

Instructional lecture

Premalignant conditions of bone

ANDREW HORVAI and K. KRISHNAN UNNI

Division of Anatomic Pathology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Introduction

The etiology of most malignant bone tumors is poorly understood, and most bone malignancies are believed to arise *de novo*. Nevertheless, a small number of malignant bone tumors arise in recognizable benign precursors, and these lesions may be divided into three conceptual categories: diseases with documented predisposition to malignant bone tumors; sporadic benign tumors with a known risk for secondary malignancy; and postradiation malignant tumors (Table 1). The following review attempts to summarize the more common entities in each category with an emphasis on clinical manifestations and pathological findings.

Congenital syndromes associated with bone tumors

A number of inherited conditions have been identified that predispose the affected individual to malignant bone tumors, typically osteosarcoma (Table 2). In general, inherited susceptibility accounts for a small number of sarcomas in most series. For example, at the Mayo Clinic, we identified only two examples each of osteosarcoma arising in the context of familial retinoblastoma, Rothmund-Thompson syndrome, and Bloom syndrome (2/1952, 0.1%). Although rare, the molecular mechanisms of the inherited syndromes may parallel the mechanisms of the more common sporadic osteosarcomas. Although a complete review of the genetic mechanisms for all of these syndromes is beyond the scope of this article, a few unifying points are discussed.

Offprint requests to: K.K. Unni

Presented at the 38th Annual Musculoskeletal Tumor Meeting of the Japanese Orthopaedic Association, Yokohama, Japan, July 2005

Received: February 20, 2006

Werner, Rothmund-Thompson, and Bloom syndromes all present with characteristic cutaneous findings during childhood and a predisposition for high-grade osteosarcoma, often at unusual locations, such as the patella. Although each of these syndromes maps to a unique genetic locus, the gene products share significant sequence homology. The latter finding is intriguing given the clinical similarities between the syndromes. Osteosarcoma is typically a diagnosis of childhood among the congenital syndromes. In contrast, chondrosarcoma presenting as part of an inherited syndrome does so late in adult life and is discussed in the context of specific precursor lesions below.

Sporadic premalignant lesions

Paget's disease

Both benign and malignant neoplasms arise in the setting of Paget's disease. The incidence of sarcoma has been estimated at approximately 1%.²⁻⁵ Osteosarcoma is by far the most common, and fibrosarcoma and chondrosarcoma are rarely observed.³⁻⁴ At the Mayo Clinic, 73 sarcomas arising in bone affected by Paget's disease have been recorded. Osteosarcoma typically affects patients with polyostotic Paget's disease, with the pelvis, femur, humerus, and tibia most often affected.^{3,6-8} With the exception of the spine, the location of the sarcomas parallels the distribution of Paget's disease. Osteosarcoma associated with Paget's disease occurs at a later age than sporadic osteosarcoma, reportedly affecting subjects during the sixth to seventh decades.^{4,9} The prognosis of sarcoma in a patient with Paget's disease is considerably worse than for similar primary tumors,^{2,3,10} with the 5-year survival as low as 8%. The discrepancy is multifactorial, related to the age of the patients, inoperative sites, fracture, and delay in diagnosis because the underlying Paget's disease can mask the clinical and radiographic findings.

Table 1. Premalignant conditions of bone

Genetic predisposition
Retinoblastoma
Rothmund Thompson syndrome
Bloom syndrome
Li-Fraumeni syndrome
Sporadic premalignant lesions
Paget's disease
Giant cell tumor
Chronic osteomyelitis, sinus tract
Osteoblastoma
Chondroid neoplasms
Osteochondroma
Synovial chondromatosis
Enchondroma
Fibrous dysplasia
Postradiation sarcoma

Radiographically, the sarcomas present (in decreasing frequency) as lytic, mixed, or sclerotic lesions (Fig. 1A)³ in the setting of the coarsened bone (Fig. 1B) affected by Paget's disease. Histologically, the tumors are high-grade osteosarcomas, with striking nuclear pleomorphism or bizarre giant cells (Fig. 1C,D).

Therapy consists of combined surgical eradication and chemotherapy and occasionally irradiation. The term "Paget's sarcoma" has been used to highlight the clinical behavior of sarcomas arising in this setting and potentially to designate patients for specific clinical trials.

Giant cell tumor

Giant cell tumor (GCT) is a perplexing entity in that it can demonstrate multiple features of malignancy (high mitotic rate, necrosis, high cellularity, vascular invasion) and behave in a relatively benign fashion. The concept of malignant giant cell tumor is further confused by the presence of cytologically benign metastases that may regress spontaneously. True malignancy in GCTs can be divided into primary and secondary types.¹¹⁻¹⁴ Of the 39 malignancies arising from a GCT in the Mayo Clinic files, 5 (13%) were primary, 26 (67%) had received radiation, and 8 (21%) were secondary but without prior irradiation. Secondary malignancy is more common, and most cases occur after radiotherapy with an interval of a decade or more.

