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Bone Sarcoma

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Bone Sarcoma

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ISBN 978-1-4614-5193-8 ISBN 978-1-4614-5194-5 (eBook)
DOI 10.1007/978-1-4614-5194-5
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2012951843

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

This book is dedicated to the memory of Alan W. Yasko, MD, who served on staff at The University of Texas MD Anderson Cancer Center for 15 years and was the former chief of the Section of Orthopaedic Oncology. A gifted and courageous surgeon, Dr. Yasko treated thousands of patients during his tenure. In addition to being a superb clinician, he was also a strong proponent of education and research. This book was originally conceived by Dr. Yasko, who wanted to develop a concise multidisciplinary manual to facilitate teaching of house staff and treatment of patients. Although he has not lived to see the project come to fruition, his spirit is alive and well in the physicians he helped train, the colleagues with whom he worked, and, most of all, the patients he treated. Many of the ideas and concepts that he strongly believed in, especially those pertaining to limb salvage and reconstruction, endure in the book.

Alan William Yasko, MD
1958–2010

Foreword

During the past 40 years, major advances have been forged in the oncologic management of malignant bone tumors. These improvements derive from therapeutic discoveries in chemotherapy, better surgical techniques, progress in the delivery of radiation therapy, improved supportive care, and new imaging methodologies. As a consequence, an increasing number of survivors of both childhood and adult bone sarcomas are being observed.

The quality of life of these patients has been improved, particularly by advances achieved in innovative surgical techniques and procedures. Amputation has been reduced to a minimum, and limb-salvage procedures have become viable options for the majority of patients. These limb-preserving procedures appear to have great potential for the treatment of the different types of skeletal defects arising from tumor resection. Better implant materials and design configurations have been developed and are being discovered; they will probably reduce the incidence of complications in the future. The improvements have been facilitated by new approaches to enhance bone transplantation procedures, special systems for internal fixation of implants, and composite reconstructions that incorporate both biological and metallic materials. The surgical advances have been integrated with advances in chemotherapy, compounding the success of both.

The first series of osteoarticular allografts in the USA were reported in 1968 by Frank Parrish from MD Anderson Cancer Center. During the subsequent years, the techniques for treating patients with bone sarcomas at MD Anderson were developed by a team of dedicated clinicians, which included two notable orthopedic surgeons. The late John A. Murray, MD, a partner in Frank Parrish's practice and a founding member of the Musculoskeletal Tumor Society, was one of the early pioneers in the treatment of osteosarcoma. His ideas were advanced and extended by the late Alan W. Yasko, MD. I had the privilege of working with both of these remarkable individuals, and their contributions, particularly to the concept of multidisciplinary care, cannot be understated. The present-day staff at MD Anderson, under the direction of Valerae O. Lewis, MD, with whom I have also had the privilege of working, has continued the work of early pioneers, with ongoing, broad research efforts that are yielding significant results in many diverse areas.

A compendium of tactics and strategies is provided in this monograph, and it serves as an invaluable guide for the optimum treatment of patients with malignant bone tumors. The volume is intended to facilitate multidisciplinary care by offering a practical, portable resource for health professionals in many different medical fields who participate in the treatment of patients with musculoskeletal tumors. The MD Anderson approach described here demonstrates effective interaction between the different disciplines deployed in the management of patients with bone sarcomas and strives to develop safe, effective, and superior forms of care for these patients.

Norman Jaffe, MD, DSc
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Preface

Sarcomas of bone form a unique topic in oncology. Apart from obvious differences in histology and etiology, a number of characteristics set this group of tumors apart from all other malignancies, including sarcomas of soft tissue. Involvement of the skeletal system creates a host of surgical, functional, and emotional issues that are not encountered in other diseases. Moreover, the response to chemotherapy, radiologic analysis, and pathologic evaluation of bone sarcomas are distinctly different from those of other malignancies. For these reasons, it seems vital to devote a book to these uncommon but fascinating neoplasms.

A multidisciplinary team approach is essential to maximize a patient's chances of having a successful outcome. Success in any one area is not sufficient. A patient may have an excellent response to chemotherapy and be rendered disease free, yet have a poor outcome because of stiffness, weakness, and pain in a limb. Many different specialties and services are involved in the care of patients with bone sarcomas. As each of these fields becomes more technologically advanced, it becomes increasingly difficult for workers in one field to understand what their coworkers do in other fields. Many team members have a surprisingly limited knowledge of what the rest of the team does.

