1 INTRODUCTION TO BONE TUMORS

The diagnosis of bone tumors frequently poses challenges to pathologists and clinicians. This is not surprising, since these tumors are uncommon, morphologically heterogeneous, possess a broad spectrum of biologic behavior, and often require specific and complex therapeutic strategies to effect a cure. Accurate diagnosis requires an integrated approach that assesses and correlates the clinical, radiologic, histologic, molecular, and prognostic characteristics of the neoplasm. The importance of correlating the histologic and radiologic findings of the lesion to ensure diagnostic accuracy cannot be overemphasized. In most instances, successful patient care is best accomplished when members of a sarcoma multidisciplinary team collaborate to diagnose and stage the tumor, and design and implement an optimal treatment plan (1).

Neoplasms of bone, and the skeletal response to them, often recapitulate the cells, tissue types, and biologic processes that form the normal skeleton during growth and development. Understanding these mechanisms and their morphologic expression is essential to correctly identify the nature and biologic potential of bone tumors and tumor-like lesions.

GROWTH, DEVELOPMENT, AND STRUCTURE OF BONE TISSUE

The skeletal system is composed of 206 bones, and each bone is composed of bone tissue, a specialized type of connective tissue. Bone tissue is unique in that it is a biphasic blend of inorganic or mineral component (calcium hydroxyapatite) and organic constituents (the cells and their secreted proteins). The term osteoid refers to bone that is unmineralized in vivo and is composed only of the organic components. Bone is the hardest and strongest tissue in the body. It undergoes constant remodeling at variable rates throughout life, which accommodates growth and development, changes in function and metabolism, and skeletal repair.

The size and shape are the determinants for the classification of individual bones. The most numerous group of bones are tubular, both long (appendicular) and short (acral); other types of bones include flat (bilaminar plates such as ilium, cranium, sternum), irregular (tarsals, carpals, vertebrae), and sesamoid bones. Anatomically, tubular bones are further divided into regions, including the epiphysis, metaphysis, and diaphysis (fig. 1-1). The epiphysis extends from the base of the articular surface to the growth

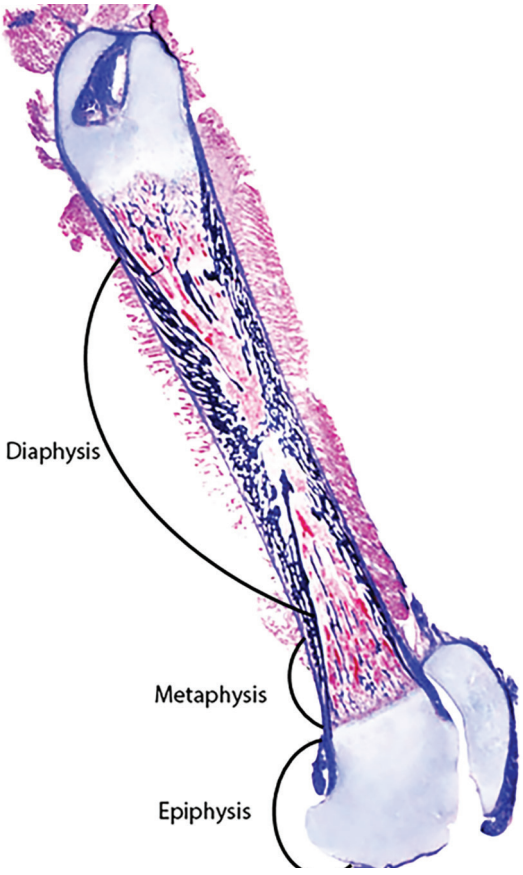

Figure 1-1
ANATOMIC REGIONS OF A LONG BONE

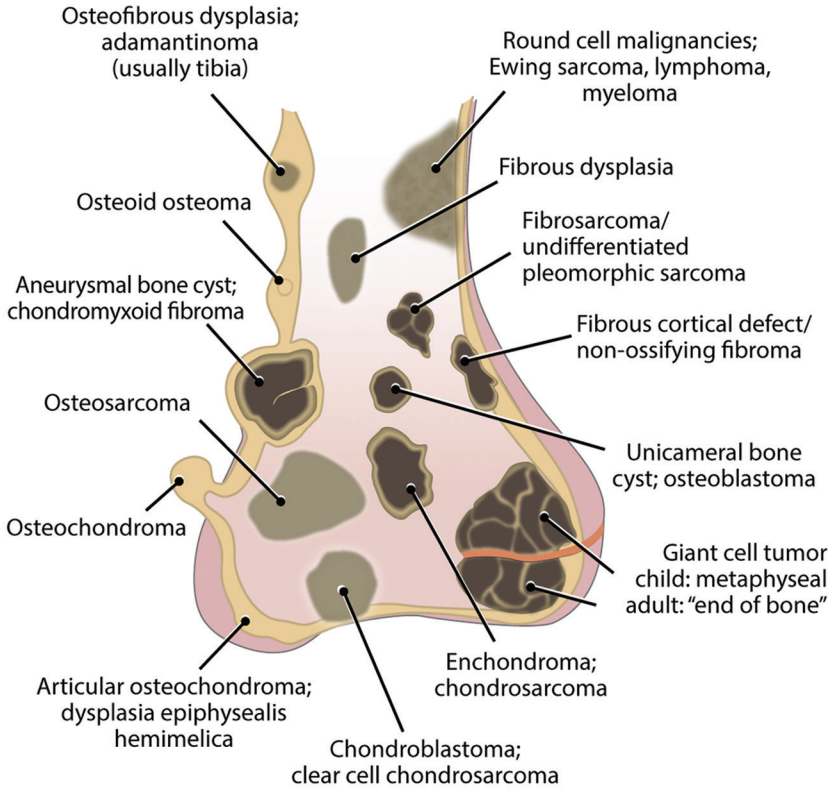

Figure 1-2

RELATIONSHIP BETWEEN TYPE OF BONE TUMOR AND LOCATION IN LONG BONE

plate or scar of the growth plate. The metaphysis embodies the region of bone that undergoes a significant decrease in diameter and extends from the growth plate or its scar to the site where the bone diameter is narrowed. The diaphysis, or shaft, extends from the base of one metaphysis (the point where the decrease in bone diameter ceases) to the base of the opposing metaphysis. During growth and development, the metaphysis is composed mainly of a cartilaginous growth plate, also known as the physis, and the primary and secondary spongiosa. Apophysis, also known as an epiphyseal equivalent, is a natural protuberance from bone for the attachment of tendons or ligaments, and includes the greater and lesser trochanters and iliac crest. There is a relationship between the location within the skeleton and the specific anatomic site, especially in long bones and vertebrae, with particular types of bone tumors (fig. 1-2).