The most frequent histologic types of secondary malignancy are osteosarcoma and fibrosarcoma. As such, the secondary sarcomas are high-grade sarcomas, and the diagnosis can usually be made with adequate clinical correlation. Primary malignant GCT can be defined by the presence of areas of typical GCT adjacent to a high-grade spindle cell sarcoma. It usually presents in a slightly older age group than conventional GCT. Importantly, the radiographic distinction from conventional

Table 2. Syndromes associated with bone sarcomas

	MOI	Locus	Gene	Associated clinical findings
Syndromes associated with osteosarcoma				
Bloom syndrome	AR	15q26	BLM	Photodistributed telangiectatic erythema, short stature
Familial retinoblastoma	AD	13q14	RB1	Bilateral retinoblastoma before age 3
Familial Paget's disease	AD	Multiple	Multiple	Pain, secondary hearing loss
Rothmund-Thompson syndrome	AR	8q24	RECQL4	Poikiloderma, short stature, premature graying and hair loss, cataracts, photosensitivity
Li-Fraumeni syndrome	AS	17p13	TP53	Scleroderma, short stature, cataracts, premature graying and hair loss
Werner syndrome	AR	8p11	WRN	Hemangiomas
Syndromes associated with chondrosarcoma				
Maffucci syndrome	Sporadic	3p21-22	PTHR1	Deformities of forearm, knee, short stature
Ollier disease	Sporadic	8q24, 11p11	EXT1	
Multiple osteochondromas	AD		EXT2	

MOI, mode of inheritance; AR, autosomal recessive; AD, autosomal dominant

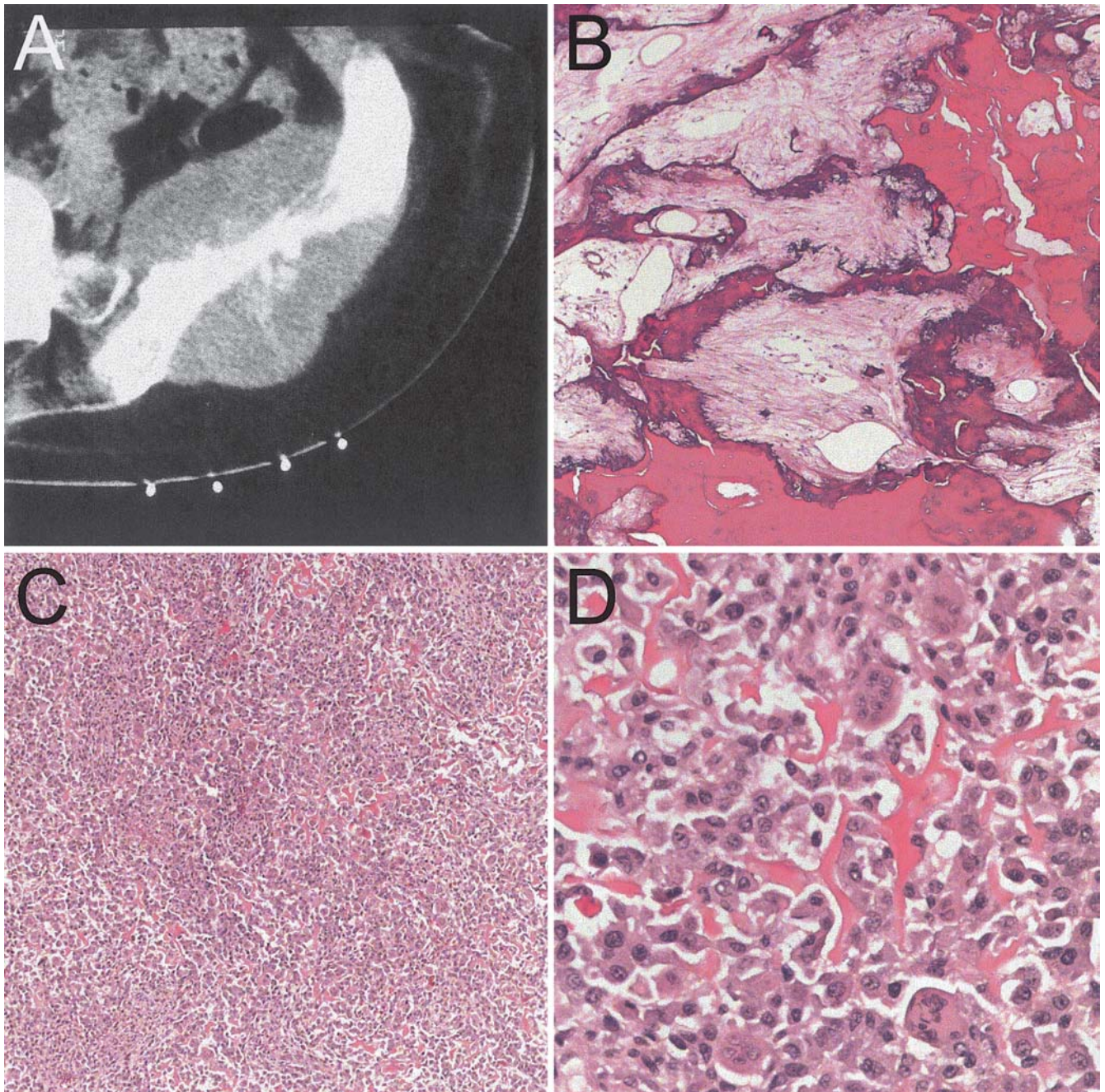


Fig. 1A–D. Osteosarcoma arising in Paget's disease. **A** Left ileum with expansile mass in a patient with Paget's disease. **B** Area of Paget's disease uninvolved by sarcoma. **C, D** Osteo-

genic sarcoma corresponding to iliac lesion with abundant hyperchromatic, pleomorphic cells and lace-like osteoid

GCT may be subtle. Histologically, the transition between GCT areas and sarcoma is gradual rather than abrupt, but the malignant component displays marked nuclear atypia in most cases. The difficulty in diagnosis occurs only when the lesion is inadequately sampled or the malignant component is overlooked when the initial impression is conventional GCT. That the malignant

component of many so-called primary malignant GCTs is osteosarcoma blurs the distinction between this entity and giant-cell-rich osteosarcoma. In any event, the presence of abnormal osteoid matrix in an otherwise unremarkable GCT should prompt careful examination of the mononuclear population for atypia and embedding additional material if available.

