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The Many Faces of Osteosarcoma[1]

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LEARNING OBJECTIVES

After reading this article and taking the test, the reader will be able to:

- Understand the radiologic spectrum of the various types of osteosarcoma.
- Describe the pathologic basis of the radiologic findings in osteosarcoma.
- Describe the important imaging features of osteosarcoma for diagnosis, staging, and preoperative planning.

Osteosarcoma is the most common primary malignant tumor of bone in adolescents and young adults. It accounts for approximately 15% of all primary bone tumors confirmed at biopsy. There are numerous types of primary osteosarcoma, including intramedullary (high grade, telangiectatic, low grade, small cell, osteosarcomatosis, and gnathic), surface (intracortical, parosteal, periosteal, and high-grade surface), and extraskeletal. Osteosarcoma may also occur as a secondary lesion in association with underlying benign conditions. The identification of osteoid matrix formation and aggressive characteristics usually allows prospective radiologic diagnosis of osteosarcoma. As with all bone tumors, differential diagnosis is best assessed with radiographs, whereas staging is performed with computed tomography or magnetic resonance imaging. Understanding and recognition of the variable appearances of the different varieties of osteosarcoma allow improved patient assessment and are vital for optimal clinical management including diagnosis, biopsy, staging, treatment, and follow-up.

■ INTRODUCTION

Osteosarcoma, which is sometimes referred to as osteogenic sarcoma, is the second most common primary malignant bone tumor, exceeded in frequency only by multiple myeloma. It is the most common primary malignant bone tumor to affect children and adolescents. Osteosarcoma accounts for approximately 15% of all primary bone tumors confirmed at biopsy (1-3).

Numerous types of osteosarcoma have been described, including intramedullary (high-grade, telangiectatic, low-grade, small cell, osteosarcomatosis, and gnathic tumors), surface (intracortical, parosteal, periosteal, and high-grade surface tumors), and extraskeletal. Osteosarcoma can also develop secondary to malignant transformation

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within a preexisting benign bone lesion, such as Paget disease, osteonecrosis, fibrous dysplasia, or chronic infection, or can arise in previously irradiated areas. These different types of osteosarcoma often have distinctive radiologic appearances that constitute the imaging spectrum for this malignant tumor.

In this article, we discuss the clinical characteristics, histologic features, various radiologic appearances, and treatment and prognosis for the different types of osteosarcoma.

■ PRIMARY INTRAMEDULLARY OSTEOSARCOMA

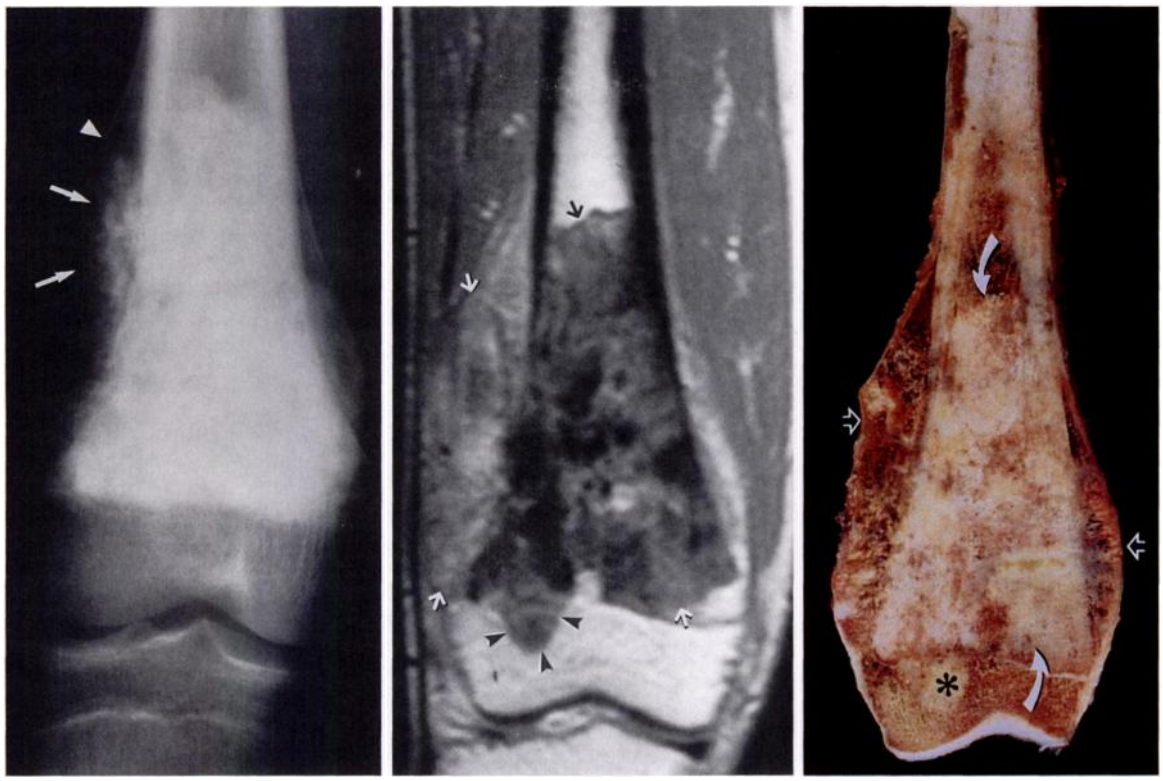
The vast majority of osteosarcomas arise in the medullary canal. The intramedullary form of osteosarcoma is defined as tumor that originates within the medullary canal and often involves the entire width of the bone. These lesions have been categorized into numerous types, largely on the basis of histologic appearance.

• High-Grade Intramedullary Osteosarcoma

The high-grade intramedullary variant of osteosarcoma accounts for approximately 75% of all lesions and is also referred to as central or conventional osteosarcoma (1–4). Most cases of high-grade intramedullary osteosarcoma are seen in patients in the 2nd and 3rd decades of life, with 75% of cases encountered in patients 15–25 years of age (1–4). Primary osteosarcoma occurring in patients younger than 6 years of age or older than 60 years of age is unusual. Osteosarcoma typically affects whites and males, with a male-to-female ratio of 1.5–2:1 (1–5). In fact, the incidence of osteosarcoma in black females is nearly five times less than that for white males (1–5). There have been isolated reports of a familial form of osteosarcoma, but the vast majority of cases occur as sporadic tumors (6). As with all types of osteosarcoma, the clinical manifestations are usually nonspecific, with pain and swelling being the most frequent symptoms. Patients commonly have a history of trauma, which brings the lesion to clinical attention. Pathologic fracture is seen in approximately 15%–20% of cases, either at presentation or during therapy (1–4).

High-grade intramedullary osteosarcoma most frequently affects long bones (70%–80% of cases), particularly about the knee (50%–55%) (1–5). Specifically, the femur is involved in 40%–45% of cases (Fig 1), the tibia in 16%–20% (Fig 2), and the humerus in 10%–15% (1–5). Involvement of the pelvis, fibula, facial bones, and spine is unusual, and the skull, clavicle, ribs, scapula, forearm, and small bones of the feet and hand are rarely affected. The majority (90%–95%) of high-grade intramedullary osteosarcomas arise in the metaphysis (1–5). Primary involvement of the diaphysis is seen in 2%–11% of cases, and these patients may have a longer duration of symptoms prior to diagnosis (Fig 3) (7,8). Although osteosarcoma with metaphyseal involvement often extends into the epiphysis (75%–88% of cases with open physis), initial manifestation within the epiphysis is very rare (<1%) (1–4,9,10).

Osteosarcoma is pathologically classified as a malignant mesenchymal neoplasm in which the tumor cells directly produce osteoid or immature bone (Fig 1d). Many lesions also contain other elements, particularly fibrous or



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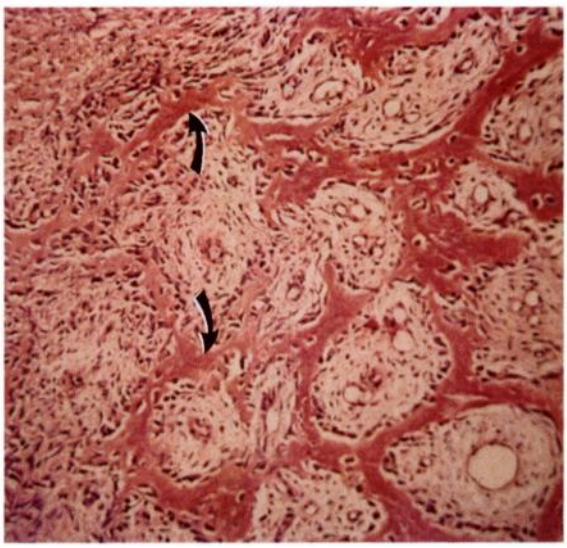

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Figure 1. High-grade intramedullary osteosarcoma of the distal femur in a 15-year-old boy with knee pain and swelling. **(a)** Anteroposterior radiograph of the knee shows extensive mineralized osteoid throughout the osteoblastic lesion, aggressive periosteal reaction (Codman triangle, arrowhead), and soft-tissue extension (arrows). **(b)** Coronal T1-weighted magnetic resonance (MR) image obtained after intravenous administration of contrast material reveals the extent of enhancing marrow and soft-tissue involvement (arrows) and transphyseal spread of tumor (arrowheads) (the latter feature was not seen on radiographs). **(c)** Photograph of the coronally sectioned gross specimen correlates well with the radiologic images, revealing the medullary (solid arrows) and soft-tissue (open arrows) extent as well as the transphyseal spread of tumor (*). **(d)** Photomicrograph (original magnification, ×150; hematoxylin-eosin stain) of the histologic specimen shows tumor cells that produced osteoid (arrows).