In an effort to foster collaboration and teamwork, we have written a succinct volume that summarizes the key elements of different specialties as they pertain to bone sarcomas. The book is not meant for any one branch of medicine but rather for all who have an interest in how the entire enterprise operates and how their efforts are intimately intertwined with those of their colleagues. The first chapter focuses upon the multidisciplinary nature of bone sarcomas. The next three chapters discuss diagnostic techniques, which include essential aspects of radiology, biopsy, and pathology. The following chapters explore in detail the three main diseases in the field—osteosarcoma, Ewing sarcoma, and chondrosarcoma. Treatment modalities, including surgery, chemotherapy, and radiation therapy, are discussed within the context of each of these diseases, since the treatment is quite different for each diagnosis. A special chapter is devoted to very rare sarcomas that arise in bone. The next portion of the book addresses important issues related to reconstruction and function.

These include growth of the skeleton in pediatric patients, soft tissue reconstruction, techniques for restoring skeletal defects, and physical rehabilitation of the patient. Finally, two chapters are more globally oriented toward algorithms for perioperative management and follow-up of patients.

It is hoped that this book will facilitate communication between health-care providers who are involved in the care of bone sarcoma patients. Through mutual understanding of each other's work, the practice of each professional can be refined, and the overall care of the patient with bone sarcoma can be optimized. Quite possibly, as a result of cross-fertilization of ideas, we may find fresh new ways to achieve a cure for our patients.

We thank Walter Pagel, Sunita Patterson, Joe Munch, and Kristi Speights of MD Anderson's Department of Scientific Publications for their encouragement, expertise, and outstanding editorial support. We are also indebted to Terri Robinson and Maribel Martinez of the Department of Orthopaedic Oncology for their invaluable assistance in the preparation of the manuscript.

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Chapter 1
A Multidisciplinary Approach to the Management of Sarcomas of Bone

Bryan S. Moon

Chapter Overview The treatment of bone sarcomas has changed dramatically over the past 30 years. Appropriate diagnosis and adequate treatment depend on a multidisciplinary approach. MD Anderson Cancer Center has designed a unique clinic system devoted to the complex treatment of bone sarcomas. Multidisciplinary providers see patients side by side. Multidisciplinary team conferences, as well as surgery-specific conferences, enable agreement on and coordination of treatment. Pathologist and physician expertise specific to bone sarcomas is crucial.

With an incidence in the USA of only approximately 2,500 cases a year, bone sarcomas are quite rare, and it can be difficult to find a team of physicians who have adequate experience and expertise in their treatment. Although there are many cancer centers across the country at which bone sarcomas can be treated, only a few of these centers have physicians from different disciplines whose practice is focused primarily on the treatment of sarcomas. At MD Anderson Cancer Center, there are not only physicians dedicated to the care of patients with sarcomas but also a unique clinic system that was designed specifically to provide a multidisciplinary team approach to the complex care of these patients.

Historically, the management of sarcomas was not so complicated. As recently as the 1970s, the majority of bone sarcomas were treated with amputation; occasionally, radiation therapy was also used. The results of this type of management

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P.P. Lin and S. Patel (eds.), *Bone Sarcoma*, MD Anderson Cancer Care Series,
DOI 10.1007/978-1-4614-5194-5_1,

were dismal, and survival rates were less than 20%. The use of modern chemotherapy and advanced imaging techniques has markedly changed the treatment and prognosis of patients with bone sarcomas, such that survival rates have increased dramatically and most patients are limb-salvage candidates.

The experience of the past few decades has demonstrated that the management of the majority of bone sarcomas requires multidisciplinary input from clinicians, musculoskeletal radiologists, and bone pathologists. The therapy for bone sarcomas is also multimodal and frequently includes chemotherapy, surgery, and/or radiation therapy. Although such multimodal therapy is required for a variety of cancers, the severity of disease and need for aggressive management seen with bone sarcomas make them a distinct entity. For these reasons, the importance of physician experience in the treatment of bone sarcomas cannot be overstated.

MD Anderson has had a Sarcoma Center since 1996. All disciplines that are involved in the care of a patient with sarcoma are represented, and providers see patients side by side, which enables close interactions among the providers and simplifies the patient's visit. Referrals to the Sarcoma Center can be made by telephone or online by physicians or by patients themselves. These referrals may be for patients with imaging results suggestive of sarcoma, patients with newly diagnosed sarcomas who are seeking definitive treatment, or those who are seeking second opinions but will be treated closer to home. Once the referral is initiated, each patient is assigned a primary physician and an advanced nurse practitioner who will coordinate the patient's care.