Chronic osteomyelitis

Although a well-recognized entity given the relative frequency of chronic osteomyelitis compared to most bone tumors, the rate of malignancy in draining sinuses is estimated to be only 0.5%.¹⁵ We have identified 56 cases in Mayo Clinic files. The interval to the develop-

ment of malignancy is highly variable, from as little as 1 year to decades. The clinical clues that suggest malignant transformation include a growing mass, increased pain, bleeding, or a purulent discharge in a long-standing sinus.¹⁶ Radiographically, an acceleration in the destructive nature of the lesion and a soft tissue mass (Fig. 2A) are the rule, although malignant change

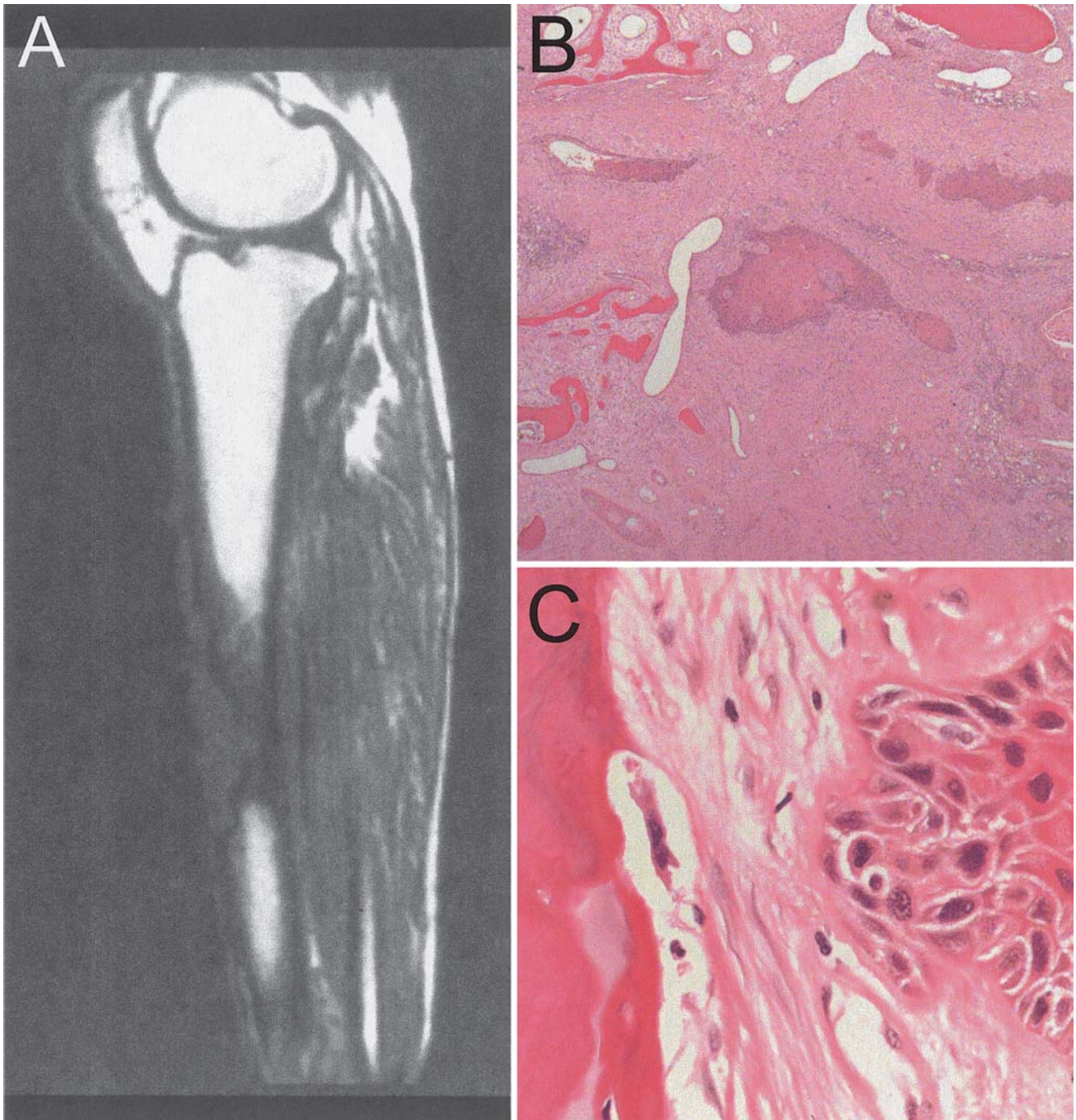


Fig. 2A–C. Squamous cell carcinoma arising in chronic osteomyelitis with a fistula tract. **A** Large, destructive lesion of the femur underneath a fistula tract noted on T1-weighted mag-

netic resonance imaging. **B, C** Squamous cell carcinoma shows diagnostic foci of keratinization and intercytoplasmic bridges

may not demonstrate a significant increase in bone destruction in some cases.^{17,18} Histologically, most cases are well-differentiated squamous cell carcinoma,^{17,19} although osteosarcoma,^{16,20} fibrosarcoma,²¹ and undifferentiated sarcoma²² have been reported. Squamous cell carcinoma does not appear to complicate chronic osteomyelitis absent a draining sinus. The presence of squamous cells invading bone is diagnostic (Fig. 2B, 2C). In the series by McGrory et al., the 5- and 10-year survival for squamous cell carcinomas (69% and 63%, respectively) were not significantly different from those of age-matched controls, although aggressive surgical management (amputation) was the rule.¹⁹ Despite limited data for clinical significance, the presence of lymph node metastasis appears to correlate with a worse outcome.^{16,23}