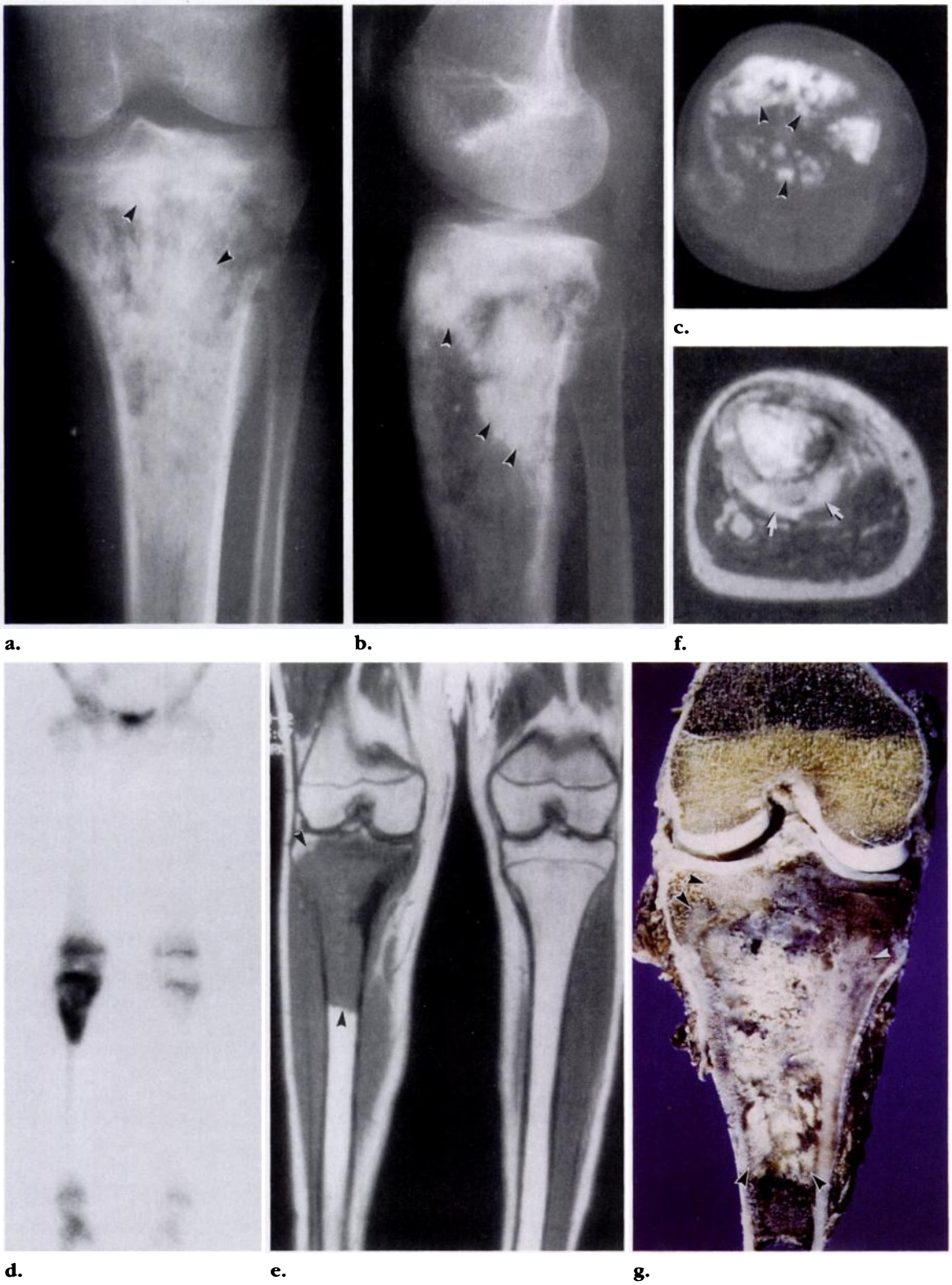
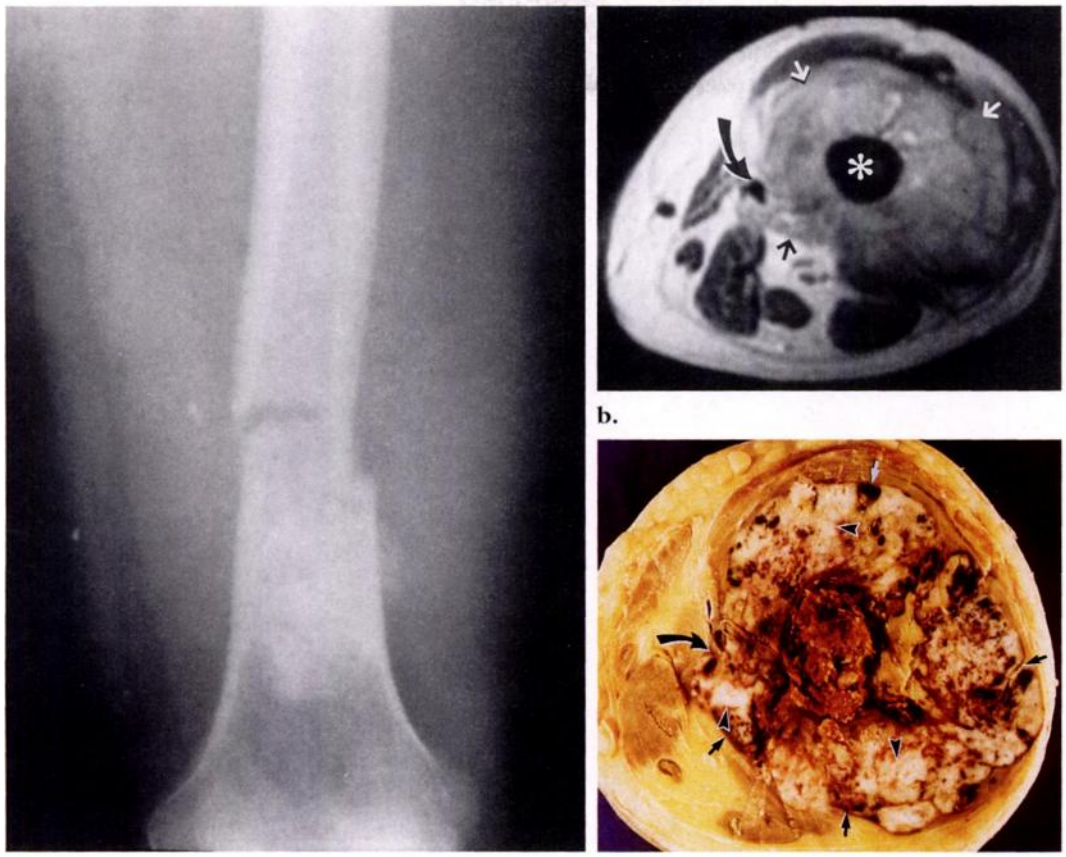


Figure 2. High-grade intramedullary osteosarcoma of the proximal tibia in a 14-year-old boy with knee pain. **(a–c)** Anteroposterior **(a)** and lateral **(b)** radiographs and computed tomographic (CT) scan **(c)** of the knee show a mixed lytic and blastic lesion with the sclerotic portion representing mineralized osteoid (arrowheads). **(d)** Bone scan shows marked increased uptake of radionuclide in the tibial lesion. Additional increased uptake resulting from hyperemia is seen in the distal femur and about the ankle. **(e–g)** Coronal T1-weighted **(e)** and axial T2-weighted **(f)** MR images and photograph of the coronally sectioned gross specimen **(g)** demonstrate the extent of intramedullary involvement including transphyseal spread (arrowheads) and a soft-tissue mass (arrows).



a. b. c.

Figure 3. High-grade intramedullary osteosarcoma of the distal femoral diaphysis in a 48-year-old man with a pathologic fracture after falling. **(a)** Anteroposterior radiograph of the distal femur shows a transverse fracture through the largely osteoblastic lesion. **(b, c)** Axial T2-weighted MR image **(b)** and photograph of the axially sectioned gross specimen **(c)** show marrow involvement (* in **b**) and a large circumferential soft-tissue mass (straight arrows) encasing the superficial femoral neurovascular bundle (curved arrow). Areas of whitish tissue in the gross specimen represent osteoid formation (arrowheads in **c**).

chondroid components, but, by convention even if only a minority of the intraosseous tumor is producing osteoid, it is designated as an osteosarcoma. Macroscopically, osteosarcoma is usually a large (5–10-cm) intraosseous tumor with frequent soft-tissue extension (Figs 1–3). Mineralized regions of osteoid and cartilage as well as hemorrhagic foci are frequent. Histologically, osteosarcoma has classically been divided into osteoblastic, chondroblastic, and fibroblastic varieties, depending on the predominant cell type present. Although many lesions have a mixed histologic appearance, the predominant pattern is osteoblastic in 50%–80% of osteosarcomas (Figs 1–3), fibroblastic-fibrohistocytic in 7%–25%, and chondroblastic in 5%–25% (1–4). At histologic analysis, reactive new bone from many reparative processes including fracture can resemble osteosarcoma, and correlation of histologic findings with radiologic results is essential to ensure correct diagnosis. As with other malignant neoplasms, osteosarcoma is graded from I to IV according to the degree of anaplasia, although the prognostic significance of this parameter is controversial.

As in all cases of a bone lesion, the primary evaluation of an osteosarcoma begins with radiographic assessment. High-grade intramedullary osteosarcomas are aggressive lesions with rapid doubling times (20–30 days) and therefore are often large (typically >6 cm) at the time of diagnosis. At radiographic examination, the vast majority (approximately 90%) of osteosarcomas demonstrate a variable amount of fluffy, cloudlike opacities within the lesion,

characteristic of osteoid matrix production (Figs 1-3) (1-4). Occasionally, the lesion may be completely blastic or lytic (fibroblastic type), but a mixed pattern of sclerosis and lucent areas is most frequent (Fig 2). High-grade intramedullary osteosarcoma tends to violate the cortex without expanding the osseous contours, a characteristic that reflects its aggressive pathologic behavior. This growth pattern is associated with aggressive periosteal reaction (Codman triangle, laminated, hair-on-end, or sunburst patterns) and soft-tissue masses in 80%-90% of cases (Figs 1-3) (1-4).

Most osteosarcomas have a radiographic appearance that poses little diagnostic dilemma. Additional imaging techniques such as CT, MR imaging, and bone scintigraphy are typically not needed to diagnose an osteosarcoma. However, unusual radiographic appearances can lead to delay in diagnosis and confusion with benign diseases (11). This situation is particularly likely when the osteosarcoma involves anatomically complex areas such as the pelvis and in the case of small lesions (often <5 cm and adjacent to the endosteum). In these cases, cross-sectional imaging may not only help confirm the presence of the lesion but also help identify mineralized matrix that is not appreciable at radiography. More important, these imaging modalities are vital in the preoperative assessment and staging of osteosarcoma (12-15).

At bone scintigraphy, marked uptake of radiotracer is seen on blood flow, blood pool, and delayed images (Fig 2d). Presently, however, the chief role of scintigraphy is in evaluating for distant metastases. Both osseous and extraosseous metastatic disease may be detected.

The aggressive characteristics of high-grade intramedullary osteosarcoma, both intraosseous and soft-tissue components, are also well seen at CT (11,15-17). Nonmineralized portions of tumor are usually of soft-tissue attenuation and replace the normal low attenuation of fatty marrow (Fig 2c). Chondroblastic components may be of low attenuation on CT scans, reflecting a higher water content. Areas of central hemorrhage or necrosis, which also have low attenuation, are frequent. Osteoid matrix production is easily appreciated in both intraosseous and soft-tissue tumor components as areas of very high attenuation (Fig 2c). The chief advantage of CT is its ability to demonstrate small areas of mineralized matrix that might not be detected with MR imaging in predominantly lytic lesions.

MR imaging has become the cross-sectional imaging modality of choice for preoperative evaluation and staging of osteosarcoma because of its superior contrast resolution and multiplanar capabilities (9,10,12-14). Tumor is seen primarily as areas of intermediate signal intensity on T1-weighted images and as areas of high signal intensity replacing the normal marrow on T2-weighted images (Figs 1, 2). Areas of low signal intensity on both T1- and T2-weighted MR images are frequent and represent mineralized matrix (Figs 1, 2). Foci of central hemorrhage (which have high signal intensity with all MR pulse sequences) and necrosis (which has low signal intensity on T1-weighted images and high signal intensity on T2-weighted MR images) are common in both the intraosseous and soft-tissue tumor components. As with other musculoskeletal neoplasms, accurate assessment of the intra- and extraosseous extent of osteosarcoma is critical in directing limb-salvage procedures. Multiplanar imaging allows assessment of the following vital information: (*a*) anatomic landmarks for the extent of marrow (Fig 4) and soft-tissue involvement and its relationship to surrounding structures, (*b*) invasion of the epiphysis, (*c*) involvement of the joint or neurovascular structures (Fig 3), and (*d*) identification of areas of viable tumor and mineralized matrix to improve biopsy accuracy (10,12,13-17). The true margins of a lesion, whether intra- or extraosseous, may be obscured by perilesional edema on MR images obtained with water-sensitive pulse sequences (inversion recovery and T2 weighting with fat suppression).

The physis has long been considered by radiologists as a barrier to tumor growth. However, pathologic evaluation has shown that approximately 75%-88% of metaphyseal osteosarcomas extend through the open physis into the epiphysis (Figs 1, 2) (18,19). Epiphyseal exten-

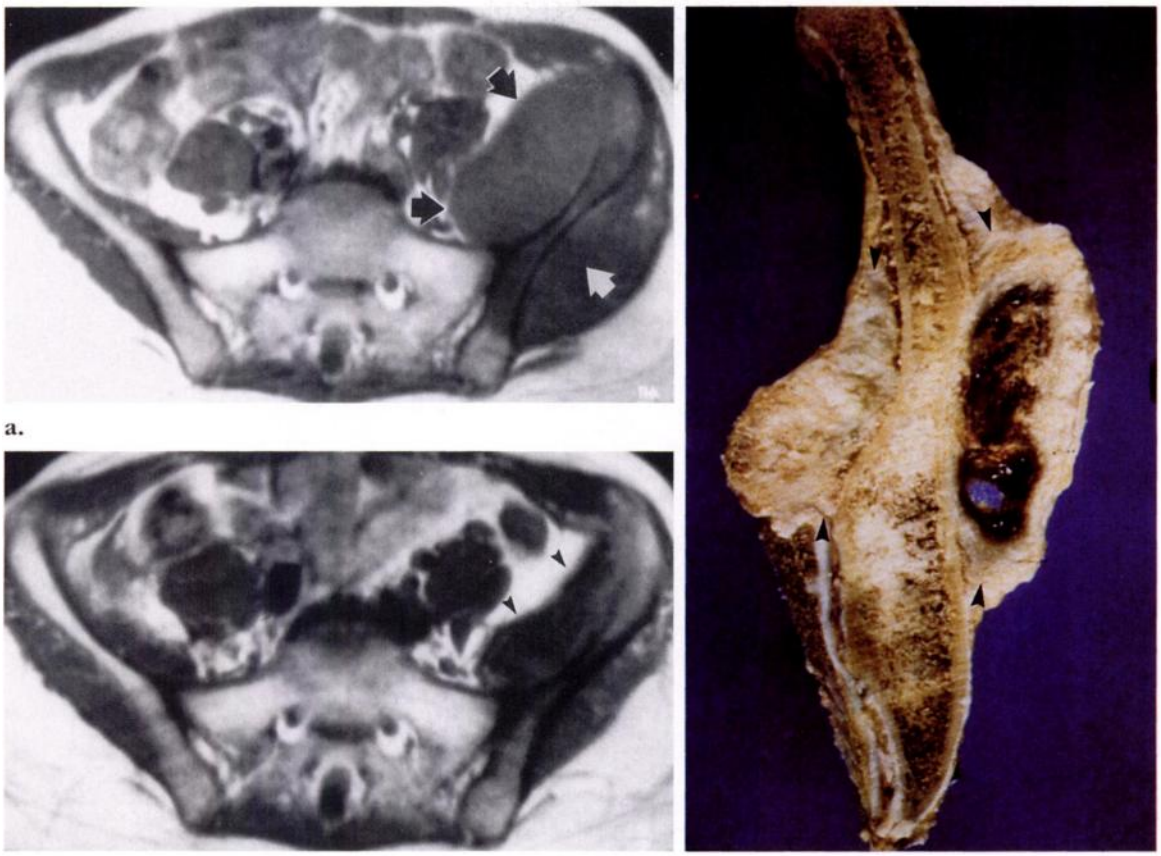


Figure 4. High-grade intramedullary osteosarcoma of the iliac bone in a 26-year-old woman treated with chemotherapy. **(a)** Axial T1-weighted MR image obtained at diagnosis (before chemotherapy) reveals a tumor with large intra- and extraosseous components (arrows). **(b, c)** On the axial T1-weighted MR image **(b)** and photograph of the sagittally sectioned gross specimen **(c)** obtained after 6 months of chemotherapy and subsequent surgical resection, there is marked shrinkage of the tumor (arrowheads).

sion may be identified at radiography in as few as 17% of osteosarcomas, although this pattern of spread is easily recognized on coronal or sagittal MR images in 80% of metaphyseal osteosarcomas (Figs 1, 2) (9,10,18,19). Joint involvement (most frequently in the knee) can be seen in 19%–24% of osteosarcomas, although the synovium is rarely violated (14). On MR images, joint involvement is suggested when the hyaline cartilage is penetrated or more commonly when tumor extends through the capsule, such as into the suprapatellar bursa anteriorly or posteriorly to encompass the cruciate ligaments (14). Fat-suppressed T1-weighted gadolinium-enhanced images are helpful for delineating extension of tumor into the joint, but enhancing synovium may mimic tumor spread. Although invasion of the joint is unlikely in the absence of an effusion, the presence of an effusion does not allow an accurate prediction of intraarticular invasion.