Commencing in the embryo until adult stature is attained, the bones of the body undergo a significant increase in size, refinement of shape, and modulation of contour. Being rigid, bone does not grow interstitially and only enlarges by the apposition of new bone on preexisting surfaces. In contrast, cartilage has the capacity for both appositional and interstitial growth; it increases its substance and enlarges in all dimensions by adding new cells that elaborate extracellular matrix internally and on its surfaces. These characteristics of bone and cartilage form the foundation of the two major processes of formation and growth of the bone, known as enchondral and intramembranous ossification. In enchondral ossification, a cartilage model is replaced by bone, and in intramembranous ossification, bone tissue is formed directly by precursor cells residing in a membranous layer of fibrous tissue.

The increase in the length of tubular bones in embryos and prepubertal children occurs as growing cartilage is replaced by bone, i.e., enchondral ossification, with most of the growth derived from the cartilage anlage (cartilage model of the future bone) and growth plate. The cartilage anlage initially develops in the early stages of embryogenesis from mesenchymal cells that form cellular condensations at the sites of future bones (fig. 1-3). These mesenchymal cells

differentiate into chondrocytes that produce a cartilage model or anlage of the forthcoming bone. This process commences at a specific time for individual bones, and the temporal sequence of anlage formation is the same in all humans.

Surrounding the newly formed cartilage anlage are mesenchymal cells that form the perichondrium. The perichondrium transforms into the periosteum once ossification is initiated. This process first occurs in the midportion of the cartilaginous shaft, where mesenchymal stem cells in the perichondrium begin to produce a layer of osteoblasts that deposit a collar of woven mineralized bone on the surface of the cartilage model. This marks the transformation of the perichondrium into the periosteum, and this anatomic region in the central part of the diaphysis, composed of different tissue types, is known as the primary center of ossification (fig. 1-4). Subsequently, the chondrocytes in the interior of the cartilaginous shaft that are encased by the periosteal shell of bone begin to hypertrophy and swell. Soon thereafter, these cells undergo apoptosis, and the surrounding matrix mineralizes. Concurrently, the periosteal vessels give rise to a capillary network, which,

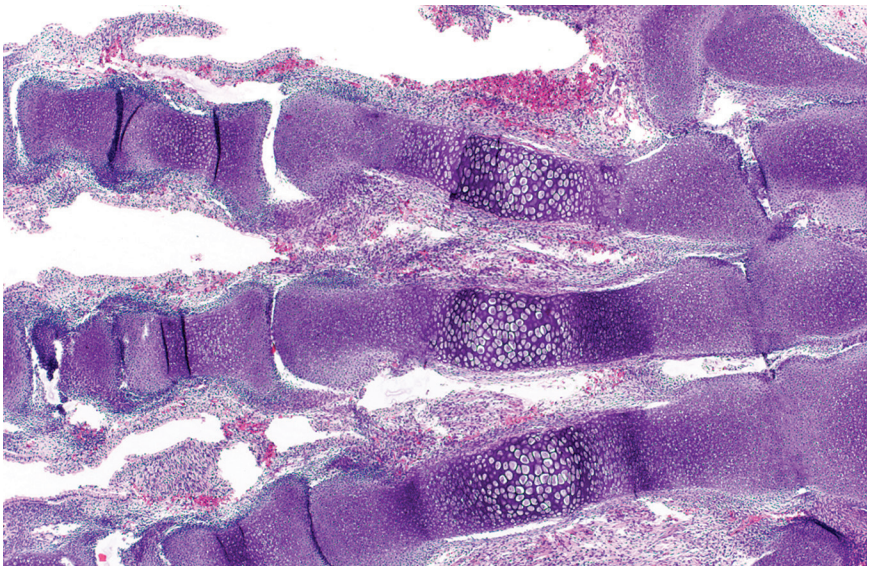

Figure 1-3

CARTILAGE ANLAGE

Cartilage anlage of the hand showing that the skeletal structures are composed of hyaline cartilage. In the center of the diaphysis, the chondrocytes are enlarged and resemble those in the zone of hypertrophy of the growth plate. These changes are occurring in preparation for the development of the primary center of ossification.

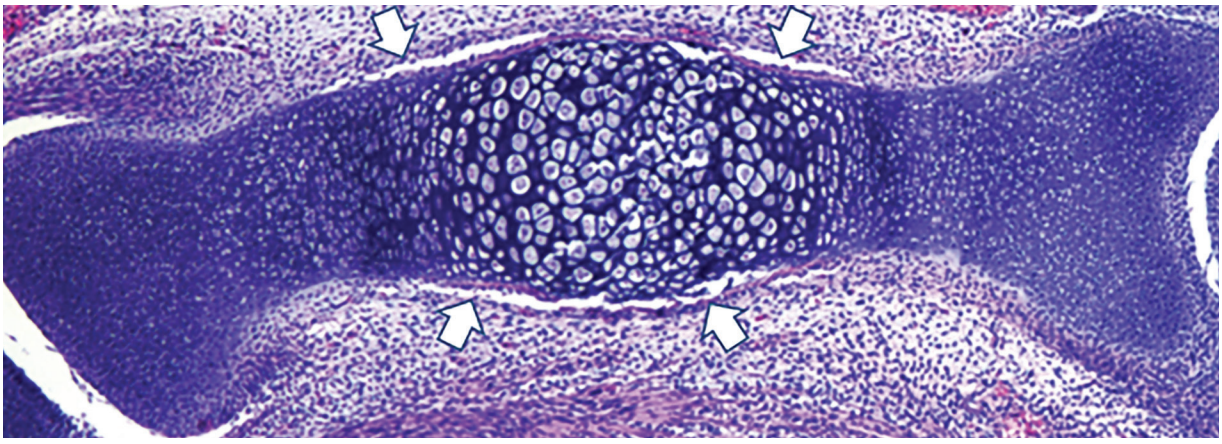

Figure 1-4

PRIMARY CENTER OF OSSIFICATION

The phalanx is composed of hyaline cartilage anlage and its surface is covered by a thin layer of newly formed bone (arrows) that is rimmed peripherally by osteoblasts, the region of the primary center of ossification.