Osteoblastoma

Osteoblastoma is, by definition, a benign bone tumor with a recurrence potential as high as 22%.²⁴ However, malignant transformation has been reported in rare cases.^{25–27} All cases of malignantly transformed osteoblastomas reported to date have shown a conversion to osteosarcomas only in recurrent tumors. In the Mayo Clinic files, only one case of malignant transformation from 108 cases of osteoblastoma has been recorded. However, the diagnosis of “malignancy” in a osteoblastoma, recurrent or otherwise, is particularly difficult because of the aggressive behavior of some osteoblastomas. Radiographic findings of cortical destruction (39%) or suggestive of malignancy (12%) are not uncommon.²⁴ Furthermore, histologic findings do not necessarily correlate with aggressive behavior even in “benign” osteoblastomas.²⁴ Rather, the clinical outcome correlates with the location such that tumors in short or flat bones or bones of the neuraxis demonstrate more aggressive behavior.^{24,28} The entity “aggressive osteoblastoma” was introduced by Dorfman and Weiss²⁹ and Lucas et al.²⁴ to describe lesions with features borderline between osteoblastoma and osteosarcoma. A permeative pattern of growth within intratrabecular spaces and lack of maturation toward the periphery of the lesion have been described as a histologic clue for distinguishing osteoblastoma from osteosarcoma.^{24,30} However, multifocal tumor growth, frequently present in osteoblastomas, may be confused with permeation.³¹ To complicate matters further, although the mortality associated with osteoblastoma-like osteosarcoma can be significant from local disease (40% in one series), the metastatic rate of osteoblastoma-like osteosarcoma may be low (9%).³² In contrast, the conventional osteosarcoma is considered a systemic disease at the time of diagnosis. Therefore, we believe a spectrum of tumors exists, with osteoblastoma at one end

and osteoblastoma-like osteosarcoma at the other, all of which are treated with either local or wide excision depending on the degree of clinical aggressiveness. Limited molecular data support a possible progression model in this disease.^{25,33,34} True transformation to malignancy, as evidenced by distant metastases, is extremely rare but should be considered a separate clinicopathologic entity from osteoblastoma-like osteosarcoma.²⁵ Osteoblastomas with conversion to osteosarcoma require aggressive surgical management combined with chemotherapy similar to conventional osteosarcomas.

Osteochondroma

The neoplastic nature of the osteochondroma has only recently come to light with the discovery of loss of heterozygosity at the EXT1 locus as well as other clonal abnormalities^{35,36} in a subset of these tumors. Osteochondroma is the most common precursor lesion for secondary chondrosarcoma. At the Mayo Clinic, 127 of 157 (81%) secondary chondrosarcomas arose at the site of an osteochondroma. Approximately two-thirds of them were from patients with the sporadic form and the remainder from patients with multiple osteochondromas. However, the rate of malignant transformation is thought to be only 1%–8% in sporadic osteochondromas.^{15,37–39} The incidence of chondrosarcoma arising in patients with multiple osteochondromas has been estimated at 5%–35%.^{37,38,40} The incidence is difficult to estimate and may be lower, as many solitary osteochondromas may go undiagnosed. Furthermore, these data are generated from large referral centers and may overestimate the true incidence secondary to selection bias.

The average age of the secondary chondrosarcoma patient is 35 years, younger than patients with primary tumors.⁴¹ Most of these tumors affect the pelvic bones. The increased thickness of the cartilage cap (normally 1–3 mm) has long been reported as an indicator of potential malignancy. However, it should be noted that in skeletally immature individuals, a cartilage cap of up to 2 cm might be identified. In addition to a thick cartilage cap, findings that should raise suspicion of malignant transformation are recent growth of an exostosis in an adult (Fig. 3A), proximal skeletal location, irregular mineralization (Fig. 3B), soft tissue invasion, a grossly irregular surface, or cystic change. Permeation of trabecular bone is not typically seen with chondrosarcomas arising in osteochondromas. Cytologically, most secondary chondrosarcomas are of low grade, although the normal columnar arrangement of chondrocytes is lost (Fig. 3C,D). Secondary chondrosarcomas arising in osteochondromas generally carry a good prognosis, and surgical treatment without adjuvant chemotherapy or

