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Bone and Soft-tissue Sarcomas: Epidemiology, Radiology, Pathology and Fundamentals of Surgical Treatment

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OVERVIEW

An understanding of the basic biology and pathology of bone and soft-tissue tumors is essential for appropriate planning of their treatment. This chapter reviews the unique biological behavior of soft-tissue and bone sarcomas, which underlies the basis for their staging, resection, and the use of appropriate adjuvant treatment modalities. A detailed description of the clinical, radiographic, and pathological characteristics for the most common sarcomas is presented.

BIOLOGY AND NATURAL HISTORY OF BONE AND SOFT-TISSUE TUMORS

Soft-tissue and bone sarcomas are a rare and heterogeneous group of tumors. Although soft tissues and bone comprise 75% of the average body weight, these neoplasms represent less than 1% of all adult and 15% of pediatric malignancies. The annual incidence in the United States, which remains relatively constant, is approximately 6000–7000 soft-tissue and 2500 bone sarcomas. Because these lesions are so rare, few pathologists have sufficient experience to deal comfortably with their diagnosis. This is further compounded by the steady evolution in the classification of soft-tissue and bone tumors, which is based on their biological behavior, ultrastructure, and results of immunohistochemical and cytogenetic studies.

Risk factors for soft-tissue and bone sarcomas include previous radiation therapy, exposure to chemicals (e.g., vinyl chloride, arsenic), immunodeficiency, prior injury (scars, burns), chronic tissue irritation (foreign-body implants, lymphedema), neurofibromatosis, Paget's disease, bone infarcts, and genetic cancer syndromes (hereditary retinoblastoma, Li–Fraumeni syndrome, Gardner's syndrome). In most patients, however, no specific etiology can be identified.

Sarcomas originate primarily from elements of the mesodermal embryonic layer. Soft-tissue sarcomas are classified according to the adult tissue that they resemble. Similarly, bone sarcomas are usually classified according to the type of matrix production: osteoid-producing sarcomas are classified as osteosarcomas, and chondroid-producing sarcomas are classified as chondrosarcomas. The three most common soft-tissue sarcomas are malignant fibrous histiocytoma (MFH), liposarcoma, and leiomyosarcoma. These tumors are anatomic site-dependent; in the extremities the common subtypes are MFH and liposarcoma, whereas liposarcomas and leiomyosarcoma are the common subtypes in the retroperitoneum and the abdominal cavity. The most common bone sarcomas are osteosarcoma, chondrosarcoma, and Ewing's sarcoma.

Although soft-tissue sarcomas can arise anywhere in the body, the lower extremities are the most common site. Incidence is as follows: lower extremities – 46%; trunk – 19%; upper extremities – 13%; retroperitoneum – 12%; head and neck – 9%; other locations – 1%. The presenting symptoms and signs of soft-tissue sarcomas are nonspecific; they commonly present as a painless, slow-growing mass. Diagnosis of sarcomas involving the abdominal and pelvic cavity is subtle; these tumors may progress for long periods without causing overt symptoms. Their location deep within the body precludes palpation of the tumor mass early in the course of the disease; consequently, these tumors often reach tremendous size prior to diagnosis.

In the past two decades, survival and the quality of life of patients with soft-tissue and bone sarcomas have dramatically improved as a result of the multimodality treatment approach. Surgery, used in combination with chemotherapy and radiation therapy, can achieve cure in the majority of patients with soft-tissue and bone sarcomas and resection is performed in lieu of amputation in more than 90% of all patients. Principles of chemotherapy and radiation therapy in the treatment of soft-tissue and bone sarcomas are discussed in Chapters 3, 4, and 5.

Biological Behavior

Tumors arising in bone and soft tissues have characteristic patterns of biological behavior because of their common mesenchymal origin and anatomical environment. Those unique patterns form the basis of the staging system and current treatment strategies. Histologically, sarcomas are graded as low, intermediate, or high grade. The grade is based on tumor morphology, extent of pleomorphism, atypia, mitosis, and necrosis. It represents its biological aggressiveness and correlates with the likelihood of metastases.

Sarcomas form a solid mass that grows centrifugally with the periphery of the lesion being the least mature. In contradistinction to the true capsule that surrounds benign lesions, which is composed of compressed normal cells, sarcomas are generally enclosed by a reactive zone, or pseudocapsule. This consists of compressed tumor cells and a fibrovascular zone of reactive tissue with a variable inflammatory component that interacts with the surrounding normal tissues. The thickness of the reactive zone varies with the histogenic type and grade of malignancy. High-grade sarcomas have a poorly defined reactive zone that may be locally invaded by the tumor (Figure 1.1).

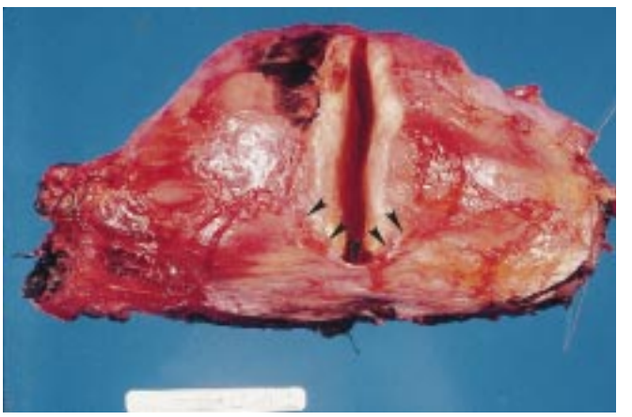
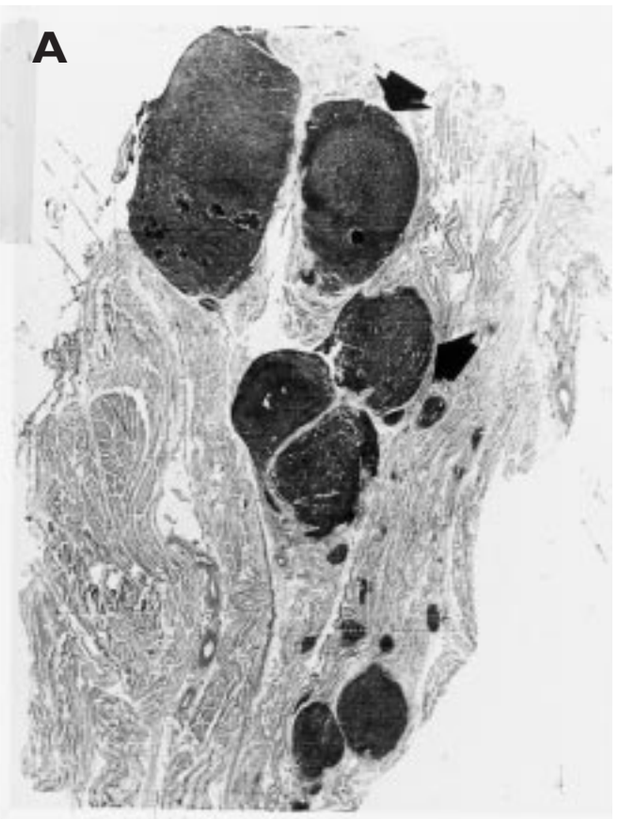


Figure 1.1 A pseudocapsule of a high-grade soft-tissue sarcoma (arrows). It is composed of compressed tumor cells and a fibrovascular zone of reactive inflammatory response.

In addition, they may break through the pseudocapsule to form metastases, termed "skip metastases", within the same anatomic compartment in which the lesion is located. By definition, these are locoregional micrometastases that have not passed through the circulation (Figure 1.2). This phenomenon may be responsible for local recurrences that develop in spite of apparently negative margins after a resection. Although low-grade sarcomas regularly interdigitate into the reactive zone, they rarely form tumor skip nodules beyond that area.

Sarcomas respect anatomical borders. Local anatomy influences tumor growth by setting natural barriers to extension. In general, sarcomas take the path of least resistance and initially grow within the anatomical compartment in which they arose. In a later stage the walls of that compartment are violated (either the cortex of a bone or aponeurosis of a muscle), and the tumor breaks into a surrounding compartment (Figure 1.3). Most bone sarcomas are bicompartmental at the time of presentation; they destroy the overlying cortex and extend directly into the adjacent soft tissues (Figures 1.4, 1.5). Soft-tissue sarcomas may arise between compartments (extracompartmental) or in an anatomical site that is not walled off by anatomical barriers such as the intermuscular or subcutaneous planes. In the latter case they remain extracompartmental and only in a later stage break into the adjacent compartment. Carcinomas, on the other hand, directly invade the surrounding tissues, irrespective of compartmental borders (Figure 1.6).



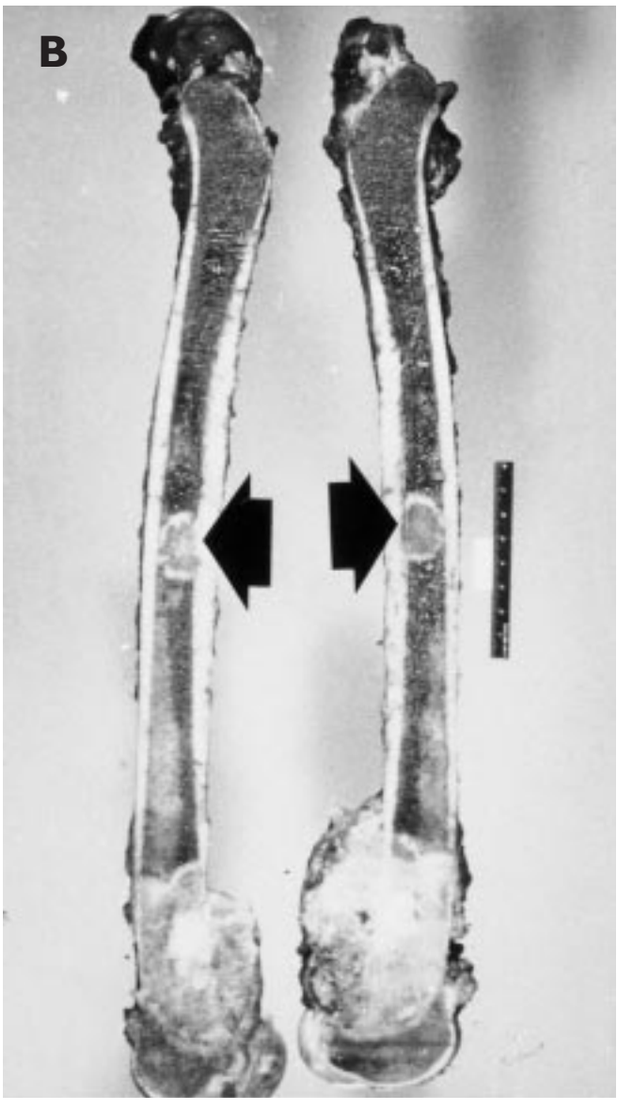
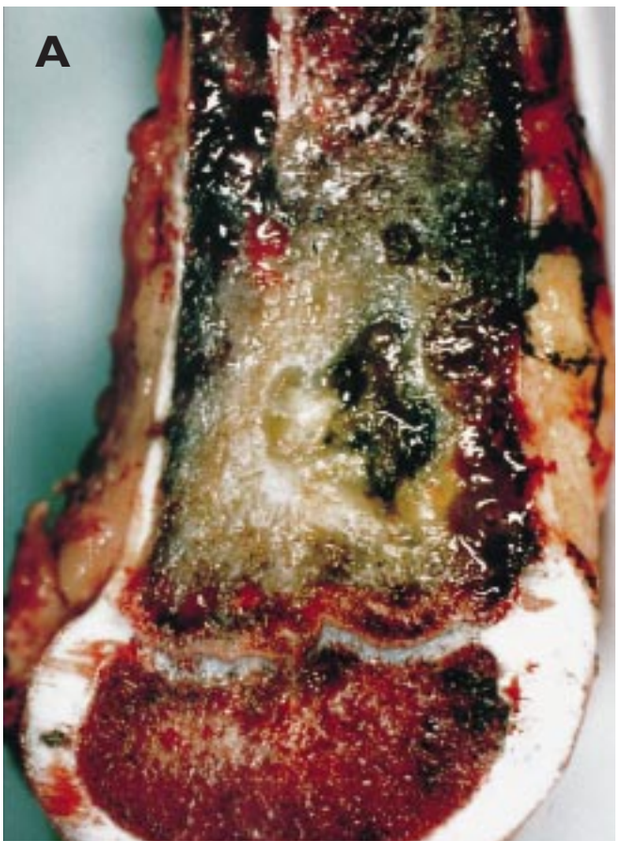
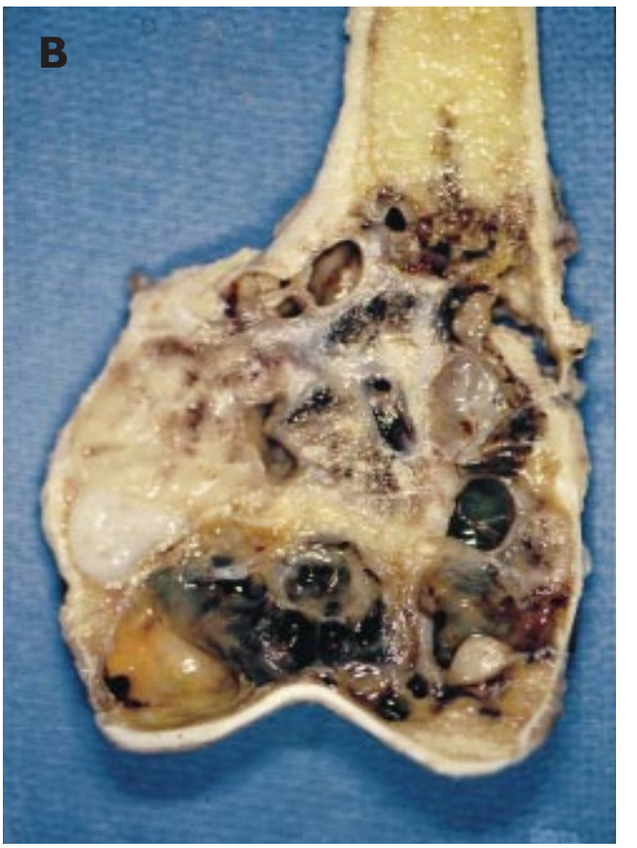


Figure 1.2 High-grade sarcomas may break through the pseudocapsule to form "skip" metastases within the same anatomical compartment. They are occasionally found with low-grade sarcomas. Skip nodules are tumor foci not in continuity with the main tumor mass that form outside the pseudocapsule. "Satellite"" nodules, by contrast, form within the pseudocapsule. (**A**) Multiple satellite nodules (arrows) associated with a high-grade MFH. Note the normal intervening tissue. (**B**) "Skip" metastases (arrows) from an osteosarcoma of the distal femur. This finding is preoperatively documented in less than 5% of patients.





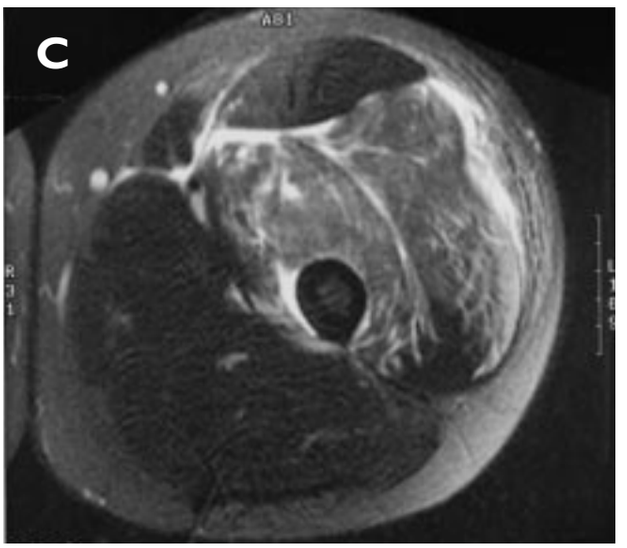


Figure 1.3 (**A**) Sagittal section of a high-grade osteosarcoma of the distal femur. The growth plate, although not invaded by the tumor in this case, is not considered an anatomical barrier to tumor extension. This is probably because of the numerous vascular channels that pass through the growth plate to the epiphysis. However, the articular cartilage is an anatomical barrier to tumor extension and very rarely is directly violated by a tumor. (**B**) Coronal section of a high-grade osteosarcoma of the distal femur. Although gross involvement of the epiphysis and medial cortical breakthrough and soft-tissue extension are evident, the articular cartilage is intact. This phenomenon allows intra-articular resection of high-grade sarcomas of the distal femur in most cases. Thick fascial planes are barriers to tumor extension. (**C**) axial MRI, showing a high-grade leiomyosarcoma of the vastus lateralis and vastus intermedius muscles. The tumor does not penetrate (clockwise) the lateral intermuscular septum, adductor compartment, and the aponeuroses of the sartorius and rectus femoris muscles.

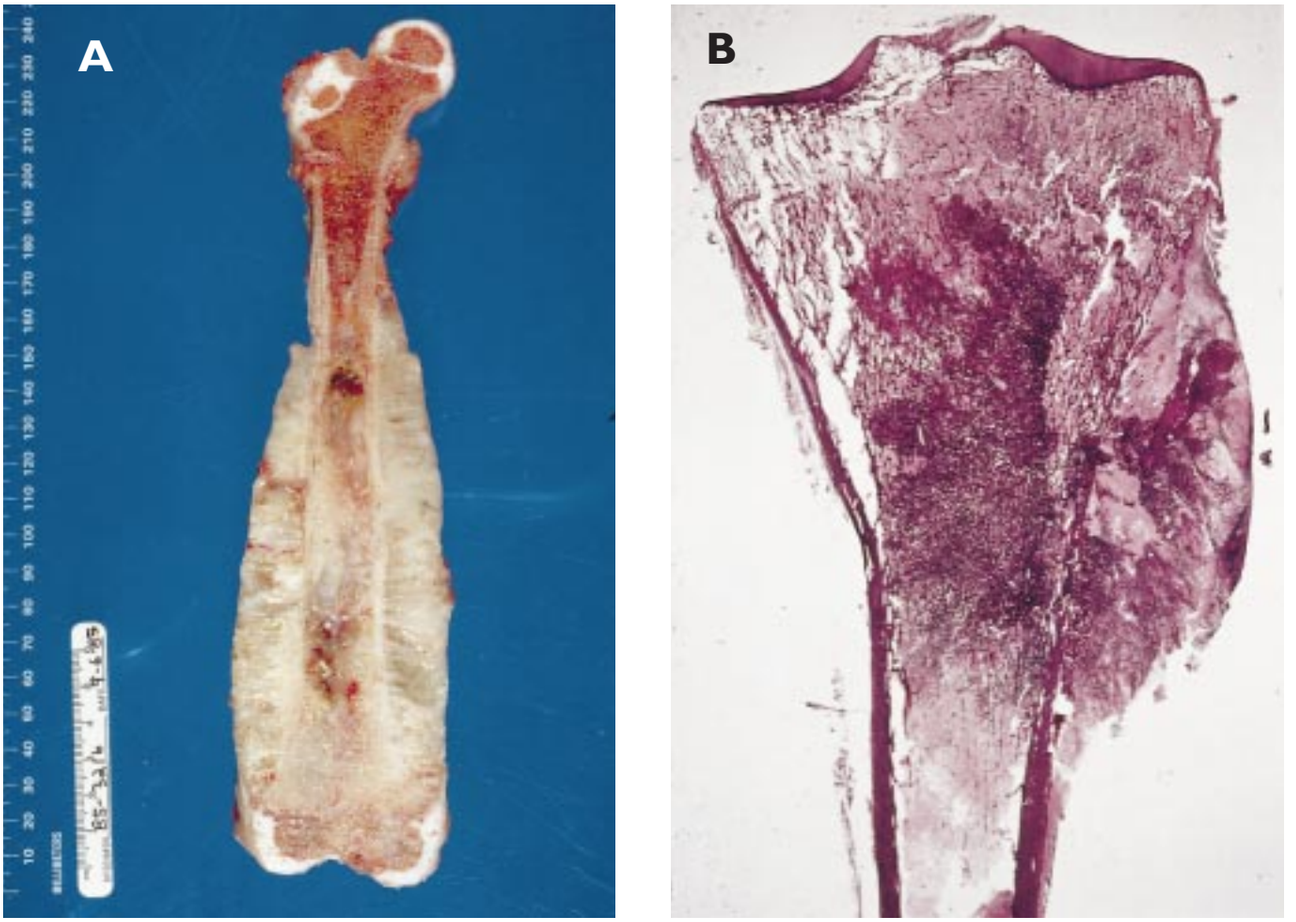


Figure 1.4 (**A**) Ewing's sarcoma of the distal two-thirds of the femur, and (**B**) osteosarcoma of the proximal tibia. Note the extraosseous component of the tumor. Most high-grade bone sarcomas are bicompartmental at the time of presentation (i.e., they involve the bone of origin as well as the adjacent soft tissues). Tumors at that extent are staged as IIB tumors (see staging of malignant bone tumors: Enneking's classification).