Treatment of high-grade intramedullary osteosarcoma consists of chemotherapy, followed by wide surgical resection and limb salvage (amputation if salvage is not possible). Clinical outcome of osteosarcoma has dramatically improved over the past 25 years.

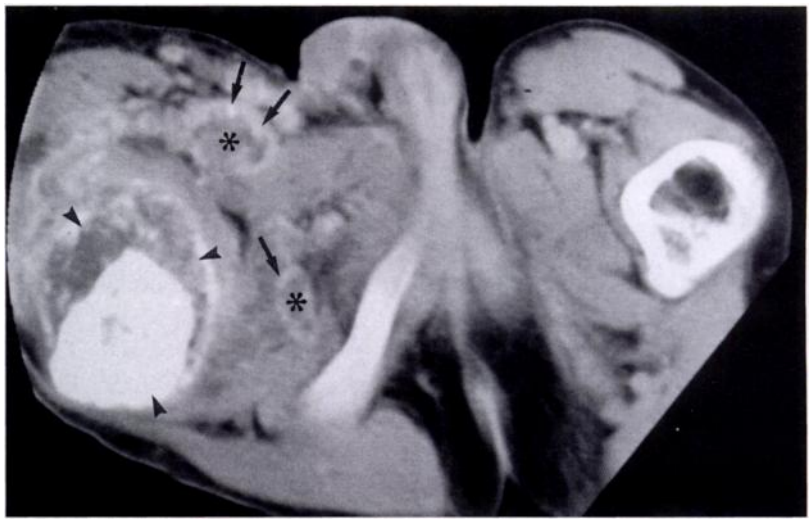


Figure 5. Regional lymph node metastases in a 17-year-old boy with high-grade intramedullary osteosarcoma of the proximal femur. Axial CT scan shows both intra- and extraosseous components (arrowheads) of a femoral lesion. Inguinal and obturator lymph node metastases (*) are also seen with small foci of mineralization (arrows).

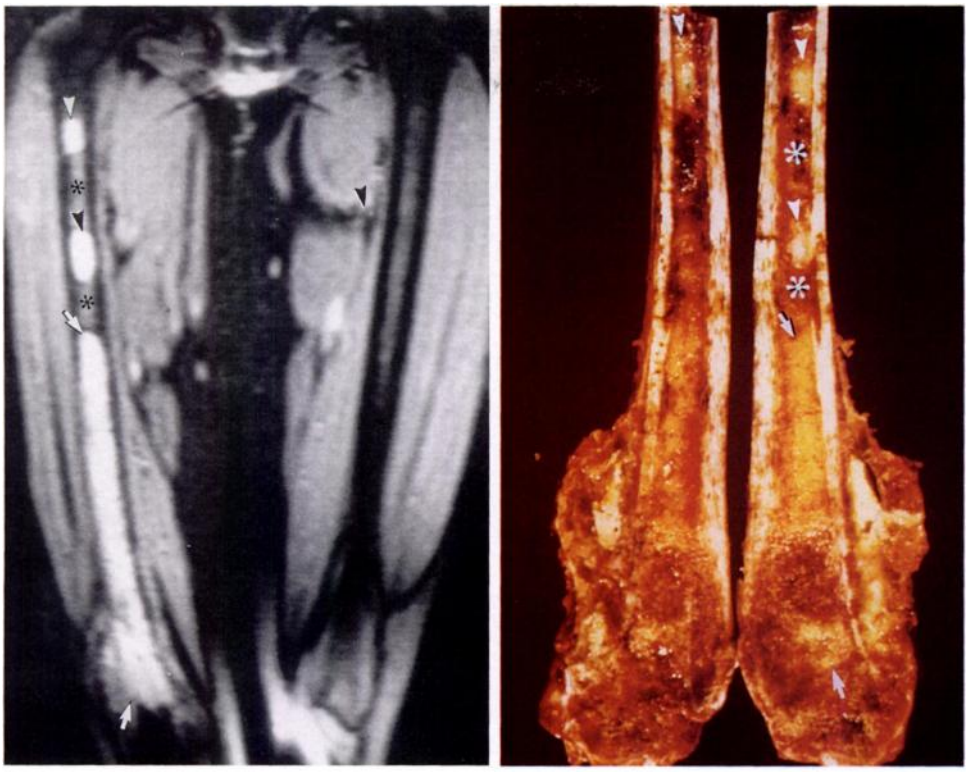
Currently, the 5-year survival rate is 60%–80% (20–22). Tumor size (>10 cm) and advanced stage at presentation are important factors that significantly worsen patient outcome. Evidence of pathologic fracture increases the likelihood of local recurrence. Perhaps the most important determinant of long-term survival of patients with osteosarcoma is tumor response to chemotherapy. Patients with greater than 90% tumor necrosis after therapy have a statistically significant higher likelihood of long-term survival (Fig 4) (20–26). Ongoing research is being conducted to quantitate the degree of tumor necrosis radiologically by using various modalities including Doppler sonography, bone scintigraphy, and MR imaging (dynamic subtraction studies) before therapy (22–26).

Metastatic disease most commonly affects the lungs, bones, and regional and distant lymph nodes (Fig 5). Ossification of pulmonary and lymph node metastases may be apparent on radiographs, CT scans, MR images, and bone scans (Fig 5). Pulmonary metastases may be associated with spontaneous pneumothorax, and, when few in number, are often treated aggressively with local resection.

Skip metastases, which are foci of tumor within the marrow of the affected bone that are distinctly separate from the primary lesion, occur in 1%–25% of high-grade intramedullary osteosarcomas (Fig 6) (27,28). In our experience, the lower percentage is much more reflective of the true prevalence of this phenomenon. The identification of skip metastases is important not only for defining the extent of disease but also prognostically since the decrement in 5-year survival for patients with skip metastases is similar to that for patients with distant metastatic disease. Skip metastases are best identified with MR imaging, and a study of the entire length of an affected bone should be performed at the time of primary evaluation (Fig 6).

• Telangiectatic Osteosarcoma

Telangiectatic osteosarcoma is an uncommon histopathologic subtype that represents 4.5%–11% of all osteosarcomas (1–4,29–36). Telangiectatic osteosarcoma was first described by Paget (37) in 1854 as a medullary cancer of bone with extensive development of vessels



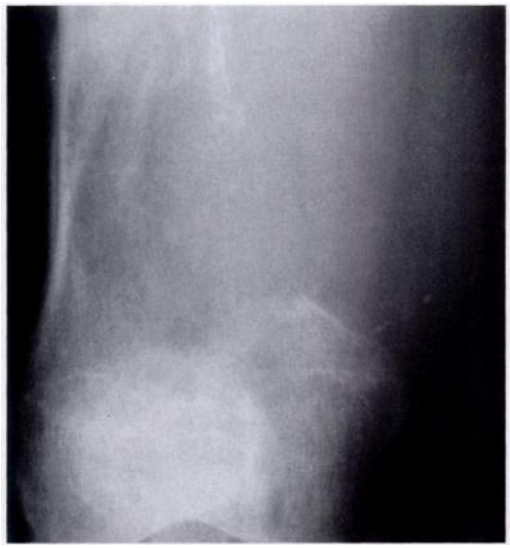
a. b.

Figure 6. Skip metastases in a 12-year-old girl with a high-grade intramedullary osteosarcoma in the distal femur. Coronal inversion recovery MR image **(a)** and photograph of the sagittally sectioned gross specimen **(b)** show a large primary focus of tumor (arrows) and two more proximally located skip lesions (arrowheads) separated from the primary region of osteosarcoma by normal marrow (*). All tumor foci show high signal intensity on MR images.

and blood-filled cysts. In 1903, Gaylord (38) used the term *malignant bone aneurysm* to describe a hemorrhagic, poorly ossified telangiectatic osteosarcoma. In 1922, Ewing (39) was the first to classify telangiectatic osteosarcoma as a distinct histologic variant, characterized by a malignant osteoid-forming sarcoma of bone with large blood-filled vascular channels.

In the largest series to date (124 patients) reported by Huvos and colleagues (30), 60% of the patients with telangiectatic osteosarcoma were male and 40% were female, with an age range of 3–67 years and a mean age of 20 years. The most frequently affected sites were around the knee, representing 62% of cases (48% in the distal femur, 14% in the proximal tibia), with the proximal humerus being the third most frequent site (16% of cases) (30). Similar to conventional osteosarcoma, telangiectatic osteosarcoma uncommonly occurs in the pelvis, scapula, ribs, and skull, and 90% of the lesions are metaphyseal. Telangiectatic osteosarcoma can also be a secondary lesion (arising in association with fibrous dysplasia or Paget disease or following radiation therapy). Two cases of extraskeletal telangiectatic osteosarcoma have also been reported (3,30).

Telangiectatic osteosarcoma must, by definition, have hemorrhagic, cystic, or necrotic spaces (both grossly and microscopically apparent) that occupy more than 90% of the lesion before therapy (Fig 7) (1–4,30,32). At histologic analysis, the cystic cavities are composed of cavernous vessels and blood-filled



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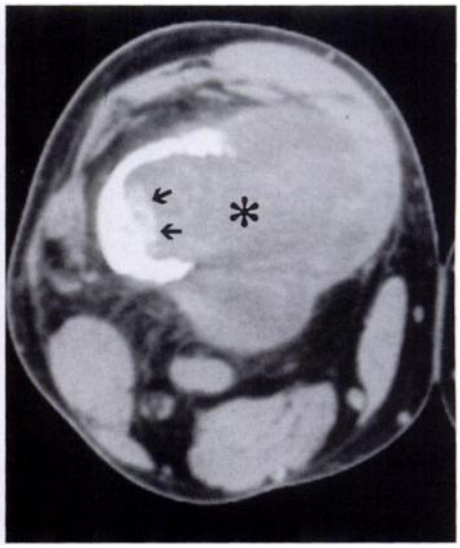

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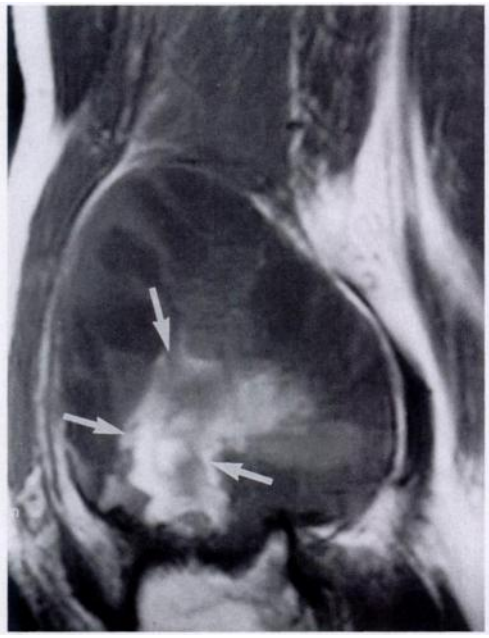

