

# Chapter 67. Skeletal Neoplasms

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## GENERAL CONSIDERATIONS

Among the acquired disorders of cartilage and bone are a variety of neoplasms. Some are malignant and cause considerable morbidity and can metastasize and kill. Others are benign and may even heal spontaneously. Rarely, skeletal tumors behave as though “transitional,” with both malignant and benign features. Diagnosis and treatment of bone tumors is a complex and specialized discipline. Only a brief overview is provided here. Additional resources include several comprehensive texts devoted to this topic.<sup>(1–7)</sup>

Classification of skeletal neoplasms begins with the apparent cell or tissue type of origin (Table 1). The source of the tumor is usually revealed by the kind of tissue that the neoplastic cells make, such as osteoid or cartilage. However, in a few instances (e.g., giant cell tumor of bone), the origin is less clear.<sup>(1,5)</sup> Chromosomal defects are detected more often in malignant than in benign skeletal neoplasms.<sup>(8)</sup>

*Biological behavior* of bone tumors importantly influences their classification. Within the two major categories, benign and malignant, there are different degrees of aggressiveness. Biological behavior reflects the capacity of the tumor to exceed its natural barriers. Such barriers may include a tumor capsule (the shell of fibrous tissue or bone around the neoplasm), a reactive zone (composed in part of fibrous tissue or bone that forms between the capsule and normal tissue), and any adjacent articular cartilage, cortical bone, or periosteum.<sup>(1,5,7)</sup>

Skeletal neoplasms will be properly managed only when there is a thorough understanding of their clinical presentation and natural history, as well as use of current staging procedures.<sup>(9)</sup> This often requires histopathological examination.<sup>(1,5,9)</sup> Proper choice of therapy may include medical and/or surgical approaches.<sup>(1–3,5,7,10–12)</sup> Optimum patient management can depend on multidisciplinary expertise.<sup>(1–7)</sup> Improved radiological imaging,<sup>(13,14)</sup> histopathological methods, cytogenetic and molecular testing, surgical techniques, and chemotherapeutic regimens have all contributed to better survival and function of patients with skeletal sarcomas. Chemotherapy has improved the treatment of early metastatic deposits.<sup>(12–18)</sup> Consequently, aggressive limb-salvaging procedures are now possible with survival rates that were previously achieved only by radical amputation.<sup>(16,19–22)</sup>

## BENIGN BONE TUMORS

*Benign skeletal tumors*, with only rare exceptions, do not metastasize.<sup>(23,24)</sup> Nevertheless, as a group, their biological behavior can still be variable and may range from completely inactive to quite aggressive. Fortunately, their behavior can often be predicted by noting the clinical presentation and examining the radiological features of the specific neoplasm;<sup>(4,25,26)</sup> sometimes, histopathological inspection is also essential.<sup>(1,6)</sup> Benign tumors can be classified generally as “inactive,” “active,” or “aggressive.”<sup>(1,6,23,24)</sup>

*Inactive* benign bone tumors are sometimes called “latent” or “static.” They are encapsulated by mature fibrous tissue or by cortical bone-like material, and do not expand or deform surrounding skeletal tissue. Individual neoplasms will have only a

minimal (if any) reactive zone, and their histopathological appearance is that of a benign tumor with a low cell-to-matrix ratio, a well-differentiated matrix, and no cellular hyperchromasia, anaplasia, or pleomorphism. Inactive benign tumors are usually asymptomatic.<sup>(1,6,23,24)</sup>

*Active* benign bone tumors can deform or destroy adjacent cortical bone or joint cartilage as they grow, but they do not metastasize. They are encapsulated within fibrous tissue, although a thin reactive zone can develop. These neoplasms generally cause mild symptoms, but may lead to pathological fractures.<sup>(1,6,23,24)</sup>

*Aggressive* benign bone tumors are not uncommon in children. They show invasive properties resembling low-grade malignancies. The reactive zone forms a capsule or pseudocapsule that prevents the neoplasm itself from extending directly into normal tissue, but the tumor can resorb and destroy adjacent bone and spread to nearby skeletal compartments. Despite their aggressive behavior, the cytological features are benign—including a well-differentiated matrix. These neoplasms cause symptoms and can engender pathological fractures.<sup>(1,6,23,24)</sup>

## MALIGNANT BONE TUMORS

*Malignant skeletal tumors* may metastasize. Nevertheless, as a group, their biological behavior also varies considerably.<sup>(1–3,5,7)</sup> Some grow slowly with a low probability of spreading elsewhere, so that there is typically a long interval between the discovery of the primary neoplasm and the development and recognition of metastases. Others are very aggressive and not only cause rapid and extensive local tissue destruction, but also have a high incidence of metastases so that primary and metastatic lesions are frequently recognized simultaneously. The biological behavior of malignant skeletal tumors can usually be predicted by their clinical, radiological,<sup>(4,25,26)</sup> and histopathological features.<sup>(1,5,6)</sup> Assessment of the histopathological type and grade is currently the best predictor of biological activity and is of paramount importance for successful treatment and accurate prognostication.<sup>(1,5,6)</sup>

*Low-grade* sarcomas invade local tissues, but grow slowly and have a low risk of metastasizing. They are usually asymptomatic and manifest as gradually growing masses. Nevertheless, the histopathological features of malignancy are present, such as anaplasia, pleomorphism, and hyperchromasia, together with a

TABLE 1. COMMON SKELETAL NEOPLASMS\*

<i>Tissue origin</i>	<i>Benign</i>	<i>Malignant</i>
Osseous		Classic osteosarcoma Parosteal osteosarcoma Periosteal osteosarcoma
Cartilaginous	Enchondroma Exostosis	Primary chondrosarcoma Secondary chondrosarcoma
Fibrous	Nonossifying fibroma	Fibrosarcoma Malignant fibrous histiocytoma
Reticuloendothelial		Ewing's sarcoma Multiple myeloma
Unknown	Giant cell tumor in bone	

\*See Refs. 1–7 for general reviews.

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few mitotic cells. The tumor capsule can be disrupted in many areas, and there may be an extensive reactive zone that forms a pseudocapsule and contains satellite tumor nodules that slowly erode the various natural barriers. Over time, and after repeatedly unsuccessful surgical excision with tumor recurrences, there is a risk of transformation to a high-grade sarcoma.<sup>(1,5,6)</sup>

*High-grade* sarcomas readily extend beyond their reactive zone. They seem to have minimal pseudoencapsulation. Their margins are poorly demarcated. Metastases may appear in seemingly uninvolved areas of the same bone and often in the medullary canal. Extension to nearby tissues destroys cortical bone, articular cartilage, and joint capsules. These tumors show all of the histopathological features that typify malignancy and produce a poorly differentiated (immature) matrix.<sup>(1,5,6)</sup>

## DIAGNOSIS OF BONE TUMORS

A thorough medical history and complete physical examination are the foundation for successful delineation and management of skeletal neoplasms.<sup>(27)</sup> The patient's age, presence or absence of predisposing conditions (e.g., Paget's disease of bone), and anatomical site of the lesion provide important clues to the precise diagnosis.

Radiological studies should be selected both to help establish the tumor type and to provide staging information that will be critical for choosing treatment and for understanding the patient's prognosis.<sup>(4,28,29)</sup> The tumor "stage" reflects the neoplasm's location and extent, as well as its biological activity or grade, and is based in part on the presence or absence of metastases.<sup>(9)</sup> Radiographs establish the tumor location, often suggest the underlying histopathological type,<sup>(4,25,26)</sup> help assess its extent, and guide the selection of additional staging studies. Clinical and radiological examination is completed before biopsy or other surgical procedures.<sup>(1,3,7,9,27)</sup>

Bone scanning helps to determine if multiple areas of neoplasm are present and if the extent of skeletal involvement exceeds conventional radiographic findings. Avidity for radionuclide uptake generally reflects the tumor's biological activity.<sup>(25,26,28,29)</sup>

CT is especially useful for precisely defining the anatomical extent of the primary lesion, detecting destruction of spongy or cortical bone, assessing compartmental changes, and locating neurovascular structures that may be impinged on by tumor or located near planned surgery.<sup>(30)</sup> This technique also supplements conventional radiography for detecting pulmonary metastases.

MRI is particularly helpful for defining soft-tissue extension and for showing any disruption of the marrow space.<sup>(29,31,32)</sup> Positron emission tomography (PET) is also proving useful.<sup>(13,33)</sup>

Angiography can help plan limb-salvage operations, because this procedure may reveal involvement of major neurovascular bundles.<sup>(4)</sup>

Arthrography assists in showing joint involvement and is therefore useful for assessing whether a cartilaginous tumor is of intra-articular or extra-articular origin.<sup>(4)</sup>

Biopsy and histopathological study are essential for successful staging and treatment of many skeletal neoplasms.<sup>(1,2,34)</sup> Open (incisional) biopsy has been the technique of choice if a malignant lesion is suspected, because it secures sufficient tissue for examination.<sup>(1,2,34)</sup> However, this procedure carries a greater risk of tumor contamination of uninvolved tissues (e.g., by dissecting hematoma) compared with closed biopsy.<sup>(35)</sup> Accordingly, open biopsy can potentially compromise a limb-salvage procedure because of added risk of local recurrence. Hence, careful attention must be paid to where the incision for biopsy is made and to the surgical technique.<sup>(1-3)</sup> Increasingly, fine-needle aspiration biopsy is used.<sup>(36)</sup> Accessible benign tumors may be removed by incisional biopsy if they are intracapsular or with en bloc marginal incision.<sup>(1-3)</sup>

## INDIVIDUAL TYPES OF SKELETAL NEOPLASIA

### Benign and Transitional Bone Tumors

*Benign* skeletal neoplasms occasionally originate from marrow elements, but most often they arise from cartilage or bone.<sup>(37)</sup> Typically, these tumors develop before skeletal maturation is complete or during the early adult years, and they are most common in areas of rapid bone growth and cellular metabolism (i.e., epiphyses and metaphyses of major long bones).<sup>(38)</sup> In some patients or families with specific heritable disorders, benign skeletal tumors (e.g., enchondromas or exostoses) are multiple and have a significantly increased risk of malignant transformation.<sup>(39,40)</sup> Most benign skeletal tumors, however, are solitary lesions and have a good prognosis.<sup>(37)</sup> The following paragraphs describe the principal types.

*Nonossifying fibroma* is the most common bone tumor.<sup>(41,42)</sup> This lesion is often called a "fibrous cortical defect." It represents a focal, developmental abnormality in periosteal bone formation that results in an area of failed ossification. Nonossifying fibromas most commonly occur in the metaphyses of the distal femur or distal tibia and are located eccentrically in or near the bony cortex.<sup>(4,25,26)</sup> They are somewhat more prevalent in boys than in girls, develop in the older pediatric population, and are active lesions that enlarge throughout childhood yet typically do not cause symptoms. However, when most of the diameter of a long bone is involved, pathological fracture can occur.<sup>(41,42)</sup> Radiological study may show a well-demarcated radiolucent zone with apparent trabecularization that results in a multilocular or even in a septated appearance (Fig. 1). Some cortical bone erosion may be present. The radiographic pattern can be considered diagnostic, and further staging is typically unnecessary.<sup>(4,26,27)</sup> After puberty with skeletal maturation, nonossifying fibromas become inactive or latent and ultimately ossify. Surgical intervention is usually unnecessary unless pathological fracture is a significant risk.<sup>(43)</sup> Intracapsular curettage is effective, but bone grafting or other stabilizing techniques for fracture prevention or treatment may be required.<sup>(41,42)</sup> Rarely, nonossifying fibromas cause oncogenic rickets.