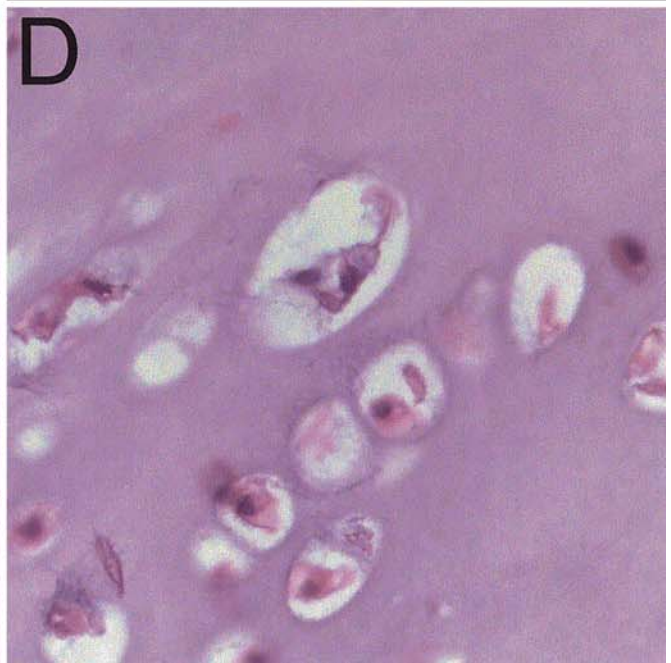
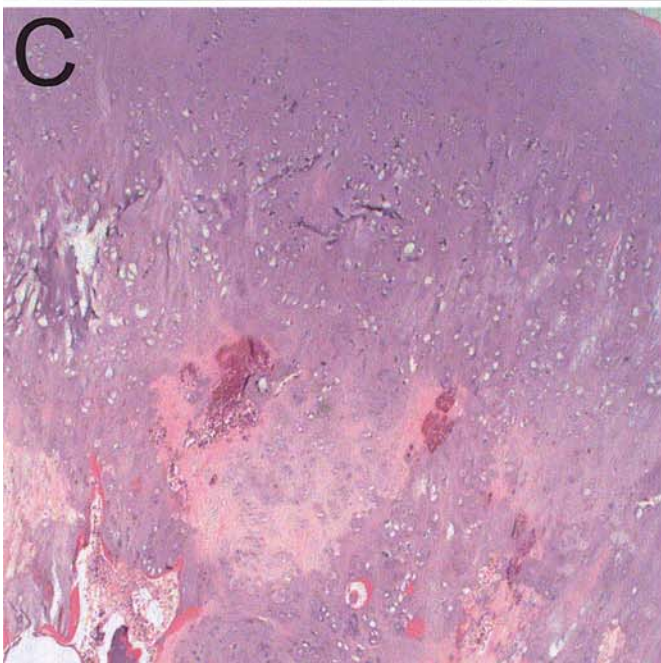
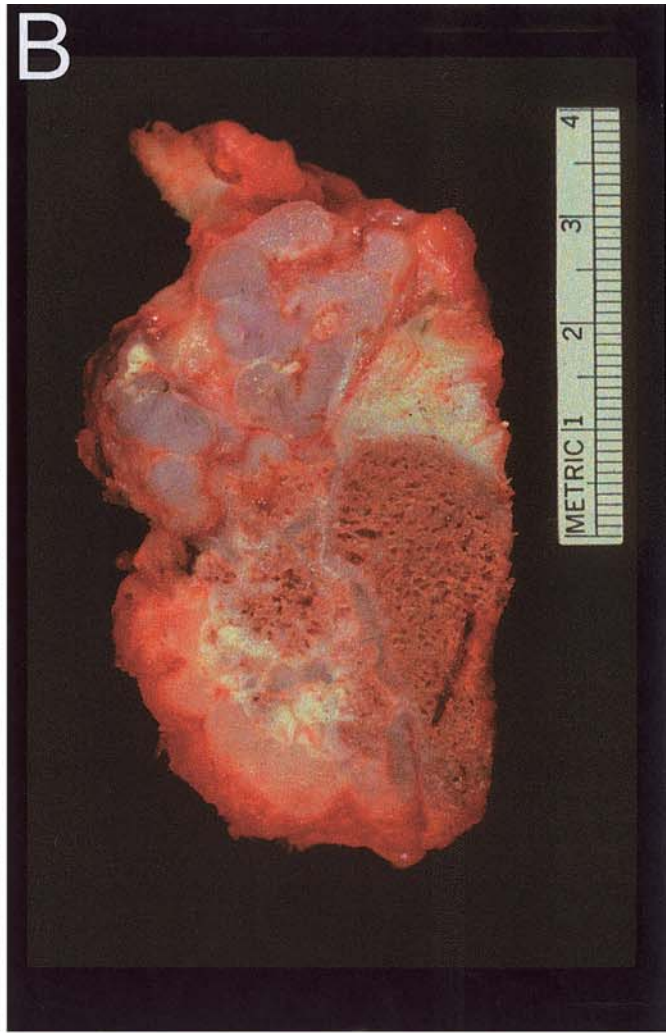


Fig. 3A–D. Chondrosarcoma arising in an osteochondroma. **A** Large, ill-defined soft tissue mass with ring-like calcifications arising at the site of prior osteochondroma in the humerus. **B** Gross pathology of chondrosarcoma arising from osteochondroma of the sacrum demonstrates irregular miner-

alization and cystic degeneration. **C** Loss of columnar architecture and thick cartilage cap (edge of cap is visible at top right) are common. **D** In a grade I chondrosarcoma cytology is typically bland

irradiation is the rule. Case reports of osteosarcoma arising within an osteochondroma have been published,^{42–44} but this event is extremely rare.