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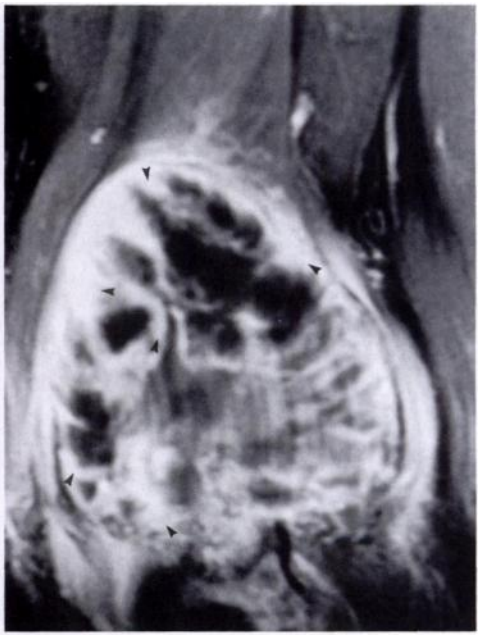

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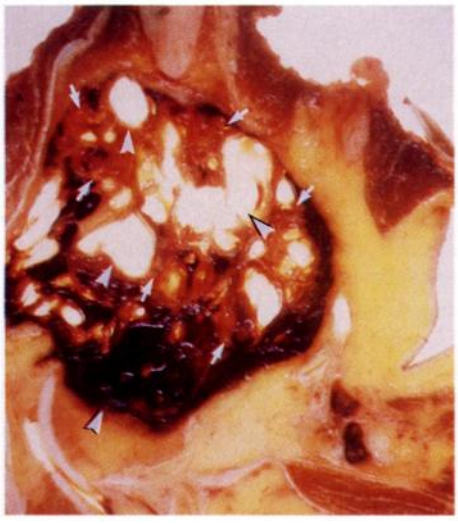

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◀ **Figure 7.** Telangiectatic osteosarcoma of the distal femur in a 56-year-old man. **(a)** Anteroposterior radiograph of the femur shows a markedly expansile, aggressive, geographic lytic lesion with a wide zone of transition; medial cortical destruction; and no definite evidence of osteoid formation. **(b)** Axial CT scan reveals similar findings, with subtle nodular osteoid mineralization peripherally (arrows) and predominantly low attenuation centrally (*). **(c, d)** Sagittal T1-weighted unenhanced **(c)** and gadolinium-enhanced **(d)** MR images demonstrate the largely hemorrhagic or cystic composition of the lesion, which has prominent areas of high signal intensity (arrows in **c**) before contrast material enhancement. The viable neoplastic cells enhance in a nodular pattern along the rim and septations (arrowheads in **d**). **(e)** Photograph of a sagittally sectioned gross specimen shows hemorrhagic or cystic spaces (arrowheads) and surrounding rinds of viable neoplastic cells (arrows), findings that correlate with the radiologic appearance.

spaces lined with osteoclastic giant cells. Viable malignant spindle cells with osteoid formation are seen in the periphery of the lesion and in the septations surrounding these cavities. In larger lesions, areas of bone expansion, cortical destruction, and soft-tissue extension are common.

Telangiectatic osteosarcoma most commonly shows geographic bone destruction with a wide zone of transition (Fig 7a). In our experience, more aggressive osseous involvement with a predominant permeative or moth-eaten pattern is rare, although others have reported that this appearance is the most frequent manifestation (33,36). Marked aneurysmal expansion of bone (Fig 7a) is not infrequent (19% of cases), and metaphyseal lesions often extend into the epiphysis (87%) (33). Aggressive periosteal reaction, cortical destruction, associated soft-tissue mass, and pathologic fracture are common features.

The cystic consistency of telangiectatic osteosarcoma is reflected by its radiologic appearance. Bone scintigraphy often demonstrates peripheral increased radionuclide uptake with central photopenia (donut sign). The CT attenuation of the central portion of the lesion is often lower than that of muscle (Fig 7b). This central region also shows very high signal intensity on T2-weighted MR images. At MR imaging, hemorrhage is frequently observed as areas of high signal intensity, regardless of MR pulse sequence (Fig 7c). Fluid-fluid levels may be seen on CT or MR images, but they are best demonstrated by MR imaging in approximately 90% of cases (33).

The lesion most often confused with telangiectatic osteosarcoma is aneurysmal bone cyst. The most important feature for distinguishing telangiectatic osteosarcoma from aneurysmal bone cyst, in our opinion, is that the former has a rim of viable tumor cells about the cystic spaces that manifests as solid tissue along the lesion periphery and septations. This viable tissue shows enhancement (often nodular) on CT or MR images after intravenous administration of contrast material (Fig 7d). Subtle osteoid formation is also frequently seen in the viable peripheral tumor (intraosseous or soft-tissue component). CT is the best modality for detecting osteoid, which appears as nodular calcific foci. In our recent review of 31 telangiectatic osteosarcomas, these foci were seen on CT scans in 81% of cases, compared with 61% in which they were seen on radiographs (Fig 7b) (33). In our opinion, these features are not seen in aneurysmal bone cyst, which allows distinction from telangiectatic osteosarcoma in most cases.

Treatment of telangiectatic osteosarcoma is similar to that of conventional osteosarcoma and consists of chemotherapy followed by wide surgical resection and limb salvage or amputation. Results of biopsy of these lesions can be misleading if specimens of only hemorrhagic tissue are obtained. Imaging can be helpful in directing the biopsy sampling to the peripheral regions of viable tumor. Prognosis of telangiectatic osteosarcoma was previously thought to be much worse than that of conventional osteosarcoma (32). However, newer studies suggest that the 5-year survival rate of telangiectatic osteosarcoma (68%) is similar to that of conventional osteosarcoma (30,34,35,37).

• Low-Grade Intraosseous Osteosarcoma

Low-grade intraosseous osteosarcoma is an unusual variant of conventional osteosarcoma and represents 4%–5% of all lesions; it has also been referred to as well-differentiated or sclerosing osteosarcoma (1–4,40–44). It occurs most frequently in patients in the 3rd decade of life (1 decade older than conventional osteosarcoma), but patients have a wide age range, and unlike high-grade intramedullary osteosarcoma, men and women are affected equally (40–44). Patients usually present after a protracted clinical course with nonspecific symptoms, but they may be asymptomatic, with the lesion being discovered incidentally. The sites of low-grade intraosseous osteosarcoma are similar to those of conventional osteosarcoma: The femur and tibia (about the knee) are most frequently affected, and the lesion most commonly involves the metaphysis, often with extension into the epiphysis (44).

Unlike conventional osteosarcoma, low-grade intraosseous osteosarcomas frequently have radiologic and pathologic characteristics that simulate a benign process, including fibrous dysplasia, nonossifying fibroma, chondrosarcoma, and chondromyxoid fibroma (38, 44). At radiologic examination, the lesion may show well-defined margins, a sclerotic rim, prominent internal trabeculation, and diffuse sclerosis, and it may cause expansile remodeling of bone (Fig 8) (43). However, radiologic evidence of a more aggressive process, such as associated bone lysis, focally indistinct margins, cortical destruction, soft-tissue mass, and, uncommonly, periosteal reaction (Fig 8), is apparent even if it is subtle (43).

Low-grade intraosseous osteosarcoma usually behaves as a locally aggressive tumor, with multiple recurrences developing after intralesional resection. Time to recurrence is variable and can be delayed up to 20 years after surgery (40,44). In general, for those patients whose lesions are initially treated by wide excision with limb salvage, the long-term prognosis is excellent. In 15% of incompletely resected lesions, Kurt et al (44) found transformation of the initial lesion into a higher-grade osteosarcoma, resulting in an increased prevalence of metastatic disease and a poor prognosis. Rarely, low-grade intraosseous osteosarcoma may manifest as a more aggressive tumor with significant metastatic potential.

• Small Cell Osteosarcoma

Small cell osteosarcoma is a distinct subtype of conventional osteosarcoma composed of small round blue cells. It was first described by Sim and coworkers in 1979 (45) and is estimated to represent between 1% and 4% of osteosarcomas (1–4,46–51). Males and females are affected equally, and the age distribution of patients and tumor locations are similar to those for conventional osteosarcoma, with the distal femur being the most common site. The lesions are typically metaphyseal with frequent extension into the epiphysis, but 15% of cases involve the diaphysis (45–48).

The pathologic characteristics of this tumor are similar to those of Ewing sarcoma: Both lesions are composed of small round blue cells. However, small cell osteosarcoma lacks the cellular uniformity seen in Ewing sarcoma and consistently produces osteoid (fine and reticular) (45,48). Ewing sarcoma does not produce osteoid, even though at times reactive bone formation may be encountered and histologic differentiation can be difficult. In this setting, molecular and immunohistochemical markers are very helpful in distinguishing between the two tumors.

At radiologic examination, small cell osteosarcoma typically manifests as a predominantly permeative, lytic medullary lesion with cortical breakthrough, aggressive periosteal reaction,

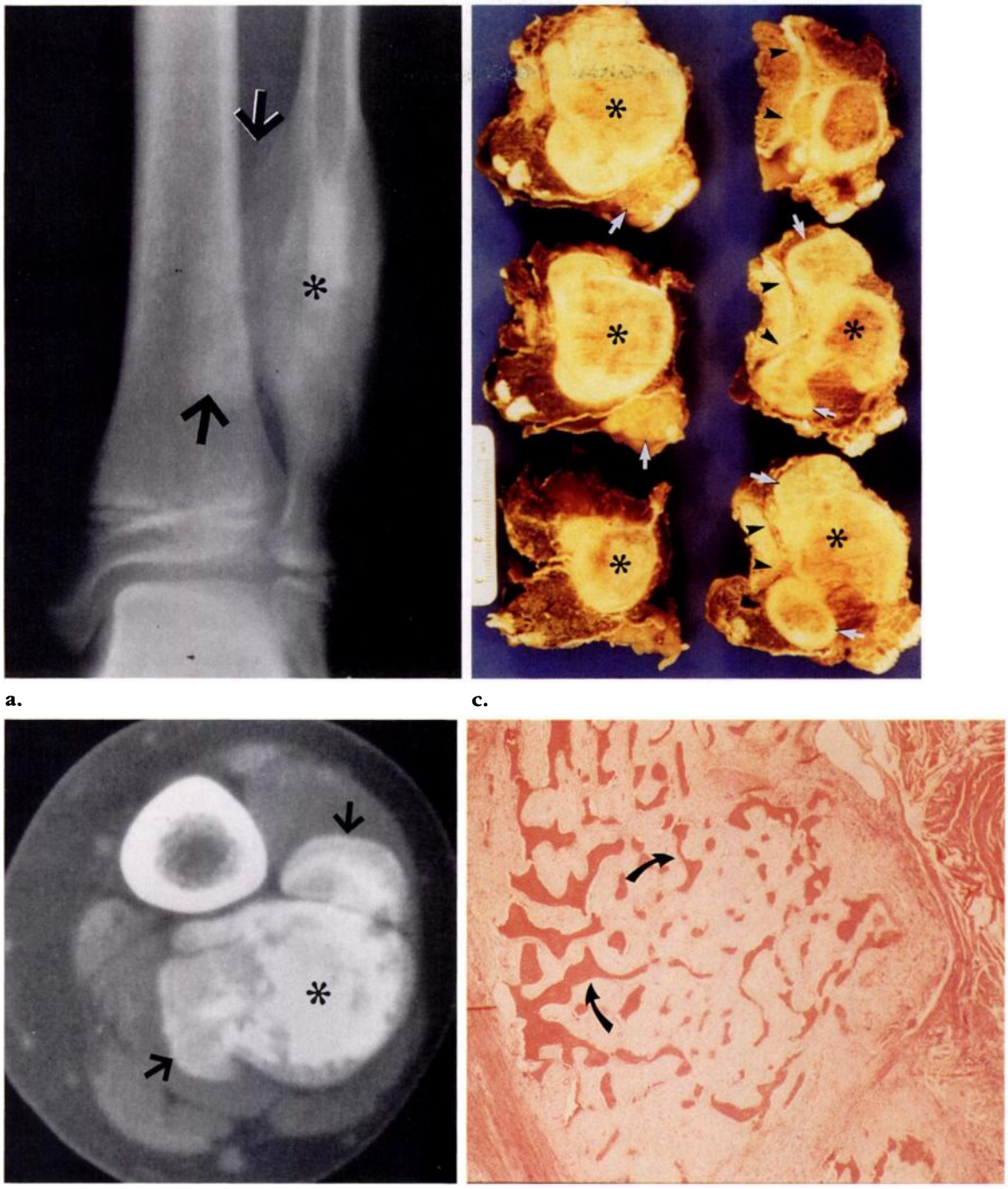
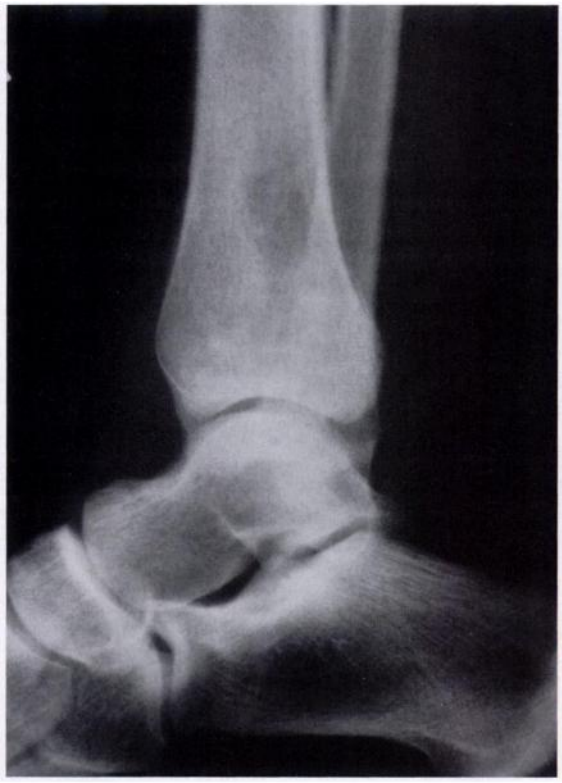
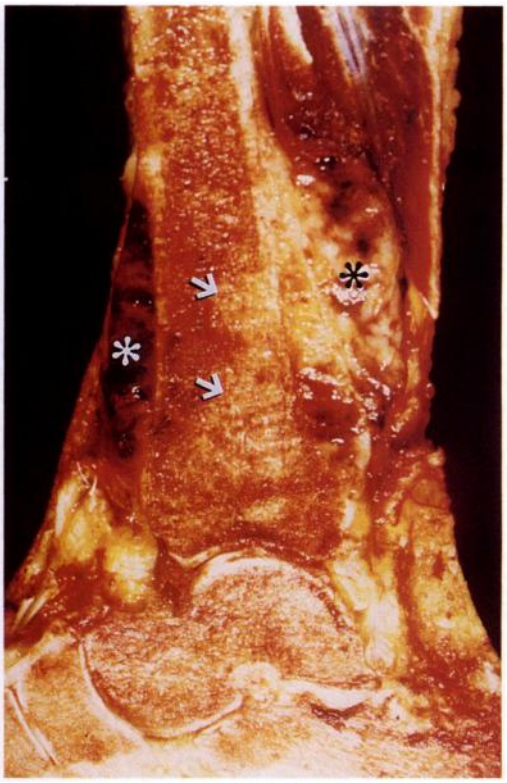


