently treated as a benign tumor can safely undergo limb salvage following a good response to induction chemotherapy. If there is a poor response, amputation is warranted.

LIMB-SPARING SURGERY AND PERIOPERATIVE PAIN MANAGEMENT

Pain after extensive limb-sparing resections of bone is severe, and patients require large amounts of narcotics. Pain after amputations in young people is especially difficult to control. Within the past decade, there has been increased interest in managing postoperative pain by various modalities in addition to the standard patient-controlled analgesia (PCA). Patients who have preoperative pain are more difficult to treat adequately and are at a higher risk of postoperative pain syndromes than are those with no preoperative pain.

The aim of postoperative pain management is to eliminate or greatly attenuate pain. The use of multiple modalities is routine. Epidural anesthesia (with or without patient control), an
intravenous PCA, and a regional block are ideal. The authors have termed this \textit{triple-modality pain control}.

The surgical author (M. M. M.) has developed a technique of \textit{perineural} anesthesia that is used in conjunction with an epidural and an intravenous PCA. Perineural anesthesia is a form of a continuous regional block that was developed specifically for the management of patients with sarcoma. Major limb-sparing procedures such as amputations expose the major nerves. This affords the surgeon the opportunity to directly catheterize all the nerves (thus the term perineural) within the operative field (e.g., in distal femoral resections, the sciatric nerve is exposed and catheterized, and in proximal humeral resections, the infraclavicular portion of the brachial plexus is similarly treated). Henshaw et al.\textsuperscript{23} reported their experience with 166 patients implanted with one or more perineural catheters; there were no catheter-related complications.

**QUALITY OF LIFE CONSIDERATIONS: LIMB-SPARING SURGERY VERSUS AMPUTATION**

During the 1990s, as the techniques of limb-sparing surgery were being developed, it had been assumed that such surgery was superior to amputation. Nonetheless, when complications occurred, many surgeons thought that an amputation might have been preferable. Despite the extensive literature on the various chemotherapy regimens, surgical techniques, and limb-sparing surgery, few studies have focused on the patients’ evaluation of their overall quality of life. Two major studies that have been published are described here.

Greenberg et al.\textsuperscript{24} from Massachusetts General Hospital and the Children's Hospital/Dana-Farber Cancer Institute evaluated 62 osteosarcoma survivors at a mean of 12 years from diagnosis. These patients responded to a comprehensive battery of psychological questions. In general, most survivors were in good mental and physical health. The results are summarized as follows:

1. The reported rates of psychopathology among amputees and those undergoing limb-sparing surgery did not differ significantly.
2. Fertility was not a problem. Twenty-three normal progeny were born after chemotherapy to eight women and the wives of five men. Only two women were considered infertile; both had undergone radiation therapy associated with other childhood cancers.
3. All responders who had undergone limb-sparing surgery believed that the effort to save their limb was worthwhile. Twenty patients rated the effort of limb salvage very worthwhile (mean, 4.5 of 5.0). Those in whom the attempt at limb salvage failed rated the effort as 4.0 (not significantly different from the successful group). Those patients who were less satisfied with surgery had secondary amputations.
4. Pain was usually minimal but, when present, was associated only with lower extremity amputation. The pain pattern suggested deafferentation syndromes. No patients undergoing upper extremity limb-sparing procedures incurred pain.
5. Among patients who did not do well, multiple symptoms, family problems, and socioeconomic problems were more common than among patients who fared well.

The authors concluded that attention to the management of depression, treatment of substance abuse, and help with financial difficulties could contribute to the quality of life of patients who undergo limb-sparing surgery or amputation. Pain management, physical and vocational rehabilitation, and sexual counseling may also be beneficial, as may psychotherapeutic counseling.

Christ et al.\textsuperscript{25} evaluated the long-term psychosocial effects of limb-sparing surgery and primary amputation for coping capacity and the degree of psychopathology. The overall incidence of emotional disturbance among these patients was no different from that in the general population. Unlike patients in other studies, those in the group with initial amputations had substantial difficulty maintaining an optimal functioning level. Their difficulty was even greater than that of limb-salvage patients with a compromised outcome, including those with late amputation. Specifically:

1. An amputee was significantly less likely to have married than a limb-spared patient.
2. Coping mechanisms of those with primary amputations were less effective than those of patients in the limb-salvage group.
3. Patients who had limb salvage without later complications were very pleased with their outcome.
4. Good work experience was an important compensation for physical loss.
5. Male dependency needs were often underestimated. Some men were left to manage their own adaptation tasks, whereas for women the opposite was true. Female patients tended to become excessively dependent.
6. Patients reported no difficulty in enjoying sexual activity. The first postsurgical sexual experience was described as no more traumatic than the first experience that required showing the leg (e.g., swimming).

Despite good social support scores, the amputees had higher psychopathology scores than did patients who had undergone limb-sparing procedures. The authors concluded that patients undergoing primary amputation need more intensive support than those whose limbs are spared. They recommend an overall approach similar to that for posttraumatic stress disorder.

**CLINICAL ANALYSIS OF LIMB-SPARING SURGERY**

Rougraff et al.\textsuperscript{26} evaluated 227 patients with nonmetastatic osteosarcoma of the distal femur treated at 26 institutions. They reported eight (11\%) local recurrences in 73 patients with a limb-salvage procedure and nine (8\%) local recurrences in 115 patients who had an above-knee amputation. No local recurrences were reported in the 39 patients who had a hip disarticulation.

Bacci et al.\textsuperscript{27} retrospectively evaluated 540 patients treated over 10 years in three multicenter studies with 63 participating institutions. The rate of local recurrence was 8\% for patients with a poor histologic response and 3\% for those with a good histologic response. A limb-sparing procedure was performed on 84\% of the 540 cases evaluated, with a local recurrence rate of 6\%. The most important determinant of local recurrence was the type of surgical margin and the response to chemotherapy. Of the 540 patients, 31 had a local recurrence. The overall outcome of this group was extremely poor. All local recurrences were accompanied by metastases, and despite treatment, only one patient remains alive (3\%). Local recurrence did not correlate with patient age, gender, histologic type, site and volume, pathologic fracture incidence, chemotherapy, or type of surgical procedure.
PROSTHESIS SURVIVAL AND COMPLICATIONS

Prosthetic replacement is commonly used for reconstruction after resection of the proximal humerus, proximal femur, distal femur, and proximal tibia. Several studies have evaluated the long-term results, prosthetic survivorship, and complications associated with prosthetic replacement.

Ruggieri et al. reported on 144 cases of nonmetastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy and limb-sparing surgery. Sixty-three percent of the patients had one or more complications. Twenty-eight complications were considered minor (i.e., no surgery was required), and 77 complications were major. The infection rate was 6.2%. Mechanical problems occurred in seven patients (5%). The average number of complications per patient was 1.3. The authors thought that the most serious problems resulting from a complication were those that required the delay of chemotherapy or deviation from the recommended dose, either of which could jeopardize survival. Such consequences were not, however, demonstrable statistically.

In 1998 Henshaw et al. reported the long-term prosthetic survival analysis of 100 patients treated with the U.S. designed modular replacement system (Howmedica and Osteonics, Inc, Allendale, New Jersey). The minimum follow-up period was 2 years. Prosthetic failure was defined as removal of the implant for any reason. Kaplan-Meier survival analysis was performed for all implants and for each site of reconstruction. The authors reported no mechanical failures of the stem, body, or taper components. No clinically significant prosthetic loosening was reported. The infection rate was 8% (four in distal femurs, three in proximal tibias, and one in proximal humerus), leading to six amputations and one prosthetic removal. The amputation rate was 7% (six infections and one local recurrence). The Kaplan-Meier survival analysis for all sites was 88% at 10 years, with a median follow-up of 64.4 months. The estimates of 10-year survival for the distal femur, proximal humerus, proximal femur, and proximal tibia were 90%, 98%, 100%, and 78%, respectively. Today, modular prostheses are forged by several manufacturers and are the standard prostheses used for most limb-sparing procedures (Fig. 45.2.5).

COST OF LIMB-SPARING SURGERY VERSUS AMPUTATION

The question of the cost effectiveness of limb-salvage surgery for bone tumors has arisen in the face of managed care, especially within the United States. The only published report on this subject is by Grimer et al. who compared the cost of a limb-salvaging procedure in lieu of an amputation. The study was based on large experience of amputations and limb-sparing procedures at the Royal Orthopaedic Hospital in Birmingham, England. They developed a formula for the cost of the limb-salvage procedure versus an above-knee amputation with subsequent prosthetic replacement over the predicted lifetime of the patient. This was calculated for tumors around the knee. They excluded tumors of the proximal humerus and of the proximal femur, because, whatever difference in cost might occur, there was a tremendous advantage in replacing the proximal femur rather than performing a hemipelvectomy or hip disarticulation. Similarly, there is a tremendous advantage in preserving the upper extremity and a functioning hand in lieu of a forequarter amputation for a proximal humeral sarcoma. They concluded the savings for an average patient undergoing a limb-salvaging surgery over a 20-year period to be approximately 70,000 British pounds (at 1977 prices), which is approximately six times the cost of the original limb-salvage procedure. They concluded that the equation can be used for any method of limb-salvage procedure. This study was performed with distal femoral resections that used a simple hinge prosthesis, which is now out of date. The modern rotating

Figure 45.2.5. Endoprosthetic survival (Kaplan-Meier analysis) following limb-sparing surgery. A: Modular prosthesis versus custom prosthesis (prior to the development of the magnetic resonance spectroscopy). B: Survival of the prosthesis versus the various anatomic sites. C: Survival of the prosthesis compared to overall patient survival. (From ref. 29, with permission.)
hinged-knee prosthesis, with an improved surface and a collar coated with porous beads, provides a much longer rate of survival. These features should provide a significantly lower rate of wear and failure, thus increasing cost effectiveness.

The surprising feature of these findings is the considerable cost of amputation. Most active young people would demand and use a sophisticated artificial limb. These individuals frequently have stump problems and require multiple replacements of the socket and prosthesis. They often require a spare prosthesis as well. Many request and use a sports limb and a limb designed for swimming. A new prosthesis is required at regular intervals. With the increasing complexity of artificial limbs, it is likely that the maintenance cost of the amputated extremity will increase.

**AMPUTATIONS**

An amputation provides definitive surgical treatment in patients in whom a limb-sparing resection is not a prudent option. Approximately 10% to 15% of patients still require amputation, despite the advent of limb-sparing surgery. In contrast to
amputations performed for noncancer causes, amputations for cancer tend to be at a more proximal anatomic level, to occur in younger people (reflecting the incidence of bone sarcomas), and to be technically more difficult. The resultant psychological and cosmetic losses are also more substantial.

**CHEMOTHERAPY FOR BONE SARCOMAS**

Before routine use of systemic chemotherapy for the therapy of osteosarcoma, fewer than 20% of patients survived more than 5 years. Further, recurrent disease developed in 50% of patients, almost exclusively in the lungs, within 6 months of surgical resection. The findings of two randomized clinical studies completed in the 1980s comparing surgery alone to surgery followed by chemotherapy demonstrated conclusively that the addition of systemic chemotherapy improved survival in patients presenting with localized high-grade osteosarcoma (Table 45.2.4).

The implications of these findings are that the vast majority of patients with apparent localized tumors have the presence of micrometastatic disease, and that available systemic chemotherapy increases the chances of survival by addressing those micrometastases. In the past 20 years, standard treatment has evolved to the routine use of neoadjuvant (pre Surgical) and adjuvant (postsurgical/chemotherapy). In addition, it is now widely accepted that the four most important drugs used for the treatment of osteosarcoma include high-dose methotrexate (HD-MTX), adriamycin (ADM), cisplatin (CDDP), and ifosfamide (IFOS). However, the optimal use of two-, three-, or four-drug combinations remains somewhat controversial.

### Table 45.2.4 Reported Results of Representative Trials Incorporating Presurgical Chemotherapy for Osteosarcoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Investigators</th>
<th>Number of Patients</th>
<th>% Relapse-Free</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDMTX + VCR + DOX + BCD (T-7 regimen)</td>
<td>MSKCC</td>
<td>54 (younger than 21 y)</td>
<td>74</td>
<td>40,126,127</td>
</tr>
<tr>
<td>HDMTX + VCR – DOX + BCD ± CDDP (depending on response) (T-10 regimen)</td>
<td>MSKCC</td>
<td>79 (younger than 21 y)</td>
<td>76</td>
<td>127</td>
</tr>
<tr>
<td>DOX + HDMTX + (BCD or CDDP) ± interferon (COSS 80)</td>
<td>GPO</td>
<td>116</td>
<td>68</td>
<td>128,129</td>
</tr>
<tr>
<td>HDMTX + DOX + CDDP</td>
<td>Mount Sinai</td>
<td>25</td>
<td>77</td>
<td>130</td>
</tr>
<tr>
<td>HDMTX + VCR + DOX + BCD ± CDDP (depending on response) (CCG-782)</td>
<td>CCG</td>
<td>231</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>HDMTX + DOX + CDDP + IFOS (COSS 82)</td>
<td>GPO</td>
<td>125</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>DOX + CDDP ≥ HDMTX</td>
<td>EOS</td>
<td>231</td>
<td>65 (~HDMTX)</td>
<td>131</td>
</tr>
<tr>
<td>IA CDDP + (HDMTX vs. IDMTX) + DOX ± BCD (depending on response)</td>
<td>Instituto Ortopedico Rizzoli</td>
<td>127</td>
<td>51 (overall)</td>
<td>132</td>
</tr>
<tr>
<td>HDMTX + DOX + IA CDDP ± etoposide, IFOS (postoperative therapy determined based on response to preoperative therapy)</td>
<td>Instituto Ortopedico Rizzoli</td>
<td>164</td>
<td>63</td>
<td>133</td>
</tr>
<tr>
<td>IA CDDP vs. HDMTX</td>
<td>M. D. Anderson Cancer Center</td>
<td>43</td>
<td>60</td>
<td>134</td>
</tr>
<tr>
<td>IA CDDP + DOX + CTX (depending on response) (TIOS I)</td>
<td>M. D. Anderson Cancer Center</td>
<td>24</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HDMTX + DOX + IFOS ± CDDP</td>
<td>CCG (selected investigators)</td>
<td>95</td>
<td>82</td>
<td>—</td>
</tr>
<tr>
<td>HDMTX + DOX + CDDP BCD (POC 8651)</td>
<td>POG</td>
<td>100</td>
<td>70 (presurgical chemotherapy)</td>
<td>—</td>
</tr>
</tbody>
</table>

BCD, bleomycin, cyclophosphamide, and dactinomycin; CCG, Children’s Cancer Group; CDDP, cisplatin; COSS, Germany-Austria-Swiss Cooperative Osteosarcoma Study; CTX, cyclophosphamide; DOX, doxorubicin; EOI, European Osteosarcoma Intergroup; EOS, First European Osteosarcoma Intergroup Study; GPO, German Society for Pediatric Oncology; HDMTX, high-dose methotrexate (12 g/m² or more) + leucovorin rescue; IA, intraarterial administration; IDMTX, intermediate-dose methotrexate (750 mg/m²) + leucovorin rescue; IFOS, ifosfamide; MTP-PE, muramyl-tripeptide phosphatidylethanolamine; MSKCC, Memorial Sloan-Kettering Cancer Center; POG, Pediatric Oncology Group; TIOS, Treatment and Investigation Osteosarcoma Study; VCR, vincristine.