One of the most critical aspects of coordinating the patient's care is obtaining complete medical records and pathologic specimens. Initially, this may seem to be an onerous task, but it is critical because it enables the multidisciplinary team to review the patient's previous workup and determine whether further testing will be required. In some instances, needed tests or imaging can be scheduled in advance and coordinated with the physician's evaluation. If imaging is done far enough in advance, the images can be submitted to the radiology team and an interpretation can be rendered even prior to the patient's arrival. Clinicians can then make sure that outside imaging is adequate in scope and quality and can verify the outside radiographic interpretations. This review can significantly expedite the workup during the patient's initial evaluation period.

A review of the biopsy specimen and pathology slides is essential. At MD Anderson, prior to the initiation of any treatment, all outside biopsies must undergo review by an MD Anderson pathologist who specializes in sarcomas. Since bone sarcomas are rare, it is mandatory that a pathologist with significant sarcoma experience evaluates the specimen. It is not at all uncommon for this review to result in a change in the diagnosed grade or type of sarcoma, and occasionally a sarcoma diagnosis will be completely overturned. As will be discussed in later chapters, bone sarcomas are not all treated alike, and the correct diagnosis is critical to appropriate management.

Once the patient has been evaluated, imaging reviewed, and pathologic diagnosis confirmed, a specific treatment plan must be designed, and a team of clinicians must be assembled to carry out the plan. In some cases, this process can be straightforward, but quite often complex factors and considerations may influence the

management of the case. Presentation at a tumor board or similar conference can be quite beneficial to address these issues and ensure that all members of the multidisciplinary team are working in concert. At MD Anderson, cases are routinely presented and discussed at the Sarcoma Multidisciplinary Conference. The conference is devoted solely to sarcomas and is attended by the appropriate specialists in the fields of orthopedic oncology, surgical oncology, medical oncology, radiation oncology, diagnostic imaging, and pathology. In addition to the attending physicians, many other health care providers participate in the conference, including clinic nurses, research nurses, physician assistants, advanced practice nurses, fellows, residents, medical students, and other trainees. The inclusion of many different disciplines and health care professionals helps foster teamwork, facilitate communication, and provide continuing education for all attendees. Another beneficial effect of having a regular forum such as this conference for discussion of cases is the development of a consistent, effective treatment philosophy and approach to these rare diseases. This approach, in essence, reflects the distilled experience of many years of practice of many specialized physicians.

Presentation of a patient's case at the conference involves a synopsis of the medical history, projection of the pertinent radiologic findings by a radiologist, review of the histologic diagnosis by a musculoskeletal pathologist, and discussion of different treatment options. Whenever appropriate, the patient's eligibility for clinical trials is also discussed. The patient's primary team (the primary provider and advanced nurse practitioner) then discuss the conference recommendations with the patient, and appropriate care is initiated.

The following case is a good illustration of the effectiveness of the Sarcoma Multidisciplinary Conference and demonstrates how different clinicians can work together to improve the care of a patient. The patient was a 72-year-old woman who presented with right shoulder pain. A workup by her local physician had revealed a lesion in the right proximal humerus. Plain radiographs showed a calcified lesion suggestive of a cartilaginous tumor (Fig. 1.1), and magnetic resonance imaging (MRI) scans revealed erosion of the tumor through the cortical bone, which would be compatible with a radiologic diagnosis of chondrosarcoma. However, surprisingly, a needle biopsy did not confirm the presence of malignant chondrocytes or cartilaginous tissue. Instead, the biopsy showed epithelioid cells with large nuclei and scattered mitotic figures. The pathologic findings alone clearly did not support the diagnosis of a conventional chondrosarcoma. With the additional input from clinicians in orthopedics and radiology, it was determined that the appropriate diagnosis was a dedifferentiated chondrosarcoma, a rare type of chondrosarcoma characterized by components of low-grade cartilaginous tumor juxtaposed with malignant, high-grade spindle cell sarcoma. The important aspect of this multidisciplinary case is that dedifferentiated chondrosarcoma is treated with chemotherapy and surgery, whereas conventional chondrosarcoma is treated with surgery alone. If not for the collaboration of the multiple teams, the patient could have been at risk of misdiagnosis and inadequate treatment.