Figure 1-5

GROWTH PLATE

Horizonal growth plate separates the epiphysis and the well-developed secondary center of ossification from the metaphysis.

with the aid of osteoclastic resorption, penetrates the woven bone of the primary center of ossification into the mineralized cartilage.

Osteoclasts continue to bore into the cartilaginous core of the bone, leaving residual, longitudinally oriented struts of matrix. These struts of cartilage act as scaffolding for newly formed bone deposited by osteoblasts originating from mesenchymal stem cells. Composed of a central cartilaginous core covered by a layer of woven bone, these first trabeculae form the primary spongiosa. A continuous breakdown of cartilage creates spaces that coalesce and form the medullary cavity. This complex process of cartilage replacement by bone, with the development of a marrow cavity, progresses toward both ends, concurrent with lengthening of the bone.

In most long bones, a similar process develops subsequently in the epiphyses, and this region is the secondary center of ossification. The maturation and replacement of the cartilage anlage in the secondary center of ossification are identical to the process in the diaphysis, except that the maturation proceeds from the center centrifugally toward the periphery. The continual growth of the primary and secondary centers of ossification eventually results in their fusion. At this time, a plate of bone demarcating the secondary center from the primary center is deposited, and henceforth, centrifugal growth of the epiphysis is hemispheric. Once the plate of bone that demarcates the secondary from the primary center of ossification forms, the final structure of the growth plate is attained (fig. 1-5).

Growth plates are responsible largely for the longitudinal growth of bones and, through the process of enchondral ossification, participate in the generation of the first cancellous bone of the skeleton. In the growth plate, the chondrocytes are arranged in merging regions that correspond to different stages of chondrocyte proliferation and maturation (fig. 1-6).

As the cells pass through different stages of their lifespan, they do not literally move within the matrix but mature in the position they occupy when first formed. The stages of maturation are reflected in their morphology, and these features form the basis of their division into different zones including: 1) a region of resting or reserve chondrocytes located nearest the ends of the bone; 2) a region of proliferating chondrocytes, which become arranged in spiral columns; 3) a region of chondrocyte hypertrophy; 4) a region of chondrocyte apoptosis and matrix mineralization; and 5) a region of cartilage resorption by osteoclasts.

The chondrocytes in the reserve zone are small, round or oval, and surrounded by abundant matrix; those at the base give rise to those that form the zone of proliferation. The chondrocytes in the zone of proliferation are flattened, undergo cell division, become arranged in spiral columns, and elaborate extracellular matrix. In the zone of hypertrophy, the chondrocytes enlarge with the cytoplasmic volume, increasing tenfold, and

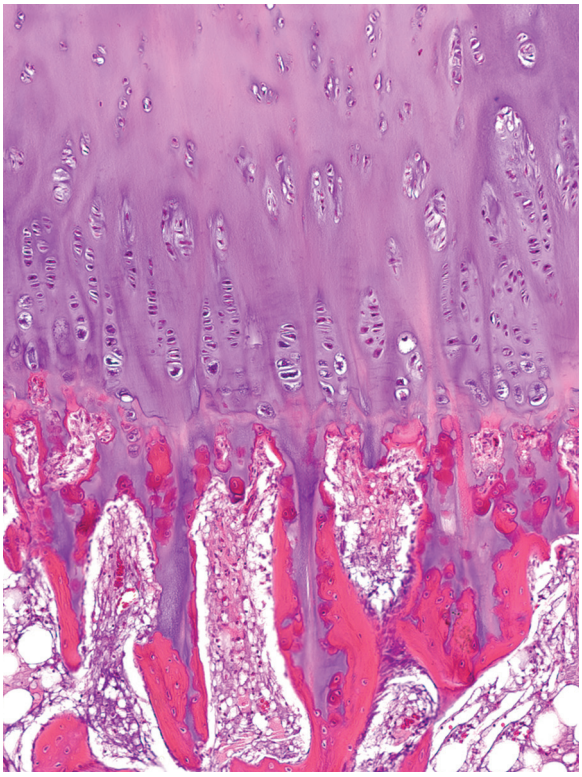

Figure 1-6

GROWTH PLATE

Growth plate cartilage undergoes enchondral ossification to produce the primary spongiosa, first bone trabeculae.

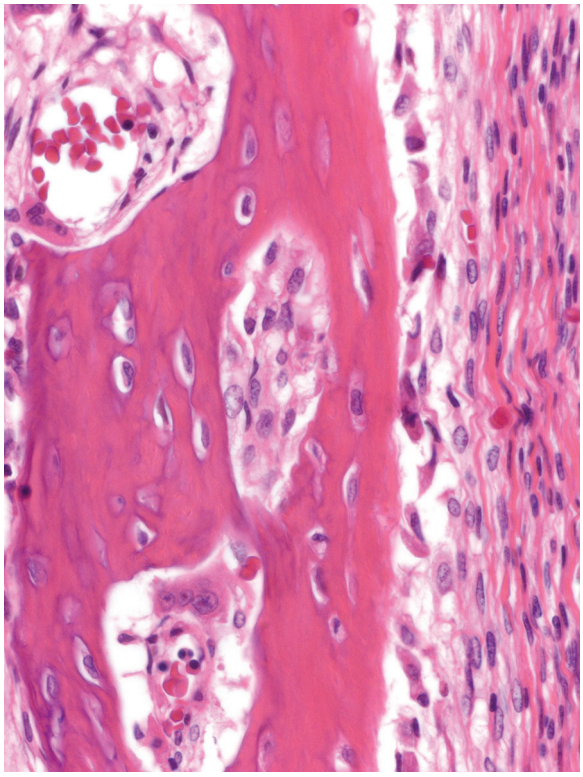

Figure 1-7

INTRAMEMBRANOUS OSSIFICATION IN GROWING BONE

Cellular periosteum overlies active osteoblasts, depositing bone onto the outer layer of the forming cortex.

the cells model the surrounding matrix as they increase in size. In the zone of mineralization or calcifying cartilage (sometimes considered a subregion of the hypertrophic zone), the chondrocytes secrete matrix vesicles that are derived from the cell membrane, which control mineralization of the surrounding extracellular matrix.