1-2 Randomized study; no significant difference in relapse-free survival for patients on each treatment arm of study.

2-3 Randomized study; favors treatment without HDMTX (some patients treated only adjuvantly).

4-5 Randomized study; difference in results of treatment significant at 7% level.

6 Randomized study; analysis of results by randomized treatment not yet available.
ADJUVANT VERSUS NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy evolved in concert with the use of limb-salvage surgical approaches. At Memorial Sloan-Kettering Cancer Center, customized endoprosthetic devices in limb-salvage procedures often required several months to manufacture. Rather than delaying treatment, investigators began to administer chemotherapy while waiting for the endoprosthesis to be made. This approach led to suggestions that preoperative chemotherapy improved survival of the patients. In addition, orthopedic oncologists developed their own opinions regarding the advantages and disadvantages of presurgical chemotherapy. These observations ultimately led to a randomized clinical study between 1986 and 1993 by the Pediatric Oncology Group (POG) comparing presurgical chemotherapy to immediate surgery followed by adjuvant chemotherapy to patients less than 30 years of age with nonmetastatic, high-grade osteosarcoma.

The investigators concluded that there is no benefit to survival whether adjuvant or neoadjuvant therapy is used, and modern-era survival for nonmetastatic osteosarcoma should be at least 65%.

ASSESSMENT OF HISTOLOGIC RESPONSES TO NEOADJUVANT CHEMOTHERAPY

Although the randomized study noted above showed no survival benefit, preoperative chemotherapy has become standard practice at most centers, in large part because of the important survival implications of histologic response to such therapy. Several issues need to be considered when evaluating the predictive value of histologic response on survival. Several related but independent systems have evolved to evaluate histologic response. These include the grading system developed at Memorial Sloan-Kettering Cancer Center by Huvos et al., the system developed by Salzer-Kuntschik et al. and used by the German-Austrian-Swiss Cooperative Osteosarcoma Study Group (COSS), and the system developed by Picci et al. at the Istituti Ortopedico Rizzoli (IOR) in Bologna. Although each of these grading systems attempts to objectively determine the effect of chemotherapy in tumor necrosis, each has a different scale applied and is subject to observer interpretation (Table 45.2.5). In addition, the timing of surgery (i.e., the duration of preoperative chemotherapy) would be expected to impact histologic response. However, in spite of these shortcomings, a consensus has emerged that uses greater than 90% necrosis

Figure 45.2.6. A: Treatment plan for induction therapy. Patients received two courses of etoposide and ifosfamide, then radiologic assessment and surgery of primary tumor. The pathologic assessment of tumor necrosis was performed after surgery. B: Continuation chemotherapy regimen started 1 to 2 weeks after surgery. CDDP, cisplatin; G-CSF, granulocyte colony-stimulating factor. (From ref. 44, with permission.)
and less than 90% necrosis as separating good and poor responses, respectively. Furthermore, most current studies use 10 to 12 weeks of preoperative chemotherapy (Fig. 45.2.7).

Using the criteria of greater than 90% as a good response and less than 90% necrosis as a poor response, several studies have reviewed 8- to 18-year experiences. The IOR reviewed data on localized-extremity osteosarcoma in patients less than 40 years of age over the 19-year period from 1983 to 2002. More than 1,000 patient records were analyzed. Fifty-nine percent of all patients had a good response to chemotherapy, and 41% had a poor response. Patients with a good histologic response to chemotherapy had a 5-year survival of 76%, whereas those with a poor response had a 5-year survival rate of 56%.

The COSS database was similarly reviewed and included 1,700 patients entered on study between 1980 and 1998. This analysis included all sites, ages, and presence or absence of metastases. The data look remarkably similar to those of the Italian study, with 55.6% of patients classified as having a good response to chemotherapy, and 44.4% having a poor response. Patients with a good histologic response to chemotherapy had a 5-year survival of 77.8%, whereas those with a poor response had a 5-year survival rate of 55.5% for poor responders. Of further note, all the patients in both of these analyses received HD-MTX, and the majority also received ADM, CDDP, with or without IFOS. Also, most patients in these two analyses received preoperative chemotherapy, with surgery occurring between weeks 9 and 11 of treatment.

The European Osteosarcoma Intergroup (EOI) from the European Organisation for Research and Treatment of Cancer, United Kingdom, and International Society of Paediatric Oncology (SIOP) analyzed data for two consecutive studies between 1983 and 1986 and 1991. A total of 570 patients were analyzed in the report. This analysis is notable for several differences compared to the COSS and IOR analyses. Only 28% of patients had a good histologic response, whereas 72% of patients had a poor histologic response. Patients with a good histologic response had a 5-year survival of 75%, whereas those with a poor response had a 5-year survival of 45%. Of note, many of the patients included in the analysis did not receive HD-MTX because many were treated on a randomized study comparing two drugs, ADM and CDDP, to more intensive therapy including HD-MTX, similar to the COSS and IOR studies. The large randomized study failed to show an advantage of multiagent therapy compared to ADM and CDDP alone. However, the 5-year survival was 55% overall in this study, which is lower than that of the other studies reported above.

**Figure 45.2.7.** Pre- and postinduction chemotherapy histology of osteosarcoma. A: Tumor prior to induction chemotherapy (hematoxylin and eosin(HE) stain, X magnification). This shows viable osteoblast tumor cells forming tumor osteoid. Osteoid formation is the hallmark of an osteosarcoma. B: A specimen following induction chemotherapy with complete tumor necrosis. Note the complete absence of osteoblasts and stromal cells. The osteoid remains present and does not resorb. This appearance of a naked lattice of osteoid is characteristic of tumor necrosis. Unlike other tumors, overall survival may not shrink following induction chemotherapy since the matrix (osteoid) always remains.
Although the findings have continued to stir debate regarding optimal therapy, it suggests that patients who have a poor response to ADM and CDDP therapy alone (the majority of patients) have a much worse 5-year survival than those who have a poor response to three- or four-drug therapy. All three studies together strongly suggest that good responders can be expected to have a 5-year survival of approximately 75%, whereas poor responders have a 5-year survival in the range of 45% to 55%, depending on the treatment. It is important to point out that, although poor responders have a worse outcome than good responders, 45% to 55% 5-year survival is still dramatically improved compared to the less than 20% 5-year survival in the prechemotherapy era.

Another factor that could possibly influence histologic response on therapy and its predictive value on survival is the histologic subtype of the tumor. The clinical and biologic relevance of histologic subtypes has generally been believed to be minimal. In the IOR and the EOI studies discussed above, histology was characterized as osteoblastic or conventional, fibroblastic, chondroblastic, or telangiectatic. In both studies approximately 70% of cases were osteoblastic, whereas approximately 10% of cases were either chondroblastic or fibroblastic, with 6% telangiectatic, a number too small to be analyzed in the EOI study. In both studies, fibroblastic tumors had a higher rate of good histologic response (approximately 80% in the IOR study), whereas chondroblastic tumors had a lower rate of good responders (43% in the IOR study). Perhaps even more importantly, unlike other histologies, 5-year survival rates were identical for good and for poor responders in chondroblastic histology, at 68%.

To summarize, treatment of patients with nonmetastatic high-grade osteosarcoma with adjuvant chemotherapy including HD-MTX and at least two other drugs among the four most active drugs in osteosarcoma can be expected to lead to a 75% 5-year survival among good histologic responders (greater than 90% necrosis) and 55% among poor histologic responders (less than 90% necrosis). However, care should be taken when assessing histologic response in patients with chondroblastic histology, as histologic responses may not be as important a predictor of survival in this subgroup.

**ADJUSTING CHEMOTHERAPY FOR POOR RESPONDERS**

Another hypothetical advantage of determining histologic response to preoperative chemotherapy is the potential to alter therapy in those patients who do not have a good response to preoperative treatment. If this “tailored therapy” approach is successful, one might expect to alter the impact of poor histologic response on survival by treating such patients with different drugs and improving their outcome. This approach has indeed proven to be successful in Hodgkin’s lymphoma and leukemia. This approach was initially pioneered in the early 1980s at Memorial Sloan-Kettering Cancer Center, where patient responders had CDDP substituted for HD-MTX in addition to continuing BCD (bleomycin, cyclophosphamide, and dactinomycin) and ADM. Although the initial analysis of this study suggested that there was no longer a difference in survival between good and poor responders, longer follow-up data demonstrated that initial response to preoperative chemotherapy continued to be predictive of survival. Furthermore, patients who had adjustments in their postoperative chemotherapy based on poor initial response did not have improvement in survival compared to those who had no modifications. More recently, the Rizzoli Institute reported long-term follow-up data on a study carried out between 1986 and 1989 on 164 patients less than 40 years of age with nonmetastatic extremity osteosarcoma. Patients with less than 90% necrosis at the time of surgical resection had IFOS and etoposide added to HD-MTX, ADM, and CDDP, whereas patients with greater than 90% necrosis continued to receive only the three drugs. The 10-year event-free survival was 67% for patients with 90% necrosis at the time of surgical resection and 51% for those with less than 90% necrosis. Although this difference in survival did not quite reach statistical significance (P = .08), it still favored those patients who had an initial good histologic response to therapy. Several other reports also have failed to demonstrate an ability to rescue poor responders. Thus, to date, it has not been possible to improve the outcome of poor responders by altering postoperative chemotherapy.

**CHEMOTHERAPY FOR METASTATIC DISEASE**

The presence of metastatic disease at presentation continues to be an extremely poor prognostic finding, with most studies showing survival rates in the range of 20%. It is therefore clear that new approaches are needed. The POG reported early data from a small phase II study for patients less than 30 years old with newly diagnosed metastatic osteosarcoma. Forty-one patients were treated with two cycles of etoposide and IFOS preoperatively, followed by 32 weeks of postoperative chemotherapy, including three additional cycles of etoposide and IFOS along with standard HD-MTX, ADM, and CDDP (Fig. 45.2.8). It should be noted that patients underwent surgical resection of all sites of disease whenever possible. The data are still immature, but the projected 2-year progression-free survival was 43%. In the large analysis of the COSS database that included more than 1,700 consecutively treated patients, the 10-year survival probability was 40% for patients who were able to have all sites of metastatic disease resected. Thus, although there is no accepted standard approach for the treatment of newly diagnosed metastatic patients, available data would suggest that such patients should be treated with currently available aggressive multiagent chemotherapy with complete surgical resection of all sites of disease if at all possible.

**CHEMOTHERAPY FOR RELAPSED OSTEOSARCOMA**

Similar to patients who present with primary metastatic disease, individuals in whom recurrent disease develops have an overall poor prognosis, with 5-year survival rates in the range of 20%. As noted for metastatic disease at presentation, new salvage strategies are needed. Although there is no standard second-line chemotherapy that currently is uniformly applied, several principles have been clearly established. Most importantly, as with primary metastatic disease, complete resection of recurrent disease appears to be mandatory for long-term survival. It also is likely that multiagent chemotherapy contributes to successful salvage of some patients. In general, patients should be treated with any of the four most active
agents noted earlier in Assessment of Histologic Responses to Neoadjuvant Chemotherapy if initial therapy did not include one or more of these agents. Patients who have recurrences more than 1 year after completing prior systemic therapy may benefit from reintroduction of at least some of the same drugs in a salvage regimen. The use of high-dose chemotherapy with autologous hematopoietic stem cell rescue has been applied to salvage therapy. However, at least two small pilot studies failed to demonstrate an advantage to standard salvage therapy approaches.45,46

LATE EFFECTS OF SYSTEMIC THERAPY
The universal application of systemic chemotherapy for all patients with osteosarcoma has led to an increased likelihood of survival as noted earlier in the introduction to Chemotherapy for Bone Sarcomas. However, with this increase in survival has come the inevitable increase in late effects secondary to chemotherapy. The most important long-term side effects that have now been well documented are ADM-induced cardiomyopathy, male infertility, and development of second malignant neoplasms. In a long-term follow-up report of 164 patients treated with cumulative doses of 480 mg/m² ADM, there were six documented cases of severe cardiomyopathy.41 It is likely that subclinical cardiac damage may occur and be underestimated.41 Although earlier reports suggested little effect on infertility, more recent inclusion of IFOS into front-line therapy has likely increased the risk of male infertility after treatment.48 In the long-term follow-up study from the IOR noted above, ten of 12 patients who underwent sperm analysis were noted to have azoospermia. All ten had received chemotherapy at the time of puberty, and nine of ten had received IFOS. As more patients survive their primary osteosarcoma, the development of second malignant neoplasms has become of increasing concern as well. In a long-term follow-up study from St. Jude’s, there were nine documented cases of second malignant neoplasms among 334 patients treated between 1962 and 1996, for an incidence of 2%. The tumors included two cases of MFH; a chondrosarcoma; carcinomas of the rectum, colon, stomach, and breast; a melanoma; and a glioblastoma.49 Although this incidence is significantly lower than that of survivors of Hodgkin’s lymphoma, it is likely that as more patients are cured of osteosarcoma, this problem will continue to increase. Because of these late sequelae of systemic treatment and continued reports of recurrences more than 5 years after treatment, these patients should be followed long term by the centers performing the initial curative treatment on these patients.