The majority of bone sarcomas will require surgical intervention. These surgeries, which are typically very complex, range from limb salvage to amputation. In

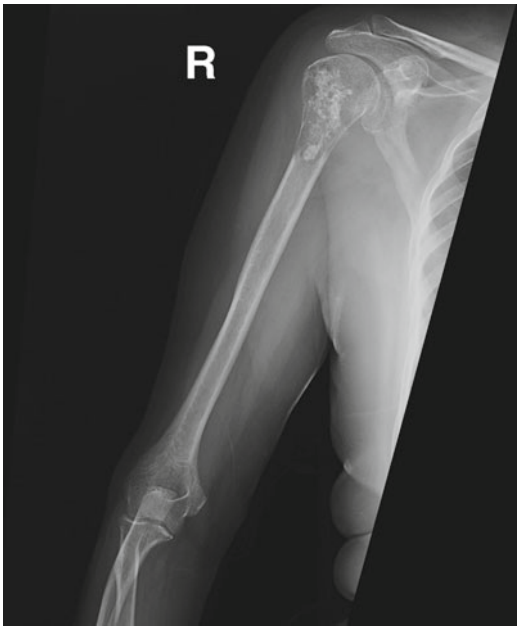

Fig. 1.1 A radiograph of the humerus demonstrates calcifications in the proximal end of the bone that are typical of a benign cartilaginous tumor. However, there is also seen lytic destruction of the surrounding cancellous bone and thinning of the overlying cortical bone. Subsequent workup revealed this tumor to be a dedifferentiated chondrosarcoma arising from an old benign enchondroma.

addition to the Sarcoma Multidisciplinary Conference, a separate surgical conference meets weekly to discuss cases that require surgery. It is attended primarily by orthopedic surgeons and musculoskeletal radiologists. At this conference, the images are again reviewed, and surgical options are discussed among the faculty. Given their rarity and heterogeneous nature, bone sarcomas can present unique challenges that may be encountered by a surgeon only a limited number of times during a surgical career. By combining the knowledge, experience, and expertise of several faculty members, the surgical conference creates a synergy that benefits the patient. It also assists in maintaining a standard of care and promotes the development of innovative surgical plans.

In summary, the major advances that have occurred in bone sarcoma management over the past 30 years demand a well-integrated, multidisciplinary approach. The chapters that follow will discuss in detail various aspects of sarcoma management and will illustrate amply how optimal treatment requires the input of many highly specialized health care professionals. Although outcomes for patients with bone sarcomas have improved over the years, there is still room for improvement. It is only through a focused, multidisciplinary approach that future improvements will emerge.

Key Practice Points

- Survival rates for patients treated for bone sarcomas have increased dramatically, and most patients are now limb-salvage candidates.
- The therapy for bone sarcomas is multimodal and frequently includes chemotherapy, surgery, and/or radiation therapy.
- Multidisciplinary conferences enable health care providers to optimize a patient's care.
- Because these diseases are rare and aggressive, we recommend evaluation and treatment by physicians and pathologists with expertise in bone sarcomas.

Suggested Readings

Federman N, Bernthal N, Eilber FC, Tap WD. The multidisciplinary management of osteosarcoma. Curr Treat Options Oncol. 2009;10:82–93.

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Chapter 2
Bone Sarcoma Imaging

John E. Madewell, Colleen M. Costelloe, Tamara Miner Haygood, Rajendra Kumar, and William A. Murphy, Jr.

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Chapter Overview Imaging studies are invaluable in the diagnosis, staging, and evaluation of response to treatment of bone sarcomas. At MD Anderson Cancer Center, the most essential initial imaging studies performed for diagnosis and staging are plain film radiography and magnetic resonance imaging (MRI), respectively.

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P.P. Lin and S. Patel (eds.), *Bone Sarcoma*, MD Anderson Cancer Care Series,
DOI 10.1007/978-1-4614-5194-5_2,

To answer specific questions, these studies are often augmented by other imaging modalities, such as computed tomography (CT), skeletal scintigraphy, positron emission tomography (PET) with fused CT (PET/CT), and ultrasonography. After treatment, plain radiography, MRI, and PET/CT may be used to evaluate tumor response. One cannot overemphasize the importance of these modalities in the comprehensive evaluation of patients with bone sarcomas. Accurate characterization of the primary lesion is key to the diagnosis, while precise identification of local, regional, and distant disease is critical to staging and treatment.

Introduction

The radiographic appearance of a tumor indicates its degree of aggressiveness, thereby suggesting whether the tumor is benign or malignant. As a standard of practice at MD Anderson Cancer Center, findings from plain radiographs are coupled with clinical information; decisions are then made about the need for additional imaging studies and procedures. Over time, as imaging studies advance into functional and metabolic realms, their impact will be incorporated more fully into the practice of radiology. Even at present, diagnosis of and treatment planning for bone sarcomas involve a multidisciplinary correlation of clinical, radiologic, and pathologic data (Morrison et al. 2005).

The multidisciplinary approach necessitates cooperation among the medical oncologist, radiologist, pathologist, radiation oncologist, and orthopedic oncologist. At our institution, the radiologist participates in the initial patient evaluation, so that imaging studies are interpreted within the clinical context.