Figure 8. Low-grade intraosseous osteosarcoma of the distal fibula in an 11-year-old boy with slowly progressive pain. **(a, b)** Anteroposterior radiograph **(a)** and CT scan **(b)** of the ankle show an expansile sclerotic lesion of the fibular diaphysis (*) that is reminiscent of the ground-glass appearance of fibrous dysplasia, although a soft-tissue mass is also apparent (arrows). **(c)** Photograph of several axial sections of the gross specimen shows the expansile osteoblastic intramedullary fibular lesion (*), soft-tissue component (arrows), and margin of the resected tibia (arrowheads). **(d)** Photomicrograph (original magnification, ×200; hematoxylin-eosin stain) of the histologic specimen reveals relatively bland osteoid with a fibrous dysplasia–like appearance (arrows).

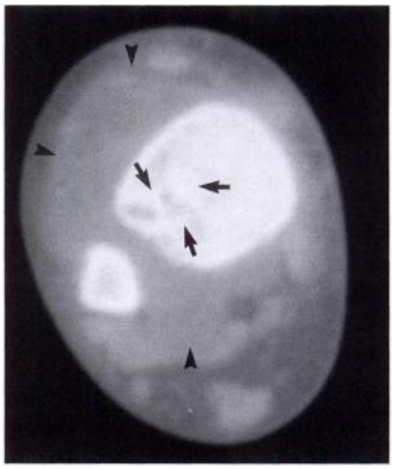


a.



c.

Figure 9. Small cell osteosarcoma of the distal tibia in an 18-year-old woman with a history of increasing pain. **(a)** Lateral radiograph shows aggressive (permeative or moth-eaten) bone destruction without obvious osteoid formation. **(b)** Axial CT scan reveals a mixed lytic and sclerotic lesion infiltrating the marrow space (arrows indicate osteoid component) and a large soft-tissue mass (arrowheads). **(c)** Photograph of the sagittally sectioned gross specimen also shows marrow (arrows) and soft-tissue (*) involvement.

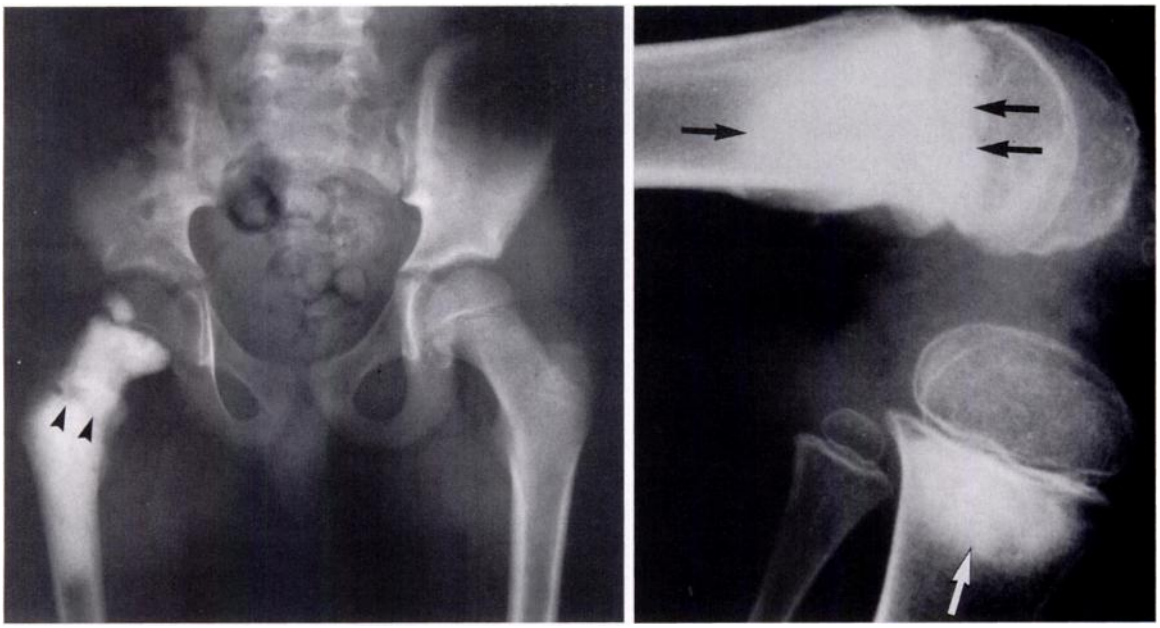


b.

and an associated soft-tissue mass (Fig 9) (45,47,48). Osteoid matrix, although subtle, is usually apparent in the medullary or soft-tissue component and is best detected with CT (Fig 9) (46,48). Occasionally, lesions are entirely lytic with no radiologic evidence of osteoid matrix to suggest the diagnosis of osteosarcoma. The prognosis for patients with small cell osteosarcoma is extremely poor, regardless of treatment.

• Osteosarcomatosis

Osteosarcomatosis (also known as multifocal osteosarcoma or multiple sclerotic osteosarcoma) describes a condition in which there are multiple intraosseous foci of osteosarcoma at the time of presentation. Previous investigators have considered osteosarcomatosis to repre-



a. b.

Figure 10. Osteosarcomatosis in a 4-year-old boy. **(a)** Anteroposterior radiograph of the pelvis shows a dominant sclerotic lesion in the proximal femur with a pathologic fracture (arrowheads). **(b)** Lateral radiograph of the knee reveals multifocal metaphyseal involvement (arrows). There was extensive pulmonary metastatic disease (not shown) that led to rapid death.

sent multicentric primary neoplasia (52–54). More recently, it has been suggested that all cases of osteosarcomatosis represent rapidly progressive metastatic disease (55,56). Although the latter concept is controversial, we strongly endorse it based on the identification of a radiographically dominant (large) lesion in most patients with otherwise symmetric disease and the presence of pulmonary metastases on chest CT scans in the majority of these patients.

Osteosarcomatosis is uncommon, accounting for approximately 3%–4% of osteosarcoma cases (1–4,52–59). However, multifocal skeletal involvement by osteosarcoma has been found at autopsy in as many as 48% of patients (55,56). Although osteosarcomatosis has been believed to be more common in skeletally immature patients, Hopper et al (56) reported a series of 29 cases in which there were relatively equal numbers of skeletally immature and mature patients. Younger, skeletally immature patients tend to have rapidly appearing, usually symmetric, sclerotic lesions, whereas older patients typically have fewer, asymmetric sclerotic lesions. In 97% of those cases reported by Hopper et al (56), a radiologically dominant skeletal tumor was seen.

The radiologic features of the dominant lesion include ill-defined margins, aggressive periosteal reaction, cortical disruption, and adjacent soft-tissue extension (52–59). Although lesions usually contain cloudlike osteoid (Fig 10), purely lytic dominant lesions may be seen. In contrast to the dominant lesions, the secondary foci are often smaller, more sclerotic, and better defined and lack periosteal reaction or cortical destruction (Fig 10b).

The existence of multifocal skeletal osteosarcoma substantially alters both treatment and anticipated prognosis. In a report on nine patients, Parham et al (59) noted that despite intensive chemotherapy all patients died, with a mean survival of 12 months (range, 6–37 months).

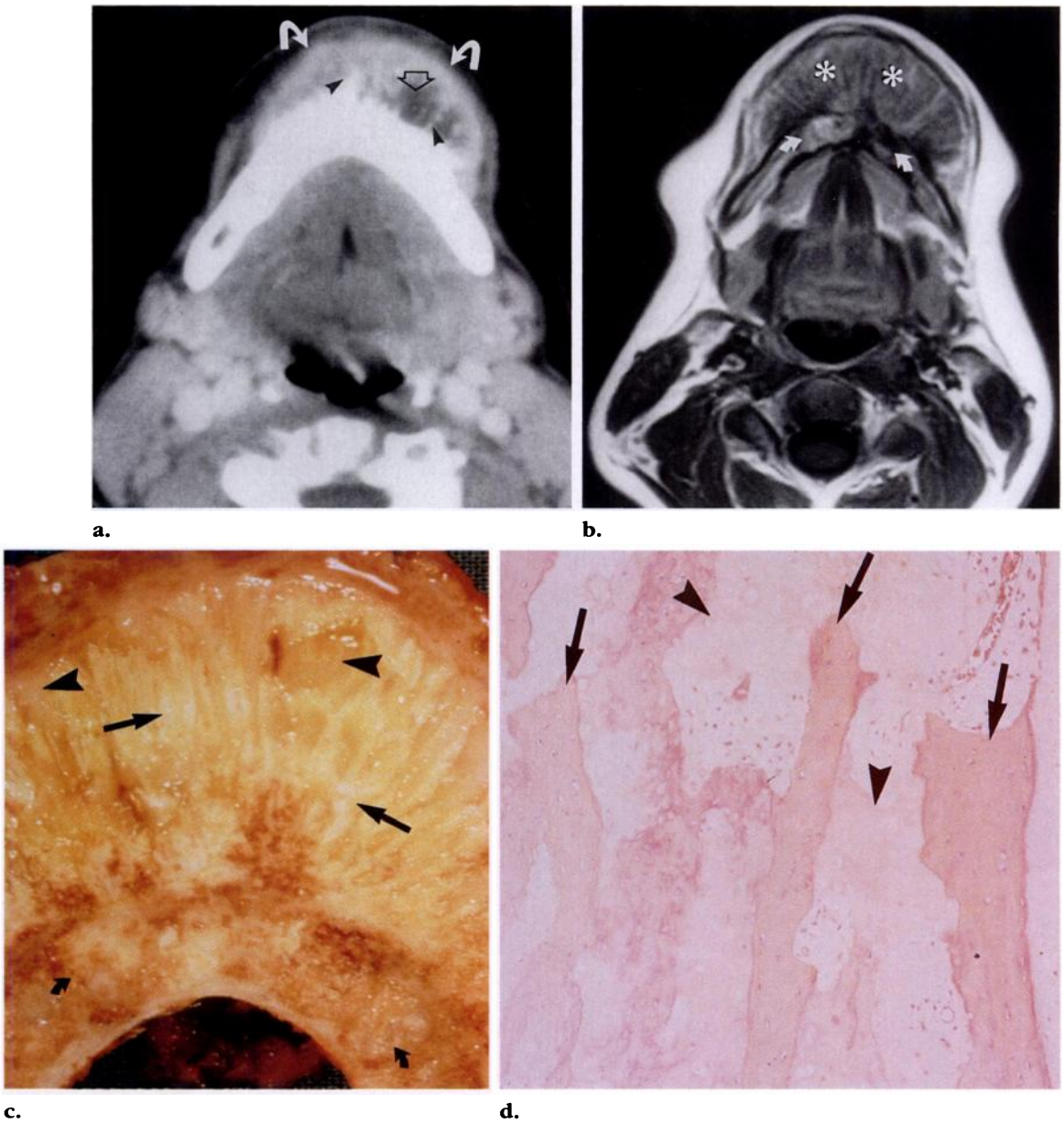
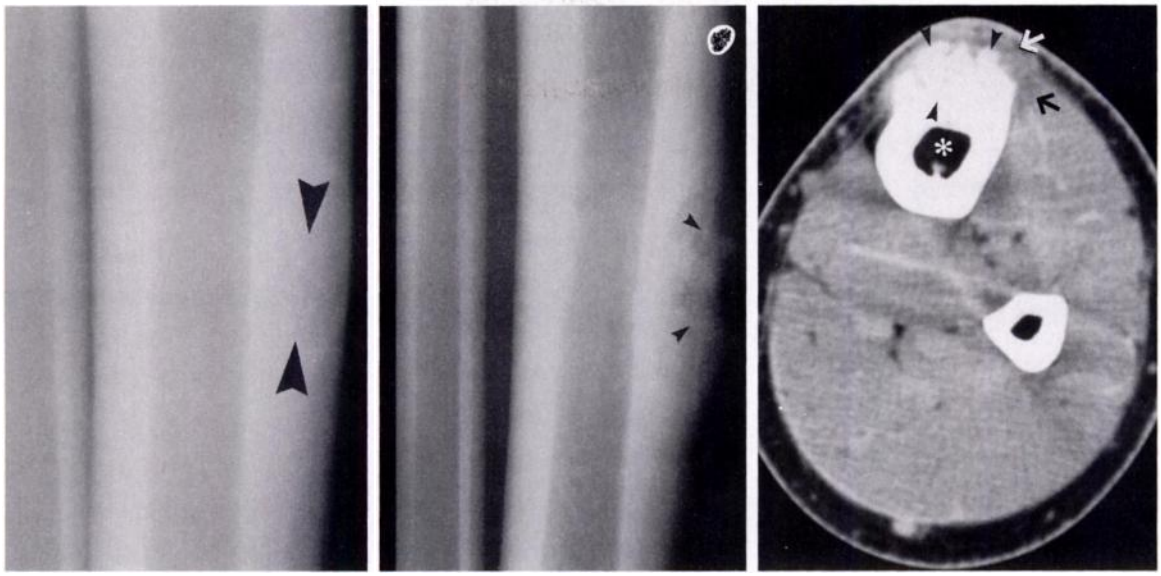