*Enchondroma* is a benign and typically asymptomatic tumor of cartilage caused by focal disruption of endochondral bone formation. It can be considered a dysplasia of the central growth plate.<sup>(23,44)</sup> Enchondromas seem to arise in metaphyses and may eventually become incorporated into the diaphysis. Solitary lesions are usually noted in adolescence or in early adulthood. They most commonly involve small tubular bones of the hands or feet or the proximal humerus. However, several distinct disorders feature multiple enchondromas (enchondromatosis, Ollier disease, and Maffucci syndrome). A mutant PTH/PTH-related peptide (PTHrP) type I receptor has been identified.<sup>(45)</sup> Fewer than 1% of the solitary asymptomatic tumors undergo malignant transformation, but with enchondromatosis the risk is estimated to be 10%.<sup>(37,42)</sup>

Radiographs show a medullary, radiolucent lesion with a well-defined (but only slightly thickened) bony margin (Fig. 2).<sup>(4,25,26)</sup> This defect may enlarge slowly during its active phase in adolescence but calcifies when the tumor becomes latent during the adult years. Then, it has a diffusely punctate or stippled appearance (Fig. 3). In time, enchondromas become surrounded by dense reactive osseous tissue. Skeletal scintigraphy typically reflects the tumor's biological activity and shows increased radioisotope uptake in the reactive zone (greatly increased uptake suggests malignant transformation). Accordingly, it is prudent to secure a "baseline" bone scan and radiographs for young adults with multiple enchondromas.

Biopsy is often not necessary because the lesion's identity is revealed by characteristic radiography.<sup>(4,25,26)</sup> Histopathologi-



**FIG. 1.** Nonossifying fibroma. This 11-year-old boy has a typical, benign-appearing lesion of his distal left tibia. It is an ovoid, radiolucent, fibrous tumor located at the metadiaphyseal junction that is slightly expansile and has a multiloculated appearance with regions of cortical scalloping and thinning.

cal examination may be required, however, to distinguish benign from low-grade malignant enchondromas. Here, the patient's age is an especially important consideration.<sup>(44)</sup>

Solitary asymptomatic enchondromas are generally benign and require no treatment, although periodic follow-up is indicated. If they become symptomatic and begin to enlarge, careful surveillance is necessary.<sup>(44)</sup> Imaging techniques may be helpful to search for evidence of malignancy.<sup>(4,29,30)</sup> Surgical treatment would then be indicated.

*Osteochondroma* (osteocartilaginous exostosis) is a common dysplasia of cartilage involving the peripheral region of a growth plate.<sup>(23,38,44)</sup> Mutations within the *EXT1* or *EXT2* genes cause heritable forms of this disorder.<sup>(46–48)</sup> The lesion can arise in any bone that derives from cartilage, but it usually occurs in a long bone. Typically, either end of a femur, the proximal humerus or tibia, the pelvis, or the scapula is affected. Exostoses present as hard, painful masses that are fixed to bone. They enlarge during childhood but become latent in adulthood. These lesions can irritate overlying soft tissues and may form a fluid-filled bursa. A painful and enlarging exostosis during adult life, especially in the pelvis or shoulder girdle, should suggest malignant transformation to a chondrosarcoma.<sup>(38,40,44,49)</sup> Generally, exostoses are solitary, but multiple hereditary exostoses is a well-characterized, autosomal domi-

nant entity that can result in significant angular deformity of the lower limbs, clubbing of the radius, and short stature.<sup>(39)</sup>

*Radiographs* may show either a flat, sessile, or pedunculated metaphyseal bony lesion of variable density that is typically well defined and covered by a radiolucent cartilaginous cap (Fig. 4). Characteristically, there is continuity of tumor and metaphyseal bone.<sup>(4,26,27)</sup> The diagnosis is rarely difficult. However, after malignant transformation, there may be a soft tissue mass on CT or MRI, and a new bone scan will show suddenly or considerably increased tracer uptake.

The cartilaginous cap of an exostosis appears histopathologically like a poorly organized growth plate. The trabeculae are not remodeled and thus contain cartilage cores (primary spongiosa).

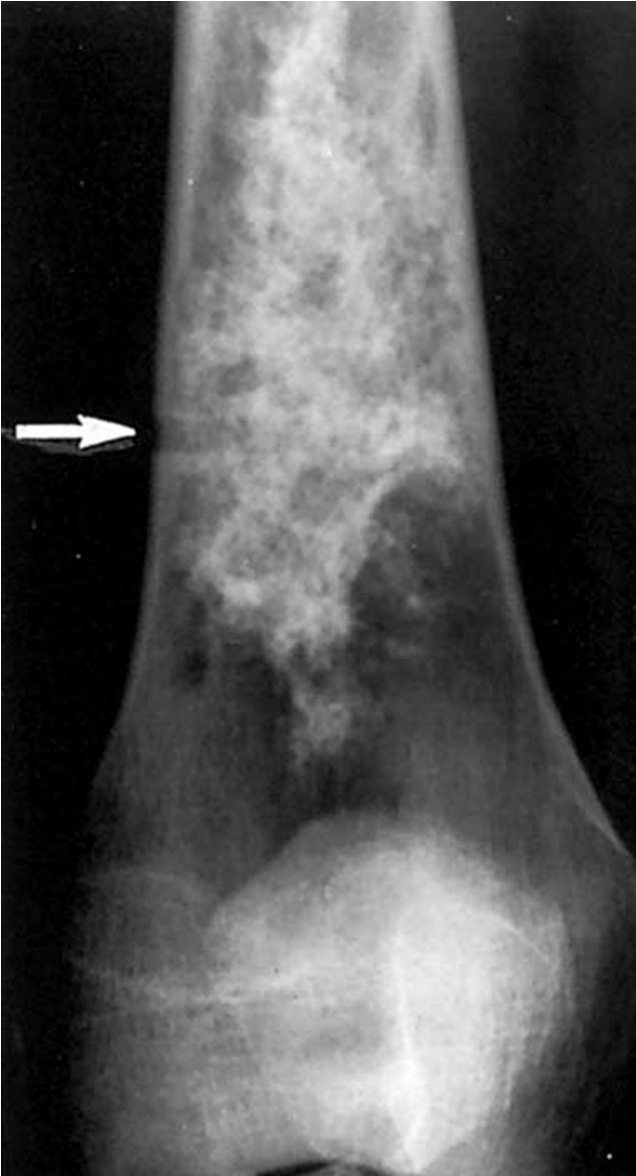
Excisional treatment of an active exostosis should include the cartilaginous cap and overlying perichondrium to minimize the chance of recurrence.<sup>(1,3,7,44)</sup> There is about a 5% recurrence rate after marginal excision of a solitary lesion. Malignant degeneration occurs in fewer than 1% of solitary lesions, but the likelihood is almost 10% for multiple hereditary exostoses.<sup>(39,40,44)</sup>

*Giant cell tumor of bone* (osteoclastoma) is a common benign bone neoplasm. The cellular origin, however, is unknown.<sup>(50–52)</sup> Men are more frequently affected than women,



**FIG. 2.** Enchondromatosis. This 13-year-old girl has multiple, lucent, benign-appearing lesions of the phalanges. Each has produced expansion of the bone as well as cortical scalloping and thinning. Several periosteum-based chondromas are present that show reactive bone formation at their margins (arrows).





**FIG. 3.** Enchondroma. This 43-year-old woman has an extensively calcified lesion of the metadiaphyseal region of her distal femur. The calcification is amorphous and dense with little radiolucent component (arrow indicates a biopsy needle track). This lesion is differentiated from a bone infarction, which typically has a dense, linearly marginated periphery.

typically at 20–40 years of age. These tumors cause chronic and deep pain that mimics an arthropathy. Pathological fracture or effusion into the knee is a common presentation. Frequently, the epiphysis of a distal femur or a proximal tibia is affected. However, the distal radius, proximal humerus, distal tibia, and sacrum are also commonly involved. Often, giant cell tumors enlarge to occupy most of the epiphysis and portions of the adjacent metaphysis, and they can penetrate into subchondral bone and may even invade articular cartilage. In contrast to other benign skeletal neoplasms, they occasionally metastasize. Accordingly, giant cell tumors of bone are sometimes referred to as “transitional” neoplasms. Overexpression of the *c-myc* oncogene correlates with occurrence of metastasis.<sup>(52)</sup>

Radiographic studies show a relatively large lucent abnormality surrounded by an obvious reactive zone.<sup>(4,26,27)</sup> The cortex can appear eroded from the endosteal surface (Fig. 5). A

trabecular bone pattern may fill in the tumor cavity. Bone scanning can manifest decreased tracer uptake at the center of the lesion (the “doughnut” sign). Histopathological examination shows numerous, scattered, multinucleated giant cells in a proliferative stroma; mitoses are occasionally present.<sup>(1,6)</sup> The findings differ from the *extraskelatal osteoclastomas* that can affect exceptional patients with Paget’s disease of bone.<sup>(53)</sup>

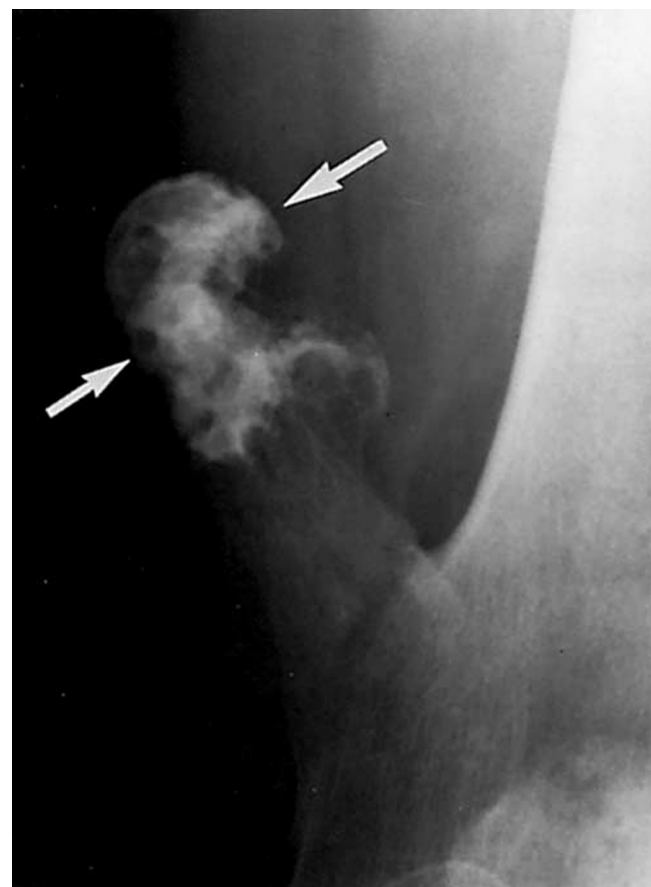
Curettage (with bone grafting or use of cement) deals with less advanced lesions. Recurrent or advanced tumors are removed with en bloc wide excision and reconstructive surgery.

### Malignant Bone Tumors

Multiple myeloma, a neoplasm of marrow origin, is the most common cancer of the skeleton. However, a considerable variety of malignant tumors arise directly from bone, cartilage, fibrous tissue, histiocytes, and perhaps endothelial tissue in the skeleton itself.<sup>(1,2,5,6)</sup>

Malignant bone tumors typically cause skeletal pain that is noted particularly at night. Accordingly, this symptom, especially in adolescents or young adults, is reason for evaluation. Treatment of malignant bone tumors is complex and primarily based on the tumor grade and staging.<sup>(1,2,5,6)</sup> Only general comments are provided here and concern the principal entities.

*Multiple myeloma* typically develops during middle age and affects many skeletal sites. Constitutional symptoms can include bone pain, fever, malaise, fatigue, and weight loss. Often



**FIG. 4.** Osteochondroma (osteocartilaginous exostosis). This 51-year-old woman has a typical pedunculated exostosis of her distal femur. The cortex and trabecular components of the exostosis are continuous with the host bone. Note how the exostosis slants away from the knee joint. The osteochondrinous cap (arrows) is densely mineralized.