Joint Involvement

Direct tumor extension through the articular cartilage is rare and usually occurs as the result of a pathological fracture with seeding of the joint cavity or by peri-capsular extension (Figure 1.7). Occasionally, structures that pass through the joint (e.g., the cruciate ligaments) act as a conduit for tumor growth (Figures 1.8, 1.9). Transcapsular skip nodules are demonstrated in 1% of all osteosarcomas.

Metastatic Pattern

Unlike carcinomas, bone and soft-tissue sarcomas disseminate almost exclusively through the blood. Hematogenous spread of extremity sarcomas is manifested by pulmonary involvement in the early stages and by bony involvement in later stages (Figure 1.10). Abdominal and pelvic soft-tissue sarcomas, on the other hand, typically metastasize to the liver and lungs. Low-grade soft-tissue sarcomas have a low (< 15%) rate of subsequent metastasis while high-grade lesions have a significantly higher (> 15%) rate of metastasis. Metastases from sarcomas to regional lymph nodes are infrequent; the condition is observed in only 13% of patients with soft-tissue sarcomas and 7% of bone sarcomas at initial presentation. The prognosis associated with such an event is similar to that of distant metastasis.

Most patients with high-grade primary bone sarcomas, unlike soft-tissue sarcomas, have distant micrometastases at presentation; an estimated 80% of patients with osteosarcomas have micrometastatic lung disease at the time of diagnosis. For that reason, in most

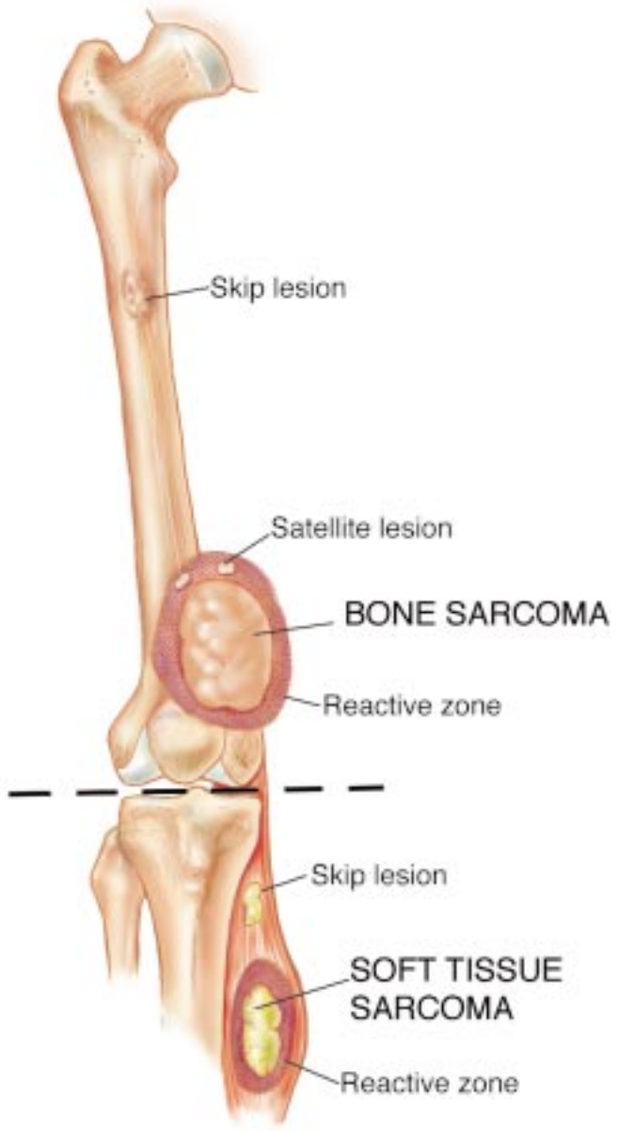


Figure 1.5 Biologic behavior of bone and soft-tissue sarcomas. Unique features are formation of reactive zone, intracompartmental growth, and, rarely, the presence of skip metastases.

cases, cure of a high-grade primary bone sarcoma can be achieved only with systemic chemotherapy and surgery. As mentioned, high-grade soft-tissue sarcomas have a smaller metastatic potential. Because of that difference in metastatic capability the role of chemotherapy in the treatment of soft-tissue sarcomas and its impact on survival are still a matter of controversy.

STAGING OF MUSCULOSKELETAL TUMORS

Staging is the process of classifying a tumor, especially a malignant tumor, with respect to its degree of differentiation, as well its local and distant extent, in order to plan the treatment and estimate the prognosis. Staging allows the surgeon to determine the type and the extent of the operation that is necessary for a specific type of tumor in a particular anatomic location, as well as the indication for neoadjuvant treatment modalities. Staging of a musculoskeletal tumor is based on the findings of the physical examination and the results of imaging studies. Biopsy and histopathological evaluation is an essential component of staging, but should always be the final step. The concept and practice of biopsy of musculoskeletal tumors is discussed in Chapter 2.

Plain radiographs remain the key imaging modality in the evaluation of bone tumors. Based on medical history, physical examination, and plain radiographs, accurate diagnosis of bone tumors can be made in more than 80% of cases. Because of the fine trabecular detail revealed by plain radiographs, bone lesions of the extremities can be detected at a very early stage; lesions of the spine and pelvis, by contrast, are not diagnosed until a large volume of bone has been destroyed. Once a bone lesion is found, computerized tomography (CT) is the imaging modality of choice to evaluate the extent of bone destruction. Magnetic resonance imaging (MRI) has been proven to be superior to CT in the evaluation of the intramedullary and extraosseous, soft-tissue extent of bone tumors (Figure 1.11).

In their early stages, soft-tissue tumors are hard to detect due to the lack of bone involvement. Occasionally, distortion of fat planes in plain radiographs implies the presence of a soft-tissue mass.

CT should be performed on a helical scanner that enables improved two-dimensional images and three-dimensional reconstruction capability. The field of view should be small enough to allow adequate resolution, particularly of the lesion and the adjacent neurovascular bundle and muscle groups. The slice thickness should be designed in order to allow at least 10–15 slices through the tumor. Intravenous contrast dye should be employed in the evaluation of soft-tissue tumors unless a clear contraindication for its use exists. On the other hand, contrast dye is of little value in the evaluation of bone tumors.

MRI is a valuable tool in the evaluation of soft-tissue tumors and of the medullary and soft-tissue components of bone tumors. The signal intensity of a tumor is assessed by comparing it with that of the adjacent soft tissues, specifically skeletal muscle and subcutaneous fat. MRI also enables one to view a lesion in all three planes (axial, sagittal, and coronal). Contrast-

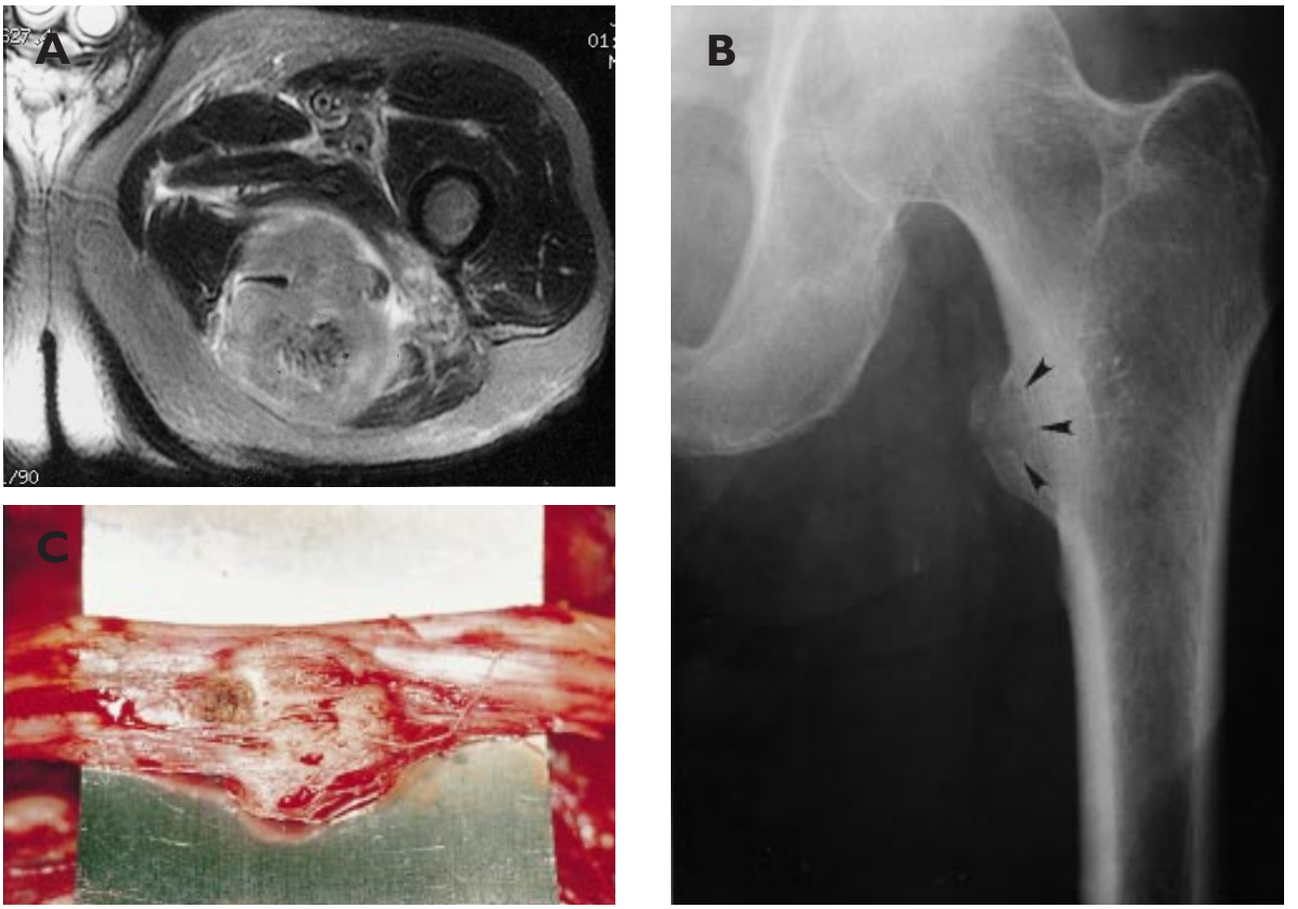


Figure 1.6 (**A**) Axial MRI, showing metastatic bladder carcinoma to the posterior thigh. (**B**) Plain radiograph of the proximal femur revealed direct invasion through the cortical bone with a pathological fracture of the lesser trochanter (arrows). (**C**) In surgery, exploration of the sciatic nerve revealed direct tumor involvement with extension under the epineural sheath.

enhanced MRI is useful in evaluating the relationship of a tumor to the adjacent blood vessels and in characterizing cystic lesions. The presence of orthopedic hardware or surgical clips is not a contraindication to the performance of MRI; however, if a lesion is immediately adjacent to the location of the hardware, the local field may be distorted.

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

Bone scintigraphy was traditionally used to assess the medullary extension of a primary bone sarcoma. As a rule the bone was cut approximately 6 cm proximal to the margin of the increased uptake. MRI allows more accurate determination of the medullary tumor extent; as a result, safer resections in narrower margins can be performed. Bone scan is currently used to determine the presence of metastatic and polystotic bone disease and the involvement of a bone by an adjacent soft-tissue sarcoma. In addition, the appearance of a bone lesion in the flow and pool phases of a three-phase bone scan reflects its biological activity and may be helpful in its diagnosis. It is also used as an indirect means of evaluating tumor response to chemotherapy.

Angiography is essential prior to surgery because vascular displacement is common in tumors that have a large extraosseous component. Blood vessels are likely

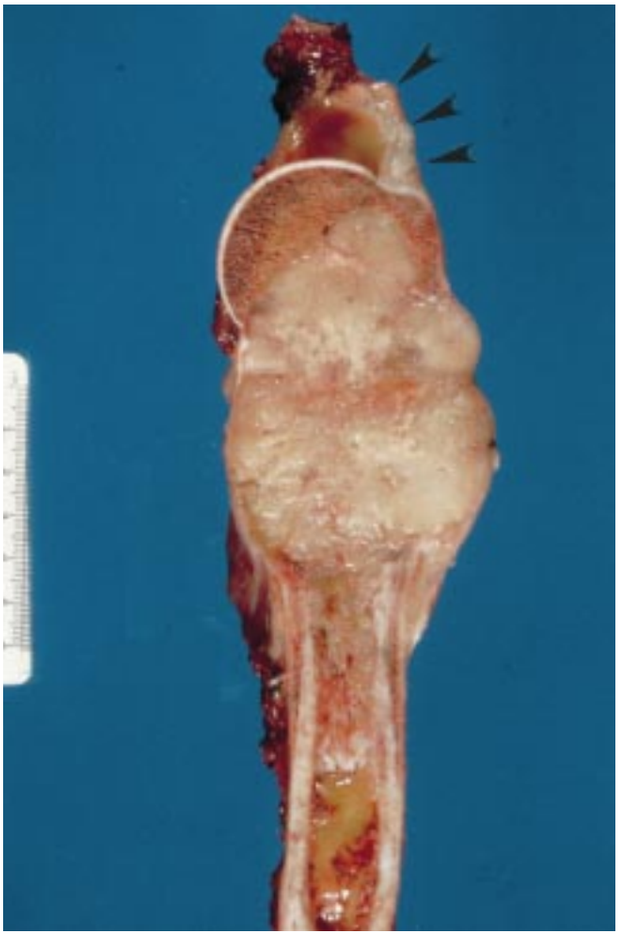


Figure 1.7 Pericapsular extension of an osteosarcoma of the proximal humerus (arrows).

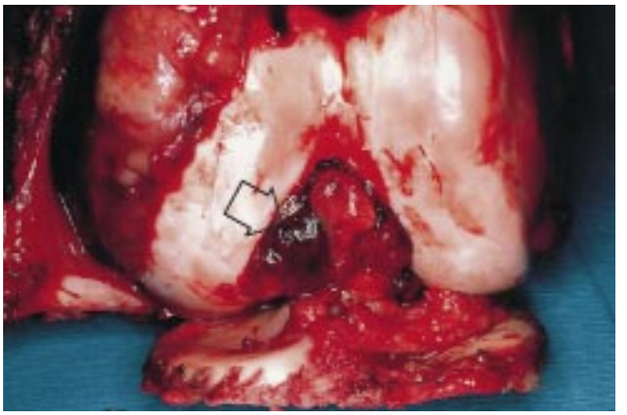


Figure 1.8 Extension of an osteosarcoma of the distal femur to the knee joint along the cruciate ligaments (arrow points to tumor); the articular cartilage is intact. Knee joint extension of a high-grade sarcoma of the distal femur is a rare event, necessitating extra-articular resection (i.e., en-bloc resection of the distal femur, knee joint, and a component of the proximal tibia), as shown in this figure.

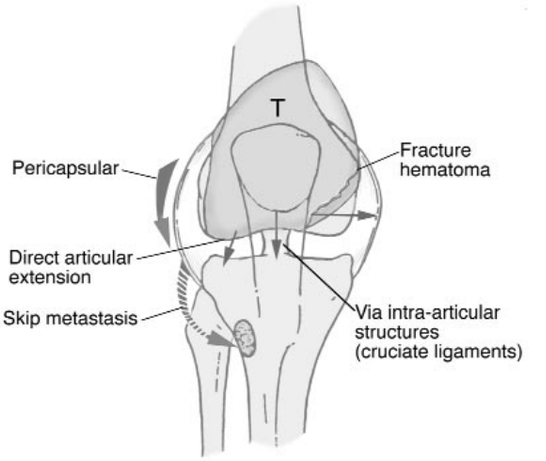


Figure 1.9 The five major mechanisms of joint involvement by a bone sarcoma. The most common mechanisms are pathologic fracture and pericapsular extension.

to be distorted or, less commonly, directly incorporated to the tumor mass. Angiography provides information that helps the surgeon plan the anatomical approach and gauge the likelihood that a major blood vessel has to be resected en-bloc with the tumor. It can also detect vascular anomalies (Figure 1.12) and establish patency of collateral vessels. Proximal femur resection, for example, frequently necessitates ligation of the profundus femoral artery (PFA). A patent superficial femoral artery (SFA) must be documented by angiography prior to surgery, otherwise the extremity will suffer severe ischemia following ligation of the PFA. Preoperative embolization may be useful in preparation for resection of metastatic vascular carcinomas if an intralesional procedure is anticipated. Metastatic hypernephroma is an extreme example of a vascular lesion that may bleed extensively and cause exsanguination upon the execution of an intralesional procedure without prior embolization.

Intra-arterial administration of chemotherapy allows the use of another type of information that can obtained from angiographs; reduction in tumor vascularity. As revealed by serial angiographs, such reduction was shown to be indicative of good response to preoperative chemotherapy. Figure 1.13 summarizes the use of the various imaging modalities in the staging process of a primary bone sarcoma.

There is no single universally accepted staging system for soft-tissue and bone sarcomas. Some systems are valuable in the determination of the operative strategy, whereas others may be more useful in the estimation of the prognosis. An important variable in any staging system for musculoskeletal tumors, unlike a staging

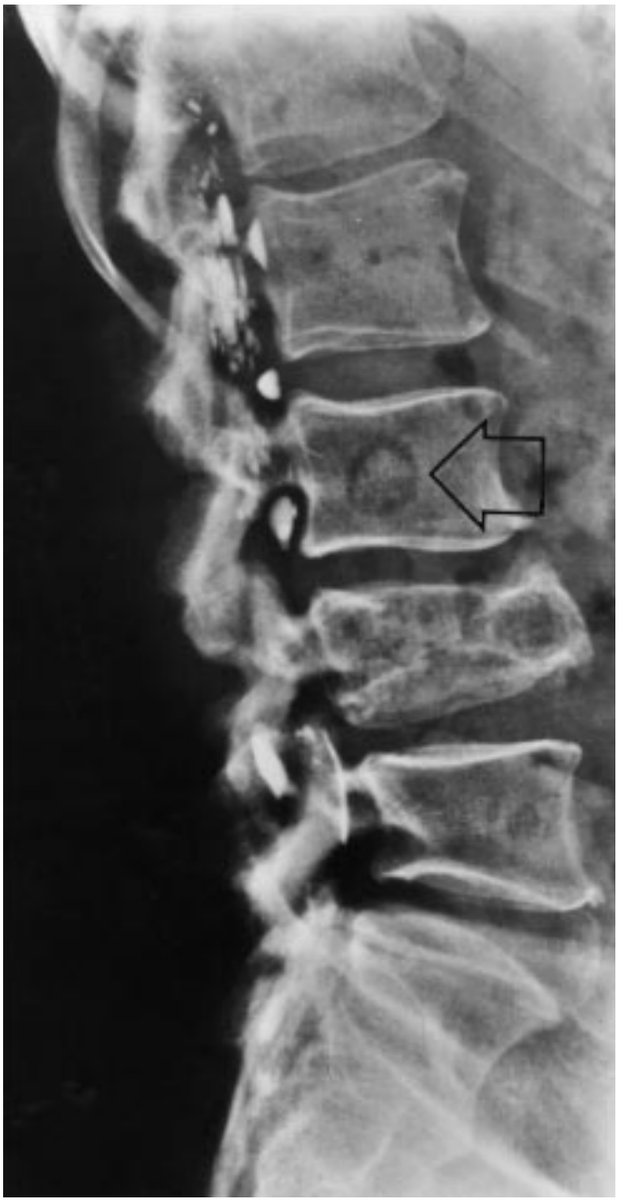


Figure 1.10 Lateral plain radiograph of the lumbar spine, showing metastatic high-grade osteosarcoma to the body of L3 vertebra (arrow).

system for carcinomas, is the grade of the tumor. The system that is most commonly used for the staging of **soft-tissue sarcomas** is that of the American Joint Committee on Cancer (Table 1.1).[1] It is based primarily on the Memorial–Sloan Kettering staging system and does not apply to rhabdomyosarcoma. Critics of this system point out that it is based largely on single-institution studies that were not subjected to multi-institutional tests of validity. The Musculoskeletal Tumor Society adopted staging systems that were originally described by Enneking *et al.*,[2,3] for malignant **soft-tissue** and **bone** tumors (Table 1.2), and the American Joint Committee on Cancer developed, with few changes, a staging system for malignant **bone** tumors (Table 1.3).[4]

Enneking's classical staging system is based on three factors: histological grade (G), site (T), and the presence or absence of metastases (M). The anatomical site (T) may be either intracompartmental (A) or extracompartmental (B). This information is obtained preoperatively on the basis of the data gained from the various imaging modalities. A tumor is classified as intracompartmental if it is bounded by natural barriers to extension, such as bone, fascia, synovial tissue, periosteum, or cartilage. An extracompartmental tumor may be either a tumor that violated the borders of the compartment from which it originated, or a tumor that originated and remained in the extracompartmental space. A tumor is assigned to stage III (M1) if a metastasis is present at a distant site or in a regional lymph node. It should be emphasized that Enneking's classification system is based on clinical data from an era in which chemotherapy was not given preoperatively and compartmental resections were much more common. Therefore, there was a clear correlation between the extent of the tumor at presentation, its relation to the boundaries of the compartment in which it is located, and the extent of surgery. A close correlation was also found between surgical stage of bone sarcoma and patient survival (Figure 1.14). Since that time the use of neoadjuvant chemotherapy was shown to decrease tumor size and facilitate limb-sparing surgery, as well as reduce the local recurrence rate. As a result, compartmental resections became rare. Nonetheless, Enneking's classification is based on the biological behavior of soft-tissue and bone sarcomas, and its underlying concept is as relevant as it was in the early 1980s.