Figure 11. Gnathic osteosarcoma of the mandible in a 30-year-old woman with a history of a swollen chin. **(a)** Axial CT scan shows a lesion with hair-on-end periosteal reaction (arrowheads) and an anterior soft-tissue mass (solid arrows). Predominant low attenuation of the soft-tissue component (open arrow) reflects the highly chondroblastic histologic characteristics. **(b–d)** Axial T1-weighted MR image **(b)** and photograph of the gross specimen **(c)** reveal the intramedullary origin of the tumor (curved arrows) and the large anterior soft-tissue mass (*). Striated osteoid (straight arrows) with intervening chondroid tissue (arrowheads), corresponding to the imaging findings, are well seen in the gross specimen **(c)** and the photomicrograph (original magnification, ×200; hematoxylin-eosin stain) of the histologic specimen **(d)**.

• Gnathic Osteosarcoma

Lesions of the mandible and maxilla constitute 6%–9% of all osteosarcomas (1–4,60–65). Gnathic osteosarcoma is often considered a distinct category because of its predilection to affect older patients (average age, 34–36 years) (60–65). Lesions affect the alveolar ridge, maxillary antrum, and body of the mandible (Fig 11). At histologic analysis, the lesions are often predominantly chondroblastic (60).

The radiologic appearance of gnathic osteosarcoma is similar to that of conventional os-



a. b. c.

Figure 12. Intracortical osteosarcoma of the anterior tibia in a 20-year-old man with shin pain. **(a)** Lateral radiograph obtained at initial presentation shows a vague, entirely intracortical area of lucency (arrowheads) in the anterior cortex of the tibial diaphysis. **(b, c)** Lateral radiograph **(b)** and axial CT scan **(c)** obtained 6 months later reveal lesion enlargement with osteoid mineralization (arrowheads) and extension into anterior soft tissues (arrows). Medullary canal is normal (*).

teosarcoma, with evidence of osteoid matrix (60%–80% of cases), aggressive periosteal reaction in mandibular lesions, and soft-tissue extension (100%) (Fig 11) (61,64). Opacification of the maxillary sinuses is also a frequent finding of maxillary lesions. CT is the optimal modality for detecting areas of mineralized osteoid in this complex anatomic location (Fig 11a). MR imaging demonstrates the intramedullary and extraosseous components to best advantage (Fig 11b).

Treatment of gnathic osteosarcoma is difficult and includes radical and local surgical resection, radiation therapy, and chemotherapy. Unfortunately, local recurrence is common (50%–80% of cases), particularly in cases of maxillary lesions, and is often uncontrollable, typically leading to patient death (60,65). Distant metastases are less frequent than in other osteosarcomas, and the 5-year survival rate is approximately 40% (60,65).

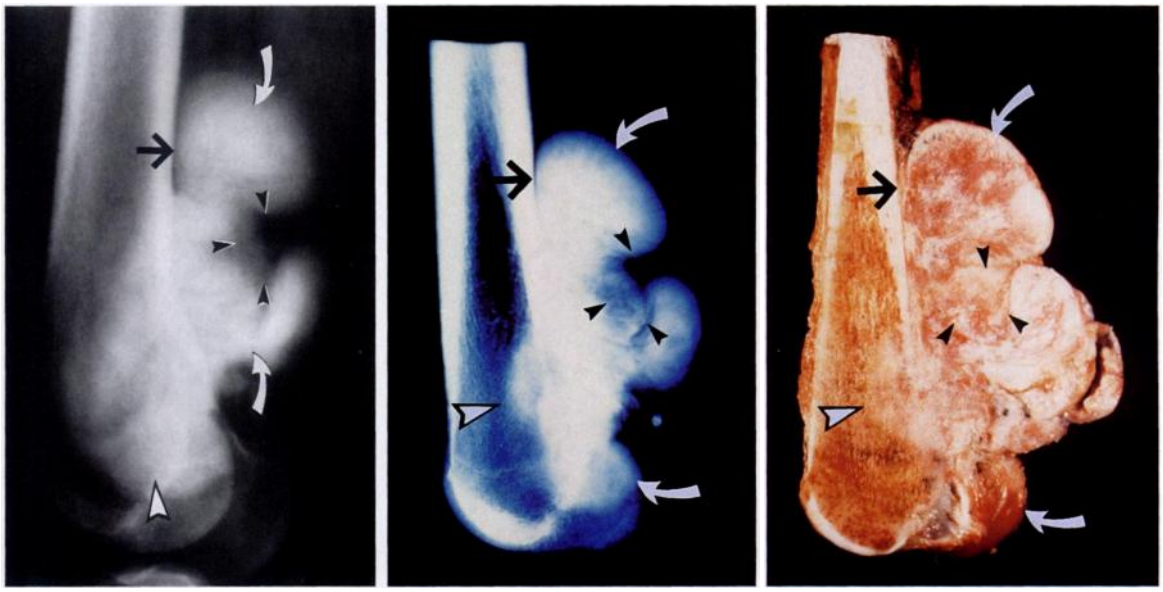
■ SURFACE OSTEOSARCOMA

Surface lesions account for 4%–10% of all osteosarcomas (1–4,66–71). Some authors prefer to group all these osteosarcomas into a single surface or "juxtacortical" category. However, we prefer to distinguish intracortical, parosteal, periosteal, and high-grade surface lesions because of differences in radiologic and pathologic appearances as well as in treatment and prognosis.

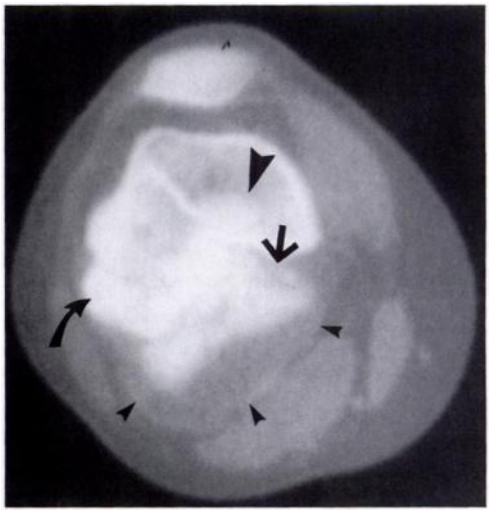
• Intracortical Osteosarcoma

Intracortical osteosarcoma is the rarest form of osteosarcoma, and the term applies to those cases in which the lesion arises within the cortex. It was originally described by Jaffee (72) in 1960 in a report of two cases, and through 1991 only nine cases had been published (72–76). The lesion is histologically characterized as a sclerosing variant of osteosarcoma, which may contain small foci of chondrosarcoma or fibrosarcoma (73–75).

Although it is difficult to make generalizations on the basis of such a small number of cases, the typical lesion shows geographic bone lysis (with small areas of mineralized osteoid), is intracortical; occurs in the femur or tibia; and measures less than 4 cm in diameter (Fig 12) (73,76). The tumor margin may be remarkably well defined with thickening of the surrounding cortex, and medullary invasion is only rarely reported (73,76).



a. c. d.



b.

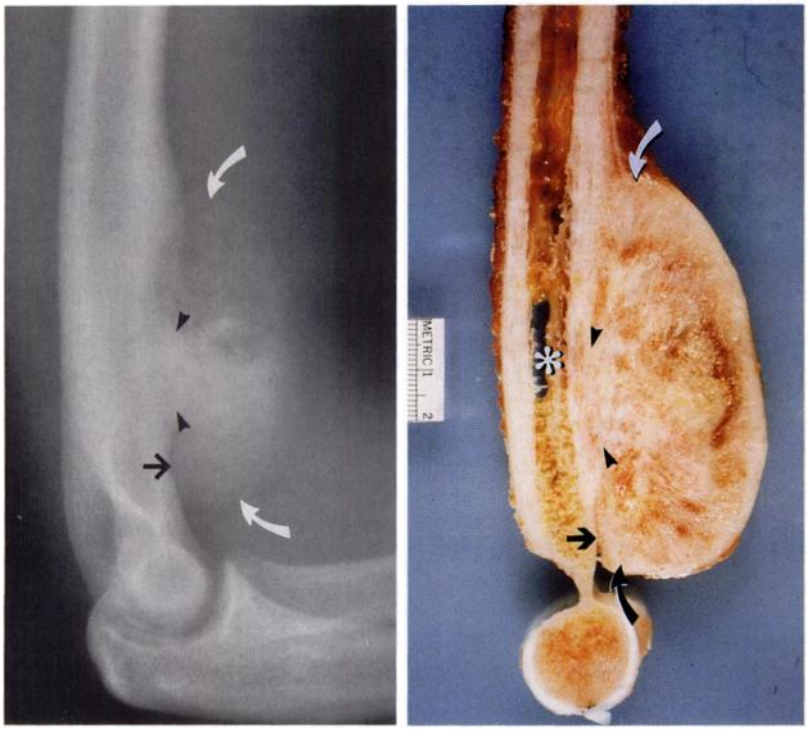
Figure 13. Parosteal osteosarcoma of the posterior distal femur in a 32-year-old man. Lateral radiograph **(a)**, axial CT scan **(b)**, and radiograph **(c)** and photograph **(d)** of the sagittally sectioned specimen show a lobulated, extensively ossified mass that is largely juxtacortical (curved arrows), with a cleavage plane superiorly (straight arrow), nonmineralized component (small arrowheads), and invasion (back growth) into the medullary canal (large arrowhead). At histologic examination, the soft-tissue component represented a higher-grade focus of the tumor.

Although long-term data are lacking, Mirra and coworkers (73) reported that in a review of seven patients, five were disease-free after 3–19 years of follow-up. One patient died of metastatic disease and another had inoperable metastases. This high rate of metastasis (29%) may be sufficient to justify adjuvant chemotherapy.

• Parosteal Osteosarcoma

Parosteal osteosarcoma accounts for 65% of all juxtacortical osteosarcomas and is thought to originate from the outer layer of periosteum (66–71,77–83). These lesions usually affect patients in the 3rd and 4th decades of life and show a slight female predilection. Clinical symptoms frequently include a palpable mass. Parosteal osteosarcomas affect the metaphyseal region of long bones (80%–90% of cases), most frequently the posterior distal femur (50%–65%) (Fig 13) (77,82). Other commonly involved regions are the proximal humerus, tibia, and fibula.

Parosteal osteosarcomas are frequently low-grade lesions (Fig 14), as suggested in the original description in 1951 by Geschickter and Copeland (78), who used the term *parosteal osteoma*. However, these large, lobulated parosteal lesions contain higher-grade regions in



a. b.

Figure 14. Parosteal osteosarcoma of the distal humerus in a 14-year-old boy who presented with an enlarging mass. Lateral radiograph **(a)** and photograph of the sagittally sectioned gross specimen **(b)** show a lobulated ossified mass (curved arrows) with a narrow stalk of attachment to the outer osseous surface (arrowheads) and a cleavage plane inferiorly (straight arrow). No nonmineralized areas, which would be suggestive of high-grade foci, are seen, and the medullary canal (* in **b**) is not involved.