As the matrix mineralizes, the chondrocytes undergo rapid apoptosis in the last row of lacunae before the ossification front. This process is associated with the release of cytokines, which attract the ingrowth of endothelial-lined blood vessels, and osteoclasts, which tunnel into the mineralized matrix, digesting the transverse septa of matrix that separate the chondrocytes from one another. As a result, vertically oriented intercolumnar struts of mineralized cartilage remain; their orientation is determined by the preexisting columnar arrangement of the chondrocytes in the proliferative and hypertrophied zones, and parallels the long axis of the bone. These struts of cartilage become the scaffolding for newly deposited bone. Cartilage that undergoes enchondral ossification recapitulating growth plate cartilage occurs in all benign and malignant bone tumors that contain cartilage as a component and in non-neoplastic conditions such as fracture callus.

Intramembranous ossification develops from the mesenchymal condensations in the embryo and the periosteum in the fetus, child, and adult (fig. 1-7). The osteoprogenitor cells within the condensations and periosteum produce offspring that differentiate into mature osteoblasts, which deposit bone matrix. Large portions of the flat bones of the skull, including the frontal, parietal, occipital, and temporal bones, form solely by this process. Also, since the cortices of all bones are largely created by osteoblasts derived from the periosteum, all bones, at least in some part, are formed by intramembranous ossification.

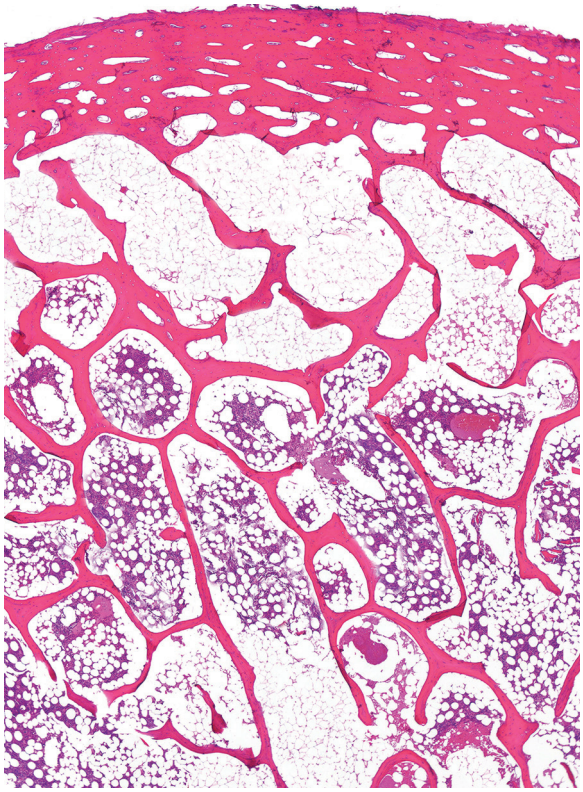

Figure 1-8

CORTICAL AND TRABECULAR BONE

Cortical bone with attached bone trabeculae and interspersed marrow elements.

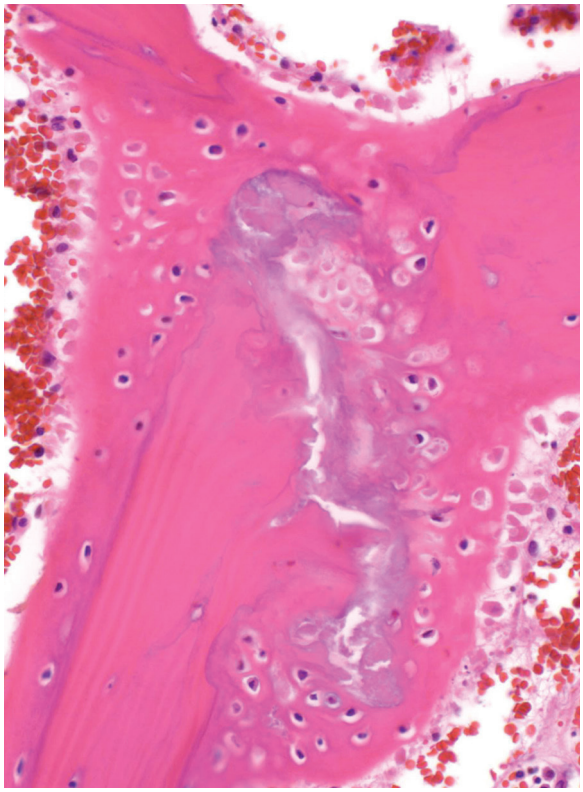

Figure 1-9

FRACTURED TRABECULA

Lamellar bone is surrounded by woven bone of the callus.

Regardless of whether bone tissue develops from the process of enchondral or intramembranous ossification, or whether it is cortical or cancellous (fig. 1-8), normal or part of a pathologic process, it is categorized into woven and lamellar types based on the organization of its type I collagen fibers, which are the major structural proteins of bone tissue. In woven bone, the collagen fibers are arranged in a seemingly haphazard feltwork, while in lamellar bone, they are deposited in parallel arrays (fig. 1-9). Neoplastic bone is usually woven and trabecular in architecture rather than cortical in appearance. Reactive bone may be woven or lamellar and trabecular or cortical in pattern.

EPIDEMIOLOGY

The overall frequency of bone tumors is unknown, as most benign tumors are asymptomatic and are only detected as incidental findings. Some benign tumors are common: fibrous cortical defect develops in 50 percent of boys and 20 percent of girls older than 2 years of age, and hemangiomas of the spine are identified in at least 10 percent of the adult population, indicating that benign tumors of bone affect billions of individuals (2). Based on this information, it is estimated that benign bone tumors outnumber their malignant counterparts by at least 71,000 to 1.