Enneking also described a staging system of benign bone tumors, which remains the one that is most commonly used (Table 1.4).[2] That system is based on the biological behavior of these tumors as suggested by their clinical manifestation and radiological findings. Benign bone tumors grow in a centrifugal fashion, as do their malignant counterparts, and a rim of reactive bone is typically formed as a response of the host bone to the tumor. The extent of that reactive rim reflects the rate at which the tumor is growing; it is usually thick and well-defined around slowly growing tumors, and barely detectable around fast-growing, aggressive tumors.

Latent benign bone tumors are classified as stage 1. Such tumors are usually asymptomatic and are commonly discovered as an incidental radiographic finding. Their natural history is to grow slowly during

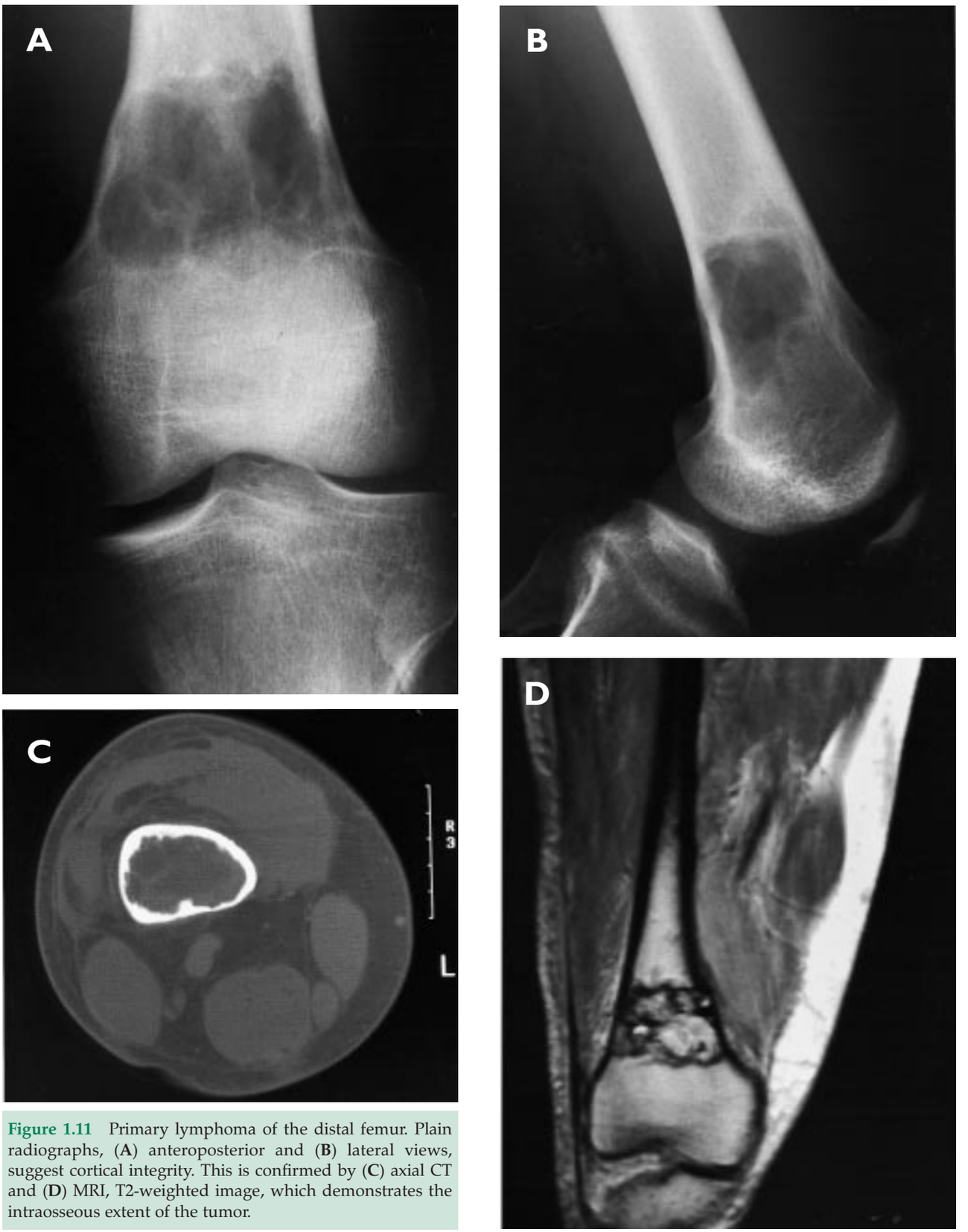


Figure 1.11 Primary lymphoma of the distal femur. Plain radiographs, (**A**) anteroposterior and (**B**) lateral views, suggest cortical integrity. This is confirmed by (**C**) axial CT and (**D**) MRI, T2-weighted image, which demonstrates the intraosseous extent of the tumor.

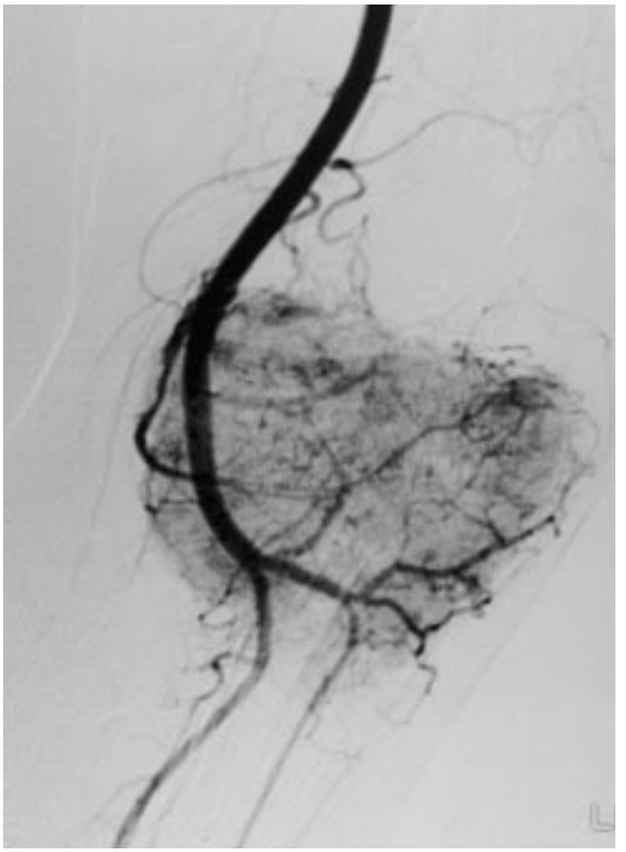


Figure 1.12 Extensive giant-cell tumor of the proximal tibia. Angiography was performed prior to a proximal tibia resection. It documented an absent peroneal artery. A successful effort was made to preserve the anterior tibial artery during the resection; otherwise, the leg would have been dependent on a single vessel.

normal growth of the individual and then to stop and, in most cases, heal spontaneously. These lesions never become malignant and usually heal following simple curettage. Examples include fibrous cortical defects and nonossifying fibromas (Figure 1.15). **Active benign** bone tumors are classified as stage 2 lesions. These tumors grow progressively but do not violate natural barriers. Associated symptoms may occur. Curettage and burr drilling are curative in most cases (Figure 1.16). **Aggressive** benign bone tumors (stage 3) may cause destruction of surrounding bone and usually break through the cortex into the surrounding soft tissues. Local control can be achieved only by curettage and meticulous burr drilling with a local adjuvant such as liquid nitrogen, or by resection of the lesion with a margin of normal tissue (i.e., wide resection) (Figure 1.17).

CLASSIFICATION OF SURGICAL PROCEDURES

There are four basic types of excisions; each is based on the relationship of the dissection plane to the tumor and its pseudocapsule. An **intralesional** excision is performed within the tumor mass and results in removal of only a portion of it; the pseudocapsule and macroscopic tumor are left behind. In a **marginal** excision, the dissection plane passes through the pseudocapsule of the tumor. Such a resection may leave microscopic disease. **Wide** (en-bloc) excision entails removal of the tumor, its pseudocapsule, and a cuff of normal tissue peripheral to the tumor in all directions. This is the desired margin for sarcoma resection; however, the adequate thickness of the normal tissue cuff is a matter of controversy. For both soft-tissue and

Table 1.1 System of the American Joint Committee on Cancer for the staging of soft-tissue sarcomas[1]

Stage[a]	*Grade*[b]	*Primary tumor*[c]	*Metastasis in regional lymph nodes*[d]	*Distant metastasis*[e]
IA	G_1 or G_2	T_{1a} or T_{1b}	N_0	M_0
IB	G_1 or G_2	T_{2a}	N_0	M_0
IIA	G_1 or G_2	T_{2b}	N_0	M_0
IIB	G_3 or G_4	T_{1a} or T_{1b}	N_0	M_0
IIC	G_3 or G_4	T_{2a}	N_0	M_0
III	G_3 or G_4	T_{2b}	N_0	M_0
IV	Any G	Any T	N_0 or N_1	M_1

[a]IA = Low-grade, small, and superficial or deep; IB = low-grade, large, and superficial; IIA = low-grade, large and deep; IIB = high-grade, small, and superficial or deep; IIC = high grade, large, and superficial; III = high-grade, large, and deep; IV = any with metastasis.
[b]G_1 = Well differentiated; G_2 = moderately well differentiated; G_3 = poorly differentiated; G_4 = undifferentiated.
[c]T_1 = Tumor is ≤ 5 cm in greatest dimension; T_{1a} = T_1 tumor is superficial (lesion does not involve the superficial fascia); T_{1b} = T_1 tumor is deep (lesion is deep to or invades the superficial fascia; that is, all intraperitoneal visceral lesions or lesions that invade major vessels or that are located in the thorax, head, or neck); T_2 = tumor that is >5 cm in greatest dimension; T_{2a} = T_2 tumor is superficial; T_{2b} = T_2 tumor is deep.
[d]N_0 = No metastasis in regional lymph nodes; N_1 = metastasis in regional lymph nodes.
[e]M_0 = No distant metastasis; M_1 = distant metastasis.

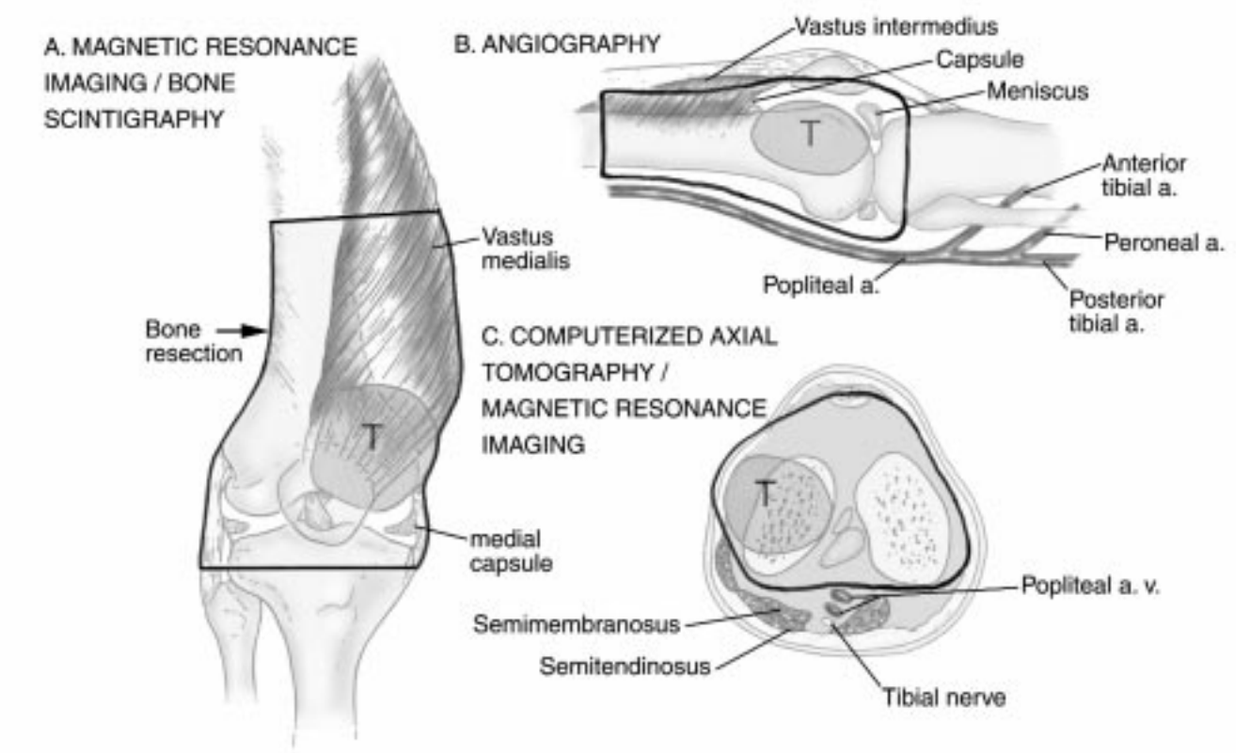


Figure 1.13 Relationship of the various imaging modalities to the different components of a bone sarcoma. Plain radiographs assess bony involvement and cortical breakdown. CT determines the exact extent of bone destruction and MRI determines the medullary and extraosseous components of the tumor. Bone scan evaluates the cortical and intraosseous extents of the tumor, as well as the presence of metastatic bone disease. Angiography reveals the anatomic relation of the tumor to the major blood vessels.

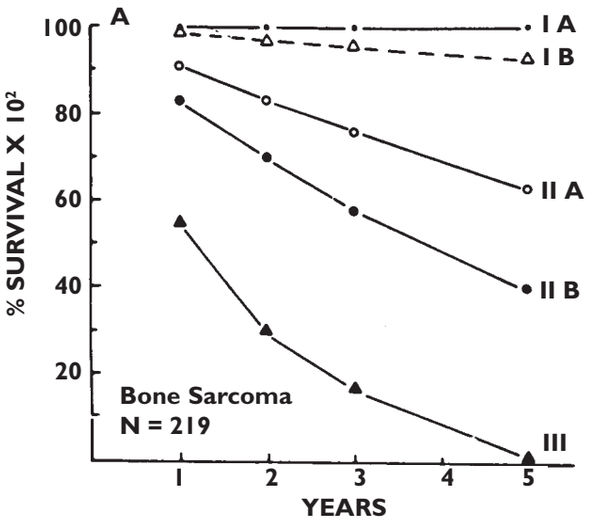


Figure 1.14 Survival by Enneking's surgical stage of 219 patients with primary bone sarcoma.

Table 1.2 System of Enneking et al.[2,3] for staging of soft-tissue and bone sarcomas

Stage	*Grade*[a]	*Site*[b]	*Metastasis*[c]
IA	G_1	T_1	M_0
IB	G_1	T_2	M_0
IIA	G_2	T_1	M_0
IIB	G_2	T_2	M_0
III	G_1 or G_2	T_1 or T_2	M_1

[a] G_1 = Low grade; G_2 = high grade.
[b] T_1 = Intracompartmental; T_2 = extracompartmental.
[c] M_0 = No regional or distant metastasis; M_1 = regional or distal metastasis.

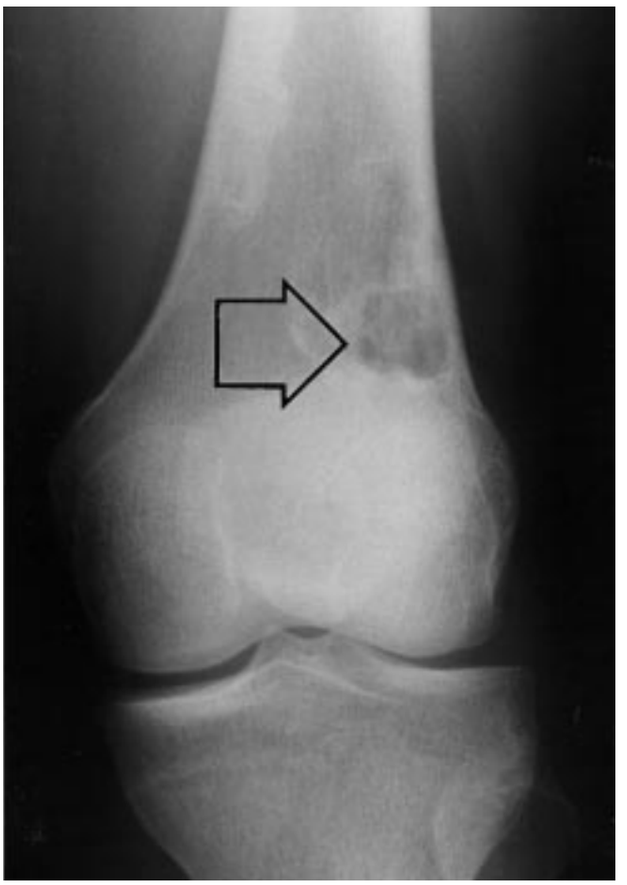
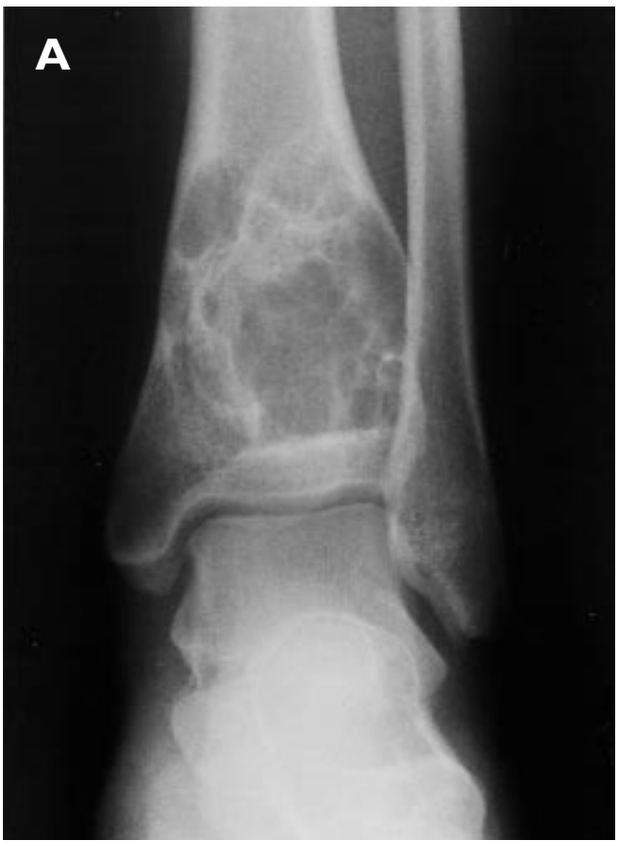


Figure 1.15 Nonossifying fibroma (NOF) of the distal femur (arrow). As in most cases of NOF, the lesion was asymptomatic and the plain radiographs were ordered because of a trauma to the knee.