RADIOTHERAPY FOR OSTEOSARCOMA
Radiation therapy is generally not used in the primary treatment of osteosarcoma, although this may change with the greater implementation of new technologies. Radiation therapy is used for patients who have refused definitive surgery, require palliation, or have lesions in axial locations. Experience with radiotherapy has been greater in the treatment of chondrosarcoma, possibly due to the lesser availability of adjuvant chemotherapy in facilitating the goals of tissue preservation. Radiotherapy assumes greater importance for tumors of the axial skeleton and facial bones where a combination of limited surgery and radiotherapy may be used since function and cosmesis preservation may be paramount. Radiotherapy is more frequently used in Ewing’s sarcoma and peripheral primitive neuroectodermal tumors of bone and are discussed in Chapter 45.
TREATMENT PLANNING

Optimal radiotherapy of bone tumors requires careful technical treatment planning and adherence to radiobiologic principles; therefore, all fields should be treated each day to ensure a continuous homogeneous distribution of dose to all areas of the target. Normal tissue should be protected from the high-dose regions wherever possible, and this is achieved using precise, three-dimensional delineation of the target volumes as well as appropriately fractionated courses of radiotherapy. The latter is also necessary to accomplish adequate tumor control by especially exploiting advantages over the tumor such as reoxygenation.

All treatments should implement megavoltage therapy beams to maximize physical reduction in absorbed dose delivered to bone. Radiotherapy is most usually planned volumetrically using computerized CT simulation technologies. Patient immobilization is also essential, especially when very precise delivery is used to avoid irradiating normal tissues.

Patient immobilization is essential to optimal radiotherapy, especially when very precise delivery is used and the margins around the target are less than usual, particularly when avoidance of normal tissues is being undertaken.

DOSE AND VOLUME CONSIDERATIONS

Large treatment volumes that include the entire clinical and radiographic extent of tumor plus a generous margin for subclinical extension of disease are needed (e.g., 45 to 50 Gy delivered over a period of approximately 5 weeks in daily fractions). For potential medullary spread (e.g., lymphoma, Ewing’s sarcoma), the standard radiation volumes previously included the entire bone, with a boost of radiation to the area of prior or persisting bulky disease. However, radiation confined to the involved area may be sufficient for small, round cell bone tumors that have responded to induction chemotherapy. If any volumes are matched, the junction should be routinely moved every 10 Gy.

The irradiated volume should encompass at least the tissue that would be resected, plus an allowance of approximately 2 cm for microscopic extension with additional allowance for patient movement. A nonirradiated strip of the limb length should be identified and maintained (or at least restricting the maximum dose in such areas to less than 40 Gy) and, wherever possible, overlap the lymphatic drainage pathways located medially in the extremity.

Additional principles involve using multiple beam-shaping devices so that shaped fields can be designed to conform to individual tumor volume and anatomy. When necessary, beam modifiers, such as compensating filters and wedge filters, or beam segmentation with multileaf collimation and intensity-modulated radiotherapy (IMRT) beams are useful aids to optimize the homogeneity of the dose within the target volume while sparing adjacent normal structures and account for individual variations in patient thickness. When chemotherapy, such as ADM and BCD, and radiotherapy are used, it is important to avoid concomitant administration of drugs that may act as radiation sensitizers to normal tissue.

PRECISION TECHNOLOGY IN RADIOTHERAPY DELIVERY

Traditional radiotherapy treatment approaches use parallel opposed or relatively standard three- or four-field plans with some beam shaping to reduce the irradiated volume where possible. This may suffice for uncomplicated presentations but for many lesions, more precise targeting with conformal plans or IMRT is necessary. Relatively inaccessible target areas previously only adequately treated with potential and unnecessary toxicity can now be successfully irradiated while avoiding adjacent vulnerable anatomy that may be partially surrounded by the target.

Precision photon methods such as IMRT can be delivered with several forms of delivery platforms. In some situations (e.g., adjacent to the spinal cord or optic chiasm) extremely accurate delivery may demand stereotactic precision for guidance to minimize interfraction differences and ensure safety in tumor coverage and avoidance of critical anatomy. Potential methods include tomotherapy, robotic linear accelerators, and standard linear accelerators modulated by additional collimation controls. A popular robotic system, the CyberKnife (Accuray, Sunnyvale, California) uses a frameless reference system for stereotactic guidance and a robotic delivery system, permitting adaptive beam pointing to account for positional variance. The absence of a frame provides great flexibility and makes it possible to treat extracranial sites with the same or better precision than other systems achieved by fixing the lesion with respect to the cranium using the frame. This is particularly applicable to spine lesions because it is difficult to firmly immobilize the torso, in contrast with limb or skull sites, for which customized physical immobilization systems are the rule. A tendency with very accurate delivery approaches is to forgo usual radiobiologic principles by delivering a relatively small number of large dose fractions to a precise target with extraordinary accuracy. This has the advantage of efficiency in treatment delivery to a complex target. Long-term results are needed to assess the ultimate safety of dose fractionation regimes delivered in this fashion, in particular when the total dose administered is high. For example, Gwak et al. recently reported preliminary results on the use of the CyberKnife to deliver hypofractionated stereotactic radiation therapy for skull base and upper cervical chordoma and chordosarcoma, but two patients developed radiation-induced myelopathy. For this reason they advise great caution with respect to the biological effects of the accumulated dose on the adjacent critical structures. So far the first large series of spinal or base of skull tumors to evaluate and report on this promising technology still contains a paucity of sarcoma lesions or may as yet lack clinical outcome from which to confidently embrace its full capability.

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CLASSIC OSTEOSARCOMA

Osteosarcoma is a high-grade malignant spindle cell tumor that arises within a bone. Its distinguishing characteristic is the production of “tumor” osteoid or immature bone directly from a malignant spindle cell stroma.

Clinical Characteristics

Osteosarcoma typically occurs during childhood and adolescence. Historically, investigators evaluated 227 patients from 1971 to 1984 and reported the peak incidence to be between 10 and 19 years of age but noted the mean and median values to
be 29 and 20 years, respectively. The overall incidence—2.1 cases per million people per year—has not changed. When osteosarcoma occurs in patients older than 40 years, it is usually associated with a pre-existing condition, such as Paget’s disease, irradiated bones, multiple hereditary exostosis, or polyostotic fibrous dysplasia. Bones of the knee joint and the proximal humerus are the most common sites, accounting for 50% and 25%, respectively, of all osteosarcomas. In general, 80% to 90% of osteosarcomas occur in the long tubular bones, and the axial skeleton is rarely affected. Fewer than 1% are found in the hands and feet.

With the exception of serum AP (SAP) levels, which are elevated in 45% to 50% of patients, laboratory findings are usually not helpful. Furthermore, elevated AP per se is not diagnostic because it is also found in association with other skeletal disease. Pain is the most common complaint. Night pain gradually develops and becomes a hallmark of skeletal involvement. Physical examination demonstrates a firm, soft mass fixed to the underlying bone with slight tenderness. No effusion is noted in the adjacent joint, and motion is normal. Incidence of pathologic fracture is less than 1%. Systemic symptoms are rare.

Radiographic Characteristics

Typical findings are increased intramedullary radiodensity (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, periosseous elevation, and extraosseous extension with soft tissue ossification. This combination of characteristics is not seen in any other lesion. Wilner classified 600 radiographs of osteosarcoma seen at the Memorial Sloan-Kettering Cancer Center into three broad categories: sclerotic (32%), osteolytic (22%), and mixed (46%). Although no statistically significant difference was found in overall survival rates among these types, the patterns are important to recognize. 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 GCT, aneurysmal bone cyst, fibrosarcoma, and MFH.

Clinical and Prognostic Considerations

Before the era of adjuvant chemotherapy, treatment of osteosarcoma consisted of amputation. Metastasis to lungs and other bones generally occurred within 24 months. A large number of series show an overall survival of 5% to 20% at 2 years. Before the era of adjuvant chemotherapy, treatment of osteosarcoma involved amputation. Metastasis to lungs and other bones generally occurred within 24 months. A large number of series show an overall survival of 5% to 20% at 2 years.

Marcove et al. reviewed 145 patients younger than 21 years of age who underwent surgery without adjuvant chemotherapy at Memorial Sloan-Kettering Cancer Center, noted no statistically significant differences with regard to race, gender, or duration of symptoms. Younger patients developed metastases sooner, but this made no difference in overall survival. Location of the osteosarcoma had no impact on the 5-year survival rate. Brostrom et al. evaluated 52 patients treated by surgery alone. They studied tumor size and site and reported that patients with distal lesions measuring less than 10 cm had a significantly higher survival (P < .01) than those with proximal lesions greater than 10 cm (43% vs. 12%, respectively).

Recently, Bacci reviewed 789 patients with nonmetastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy, following them for a minimum of 5 years at the Rizzoli Institute in Bologna, Italy. The significant treatment-related factors were patients’ age of 14 years or younger, elevated serum alkaline phosphatase at presentation, tumor volume of 200 mL or more, inadequate surgical margins, and poor histological response to preoperative chemotherapy. Each independently predicted a high risk of systemic recurrence. These are significant findings from an extremely large group of patients treated at an institution devoted to the care of osteosarcoma patients.

Alkaline Phosphatase

SAP level is an important biologic marker of tumor activity in patients with osteosarcoma. The early studies of the relationship between AP activity and survival were performed before the introduction of adjuvant chemotherapy (i.e., in patients treated with surgery alone). SAP continues to be a significant prognostic marker following neoadjuvant and adjuvant chemotherapy.

Marcove et al. reported on an evaluation of the SAP levels among 560 patients with high-grade osteosarcomas of the extremity who were treated at a single institution. Forty-six percent of these patients had elevated SAP levels before treatment; such levels were most commonly found in males older than 14 years and in patients with tumors greater than 150 mL of the osteoblastic type. Only two factors by a multivariate analysis were independently correlated with 5-year event-free survival: SAP levels (P < .002) and grade of chemotherapy-induced tumor necrosis (P < .0001). The authors recommend that, in planning randomized trials, patients be stratified according to SAP levels.

Biology and Prognostic Factors

Although the etiology of osteosarcoma remains for the most part unknown, several predisposing conditions have been clearly identified. The most common known risk factor is radiation exposure, and osteosarcoma is the most common histology found in radiation-associated second malignancies. Several hereditary risk factors are known to predispose toward osteosarcoma. Hereditary retinoblastoma associated with germline mutations in the RB gene is associated with a 100-fold increase in the risk of osteosarcoma, even in the absence of radiation exposure, which further increases the risk of osteosarcoma development. Li-Fraumeni syndrome is associated with germline mutations in the p53 gene and also with an increased risk for the development of osteosarcoma. Rothmund-Thomson syndrome is an autosomal recessive disorder characterized by cataracts; skeletal, dental, and nail abnormalities; skin rash; and short stature and is known to be associated with an increased risk of osteosarcoma. This syndrome is now known to be associated with mutations in the DNA helicase RECQL4, and a report has demonstrated that all patients with Rothmund-Thomson syndrome in whom osteosarcomas developed had evidence of truncating mutations of the RECQL4 gene. This is of particular note because alterations in a related RecQ DNA helicase in Werner’s syndrome are associated with an increased risk of osteosarcoma.
In view of these genetic predisposition syndromes, it is not surprising that RB1 and p53 are frequently found to be altered in patients with osteosarcoma. For p53, numerous studies have found the frequency of p53 mutations to be in the 18% to 30% range. The presence or absence of p53 mutations at diagnosis does not appear to carry prognostic implications. Alterations in the RB1 gene appear to be even more common than p53 alterations, with loss of heterozygosity reported in more than 50% of informative cases. The more sensitive technique of allelotyping found high frequencies of RB1 and p53 allelic imbalances, with no association with prognosis. The p53 and RB pathways are regulated by a series of activators and inhibitors, and these can be altered in tumors. In osteosarcomas, the incidence of alterations in either p15ARF or HDM2, positive and negative regulators of p53 function, respectively, is quite low. In contrast, alterations in the positive regulator of RB1 function, p16, Ink4a, was found to be greater than 15%, making overall incidence of RB pathway abnormalities in osteosarcoma likely to be even higher than 50%. No large studies of RECQL4 status in sporadic osteosarcomas have been reported.