Bone sarcomas are rare: they account for 0.2 percent of all malignancies. In 2019, approximately 3,500 bone sarcomas were diagnosed in the United States resulting in an estimated 1,660 deaths (960 males and 790 females) (3,4). The adjusted incidence rate for all bone and joint malignancies is 0.9 per 100,000 person-years.

Bone tumors develop in all age groups, however, most affect young individuals who are less than 20 years of age. In many instances, there is a relationship between the age of the patient and

the specific location and type of tumor. Bone sarcomas have a bimodal age distribution: the first peak occurs in patients 10 to 20 years old, and the second develops during the seventh decade of life. The risk of developing a bone sarcoma is equal in both of these age groups, but in absolute numbers, more bone sarcomas are diagnosed during the second decade of life. Statistically, the younger the patient, the more likely a bone tumor is benign, since benign tumors outnumber sarcomas, commonly occur in childhood, and their frequency diminishes with age.

There is a paucity of information available regarding the distribution of benign bone tumors in relation to patient gender, which reflects the fact that most benign tumors are asymptomatic and do not undergo diagnostic evaluation. Existing estimates suggest, however, that benign tumors occur more frequently in males, although there is no scientific information that explains this association. Data concerning bone sarcomas are more comprehensive and reveal that males and females are affected at a ratio of 1.38 to 1.0 (3).

Although primary bone tumors develop in all parts of the skeleton, most have a predilection for the long tubular bones. Benign tumors tend to arise in the appendicular skeleton, with approximately 45 percent developing in the femur and tibia, usually about the knee. In comparison, bone sarcomas more frequently involve the pelvis, axial skeleton, and major long bones, especially distal femur and proximal tibia, and rarely affect the small bones of the hands and feet. The observation that many bone tumors arise in the distal femur and proximal tibia may be related to the fact that these sites possess the most active physeal plates in the body, which contain many mesenchymal stem cells that may experience mutational events.

ETIOLOGY

The etiology and pathogenesis of most bone tumors are uncertain. Current hypotheses indicate that clonal chromosomal aberrations in mesenchymal stem cells develop, the mutations activate genes, and the gene expression profile determines the specific phenotype and biologic potential of the newly formed neoplasm (see chapter 2). The specific molecular genetic changes and their related alterations in signaling pathways have resulted in a better understanding of the pathogenesis of some bone tumors and have helped identify diagnostic markers, prognostic factors, and new forms of targeted therapy.

Most bone sarcomas arise de novo; some, however, develop in association with a variety of genetic syndromes. Additionally, sarcomas have an increased incidence in certain disease states affecting bone, including radiation injury, Paget disease, bone infarction, and chronic osteomyelitis (1). Malignant transformation of preexisting benign tumors is infrequent, and those that do so are most commonly enchondroma and osteochondroma; rarely does it occur with fibrous dysplasia. There have been documented reports of sarcoma arising adjacent to orthopedic implants; however, the incidence of this dreaded complication is exceedingly small, and the sarcomagenic properties of the chemical components of the implants in humans are thought to be minimal (5,6). Nonetheless, this phenomenon deserves further investigation and monitoring.

CLASSIFICATION

The classification of bone tumors is based on the normal cell or tissue type that they recapitulate (Table 1-1) (1,7). Most differentiate along the cell lines or tissue types that compose the skeletal system; a small number have consistent and distinctive clinicopathologic features but lack an identified normal tissue counterpart. Further subclassification of bone sarcomas is based on their specific histologic characteristics, their relationship to the underlying bone, their genetic aberration, and the presence of preexisting conditions. A variety of non-neoplastic conditions and diseases may present as a mass involving bone, and these must be distinguished from primary bone neoplasms to ensure appropriate treatment (Table 1-2).

Bone tumors are also classified according to their biologic potential. The nomenclature of these categories reflects their anticipated behavior and has been espoused by the World Health Organization (WHO) classification of bone tumors (7). *Benign* tumors are considered indolent neoplasms with no metastatic potential and are associated with a low rate of local recurrence. *Intermediate-locally aggressive* tumors are locally destructive, associated with an increased risk of local recurrence, and have no risk of metastasis. *Intermediate-rarely metastasizing*

Table 1-1

CATEGORIES OF PRIMARY NEOPLASMS OF BONE BASED ON PHENOTYPE

Neoplasms of osteoblastic phenotype: bone-forming tumors
Neoplasms of chondrocytic phenotype: cartilage-forming tumors
Neoplasms of fibroblastic phenotype: fibrous and fibrohistiocytic tumors
Neoplasms of osteoblastic and fibroblastic phenotype: fibro-osseous tumors
Neoplasms of epithelial, osteoblastic, and fibroblastic phenotype: osteofibrous dysplasia and adamantinoma
Neoplasms of endothelial phenotype: vascular tumors
Neoplasms of notochordal phenotype: notochordal cell tumors
Neoplasms of primitive neuroectodermal phenotype: Ewing sarcoma
Neoplasms of malignant round cells of uncertain phenotype: undifferentiated round cell sarcomas
Neoplasms of malignant spindle and/or epithelioid cells of uncertain phenotype: undifferentiated pleomorphic sarcoma
Neoplasms of uncertain phenotype with osteoclastic giant cells: giant cell-rich tumors
Neoplasms of hematopoietic phenotype: lymphoid, myeloid, plasmacytic, histiocytic, and dendritic tumors
Neoplasms of smooth muscle phenotype: smooth muscle tumors
Neoplasms of Schwann cell phenotype: Schwann cell tumors
Neoplasms of adipocytic phenotype: adipocytic tumors
Neoplasms of myoepithelial phenotype: myoepithelial tumors

Table 1-2

NON-NEOPLASTIC TUMOR-LIKE LESIONS OF BONE

Stress fracture
Florid fracture callus
Brown tumor of hyperparathyroidism
Melorheostosis
Amyloidoma
Gaucher disease
Bone infarct
Intraosseous ganglion and synovial cyst
Subchondral cyst
Epidermoid inclusion cyst
Osteomyelitis/bone abscess

are locally aggressive tumors that have a low rate of metastasis, which is 2 percent or less. *Malignant* tumors or sarcomas are locally destructive, have a high rate of local recurrence when not widely excised, and possess a significant risk of dissemination.