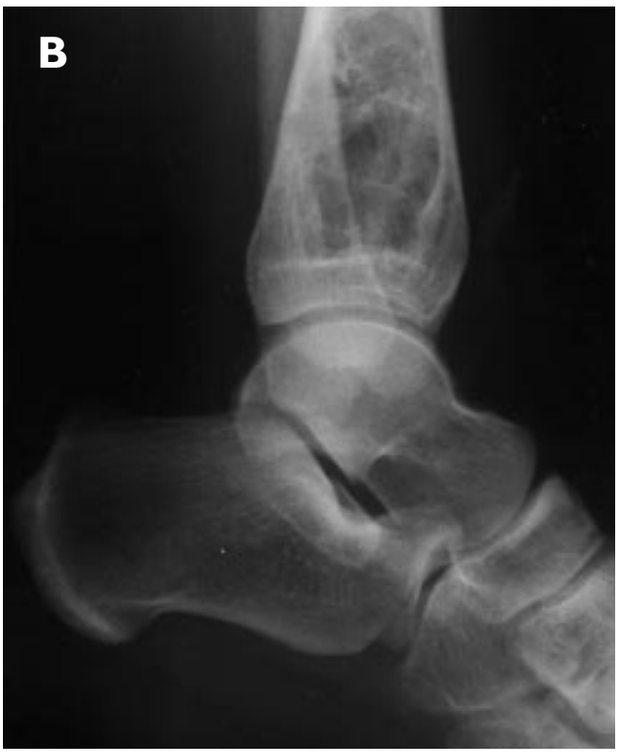


Figure 1.16 *(see above right and bottom right)* Aneurysmal bone cyst of the distal tibia as seen by plain radiographs, (**A**) anteroposterior and (**B**) lateral views.

Table 1.3 System of the American Joint Committee on Cancer for the staging of sarcomas of bone[4]

Stage	*Grade*[a]	*Primary tumor*[b]	*Metastasis in regional lymph nodes*[c]	*Distant metastasis*[d]
IA	G_1 or G_2	T_1	N_0	M_0
IB	G_1 or G_2	T_2	N_0	M_0
IIA	G_3 or G_4	T_1	N_0	M_0
IIB	G_3 or G_4	T_2	N_0	M_0
III	Not defined			
IVA	Any G	Any T	N_1	M_0
IVB	Any G	Any T	Any N	M_1

[a]G_1 = Well differentiated; G_2 = moderately differentiated; G_3 = poorly differentiated; G_4 = undifferentiated. Ewing's sarcoma and malignant lymphoma are graded as G_4.
[b]T_1 = Tumor confined within the cortex; T_2 = tumor extends beyond the cortex.
[c]N_0 = No metastasis in regional lymph nodes; N_1 = metastasis in regional lymph nodes.
[d]M_0 = No distant metastasis; M_1 = distant metastasis.

Table 1.4 Enneking's system for the staging of benign bone tumors[2]

			Typical example	
Stage	*Definition*	*Biological Behavior*	*Soft-tissue tumor*	*Bone tumor*
1	Latent	Remains static or heals spontaneously	Lipoma	Nonossifying fibroma
2	Active	Progressive growth, limited by natural barriers	Angiolipoma	Aneurysmal bone cyst
3	Aggressive	Progressive growth, invasive, not limited by natural barriers	Aggressive fibromatosis	Giant-cell tumor

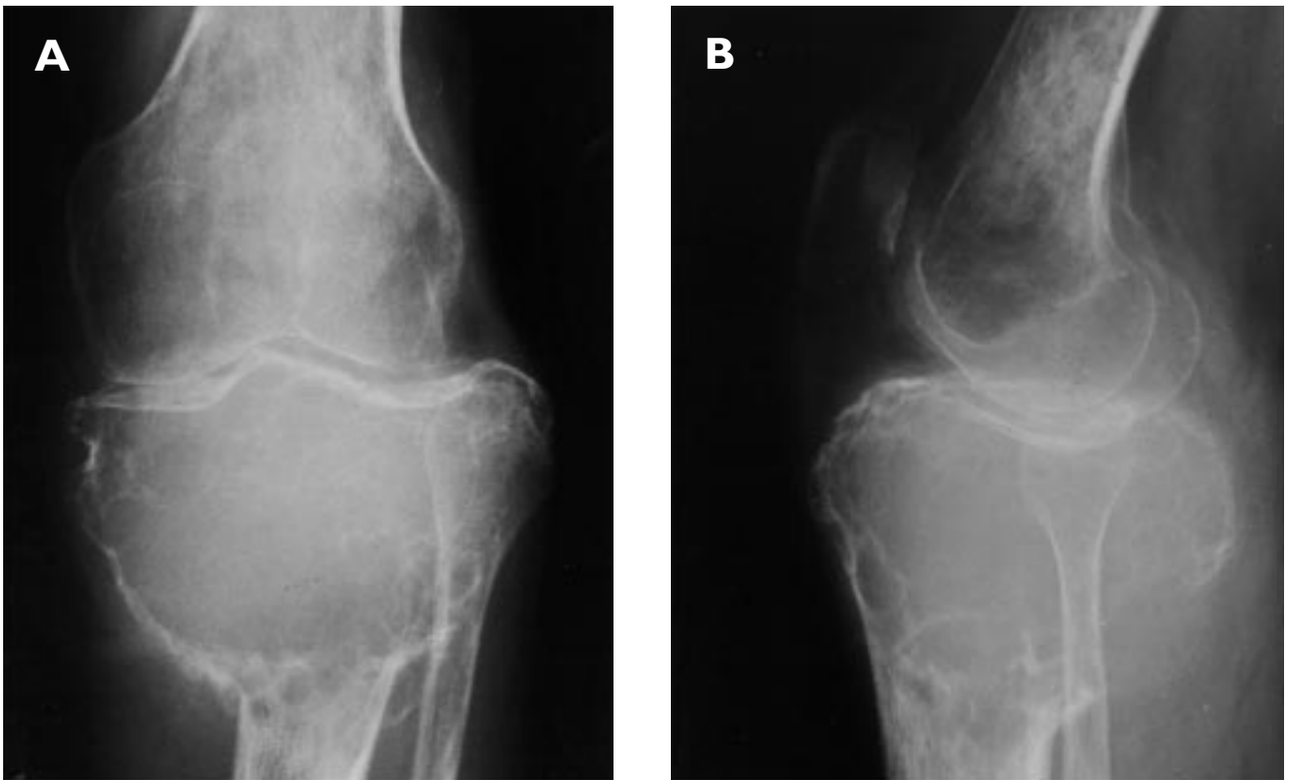


Figure 1.17 Plain radiographs, (**A**) anteroposterior and (**B**) lateral views of benign giant-cell tumor of the proximal tibia. The tumor was neglected for 18 months and necessitated proximal tibia resection and reconstruction with endoprosthesis.

bone sarcomas, it is generally believed to be a few centimeters.

Radical excision involves removal of the tumor and the entire anatomical compartment within which it is located (Figures 1.18, 1.19). Although traditionally mentioned as the fourth excision type, it does not define the component of the tumor that is left behind. In other words, a radical excision can achieve a marginal or a wide margin, depending on how close the tumor is to the border of the compartment. However, radical excision excludes the possibility of skip metastases.

In general, benign bone tumors are adequately treated by either an intralesional procedure (curettage and burr drilling, cryosurgery) or by marginal excision. Primary bone sarcomas are treated with wide excision. Metastatic tumors are treated according to the general intent of the surgery. When a palliative surgery is performed, metastatic lesions are treated by an intralesional procedure. If a curative procedure is performed, as in the case of solitary breast metastasis, for example, the lesion is treated as if it was a primary bone sarcoma (i.e., wide excision). It is important to emphasize that any of these excision types may be accomplished by a limb-sparing procedure or by amputation. An amputation is *not* necessarily an adequate cancer operation, but it is a method of achieving a specific margin. It may entail a marginal, wide, or radical excision, depending upon the plane in which it passes. Staging studies are used to assess local tumor extent and relevant local anatomy, and thereby determine how a desired surgical margin may be achieved.

SOFT-TISSUE SARCOMAS

Soft-tissue sarcomas are a heterogeneous group of rare tumors that arise from the supporting extraskeletal

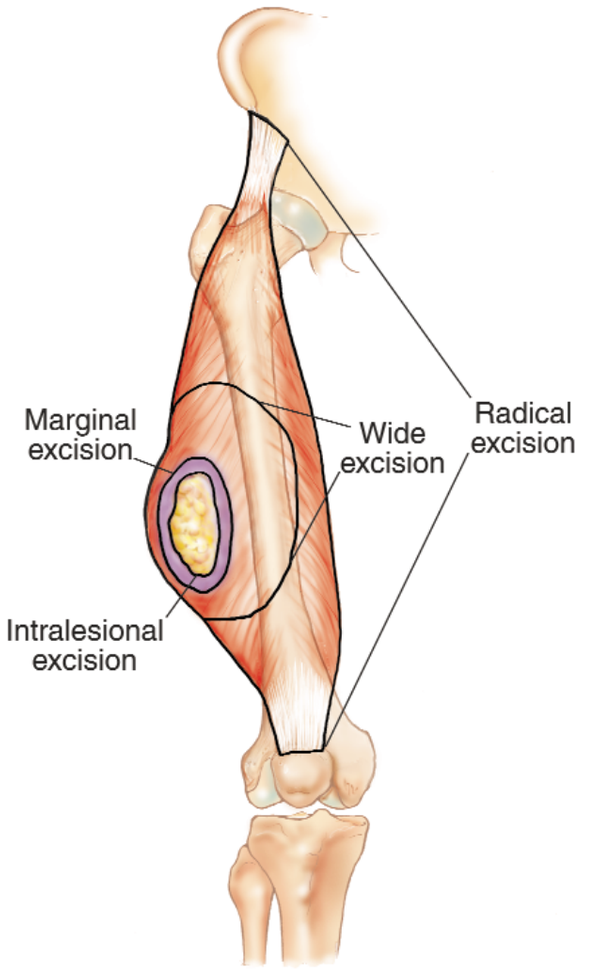


Figure 1.18 Various excision types for soft-tissue sarcoma.

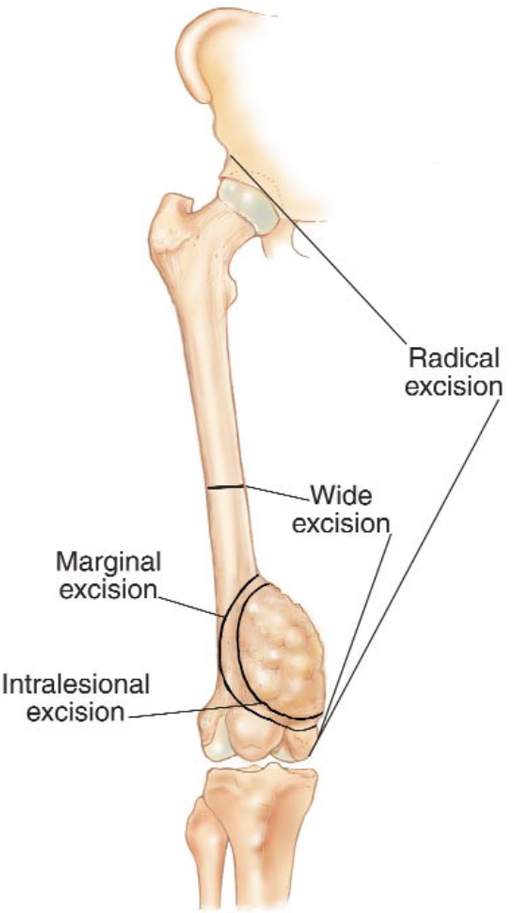


Figure 1.19 Various excision types for bone sarcoma.

tissues (i.e., muscle, fascia, nerve, connective, fibrous, and fatty tissues). Although they share biological characteristics, and are treated in a similar fashion, each of the various soft-tissue sarcomas has a unique morphology, biological behavior, and prognosis. Pathologic grading is at times difficult. In general, the extent of pleomorphism, atypia, mitosis, and necrosis correlates with the grade of malignancy. Notable exceptions are synovial sarcomas, which tend to behave like high-grade lesions even in the absence of histopathological high-grade characteristics. The exact histogenesis often cannot be accurately defined, although the grade can be determined.

Pathologic Characteristics of Specific Soft-tissue Sarcomas

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma (MFH) is the most common soft-tissue sarcoma in adults. It most commonly affects the lower extremity and has a predilection for originating in deep-seated skeletal muscles. The tumor usually presents as a multinodular mass with well-circumscribed or ill-defined infiltrative borders. The size at the time of diagnosis often correlates with the ease of clinical detection: superficial variants, presenting as dermal or subcutaneous masses, may be only a few centimeters in diameter, whereas those arising in the retroperitoneum often attain a diameter of 15 cm or greater. Color and consistency vary considerably and reflect, in part, the cellular composition. Red–brown areas of hemorrhage and necrosis are not uncommon (Figure 1.20).

The myxoid variant of MFH contains a predominance of white–gray, soft, mucoid tumor lobules, created by the high content of myxoid ground substance. Approximately 5% of MFHs undergo extensive hemorrhagic cystification, often leading to a clinical and radiologic diagnosis of hematoma. A needle biopsy can result in a benign diagnosis if only the hemorrhagic center of the tumor is sampled. For these reasons, until proven otherwise, one should assume that an underlying soft-tissue sarcoma is present in any adult patient with a deep-seated hematoma that does not resolve after a few weeks, even when there is a history of trauma to that site.

The currently accepted broad histologic spectrum of MFH encompasses many variants that were formerly considered to be distinct clinicopathologic entities. These lesions, which had been named according to the predominant cell type, include fibroxanthoma, malignant fibroxanthoma, inflammatory fibrous histiocytoma, and giant cell tumor of soft part. Immunohistochemical studies and electron microscopy can assist in the accurate diagnosis of a significant percentage of these tumors. The basic neoplastic cellular constituents of all fibrohistiocytic tumors include fibroblasts, histiocyte-like cells, and primitive mesenchymal cells (Figure 1.21). In addition, there is usually an acute and a chronic inflammatory cell component. The proportion of these malignant and reactive cell elements, the degree of pleomorphism of the neoplastic cells, and the predominant pattern accounts for the wide histologic variances.

The most common histologic pattern associated with MFH is a storiform arrangement of the tumor cells. This is characterized by fascicles of spindle cells that

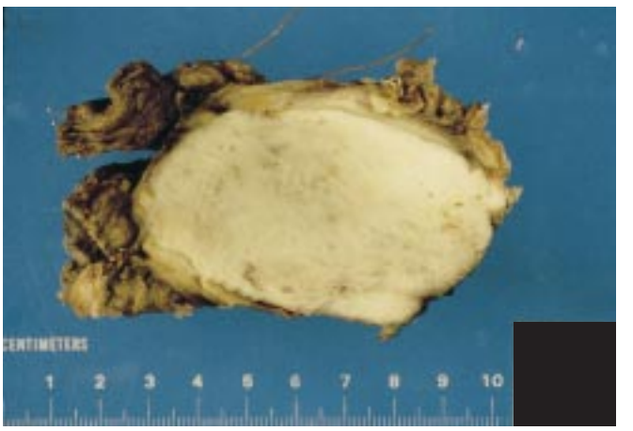


Figure 1.20 Deep-seated malignant fibrous histiocytoma (MFH) presents as a soft, white–tan mass, often with areas of hemorrhage and necrosis. Occasionally, cysts and hematoma-like changes are present.

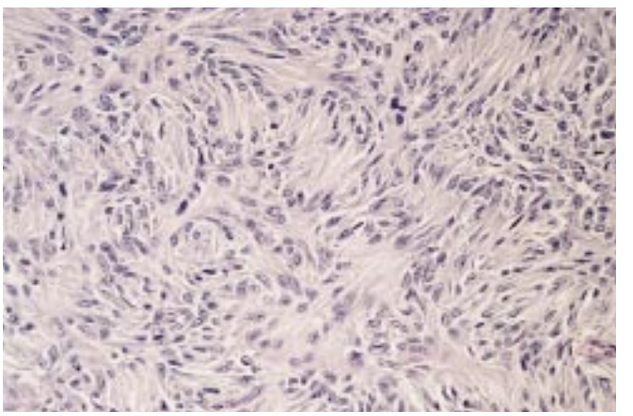


Figure 1.21 MFH, a high-grade sarcoma, is characterized by pleomorphic spindle cells forming fascicular or typical storiform patterns. Bizarre tumor giant cells are interspersed throughout the mass. Atypical mitotic figures are frequently seen.

intersect to form a pinwheel or cartwheel pattern (Figure 1.21). Atypical and bizarre giant cells, often containing abnormal mitotic figures, may occur. The histologic grade (almost always intermediate to high) is a good prognosticator of metastatic disease. In the myxoid variant, the second most common histologic type, the tumor cells are dispersed in a richly myxoid matrix (Figure 1.22). The less common giant cell type (malignant giant cell of soft parts) is characterized by abundant osteoclast-like giant cells that are diffusely distributed among the malignant fibrohistiocytic elements. Myxoid MFH has a more favorable prognosis than other subtypes.

Liposarcoma

Liposarcoma is the second most common soft-tissue sarcoma in adults. It has a wide range of malignant potential that correlates well with the histologic classification of the individual tumor. The lower extremity is the most common site and accounts for greater than 40% of the cases. These tumors, particularly those arising in the retroperitoneum, can attain enormous size; specimens measuring 10–15 cm and weighing greater than 5 kg are not uncommon (Figure 1.23). Liposarcomas tend to be well circumscribed and multilobulated. Gross features usually correlate with the histologic composition. Well-differentiated liposarcomas contain variable proportions of relatively mature fat and fibrocollagenous tissues, vary from yellow to white–gray and can be soft, firm, or rubbery. A tumor that is soft, pink–tan, and reveals a mucinous surface is probably a myxoid liposarcoma, which is the most common histologic type. The high-grade liposarcomas (round cell and pleomorphic) vary from pink–tan to brown and may disclose extensive hemorrhage and necrosis.

Identification of typical lipoblasts is mandatory to establish the diagnosis of liposarcoma. This diagnostic cell contains one or more round, cytoplasmic fat droplets that form sharp, scalloped indentations on the central or peripheral nucleus. Well-differentiated liposarcomas often contain a predominance of mature fat cells and only a few, widely scattered lipoblasts. Inadequate sampling can therefore lead to a misdiagnosis of a benign lipoma (Figure 1.24). Well-differentiated liposarcomas that arise in the superficial soft tissues have been called "atypical lipomas." In the sclerosing variant of a well-differentiated liposarcoma, delicate collagen fibrils that encircle fat cells and lipoblasts comprise a prominent part of the matrix

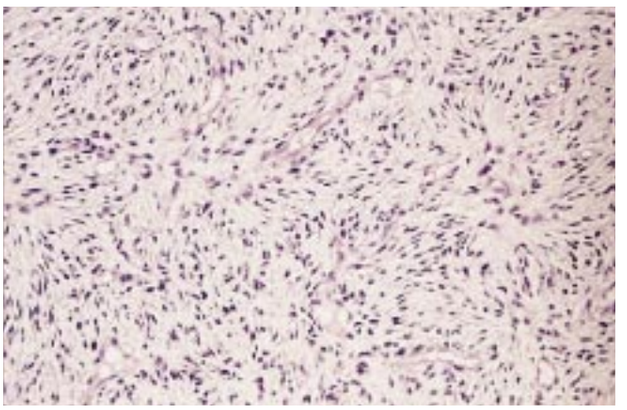


Figure 1.22 The myxoid variant of MFH discloses copious mucinous-like interstitial substance that consists predominantly of hyaluronic acid. The cellular components can be widely dispersed, imparting a deceptively bland appearance, particularly on a needle-biopsy specimen. Thorough sampling of the tumor usually discloses more diagnostic features.

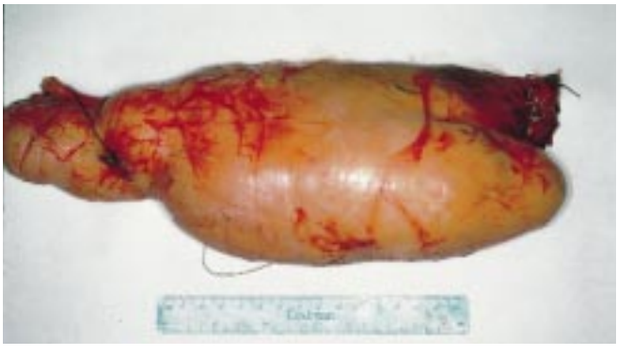


Figure 1.23 Large, low-grade liposarcoma of the posterior thigh.