**FIG. 5.** Giant cell tumor. This 25-year-old man has an expansile, destructive, lucent lesion of the distal ulna. The lesion extends to the end of the bone.

there is anemia, thrombocytopenia, and renal failure.<sup>(54,55)</sup> Hypercalcemia, caused by elaboration of osteoclast-activating factors,<sup>(56)</sup> occurs in about 20–40% of patients.<sup>(57)</sup> The diagnosis is made by showing paraproteinemia using serum and urine immunoelectrophoresis and by examining bone marrow for plasmacytosis.<sup>(54)</sup> Infection with Kaposi's sarcoma-associated herpes virus<sup>(58)</sup> and overexpression of *DKK-1* leading to inactive bone formation<sup>(59)</sup> may be involved in the pathogenesis.

Radiographic findings classically include discrete, circular, osteolytic lesions, but generalized osteopenia is actually a more common presentation. Bone scintigraphy can seem unusual because of little tracer uptake in foci of osteolysis.<sup>(4,25,26,28)</sup>

Myeloma is radiation sensitive and treatable by chemotherapy. Reossification of tumor sites can occur within several months of therapy. Prevention of pathological fractures may require surgical stabilization.<sup>(54)</sup> The primary mechanism of bone destruction is increased osteoclastic action.<sup>(56)</sup> Bisphosphonate treatment has helped to decrease fractures and pain.<sup>(60,61)</sup>

*Osteosarcoma* (osteogenic sarcoma) is the most common primary malignancy of the skeleton.<sup>(1,7,62,63)</sup> There are about 1100–1500 new cases in the United States yearly. This cancer typically develops before age 30 and is somewhat more common in males than in females. Although most of the tumors are the “classic” variety, variants include parosteal, periosteal, and telangiectatic types that have different presentations and prognoses. Cytogenetic aberrations have been characterized.<sup>(63,64)</sup>

*Classic osteosarcoma* characteristically arises in the metaphysis of a long bone where there is the most rapid growth. Teenagers are usually affected. In about 50% of cases, these tumors develop near the knee in the distal femur or proximal tibia. Other commonly involved sites are the humerus, proxi-

mal femur, and pelvis, but they can begin de novo anywhere in the skeleton. Classic osteosarcomas also derive from malignant transformation of Paget's disease of bone.<sup>(65)</sup>

Typically, an osteosarcoma presents as a tender bony mass. Pain is severe and unremitting. Pathological fracture can occur. They are aggressive neoplasms that readily penetrate metaphyseal cortical bone, and the majority have already infiltrated surrounding soft tissues at the time of diagnosis. At presentation, about 50% of affected adolescents show penetration of their growth plates with epiphyseal involvement, about 20% have metastases elsewhere in the cancerous bone and, in approximately 10%, the tumor has spread to lymph nodes or to lung.<sup>(62)</sup>

Radiographic study shows a destructive lesion that is composed of amorphous osseous tissue with poorly defined margins.<sup>(4,25,26,66)</sup> Some osteosarcomas are predominantly osteoblastic and radiographically dense; others are predominantly osteolytic and radiolucent. Some have a mixed pattern.<sup>(25,26)</sup> Cortical bone destruction is often apparent (Fig. 6). A characteristic “sunburst” configuration results from spicules of amorphous neoplastic osseous tissue forming perpendicularly to the long axis of the affected bone. This is in contrast to the parallel



**FIG. 6.** Central (medullary) osteosarcoma. This 12-year-old boy has a sclerotic diaphyseal lesion that arose in the medullary cavity. It has penetrated the cortex and produced a densely mineralized mass surrounding the femur. Portions of the cortex seem to have been destroyed (arrow), whereas other regions are thickened.

or “onion skin” appearance of reactive periosteal new bone. Codman’s triangle results from reaction and elevation of the periosteum that demarcates a triangular area of cortical bone (see Fig. 8). Bone scintigraphy shows intense uptake of tracer and may disclose more widespread disease than by conventional radiography.<sup>(65)</sup> CT, MRI, PET, and angiography are helpful, as discussed previously. Microscopic examination typically shows a very malignant stroma that produces an amorphous and immature osteoid in a trabecular pattern.<sup>(1–7)</sup>

Use of chemotherapy preoperatively<sup>(11,18,25,62)</sup> has significantly improved the prognosis for this malignancy, and has enabled many osteosarcoma patients to be managed by limb-salvage procedures instead of radical amputation.<sup>(7,10,21)</sup>

*Parosteal osteosarcomas* are juxtacortical (i.e., they develop between the bony cortex and the soft tissue as a surface neoplasm). Adolescents and young adults are most commonly affected by these slowly growing, low-grade tumors that typically occur as a fixed and painless mass posteriorly on the distal femur or medially on the proximal humerus. They are less aggressive than classic osteosarcomas and can remain separated for a considerable length of time from the parent bone by a narrow radiolucent region of soft tissue. Eventually, they may involve the underlying skeleton and degenerate into a high-grade osteosarcoma.<sup>(62)</sup>

Radiographic study typically reveals a densely ossified, broad-based, fusiform mass that seems to encircle the metaphyseal region of a long bone (Fig. 7).<sup>(4,25,26,66)</sup> Reactive tissue initially separates the neoplasm from the underlying bone that is destroyed once the tumor penetrates the normal cortex into the medullary canal. Parosteal osteosarcomas have mature trabeculae with cement lines resembling Paget’s disease of bone,<sup>(10)</sup> however, a low-grade malignant stroma is present. This tumor is often misdiagnosed as benign. Limb-salvage with wide marginal excision is the usual treatment for less advanced disease. The prognosis is good. Chemotherapy is typically not used unless there has been dedifferentiation of the neoplasm.<sup>(10,18,62)</sup>

*Periosteal osteosarcoma* often presents as a painless growing mass that extends from the surface of a bone into soft tissue.<sup>(62)</sup> This uncommon variant of classic osteosarcoma typically affects young adults. Radiological study shows a poorly mineralized mass primarily on a bone surface in an area of cortical erosion. The crater-like lesion has irregular margins with periosteal reaction.<sup>(4,25,26)</sup> Penetration through cortical bone into the medullary canal occurs more rapidly than with parosteal osteosarcoma. If this complication has occurred, the likelihood of pulmonary metastasis is greater—contributing to its poorer prognosis. Bone scintigraphy shows avid tracer uptake.<sup>(66)</sup> CT reveals a mass that fills a shallow cortical bone defect but contains minimal calcification. Malignant mesenchymal stroma with neoplastic osteoid occurs in, and around, areas of mature cartilage.<sup>(4,6,25,26)</sup>

Periosteal osteosarcoma is often treated by excision with a wide margin.<sup>(56)</sup> Adjuvant chemotherapy is used when the tumor has regions of high-grade malignancy.<sup>(15,18)</sup>

*Chondrosarcoma* occurs most often between 40 and 60 years of age, when this neoplasm develops as a primary tumor.<sup>(44,67)</sup> About 25% of patients manifest malignant transformation in a pre-existing enchondroma or osteochondromatous exostosis. Thus, chondrosarcomas usually involve the pelvis, proximal femur, or shoulder girdle. Patients initially experience a persistent dull ache that can mimic arthritis. Variants of the classic form of chondrosarcoma include a high-grade, dedifferentiated neoplasm, an intermediate-grade, clear cell type, and a low-grade, juxtacortical tumor. The particular designation depends on the histopathological pattern and anatomical location.<sup>(44,67)</sup>

Radiographs show a subtle radiolucent lesion that contains hazy or speckled calcification in a diffuse “salt and pepper” or



**FIG. 7.** Parosteal osteosarcoma. This 30-year-old woman has a very densely mineralized mass arising from the periosteal surface of the distal femoral metaphysis posteriorly. This tumor has lobular calcification and is attached to the femur by a broad pedicle.

“popcorn” pattern.<sup>(4,25,26)</sup> Primary chondrosarcomas can develop either within the medullary canal or on the surface of a bone where they may destroy the cortex and form a mass. On histopathological examination, it can be difficult to show that high-grade tumors are cartilaginous in origin, or that low-grade tumors are actually malignant.<sup>(44,50)</sup>

Treatment of chondrosarcomas depends on the tumor stage. Limb amputation may be necessary for higher grade tumors. Adjuvant chemotherapy or radiation therapy has been disappointing.<sup>(44)</sup>

*Ewing sarcoma* is a highly malignant neoplasm that arises from nonmesenchymal cells in the bone marrow.<sup>(68–71)</sup> This cancer usually harbors a pathognomonic  $t(11:12)(q24;q12)$  translocation<sup>(72)</sup> and represents a form of primitive neuroectodermal tumor.<sup>(66)</sup> It typically presents in 10- to 15-year-old children and more commonly affects boys than girls.<sup>(1,68–71)</sup> Initial manifestations include an enlarging and tender soft tissue swelling together with weight loss, malaise, fever, and lethargy. The erythrocyte sedimentation rate may be elevated, and there can be leukocytosis and anemia. The diaphysis of the femur is most commonly involved; alternatively, an ilium, tibia, fibula, or rib is affected. When this cancer occurs in the pelvis, it is usually found late and has an especially poor prognosis.<sup>(1,68–71)</sup>





**FIG. 8.** Ewing sarcoma. This 5-year-old boy has a subtle permeative lesion of the proximal diaphysis of his fibula. The tumor is characterized by layered (onion skin) periosteal reaction forming a Codman's triangle (arrows) and by "sunburst" new bone formation more proximally, which is characteristically perpendicular to the bone's long axis. A large soft tissue mass is associated with the skeletal defects.

Radiological study typically reveals a diaphyseal lesion of patchy density that destroys cortical bone and frequently causes an "onion skin" appearance of reactive periosteum (Fig. 8).<sup>(4,25,26)</sup> Bone scanning may show intense tracer uptake that extends considerably beyond the radiographic abnormality.

Chemotherapy can be followed by wide excision or radiation therapy, depending on, among other factors, the anatomical site. Newer therapeutic approaches have reduced the incidence of pulmonary metastases and have markedly improved survival.<sup>(1,73)</sup> Zoledronic acid may be helpful.<sup>(74)</sup> Histological response to preoperative chemotherapy and tumor size are important predictors of event-free survival.<sup>(17)</sup>

*Malignant fibrous histiocytoma* occurs more frequently in soft tissues than in the skeleton and is less common than benign fibrous tumors.<sup>(1,3,42)</sup> This cancer affects adults and often originates in Paget's disease of bone or at the site of a skeletal infarct. Typically, this is an aggressive sarcoma that readily spreads within the lymphatics. Bone is infiltrated early on, and pathological fracture is a common presentation.