Osteosarcomas are genetically characterized by complex karyotypes characteristic of severe disturbances in genomic stability. This virtually invariant presence of a complex karyotype is the cytogenetic hallmark of marked telomere dysfunction. A small, retrospective analysis of 62 patients with osteosarcoma revealed that 11 had no evidence of telomere maintenance. These individuals had significantly increased 5-year survival (90%) compared with the 51 patients with evidence of activation of telomere maintenance, who had a 5-year survival rate of 60%. Although these data require confirmation, they raise the possibility that, although the vast majority of patients with osteosarcoma have activation of telomere maintenance mechanisms leading to chromosomal instability, a minority may have normal telomere function and may constitute a particularly favorable subset.

Initial enthusiasm was shown in regard to the prognostic significance of expression of the multidrug resistance gene, MDR1 or P-glycoprotein, in osteosarcoma. The IOR group reported that increased expression of P-glycoprotein was associated with poor prognoses. However, subsequent studies have failed to confirm these observations; for example, a prospective multicenter study showed no correlation between MDR1 messenger RNA expression and disease.

In summary, although the overwhelming majority of osteosarcomas occur sporadically, there are several known hereditary risk factors for the development of this tumor. These risk factors have pointed out several key genetic alterations that occur commonly in sporadic osteosarcomas and likely play a major role in the biology of these tumors. The genetic hallmark of osteosarcoma is the presence of complex karyotypes, suggesting that chromosomal instability and mechanisms contributing to this phenotype also contribute to the biology of these tumors.

**Changing Pattern of Metastasis**

The classic pattern and time frame of metastatic dissemination of osteosarcoma has been modified by the use of adjuvant chemotherapy and thoracotomy. Bacci, in a recent report of 789 nonmetastatic osteosarcoma patients, described the present pattern of metastases, disease-free interval, and overall survival. In the 313 patients who experienced recurrence, the first recurrences were isolated lung metastases in 243 (77.6%) patients, isolated bone metastases in 26 (8.3%), lung and bone metastases in 51 (16%) cases, metastases in other sites in 3 (0.9%) (Kidney, brain, heart), metastases in more than two sites in 2, isolated local recurrence in 20 (6.4%), local recurrences combined with bone metastases in 8 (2.6%), and local recurrence combined with lung metastases in 6 (1.9%).

**Histologic Subtype and Influence on Chemotherapy Response**

Within the past decade, as more patients have been treated in cooperative studies and the number of patients treated with induction chemotherapy has increased, the question of the significance of the histologic subtype on the chemotherapy response of an osteosarcoma has begun to be examined. Bacci et al. analyzed the factors that determined the rate of chemotherapy response in the subgroup of patients who attained total (100%) tumor necrosis. Of 510 patients treated between 1983 and 1995, a 100% tumor necrosis was not related to gender, age, tumor size, SAP, or route of CDDP administration. The histologic complete response was related to only two factors: the number of drugs used and histologic subtype. According to the drugs used, the percentage of total necrosis was 31% for a four-drug regimen, 18% for a three-drug regimen, and only 1.5% for a two-drug regimen. According to the histologic subtypes, the rates of 100% total necrosis were telangiectatic tumors (41%), fibroblastic tumors (31%), and chondroblastic tumors (3%) (Fig. 45.2.9).

**Limb-Sparing Surgery and Pathologic Fracture**

Traditionally, a fracture through an osteosarcoma was treated by amputation. As experience with induction chemotherapy and limb-sparing surgery has increased, however, several centers have attempted limb-sparing surgery in this high-risk patient population. The assumption has been that if the fracture can be immobilized during the induction period and the tumor shows clear signs of necrosis and secondary fracture healing, an amputation may be avoided. The earlier strategy, immediate amputation, was based on the presumed high risk of local recurrence after a limb-sparing procedure. A limb-sparing procedure can now be safely performed if the response to induction chemotherapy is good, as evidenced by fracture healing.

Steadman et al. evaluated their experience with patients who had osteosarcoma-induced pathologic fractures between 1970 and 1995. Nine primary instances of limb salvage in patients with preoperative chemotherapy and eight primary cases of amputation with postoperative chemotherapy were studied. No significant difference in survival was found. One local recurrence occurred in the limb-salvage group and none in the amputation group. This retrospective analysis, combined with other reported results, makes a convincing case that a pathologic fracture does not indicate the need for an immediate amputation. The strategy today is to immobilize the extremity and proceed with induction chemotherapy. If the fracture heals...
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and the tumor appears to respond to chemotherapy, a limb-sparing operation is warranted. Repeat staging studies after induction chemotherapy and close serial observation during the induction period are essential.

The most recent study of pathological fracture was reported by Ebied and Abdelmegid from the Lee Moffitt Cancer Center and Research Institute. They evaluated 31 patients with primary malignant bone tumors who either sustained a pathological fracture prior to treatment or during the course of treatment. Seventeen of these 31 patients had osteosarcoma. All patients received preoperative induction chemotherapy. The overall local recurrence rate was two of 31 patients (6%). Both occurred in the osteosarcoma subgroup. Twenty-six of the 31 fractures healed, and those patients underwent a limb-sparing procedure. The main conclusion is that pathological fractures are capable of healing, indicating a high propensity for a good response to induction chemotherapy. Amputation is not automatically warranted, and limb-sparing surgery is preferred if a wide margin can be obtained during surgical resection.

Surgical Resection of Localized-Extremity Osteosarcoma

Rougraff et al. updated a combined study from the MSTS of 227 patients from 26 institutions treated for osteosarcoma of the distal femur; 109 patients (48%) were alive at an average of 11 years after surgery. No differences in local recurrence, overall survival, or duration of disease-free survival were noted between amputation and limb-sparing groups. The local recurrence rate (10%) was identical for above-knee amputation and limb-sparing surgery. The most common causes of failed limb-sparing procedures were infection and local recurrence. The authors concluded that the type of surgery did not affect outcomes. No difference was noted among patients treated with endoprostheses, allografts, composites, rotationplasties, and arthrodesis; however, the numbers of patients in those categories were small.

Bacci et al. analyzed the type of surgical margin and the responses to chemotherapy compared to local recurrence following induction chemotherapy to a limb-sparing procedure. The differences in outcome were dramatic. The patients with poor necrosis (fewer than 60%) and wide margins had ten times the risk of local recurrence. The worst combination was poor necrosis and less than wide margins. This study emphasizes the need for wide margins following a good response to induction chemotherapy for a safe limb-sparing procedure.

Treatment by Anatomic Site

The unique features of evaluation, management, and resection of tumors of the most common anatomic areas, the shoulder and knee, are described and illustrated in this section.

SHOULDER GIRDLE. A surgical classification for shoulder girdle resections has been described. This classification is useful for all limb-sparing procedures of the shoulder girdle. It is
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Extra-articular resection of the glenohumeral joint by medial scapulosteotomy is safer than intra-articular resection (Fig. 45.2.12).

Wittig et al. described the technique of extra-articular resection and reported that, of 23 patients with high-grade, stage IIIB osteosarcoma of the proximal humerus, 22 were treated by an extra-articular resection; there were no local recurrences. The authors reviewed the published data regarding intra-articular resections versus extra-articular resections for osteosarcoma and reported local recurrence rates of 16% and 4%, respectively. A modular endoprosthesis is used for reconstruction. Soft tissue reconstruction and suspension are essential to avoid post-operative pain, instability, and fatigability.

Alternatively, resection of the proximal humerus for osteosarcomas can be performed by an intra-articular resection that preserves the glenoid and the adjacent deltoid muscle (Fig. 45.2.13). The problems associated with this procedure include significant local recurrence and instability of the reconstructed prosthesis or allograft. When the glenoid and deltoid are preserved in this procedure, minimum margins are obtained along the shoulder joint, deltoid muscle, and axillary nerve. Because of this serious drawback, this technique is not recommended by the surgical author (M. M. M.). Fewer than 5% of osteosarcomas of the proximal humerus, usually those without an extraosseous component (stage IIA), can be treated by an intra-articular resection.

SCAPULA. The scapula is an uncommon site for osteosarcoma (less than 5%); however, it is a common site for round cell tumors (Ewing’s sarcoma) and metastatic cancers in adults. A fair amount of knowledge regarding scapular prosthetic design, indications, and techniques of resection and reconstruction has been developed. Most high-grade sarcomas of the scapula involve the body as well as the glenoid. The glenoid cannot be preserved. The classic operation for high-grade tumors of the scapula has been the Tikhoff-Linberg resection, originally described in 1928 and now identified as Malawer’s classification type IVB. The Tikhoff-Linberg resection is a complete (extra-articular) en bloc resection of the scapula and the proximal humerus. Reconstruction is by a hanging shoulder and, more recently, by scapular endoprosthetic replacement.

Malawer et al. (American Academy of Orthopaedic Surgeons 2007) reported a retrospective comparison of patients undergoing scapular resection and reconstruction with and without an endoprostheses. Patients with endoprosthetic reconstruction had a higher MSTS score than did patients with no endoprosthesis. The former group also had a larger arc of abduction (60% to 90% vs. 10% to 20%), better forward flexion, and improved cosmesis. Most bony sarcomas of the scapula are “contained” by the two surrounding muscles, the infraspinatus posteriorly and the subscapularis muscle anteriorly. Therefore, most tumors of the scapula, irrespective of size, are amenable to endoprosthetic replacement.

DISTAL FEMUR. Adequate en bloc resection includes 15 to 20 cm of the distal femur and proximal tibia and portions of the adjacent quadriceps. Angiography (or three-dimensional CT-angiogram) is crucial to determine popliteal vessel involvement. MRA has been used more recently. Biopsy must avoid the sartorial canal and the knee joint. Contraindications

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**Figure 45.2.10.** Surgical classification of shoulder girdle resections. This classification was described in 1991 by Malawer. (From Clin Orthop 1991; June(267):33–44.)

Recommended that osteosarcomas arising from the proximal humerus be treated by a type VB resection (Fig. 45.2.10).

**PROXIMAL HUMERUS.** The proximal humerus is the third most common site for osteosarcoma. Joint involvement is common in patients with high-grade malignancies of the proximal humerus; for this reason, an extra-articular resection is commonly performed. Intra-articular resections are reserved for small, intraosseous (stage IIA) lesions. The aim of surgery is to create a stable new “shoulder” that permits the placement of the hand in space and enables the patient to retain elbow function (Fig. 45.2.11). Proximal humeral lesions should not be biopsied through the deltopectoral interval. Biopsy under fluoroscopy through the anterior one third of the deltoid by a trocar is preferred. Angiography is the most useful preoperative study. If the neurovascular bundle is clear, resection is feasible.

Adequate resection of the proximal humerus requires removal of 15 to 20 cm of the humerus and shoulder joint with the deltoid, rotator cuff, and portions of the biceps and triceps muscles. The procedure involves suspension of the arm, motor reconstruction, and provision of adequate soft tissue coverage.
to resection are popliteal vessel involvement, massive soft tissue contamination from previous biopsy, and displaced pathologic fracture. Large tumors requiring removal of the entire quadriceps or hamstrings can be adequately reconstructed by an arthrodesis. Segmental endoprostheses are routinely used for the bony reconstruction. The use of large segmental allografts or allograft composite (with an endoprosthesis) has become less frequent within the past decade. Bickels et al.\textsuperscript{67} reported a low prosthetic failure in 110 consecutive modular distal femoral endoprostheses. Several surgical techniques

\begin{figure}[h]
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\caption{Osteosarcoma of the proximal humerus. A: Bone scan demonstrating the length of the humerus needed to be resected. The ipsilateral glenoid is routinely removed for large tumors. B: Plain radiograph showing the magnetic resonance spectroscopy prosthesis in place 6 years following limb-sparing surgery. C: Schematic of muscle transfers and soft tissue reconstruction following a proximal humeral resection. (From \textit{Seminars in Arthroplasty} 10(3 July):142–153.)}
\end{figure}
were consistently used, including routine cementation of the stem and gastrocnemius rotation flaps for adequate soft tissue coverage when needed. The 5- and 10-year survival rates of persons with distal femoral prostheses were 93% and 88%, respectively (Fig. 45.2.14).

**Figure 45.2.12.** Tikhoff-Linberg resection of the scapula and proximal humerus. A: Gross specimen showing all of the muscles attaching and arising from the scapula have been transected. Note the biopsy site has been removed *en bloc*. The proximal humeral joint cannot be visualized and is covered by the deltoïd muscle. B: Intraoperative photograph showing the placement and muscle reconstruction of a scapula prosthesis. C: Schematic drawing of a scapular prosthesis and muscle reconstruction. D: Gore-Tex reconstruction of the (shoulder joint) capsule. Gore-Tex is routinely used with all scapula reconstructions. E: Plain radiograph showing a bipolar proximal humeral and scapula replacement postoperatively. The function following a scapula replacement in contrast to a “hanging shoulder” reconstruction is superior (see text). (From Wittig JC, Bickels J, Wodajo F, Kellar-Graney KL, Malawer MM. Constrained total scapula reconstruction after resection of a high-grade sarcoma. *Clin Orthop* 2002; 397:143.)

**PROXIMAL TIBIA.** Today, limb-sparing procedures often are feasible for tumors of the proximal tibia after induction chemotherapy. It is more difficult to obtain an adequate margin of resection and a good functional result with lesions of the proximal tibia, which tend to have a higher
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incidence of local complications than do distal femoral tumors. These problems are directly related to the anatomic constraints: minimal adjacent soft tissue and the normal subcutaneous location of the medial tibial border. It is extremely important that the biopsy be small and that it avoid the knee joint. A core biopsy of medial flare is preferred to avoid contamination of the anterior musculature and peroneal nerve (Fig. 45.2.15).