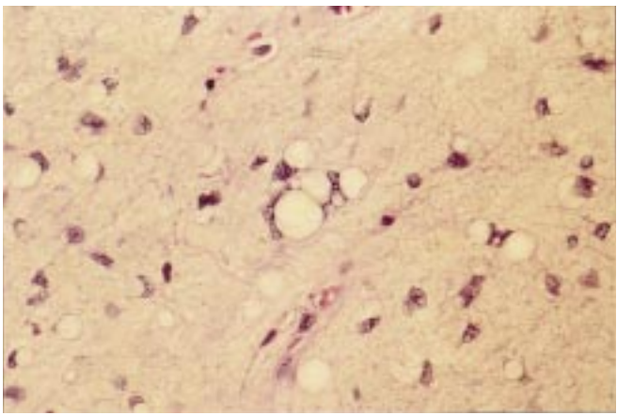


Figure 1.24 The diagnosis of a well-differentiated liposarcoma depends on the identification of characteristic lipoblasts. These cells can be mono- or multivacuolated with hyperchromatic, scalloped nuclei. This variant can closely mimic ordinary lipoma.

(Figure 1.25). In rare cases, well-differentiated liposarcomas, usually after multiple local recurrences, transform into a high-grade spindle-cell sarcoma, often with MFH-like features ("dedifferentiated liposarcoma"). This change imparts a high risk of metastases.

A diagnosis of myxoid liposarcoma requires the observation of a delicate plexiform capillary network associated with both primitive mesenchyme-like cells and a variable number of lipoblasts (Figure 1.26). The stroma contains a high proportion of myxoid ground substance that may form numerous microcysts. In round-cell liposarcomas, the lipoblasts are interspersed within sheets of poorly differentiated round cells (Figure 1.27). There is convincing evidence that myxoid and round-cell liposarcomas are the divergent ends of a continuous spectrum of the same neoplasm. This is supported by the fact that both tumors have the same chromosomal translocation. Finally, pleomorphic liposarcoma discloses a mixture of bizarre, often multivacuolated, lipoblasts and atypical stromal cells, many of which contain abnormal mitotic figures (Figure 1.28). Areas of necrosis and hemorrhage are common. The presence of lipoblasts distinguishes this high-grade sarcoma from MFH and other pleomorphic sarcomas.

Unlike other soft-tissue sarcomas, liposarcomas may be multiple and occur in unusual sites in the same individual. Therefore, careful evaluation of other masses in a patient with a liposarcoma is mandatory. Accurate determination of the morphologic subtype and its grade is essential. Low-grade liposarcomas are

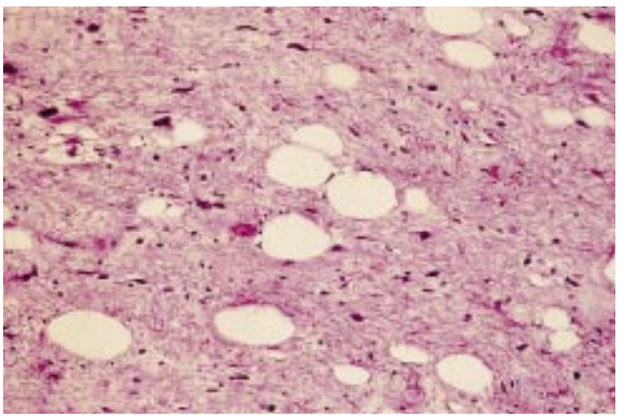


Figure 1.25 The sclerosing variant of well-differentiated liposarcoma contains a background of coarse wavy collagen fibers. The lipoblasts are dispersed among these fibers.

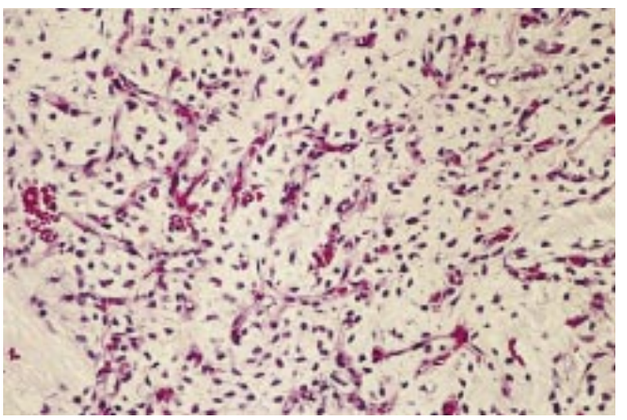


Figure 1.26 Lipoblasts associated with a plexiform capillary network in a diffusely myxoid stroma define the myxoid liposarcoma. Cyst-like areas are occasionally present.

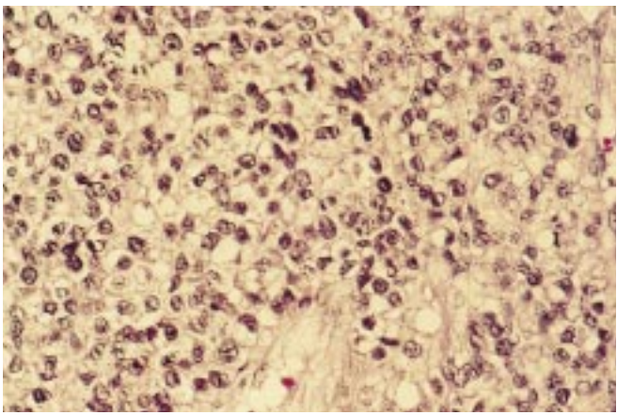


Figure 1.27 Sheets of round blue cells with clear to eosinophilic cytoplasm are typical of round-cell liposarcoma, a high-grade neoplasm. It has the identical chromosomal abnormality found in myxoid liposarcoma, evidence that these are morphologic variants of the same tumor.

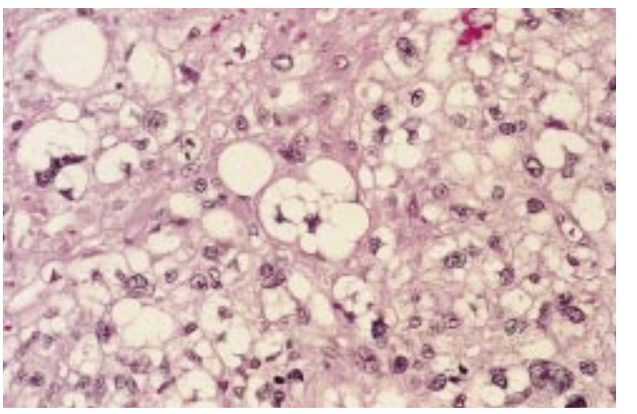


Figure 1.28 The pleomorphic liposarcoma is another high-grade form of lipomatous malignancy. It is characterized by numerous large, bizarre lipoblasts, abnormal mitotic figures, and necrosis. Many of its features overlap with malignant fibrous histiocytoma.

treated with wide excision and adjuvant radiation therapy is recommended only if marginal margins were achieved. The authors treat high-grade liposarcomas as any other high-grade soft tissue sarcoma; neoadjuvant chemotherapy, wide excision, and adjuvant chemotherapy. Radiation therapy is indicated if wide margins were not achieved. The role of chemotherapy and radiation therapy in the treatment of soft tissue is discussed in Chapters 3 and 5, respectively.

Fibrosarcoma

Fibrosarcoma used to be considered the most common soft-tissue sarcoma. Following the histopathologic definition of MFH as a distinct entity and the subsequent assignment of "pleomorphic fibrosarcoma" to that category, fibrosarcoma has become uncommon. Fibrosarcomas usually arise from the fascial and aponeurotic structures of the deep soft tissues. Superficial variants are rare. Relatively small tumors present as firm, gray–white, partially to completely circumscribed masses (Figure 1.29). As these lesions enlarge, a more diffusely infiltrative pattern predominates.

The fundamental cell of this neoplasm is the fibroblast, which is a spindle cell capable of producing collagen fibers. The collagen matrix, appearing as birefringent wavy fibers, can be easily recognized in the more differentiated fibrosarcomas (Figure 1.30). Its presence can be confirmed with the application of Masson trichrome stain. Well-differentiated fibrosarcoma is characterized by intersecting fascicles of relatively uniform spindle cells showing minimal atypical features and sparse mitotic figures. The fascicles often intersect at acute angles to form the typical herringbone pattern. Differentiating low-grade fibrosarcomas from fibromatosis and its variants may be difficult. In contrast, poorly differentiated fibrosarcoma reveals a barely discernible fascicular arrangement. The smaller cells show significant pleomorphism, nuclear atypia, and often have a high mitotic rate. Necrosis and hemorrhage commonly occur in high-grade fibrosarcomas. In this situation, particularly in the presence of pleomorphic tumor cells, distinguishing fibrosarcoma from MFH is exceedingly difficult.

Synovial Sarcoma

Synovial sarcoma ranks as the fourth most common soft-tissue sarcoma. In spite of its name, this tumor rarely arises directly from a joint but rather arises in proximity to it with a propensity for the distal portion of the extremities. Synovial sarcomas occur in a younger age group than do most other sarcomas: most patients are below the age of 40. The tumor typically presents as a deep-seated, well-circumscribed, multinodular, firm mass. Contiguity with a synovium-lined space is rare and, occasionally, lymphatic spread occurs. Unlike most soft-tissue sarcomas, synovial sarcomas may be present as a painless mass for a few years. Plain radiographs often show small calcifications within the mass. That finding should alert the physician to the diagnosis.

Virtually all synovial sarcomas are high-grade. The poorly differentiated neoplasms usually present as ill-defined, infiltrative lesions with a soft, somewhat gelatinous consistency. The classic histologic presentation of this tumor is a biphasic pattern. This implies the presence of coexisting but distinct cell populations, namely, spindle cells and epithelioid cells (Figure 1.31).

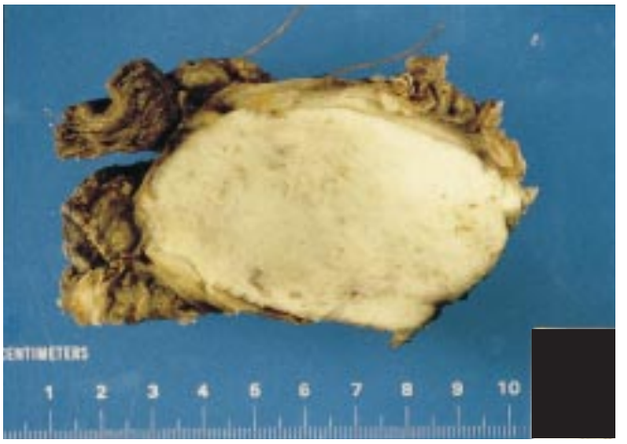


Figure 1.29 The gross appearance of a well-differentiated fibrosarcoma is that of a white–gray whorled nodules. It has a firm rubbery consistency.

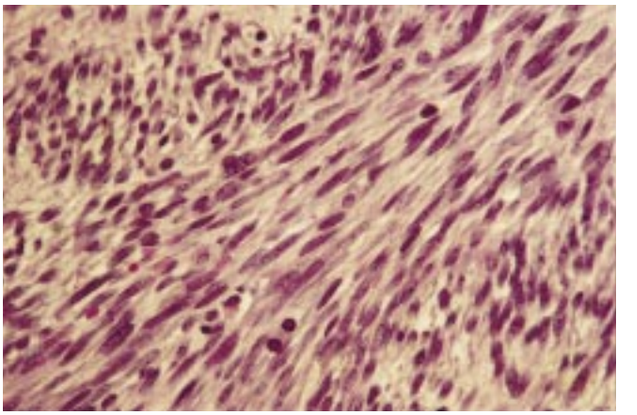


Figure 1.30 Low-grade fibrosarcoma is composed of slender, relatively uniform spindle cells forming elongated fascicles. These nodules often intersect at acute angles forming the typical herringbone pattern.

The plump spindle cells, usually the predominant component, form an interlacing fascicular pattern that is reminiscent of fibrosarcoma. Within the spindle-cell portion of the tumor, areas resembling the acutely branching vascular pattern of hemangiopericytoma are common. The arrangement of epithelioid cells varies from merely solid nests to distinct, gland-like structures (Figure 1.32). When comprising glandular spaces the constituent cells range from cuboidal to tall columnar; rarely do they undergo squamous metaplasia. The application of histochemical stains demonstrates that the glandular lamina contain epithelial-type acid mucins. The neoplasm may contain extensive areas of dense stromal hyalinization, and focal calcification is common. The presence of extensive areas of calcification, sometimes with modulation to benign osteoid, deserves recognition because this rare variant imparts a significantly more favorable prognosis than other forms of synovial sarcoma. The existence of a monophasic spindle cell synovial sarcoma has been recognized, although distinguishing it from fibrosarcoma can be difficult. In contrast to fibrosarcoma, the spindle cell variant of synovial sarcoma may contain cytokeratins, as demonstrated with immunohistochemical studies.

PATHOLOGIC CHARACTERISTICS OF SPECIFIC PRIMARY BONE SARCOMAS

Osteosarcoma

Osteosarcoma is the most common primary bone sarcoma. Its distinguishing characteristic is the production of "tumor" osteoid or immature bone matrix. Osteosarcoma typically occurs during childhood and adolescence. In patients over the age of 40 it is usually associated with a pre-existent condition such as Paget's disease or irradiated bone. Between 80% and 90% of the tumors occur in the metaphysis of long bone with the most common sites being the distal femur, proximal tibia, and proximal humerus. Pain, accompanied by a tender, soft tissue swelling, is the most common complaint.

The classical radiologic appearance is a destructive tumor with increased intramedullary radiodensity, an area of radiolucency, and a pattern of permeative invasion of the surrounding bone with poorly defined borders, cortical destruction, periosteal elevation, extraosseous extension, and soft-tissue calcification. On the basis of radiological presentation, osteosarcomas are classified into three broad categories: sclerotic osteosarcomas (30%), osteolytic osteosarcomas (25%), and mixed pattern (45%) (Figure 1.33). The differential diagnosis of this tumor includes giant-cell tumor, aneurysmal bone cyst, fibrosarcoma, and MFH of bone. Errors in diagnosis most often occur with pure osteolytic osteosarcoma.

As the neoplasm permeates the cortex, the periosteum may be elevated. This stimulates reactive bone formation and accounts for a distinctive radiologic feature called "Codman's triangle". Longitudinal sectioning of the involved bone often reveals wide extension within the marrow cavity. Rarely, skip areas within the medullary canal can be demonstrated. There may be necrotic and hemorrhagic foci. At the time of diagnosis, most tumors have already caused substantial cortical destruction. Continued tumor growth results in involvement of the adjacent soft tissues (Figure 1.34).

The definitive diagnosis of osteosarcoma rests on the identification of a malignant stroma that produces an osteoid matrix. The stroma consists of a haphazard

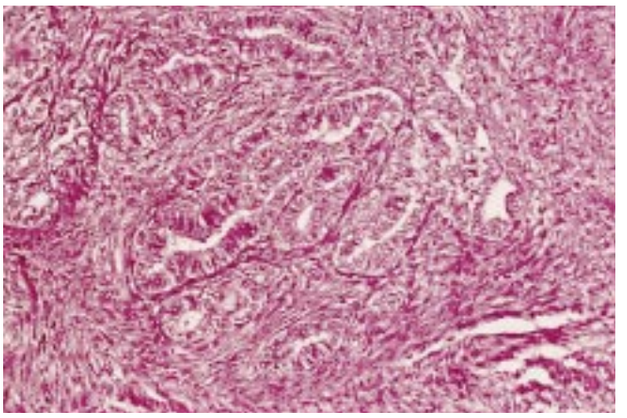


Figure 1.31 Synovial sarcoma is characterized by a distinctive biphasic pattern. This implies an admixture of spindle-cell areas along with epithelioid cells forming gland-like structures. The proportion of these two components is variable.

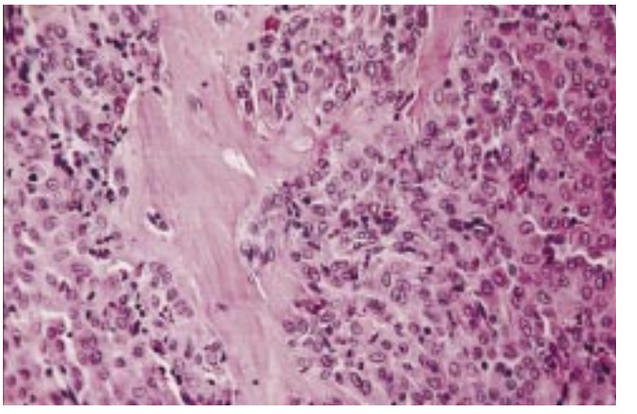


Figure 1.32 When only one of the elements of synovial sarcoma is present, almost invariably the spindle-cell component, it is termed monophasic synovial sarcoma.

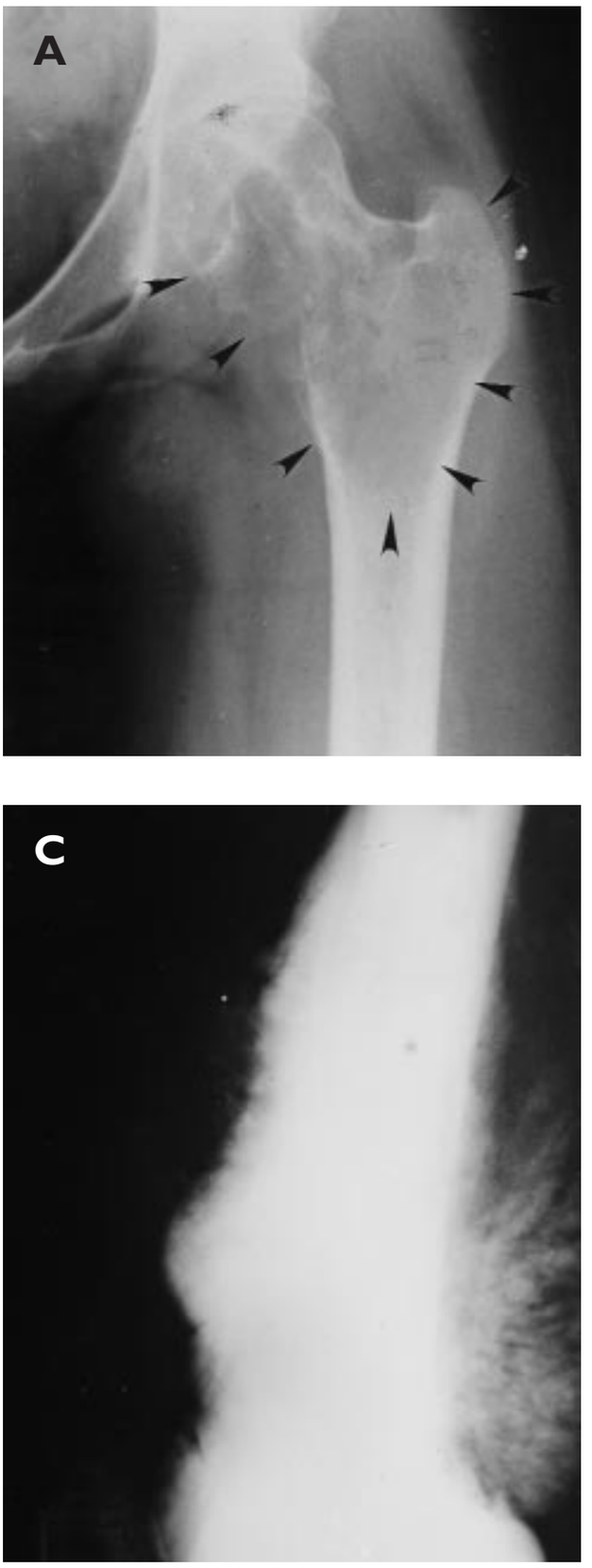


Figure 1.33 The three radiographic matrix types of osteosarcoma: (**A**) osteolytic (arrows indicate tumor), (**B**) mixed, and (**C**) sclerosing. There is no prognostic difference in survival based on the radiographic type of matrix formation.

arrangement of pleomorphic cells that contain hyperchromatic and irregular nuclei. Mitotic figures, often atypical, are usually numerous. Deposited between these cells is a lace-like eosinophilic matrix that is assumed to be malignant osteoid (Figure 1.35). Both malignant and benign osteoblast-like giant cells can be found in the stroma. An abundance of the latter type can create confusion with giant-cell tumor of bone. The predominance of one tissue type in many osteosarcomas has led to a histologic subclassification of this neoplasm. Thus, "osteoblastic osteosarcoma" refers to those tumors in which the production of malignant osteoid prevails. The pattern is usually that of a delicate meshwork of osteoid, as noted above, although broader confluent areas may be present. Calcification of the matrix is variable. Alternatively, some tumors reveal a

predominance of malignant cartilage production; hence, the term "chondroblastic osteosarcoma". Even though the malignant cartilaginous elements may be overwhelming, the presence of a malignant osteoid matrix warrants the diagnosis of osteosarcoma. Another variant, fibroblastic osteosarcoma, is characterized by large areas of proliferating fibroblasts arranged in intersecting fascicles. Such areas are indistinguishable from fibrosarcomas, and thorough sampling may be necessary to identify the malignant osteoid component. The so-called telangiectatic osteosarcoma contains multiple blood-filled cystic and sinusoidal spaces of variable size. Identification of marked cytologic atypia in the septae and more solid areas rule out the diagnosis of aneurysmal bone cyst.