Radiological study reveals a poorly defined radiolucent le-

sion that causes cortical bone erosion.<sup>(4,23,25)</sup> The histopathological pattern is variable from area to area; extremely large and bizarre histiocytic cells are found in some sections, and undifferentiated cells that resemble histiocytic lymphoma are noted in others. Areas that contain fibrous tissue may suggest that the tumor is a fibrosarcoma. Special stains and electron microscopy can be required to establish the diagnosis.<sup>(5,6,75)</sup> Staging studies direct the therapy, which may require radical resection or amputation and perhaps chemotherapy.<sup>(1,44)</sup> The prognosis is guarded.<sup>(44,75)</sup>

*Fibrosarcoma* causes pain and typically arises in a major long bone of an adolescent or young adult.<sup>(1-5,42)</sup> Radiological study reveals a poorly defined and destructive lucent lesion in a metaphysis.<sup>(4,25,26)</sup> Low-grade and high-grade fibrosarcomas have similar radiological and histopathological appearances. Accordingly, electron microscopy may be necessary to reveal the collagenous composition of the matrix of a high-grade tumor.<sup>(6,42)</sup> Therapy depends on the staging results.<sup>(1,3,5)</sup>

*Metastatic bone tumors* are considerably more common than primary skeletal malignancies (with a ratio of about 25 to 1).<sup>(1,4,5)</sup> Prostate, breast, thyroid, lung, and kidney cancers are the principal neoplasms that metastasize to bone. There is predilection for malignant cells to deposit within blood-forming marrow spaces in the spine, ribs, skull, pelvis, and metaphyses of long bones (particularly the femur and humerus). In children, metastases within the skeleton usually reflect a neuroblastoma, leukemia, or Ewing sarcoma. In teenagers or young adults, lymphomas are the predominant source. After age 30, an adenocarcinoma is the likely primary. Osteoblastic metastases most commonly derive from carcinoma of the prostate or breast. Osteolytic metastases may come from the lung, thyroid, kidney, or gastrointestinal tract.<sup>(4,25,27)</sup> In a significant number of patients, the origin is not evident, and staging studies with biopsy<sup>(36)</sup> are performed to explore the possibility of an intrinsic skeletal sarcoma.<sup>(1-3,5,6)</sup>

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# Chapter 68. Mechanisms of Bone Destruction and Formation by Metastatic Tumors

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## INTRODUCTION

Cancer adversely affects bone and mineral metabolism through a broad spectrum of mechanisms. These include focal osteolysis at sites of metastases, hypercalcemia, and diffuse osteopenia. As early as 1889, Stephen Paget recognized the diversity of effects, stating that “in a cancer of the breast the bones suffer in a special way, which cannot be explained by any theory of embolism alone. . . the same thing is seen much more clearly in those cases of cancer of the thyroid body where secondary deposition occurs in bones with astonishing frequency.” He further observed, “A general degradation of the bones sometimes occurs in carcinoma of the breast, yet without any distinct deposition of cancer in them.” These were prescient observations, as it is now recognized that cancer affects bone through systemic humoral mechanisms and by direct metastatic invasion.<sup>(1,2)</sup> This review will focus on pathogenic bone remodeling as a consequence of cancer metastasis to bone.

The potential for tumor metastasis, especially to bone, is greater with certain types of cancers. Breast, prostate, lung, and renal cancers all frequently metastasize to bone, and bone metastases are present in nearly all patients with advanced breast or prostate cancer. Bone is the third most common site of metastasis of solid tumors after the liver and the lung. Metastatic bone disease is often classified as osteoblastic or osteolytic, but in reality, most bone lesions fall in between these two extremes. In fact, bone metastases may display extreme heterogeneity even in the same patient.<sup>(3)</sup>

Breast cancer is one of a limited number of primary neoplasms that display osteotropism, an extraordinary affinity to grow in bone. This property has provided a key paradigm for our understanding of the metastatic process. Paget, during his observations of breast cancer in 1889, proposed the “seed and soil” hypothesis to explain this phenomenon. “When a plant goes to seed, its seeds are carried in all directions; but they can only grow if they fall on congenial soil.” In essence, the microenvironment of the organ to which the cancer cells metastasize may serve as a fertile soil on which the seeds (or cancer cells) may grow. This century-old concept remains a basic principle of our understanding of cancer metastasis, guiding current progress in the research of molecules produced by bones and tumor cells to enrich the vicious cycle of secondary tumor growth.

## CHEMOTAXIS, INVASION, AND ADHESION

For metastasis to occur, a tumor cell must (1) detach from the primary site; (2) enter the systemic vasculature through the permeable neovasculature of the tumor; (3) survive host immune response and physical forces in the circulation; (4) arrest in a distant capillary bed; (5) escape the capillary bed; and (6) proliferate in the metastatic site.<sup>(1)</sup> A number of molecules have been identified that promote tumor cell escape, including E-cadherin, osteonectin, osteopontin, and urokinase. However, the chemokine system, integrins, and matrix metalloproteinases

have convincingly been shown to play a more direct role in bone metastasis. Platelets may also assist circulating cancer cells in the development of metastasis.

## CXCR4

The chemokine receptor CXCR4 is abundantly expressed in breast cancer cells and involved in cellular migration. The CXCR4 ligand, stromal cell derived factor 1 (SDF-1) (CXCL12), is present in tissues that represent common sites of metastasis, including bone marrow. CXCR4 was one of a tool box of genes, upregulated in the highly bone metastatic MDA-MB-231 breast cancer,<sup>(4)</sup> that likely causes the breast cancer cells to home to bone. Neutralizing antibodies to CXCR4 impaired breast cancer metastasis to regional lymph nodes and lung in a mouse model,<sup>(5)</sup> as well as PC3 prostate cancer metastases to bone.<sup>(6)</sup> CXCR4-expressing prostate cancer cell lines adhered to bone marrow endothelial cells when treated with SDF-1 and migrated across an SDF-1 gradient.<sup>(7)</sup> Recent evidence indicates that bisphosphonates may affect this process because YM529 (minodronate) decreased CXCR4 expression and invasiveness of prostate cancer cell lines in an animal model of bone metastasis.<sup>(8)</sup>

## Integrins

Bone marrow stromal cells express the vascular cell adhesion molecule-1 (VCAM-1), a ligand for  $\alpha_4\beta_1$  integrin.<sup>(9)</sup> CHO cells transfected with an  $\alpha_4\beta_1$  integrin expression construct invaded bone and lung when inoculated intravenously into nude mice compared with lung invasion alone in mice inoculated with parental Chinese hamster ovary (CHO) cells.<sup>(10)</sup> Neutralizing antibodies to  $\alpha_4\beta_1$  integrin or VCAM-1 inhibited development of these bone lesions. However, overexpression of  $\alpha_3\beta_1$ ,  $\alpha_6\beta_1$ , or  $\alpha_v\beta_1$  integrins did not produce similar results in this animal model. The  $\alpha_v\beta_3$  integrin receptor binds the arginine-glycine-aspartic acid (RGD) peptide sequence present on a variety of extracellular matrix proteins, including osteopontin, vitronectin, and bone sialoprotein. This integrin is important in homing and, possibly, invasion of tumor cells into the bone endosteum.<sup>(11)</sup> In an animal model of bone metastasis, an  $\alpha_v\beta_3$  antagonist suppressed the development of bone lesions after intracardiac inoculation of MDA-MB-435 breast cancer cells.<sup>(12)</sup>

## Matrix Metalloproteinases

The matrix metalloproteinases (MMPs) are a family of at least 28 zinc-dependent proteinases that are either bound to the extracellular membrane or secreted within the local environment.<sup>(13)</sup> The expression of MMPs has been found to be increased in most cancer types including breast and prostate.<sup>(14,15)</sup> High levels of MMPs have been associated with poor prognosis.<sup>(16)</sup> MMPs participate in the progression of cancer metastasis not only by the degradation of matrix leading to invasion but also by the alteration of signaling molecules affecting tumor growth and migration. This process is manifested through the cleavage of tethered signaling molecules such as insulin-like growth factor binding protein 1, E-cadherin, fibroblast growth factor (FGF) receptor 1, and pro-TGF- $\beta$ .<sup>(17-19)</sup> MMP-3 and MMP-7 cleave cell membrane-associated RANKL to a soluble form, resulting in osteoclast activation in an

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vitro model, suggesting MMPs have a role in osteolytic bone metastasis.<sup>(20)</sup> Furthermore, MMP-1 was upregulated in the highly bone metastatic MDA-MB-231 breast cancer.<sup>(4)</sup> MMP-1 may contribute to osteolysis by promoting collagen degradation at the bone surface to make such a surface more attractive to osteoclastic bone resorption.

### Platelets

Collective evidence from recent studies supports the role of platelets in promoting metastasis. While it has long been recognized that cancer patients are hypercoagulable, this association may be caused by direct and reciprocal interactions between the cancer cells and platelets. Platelets may “coat” circulating tumor cells thereby protecting them from attack from the immune system and enhancing their ability to adhere to disrupted vascular endothelium.<sup>(21)</sup> Cancer cell-mediated platelet aggregation may also result in the release of platelet vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and thrombospondin-1 promoting cancer cell survival and angiogenesis. MDA-MB-231 breast cancer cells promote platelet aggregation and release of lysophosphatidic acid (LPA).<sup>(22)</sup> LPA receptors on cancer cells enhanced cellular proliferation, stimulated the production of osteolytic factors, such as interleukin (IL)-8, and increased the size of MDA-MB-231 subcutaneous tumors and osteolytic bone lesions in a mouse model of osteolytic bone metastasis. Moreover, integrilin, an  $\alpha_{IIb}\beta_3$  antagonist and inhibitor of platelet aggregation, reduced osteolytic bone lesion area in this model.<sup>(22)</sup>

## LOCAL TUMOR SYNDROMES IN BONE

### Osteolytic Metastasis

Secondary tumor deposition in bone frequently causes osteolysis or bone destruction at the site of deposition. Breast cancer is the most common tumor type to do so, although prostate, lung, renal, and thyroid tumors are all associated with osteolytic lesions. The following discussion will focus on breast cancer as a model for cancer-mediated osteolysis.

**Breast Cancer as the “Seed.”** Osteolysis is the ability to cause destruction of the hard, mineralized matrix. Breast cancer cells in vitro secrete proteolytic enzymes capable of destroying bone. In vivo, however, it seems that tumor cells are not active effectors of bone destruction, particularly during the establishment of metastasis. Histological analysis and scanning electron microscopy of osteolytic bone metastases indicate that osteoclasts adjacent to tumor cells actively resorb bone. This would suggest that breast cancer cells have the ability to stimulate osteoclastic bone resorption.

**PTH-Related Peptide as a Mediator of Osteolysis.** PTH-related peptide (PTHrP) plays a local paracrine role in the establishment and progression of breast cancer bone metastasis even in the absence of detectable increases in its plasma concentration with malignant hypercalcemia.<sup>(23)</sup> PTHrP is expressed by 50–60% of human primary breast cancers. In a mouse model of bone metastasis using the breast cancer cell line MDA-MB-231, a neutralizing antibody to PTHrP(1-34) reduced the number and size of osteolytic bone lesions. Histomorphometric analysis of long bones of mice treated with the PTHrP antibody revealed significantly fewer osteoclasts at the tumor-bone interface and less tumor than controls.<sup>(23)</sup> When mice with established osteolytic metastases caused by MDA-MB-231 were treated with the PTHrP antibody, an appreciable decrease in the rate of progression of disease compared with controls was observed.<sup>(24,25)</sup> Conversely, when MDA-MB-231

cells were engineered to overproduce PTHrP, an increase in the number of osteolytic lesions was seen.<sup>(26)</sup> The breast cancer cell line, MCF-7, does not express PTHrP and is not associated with osteolytic lesions. However, when engineered to overexpress PTHrP, MCF-7 cells induced marked bone destruction and increased osteoclast formation as compared with controls.<sup>(27)</sup>

Tumor-produced PTHrP drives the expression of RANKL and inhibits osteoprotegerin (OPG) secretion from osteoblasts and stromal cells. This stimulates osteoclastogenesis through the RANK located on osteoclast precursors.<sup>(2)</sup> While PTHrP expression by tumor cells within the bone microenvironment results in osteolysis, PTHrP expression by the primary tumor does not predict the development of bone metastasis. Overexpression of PTHrP in a murine primary mammary cancer in vivo resulted in the development of hypercalcemia but not bone metastasis.<sup>(28)</sup> Consistent with this, and in contrast to early, smaller clinical studies, are data from the largest prospective study of >300 breast cancer patients. Here, women with PTHrP-negative primary tumors were more likely to develop bone metastases than patients with PTHrP-positive primary tumors.<sup>(29)</sup>

**Differences in PTHrP Expression Between Primary Tumor and Metastases.** Interestingly, it is now known that PTHrP expression by tumor cells at the primary site differs significantly from PTHrP expression of tumor cells at sites of metastasis. PTHrP expression is higher in breast cancer cells that have metastasized to bone compared with nonbone sites.<sup>(1,2)</sup> Breast cancer tissue from primary tumors and bone metastases in three patients were analyzed. In these three cases, the bone metastases were PTHrP positive and the respective primary tumors were PTHrP negative. This is the only published study able to compare, in an individual patient, PTHrP expression in the primary tumor and at the metastatic site.<sup>(29)</sup> Two theories, which are not mutually exclusive, can be made from these observations. First, PTHrP stimulates osteolysis, thus promoting tumor growth in bone. Second, the bone microenvironment enhances expression of PTHrP in metastatic cancer cells. Studies with larger numbers of patients are needed to confirm these observations. Taken together, the data suggest that PTHrP is not important in the establishment of osteolytic bone metastases but is critical in the progression of osteolytic bone destruction.