The initial analysis of imaging features of bone sarcomas, derived mostly from plain radiographs, includes consideration of the location of the lesion within a bone, the appearance of its margins, the pattern of periosteal reaction (if present), the pattern of osteolysis (bone destruction), and the type of matrix mineralization. The data about the bone lesion derived from the plain radiographs facilitate the radiographic diagnosis and at times even influence the pathologic diagnosis. After the radiographic diagnosis, further radiologic imaging becomes essential for staging the local disease. During preoperative treatment (usually with chemotherapy), imaging of the tumor is important for evaluating response and can help guide the oncologist in deciding whether to continue or alter treatment. Specific considerations for the role of imaging in diagnosis, in assessing extent of disease, and in evaluating response to treatment are described in this chapter.

Lesion Location

Bone sarcomas occur in predictable locations; most arise in the metaphysis of a long bone, especially around the knee in either the distal femur or the proximal tibia. The dominant anatomic sites of many bone tumors have been described (Johnson 1953; Madewell et al. 1981). The locations in which these tumors arise (Fig. 2.1) reflect

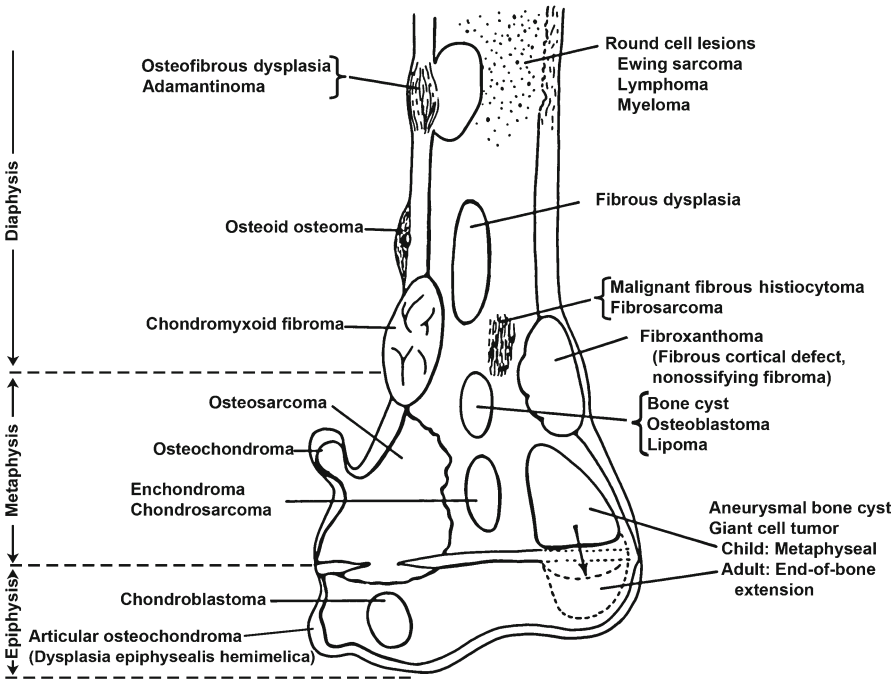

Fig. 2.1 Frequent sites of common primary bone tumors, depicted in the end of a long bone, which is divided into the epiphysis, metaphysis, and diaphysis. Adapted from Madewell et al. (1981).

increased underlying cellular activity. Because the distal femur and proximal tibia are the most rapidly growing areas of the skeleton, it is understandable that they are the most common sites for many bone neoplasms. However, bone sarcomas may arise at other sites in a long bone, and any bone in the body may be involved.

An important aspect of imaging bone sarcomas is the relationship of the tumor to the adjoining normal soft tissues and other vital structures, such as the neurovascular bundle. Description of the relationship between the tumor and these adjacent normal structures is critical to local staging of the bone sarcoma and to the planning of surgical intervention.

Diagnostic Imaging

As described below, plain radiography remains the primary imaging modality for the initial evaluation of skeletal neoplasms because of its utility for detecting, characterizing, and quantifying bone alterations. Magnetic resonance imaging (MRI) has distinct advantages in detection of bone marrow and soft tissue extension, and computed tomography (CT) is useful in certain circumstances, especially in instances of complex bony anatomy. Skeletal scintigraphy (radionuclide bone

scanning) can help in the detection of multiple lesions, either within a single anatomic compartment (skip lesions) or in distant sites. Other modalities used on occasion in workup of patients with potential bone sarcomas are positron emission tomography (PET), fluoroscopy, and ultrasonography.

Radiography

At the time of presentation, primary bone sarcomas usually are characterized by fairly extensive local disease. Plain radiographs usually demonstrate osteolysis, periosteal reaction, and even matrix mineralization, depending on the type of bone tumor. Besides these tumor characteristics, radiographs also show the specific location of the tumor within the bone: whether it is located in the epiphysis, the metaphysis, the diaphysis, or a combination of these sites (Fig. 2.1).