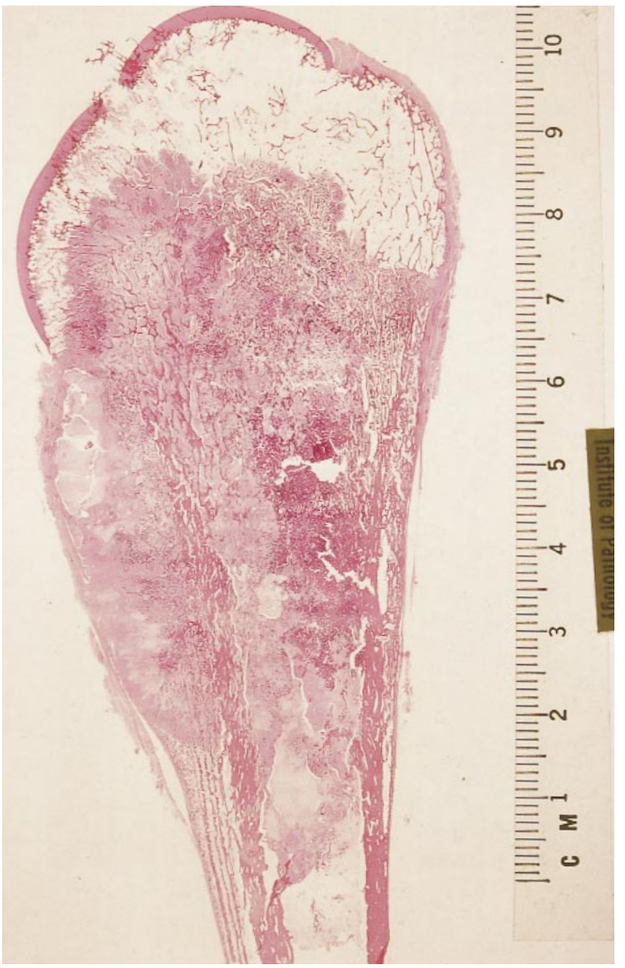


Figure 1.34 High-grade osteosarcoma of the proximal humerus with cortical breakthrough and tumor extension into the soft tissues.

Variants of Osteosarcoma

There are 11 recognizable variants of osteosarcoma, with parosteal and periosteal osteosarcomas being the most common. In contrast to the classical osteosarcoma, which arises within bone, parosteal and periosteal osteosarcomas arise in the surface of the bone.

Parosteal Osteosarcoma

Parosteal osteosarcoma is a distinct variant of osteosarcoma. Its prevalence is estimated to be 4%. It arises from the cortical bone and generally occurs in an older age group and has a better overall prognosis than osteosarcoma. As in osteosarcoma, the distal femur is the most common location; characteristically, the tumor attached to its posterior aspect. The proximal humerus and the proximal tibia are the next most frequent sites. Parosteal osteosarcomas usually present as a mass, occasionally associated with pain. The natural history is slow growth and late metastasis. The long-term survival rate is 75% to 85%. The tumor arises from the cortical surface and presents as a protuberant multinodular mass. The surface of the lesion may be covered in part by a cartilaginous cap resembling an osteochondroma; other areas may infiltrate into the adjacent soft tissues. The tumor usually encircles, partially or completely, the shaft of the underlying bone. In contrast to osteochondromas, the medullary canal of the bone is not contiguous with that of the neoplasm. Radiologically, parosteal osteosarcoma presents as a large, dense, tabulated mass that is broadly attached to the underlying bone without

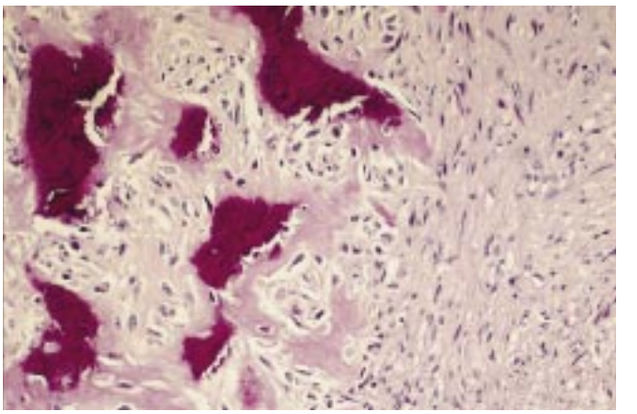


Figure 1.35 Classical high-grade osteosarcoma reveals a population of pleomorphic spindle cells intimately associated with a mesh of immature lacy osteoid. Occasionally the amount of osteoid can be minimal, or it may be a predominant element forming wide intersecting trabeculae lined by the malignant osteoblasts. Giant cells can also be present.

involvement of the medullary canal (Figure 1.36). If present long enough, the tumor may encircle the entire bone. The periphery of the lesion is typically less mature than the base. Despite careful evaluation, intramedullary extension is difficult to determine from the plain radiographs. It is more accurately detected with CT scan (Figure 1.37).

Diagnosis of parosteal osteosarcoma, more than that of other bone tumors, must be based on the clinical, radiological, and pathological findings. Most parosteal osteosarcomas are low-grade; they do not require neoadjuvant and adjuvant chemotherapy, and are best treated with wide excision. This tumor is commonly mistaken by inexperienced clinicians and pathologists as osteochondroma, myositis ossificans, or conventional osteosarcoma. In the classical low-grade lesion, irregularly formed osteoid trabeculae, usually of woven bone, are surrounded by a spindle-cell stroma containing widely spaced, bland-appearing fibroblastic spindle cells (Figure 1.38). There may be foci of atypical chondroid differentiation. With the higher grades the likelihood of intramedullary involvement is increased. This, in turn, correlates well with the presence of distant metastases.

Periosteal Osteosarcoma

Periosteal osteosarcoma is a rare cortical variant of osteosarcoma that arises superficially on the cortex, most often on the tibial shaft. It projects into the adjacent soft tissues as a well-circumscribed tabulated mass. Radiologically, it is a small, radiolucent lesion with some evidence of bone spiculation. The cortex is characteristically intact with scooped-out appearance and a Codman's triangle (Figure 1.39). On section, the tumor reveals a dominant chondroid consistency. The histologic features are essentially those of intermediate-grade chondroblastic osteosarcoma. The cartilaginous lobules may contain markedly atypical chondrocytes. At the periphery of the lobule is situated a cellular

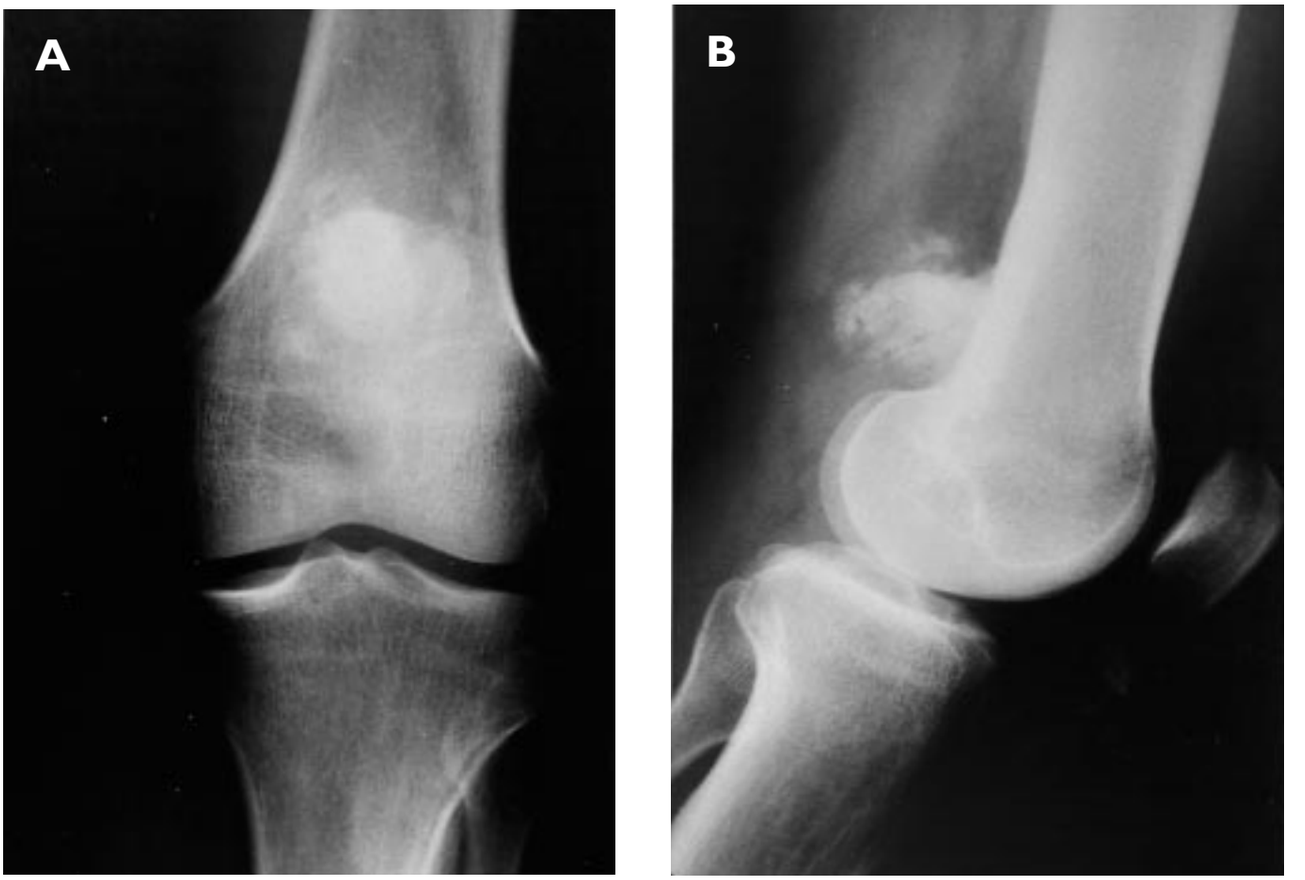
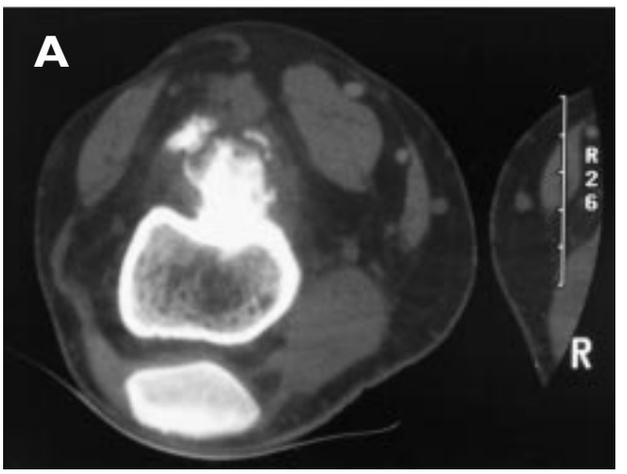
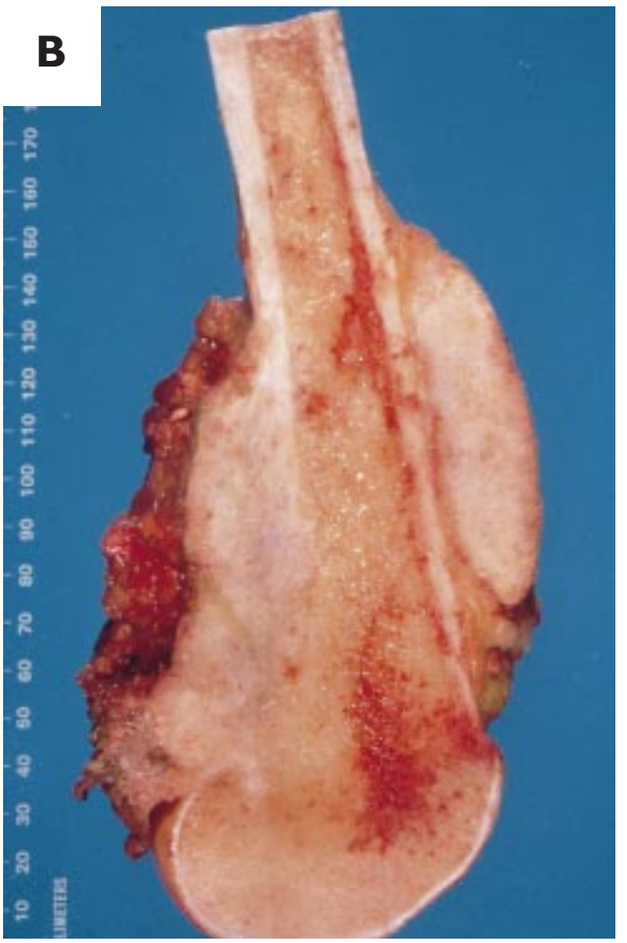


Figure 1.36 Parosteal osteosarcoma. Plain radiographs of the distal femur, (**A**) anteroposterior and (**B**) lateral views, show a dense, irregular, sclerotic lesion, attached to the posterior femoral cortex. The posterior aspect of the distal femur is a classical location for parosteal osteosarcomas and that diagnosis should be considered for any sclerotic lesion in that location.





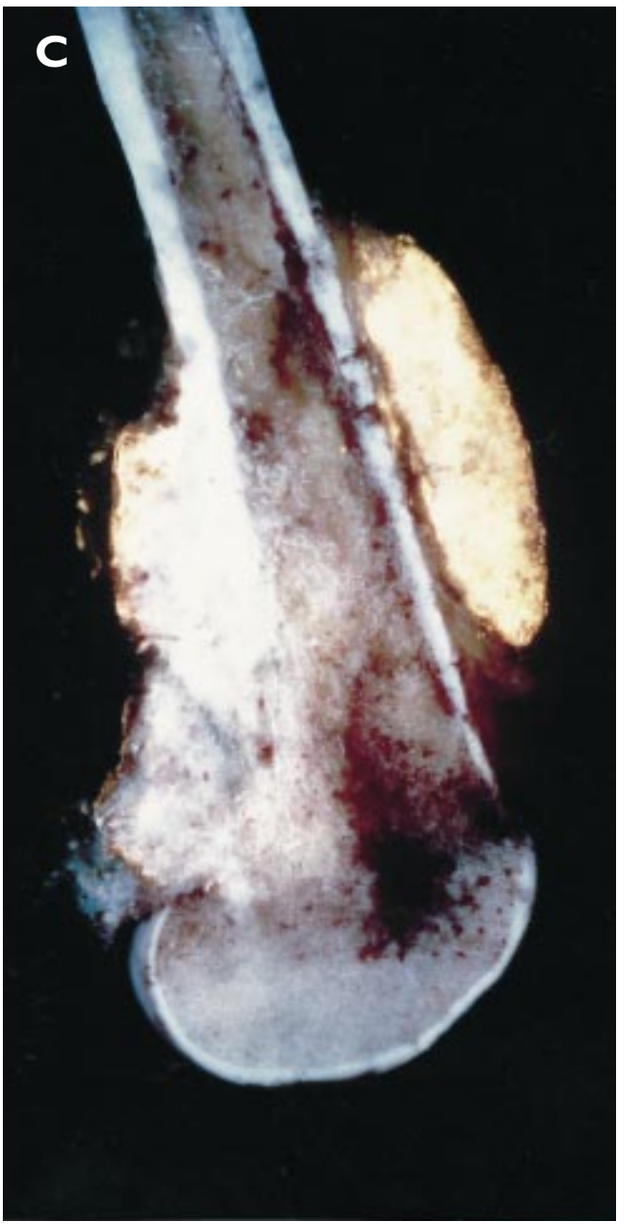


Figure 1.37 (**A**) The relation of parosteal osteosarcoma to the medullary canal is better viewed on CT that shows no tumor extension to the canal. In contrast to osteochondromas, the medullary canal of the bone is not contiguous with that of the tumor. (**B**) Surgical specimen, (**C**) illuminated with tetracycline fluorescence, demonstrates minimal medullary tumor extension through the posterior cortex. Medullary extension of parosteal osteosarcomas has no impact on survival; however, the extent of surgical resection must be changed to achieve wide margins.

spindle-cell component wherein a fine intercellular osteoid matrix is produced. Areas of malignant osteoid and chondroid can be seen to infiltrate into the cortical bone at the base of the neoplasm.

Small-cell Osteosarcoma

In small-cell osteosarcoma the neoplastic cells are round rather than spindle-shaped. The tumor consists of nests and sheets of small round cells separated by fibrous septae, a pattern reminiscent of Ewing's sarcoma. Occasionally, transition to spindle cells is noted. The cells have well-defined borders and a distinct rim of cytoplasm. The round nuclei disclose a delicate chromatin pattern. The presence of a characteristic lace-like osteoid matrix, often surrounding individual or small nests of cells, confirms the diagnosis (Figure 1.40). The recommendations for treatment vary. Radiation and chemotherapy are used at some institutions while others choose primary surgical ablation with neoadjuvant and/or adjuvant chemotherapy. Too few cases have been reported to make definitive recommendations.

Chondrosarcoma

Chondrosarcoma is the second most common primary bone sarcoma. It is a heterogeneous group of tumors whose basic neoplastic tissue is cartilaginous and shows no evidence of primary osteoid formation. It is subdivided in a variety of ways, including by histological grade and by whether it is primary or secondary or peripheral or central. The single most useful classification, both in terms of planning the surgical procedure and determining the prognosis, is histological grade. There are a few distinct, relatively rare, histological variants of chondrosarcoma. These include clear-cell, mesenchymal, and dedifferentiated chondrosarcoma.

Primary chondrosarcomas are not associated with a pre-existing lesion. Secondary chondrosarcomas are associated with a pre-existing chondroid lesion such as

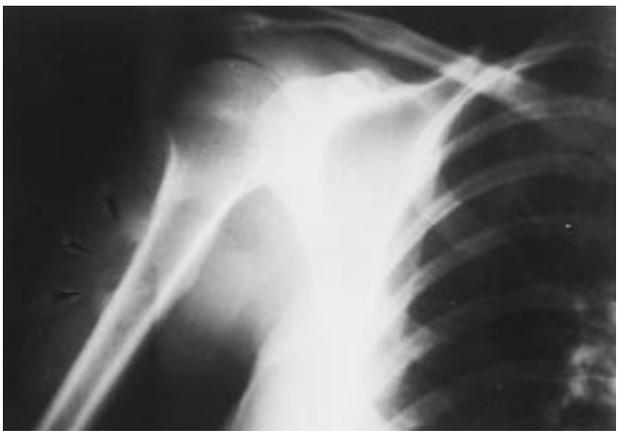


Figure 1.39 Periosteal osteosarcoma of the proximal humerus. Plain radiograph shows a typical "scooped-out" appearance of a cortical lesion (arrows). The center of the lesion has a lytic appearance because of its chondroblastic features.

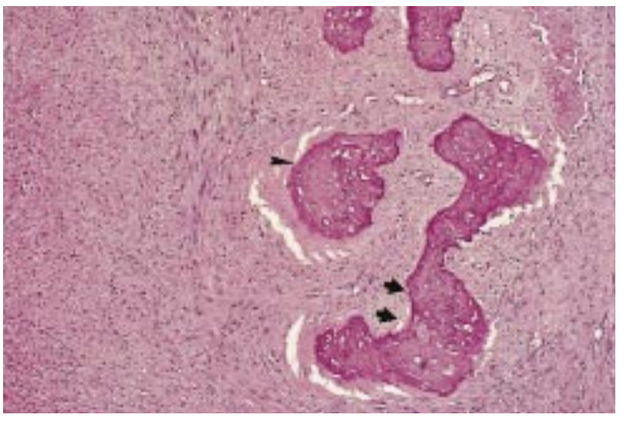


Figure 1.38 Parosteal osteosarcoma belongs to a group of bone surface sarcomas. It is usually a low-grade neoplasm. There are parallel or intersecting osseous trabeculae that may be either lamellar or woven-bone-type matrix. The intervening fibrocollagenous tissue is composed of bland, widely spaced fibroblastic cells.