CLINICAL PRESENTATION

Clinically, bone tumors have a broad spectrum of presentations, ranging from a small asymptomatic mass that is an incidental finding to a large, growing, painful, fungating tumor. Many tumors that lead to diagnostic evaluation cause localized pain, with or without a detectable mass. The pain may be intermittent, constant, progressive, and radiating. Rapid swelling, in conjunction with skin changes, such as red-violaceous discoloration and the development of prominent blood vessels, are other harbingers of malignancy. Systemic symptoms of fever, fatigue, and weight loss are usually associated with the most aggressive bone neoplasms. Mechanical dysfunction in the form of restricted movement results from tumor bulk or synovitis caused by a periarticular mass. The continued growth of the tumor can result in a pathologic fracture, which in a minority of patients is the heralding event, producing sudden excruciating pain, swelling, and hemorrhage.

GRADING AND STAGING BONE SARCOMAS

The pathologist's attempt to predict the biologic behavior of bone sarcomas is reflected in the histologic grade, which is translated into the

Table 1-3

AMERICAN JOINT COMMITTEE ON CANCER 8TH EDITION STAGING SYSTEM OF BONE SARCOMAS[a,b]

Stage	Tumor	Nodes	Metastases	Grade	Brief Summary of the Stage
IA	T1	N0	M0	G1 or Gx	T1 low-grade
IB	T2 or T3	N0	M0	G1 or Gx	T2 or T3 low-grade
IIA	T1	N0	M0	G2 or G3	T1 high-grade
IIB	T2	N0	M0	G2 or G3	T2 high-grade
III	T3	N0	M0	G2 or G3	T3 high-grade
IVA	Any T	N0	M1a	Any G	Lung metastases
IVB	Any T	N1	Any M	Any G	Regional lymph node involved
IVB	Any T	Any N	M1b	Any G	Bone or other distant metastases

[a]T0 = no evidence of a primary tumor, TX = a primary tumor cannot be assessed.
[b]General tumors of the appendicular skeleton: T1 = ≤8 cm in greatest dimension, T2 = >8 cm in greatest dimension, T3 = "skip lesions" (discontinuous tumors within a primary bone site).
Spine tumors: T1 = one to two adjacent vertebral segments, T2 = three adjacent vertebral segments, T3 = ≥4 adjacent vertebral segments or nonadjacent segments, T4 = extension into the spinal canal (T4a) or great vessels (T4b).
Pelvic tumors: GX = grade cannot be assessed, G1 = well-differentiated, low-grade, G2 = moderately differentiated, high-grade, G3 = poorly differentiated, high-grade, M0 = no distant metastasis, M1 = distant metastasis to the lungs (M1a) or bone/other distant sites (M1b), N0 = no regional lymph node metastasis (if nodes cannot be assessed, N0 is assumed because of the rarity of lymph node involvement in bone sarcomas), N1 = regional lymph node metastasis, T1 = confined to one pelvic segment; size ≤8 cm (T1a) or >8 cm (T1b) in greatest dimension, T2 = one segment extraosseous extension or two segments without extraosseous extension; size ≤8 cm (T2a) or >8 cm (T2b) in greatest dimension, T3 = two segments, extraosseous extension: size ≤8 cm (T3a) or >8 cm (T3b) in greatest dimension. T4 = three segments or crossing sacroiliac joint; sacroiliac joint involvement medial to the sacral neuroforamen (T4a) or the encasement of the external iliac vessels/gross tumor thrombus in major pelvic vessels (T4b).

biologic grades of low and high grade. Grading systems like the National Cancer Institute (NCI) and French Federation Nationale des Centres de Lutte le Cancer (FNCLCC) schemes devised for soft tissue sarcomas have not been developed and universally applied to bone sarcomas. There are, however, grading systems that some investigators have proposed for specific types of sarcomas, especially chondrosarcoma (8).

For many bone sarcomas, a three-tiered system based on the assessment of standard morphologic criteria, including the degree of differentiation, cytologic atypia, mitotic activity, and necrosis, can be used. The goal of the grading system is to distinguish sarcomas associated with a low probability of dissemination (biologically low grade; less than 10 percent chance of metastasis) from those that are aggressive and have a significant risk of systemic spread (biologically high grade; greater than 10 percent chance of metastasis). Grade 1 sarcomas are biologically low grade and are usually hypocellular to moderately cellular. The tumor cells demonstrate mild cytologic atypia, closely resemble their normal tissue counterparts, and have few if any mitoses and minimal necrosis.

Grades 2 and 3 sarcomas are considered biologically high grade for treatment purposes, and are moderately to densely cellular. The cells are moderately to severely pleomorphic and hyperchromatic, and are mitotically active with atypical forms, and the tumor contains areas of necrosis.

There are select bone sarcomas for which the histologic subtype reflects the biologic potential and, therefore, also the grade; for instance, Ewing sarcoma is high grade. There are other primary malignancies, such as adamantinoma and chordoma, that are not traditionally graded. Generally, the focus of treatment of low-grade sarcomas is local control, whereas systemic therapy combined with local control is used for patients with high-grade sarcomas.

The pathologic staging of bone sarcomas provides important prognostic information and offers guidelines for effective treatment. The two major staging systems used are those endorsed by the American Joint Commission on Cancer (AJCC) (Table 1-3) and the Musculoskeletal Tumor Society (Table 1-4) (9,10). The AJCC system incorporates tumor size, location (appendicular skeleton, trunk, skull, facial bones/pelvis/spine),

Table 1-4

MUSCULOSKELETAL TUMOR SOCIETY STAGING SYSTEM OF BONE SARCOMAS

Stage	Grade	Site	Metastases
IA	Low	lntracompartmental	------
IB	Low	Extracompartmental	------
IIA	High	lntracompartmental	------
IIB	High	Extracompartmental	------
III	Any	Any	Present (regional or distant)

grade, and presence of metastases, and whether metastases are in the lungs or bone and other sites. In contrast, the Musculoskeletal Tumor Society staging scheme is more focused on surgical staging and integrates tumor grade, anatomic extent, and presence of metastases (10). Assessment of tumor size on biopsy specimens requires knowledge of the imaging findings, which can also provide information regarding the extent of local and distant disease (11).