Osteolytic Margin Pattern

One of the important types of diagnostic information identified with radiography is the nature of the tumor margins. A lytic lesion's appearance on radiographs depends on the structure of the underlying bone, whether it is cancellous (trabecular) or cortical (compact) bone, the degree of adjoining bone loss, and the amount of contrast between the lesion and the surrounding bone (Madewell et al. 1981). For example, a small, focal area of bone loss within the dense cortical bone is easily seen with radiography, but a similar focus of destruction in the cancellous bone of the marrow may be difficult to see because there is less adjacent bone to produce visual contrast. Thus, a greater volume of osteolysis is needed for perceiving abnormalities in cancellous bone than for perceiving them in cortical bone. An example of this background contrast effect can be seen in the elderly patient with osteoporosis, in whom early destructive lesions are more difficult to detect; even advanced infiltrative destructive processes may not be appreciated because of lack of contrast due to density loss within the cancellous bone. In such radiographic settings, other more sensitive imaging modalities, such as MRI, CT, or skeletal scintigraphy, are most helpful in detection of the lesion.

The growth of bone sarcomas induces host osteoclastic activity and modifies bone structure locally and regionally to produce the fundamental radiographic patterns referred to as *geographic* (type I), *moth-eaten* (type II), and *permeative* (type III) bone destruction (Fig. 2.2). These lucency patterns serve as an index of tumor growth rates (Lodwick et al. 1980; Oudenhoven et al. 2006).

Geographic osteolysis creates a well-circumscribed lesion with a narrow zone of transition. Arcuate, lobulated, or scalloped borders are commonly associated with slow-growing, benign lesions, such as enchondroma, fibrous dysplasia, fibroxanthoma, chronic osteomyelitis (Brodie abscess), and bone cysts. These nonaggressive types of margin are also sometimes associated with low-grade (grade 1)

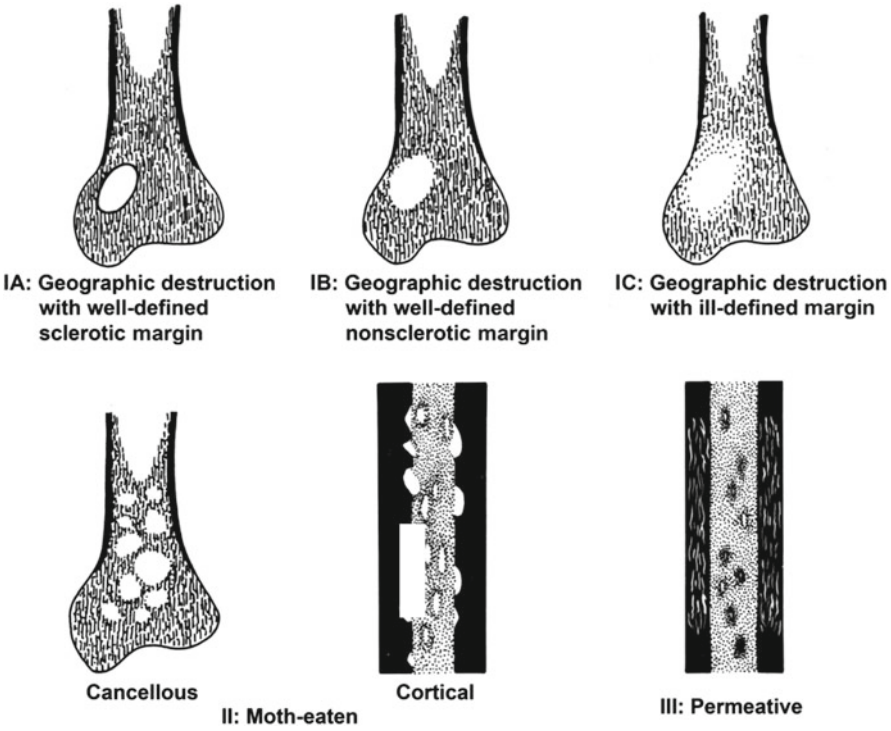

Fig. 2.2 Patterns of osteolysis (types IA, IB, IC, II, and III) and their margins. Transitions from a lower numbered pattern to a higher numbered pattern imply increased activity and a greater probability of an aggressive process or malignancy. Adapted from Madewell et al. (1981).

malignancies. Tumors with the geographic pattern of radiolucency may have rims with margins that are *sclerotic* (IA), *nonsclerotic* (IB), or *ill defined* (IC). These three different phases of the geographic pattern, described below, correspond to progressive tumor aggression.