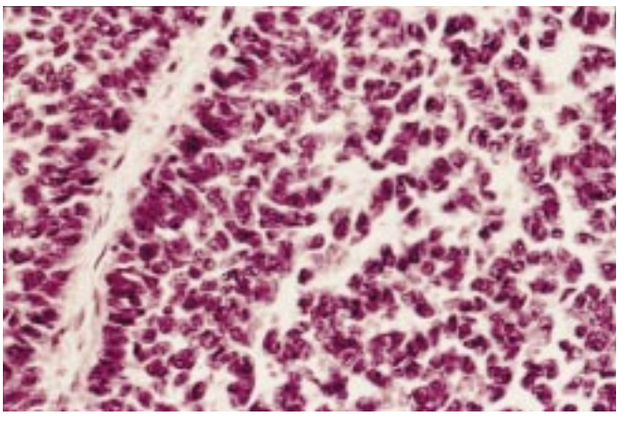


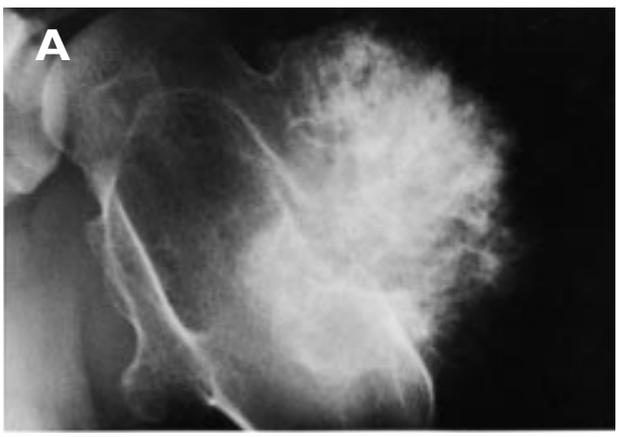
Figure 1.40 A rare variant of high-grade osteosarcoma is the so-called small-cell type. It is composed of small round blue cells, often with only sparse osteoid matrix to reveal the true diagnosis. Consequently extensive tumor sampling is necessary to differentiate it from Ewing's sarcoma, rhabdomyosarcoma, and lymphoma.

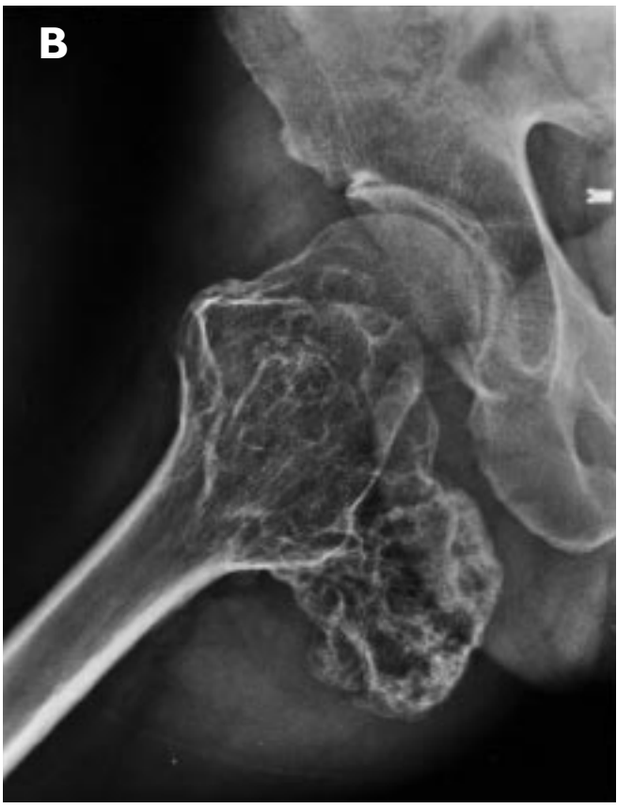
enchondroma, osteochondroma, chondroblastoma, chondromyxofibroma, periosteal chondroma, and synovial chondromatosis (Figures 1.41, 1.42). Central chondrosarcomas arise from within the medullary canal, and peripheral chondrosarcomas arise from the surface of the bone. Primary chondrosarcomas are virtually always central; secondary chondrosarcomas can be central or peripheral. The treatment and prognosis of primary and central secondary chondrosarcomas are identical, and that distinction is made only to clarify the underlying pathogenesis.

The majority of the "conventional" chondrosarcomas occur between the ages of 40 and 60. The most common sites are the pelvis, femur, and shoulder girdle. Pelvic chondrosarcomas are often large and present with referred pain to the lower back, sciatic pain, urinary symptoms from pressure on the bladder neck, unilateral swelling of the lower extremity due to iliac vein obstruction, or a painless pelvic mass. Central chondrosarcomas usually present with pain. Correlation of the clinical, radiographic, and histological data is essential for accurate diagnosis and evaluation of the aggressiveness and metastatic potential of a cartilage tumor. In general, proximal or axial location, skeletal maturity, and pain point toward malignancy. Radiologically, central chondrosarcoma presents as a well-defined lytic lesion with a narrow zone of transition and surrounding sclerosis with faint calcification or with no sclerotic rim at all (Figure 1.43). Endosteal scalloping is the key sign of malignancy (Figure 1.44).

Central chondrosarcoma is an expansive lesion that commonly causes cortical destruction and subsequent extension to the soft tissues. Typically, the tumor consists of fused, variably sized nodules that, on cut section, are composed of white–gray hyaline tissue, areas of calcification and even ossification. There may be focal myxoid areas (Figure 1.45).

The histological spectrum and the ease of diagnosis vary tremendously. High-grade tumors can be easily identified; in contrast, it may be exceedingly difficult to distinguish low-grade tumors from other benign cartilage tumors. When this diagnostic dilemma arises, correlation of the histological features with both the





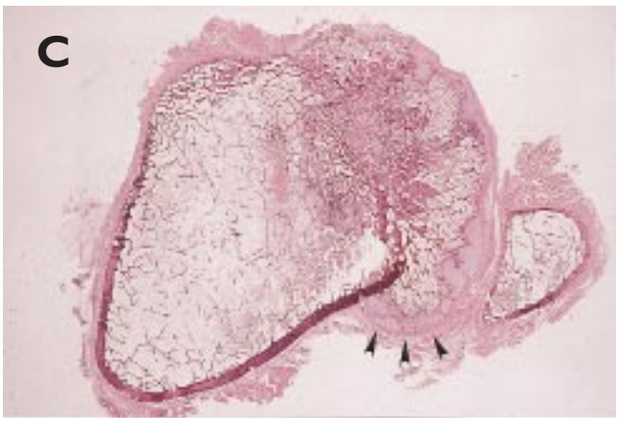


Figure 1.41 Secondary, low-grade chondrosarcomas, arising from osteochondromas of the (**A**) proximal humerus, (**B**) proximal femur, and (**C**) proximal tibia (arrows point to the region of the cartilage cap that has undergone malignant transformation).

clinical setting and the radiographic changes becomes extremely important. Chondrosarcomas are histologically graded as I (low), II (intermediate), or III (high); the majority are grade I or II. Grade I tumors are characterized by a slightly increased number of chondrocytes, set in lobular chondroid matrix. The cells contain hyperchromatic nuclei, occasionally binucleate forms that show minimal variation in size (Figure 1.46). Areas of markedly increased cellularity with more prominent pleomorphism and significant nuclear atypia define a grade II tumor. Myxoid matrix changes are indicative of a grade II tumor, or even higher. Grade III chondrosarcoma, which accounts for approximately 10% of all chondrosarcomas, discloses greater cellularity, often with spindle-cell areas, and prominent mitotic activity. Areas of myxoid changes are common, and the malignant chondrocytes may contain large, bizarre nuclei (Figure 1.47). Calcification and enchondral ossification can be observed in tumors of all grades; however, the presence of unequivocal malignant osteoid production, even in the face of chondrosarcomatous areas, dictates that the tumor be classified as osteosarcoma.

Resection is the treatment of choice for all chondrosarcomas. Low-grade chondrosarcomas or enchondrosarcomas may be treated by intralesional resection. Curettage, burr drilling, and, in most cases, the use of adjuvant liquid nitrogen should be considered. Intermediate- and high-grade chondrosarcomas, on the other hand, are treated surgically by wide resection. The use of neoadjuvant and adjuvant chemotherapy for chondrosarcomas is controversial. Low- and intermediate-grade chondrosarcomas respond poorly to chemotherapy. Although there are few data on the efficacy of chemotherapy in the treatment of high-grade chondrosarcomas, it should be considered in any young patient with a high-grade tumor. Radiation is recommended when anything other than wide excision is performed for a chondrosarcoma of any grade.

Ewing's Sarcoma

Ewing's sarcoma is a distinct round-cell sarcoma that occurs predominantly in the long bones of skeletally immature patients. The tumor is composed of undifferentiated, round, mesenchymal cells that are rich in glycogen and typically manifest a unique reciprocal chromosomal translocation, t(11;22)(q24;q12) that results in a chimeric protein, EWS/FLI-1. This translocation occurs in approximately 90% of these tumors. Very few other human tumors exhibit such consistent karyotypic alterations, which might play a significant role in their pathogenesis.

Ewing's sarcoma is the third most common primary bone sarcoma. It has a significant predilection for the White population; it is rare to diagnose Ewing's sarcoma in a Black patient. The peak incidence is the second decade of life. In very young patients, and in patients over the age of 30, a diagnosis of Ewing's sarcoma should be questioned, because it occurs so rarely in these age groups. Common differential diagnoses include metastatic neuroblastoma and acute leukemia (in the young age group) and small-cell carcinoma and large-cell lymphoma (in patients older than 30). With the advent of molecular probes and

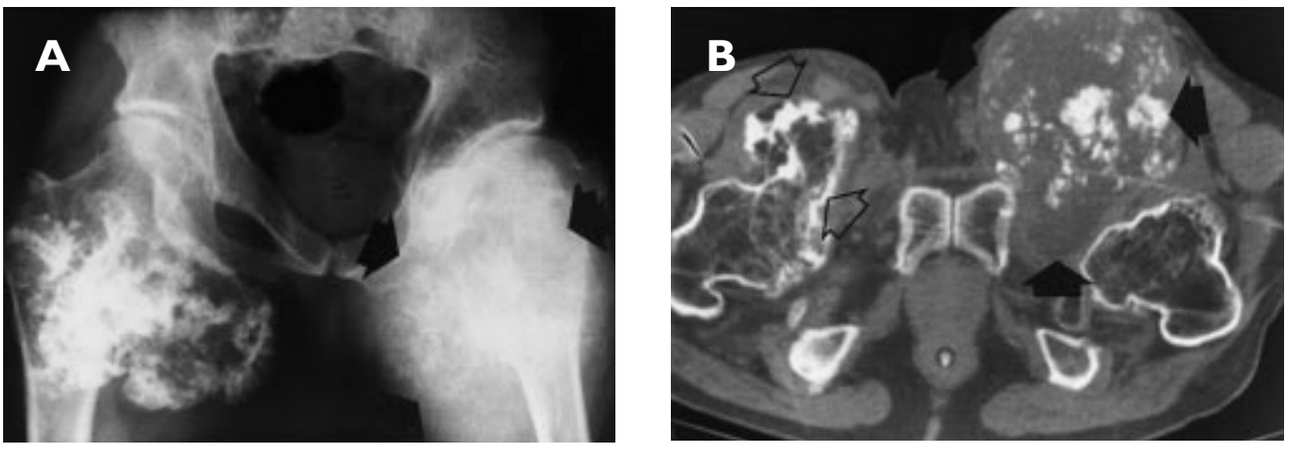


Figure 1.42 Secondary chondrosarcoma arising from the left proximal femur in a patient with multiple hereditary enchondromatosis. (**A**) Plain radiograph shows a large, benign-appearing enchondroma arising from the right proximal femur and a large, poorly demarcated cartilage tumor, arising from the left. (**B**) CT shows a marked difference between the two lesions. The destructive neoplastic tissue has completely replaced the enchondroma on the left, and it is almost fungating through the skin. The patient underwent modified hemipelvectomy and remains disease-free after more than 10 years of follow-up.

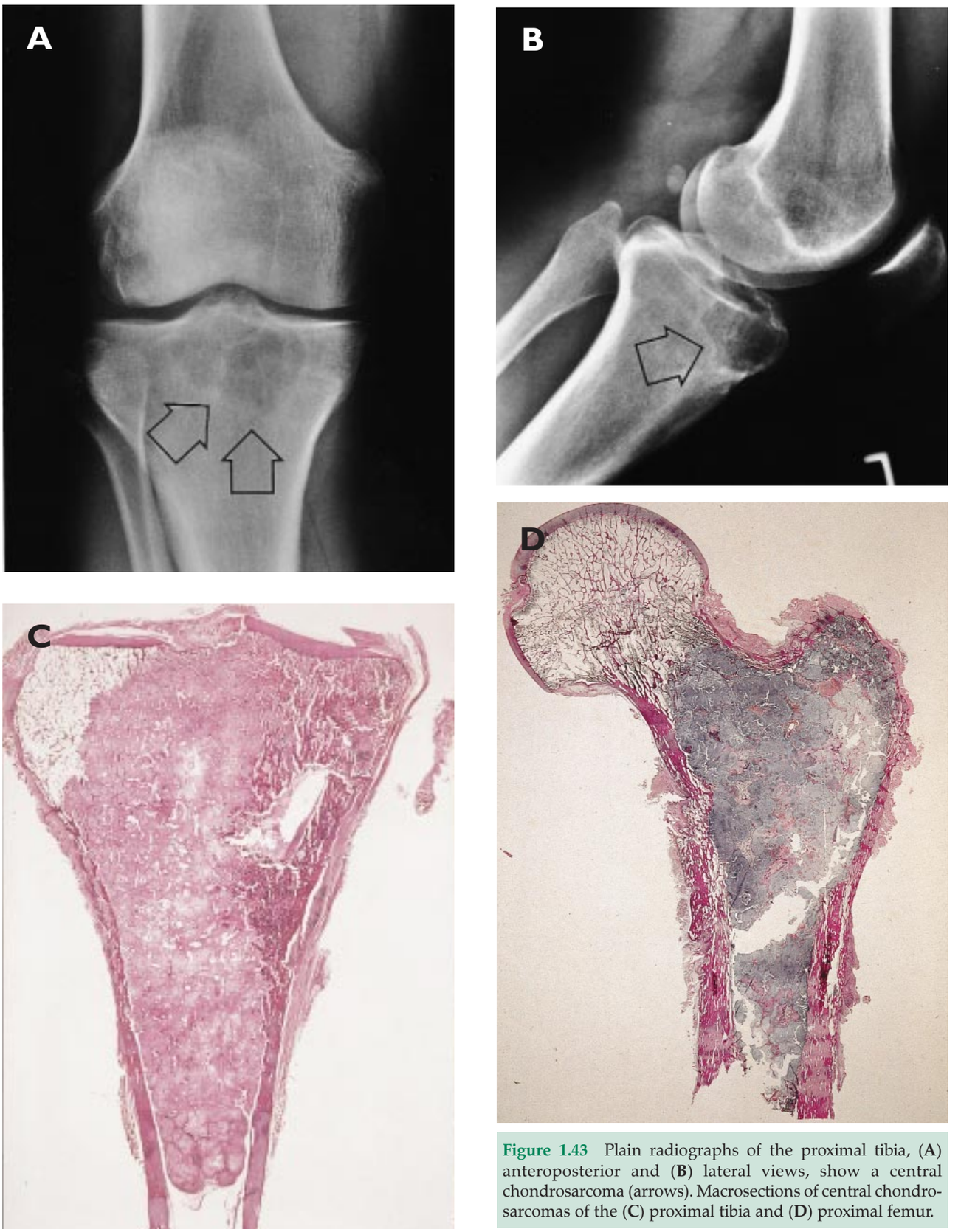


Figure 1.43 Plain radiographs of the proximal tibia, (**A**) anteroposterior and (**B**) lateral views, show a central chondrosarcoma (arrows). Macrosections of central chondrosarcomas of the (**C**) proximal tibia and (**D**) proximal femur.

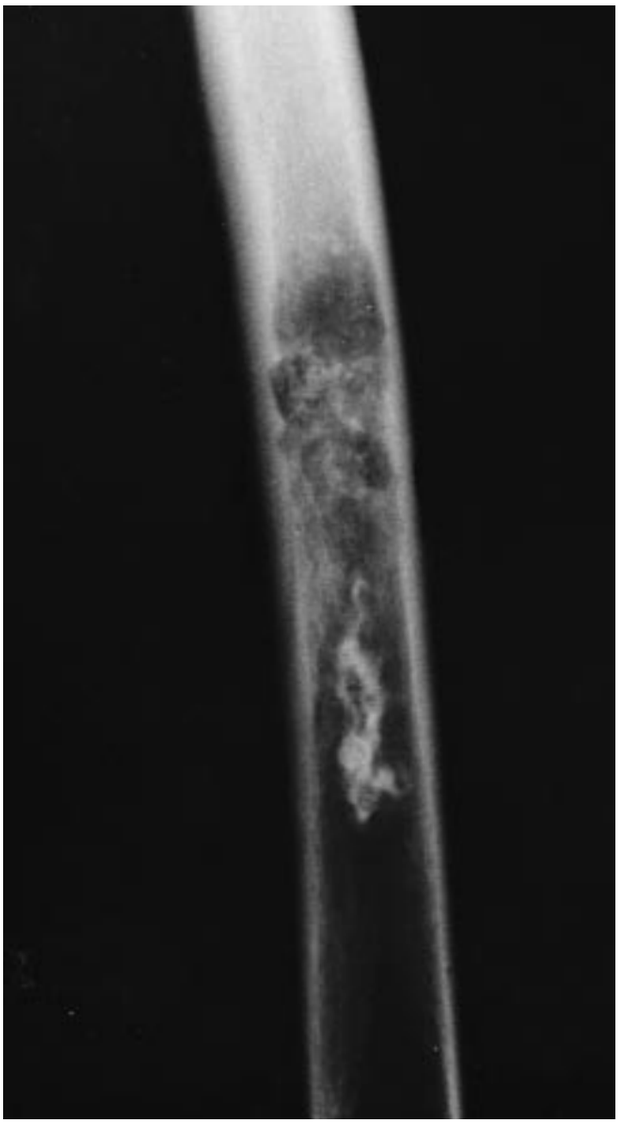


Figure 1.44 Plain radiograph of the femoral shaft, showing a central chondrosarcoma, presenting as a well-defined lytic lesion with a sharp transition zone, calcifications, and endosteal scalloping.

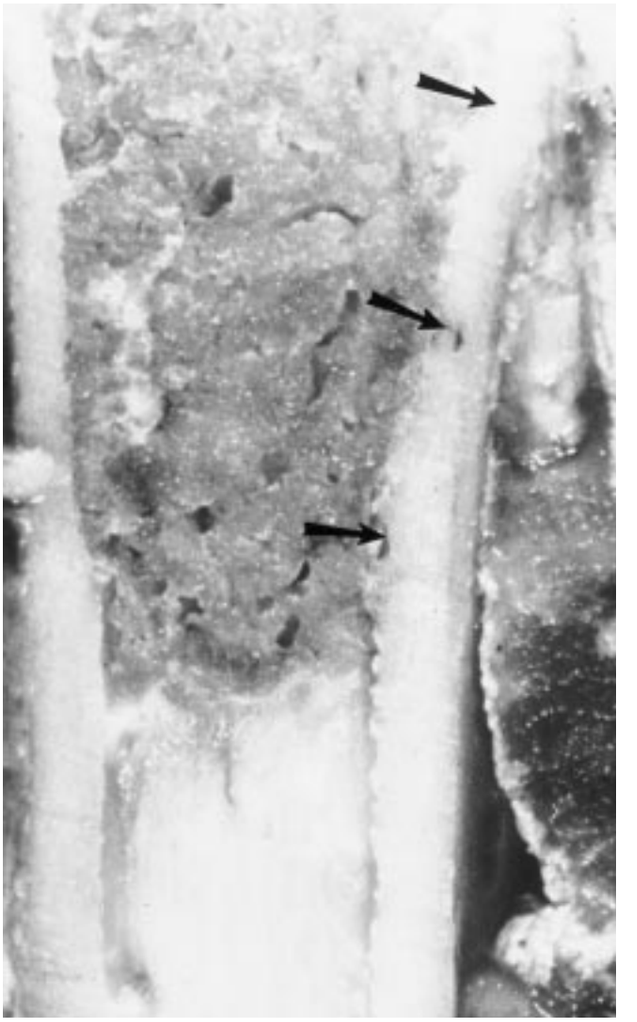


Figure 1.45 Cross-section of an intramedullary chondrosarcoma discloses its lobular architecture and translucent, hyaline-like matrix. Note the characteristic endosteal erosions (arrows).

immunohistochemical stains, differentiation among these tumors has become simpler.