TREATMENT AND PROGNOSIS

The treatment of benign bone tumors depends on the type, size, location, and symptoms. Some tumors, such as fibrous cortical defect, nonossifying fibroma, unicameral bone cyst, fibrous dysplasia, osteochondroma, and enchondroma, may be observed if the patient is asymptomatic, the lesion is small, and there are no worrisome radiologic features. Symptomatic benign tumors usually require surgical removal in the form of curettage, with or without an adjuvant (liquid nitrogen, phenol, polymethylmethacrylate, or thermal cautery) or en bloc resection for tumors in specific locations such as the proximal fibula that do not result in significant loss of function. Sarcomas, in contrast, usually require excision with widely negative margins, which may require amputation. High-grade sarcomas are also often treated with neoadjuvant systemic therapy. Radiation is usually reserved for unresectable tumors or when resection is associated with positive margins (skull base, spine, pelvis).

The prognosis of patients with bone tumors depends on the size, location, type, and biologic potential of the neoplasm. Some benign tumors have a low rate of recurrence following curettage or en bloc resection, such as nonossifying fibroma, fibrous dysplasia, osteochondroma, and enchondroma, while the rate of recurrence of more aggressive lesions such as chondroblastoma, osteoblastoma, aneurysmal bone cyst, and giant cell tumor is 10 to 20 percent.

The prognosis of patients with sarcoma also depends on the specific type, size, location, grade, and stage of the tumor. For some tumors, such as osteosarcoma and Ewing sarcoma, other variables, including patient age and response to chemotherapy, have prognostic importance (12). Important independent prognostic factors associated with a poor outcome include proximal location in an extremity or in the axial skeleton, large tumor size, clinically detectable metastases at the time of initial diagnosis, and poor response of the tumor to preoperative chemotherapy.

Overall, the 5-year survival rate for adults with bone sarcoma is approximately 66 percent and for children approaches 80 percent (3,4). The 5-year survival rate for patients with metastatic disease is much lower and ranges from 30 to 40 percent.

HANDLING BONE TUMOR SPECIMENS

The ability to make a primary diagnosis, document recurrence or metastasis, and assess treatment effect is based on the assessment of bone tumor specimens. The different types of tissue specimens include fine-needle aspiration (FNA) cytology, needle core biopsy, open curettage (which yields multiple, irregular fragments of tissue), and en bloc resection. In specific instances, frozen section analysis can be performed to facilitate diagnosis and assess margin status.

Cytologic evaluation has been reliably and successfully used for many years in the investigation and diagnosis of metastases to the skeleton. FNA diagnosis of primary bone tumors is challenging because of the morphologic heterogeneity of the tumors and their relative rarity. Studies have shown that the FNA diagnosis of primary bone tumors has an accuracy rate of 70 to 90 percent when the goal is distinguishing benign from malignant lesions. It is not a technique that is usually used to render the primary diagnosis and grade the tumor, except in the hands of the most experienced cytologists. Knowledge of the

cytologic appearance of primary bone tumors is important, however, because they may be aspirated during the workup for suspected metastatic disease, from which they must be distinguished.

Needle core biopsy is often performed with computerized tomography (CT) scan or ultrasound guidance; we recommend that a minimum of three cores of tumor-bearing tissue be obtained for diagnosis. A frozen section can be performed on one core to confirm that diagnostic tissue is present, provide a provisional diagnosis, and facilitate triage of the remaining tissue, including generating touch preparation slides for fluorescence in situ hybridization (FISH) analysis, if appropriate. The remaining cores can be fixed in formalin and processed routinely for standard hematoxylin and eosin (H&E)-stained slides. If the tissue requires decalcification, it should be done with solutions that preserve RNA and DNA, or a representative core should be kept frozen or embedded in paraffin and not decalcified, to enable molecular testing.

Open biopsy for primary diagnosis typically generates specimens that are amenable to frozen section analysis. The tissue, including bone (except for pieces of cortex), can be frozen to construct a working diagnosis and allow for the appropriate triage of tissue. If curettage is going to be immediately followed by a definitive procedure during the same operation, then all the tissue submitted for initial diagnosis should undergo frozen section analysis so that errors based on sampling can be avoided. Definitive curettage specimens should be fixed, decalcified, and thoroughly sampled (minimum of ten cassettes if enough tissue is present).

Most malignancies and some benign tumors are resected en bloc with a rim of normal tissue. The specimen should be oriented, and the soft tissue and bone margins should be carefully assessed grossly. The margins can be inked, and the specimen transected with a bone saw along the plane of the greatest dimension of the tumor and its relationship to the closest soft tissue and bone margins. If needed, fresh tumor can be frozen for both diagnostic purposes and tissue triage. Subsequently, in most instances, a longitudinal slab 0.5 to 1.0 cm thick can be cut from the center of the specimen. The remaining two hemispheres of tissue can then be "bread loafed" at 0.5- to 1.0-cm intervals in the plane perpendicular to the cut surface of the slab to facilitate the evaluation of the circumferential soft tissue margins, the dimensions of the soft tissue component, and the percent circumference involved by tumor. Alternatively, the tumor can be "bread loafed" parallel to the long axis of the bone.

Sections demonstrating the proximity of the tumor to the closest soft tissue and bone margins should be submitted, and the tumor carefully dissected and sampled. This usually requires processing a minimum of one cassette per centimeter of tumor. The relationship between the tumor and the surrounding cancellous bone, cortex, articular surfaces, and neighboring soft tissues should be illustrated in appropriate sections.

Resected tumors that have been treated with preoperative chemotherapy require determination of percent tumor necrosis. The process to determine percent necrosis is not standardized internationally. There is agreement that at a minimum a central slab of tumor through its largest dimension should be mapped and blocked out in its entirety (fig. 1-10). Most protocols recommend that in addition, a section of tumor per centimeter (as determined by its greatest dimension) be processed from each of the remaining two hemispheres of the specimen. During the histologic review, the amount of tumor necrosis on each slide can be estimated, and these scores then be averaged to calculate the overall percentage of tumor necrosis. The location of the areas of viable and necrotic tumor can then be located on the map of the slab section, if necessary.