Enchondroma

Controversy exists in the literature about the development of secondary chondrosarcoma from enchondroma. In the Mayo Clinic series of 157 secondary chondrosarcomas, none had a documented history of a precursor solitary enchondroma. It is important to note that even benign enchondromas of the small bones of the hands and feet may show histological features of malignancy (hypercellularity, myxoid change, nuclear hyperchromasia) but nevertheless behave in a benign fashion. Indeed, an unequivocal diagnosis of malignancy at these sites requires extensive destructive or permeative soft tissue growth or evidence of metastasis.^{45,46}

Multiple enchondromas

Patients with multiple enchondromas (enchondromatosis) in the setting of Ollier's disease or Maffucci's syndrome carry a significantly higher risk of transformation to secondary chondrosarcoma than those with solitary enchondromas discussed above. Of 158 secondary chondrosarcomas seen at the Mayo Clinic, 21 (13%) had preexisting enchondromatosis.

The genetic mechanisms of these diseases are poorly understood but may involve mutations in the parathyroid hormone receptor 1 (*PTHRI*) gene in some cases,^{47,48} although the diseases are not heritable. Ollier's disease usually presents with multiple enchondromas of varying size affecting any bones undergoing endochondral ossification but with a predilection for the femur and tibia. Although involvement may be unilateral, it is often bilateral in the hands and feet (Fig. 4A). The rate of chondrosarcoma in Ollier's disease has been estimated at 30%–50%.^{49,50} Given the hypercellularity of enchondromas in Ollier's disease, the histological distinction may be difficult. However, radiographic evidence of cortical destruction and soft tissue extension (Fig. 4B) and the histological findings of abundant myxoid change, cyst formation, and permeation of existing trabeculae (Fig. 4C) suggest malignancy. Maffucci's syndrome demonstrates multiple chondroid masses similar to Ollier's disease in addition to soft tissue hemangiomas. The risk of chondrosarcoma is approximately 15%–35%.^{51,52} The appearance of the chondromas and the criteria for chondrosarcoma in Maffucci's syndrome are similar to those for Ollier's disease.

Synovial chondromatosis

Secondary malignancy in synovial chondromatosis has been reported^{53,54} but is exceedingly rare. Synovial chondrosarcoma, without prior evidence of chondromatosis, was first described by Goldman and Lichtenstein.⁵⁵ In the Mayo Clinic series, only 3 of 158 (2%) of secondary chondrosarcomas arose in synovial chondromatosis.³⁷ Synovial chondromatosis has morphological and clinical overlap with soft tissue chondroma and is distinct from cartilaginous loose bodies (so-called secondary synovial chondrometaplasia).^{56,57} Specifically, the cartilage grows in lobules of solid matrix, with chondrocytes arranged in clusters (Fig. 5A,B). The soft tissue location, its locally aggressive nature, and common histological findings of clustering, hypercellularity, and frequent nuclear hyperchromasia or binucleation may lead to overdiagnosis of chondrosarcoma. A true diagnosis of chondrosarcoma requires the presence of a sheet-like growth pattern, loss of clustering of chondrocytes, or spindling at the periphery of lobules (Fig. 5C,D).⁵⁸

Fibrous dysplasia

Fibrous dysplasia is a relatively common lesion, and therefore fairly large series have reviewed its premalignant potential. Malignant transformation in fibrous dysplasia, most commonly to osteosarcoma, has been documented^{15,59,60,61} at a rate of 0.4%–2.0%. However, approximately half of the patients in the Mayo Clinic series also had a history of irradiation.⁶⁰ The risk of osteosarcoma appears to be somewhat higher in polyostotic fibrous dysplasia,^{16,61} although it is unclear whether patients with the McCune-Albright or Mazabraud syndromes are still at further increased risk. Fibrosarcoma and “malignant fibrous histiocytoma” have been associated with fibrous dysplasia but not specifically with the McCune-Albright or Mazabraud syndrome.

The most common sites of malignant transformation tend to parallel the common sites of fibrous dysplasia: craniofacial bones, proximal femur, humerus, and pelvis (in order of decreasing incidence).⁶² Typically, fibrous dysplasia represents a benign developmental abnormality in which the medulla is replaced by immature fibrous tissue and distorted trabeculae of primitive bone. The radiographic and histological features of secondary osteosarcomas are usually high grade and carry a poor prognosis. The histological findings of benign fibrous dysplasia may raise the differential diagnosis of low-grade central osteosarcoma,^{63,64} although these entities are likely unrelated. Degenerative nuclear changes mimicking atypia may be seen with fibrous dysplasia,⁶⁵ but fibrous dysplasia should not demonstrate an infiltrating pattern along the peripheral native bone, even if radiographic features suggest a benign lesion.