Reconstruction is achieved by endoprosthetic replacement, arthrodesis, or allograft. The medial gastrocnemius is routinely transferred to provide soft tissue coverage of the reconstructed area. The proximal tibia remains the most difficult site in which to perform a limb-sparing resection and reconstruction. As a result of the development of smaller, modular prostheses, which are easier to cover with muscle; the routine use of the medial gastrocnemius flaps for prosthetic coverage; and reconstruction of the extensor mechanism, limb-survival rates have almost doubled from the early 1980s (from 35% to 40% of all cases to 70% to 80%).

Figure 45.2.13. Clinical photograph showing the cosmetic appearance and the use of a custom orthosis to smooth out the shoulder girdle appearance.

Figure 45.2.14. A: Long-term results of 110 patients with osteosarcoma of the distal femur treated with an endoprosthesis replacement. The overall limb-salvage rate reported was 96% and the overall functional evaluation was good to excellent in 85%. (From ref. 67, with permission.) B: The original distal femoral Guepar replacement was a simple hinge knee joint utilized in the early 1980s. C: The modular replacement system. This system consists of three basic components: joint, body (of various lengths), and stems (of various diameters). The magnetic resonance spectroscopy is designed to replace large segments of bone and the adjacent joints: proximal femur, distal femur, total femur, proximal tibia, and proximal humerus (scapula prosthesis not shown).
PROXIMAL FIBULA. Tumors of the proximal fibula require the same evaluation as do proximal tibial lesions. Unique considerations are early soft tissue extension, proximity to the lateral tibial condyle, necessity of ligation of the anterior and peroneal arteries, sacrifice of the peroneal nerve, and tumor infiltration of the tibiofibular joint capsule. Contraindications to resection are direct tibial involvement, an anomalously absent posterior tibial artery, and intra-articular knee joint extension. Adequate resection includes the fibula, the tibiofibular joint, the anterior and lateral muscle compartments, and a portion of the lateral gastrocnemius muscle. After surgery, the only functional deficit is foot drop, which is treated by an orthosis. Knee function is normal.

OSTEOSARCOMA OF THE PELVIS AND PROXIMAL FEMUR

Osteosarcomas of the pelvis and proximal femur are less common than those occurring at other anatomic areas. They account for 10% and 5%, respectively, of all osteosarcomas. Tumors arising from these structures are often large, involve important structures, and are difficult to resect. Hemipelvectomy often is required for pelvic tumors, whereas modified hemipelvectomy is used for tumors of the proximal femur. The limb-sparing options, when feasible, are all functionally superior to amputation at this level. Adequate resection includes the fibula, the tibiofibular joint, the anterior and lateral muscle compartments, and a portion of the lateral gastrocnemius muscle. After surgery, the only functional deficit is foot drop, which is treated by an orthosis. Knee function is normal.

The high incidence of venous invasion requires that the iliac vessels be evaluated preoperatively and intraoperatively. Radiographic staging studies should include a thorough evaluation of the iliac vessels. This can best be performed by CT, MRI with contrast, and pelvic venography. Survival for patients with pelvic osteosarcomas is approximately one half of extremity osteosarcomas.

EXPANDABLE PROSTHESES FOR YOUNG CHILDREN

Use of endoprosthetic (or allograft) replacement in young children continues to present problems because of the effect of the procedure on subsequent bone growth. Approximately 70% of the total growth of the lower limb is a result of growth of the distal femoral and proximal tibial growth plates. A new expandable prosthesis, manufactured in France and approved by the U.S. Food and Drug Administration for the lower extremity, was described at the 2002 MSTS meeting. Neel et al. reported on the short-term and intermediate results of the Phenix (Wright Medical, Inc, Memphis, Tennessee) prosthesis in 16 patients. Repeat surgical expansions have been avoided by a novel design. The device uses an externally applied electromagnetic field to control lengthening. This procedure does not require anesthesia. At an average of 25 months, 58 lengthening procedures have been performed, resulting in a total lengthening of 34 mm. Although this technique appears promising, more experience is required in the design and application. Today, many manufacturers and surgeons are concentrating on designing prostheses that do not require an open surgical procedure for expansion.

CLINICAL PRESENTATIONS OF OSTEOSARCOMA AND TREATMENT

TREATMENT CONSIDERATIONS

LOCALIZED-EXTREMITY DISEASE. Management of osteosarcoma requires the expertise of a multidisciplinary team familiar
with the various management options. Before biopsy, patients
with a suspected diagnosis of osteosarcoma (based on radi-
ographic findings) should be referred to centers with treatment
programs. The biopsy should be performed by an orthopedic
surgeon familiar with the management of malignant bone tu-
mors and experienced in the required techniques. Whenever
possible, this should be the surgeon who will ultimately perform
the definitive surgical procedure because the biopsy must be
planned carefully, with a consideration of subsequent definitive
surgery. A poorly conceived and poorly placed biopsy may jeop-
ardize the subsequent treatment, especially a subsequent limb-
salvage procedure.

The patient with a primary tumor of the extremity without ev-
idence of metastases requires surgery to control the primary
tumor and chemotherapy to control micrometastatic disease.
The choice between amputation and limb-sparing resection
must be made by an experienced orthopedic 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 pref-
erece. Routine amputations are no longer performed; all pa-
tients should be evaluated for limb-sparing options. Intensive,
multiagent chemotherapeutic regimens have provided the best
results to date. Patients who are judged unsuitable for limb-spar-
ing options may be candidates for presurgical chemotherapy;
those with a good response may then become suitable candidates
for limb-sparing operations. In addition, the possibility of radio-
therapy as a treatment also exists for adverse presentations and is
discussed later (see Radiotherapy in the Radical Setting). The
management of these patients mandates close cooperation be-
tween the medical oncologist, radiation oncologist, and surgeon.

PELVIC TUMORS AND UNRESECTABLE DISEASE. In some
pelvic and most vertebral primary tumors, complete resection
often is not possible. Most pelvic osteosarcomas can be treated by
hemipelvectomy; more centrally located pelvic tumors, especially
those involving the sacrum, are unresectable. Only a few pelvic
osteosarcomas can be treated by limb-sparing resection (internal
hemipelvectomy). Contraindications to resection are unusually
large extraosseous extensions with sacral plexus or major vascu-
lar involvement. On rare occasions, vertebral and sacral resec-
tions have been attempted. In general, these tumors cannot be

Figure 45.2.16. Sclerosing osteosarcoma of the proximal femur. A: Plain ra-
diograph showing a skip metastasis to
the acetabulum. Proximal femur repre-
sents approximately 5% of overall sur-
vival. B: Gross specimen following a
limb-sparing resection of the proximal
femur and acetabulum. Note the tumor
in the ligamentum teres. Any anatomical
structure that crosses a joint can act as
an “anatomical bridge” to the ipsilateral
juxta-articular area.

Figure 45.2.17. Osteosarcoma of the pelvis. Computed tomogra-
phy of a large pelvic osteosarcoma. Pelvic overall survival is often large
and may require a hemipelvectomy. The ilium is most commonly in-
volved. Extension to the SI-joint and/or hip joint makes a safe resec-
tion often difficult. In general, the survival rate of pelvic osteosarcomas
is one half of other appendicular sites. A unique characteristic of pelvic
overall survival is the propensity to involve the microvasculature as well
as the larger veins of the pelvis (see text).
Metastatic disease detected at initial diagnosis does not preclude a curative treatment strategy, although the presence of extrathoracic metastases makes cure extremely unlikely. In general, the surgical principles outlined for the treatment of relapsing patients apply equally to the patient presenting with macroscopic disease in primary and metastatic sites. Arguments advanced to justify this approach are similar to those used to support preoperative chemotherapy in general, and the theoretic advantages and disadvantages of this strategy as discussed for patients with nonmetastatic osteosarcoma apply here as well. The risk for the patient with metastases is that growth of tumor nodules in the face of chemotherapy may render small, operable metastases unresectable and prevent cure. Although the timing of the surgery of the primary tumor and metastatic sites has been variable, most modern approaches entail alternating chemotherapy and surgery. The initial treatment is usually a course of chemotherapy, followed by surgical resection of the primary tumor, followed by a second course of chemotherapy and surgical ablation of metastatic sites, followed by the remaining courses of chemotherapy. Patients with tumors that respond to presurgical chemotherapy are more likely to be cured. In those with inoperable metastases, primary treatment with chemotherapy is probably appropriate; metastases may respond sufficiently to allow complete resection. Because these patients usually require surgery for the primary tumor as a palliative procedure, early surgery may be recommended, despite unresectable pulmonary disease. Although improving, the outlook for patients presenting with metastatic disease remains poor.

New Systemic Therapeutic Approaches

Over the years, there has been interest in developing immunostimulatory agents that might be of benefit in the treatment of osteosarcoma. A randomized, double-blind study performed in spontaneous canine osteosarcoma in 1989 demonstrated that the macrophage activator, muramyl tripeptide (MTP), prolonged survival in dogs after amputation. Subsequent clinical studies in patients with pulmonary metastases at M. D. Anderson Cancer Clinic showed a median time to relapse of 9 months after metastasectomy and 24 weeks of liposomal MTP (MTP-PE), compared to 4.5 months for historical control patients. Based on these promising results, the POG and Children’s Cancer Group performed a joint randomized study to determine whether the addition of MTP-PE to chemotherapy would enhance survival in newly diagnosed patients. The study also evaluated whether the addition of IFOS to HD-MTX, ADM, and CDDP improved survival. The results of this study, which accrued almost 800 patients, were somewhat surprising in that the addition of MTP-PE appeared to improve survival only in the patients who received IFOS. The 4-year event-free survival in this group is 70%, compared to 57% for patients receiving IFOS but no MTP-PE. However, patients treated with the standard three-drug combination of HD-MTX, ADM, and CDDP had a 4-year disease-free survival of 65% compared to 62% for those patients who also received MTP-PE. These results suggest that there may be some modest benefit to patients treated with the macrophage-activating agent MTP. However, there appears to be specific drug interactions because this benefit is only seen in patients receiving IFOS. Similarly, a group from the Karolinska Hospital has reported that the use of leukocyte interferon may enhance survival for high-risk osteosarcoma patients and suggested that this should be studied in more detail in high-risk patients.

Because the overwhelming majority of metastases in osteosarcoma occur in the lung, many investigators have sought to develop therapies that target microscopic and macroscopic disease in the lungs. Toward that end, investigators at the Mayo Clinic have reported the results of early clinical studies using aerosolized granulocyte-macrophage colony-stimulating factor for patients with a variety of tumors and pulmonary metastases. The results of this study were promising, and the Children’s Oncology Group is planning a phase II study for patients with osteosarcoma and pulmonary metastases.

Several groups have recently reported that the expression of the Her2/neu/ErbB-2 protein occurs in osteosarcoma. In a retrospective study of 26 patients with osteosarcoma treated at the University of Tokyo, 42% of tumors expressed Her2 protein, and expression was associated with early pulmonary metastases and poor survival. Another retrospective study of 53 patients at Memorial Sloan-Kettering Cancer Center also found Her2 expression in 42% of tumors at presentation and confirmed that expression was associated with a worse event-free survival. Other groups have reported similar findings. This is of potential therapeutic interest because breast cancers that express Her2/neu have been shown to respond to the humanized monoclonal antibody trastuzumab directed against Her2/neu. However, these data have been contradicted by several reports, one finding Her2/neu expression to be correlated with increased survival in osteosarcoma and another study finding no Her2/neu membranous staining (that is characteristic of breast cancer) in 60 osteosarcoma samples.
Nonetheless, based on the findings of expression and the promising results of the use of trastuzumab in Her2-positive breast cancer, the Children’s Oncology Group is conducting a study that includes the use of trastuzumab in high-risk osteosarcoma patients with documented expression of Her2/neu. This has just begun to accrue patients.

Radiation Therapy in the Treatment of Osteosarcoma

BACKGROUND. Past experience with primary radiotherapy for osteosarcomas has shown that high radiation doses can sterilize some tumors but is also associated with significant necrosis of normal tissue. Radiotherapy has, however, been shown to be successful in several distinct clinical situations—facial lesions, palliation, and, possibly, as a postoperative adjuvant.

RADIOTHERAPY IN THE RADICAL SETTING. As was evident in the local management of patients on randomized trials addressing the role of adjuvant whole lung irradiation, radiotherapy, alone or as a local adjuvant, was used relatively frequently. With the high local control expectation of surgery after induction chemotherapy and pathologic response assessment, the role for radiotherapy in osteosarcoma is now restricted to selected circumstances. For the most part, these are determined by critical and life-threatening locations of primary disease where adequate surgical removal is unlikely. These are represented by lesions in critical areas of the head and neck, spine, and pelvis where surgery has already been attempted or has been deemed not to be possible.

Palliation

EXTERNAL-BEAM AND RADIATION SENSITIZERS. Radiation therapy is extremely beneficial in patients requiring palliation of metastatic bony sarcomas; tumors at axial sites, which are unsectable; and advanced, inoperable lesions of the pelvis or extremities.

BONE-SEEKING TARGETED RADIOISOTOPES. An additional interesting approach is the use of the isotope 153Sm-EDTMP to target “bone-specific” radiotherapy to osteoblastic osteosarcomas. Originally introduced for palliation of bone pain arising from osteoblastic bone metastasis, preliminary evidence suggests that 153Sm-EDTMP has attractive possibilities to target bone-forming tumors in surgically inaccessible sites and in refractory tumors, possibly in combination with external-beam radiotherapy. The therapeutic effect of this compound comes from its β-emitting capability derived by neutron capture from samarium-153 (153Sm). The circumstanes for the use of this treatment are almost ideal because there is rapid bone uptake and bone surface retention of 153Sm-EDTMP for many months, and unbound compound undergoes rapid urinary excretion. Unfortunately, the β-emitting property can also result in myeloablation due to marrow tolerance, necessitating autologous peripheral blood stem cell support. Anderson et al.79 from the Mayo Clinic reported a dose-escalation trial of 153Sm-EDTMP and showed this to be of particular risk with high doses of 153Sm-EDTMP (30 mCi/kg). Of note, however, nonhematologic sequelae are minimal, and reduction or elimination of opiates is a uniform finding in all cases.