Geographic lesions with sclerotic and nonsclerotic margins represent a narrow zone of transition. In both these margin types, the normal cancellous bone is present up to the peripheral edge of the tumor, but the degrees of remodeling vary. Lesions with nonsclerotic margins are more aggressive but are still generally associated with benign bone tumors, such as giant cell tumor, chondromyxoid fibroma, enchondroma, and chondroblastoma. Occasionally, deceptive low-grade sarcomas, such as chondrosarcoma, may exhibit a similar radiographic appearance. Hence, the possibility of a bone sarcoma increases when the geographic pattern with nonsclerotic margins is detected. The likelihood of malignancy increases even further when the tumor margin is ill defined or fuzzy. This type of geographic lesion represents a locally infiltrating, poorly contained lytic process and is indicative of local aggression. The tumor usually extends into the bone marrow beyond the main, perceived

margin of the lytic lesion, and the true extent of the lesion is best appreciated with MRI. Such locally invasive tumors may include giant cell tumor, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, and chondrosarcoma.

Moth-eaten osteolysis consists of multiple scattered holes that vary in size and may arise separately or originate from the edge of a major central, lytic component. They can coalesce into a more focal or larger destructive lesion and may affect cancellous bone, cortical bone, or both. In the cancellous bone, the normal trabecular markings can usually be seen between the holes. The holes are caused by regional infiltration from more aggressive processes, which tend to spare the intervening normal bone. In the cortical bone, the destructive holes that create this moth-eaten pattern usually begin on the endosteal surface and progress along the cortical axis outward to the periosteum. The defects filled with neoplasm are usually oval and represent active osteoclastic resorption at the cancellous and cortical bone. Bone lesions with a moth-eaten pattern of osteolysis may have cortical penetration and soft tissue extension. Evaluation for such extension is best accomplished with MRI. The moth-eaten osteolytic pattern is frequently seen in malignant neoplasms such as osteosarcoma, chondrosarcoma, Ewing sarcoma, malignant fibrous histiocytoma, fibrosarcoma, and primary bone lymphoma. This pattern may also be seen with osteomyelitis, which may cause aggressive osteolysis, especially in its acute/subacute form. However, osteomyelitis is usually associated with clinical and laboratory findings indicative of an inflammatory process. Subacute/chronic osteomyelitis and other inflammatory diseases, such as Langerhans cell histiocytosis, may masquerade as neoplasms, and biopsy of the lesion may be the only way to differentiate them from bone sarcomas.

Permeative osteolysis is predominantly cortical bone destruction in which multiple uniform, tiny, oval areas of lucency or streaks are seen within the cortex. These streaks are created by cortical tunneling from osteoclastic cutting cones in an accelerated phase of normal cortical remodeling that is stimulated by hypervascularity and tumor extension. These cortical permeations are usually seen with highly aggressive neoplasms such as Ewing sarcoma and osteosarcoma. However, they can also be seen with aggressive benign bone lesions, such as stress fractures and acute osteomyelitis. Again, clinical and laboratory features are helpful in excluding malignancy in such cases. Even metabolic diseases with active cortical remodeling, such as hyperparathyroidism, can exhibit this permeative lytic pattern, usually in metaphyseal cutback areas such as the concave portion of the metaphysis or at points of greatest stress. Cortical permeation caused by metabolic disease is usually more generalized and multifocal than the focal cortical permeation caused by a bone sarcoma.

Bone sarcomas may simultaneously exhibit more than one type of osteolytic margin pattern. The area of most aggressive destruction is the most ominous and relevant in regard to patient management and prediction of the biologic activity of the tumor. Such areas of aggressive osteolysis should be biopsied to obtain representative tissue samples from the tumor. Another important feature of margin evaluation is its change over time. A prior radiograph that shows a well-defined or sclerotic rim of a bone lesion, paired with a follow-up radiograph that shows aggressive destruction, suggests biological change and a more malignant neoplasm.

Table 2.1 Relationship of biologic activity to osteolytic margin pattern and periosteal reaction

Growth rate	Osteolytic margin pattern	Periosteal reaction
Slow	Geographic (I)	Solid
	IA	
	IB	
	IC	
Intermediate	Moth-eaten (II)	Shells
		Ridged
		Lobulated
		Smooth
Fast	Permeative (III)	Lamellated
Fastest	Nonvisible	Spiculated or none

IA, well-defined sclerotic margin; IB, well-defined nonsclerotic margin; IC, ill-defined margin. Adapted from Madewell et al. (1981).