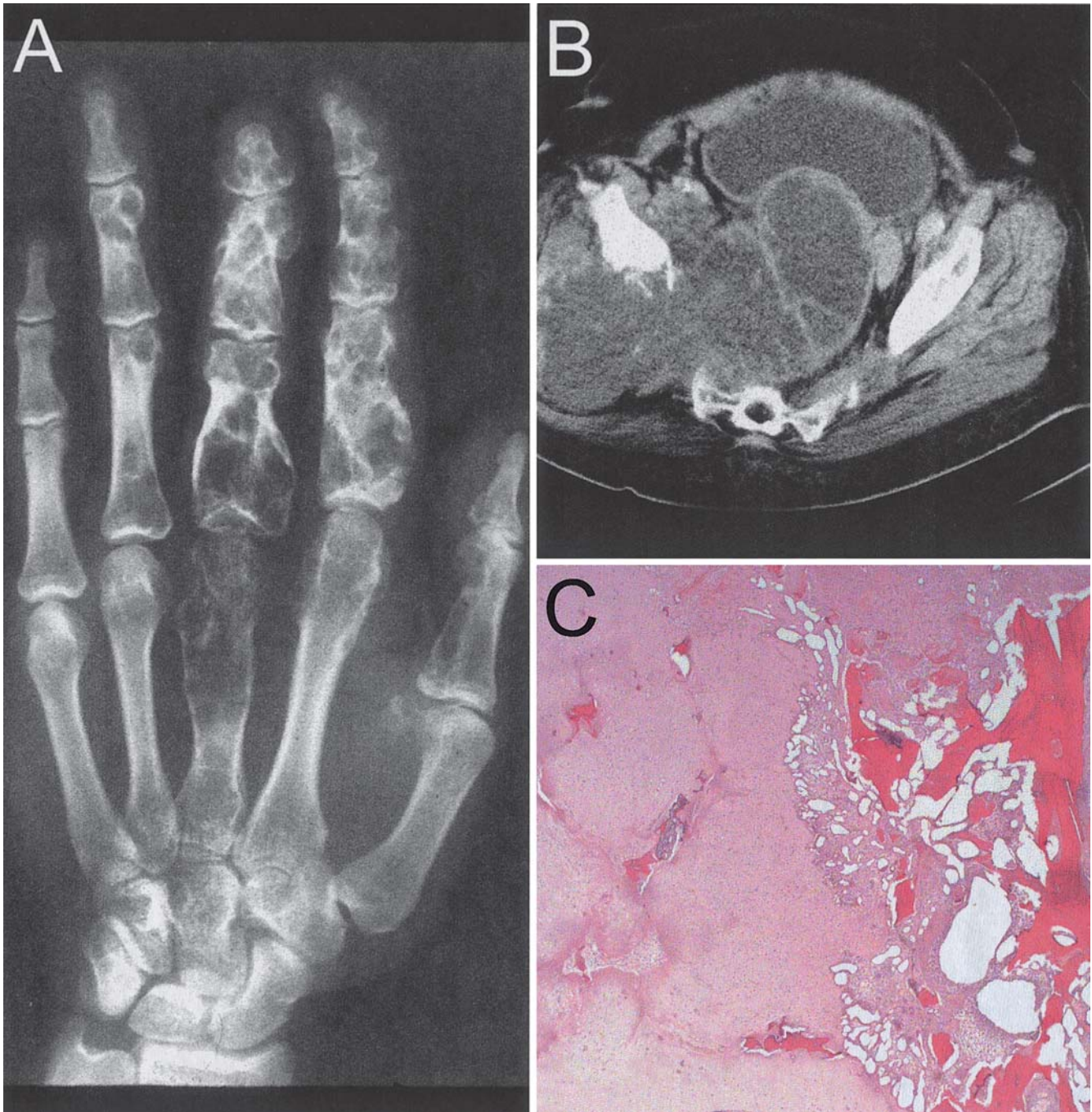


Fig. 4A–C. Chondrosarcoma arising in the setting of multiple enchondromas. **A** Plain radiograph from an Ollier disease patient demonstrating multiple enchondromas of the digits. **B**

Computed tomography scan from an Ollier disease patient showing a large, destructive mass of the ileum. **C** Permeation of existing trabecular bone is diagnostic of chondrosarcoma

Postradiation sarcoma

The first description of sarcoma arising in irradiated bone was recorded by Cahan et al.,⁶⁶ and sarcoma is now a well-studied, albeit rare, detrimental effect of ionizing radiation. The term postradiation sarcoma is preferred to radiation-induced sarcoma. To be classified as a

postradiation sarcoma requires at least three conditions: (1) the bone must have been included in the radiation field; (2) a latency period; and (3) histological confirmation of sarcoma.¹⁶ Histological confirmation is of particular import to confirm that the sarcoma differs from the original lesion. The incidence of postradiation sarcoma is not known, in part, because early studies