22%–64% of cases and may demonstrate invasion (back growth) into the medullary canal (8%–59%) (66,67,70,77,80,82). Fibrous stroma and extensive osteoid are the predominant histologic characteristics, although smaller foci of cartilage are also frequent.

The radiologic appearance of parosteal osteosarcoma is often characterized by a large, lobulated (cauliflower-like), ossific (denser centrally), juxtacortical mass (Figs 13, 14). Initially, only a narrow zone (stalk) of attachment to the cortex may be apparent, creating a partial radiolucent cleavage plane (Figs 13, 14) between the lobulated ossific mass and the remaining bone (68,79). However, continued tumor growth often obliterates the cleavage plane. Cortical thickening without aggressive periosteal reaction may be seen. CT and MR imaging can demonstrate both the soft-tissue extent and evidence of medullary involvement (Fig 13b). The ossified regions show high attenuation on CT scans and low signal intensity on all MR images, regardless of pulse sequence. In addition, Jelinek and coworkers (79) have recently shown that nonmineralized soft-tissue components larger than 1 cm^3 identified at CT or MR imaging correspond to high-grade foci (Fig 13). Parosteal osteosarcomas may be confused both pathologically and radiologically with myositis ossificans (84). However, in contradistinction to parosteal osteosarcoma, myositis ossificans is denser peripherally and is usually not attached to the cortex.

Prognosis for patients with parosteal osteosarcoma is excellent, with 5- and 10-year survival rates of 80%–90% (77,82). Detection of higher-grade foci may alter therapy, and presurgical biopsy should be directed toward these sites. Higher-grade parosteal osteosarcomas may warrant neoadjuvant chemotherapy.

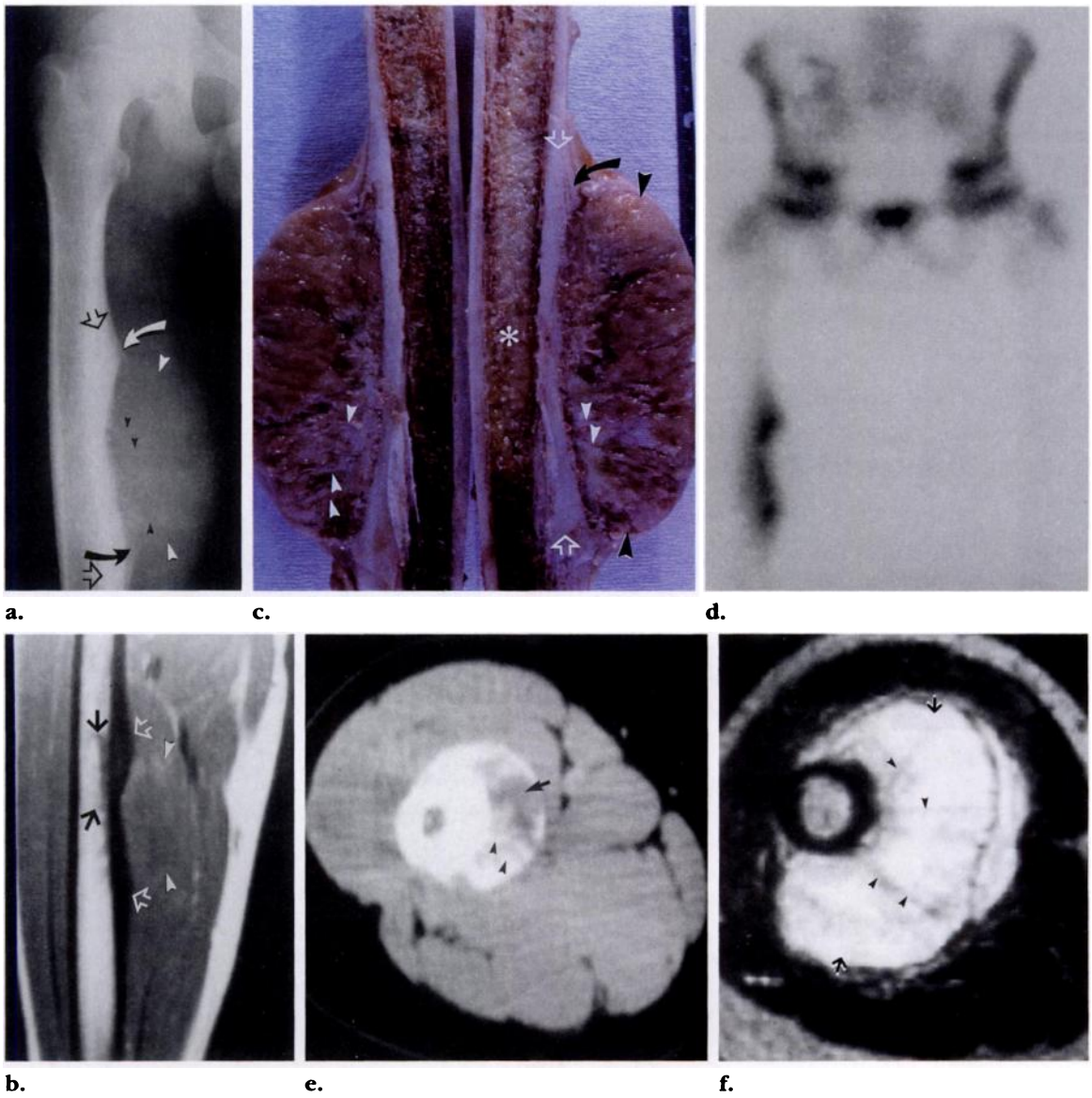


Figure 15. Periosteal osteosarcoma of the femoral diaphysis in a 14-year-old boy. **(a–c)** Anteroposterior radiograph **(a)**, coronal T1-weighted MR image **(b)**, and photograph of the sagittally sectioned gross specimen **(c)** show cortical periosteal reaction (Codman triangle, curved arrows) and cortical thickening (open arrows). The cortex is scalloped with hair-on-end periosteal reaction (small arrowheads) extending into a broad-based soft-tissue mass (large arrowheads). **(d)** Bone scan reveals similar findings, with increased radionuclide uptake seen along the juxtacortical lesion. **(e, f)** Axial CT scan **(e)** and axial T2-weighted MR image **(f)** show perpendicular periosteal reaction (arrowheads) and chondroblastic nonmineralized component (arrows) as low attenuation and very high signal intensity, respectively. On the T1-weighted MR image **(b)**, the small areas of low signal intensity in the marrow space (solid arrows) are separated from the juxtacortical mass and represent reactive changes and not marrow invasion. This finding was proved pathologically, as shown by lack of marrow involvement (*) in the gross specimen **(c)**.

Lesions of higher grade have been called dedifferentiated parosteal osteosarcoma, although we reserve this term for those lesions that contain a second tumor cell line (often fibrosarcoma or malignant fibrous histiocytoma) (83). The presence of intramedullary back growth has previously been reported to imply a worse prognosis. More recent studies suggest that this finding does not change the overall excellent prognosis of patients with parosteal osteosarcoma (79,80,83). However, it remains important to identify medullary extension to ensure adequate surgical resection during limb-salvage operations (Fig 13).

• Periosteal Osteosarcoma

Periosteal osteosarcoma accounts for 25% of all juxtacortical osteosarcomas and was originally described in 1976 by Unni and coworkers (66, 69,85). The age group affected is similar to that for conventional osteosarcoma (patients in the 2nd and 3rd decades of life). However, unlike conventional osteosarcoma, these lesions show a strong propensity to arise in the diaphysis (Fig 15) or metadiaphysis of bone. The most commonly affected sites are the femur and tibia (85%–95% of cases), followed by the ulna and humerus (5%–10%) (85–87).

Periosteal osteosarcomas are intermediate-grade lesions that arise from the deep layer of periosteum and cause cortical scalloping typically without intramedullary invasion (85). Pathologic assessment demonstrates a highly chondroblastic lesion with smaller areas of osteoid formation (Fig 15).

The radiologic appearance of periosteal osteosarcomas is usually characteristic and distinctive from that of parosteal lesions. The surface of the thickened diaphyseal cortex is scalloped, with perpendicular periosteal reaction extending into a broad-based soft-tissue mass (Fig 15a) (86,87). Solid (cortical thickening) or aggressive (Codman triangle) periosteal reaction may also be apparent at the upper and lower margins of the lesion. CT and MR imaging show similar findings, with the highly chondroblastic areas corresponding to relatively low-attenuation regions on CT scans, low-signal-intensity areas on T1-weighted images, and very high-signal-intensity areas on T2-weighted MR images (Fig 15b, 15e, 15f) (86,87). In our recent study, we demonstrated that these lesions usually involve approximately 50% of the osseous circumference and that the perpendicular periosteal reaction is seen as rays of low signal intensity with all MR pulse sequences (87). Marrow invasion is rare and, when seen, is directly continuous with the surface mass. Marrow invasion should be distinguished from reactive marrow changes (Fig 15b), which appear as foci of marrow replacement (low signal intensity on T1-weighted MR images and high signal intensity on T2-weighted or inversion recovery images) adjacent to but noncontiguous with the surface mass, as described in more than 50% of cases by Murphey and coworkers (87).

Prognosis for patients with periosteal osteosarcoma is improved compared with that for patients with conventional osteosarcoma, but it is not as good as that for patients with parosteal lesions. Metastatic disease leads to patient death in 8%–16% of cases (85,88). Surgical treatment is usually wide local excision with an associated limb-salvage procedure.

• High-Grade Surface Osteosarcoma

High-grade surface osteosarcoma is rare and accounts for 10% of all juxtacortical osteosarcomas (69,89). These lesions have a high predilection to involve the diaphysis of bone and most commonly affect the femur, humerus, and fibula. Pathologically and prognostically, high-grade surface osteosarcomas are identical to conventional intramedullary lesions (69). Radiologically, these lesions are similar in appearance to periosteal osteosarcoma (Fig 16)