**Other Factors.** Tumor cells also produce other important factors that lead to osteolysis. When IL-6, IL-11, and VEGF are secreted by osteolytic breast cancer cell lines after TGF- $\beta$  stimulation, they potentiate the effects of PTHrP on osteoclastic bone resorption.<sup>(30,31)</sup> IL-8 production correlates with an increased metastatic potential in MDA-MB-231 cells but seems to be independent of PTHrP secretion.<sup>(32)</sup> IL-8, a potent osteolytic factor, is produced by tumor cells in response to activated platelet production of lysophosphatidic acid.<sup>(22)</sup> IL-11 was one of a cohort of genes upregulated in the highly bone metastatic MDA-MB-231 breast cancer cell line.<sup>(4)</sup> Its contribution to breast cancer osteolysis is obvious, by promoting osteoclastic bone resorption.

Interestingly, breast cancer cells express genes thought to be restricted to osteoblasts, bone sialoprotein and osteopontin; these genes are regulated by Runx2. The transcription factor Runx2 (Cbfa1) directs mesenchymal cells to the osteoblast lineage and is critical for osteoblast development. Stable expression of a dominant-negative Runx2 mutant or of a Runx2 mutant containing a point mutation in the nuclear matrix-targeting signal sequence in MDA-MB-231 cells blocked the cells' ability to form osteolytic bone lesions in animal mod-

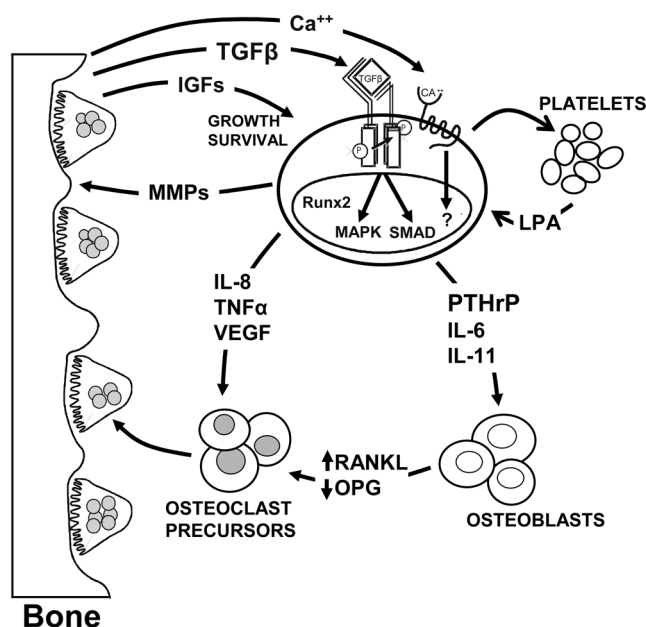
els.<sup>(33,34)</sup> Thus, breast cancer cells may act as surrogate osteoblasts to support osteoclast formation.

**Bone Microenvironment as the “Soil.”** Immobilized within the mineralized bone matrix is a rich trove of growth factors. These growth factors are released from the matrix by osteoclastic bone resorption during the normal course of physiological bone remodeling required to maintain structural integrity of bone. Thus, once tumor cells arrest in bone, the high concentrations of cytokines and growth factors in the microenvironment provide a fertile soil in which to grow. The environment is further enriched as the tumor cells stimulate osteoclastic bone resorption, leading to the release of more bone-derived growth factors that enhance survival and growth of the cancer, while simultaneously disrupting normal bone remodeling thus resulting in bone destruction.

**TGF- $\beta$ .** TGF- $\beta$  promotes invasion and metastasis in the transformed cancer cell and has a distinct role to promote bone metastasis through its effects to stimulate tumor production of osteolytic factors. TGF- $\beta$  mobilized from the bone matrix increases metastasis of breast cancer by stimulating tumor production of PTHrP.<sup>(19)</sup> The signaling pathways by which TGF- $\beta$  stimulates osteolytic factor production is cell and context specific. For example, the effects of TGF- $\beta$  to stimulate PTHrP are mediated by both the Smad and p38 mitogen-activated protein kinase (MAPK) pathways in the MDA-MB-231 breast cancer cell line.<sup>(35)</sup> TGF- $\beta$  stimulates production of the osteolytic factor, IL-11, and the pro-metastatic factor connective tissue growth factor (CTGF) through the Smad pathway in another variant of the MDA-MB-231 line.<sup>(4)</sup> Furthermore, knockdown of Smad4 through the siRNA approach reduced bone metastases by MDA-MB-231. Through immunohistochemical analysis of human breast cancer bone metastasis and functional imaging of the Smad pathway in this mouse xenograft model, Kang et al.<sup>(36)</sup> provided evidence for active Smad signaling in human and mouse bone metastatic lesions.

**Other Osteolysis-Stimulating Factors.** Osteoclastic resorption of bone releases high concentrations of ionized calcium and phosphate from the dissolution of the bone mineral. The calcium-sensing receptor (CaSR) is a G protein-coupled, seven-transmembrane domain receptor, which responds to small variations in the concentration of extracellular calcium.<sup>(37)</sup> CaSR is expressed by breast cancer cells and regulates tumor secretion of PTHrP,<sup>(38,39)</sup> an effect that is enhanced by TGF- $\beta$ . Thus, the high concentrations of ionized calcium in bone may contribute to the vicious cycle by increasing PTHrP production and osteolysis. Small molecule agonists and antagonists of CaSR have been developed and are in clinical trials.<sup>(40)</sup> Such agents might be effective against breast cancer bone metastasis. The IGFs are also released into the local bone environment during osteolysis and likely also have a role in the proliferation of bone metastasis.<sup>(41,42)</sup> Hauschka et al.<sup>(43)</sup> found that IGF-II, then -I, was the most abundant factor in bone matrix, followed by TGF- $\beta$ , after which were lower concentrations of bone morphogenetic proteins (BMPs), FGF-1 and -2, and PDGF.

**Interactions Between Tumor and Bone—the “Vicious Cycle.”** The arrival of tumor cells in bone marks the beginning of complex interactions that occur with the bone-forming osteoblasts, bone-destroying osteoclasts, and the mineralized bone matrix (Fig. 1). Tumor cells secrete factors into the bone microenvironment that stimulate osteoclastic bone resorption directly (IL-8, TNF- $\alpha$ , and VEGF) or indirectly (PTHrP, IL-6,



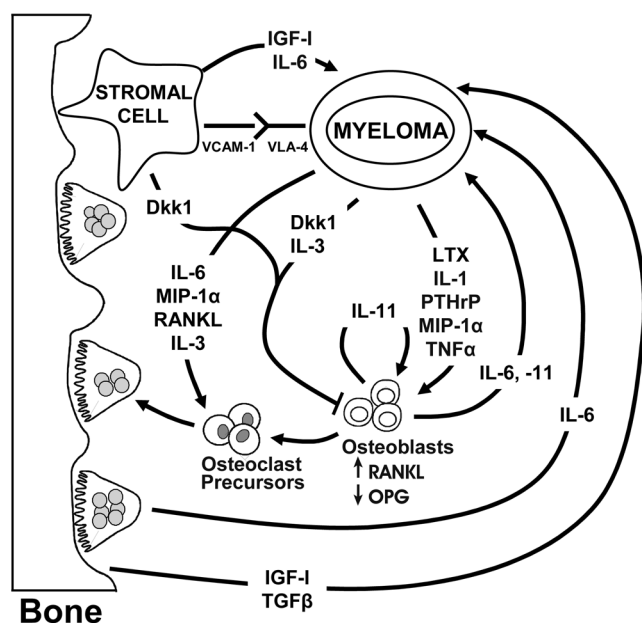
**FIG. 1.** Bone resorption in breast cancer osteolytic metastasis. Tumor cells secrete factors into the bone microenvironment that support osteoclastogenesis. Tumor-produced PTHrP, IL-6, and IL-11 increase osteoblast RANKL and decrease OPG activity, resulting in increased osteoclastogenesis. IL-8, TNF- $\alpha$ , and VEGF secreted by tumor cells also enhance osteoclast formation but are independent of the RANK/RANKL axis. MMPs produced from tumor cells may prime the bone surface for osteoclast attachment. The escalation in bone resorption leads to the release of factors immobilized in the mineralized bone matrix such as TGF- $\beta$ . TGF- $\beta$  stimulates tumor cells to produce even more osteolytic factors; thus, the “vicious cycle” of osteolytic bone metastases begins. The transcription factor Runx2 also plays a role in tumor cell activation. Other factors immobilized in bone that are released during osteoclast-mediated resorption include members of the IGF family. Increased calcium concentration as a consequence of enhanced bone resorption may also lead to tumor cell activation.

and IL-11) through the osteoblast through modulation of the RANK/RANKL axis. The dissolution of the bone matrix results in the release of a vast storehouse of matrix-immobilized growth factors, such as IGFs and TGF- $\beta$ . These are synthesized by osteoblasts during the deposition of osteoid. Increasing concentrations of these factors in the bone metastasis microenvironment further stimulate nearby tumor cells to produce even more osteolytic factors. Therapies targeting this vicious cycle would be expected to reduce metastasis by decreasing growth factor concentrations in bone.

### Multiple Myeloma

Although multiple myeloma bone disease is not a metastatic process per se, this malignancy shares similarities with breast cancer metastasis in that tumor-produced factors stimulate osteolysis resulting in the release of immobilized factors that further stimulate myeloma cells (Fig. 2). Almost all patients with multiple myeloma have extensive bone destruction that may occur either as discrete local lesions or as diffuse involvement throughout the axial skeleton. The increased bone resorption is responsible for a number of disabling features, including susceptibility to pathological fracture, intractable bone pain, and in some patients, hypercalcemia. Approximately 80% of patients with myeloma present with the chief complaint of bone pain. Hypercalcemia occurs in between 20% and 40% of patients at some time during the course of the disease.





**FIG. 2.** Bone resorption in multiple myeloma. Numerous local factors have been identified in the bone microenvironment that contribute to increased bone resorption and osteolytic disease. IGF-I and IL-6 secreted by bone marrow stromal cells and the VLA-4/VCAM-1 interaction increase myeloma proliferation and survival. Myeloma cells produce IL-6, RANKL, and MIP-1 $\alpha$  that ultimately lead to an increase in osteoclast activity and numbers. Myeloma cells also secrete Dkk1 and IL-3, resulting in suppression of osteoblast activity.