VARIANTS OF CLASSIC OSTEOSARCOMA

Dahlin and Unni have identified 11 variants of the classic osteosarcoma. These accounted for 268 of 1,021 (26%) cases reviewed at the Mayo Clinic. Osteosarcoma arising in the jawbone, the most common variant, is characterized by well-differentiated cells with a low metastatic potential. Excluding tumors arising secondary to Paget’s disease, irradiation, or dedifferentiation of a chondrosarcoma, parosteal and periosseous osteosarcomas are the most common variants of classic osteosarcoma arising in the extremities. In contrast to classic osteosarcoma, which arises within a bone, parosteal and periosseous osteosarcomas arise on the surface of the bone (juxtacortical).

The three types of surface osteosarcomas are parosteal osteosarcoma, periosseous osteosarcoma, and high-grade surface osteosarcoma. The Mayo Clinic reported 518 surface osteosarcomas seen between 1926 and 1996. The incidence was 335 parosteal osteosarcomas (64.7%), 137 periosseous osteosarcomas (26.4%), and 46 high-grade surface osteosarcomas (8.9%). These 518 surface osteosarcomas were from a pool of 4,365 osteosarcoma tumors (i.e., a ratio of 1:0.84 cases).80

Parosteal Osteosarcoma

CLINICAL CHARACTERISTICS. Parosteal osteosarcoma is a distinct variant of conventional osteosarcoma that accounts for 4% of all osteosarcomas. It arises from the cortex of a bone and generally occurs in older individuals. It has a better prognosis than classic osteosarcoma.

RADIOGRAPHIC FINDINGS. A slight predominance of parosteal osteosarcoma is found in women. The distal posterior femur is involved in 72% of all cases; the proximal humerus and proximal tibia are the next most frequent sites. Parosteal osteosarcoma metastasizes slowly and has an overall survival rate of 75% to 85%. Unni et al.81 noted that all patients who died of tumor lived longer than 5 years after treatment. The natural history of parosteal osteosarcoma is progressive enlargement and late metastasis. Parosteal osteosarcoma presents a mass and occasionally is associated with pain. In contrast to conventional osteosarcoma, duration of symptoms varies from months to years. Unni et al. reported that 50 of 79 patients had complaints of longer than 1 year, and one third of this group had pain for more than 5 years. Tumor size, location, and duration of symptoms did not correlate with survival (Fig. 45.2.18).

PATHOLOGY AND GRADING. Parosteal osteosarcoma is characterized by well-formed lamellar or woven bone with a mature spindle cell stroma and few signs of malignancy. The cellularity of the spindle cell components varies; generally, it is not anaplastic, with few mitoses. The differential diagnosis is osteochondroma, myositis ossificans, and conventional osteosarcoma. Cortical tumors of the posterior femur should always be suspected of being malignant; this is a rare location for a benign osteochondroma. In contrast to sarcoma, myositis ossificans is rarely attached to the underlying bone. In addition, the periphery is more mature radiographically and histologically. Ahuja et al.82 reviewed all cases of parosteal osteosarcoma at Memorial Sloan-Kettering Cancer Center from 1934 to 1975 and described three grades: grade I (low grade), grade II (intermediate), and grade III (high grade). They emphasized the
Wide excision of the tumor is the treatment of choice for parosteal osteosarcoma of the distal femur.

The authors stressed the need for long-term follow-up. Eleven of the 67 patients managed at their institution died at an average of 14 years (range, 2 to 41 years). Ten of the 11 patients died from a dedifferentiated tumor.

**TREATMENT.** Wide excision of the tumor is the treatment of choice. This may be accomplished either by an amputation or a limb-sparing procedure. No experience with preoperative chemotherapy or radiotherapy has been reported. Parosteal osteosarcomas are often amenable to limb preservation due to their distal location, low grade, and lack of local invasiveness. If the adjacent neurovascular bundle is free of tumor, resection is feasible. Vascular displacement is not a contraindication for resection. The major surgical decision usually is whether to remove the entire end of the bone and the adjacent joint or to preserve the joint. Small lesions can be resected with joint preservation. If the medullary canal is involved, the joint cannot be preserved. A second factor mitigating against joint preservation is extensive cortical involvement. Techniques of resection and reconstruction are similar to those described for conventional osteosarcoma. The major difference is that only a small amount of soft tissue usually must be resected; consequently, a good functional result is obtained. Grade III parosteal lesions warrant systemic therapy because of the risk of metastasis.

**Dedifferentiated Parosteal Osteosarcoma**

**Figure 45.2.18.** Parosteal osteosarcoma of the distal femur. Computed tomography scan showing the tumor arising from the posterior cortex with some intramedullary extension. Intramedullary extension is not a worse prognostic finding but must be taken into consideration when planning the surgical procedure.

Bertoni et al., in the largest report of dedifferentiated parosteal osteosarcoma (DPOS), described the clinical and radiological features, histological specimens, treatments, and outcomes of 29 patients. The average age of patients with DPOS in this study was 36 years, and the most common anatomic sites in order of frequency included femur, humerus, and tibia. They emphasized that the finding of radiographic areas of lucency in an otherwise sclerotic lesion was a clue to the diagnosis of DPOS in 18 of the 29 patients. The histological subtypes of the dedifferentiated components were high-grade osteoblastic osteosarcoma in 14 patients, fibroblastic osteosarcoma in ten patients, giant cell-rich osteosarcoma in three patients, and chondroblastic osteosarcoma in two patients. Two thirds of the patients had intramedullary involvement. Twenty of 29 patients (69%) remained disease free at an average follow-up of 107 months. All patients received adjuvant chemotherapy. No conclusion could be made regarding the role of adjuvant chemotherapy for DPOS, although the tendency today is to utilize chemotherapy for all patients with DPOS.

**Periosteal Osteosarcoma**

Periosteal osteosarcoma is a rare cortical variant of osteosarcoma that arises superficially on the cortex, most often on the tibia shaft. Radiographically, it is a small radiolucent lesion with some evidence of bone spiculation. The cortex is characteristically intact, with a scooped-out appearance and a Codman’s triangle. Histologically, periosteal osteosarcomas are relatively high-grade chondroblastic osteosarcomas composed of a malignant cartilage with areas of anaplastic spindle cells and osteoid production. Unni et al., in a report of 23 cases, found periosteal osteosarcomas to occur one-third as frequently as the parosteal variant. The largest tumor measured 2.5 by 3.5 cm. Four of the 23 patients died of metastatic disease.
One of the largest reported series was by Okada et al.\(^8^0\) from the Mayo Clinic. They evaluated 46 patients and described their radiographic, clinical, and pathologic evaluation. All the tumors were broad based and attached to the underlying cortex. Nineteen of the 46 tumors (41%) showed infiltration into the cortex of the underlying bone. The authors attempted to evaluate the effectiveness of chemotherapy in this very rare subtype of osteosarcoma. Fifteen of the 21 patients receiving systemic treatment showed no response to chemotherapy. Among these 15, only one patient remains alive. All six patients who showed a good response to chemotherapy are alive. Medullary involvement did not affect prognosis. The survival rate was 57.5% at 3 years and 46.1% at 5 years. Treatment is similar to that of other high-grade lesions. \(\text{En bloc}\) resection should be performed when feasible; amputation is rarely indicated.

**Paget’s Sarcoma**

In approximately 1% of patients with Paget’s disease, a primary bone sarcoma will develop. Greditzer et al.\(^8^6\) reported 41 sarcomas among 4,415 patients with Paget’s disease followed at the Mayo Clinic; 35 were osteosarcomas and six were fibrosarcomas. The average patient age was 64 years, and the most common sites were the pelvis, femur, and humerus. One half of these lesions were osteolytic; the remainder had a mixed pattern. Cortical destruction and a soft tissue component were the most common signs noted; periosteal elevation was rare. Most patients with this condition present with pain; thus, a patient with known Paget’s disease who complains of increasing pain, especially when it is well localized, should be evaluated radiographically. The diagnosis is usually made by plain radiography and confirmed by biopsy. Traditionally, fewer than 8% of patients survive, and most deaths occur within 2 years. Treatment is similar to that recommended for adolescent patients with osteosarcoma without metastatic disease, while recognizing that the characteristic older age of Paget’s-associated patients often influences the intensity of treatment that can be offered.

**High-Grade Surface Osteosarcoma**

High-grade surface osteosarcoma (peripheral conventional osteosarcoma) is the rarest variant of surface osteosarcoma. The parosteal and periosteal osteosarcomas have a better prognosis, whereas the high-grade surface variant has the same prognosis as the conventional, intramedullary lesion. Schajowicz et al.\(^8^7\) studied the different surface osteosarcomas. They reported that only seven of 80 surface osteosarcomas (9%) were considered to be the high-grade variant. Clinically, the median age was 13.5 years (younger than that of patients with other surface lesions), and almost all were located in the diaphyseal region of the bone. The femur was the most common site. This tumor may show extensive intramedullary involvement. Radiographically, it appears as a small or moderate-size lesion with slight to heavy calcification. The broad base of the lesion abuts the cortex. The radiographic features often are misleading and may suggest the periosteal variant; thus, the preoperative diagnosis may be difficult. However, the young age, the diaphyseal location, and, most importantly, the highly malignant histologic features indicate the correct diagnosis. Wide excision with limb preservation has been reported. Adjuvant chemotherapy is warranted due to the high rate of metastases.

**Small Cell Osteosarcoma**

The small cell osteosarcoma, a rare variant of osteosarcomas, resembles an Ewing’s sarcoma and is often classified as an “atypical” Ewing’s sarcoma. Characteristically, areas of osteoid and, on occasion, chondroid formation are present. The differential diagnosis includes Ewing’s sarcoma, atypical Ewing’s sarcoma, primitive neuroectodermal tumor, mesenchymal chondrosarcoma, lymphoma, and Askin’s tumor. Differentiation from Ewing’s sarcoma and the typical osteosarcoma is important because the response of small cell osteosarcoma to treatment is poorly defined.

Sim et al.\(^8^8\) recommend surgery. At the pediatric branch of the National Cancer Institute, however, these tumors, like other pediatric round cell tumors, are treated by a combination of surgical resection, radiation therapy, and chemotherapy.

**Radiation-Induced Osteosarcoma**

Radiation-induced osteosarcomas arise in a previously irradiated field and meet the general criteria of a radiation-induced sarcoma (i.e., they appear after a latent period of 5 to 20 years, are documented to be secondary [different from the original one], and occur in a documented irradiated field). Amendola et al.\(^8^9\) from the University of Michigan reviewed 22,306 patients treated with radiation between 1934 and 1983 and reported 23 patients with radiation-associated sarcoma (prevalence, 0.1%). The median latent period was 13 years (range, 3 to 34 years). The radiation doses ranged from 25 to 72 Gy. The data suggest that intensive chemotherapy may have shortened the latency period. In two nested case-control studies of 3-year cancer survivors from France and the United Kingdom, the risk of osteosarcoma was found to be a linear function of radiation dose and alkylating agent chemotherapy;\(^9^0\) The 20-year risk of osteosarcoma among survivors of retinoblastoma (7.2%), Ewing’s sarcoma (5.4%), and other bone tumors (2.2%) suggests a genetic influence in the induction of secondary osteosarcoma. However, the risk of developing bone sarcoma within 20 years for the majority of survivors of childhood cancer is less than 0.9%.

The treatment of radiation-associated osteosarcoma is wide resection, when possible, combined with adjuvant chemotherapy. A previously irradiated field presents a unique challenge for the surgeon—choosing the best local option. The likelihood of local complications is greater in such cases. Tabone et al.\(^9^1\) reported results from the French Society of Pediatric Oncology indicating that an intensive approach using chemotherapy and surgery will yield 8-year overall and event-free survival rates of 50% and 41%, respectively.

**CHONDROSARCOMA**

Chondrosarcomas are the second most common primary malignant spindle cell tumors of bone. They form a heterogeneous group of tumors whose basic neoplastic tissue is cartilaginous without evidence of direct osteoid formation. Occasionally, bone formation occurs from differentiation of cartilage. If evidence is found of direct osteoid or bone production, the lesion is classified as an osteosarcoma. The five
types of chondrosarcomas are central, peripheral, mesenchymal, differentiated, and clear cell. The classic chondrosarcomas are central (arising within a bone) or peripheral (arising from the surface of a bone). The other three are variants and have distinct histologic and clinical characteristics.

Central and peripheral chondrosarcomas can arise as primary tumors or secondary to underlying neoplasm. Seventy-six percent of primary chondrosarcomas arise centrally. Secondary chondrosarcomas most often arise from benign cartilage tumors. The multiple forms of benign osteochondromas or enchondromas have a higher rate of malignant transformation than the corresponding solitary lesions.

Central and Peripheral Chondrosarcomas

CLINICAL CHARACTERISTICS. One half of all chondrosarcomas occur in persons older than 40 years of age; only 3.8% develop in those younger than 20 years. The most common sites are the pelvis (31%), femur (21%), and shoulder girdle (13%). Chondrosarcomas are the most common malignant tumors of the sternum and scapula. The clinical presentation varies. Peripheral chondrosarcomas may become large without causing pain, and local symptoms develop only because of mechanical irritation. Pelvic chondrosarcomas are often 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 a painless abdominal mass. Conversely, central chondrosarcomas present with dull pain; a mass is rare. 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 associated with pain most likely has a chondrosarcoma (Fig. 45.2.19).