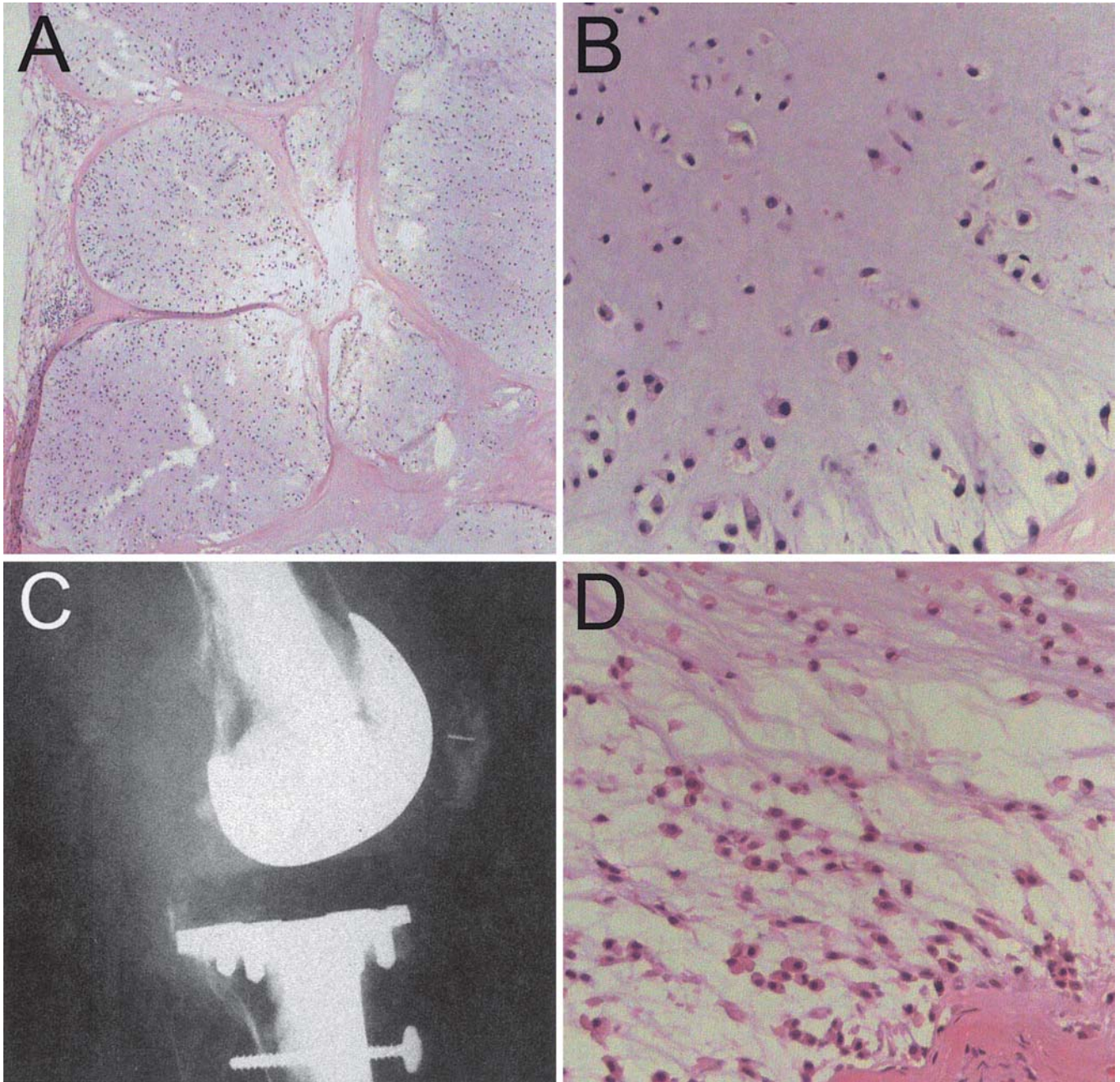


Fig. 5A–C. Chondrosarcoma in synovial chondromatosis. **A** The benign cartilage of synovial chondromatosis shows a lobular growth pattern at low power. **B** Synovial chondromatosis often demonstrates chondrocyte clustering, nuclear hyperchromasia, and binucleation and should not be mistaken for chondrosarcoma. **C** Plain radiograph of a patient

with synovial chondromatosis and knee hemiarthroplasty with a new ill-defined soft tissue density adjacent to the knee joint. **D** Loss of clustering and spindling of chondrocytes at the periphery of a lobule are suggestive of chondrosarcoma in this setting

reported the effects of irradiation for benign processes,^{66–72} whereas more recent work has focused on irradiation of malignancies, particularly breast cancer.^{73–78} The overall incidence in adults ranges from 0.1% to 0.78%,^{67,79} although these figures include soft tissue as well as bone sarcomas. In children, particularly those treated for Ewing's sarcoma, the rate has been

reported to be as high as 22% if followed more than 20 years,⁸⁰ although rates as low as 1% have also been reported.^{81–83}

In the Mayo Clinic series of postirradiation sarcoma, the most common indication for the irradiation was a benign bone lesion (giant cell tumor or fibrous dysplasia).⁸⁴ Although there is no absolute minimum interval

between irradiation and the sarcoma, most cases present at least 4 years after irradiation (mean 13 years).^{67,85,86} The most common interval was 5–9 years (33.5% of cases) in the Mayo Clinic series,⁸⁴ and the most common postirradiation sarcoma was osteosarcoma (62%). However, irradiation of breast carcinoma tends to produce sarcomas of soft tissues (most commonly angiosarcoma) rather than of bone.⁸⁷ Thus, given the unfortunately high incidence of breast carcinoma requiring radiation therapy, and the decrease in the use of irradiation for benign bone lesions, the incidence of postradiation bone sarcomas may decrease. In general, the prognosis of postradiation sarcoma of bone has been regarded as very poor, with the 5-year survival ranging from 9% to 29%.^{67,85,88–90} However, in the Mayo Clinic series, those with operable extremity sarcomas showed a 5-year survival of 68%.⁸⁴ Unfortunately, this group represented only 23% of the patients, and particularly unfavorable outcomes were associated with tumors of the pelvis, spine, shoulder girdle, and skull. Central lesions may predict a worse prognosis because of delay in diagnosis and unresectability. Often the only clinical clue to the development of a postradiation sarcoma is bone pain, which may be a relatively nonspecific symptom in patients with cancer. Radiographically, the presence of cortical bone destruction or a mineralized soft tissue mass in an irradiated field should prompt needle biopsy of the lesion.⁸⁴ Patients with postradiation sarcoma of the extremity should undergo aggressive wide resection if possible.

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