**Stimulation of Myeloma Cells by the Bone Microenvironment.** Identification of myeloma-stimulating factors within the bone microenvironment has been elusive. IL-6 produced by both osteoclasts and osteoblasts is mitogenic and reduces apoptosis in myeloma cells.<sup>(2)</sup> IGF-I produced by bone marrow stromal cells also contributes to myeloma survival and activates a signal transduction pathway that is independent of IL-6 signaling.<sup>(44)</sup> Osteoclast activity promotes myeloma survival; severe combined immunodeficient (SCID) mice inoculated with human myeloma cells show inhibition of myeloma growth in the presence of the bisphosphonates pamidronate and zoledronic acid.<sup>(45)</sup>

**Stimulation of Osteoclastogenesis by Myeloma Cells.** The bone destruction that occurs in myeloma is caused by an increase in the number and activity of osteoclasts. Myeloma cells in the marrow cavity produce cytokines that activate adjacent endosteal osteoclasts to resorb bone. IL-6 is secreted by myeloma cells and osteoblast precursors as a consequence of myeloma cell adherence. Myeloma cells also induce osteoblast production of IL-11. However, neither IL-11 nor IL-6 are potent bone-resorbing factors alone and likely cooperate with other factors. IL-3 is increased in multiple myeloma patients and promotes osteoclastogenesis.<sup>(46,47)</sup>

Myeloma-produced macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ) is a member of the RANTES family of chemokines. MIP-1 $\alpha$  is a potent osteoclast stimulatory factor with an increased marrow plasma concentration in 70% of myeloma patients.<sup>(47)</sup> MIP-1 $\alpha$  enhances osteoclast formation induced by IL-6, PTHrP, and RANKL.<sup>(48)</sup> MIP-1 $\alpha$  neutralizing antibodies blocked osteoclast formation in bone marrow cultures treated with human myeloma bone marrow plasma<sup>(49)</sup> and reduced osteolysis in an in vivo mouse myeloma model.<sup>(50)</sup>

An important mediator of osteoclastogenesis in myeloma

bone disease is RANKL. Association of this factor with RANK on osteoclast precursors is key to the development of mature osteoclasts. Marrow stromal cells from myeloma patients have increased expression of RANKL, presumably as a consequence of the myeloma cells.<sup>(51)</sup> Another source of RANKL is from myeloma cells themselves,<sup>(52)</sup> bypassing osteoblast and bone marrow stromal cell intermediaries. In a mouse model of multiple myeloma, a RANKL neutralizing antibody prevented myeloma bone destruction.<sup>(53)</sup>

Myeloma cells express the cell surface molecule VLA-4 ( $\alpha 4\beta 1$ -integrin), a receptor that has affinity for fibronectin and vascular cell adhesion molecule-1 (VCAM-1). Bone marrow stromal cells express VCAM-1, thereby presumably promoting recruitment of myeloma to bone. Disruption of the VLA-4/VCAM-1 interaction in vitro resulted in decreased osteoclastic activity and was independent of other bone microenvironment cytokines, including IL-1, IL-6, TNF- $\alpha$ , and PTHrP.<sup>(9)</sup> The VLA-4/VCAM-1 system also has a role in the regulation of RANKL and OPG. Bone marrow stromal cells had increased RANKL and decreased OPG expression when co-cultured with myeloma cells, thereby promoting an environment for enhanced osteoclastogenesis. This imbalance of RANKL/OPG was inhibited in the presence of a VLA-4 neutralizing antibody.<sup>(54)</sup>

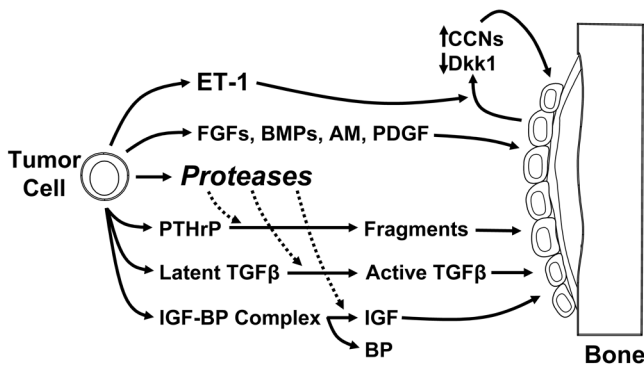
#### **Suppression of Bone Formation in Myeloma Bone Disease.**

Dickkopf homolog 1 (Dkk1) is involved in the suppression of osteoblast activity in multiple myeloma.<sup>(55)</sup> Dkk1 mRNA concentrations were increased in plasma cells of patients with more advanced disease, and Dkk1 protein levels were higher in the bone marrow plasma and peripheral blood of patients with myeloma bone disease compared with controls. Dkk1 is a secreted inhibitor of the Wnt signaling pathway and binds to the LDL receptor-related proteins 5 and 6 (LRP5 and 6), preventing interaction of these co-receptors with the frizzled (Frz) receptor family.<sup>(56)</sup>

The Wnt pathway is important in the differentiation of mesenchymal stem cells to mature osteoblasts. Dkk1 seems to alter the bone microenvironment by suppressing osteoblast differentiation.<sup>(55)</sup> In vitro experiments support this statement. The addition of recombinant Dkk1 to osteoblast cultures decreased BMP-2-mediated increases in alkaline phosphatase, a marker of osteoblast differentiation.<sup>(55)</sup> Dkk1 also blocked the osteoblast proliferative effects of endothelin-1.<sup>(57)</sup> Low concentrations of this factor may have a role in promoting osteoblastic disease of prostate cancer and some breast cancers. Preclinical studies with a Dkk1 neutralizing antibody shows promise. In a mouse model of myeloma bone disease, an anti-Dkk1 antibody increased osteoblast activation and osteoclast inactivation and decreased bone loss and tumor burden.<sup>(58)</sup>

An additional role for Dkk1 in other osteolytic diseases is likely. Human prostate cancer PC-3 cells produce osteolytic lesions in a mouse model of bone metastasis. PC-3 cells abundantly expressed Dkk1 compared with the osteoblastic prostate cancer cell lines C4-2B and LuCaP-35. PC-3 cells were stably transfected with a Dkk1 siRNA construct and tested in an in vitro mineralization assay. These clones failed to stimulate mineralization. Furthermore, an opposite response was observed in C4-2B cells that overexpress Dkk1.<sup>(59)</sup>

Increased concentrations of IL-3 in the bone marrow plasma of myeloma patients stimulate osteoclast formation but may also inhibit osteoblast differentiation. In a recent report, IL-3 decreased osteoblast differentiation of murine stromal cell cultures and human bone marrow aspirates and blocked BMP-2-mediated osteoblast differentiation. Additionally, an IL-3 neutralizing antibody enhanced osteoblast differentiation from bone marrow plasma derived from myeloma patients.<sup>(60)</sup>



**FIG. 3.** Bone formation in prostate cancer osteoblastic metastasis. Prostate cancer cells stimulate osteoblast proliferation and new bone formation through secretion of factors into the bone microenvironment, including ET-1, FGFs, BMPs, adrenomedullin, and PDGF. Tumor-produced ET-1 stimulates osteoblast activity by decreasing secretion of the Wnt pathway inhibitor Dkk1. ET-1 may also lead to an increase in CCN proteins, which may further support osteoblastic bone metastasis. Tumor production of proteases, most notably prostate specific antigen, cleaves PTHrP, TGF- $\beta$ , and IGF from its binding protein, resulting in the generation of fragments with osteoblast stimulating activity.

### Osteoblastic Metastasis

Osteoblastic bone metastasis is commonly associated with prostate cancer and to a lesser degree with breast cancer. Just as with breast cancer-mediated osteolysis, the seed and soil hypothesis applies to prostate cancer in that the bone microenvironment readily supports the growth of prostate cancer cells. The key difference, however, is that prostate tumor cells secrete factors that stimulate bone formation rather than destruction (Fig. 3).

**Endothelin-1.** Endothelin-1 (ET-1) is a 21 amino acid peptide that was first identified as a potent vasoconstrictor but has since been found to have multiple physiologic functions and an important role in osteoblastic bone metastasis.<sup>(61)</sup> The biological actions of ET-1 are transmitted through activation of specific G protein-coupled receptors. Two receptors have been identified: the endothelin A receptor (ETAR) and the endothelin B receptor (ETBR).<sup>(61)</sup>

Tumor-produced ET-1 is implicated in the pathogenesis of osteoblastic metastasis.<sup>(62)</sup> The human breast cancer cell line ZR-75-1 produces osteoblastic bone lesions in nude mice and abundantly secretes ET-1. ET-1 stimulated osteoblast activity and new bone formation; these responses were blocked by an ETAR antagonist, ABT-627, but not by ETBR blockade. ABT-627 blocked development and progression of ZR-75-1 osteoblastic bone metastases in nude mice. The drug had no effect on mammary tumors or on bone metastases because of ET-1-negative MDA-MB-231 breast cancer cells. The former result suggests that ETAR blockade may have a bone-specific effect on metastasis, a fact that was borne out in clinical trials described below.

ET-1 also contributes to bone metastasis of human prostate cancer. (1) Prostate epithelial cells secrete large amounts of ET-1 into seminal fluid compared with plasma.<sup>(63,64)</sup> (2) ET-1 is secreted by the majority of prostate cancer cell lines.<sup>(65)</sup> (3) Plasma ET-1 concentrations are higher in men with advanced prostate cancer than in men with local disease or in age-matched controls.<sup>(65)</sup> (4) Prostate cancer expression of ETAR is higher in men with more aggressive disease.<sup>(66)</sup> (5) ETAR blockade benefits prostate cancer patients with bone metastases. In a phase II clinical study, the ETAR antagonist atrasentan (ABT-627) delayed progression and decreased prostate-

specific antigen (PSA) compared with the control group in men with hormone refractory disease.<sup>(67)</sup> In addition, atrasentan reduced markers of bone formation (bone alkaline phosphatase) and bone resorption (N-telopeptide) in men with prostate cancer bone metastases.<sup>(68)</sup> In a large phase III placebo-controlled trial of atrasentan in men with advanced prostate cancer,<sup>(69)</sup> there was a significant decrease in the progression of bone metastasis but not in overall disease progression.<sup>(70)</sup> These clinical data again suggest that the effects of ETAR blockade are bone specific.

Results from animal and human clinical studies support a model in which tumor-produced ET-1 mediates pathological bone formation by acting on osteoblast ETAR. These findings also suggest that the effect of ET-1 to stimulate tumor growth is dependent on the osteoblast. The vicious cycle model predicts that osteoblasts, osteoclasts, and tumor cells cooperate to cause the pathology of bone metastases. The endothelin receptor antagonist blocks the activation of osteoblasts by tumor-produced ET-1. This reduction in osteoblast activity was associated with a reduction in bone resorption and suggests that the bone resorption associated with osteoblastic bone metastasis may be a secondary event because ETAR antagonists have no direct effects on osteoclastic bone resorption.<sup>(68)</sup>

Downstream mediators of the effects of ET-1 on the osteoblast were identified by microgene array analysis of ET-1-treated osteoblasts. ET-1 suppressed osteoblast production of Dkk1, and Dkk1 blocked osteoblast activation by ET-1. These results suggest that ET-1 mediates its effects on bone formation by activating the Wnt signaling pathway, findings that are consistent with dysregulation of this pathway in multiple myeloma. ET-1 also stimulated osteoblast production of IL-6 and CCN proteins, CTGF and Cyr61—factors that could contribute to the vicious cycle by affecting bone cell function, tumor growth, and angiogenesis.<sup>(57)</sup>

**Other Osteoblastic Factors.** Other factors that may contribute to osteoblastic metastasis include IGFs, PSA, and TGF- $\beta$ . However, these factors remain to be critically tested. Such factors need to meet two initial criteria: (1) ability to stimulate osteoblastic new bone formation and (2) expression by cancer cells. Adrenomedullin (AM) is a 52 amino acid vasoactive peptide with potent bone stimulatory actions,<sup>(71)</sup> which is produced by many cancers.<sup>(72)</sup> In lung and prostate cancer cell lines, AM increases bone metastases *in vivo*.<sup>(73)</sup> It is also an autocrine growth factor for breast cancer cells,<sup>(74)</sup> but its role in breast cancer bone metastasis has not yet been investigated. Yi et al.<sup>(75)</sup> overexpressed platelet-derived growth factor B-chain (PDGF-BB) in MDA-MB-231 cells and observed osteosclerotic rather than osteolytic metastases.