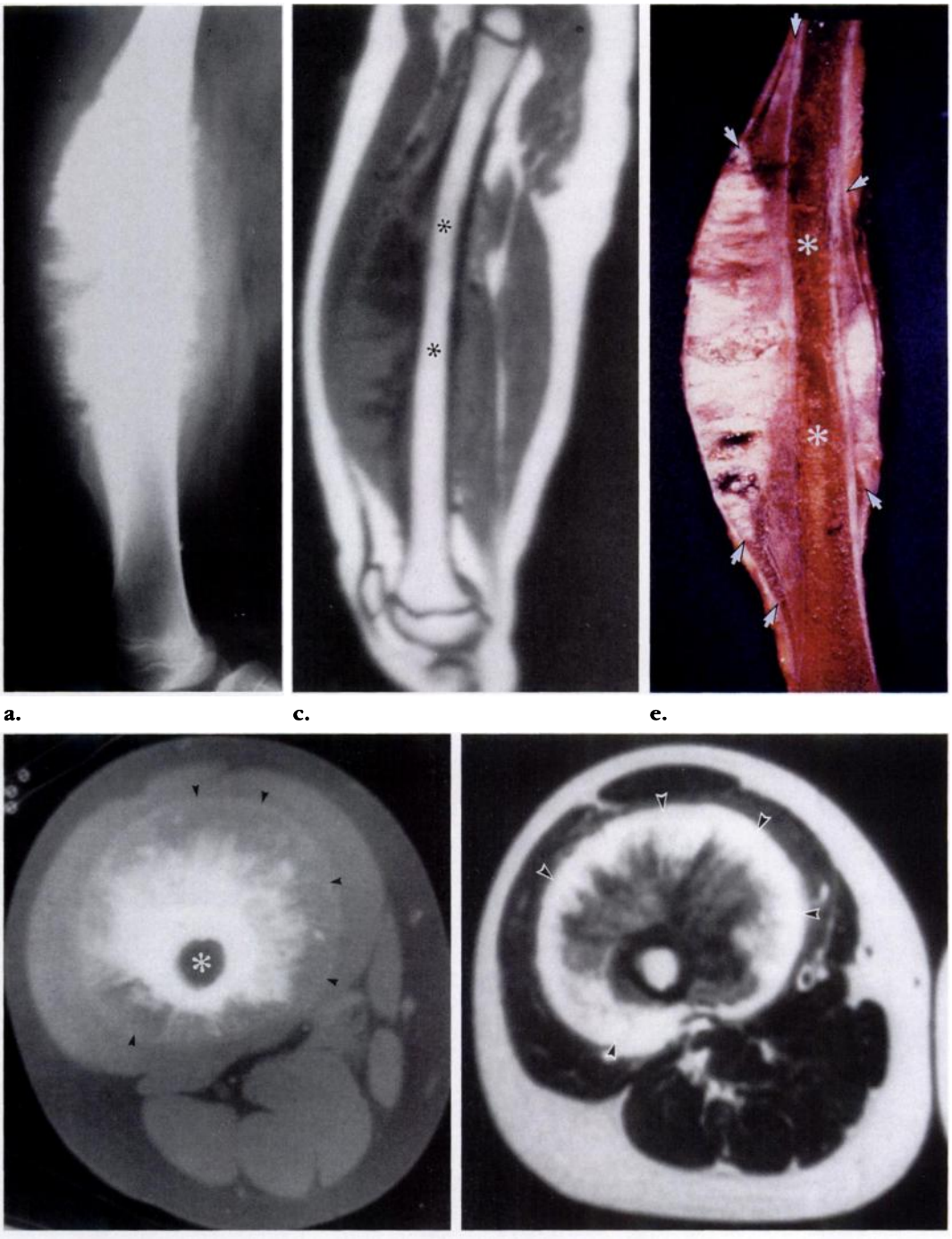
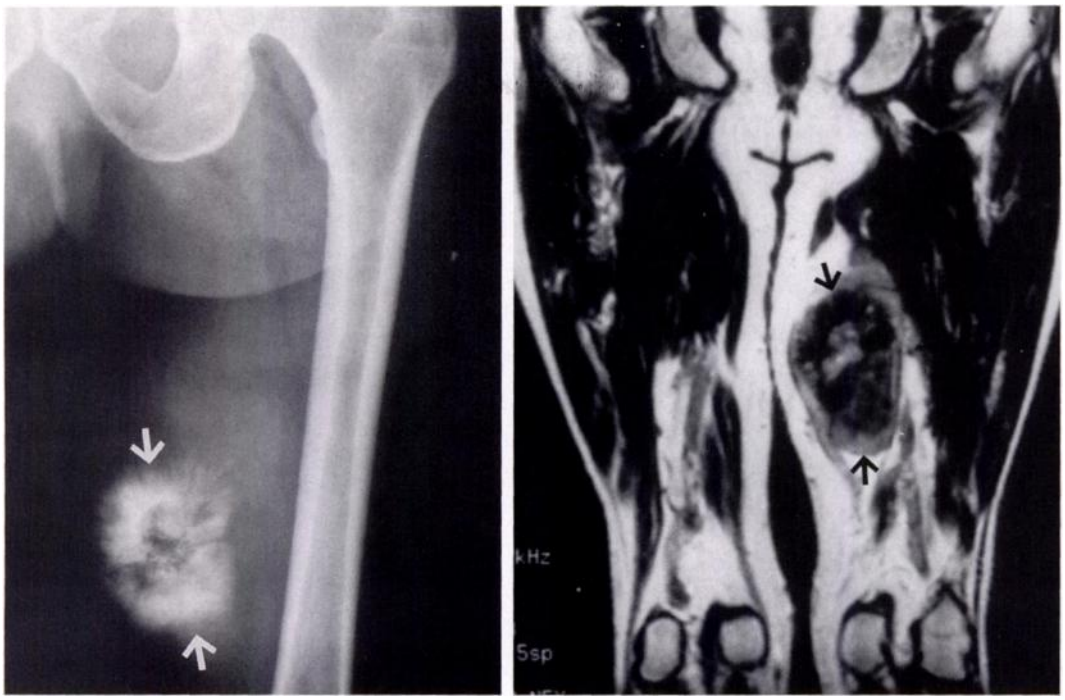
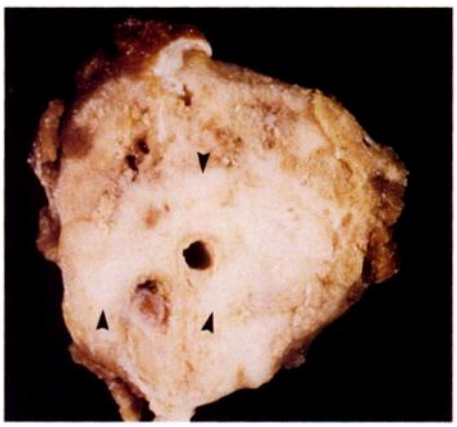


Figure 16. High-grade surface osteosarcoma of the femoral diaphysis in a 10-year-old boy with clinical symptoms of an enlarging mass. **(a, b)** Lateral radiograph **(a)** and axial CT scan **(b)** show an osteoblastic lesion with aggressive periosteal (hair-on-end) reaction. On the CT scan, the lesion involves the bone surface circumferentially without marrow abnormality (*) and has a peripheral soft-tissue component (arrowheads). **(c)** Sagittal T1-weighted MR image also shows normal signal intensity in the marrow (*). **(d)** Axial T2-weighted MR image demonstrates the soft-tissue component peripherally (arrowheads) with the very high signal intensity characteristic of chondroid matrix (which has low attenuation on the corresponding CT scan **[b]**). **(e)** Photograph of the sagittally sectioned gross specimen shows extent of involvement on the osseous surface (arrows) and the uninvolved marrow cavity (*).



a. b.



c.

Figure 17. Extraskeletal osteosarcoma in an 87-year-old man with an enlarging soft-tissue mass in his left thigh. **(a)** Anteroposterior radiograph shows an extensively mineralized soft-tissue mass distally (arrows). **(b, c)** Coronal T2-weighted MR image **(b)** reveals predominantly low signal intensity within the large mass (arrows), owing to extensive mineralization (arrowheads), as seen on the photograph of the sectioned gross specimen **(c)**.

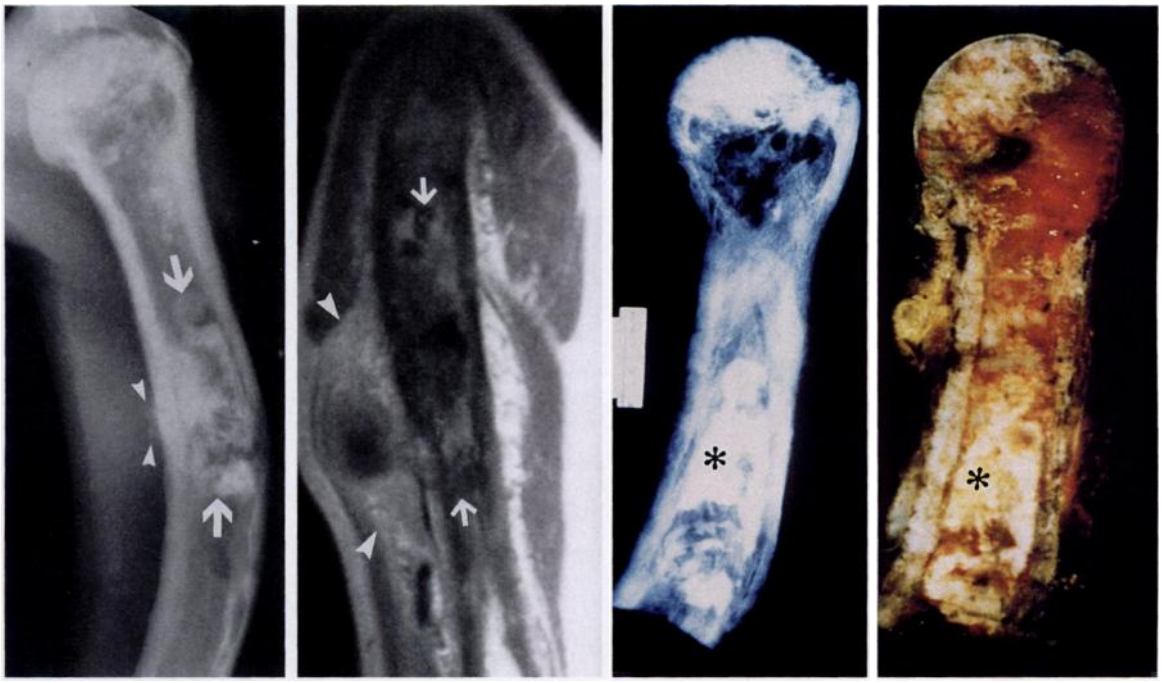
(69,89). However, in our experience, high-grade surface osteosarcomas often involve the entire circumference of bone and frequently invade the medullary canal.

■ EXTRASKELETAL OSTEOSARCOMA

Extraskeletal or soft-tissue osteosarcoma is rare, representing approximately 1.2% of all soft-tissue sarcomas and 4% of all osteosarcomas (1–3,90–94). The peak prevalence occurs in patients in the 6th decade of life, and men are slightly more frequently affected. Symptoms often include a slowly growing painful mass, and a history of trauma is not infrequent (12% of cases) (92). Common sites of involvement are the deep soft tissues of the thigh (47% of cases), upper extremity (20%), and retroperitoneum (17%) (90–94).

Extraskeletal osteosarcomas are usually large (average, 9 cm in diameter) with variable amounts of neoplastic osteoid and bone (91). Other histologic components, including cartilage, fibrosarcoma, malignant fibrous histiocytoma, and malignant peripheral nerve sheath tumor, are also frequently seen within extraskeletal osteosarcoma (90).

Radiologic studies show large soft-tissue masses with focal to massive areas of mineralization and a lack of osseous involvement (Fig 17) (94,95). Nonmineralized areas have muscle attenuation values on CT scans, nonspecific intermediate signal intensity on T1-weighted images, and high signal intensity on T2-weighted MR images and show contrast enhancement (95). A pseudocapsule may also be apparent. Scintigraphy often reveals increased radionuclide uptake in both primary and metastatic foci.



a. b. c. d.

Figure 18. Secondary osteosarcoma of the humerus in a 77-year-old woman with long-standing Paget disease and new pain and a soft-tissue mass. **(a)** Anteroposterior radiograph shows extensive underlying changes of Paget disease. Focal sclerosis in the medullary canal (arrows) and subtle calcification in the soft-tissue component (arrowheads) represent osteoid mineralization. **(b)** Sagittal proton-density-weighted MR image reveals large intraosseous (arrows) and extraosseous (arrowheads) areas of malignant transformation. **(c, d)** Radiograph **(c)** and photograph **(d)** of the coronally sectioned gross specimen also show osteoid in the medullary and soft-tissue components (*) of the osteosarcoma, as well as underlying changes of Paget disease.

Treatment consists of amputation or wide surgical resection with neoadjuvant chemotherapy or radiation therapy. Tumor size is the most important prognostic factor, with patients with lesions larger than 5 cm having a worse outcome (90–94). Despite aggressive therapy, overall prognosis is poor, with patient death occurring in at least 60% of cases (90–92). Metastases are frequent and most commonly involve the lung, regional lymph nodes, and bone.

■ SECONDARY OSTEOSARCOMA

Most osteosarcomas occur as primary neoplasms. However, both osseous and soft-tissue osteosarcomas can be secondary lesions (5%–7% of all osteosarcomas) resulting from malignant transformation within a benign process (1). The vast majority of these secondary osteosarcomas are associated with Paget disease (67%–90% of cases) (Fig 18) or previous osseous or extraskeletal irradiation (6%–22%) (1–3). The frequency of malignant transformation to osteosarcoma in Paget disease varies widely, from 0.2% in patients with limited involvement to as much as 7.5% in those with extensive skeletal manifestations (96,97). Similarly, the estimates of radiation-induced osteosarcoma show a wide range of prevalence, from 0.02% to 4%, that is related to exposure dose (usually >1,000 cGy) (98,99). Preexisting conditions that less commonly lead to osteosarcoma include osteonecrosis, fibrous dysplasia, metallic implants, osteogenesis imperfecta, chronic osteomyelitis, and retinoblastoma (particularly the familial bilateral type associated with a deficient oncogene suppressor on chromosome 13) (1).

Patients with secondary osteosarcoma are usually middle-aged or in late adulthood, accounting for a small second peak of prevalence in this older age group. Radiologic evidence of the long-standing underlying condition is usually obvious, as is the more aggressive bone destruction in the area of malignant transformation. Large, associated soft-tissue masses are also typical of secondary osteosarcoma (Fig 18).

Pathologically, the lesions are usually composed of high-grade anaplastic tissue and produce little or no mineralized matrix, and this aggressiveness results in a dismal prognosis. Despite all the treatment regimens that have been employed, the 5-10-year survival rate is often extremely poor and less than 5% (1-3).

■ CONCLUSIONS

Osteosarcoma is the most common primary malignant bone tumor in children. Its radiologic appearances vary over a wide spectrum. We have reviewed the radiologic and pathologic features of the various types of primary osteosarcoma, including intramedullary (high-grade, telangiectatic, low-grade, small cell, osteosarcomatosis, and gnathic), surface (intracortical, parosteal, periosteal, and high-grade surface), extraskeletal, and secondary lesions. The radiographic appearances of these lesions are often characteristic and suggestive of the specific diagnosis. Perhaps more important, additional imaging modalities, including bone scintigraphy, CT, and MR imaging, provide vital information for preoperative staging in planning surgical management. Radiologic examination also allows evaluation of tumor response to chemotherapy, identification of metastatic disease, and postoperative evaluation of recurrent neoplasm, all of which have important prognostic implications. Recognition of these imaging features is an important guide to our clinical colleagues throughout the often difficult and complex treatment of patients with osteosarcoma and results in improved clinical outcome.

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