HISTOLOGY AND GRADING. Chondrosarcomas are categorized as grade I, II, or III. The metastatic rate of moderate-grade lesions is 15% to 40% (Fig. 45.2.20).

RADIOGRAPHIC DIAGNOSIS AND EVALUATION. Central chondrosarcomas have two distinct radiologic 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, which may appear radiographically benign. The second type has no sclerotic border and is difficult to localize. The key sign of malignancy is endosteal scalloping. It is difficult to diagnose on plain radiographs and may go undetected for a long period. In contrast, peripheral chondrosarcoma is recognized easily as a large, calcified mass protruding from a bone. Proximal or axial location, skeletal maturity, and pain point toward malignancy, even though the cartilage may appear benign.

PROGNOSIS. Metastatic potential tends to correlate with the histologic grade of the lesions. Marcove et al., reported on long-term follow-up of 113 chondrosarcomas of the proximal femur and the pelvis. The survival rates in patients with grade I, II, or III lesions were 47%, 38%, and 15%, respectively; the overall survival rate was 52%. No significant difference was noted between grades I and II; however, the mortality for grade III was significantly higher (P < .02) than for the other two. Eleven of 59 deaths occurred after 5 years. The authors emphasized that the meaningful survival interval should be considered 10 or 15 years. No relationship between grade, age, gender, or location was found, and there was no statistical difference between primary and secondary chondrosarcomas. Adequacy of surgical removal was the main determinant of recurrence. In general, chondrosarcomas occurring during childhood have a worse prognosis than those of adult onset.
In general, peripheral chondrosarcomas have a lower grade than central lesions. Gitelis et al.\textsuperscript{93} reported that 43% of peripheral lesions, compared with 13% of central lesions, were grade I. The 10-year survival rate among those with peripheral lesions was 77%, and among those with central lesions it was 32%. Secondary chondrosarcomas arising from osteochondromas also have a low malignant potential. Eighty-five percent are grade I. Garrison et al.\textsuperscript{94} reported that only 3% of 75 patients with secondary chondrosarcoma from an osteochondroma developed metastases, although 12% died of local recurrence. Ahmed et al.\textsuperscript{95} described the largest reported series of secondary chondrosarcoma. The report included a total of 107 patients. Sixty-one of the secondary lesions occurred in patients with solitary osteochondromas and 47 in patients with multiple exostoses. The 5- and 10-year mortality was 1.6% and 4.8%, respectively. Metastases developed in only five patients. Most of the deaths were caused by the sequelae of local recurrences.

TREATMENT. The treatment of chondrosarcomas is surgical removal. No reports of effective adjuvant chemotherapy have been published. Resection guidelines for high-grade chondrosarcomas are similar to those for osteosarcoma. The shoulder and pelvic girdle are the most common sites for chondrosarcomas. This, combined with the fact that chondrosarcomas tend to be low grade, makes them amenable to limb-sparing procedures. Lesions of the ribs and sternum are treated by wide excision. Cryosurgery, a technique using liquid nitrogen after thorough curettage of the lesion, has been used for central, low-grade chondrosarcomas. A few reports have been published of effective radiation therapy for axial chondrosarcomas.

Limb-Sparing Procedures: Specific Anatomic Sites

The four most common sites of chondrosarcomas are the pelvis, proximal femur, shoulder girdle, and diaphyseal portions of long bones. The unique characteristics of each are described in the following sections.

PELVIS. The pelvis consists of three areas: ilium, periacetabulum, and pubic rami. Each site can be resected independent of the others. Resections are classified as type I (iliac wing), type II (acetabulum), or type III (pubic rami, pelvic floor). Bone scan most accurately determines specific bony involvement, whereas CT and MRI delineate the extraosseous component. Contraindications to resection are vascular (iliac artery and vein), peritoneal, and sacroiliac joint and/or sacroiliac involvement (Fig. 45.2.21).

Long-term results of these procedures have been published by Enneking and Dunham who reported that local recurrence was only 4% if adequate margins were obtained. Function was nearly normal if the hip joint was preserved. If the hip joint was removed and fusion was obtained, results were good. A saddle prosthesis has been developed, permitting reconstruction after periacetabular resections. Pelvic allograft combined with hip arthroplasty is an alternative technique of reconstruction. In general, this approach has had a high failure rate as a result of infection, fracture, and dislocation.

PROXIMAL FEMUR. Chondrosarcoma of the proximal femur can often be treated successfully by resection and prosthetic replacement. A lateral trephine or core biopsy is recommended. Care must be taken to avoid intra-articular, groin, or retrogluteal contamination. A posterior approach should be avoided because of potential contamination of the posterior flap in the event that a hemipelvectomy is required.

SHOULDER. The technique of resection of chondrosarcoma of the proximal humerus and scapula is similar to that described for osteosarcomas. In low-grade intracompartmental (stage IA) tumors, preservation of the deltoid, rotator cuff musculature, and glenoid is possible, and alternatives for reconstruction are more variable.\textsuperscript{96} Endoprostheses, fibula autografts, and allografts all have a high rate of success. Wittig et al.\textsuperscript{97} have described a technique of intra-articular resection and reconstruction using a GoreTex sleeve as a new capsule. The use of GoreTex capsular reconstruction reduces the incidence of shoulder subluxation or dislocation.

DIAPHYSEAL SEGMENTS OF THE TIBIA, FEMUR, AND HUMERUS. Central diaphyseal chondrosarcomas can be adequately treated by segmental resection without sacrificing the adjacent joint. Because the ends of the bones are not involved, function is excellent. Reconstruction is performed by allografts or autografts combined with internal fixation.

Variants of Chondrosarcoma

CLEAR CELL CHONDROSARCOMA. Clear cell chondrosarcoma, the rarest form of chondrosarcoma, is a slow-growing, locally recurrent tumor resembling a chondroblastoma but with some malignant potential. It generally occurs in adults. The most difficult clinical problem of this entity is early recognition. It is often confused with chondroblastoma. Metastases occur only after multiple local recurrences. Primary treatment is wide excision. Systemic therapy is not required. Cryosurgery may avoid an extensive resection.

MESENCHYMAL CHONDROSARCOMA. Mesenchymal chondrosarcoma is a rare aggressive variant of chondrosarcoma characterized by a biphasic histologic pattern (i.e., small compact cells intermixed with islands of cartilaginous matrix). It has a predilection for flat bones; long tubular bones are rarely affected. It tends to occur in younger individuals and has high rates of metastatic
potential. Harwood et al.\textsuperscript{97} reported that eight of 17 patients died within 1 year of diagnosis. The 10-year survival rate is 28%. This entity responds favorably to radiotherapy. It is hypothesized that the round cell component, similar to other round cell sarcomas, is relatively radiosensitive. Treatment is surgical removal combined with adjuvant chemotherapy. Radiotherapy is recommended if the tumor cannot be completely removed.

**DEDIFFERENTIATED CHONDROSARCOMA.** Approximately 10% of chondrosarcomas may be dedifferentiated into a fibrosarcoma or osteosarcoma. This occurs in older individuals and is highly fatal. Surgical treatment is similar to that described for other high-grade sarcomas. Adjuvant therapy is warranted.

**Radiation Therapy in the Treatment of Chondrosarcoma**

Although chondrosarcomas have generally been considered radioresistant, data in fact exist from several sources to show that some of these lesions are radiocurable, although it is preferable if it can be combined with surgery. Unresectable or inoperable chondrosarcomas arising within the axial skeleton and pelvic or shoulder girdle, or both, can be controlled and, in some cases, cured by radiation therapy. A unique situation is chondrosarcomas of the facial bones and skill, in which a combination of radiotherapy and surgery has been shown to be successful, and the authors have already noted the results from Massachusetts General Hospital.\textsuperscript{104} Radiotherapy is almost always used in situations in which adequate surgery is either not possible to accomplish or the patient is not suitable for surgery because of medical reasons. Alternatively, the functional and cosmetic circumstances may make it undesirable to proceed with the type of ablation needed to accomplish complete resection. In addition there are lesions that can still be managed with surgery, but where margins are not adequate, radiotherapy can play a role as an adjuvant treatment.

**GIANT CELL TUMOR OF BONE**

GCT is an aggressive, locally recurrent tumor with a low metastatic potential. It consists of spindle-shaped and ovoid cells uniformly interspersed with multinucleated giant cells. Giant cell sarcoma of bone is a term that refers to the de novo malignant GCT, not the tumor that arises from the transformation of this entity. They defined a primary GCT as a high-grade sarcoma that arises side-to-side with a benign GCT. A secondary malignant GCT was defined as a high-grade sarcoma that arises at a previously treated GCT site. The mean age for the primary malignant GCT was 67 years; for the secondary malignant GCT group it was 40 years. Patients in both age groups were older than those with the typical benign GCT, which is between 20 and 30 years. They concluded that malignancy associated with GCTs is always high grade with a poor prognosis.

**Natural History and Malignancy**

Although GCTs are rarely malignant de novo (2% to 8%), they may undergo transformation and demonstrate malignant potential histologically and clinically after multiple local recurrences. Local recurrence of a GCT is determined by the adequacy of surgical removal rather than histologic grade. Between 9% and 22% of known GCTs become malignant after local recurrence. This rate decreases to less than 10% if patients who have undergone radiotherapy are excluded from the series.

Bertoni et al.\textsuperscript{98} reviewed all the cases of primary and secondary malignant GCTs at the Rizzoli Institute. They reported on only 17 patients, five with primary and 12 with secondary malignant GCTs. Half of the secondary GCTs occurred after radiation. This small number of malignant GCTs attests to the rarity of this entity. They defined a primary GCT as a high-grade sarcoma that arises side-to-side with a benign GCT. A secondary malignant GCT was defined as a high-grade sarcoma that arises at a previously treated GCT site. The mean age for the primary malignant GCT was 67 years; for the secondary malignant GCT group it was 40 years. Patients in both age groups were older than those with the typical benign GCT, which is between 20 and 30 years. They concluded that malignancy associated with GCTs is always high grade with a poor prognosis.

**Radiographic and Clinical Evaluation**

GCTs are eccentric lytic lesions without matrix production. They have poorly defined borders with a wide area of transition. They are juxtaepiphyseal with a metaphyseal component. Although the cortex is expanded and appears destroyed at surgery, it is usually found to be attenuated but intact. Periosteal elevation is rare; soft tissue extension is common.

**Clinical Characteristics**

GCTs occur slightly more often in females than in males. Pain, mass, local tenderness, and decreased motion in the adjacent joint are the most common clinical symptoms. Eighty percent of GCTs in the long bones occur after skeletal maturity, and 75% of these develop around the knee joint. An effusion or pathologic fracture, uncommon with other sarcomas, is common with GCTs. GCTs occasionally occur in the vertebral body (2% to 5%) and the sacrum (10%).\textsuperscript{1}

**Grading and Pathologic Characteristics**

Jaffe\textsuperscript{1} attempted to grade GCTs as grade I (completely benign), grade II (borderline), and grade III (frankly sarcomatous). In general, grades I and II do not correlate well with biologic behavior. The correlation is also poor between the histologic pattern and the tendency for recurrence or malignant transformation. Nineteen percent to 25% of GCTs have some osteoid product. When osteoid formation is noted, care must be exercised in differentiating a GCT from an osteosarcoma. Conversely, an osteosarcoma with giant cells may be misinterpreted as a benign GCT. No correlation has been found between osteoid formation and increased risk of recurrence or metastasis. Necrosis or hemorrhage is often noted. Neither has a relationship to malignant potential or local recurrence rate.

**Radiation Therapy in the Treatment of**

**Chondrosarcoma**

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using curettes and a mechanical burr. This extensive technique has been termed curettage resection and has decreased the rate of local recurrence to approximately 15% to 25%. Bone graft and PMMA are used to reconstruct the surgical defect. Results of a Canadian multicenter study of 186 cases shows no difference in function, health status, or recurrence rate whether cement or bone graft was used after curettage.102

O’Donnell et al.101 reviewed the experience at the Massachusetts General Hospital of 60 patients with GCTs treated by curettage and packing with PMMA. The overall rate of local recurrence was 25% (15 of 60 patients), occurring at an average of 4 years. Risk factors for local recurrence were pathologic fracture, stage III disease, anatomic site, and the use of adjuvant treatment. The distal radius and the proximal tibia had the highest rate of local recurrence: 50% (five of ten patients) and 28% (seven of 25 patients), respectively.

Amputation is reserved for massive recurrence, malignant transformation, or infection. Because of the putative biologic propensity for malignant transformation, radiation is reserved for specific lesions, usually lesions of the spine that cause bone destruction in a confined area and can lead to spinal cord compression and severe deformity. Thus, treatment of GCT of the vertebrae and sacrum must be individualized. A combination of surgical excision and cryosurgery or radiotherapy is required to eradicate the tumor and prevent neurologic impairment.

Cryosurgery

Cryosurgery has been used more successfully for GCTs than for any other type of bone tumor. Dr. Ralph C. Marcove developed the technique of cryosurgery for bone tumors (in 1968) because of the high recurrence rates after curettage and the significant risk of sarcomatous degeneration in GCTs treated by irradiation. They found cryosurgery effective in eradicating the tumor while preserving joint motion and avoiding resection or amputation. These authors reported a 17-year experience of 100 GCTs treated by thorough curettage and cryosurgery. They noted a recurrence rate of 16% in the first 50 cases and 2% in the following 50 cases. The major complications of cryosurgery are necrosis of the adjacent bones, which are liable to develop a late pathologic fracture and delayed union. The rate of secondary pathologic fracture has been decreased by a combination of PMMA, augmentation, bone graft, internal fixation of the cavity, and postoperative use of a long-leg brace with a quadrilateral socket.