A puzzling question has been the role of PTHrP in osteoblastic metastasis, especially those caused by prostate cancer, which nearly always express PTHrP. A partial explanation was provided by the observation that PSA is a serine proteinase, which cleaves PTHrP after residue 23.<sup>(1,2)</sup> The resulting fragment fails to activate the classical PTH/PTHrP receptor. It was later observed that the inactive fragment PTHrP1-16 increased cAMP in cardiomyocytes by activating ETAR. Binding was attributed to a four amino acid near-identity between the two peptides.<sup>(76)</sup> PTHrP-1-23 is a potent stimulator of new bone formation. The results suggest that PSA proteolysis, rather than inactivating PTHrP, converts it from an osteolytic factor to a potent osteoblastic one. This process may occur in breast and prostate cancer bone metastasis. Proteolytic cleavage of IGF from its binding protein and the processing of latent TGF- $\beta$  to the active form may also contribute to osteoblast stimulation.<sup>(1,2)</sup>

Tumor cells may also secrete factors that oppose the devel-

opment and progression of bone metastasis. IL-18, which decreases osteoclast formation, is one such factor made by cancer cells.<sup>(77,78)</sup> This unexplored territory may reveal exciting new approaches for future anti-metastatic therapies. Similarly, the role of the immune system in bone metastasis is understudied,<sup>(79)</sup> as is angiogenesis.<sup>(80)</sup>

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# Chapter 69. Treatment and Prevention of Bone Metastases and Myeloma Bone Disease

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## CLINICAL ASPECTS

According to various large series, up to 90% of patients with advanced cancer will develop bone metastases. The skeleton is the most common site of metastatic disease. It is also the most frequent site of first distant relapse in breast and prostate cancers.

### Breast Cancer

Metastatic bone disease causes considerable distress to breast cancer patients. Because of the long clinical course breast cancer may follow, morbidity caused by tumor bone disease also makes major demands on resources for health care provision. The term skeletal-related events (SREs) refers to the major complications of tumor bone disease, namely pathological fractures, need for radiotherapy, need for bone surgery, spinal cord compression, and hypercalcemia.<sup>(1,2)</sup> Such major complications will be observed in up to one third of the patients whose first relapse is in bone. Bone pain can be the source of great suffering, causing most patient concern and physician visits.<sup>(3)</sup> Hypercalcemia classically occurs in 10–15% of the cases, spinal cord compression in about 10%, and when long bones are invaded, fractures will occur in 10–20% of the cases.<sup>(4,5)</sup> Pathological fractures are a dramatic consequence of tumor bone disease and they occur with a median onset of 11 months from the initial diagnosis of bone involvement.<sup>(6)</sup> Across all tumor types, patients with breast cancer have the highest incidence of skeletal complications. Taken from data in placebo groups of randomized bisphosphonates trials, the mean skeletal morbidity rate (i.e., the mean number of SREs per year) varies between 2.2 and 4.0.<sup>(4–9)</sup> Patients who have metastases only in the skeleton have a higher rate of SREs than patients who have bone and visceral metastases (e.g., a 2- to 3-fold increase in pathological fractures).<sup>(9)</sup> The same authors also confirmed that survival from diagnosis of bone metastases was longest for patients with only bone metastases (median survival, 24 months) and was least for patients with concomitant bone and liver metastases (median survival, 5.5 months).<sup>(9)</sup>

### Multiple Myeloma

Bone pain is a presenting feature in three fourths of patients with multiple myeloma. Back pain correlates with the presence of vertebral fractures that are present in more than one half of the patients at diagnosis. Extensive osteolytic lesions are frequent in this aggressive bone disease and, typically, they do not heal despite successful antineoplastic treatment.<sup>(10)</sup> Diffuse osteoporosis can also be a presenting and misleading feature. The increased fracture rate seems to be especially high around the time of diagnosis. In a large retrospective cohort study, fracture risk was increased 16-fold in the year before diagnosis and 9-fold thereafter. Fractures of the vertebrae and ribs were the most frequent, and oral corticosteroids were the most important predictor.<sup>(11)</sup>

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### Prostate Cancer

Surprisingly, there are only few studies to document the frequency and the nature of bone metastatic complications in hormone-refractory prostate cancer patients.<sup>(12–15)</sup> The incidence of SREs can probably be best estimated by analyzing the placebo group of the controlled trial that has shown the efficacy of the bisphosphonate zoledronic acid.<sup>(14,15)</sup> Inclusion criteria required that patients had at least one bone metastasis and an augmentation of prostate-specific antigen (PSA) levels while on hormonal therapy. During a follow-up period of 2 years, nearly one half of the patients developed one or more SREs, which were defined as the necessity of radiation therapy or surgery to bone, pathological fracture, spinal cord compression, or a change in antineoplastic therapy to treat bone pain. The two most frequent complications were the need for radiation therapy and the occurrence of pathological fractures. These fractures appeared more frequently at peripheral than at vertebral sites. The median time to the first SRE was 10.5 months, whereas the mean skeletal morbidity rate per year was nearly 1.5. The median survival was 9.5 months.<sup>(15)</sup>

The following sections relate to the use of bisphosphonates in tumor bone disease. The reader is referred to other sources for the other therapeutic modalities of bone metastases, namely analgesics,<sup>(16)</sup> radiotherapy,<sup>(17)</sup> radioisotopes,<sup>(18)</sup> surgery,<sup>(19)</sup> vertebroplasty,<sup>(20)</sup> or kyphoplasty.<sup>(21)</sup>

## CURRENT USE OF BISPHOSPHONATES IN TUMOR BONE DISEASE

Bisphosphonates bind to active sites of bone remodeling, are released from the bone matrix during bone resorption, and are taken up by osteoclasts. They potently inhibit osteoclast-mediated bone resorption and eventually cause osteoclast apoptosis.<sup>(22)</sup>

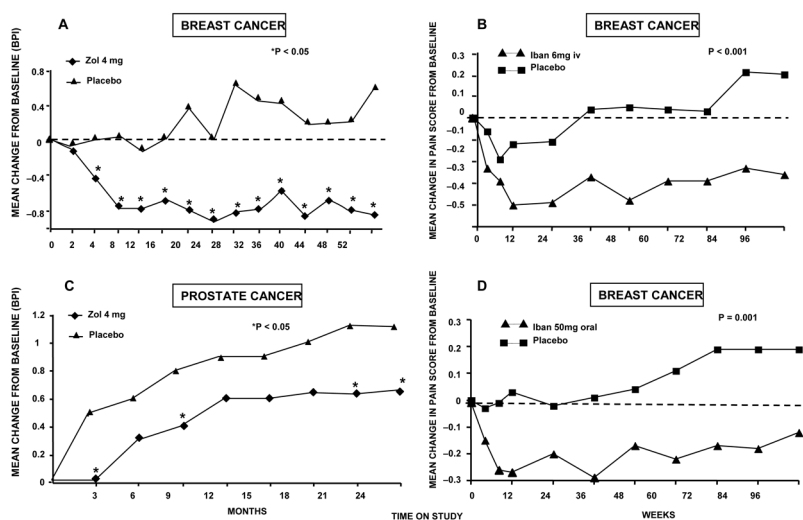
### Cancer Hypercalcemia

This complication of metastatic bone disease is reviewed elsewhere.

### Metastatic Bone Pain

Bisphosphonates can relieve metastatic bone pain and improve patient functioning and quality of life even if the mechanism of this analgesic effect remains largely unknown. The relative inability of first-generation oral bisphosphonates to reduce metastatic bone pain has been confirmed in a placebo-controlled study of oral clodronate after a median time on study of almost 2 months in patients with progressing bone metastases.<sup>(23)</sup> In another short-term study, clodronate was inferior to intravenous pamidronate in relieving metastatic bone pain ( $p < 0.01$ ) after 3 months.<sup>(24)</sup> The current opinion is that the intravenous route has to be selected to obtain optimal analgesic effects, but this statement is now challenged by the analgesic effects of oral ibandronate that have been shown in a placebo-controlled study.<sup>(25)</sup>

Short-term placebo-controlled trials have established that both clodronate and pamidronate given intravenously can exert significant and rapid analgesic effects.<sup>(26,27)</sup> A clinically meaningful relief of bone pain seems to occur in one



**FIG. 1.** Analgesic activity of long-term therapy with bisphosphonates in placebo-controlled trials. Effects of zoledronic acid (Zol) are shown in left panels (pain assessed by the Brief Pain Inventory score, quantitative 10-point scale): (A) breast cancer<sup>(33)</sup> and (C) prostate cancer<sup>(14,15)</sup>. Effects of ibandronate (Iban) in breast cancer are shown in the right panels (pain assessed on a qualitative five-point scale): (B) intravenous route<sup>(7)</sup> and (D) oral route.<sup>(34)</sup>

half to two thirds of the patients treated with pamidronate, and most of the effect is obtained after only one or two infusions.<sup>(1,27)</sup> More recently, open phase II studies have shown that intensive ibandronate dosing provides rapid and effective relief from severe metastatic bone pain.<sup>(28,29)</sup>

Over the long term, randomized placebo-controlled trials have shown that intravenous clodronate, pamidronate, ibandronate, and zoledronic acid exert useful pain relief. The American Society of Clinical Oncology (ASCO) panel considered it “reasonable” to start intravenous bisphosphonates in women with abnormal bone scans with localized pain and normal plain radiographs but not if the abnormal bone scan is asymptomatic.<sup>(30)</sup> In two randomized, placebo-controlled trials, mean pain scores and use of analgesics in patients treated with pamidronate 90 mg monthly for 2 years increased significantly less than in the placebo group.<sup>(31)</sup> In a phase III trial of patients with breast cancer, pain and analgesic scores were reduced to a similar extent with zoledronic acid 4 mg and pamidronate 90 mg at 13 months.<sup>(32)</sup> Performance status also improved in both groups. Bone pain levels were recently assessed in a randomized, placebo-controlled study of zoledronic acid in Japanese patients with breast cancer and bone metastases.<sup>(33)</sup> Patients receiving zoledronic acid 4 mg for 12 months experienced a significant decrease from baseline ( $p < 0.001$ ) in their mean composite Brief Pain Inventory (BPI) score (Fig. 1A). In phase III trials of intravenous and oral ibandronate, bone pain was reduced and similarly maintained below baseline for 2 years (Figs. 1B and 1D).<sup>(34)</sup> There were also significant improvements in global quality of life and physical functioning with intravenous or oral ibandronate versus placebo.<sup>(35)</sup> Given the variations in the endpoints used between studies, direct comparative trials are warranted to further evaluate the efficacy of bisphosphonates against bone pain.

In prostate cancer, uncontrolled trials have often been positive, whereas placebo-controlled studies were usually negative, whether for clodronate or for pamidronate. Initial pamidronate uncontrolled trials reported impressive results,<sup>(36)</sup> but a more recent controlled trial suggests that pamidronate is no more effective than placebo in reducing bone pain or SREs over 6 months.<sup>(13)</sup> A posthoc analysis showed pain reduction in patients whose pain was “moderate” at baseline, although the effect was only transitory. In the large scale, placebo-controlled study of zoledronic acid,

the effect on bone pain was not impressive (Fig. 1C)<sup>(14,15)</sup> compared with the analgesic effects observed in breast cancer. There was, however, a marked reduction in the frequency of SREs in the zoledronic acid group, which was not the case in the pamidronate trial.<sup>(13)</sup> However, the selection of bone pain (rather than SREs) as a primary endpoint in the latter study and the advanced disease state of the patients reduce the validity of cross-trial comparisons. In the placebo-controlled clinical trial in patients with bone metastases from other tumors, zoledronic acid had no significant effects on bone pain or quality of life.<sup>(37,38)</sup>

The analgesic effect of bisphosphonates is thus well established in patients with breast cancer or myeloma but seems to be less in patients with other tumor types. Last, the role of bisphosphonates as an alternative or an adjunct to radiotherapy remains unclear.