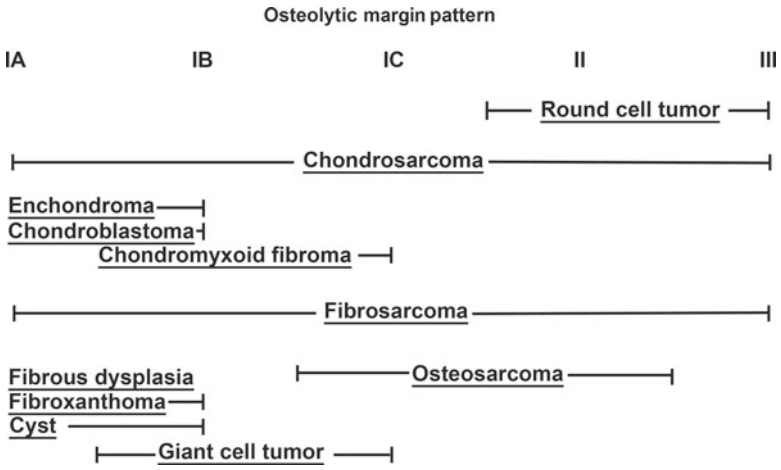

Fig. 2.3 Common bone tumors classified by their typical patterns of osteolysis. IA, geographic destruction with well-defined sclerotic margin; IB, geographic destruction with well-defined nonsclerotic margin; IC, geographic destruction with ill-defined margin; II, moth-eaten destruction (regionally invasive); III, permeative destruction (diffusely invasive). Note that most benign tumors occur on the left side of this spectrum, with patterns from IA to IC, whereas most malignant tumors occur on the right side, with patterns from IC to III. This distribution illustrates the general principle that the biologic activity and probability of malignancy increase from left to right. Adapted from Madewell et al. (1981).

To summarize, the defining margin or interface between the tumor and adjacent normal bone in cortical and/or cancellous locations is an indicator of the underlying biologic process of the tumor and its aggressiveness (Table 2.1, Fig. 2.3). The radiographic image shows best the location in bone and represents a summation of bone osteolysis (osteoclastic activity) and osteosclerosis (osteoblastic activity). Sarcomas may arise in preexisting benign lesions or may be lower-grade tumors. In such

cases, the radiographic pattern may lag behind the histologic activity, producing a radiographic discrepancy (a lesion that appears to be growing slowly but has a malignant histologic type). A careful analysis of these radiographic patterns, when integrated with clinical data, will enable accurate diagnosis in the initial evaluation of suspected bone sarcomas in most patients.

Periosteal Reactions

The periosteum is traditionally defined as an envelope consisting of inner cellular and outer fibrous components that separate the bone from surrounding soft tissue. In the child, it is a rich source of uncommitted mesenchymal stem cells and preosteoblasts. In the adult, even though the periosteum may not be as substantial as it is in children, periosteal reactions are common sequelae of underlying bone marrow processes, including bone sarcomas, and are helpful in predicting the biologic activity of the bone lesions.

The various patterns of periosteal reactions in a bone (Fig. 2.4) represent the periosteum's attempt to contain a bone lesion, and the radiographic appearance of the periosteal reaction relates to the manner, time, and course of periosteal bone production and mineralization (Ragsdale et al. 1981). Periosteal reactions are biologic measures of the intensity, aggression, and duration of the inciting underlying bone processes. These reactions involve the reawakening and acceleration of mechanisms that modify the surface of bone in normal growth by production of new bone from the cambian layer of the periosteum. The periosteal reaction must be mineralized in order for radiography to demonstrate its presence. This mineralization may require as much as 10 days to 3 weeks from the initial stimulus, depending on the nature of the stimulus and the age of the patient. When the periosteal reaction is continuous and solid, it is an indicator of slow underlying biologic activity and is commonly associated with benign or slow-growing processes. However, if the periosteal reaction is interrupted, spiculated, or lamellated or demonstrates a Codman angle or buttress angle, it is indicative of an aggressive process, and, with the exclusion of certain conditions such as infection and trauma, it is associated with a high probability of a malignant bone tumor.

Matrix Production and Mineralization

The term *matrix* refers to an acellular intercellular substance produced by mesenchymal cells and may include osteoid, chondroid, myxomatous material, and/or collagen. Bone tumors may be divided into matrix-producing and non-matrix-producing lesions. When radiographic mineralized matrix patterns of increased density (Fig. 2.5) are present, their significance in predicting the specific diagnosis of bone tumors is well recognized (Sweet et al. 1981). Specific patterns of mineralized matrix can indicate the underlying histologic composition of either chondroid- or osteoid-producing bone tumors (Figs. 2.6b, c, 2.7, and 2.8). These patterns may also be helpful to the