Radiologically, Ewing's sarcoma presents as an ill-defined, permeative or focally moth-eaten, destructive intramedullary lesion that affects the diaphysis. Ewing's sarcomas are frequently lytic or have a mixed pattern; however, in approximately 40% of the cases a sclerotic appearance is dominant. Ewing's sarcomas are associated with a diffuse, irregular, and wavy periosteal reaction consisting of multiple parallel layers. That reaction has been the named "onion-skin appearance". The large majority of these tumors break through the cortex and have an extensive soft-tissue component (Figure 1.48). Histologically, the small round cells grow in solid, densely packed sheets and nests that fill the intertrabecular spaces. They have round, centrally located nuclei with indistinct cytoplasmic features. The nuclear chromatin is granular, and there are usually one to three clearly identifiable small- to intermediate-sized nucleoli (Figure 1.49). Often a biphasic pattern is simulated by the presence of "light" and "dark" cells (i.e., cells with an open chromatin structure and cells with dark condensed nuclei, respectively). The latter represent apoptotic tumor cells. The ratio between light

and dark cells varies from tumor to tumor and even in different areas of the same lesion.

Ewing's sarcoma is an extremely malignant tumor with high rates of metastatic disease and local recurrence following surgery alone. The 5-year survival rate has risen dramatically, from 5% to more than 60%, because of the use of multimodality treatment that includes chemotherapy, surgery, and radiation therapy in selected cases in which wide margins were not or could not be achieved at surgery. As with any high-grade primary bone sarcoma, the surgical aim is wide resection.

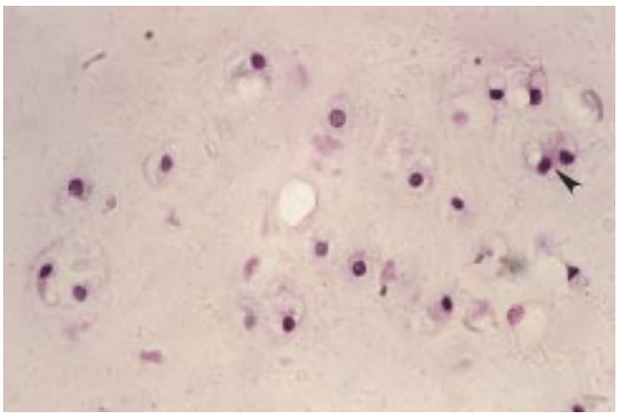


Figure 1.46 Low-grade chondrosarcoma maintains a lobular architecture. There is slightly increased cellularity, occasional binucleate cells and nuclear atypia. These cells are typically found in lacunae. The tumor tends to permeate between the normal osseous trabeculae.

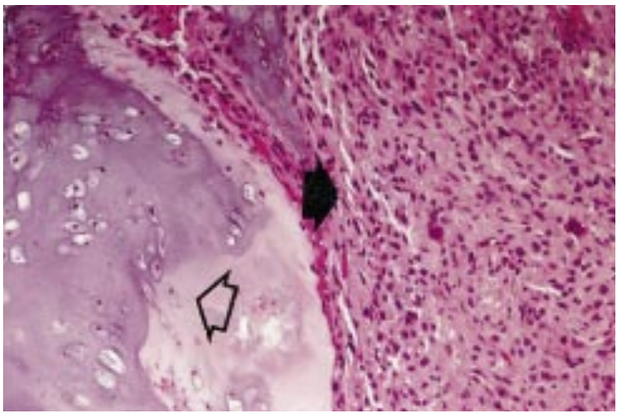


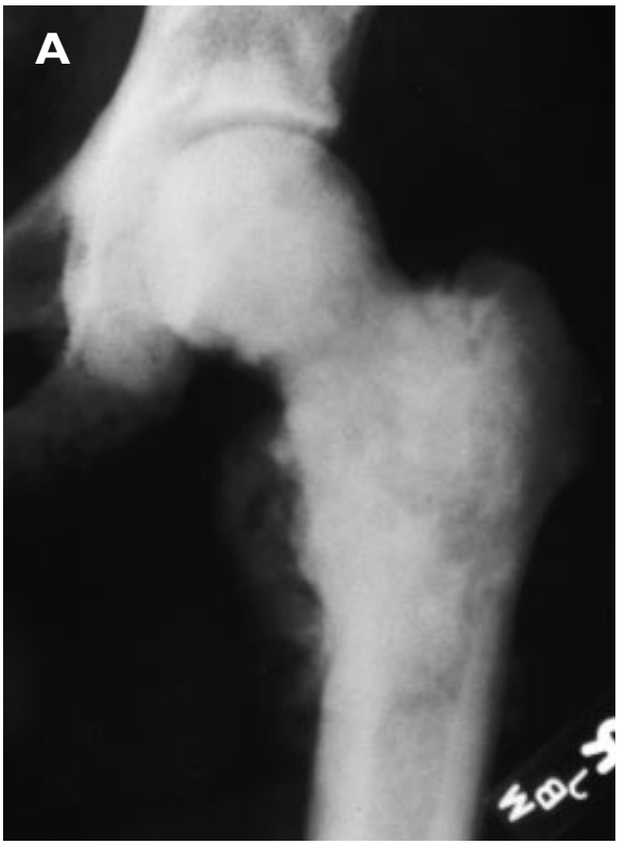
Figure 1.47 The juxtaposition of high-grade spindle sarcoma with lobules of low-grade chondrosarcoma is the hallmark of dedifferentiated chondrosarcoma. The spindle-cell component usually reveals features of malignant fibrous histiocytoma, osteosarcoma, or it may be unclassifiable. This neoplasm pursues an aggressive clinical course with very low long-term survival.

Giant-cell Tumor of Bone

Giant-cell tumor (GCT) is a locally aggressive tumor with a low metastatic potential. It occurs slightly more often in females than in males. The primary areas of involvement are the femoral condyles, tibial plateau, proximal humerus, and distal radius. The tumor is thought to arise in the metaphyseal–epiphyseal junction. Large tumors may extend into the metaphysis and, more rarely, into the diaphysis. GCT occasionally occurs in the vertebrae and sacrum. The descriptor "benign" was first applied to GCT to differentiate it from other bony malignancies that required amputation. The quotation marks were gradually removed and GCT is now considered a benign aggressive lesion. This descriptor is misleading, because 3% of GCTs are primarily malignant or will undergo malignant transformation either after radiation therapy or after several local recurrences. GCT is, therefore, considered by the authors to be a low-grade primary bone sarcoma and is treated as such.

Radiologically, GCTs are eccentric lytic lesions without matrix formation. They have well-defined borders and a very sharp transition between the tumor and the host bone. Periosteal elevation is rare unless a pathological fracture is present (Figure 1.50). Expanded and thinned cortex and, occasionally, cortical breakthrough and soft-tissue extension are common (Figure 1.51). Histologically, two basic cell types comprise the typical GCT. The stroma consists of polygonal to somewhat spindle cells containing central round nuclei. Typical mitotic figures, sometimes numerous, are often noted. Scattered diffusely throughout the stroma are benign osteoclast-like giant cells (Figure 1.52). Small foci of osteoid matrix, produced by the stromal cells, can be observed. Chondroid matrix never occurs. Extensive hemorrhage, pathologic fracture, or previous surgery can alter significantly the usual histologic picture of GCT and make it resemble a primary bone sarcoma. These events must be recognized at the time of histologic interpretation in order to prevent diagnostic errors. Cystic areas with surrounding hemosiderin pigment and xanthoma cells correspond to the grossly observed cyst. A malignant GCT contains areas of unequivocal sarcomatous transformation, usually typical of fibrosarcoma or osteosarcoma. The sarcomatous component is devoid of ordinary GCT features; thus, it is only by the recognition of foci of residual GCT, or by the confirmation of pre-existing GCT, that an accurate diagnosis of malignant GCT can be established.

Treatment of GCT is surgical removal. During the past several decades, surgeons have used the following: (1) curettage; (2) curettage and cytotoxic agents such as phenol, zinc chloride, alcohol, H_2O_2, or



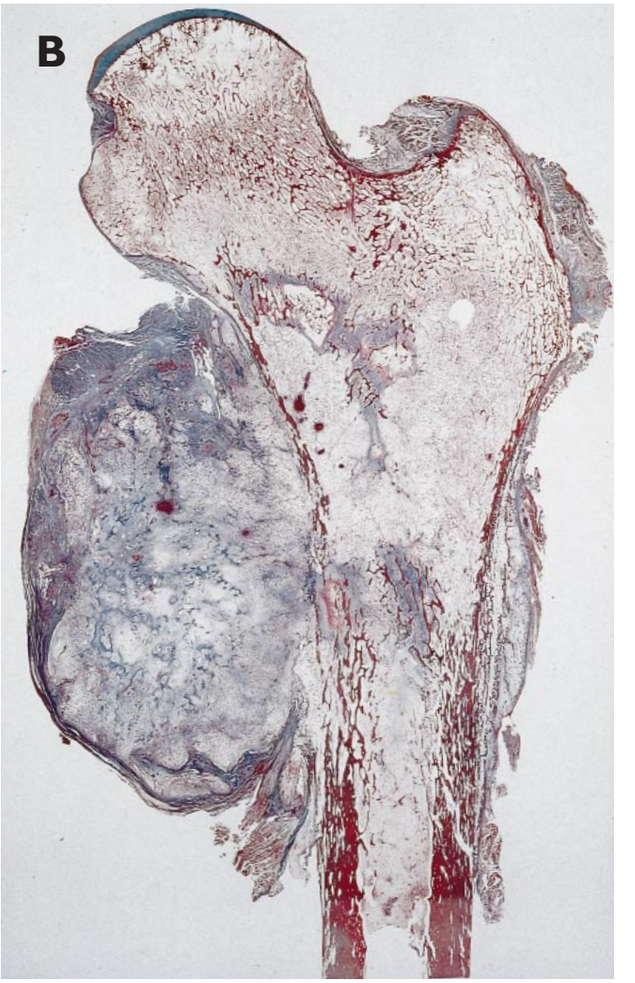


Figure 1.48 *(above and above right)* (**A**) Plain radiograph of the proximal femur, showing Ewing's sarcoma presenting as an ill-defined, permeative, destructive intramedullary diaphyseal lesion. Extensive periosteal reaction, cortical breakthrough, and soft-tissue extension are noted. (**B**) Macrosection of a proximal femur, showing Ewing's sarcoma with medial cortical breakthrough and soft-tissue extension.

carbolic acid; (3) curettage and a physical adjuvant (polymethylmethacrylate and cryosurgery); (4) primary resection; (5) radiation therapy; and (6) embolization, which is practiced in unresectable tumors. Simple curettage, with or without cytotoxic agents, has a significantly high rate of local recurrence of up to 57%. Treatment of GCT with curettage, burr drilling, and cryosurgery using application of liquid nitrogen to the tumor cavity has achieved a recurrence rate of less than 3% among patients who were primarily treated with that modality. This is among the lowest reported recurrence rate after any surgical intervention for GCT of bone. Cryosurgery is, therefore, recommended as a physical adjuvant to curettage in the treatment of GCTs of bone.

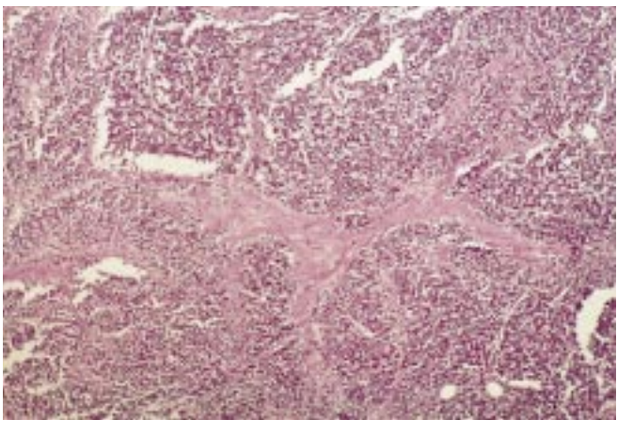
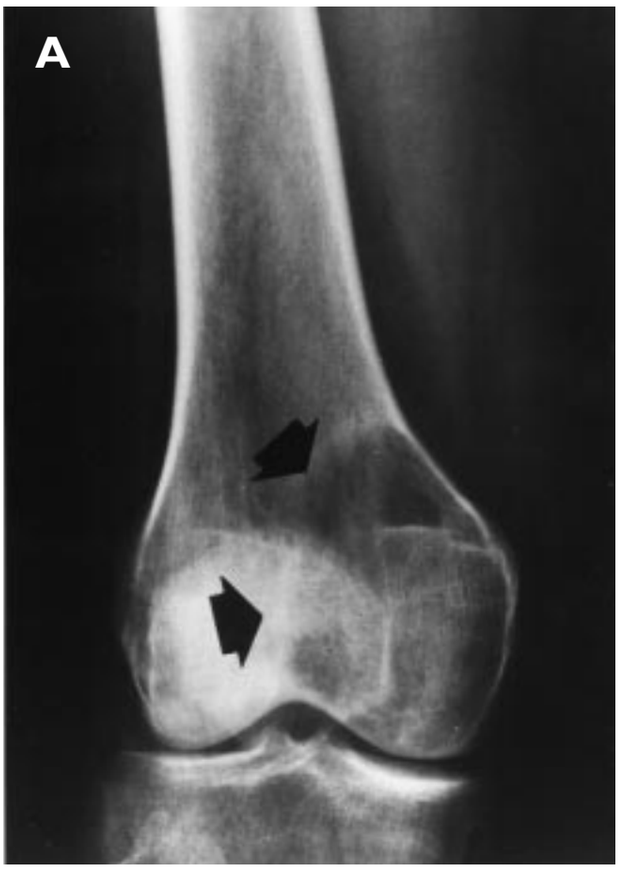
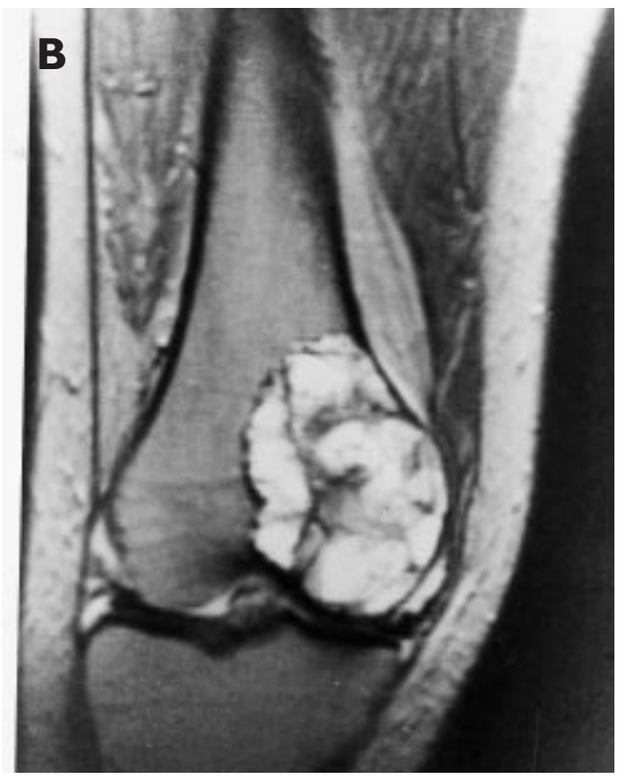


Figure 1.49 Ewing's sarcoma belongs to the ever-expanding category of small, round, blue-cell tumors. It is composed of round cells with scanty cytoplasm and round to oval nuclei. The nuclear chromatin tends to be fine homogeneous. Differentiation from the other members of the round-cell family may require the use of immunohistochemistry, electron microscopy, and cytogenetic and oncogene markers.





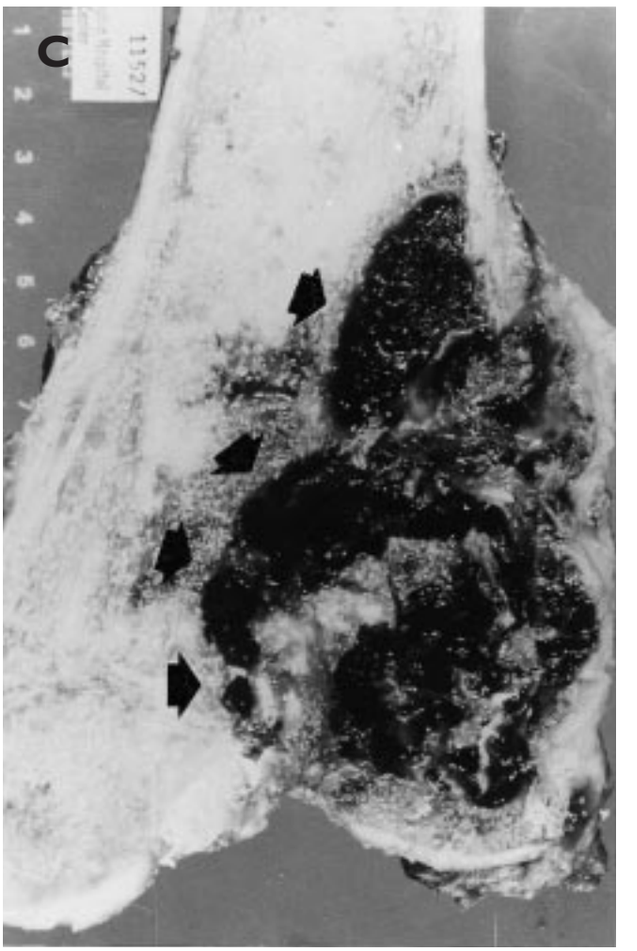


Figure 1.50 GCT of the distal femur. (**A**) Plain radiograph demonstrating a typical eccentric, osteolytic lesion with a thinned cortex without periosteal elevation. There is no evidence of matrix formation. (**B**) Corresponding T2-weighted image MRI and (**C**) gross specimen show hemorrhage with an expanded but intact cortex. The major radiological differential diagnosis is telangiectatic osteosarcoma, MFH, or fibrosarcoma of bone.

SUMMARY

The unique biological behavior of soft-tissue and bone sarcomas is reviewed. In addition to serving as the basis for the various staging systems, biological behavior dictates the surgical planning and the choice of adjuvant treatment modalities such as chemotherapy and radiation therapy. Although each soft-tissue and bone sarcoma is a distinct clinical and pathological entity, the principles of evaluation and management presented in this chapter apply to all.

Figure 1.51 Macrosection of the proximal femur, showing giant-cell tumor of bone with medial cortical breakthrough and extension to the surrounding soft-tissues.

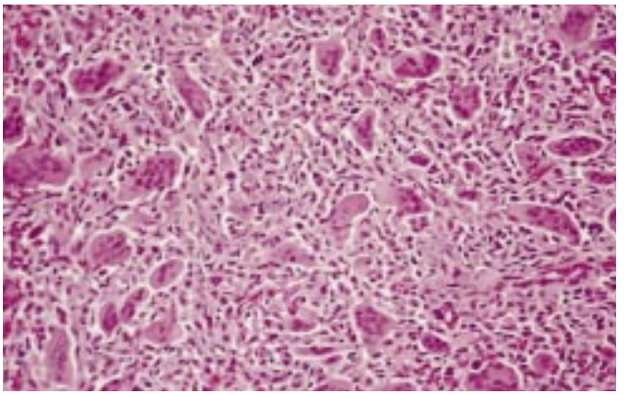


Figure 1.52 Giant cell tumor of bone reveals a rather uniform distribution of osteoclastic giant cells. The background contains round to polygonal histiocytic cells. Normal mitotic figures can be seen. Hemorrhage with aneurysmal bone cyst changes is not unusual.

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