HISTOLOGIC DISTINCTION OF BENIGN FROM MALIGNANT TUMORS

Distinguishing benign from malignant bone tumors is not always easily accomplished through the assessment of conventional histologic features such as the degree of cellularity, mitotic activity, and necrosis. This is because benign or locally aggressive tumors such as chondroblastoma, osteoblastoma, giant cell tumor, and solid aneurysmal bone cyst can be densely cellular, demonstrate many mitoses, and have large areas of necrosis, whereas variants of osteosarcoma or chondrosarcoma may be relatively hypocellular and have few mitoses and little or no necrosis. Significant

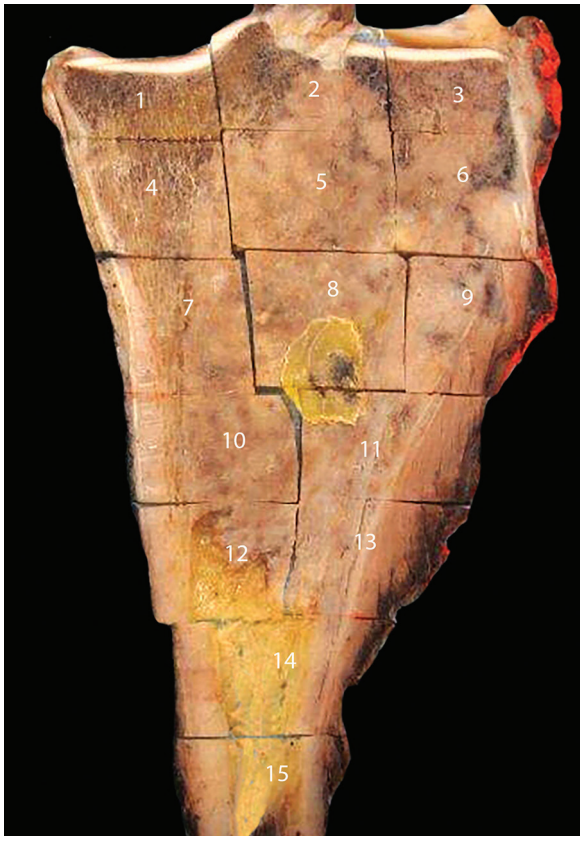

Figure 1-10

RESECTED TUMOR

Longitudinal section of tumor cut and coded.

pleomorphism and atypia are telltale signs of malignancy when accompanied by concurrent cellularity and mitotic activity. The absence of these features, however, should be interpreted with caution, as degenerative nuclear atypia, as seen in ancient schwannoma, is occasionally present in a variety of benign or locally aggressive neoplasms, including osteoblastoma, fibrous dysplasia, giant cell tumor, and chondromyxoid fibroma.

An important morphologic feature indicative of malignancy is an infiltrative growth pattern (also referred to as entrapment) in which the tumor replaces the marrow elements, encases preexisting bony trabeculae manifested by all surfaces of the trabecula covered by the tumor, and percolates within haversian systems (fig. 1-11). This finding is strongly suspicious of malignancy, especially for bone- and cartilage-forming neoplasms. Hemangioma and the histiocytoses, including Langerhans cell histiocytosis, Rosai-Dorfman disease, and Erdheim-Chester disease, are the only benign neoplasms that routinely infiltrate the marrow cavity, although infiltration may also be present focally but infrequently in desmoplastic fibroma. Other processes that can cause confusion with infiltration are fracture callus, infection, and a tangential plane of section through a well-delineated, but an undulating interface

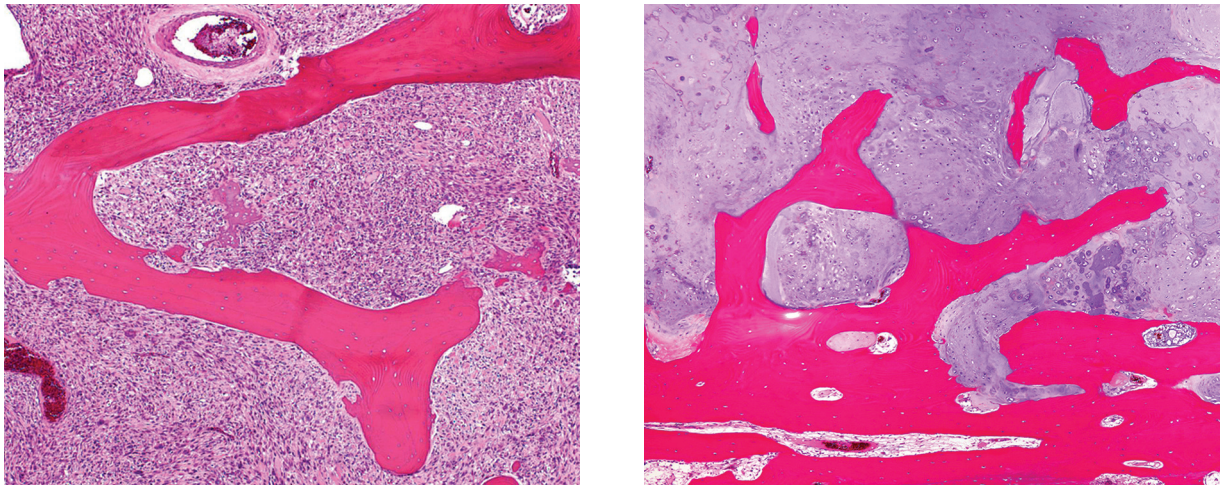

Figure 1-11

INFILTRATIVE GROWTH PATTERN

Left: Fibroblastic osteosarcoma with an infiltrative growth pattern replaces bone marrow and surrounds bony trabeculae.
Right: An infiltrative pattern of growth of chondrosarcoma in the ilium.

between tumor and surrounding bone. The converse is also important in that most benign tumors have well-circumscribed margins, and it is uncommon for bone sarcomas to be well-delineated along their entire margin.

PATHOLOGY REPORTING

The pathologic report of bone tumors should include tumor type, grade, and percentage of necrosis when appropriate; immunohistochemical and molecular findings; margin status and clearances when appropriate; relationship to important anatomic structures when appropriate; and coexisting diseases or conditions. In the United States, the College of American Pathologists (CAP)-approved synoptic reports are completed for all sarcomas. International guidelines for reporting are available through the International Collaboration on Cancer Reporting (ICCR).

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