Malawer et al.103 in a multicenter study of 100 cases of GCTs of the extremities (treated with wide curettage, high-speed burr, and either a single or double cycle of cryosurgery with liquid nitrogen), reported a local recurrence rate of 9% (nine of 100 patients). They used the direct-pour technique described and developed by Dr. Ralph C. Marcove. Reconstruction of the surgical defect was performed with PMMA (combined with internal fixation in most cases). The secondary fracture rate was 5%. Only two patients required a secondary resection and prosthetic replacement. Malawer et al. recommended liquid nitrogen adjuvant after curettage in the treatment of GCTs.

Bickels et al.104 reported on 102 patients treated by curettage and cryosurgery at two institutions between 1983 and 1993. The surgical stage was I in 15 cases, II in 47 cases, and III in 40 cases. Sixteen percent of the patients had presented with local recurrences. The local recurrence rate among 86 patients treated primarily with cryosurgery was 2.3%. Six local recurrences occurred among 16 patients who were referred with recurrent disease. The overall recurrence rate was 7.9%. The most common complication was pathologic fracture (5.9%). No pathologic fractures occurred when internal fixation was used along with PMMA. This study emphasized that the overall function was good to excellent in 92% of the patients. All 102 patients were free of disease at final follow-up. Cryosurgery is a powerful physical adjunct to curettage in the treatment of GCTs of bone. These authors recommend routine use of cryosurgery for all GCTs of long bones, as well as for all aggressive benign and active bone tumors.

Giant Cell Tumors and Bisphosphonates

A novel approach suggested by Chuang et al.14 is the possible use of bisphosphonates as a surgical adjuvant. A recent study by Chang et al.105 suggested that bisphosphonates may reduce the rate of giant cell tumor recurrence by inducing apoptosis. The bisphosphonates pamidronate and zoledronate can induce apoptosis in giant cell tumor culture in a dose dependent manner. Topical systemic use of pamidronate or zoledronate can be a novel therapy for giant cell tumors by targeting osteoclastlike giant cells, the mononuclear giant cell precursor cells, and the autocrine loop of tumor osteoclastogenesis. Additional work by other investigators with blocking the RANK-L pathway has been suggested and is presently being investigated (Amgen Inc, Thousand Oaks, California). Roudier et al.106 presented data at the 2006 Connective Tissue Oncology Society Meeting (Venice, Italy). The conclusions of their study analyzing 31 formalin-fixed and paraffin-embedded archival specimens of GCT were RANK-L expression was observed in all sample GCT in spindle shaped cells, suggesting that these cells possess an osteoblast lineage marker and that RANK-L is a key factor of osteoclast formation, differentiation, and survival.

Giant Cell Tumors of the Sacrum

GCTs of the sacrum are difficult to treat. Patients often present with back pain, neurologic deficits, and rectal symptoms. The diagnosis is often delayed. CT, MRI, and bone scintigraphy are required for accurate local anatomic staging. Turcotte et al.107 reviewed the treatment of 26 patients treated at the Mayo Clinic between 1960 and 1986 with an average follow-up of 7.8 years. Neurologic deficit was present in 88%. The local recurrence rate for patients treated by curettage was 33%. Twenty-one patients had radiation therapy; malignant transformation occurred in three. These authors suggested complete curettage for initial treatment. Radiation therapy is recommended for incomplete resection and local recurrence. Resection of the sacrum should be reserved for extensive recurrences. The technique of surgical resection of the sacrum is similar to the combined anterior and posterior approach described for chordomas. Cryosurgery has been used in conjunction with curettage in lieu of resections. Surprisingly, there is minimal effect on the “frozen” nerves in the operative field. Increased interest has been shown in sacral-sparing surgery, be it a combination of cryosurgery or newer techniques of radiation therapy. Although the doses of radiotherapy are usually modest and well tolerated, for example, 50 Gy in 25 fractions, it is likely that IMRT or other conformal or stereotactic approaches may be of use to minimize dose to nontarget structures.
Radiation Therapy

GCT is not radioresistant, as was once believed. Local control rates range from 75% to 85% in more recent series. At Princess Margaret Hospital, local control was achieved in 19 of 21 patients selected with adverse prognosis GCT treated with one course of megavoltage radiation. The two only local failures seen were subsequently salvaged, for an ultimate control rate of 100% without any malignant transformation.108 The M. D. Anderson Cancer Center recently advised that radiotherapy should be considered an adjuvant to surgery or alternative therapy in cases of GCT that are unresectable or in which excision would result in substantial functional deficits. When RT is used as primary therapy, the rate of local control seems to be satisfactory.109 Doses of 35 to 50 Gy in 4.0 to 5.5 weeks using megavoltage equipment are recommended. After radiotherapy, slow radiographic resolution is common and may take many years. In some cases, bone reconstitution may never be complete.

Malignant Fibrous Histiocytoma

MFH is a high-grade bone tumor that is histologically similar to its soft tissue counterpart. It is a disease of adulthood. The most common sites are the metaphyseal ends of long bones, especially around the knee. AP values are normal. Pathologic fracture is common. Huvos110 emphasized that a lytic metaphyseal lesion with a pathologic fracture in an adult with a normal SAP level suggests a primary MFH rather than an osteosarcoma or fibrosarcoma. MFH disseminates rapidly. Spanier et al.111 reported that nine of 11 patients died of the tumor. The average disease-free survival was 6 months. One third of patients (three of nine) with pulmonary metastasis had lymph node dissemination. The author hypothesized that lymphatic spread was due to the histiocytic component of the tumor.

Radiographic Characteristics

MFH is an osteolytic lesion associated with marked cortical disruption, minimal cortical or periosteal reaction, and no evidence of matrix formation. The extent of the tumor routinely exceeds plain radiographic signs. McCarthy et al.112 reporting on 35 patients with MFH, noted that four tumors were multicentric and four were associated with bone infarcts.

Treatment

Today MFH and osteosarcoma of bone are treated in much the same way. Data demonstrate that results of limb-sparing surgery for MFH of bone, as well as responses to chemotherapy among MFH patients, are very similar to those of patients with primary osteosarcoma. Picci et al.113 in the largest review to date, evaluated the effects of neoadjuvant chemotherapy of MFH of bone and extremity osteosarcomas. They reported 51 patients treated with high-grade MFH of bone and 390 patients with high-grade osteosarcoma treated with identical regimens of neoadjuvant chemotherapy at the Rizzoli Institute between 1982 and 1994. Rates of limb salvage were approximately the same for MFH (92%) and osteosarcoma (85%), although MFH patients showed a statistically significantly lower rate of good histologic response. Despite this low chemosensitivity, the disease-free survival rates for the two neoplasms were similar (67% vs. 65%). Nevertheless, the two tumors had similar prognoses when treated with chemotherapy regimens based on MTX, CDDP, ADM, and IFOS. The surgical procedures were similar limb-sparing procedures. This study emphasized that induction chemotherapy, followed by limb-sparing surgery and subsequent postoperative chemotherapy, was just as effective for MFH of bone as for the osteosarcomas.

Bacci et al.,114 again from the Rizzoli Institute, reported on 65 patients treated with MFH of bone in the extremities with neoadjuvant chemotherapy. The limb-salvage rate was 89% (58 patients), and the amputation rate was 11% in seven patients. The histologic response to preoperative chemotherapy was good (90% or more tumor necrosis) in 16 patients (25%) and poor in 49 patients (75%). At a median follow-up of 7 years, 40 patients (62%) remained free of disease and 20 patients experienced relapse. The rate of disease-free survival was significantly higher for patients who had a good response than for those who had a poor response (94% vs. 61%). Similarly, these authors concluded that a high percentage of patients with MFH of the extremities can be cured with neoadjuvant chemotherapy and that it is usually possible to avoid amputation.

Fibrosarcoma of Bone

Clinical Characteristics

Fibrosarcoma of bone is a rare entity characterized by interlacing bundles of collagen fibers (herringbone pattern) without any evidence of tumor bone or osteoid formation. Fibrosarcoma occurs in middle age. The long bones are most affected. Fifteen percent of tumors are found in the bones of the head and neck. Fibrosarcomas occasionally arise in conjunction with an underlying disease, such as fibrous dysplasia, Paget’s disease, bone infarcts, osteomyelitis, and postirradiation bone and GCT. Fibrosarcoma may be either central or cortical (periosteal). The histologic grade is a good prognosticator of metastatic potential. Huvos and Higinbotham115 reported overall survival rates of 27% and 32% for central and peripheral lesions, respectively. Late metastases do occur, and 10- and 15-year survival rates vary. In general, periosteal tumors have a better prognosis than central lesions.

Radiographic Features

Fibrosarcoma is a radiolucent lesion that shows minimal periosteal and cortical reaction. The radiographic appearance closely correlates with the histologic grade of the tumor. Low-grade tumors are well defined, whereas high-grade lesions demonstrate indistinct margins and bone destruction similar to those of osteolytic osteosarcoma. In general, plain radiographs underestimate the extent of the lesion. Pathologic fracture is common (30%) owing to the lack of matrix formation. Differential diagnosis includes GCT, aneurysmal bone cyst, MFH, and osteolytic osteosarcoma.

Chordoma

Chordoma is a rare neoplasm arising from notochordal remnants in the midline of the neural axis and involving the adjacent bone. The ends of the spine are the most common sites. The sacrococcyx and the base of the skull (35%) near the
spheno-occipital area are most commonly involved, accounting for 50% and 35%, respectively, of all chordomas. Histologically, the physaliferous cell is pathognomonic. Large areas of synechial strands of cells lying in a mass of mucus are typically present. Myxoid chondrosarcoma and metastatic carcinoma must be differentiated. This tumor is highly fatal because of the high rate of local recurrence and local complications. Death is most commonly due to local disease. Gray et al.\textsuperscript{116} reviewed 222 cases from the literature and noted that only two patients were disease free at 10 years. Average survival was 5.7 years. Mindell\textsuperscript{117} emphasized that the main malignant potential of chordomas resides in their critical locations adjacent to important structures, their locally aggressive nature, and their extremely high rate of recurrence. Chordomas at the base of the skull are often described as chondroid chordomas. Patients with these lesions at this site tend to survive longer than those with the sacrococcygeal tumors. The most common complaint of patients with sacrococcygeal tumors is dull pain; constipation is an occasional symptom. Bladder and sensory loss are late complaints. Clinical suspicion is the key to early diagnosis. Rectal examination characteristically reveals a large presacral mass. Spheno-occipital tumors present with signs of cranial nerve or pituitary dysfunction or both. CT and MRI are essential for accurate evaluation. A transrectal biopsy should not be performed because of potential contamination. A small midline posterior incision or trocar biopsy is recommended.

**Treatment**

The first surgical procedure has the best chance of cure. Inadequate surgery results in local recurrence, with little chance of subsequent surgical removal. Sacrococcygeal tumors are best removed by a combined abdominosacral approach, as described by Localio et al.\textsuperscript{118} They emphasized wide excision of the sacrum one level higher than the lesion. A lateral position is used. The rectum can be controlled anteriorly and removed with the sacrum if necessary. Guterberg et al.\textsuperscript{119} reported that if only one half of the first sacral vertebra remains bilaterally, the pelvic girdle is still stable enough to allow immediate mobilization.

**Radiation Therapy**

Because local recurrence is common with chordomas, radiation therapy is an integral treatment modality, particularly for tumors of the base of the skull and sphen-occipital region. Results of conventional radiation therapy have been disappointing, but series using proton beam and carbon ion radiotherapy appear to provide promising results.

Amendola et al.\textsuperscript{120} reported on 21 patients with a 5-year survival rate of 50% but a disappointing 10-year survival rate of only 20%. This is not surprising, because chordomas are relatively slow growing; in fact, long-term survival free of tumor regrowth over 10 years is relatively rare. These authors emphasized the importance of using CT in planning the radiation field, administering high radiation doses (i.e., 5500 to 7000 cGy with megavoltage equipment), and use of irradiation immediately after surgery to prolong local control, rather than reserving it until recurrence. The Princess Margaret Hospital group investigated various fraction schedules in an effort to improve local control. With a median survival of 65 months, the authors concluded that external-beam radiation provided useful palliation but was rarely curative, although this involved the use of conventional phone irradiation alone.\textsuperscript{121,122} In contrast, long-term experience at the Massachusetts General Hospital has shown significantly improved control rates with high-dose radiotherapy (often approximating or exceeding 75 cGy [cobalt gray equivalent]) using mixed photon and proton beam approaches. This effect seems particularly true for primary (as opposed to recurrent) cases of sacral chordoma in their most recent report.\textsuperscript{123}

The most recent proton beam radiotherapy series was reported by Rutz et al.\textsuperscript{124} at the proton facility in Villigen, Switzerland, where patients with extracranial chordoma were treated with function-preserving surgery followed by spot-scanning proton beam irradiation. In 26 patients the 3-year actuarial overall survival and progression-free survival rates were 84% and 77%, respectively. Noel et al.\textsuperscript{125} from the Institute Curie, France, recently described local control and survival in 100 consecutive patients treated by fractionated photon and proton radiation for chordoma of the skull base and upper cervical spine. With a median follow-up of 31 months (range, 1 to 87), 25 tumors failed locally. The 2- and 4-year local control rates were 86.3% (plus or minus 3.9%) and 53.8% (plus or minus 7.5%), respectively, and the 2- and 5-year overall survival rates were 94.3% (plus or minus 2.5%) and 80.3% (plus or minus 7.2%). Radiation therapy for chordomas is considered palliative and rarely curative.

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