### Prevention of Skeletal-Related Events

**Breast Cancer.** Bisphosphonates constitute a highly effective therapeutic option for the prevention of skeletal complications secondary to bone metastases in breast cancer. Several placebo-controlled trials and fewer comparative trials against another bisphosphonate have been performed. Assessment of treatment effects has often used the first-event analyses, such as the proportion of patients with at least one SRE or time to the first event. These are quite objective and conservative endpoints but they do not take into account all subsequent events that occur in any given patient. From a clinical perspective, an aggregate score of symptomatic SREs is more relevant. Skeletal morbidity rate (SMR) or skeletal morbidity period rate (SMPR, number of periods with at least one SRE) take into account the occurrence of multiple SREs. SMPR is better than SMR because events often occur in clusters and SMPR thus reduces the risk of multiple counting of the same event (e.g., fracture of a long bone, followed by surgery and radiotherapy). More recently, more sophisticated analyses have emerged. Multiple-event analyses are able to model all events and the time between events. Thus, Andersen-Gill multiple-event analysis calculates a hazard ratio that indicates the relative risk of skeletal events between two treatment groups.

Until quite recently, the bisphosphonates clodronate, in Europe, and pamidronate, in the United States and Europe, were most often used in practice. Clinical trials of these agents have established their effectiveness in breast cancer patients with



bone metastases.<sup>(8,31,39–42)</sup> In these trials, clodronate has been shown to increase the time to the first event and to reduce the incidence of hypercalcemia and of vertebral fractures. However, clodronate is considered to be less effective than pamidronate for the prevention of SREs.<sup>(43)</sup> This has been shown in a limited comparative trial against pamidronate.<sup>(24)</sup> Two double-blind randomized placebo-controlled trials comparing 90 mg pamidronate infusions every 4 weeks to placebo infusions for up to 2 years in addition to chemo- or hormonal therapy in large series of breast cancer patients with at least one lytic bone metastasis showed that bisphosphonates can reduce SMR by more than one third, increase the median time to the occurrence of the first SRE by almost 50%, and reduce the proportion of patients having any SRE.<sup>(8,42)</sup> The results were more impressive in the chemotherapy trial<sup>(8)</sup> than in the hormone therapy trial,<sup>(42)</sup> probably because the skeletal disease was more aggressive at the beginning of the chemotherapy study.

In the past few years, more convenient and somewhat more effective aminobisphosphonates have emerged. Zoledronic acid is widely used for patients with bone metastases from various tumors,<sup>(14,32,37,38,44)</sup> and ibandronate has since been approved in many countries, but not in the United States, for the prevention of skeletal events in patients with breast cancer and bone metastases.

Three randomized double-blind multicenter trials assessed the efficacy of zoledronic acid in patients with breast cancer and multiple myeloma, in prostate cancer, and in lung or other solid tumors. The primary efficacy endpoint was the proportion of patients with at least one SRE, defined as pathological fracture, spinal cord compression, radiation therapy to bone, and surgery to bone. Secondary endpoints included time to first SRE, SMR, and Andersen-Gill multiple-event analysis. Patients with breast cancer or multiple myeloma ( $n = 1648$ ) were randomized to a 15-minute infusion of zoledronic acid 4 or 8 mg or a 2-h infusion of pamidronate 90 mg every 3–4 weeks.<sup>(32,44)</sup> The proportion of patients with at least one SRE was similar in all treatment groups (46%, 44%, and 46% for zoledronic acid 8/4 mg, zoledronic acid 4 mg, and pamidronate, respectively). The pre-established criterion for non-inferiority of zoledronic acid to pamidronate was thus met. Zoledronic acid 8 mg was no more effective than the 4-mg dose but was associated with an increased frequency of renal adverse events, explaining why all patients in that treatment arm were switched to the lower dose of zoledronic acid during all zoledronic acid trials. Median time to first SRE was ~1 year in all three treatment groups, and SMRs were also not significantly different. A preplanned multiple-event analysis, according to the Andersen-Gill model, showed that zoledronic acid 4 mg reduced the risk of developing a skeletal complication by an additional 20% over that achieved by pamidronate 90 mg in the breast cancer subgroup ( $p < 0.05$ ; Fig. 2, top).<sup>(44)</sup> The short infusion time (15 minutes compared with 1 or 2 h for pamidronate) offers a quite convenient therapy and is another advantage of zoledronic acid compared with pamidronate.<sup>(45)</sup>

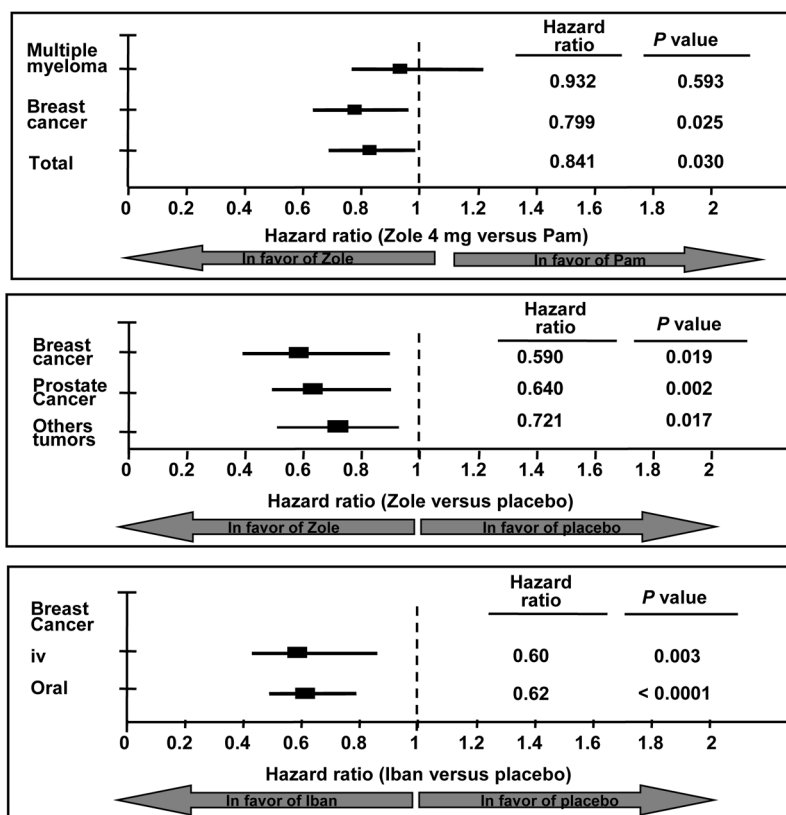
The efficacy of intravenous and oral ibandronate has been assessed in randomized double-blind, placebo-controlled studies.<sup>(7,25)</sup> Breast cancer patients were randomized to ibandronate 6 mg or placebo infused over 1–2 h every 3–4 weeks in the intravenous trial. Oral ibandronate 50 mg was given once daily 1 h before breakfast in two trials of identical design that were pooled for analysis. The primary efficacy endpoint was the SMPR, loosely defined as the number of 12-week periods with skeletal complications (vertebral fractures, nonvertebral fractures, radiotherapy to bone, and surgery to bone) divided by the total observation time. Second-

ary endpoints also included a multiple-event analysis. Intravenous ibandronate 6 mg and oral ibandronate 50 mg significantly reduced SMPRs compared with placebo ( $p < 0.005$  for both). Multiple-event Poisson regression analysis showed that intravenous ibandronate led to a statistically significant 40% reduction in the risk of SREs compared with placebo (Fig. 2, bottom;  $p < 0.005$ ). The effect of oral ibandronate 50 mg on the risk of SREs was similar (Fig. 2, bottom; 38% reduction versus placebo;  $p < 0.0001$ ). Posthoc Andersen-Gill analysis showed a 29% reduction in SREs for intravenous ibandronate ( $p < 0.05$ ) and a 35–42% reduction for oral ibandronate ( $p < 0.005$ ) compared with placebo.<sup>(46)</sup>

**Myeloma.** Bisphosphonates are of great benefit in myeloma patients. Chemotherapy may reduce tumor burden but has little effect on the underlying bone disease. A recent systematic review of the various therapeutic options for the management of multiple myeloma has considered the introduction of bisphosphonates as one of the two most important therapeutic advances for this disease, the other one being the use of high-dose chemotherapy.<sup>(47)</sup> Recently published ASCO guidelines recommend to start bisphosphonates in patients with lytic disease on plain X-rays and consider “reasonable” to start them in osteopenic patients without lytic disease. However, bisphosphonates are not suggested in other situations such as a solitary plasmacytoma or indolent myeloma.<sup>(48)</sup> The Cochrane Myeloma Review Group has reported a meta-analysis based on 11 trials and involving 2183 assessable patients. This review concluded that both pamidronate and clodronate reduce the incidence of hypercalcemia, the pain index, and the number of vertebral fractures in myeloma patients.<sup>(49)</sup>

The efficacy of repeated pamidronate infusions has been best shown in a placebo-controlled trial including 392 patients with at least one osteolytic lesion. Patients received either 90 mg pamidronate or placebo infusions monthly in addition to their antimyeloma regimen. The proportion of patients developing any SRE (defined as a pathological fracture, irradiation of bone, surgery on bone, hypercalcemia, or spinal cord compression) was significantly ( $p < 0.001$ ) smaller in the pamidronate than in the placebo group (24% versus 41%). The effect was already evident after 3 months of therapy.<sup>(50)</sup> At the end of a second year extension of the trial, the mean number of skeletal events per year was 1.3 in the pamidronate group versus 2.2 in the placebo group.<sup>(51)</sup> Vertebral fractures were significantly reduced by pamidronate therapy, but nonvertebral fractures were not significantly affected, consistent with a better effect of bisphosphonates on trabecular than on cortical bone. Quality of life score, performance status, and pain score were all favorably affected by pamidronate therapy. The data also suggested a prolongation of survival in the pamidronate group in patients receiving second or subsequent lines of chemotherapy.<sup>(51)</sup>

The newer more potent bisphosphonate zoledronic acid has been shown to have a comparable efficacy to pamidronate in a randomized phase III trial including breast cancer and myeloma patients (Fig. 2, top).<sup>(44)</sup> Ibandronate has been tested in myeloma at a too low dose (2 mg monthly), but there was a significant reduction in SMR in ibandronate-treated patients who had a suppression of their bone resorption markers.<sup>(52)</sup> Although there is no direct comparative trial between clodronate and pamidronate or zoledronic acid, the ASCO Panel recommends only intravenous pamidronate or zoledronic acid in light of the use of the time to the first event as the primary endpoint and a more complete assessment of bony complications.<sup>(48)</sup>



**FIG. 2.** Effects of long-term therapy with bisphosphonates on the risk of developing a skeletal complication in patients with bone metastases. Data are summarized by a multiple-event analysis (Andersen-Gill model for zoledronic acid and Poisson regression analysis for ibandronate). Hazard ratios (and 95% CI) are shown in the left part of each graph with corresponding *p* values indicated in the right parts. [Data from the top graph appear from Cancer **98**:1735–1744 (Ref. 44) with permission; data in the middle graph appear from Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, Iino Y, Watanabe T, Goessl C, Ohashi Y, Takashima S 2005 Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: A randomized, placebo-controlled trial. *J Clin Oncol* **23**:3314–3321 (Ref. 33) with permission from the American Society of Clinical Oncology, Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Zheng M, Zoledronic Acid Prostate Cancer Study Group 2004 Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer* **96**:879–882 (Ref. 15) with permission from the Oxford University Press, and Rosen LS, Gordon D, Tchekmedyian S, Yanagihara R, Hirsch V, Krzakowski M, Pawlicki M, de Souza P, Zheng M, Urbanowitz G, Reitsma D, Seaman JJ 2003 Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase II, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* **21**:3150–3157 (Ref. 37) with permission from the American Society of Clinical Oncology; data in the bottom graph relate to ibandronate and appear from Body JJ 2006 Bisphosphonates for malignancy-related bone disease: Current status, future developments. *Support Care Cancer* (in press). (Ref. 46) with kind permission of Springer Science and Business Media.]

**Prostate Cancer.** Skeletal metastases from prostate cancer are typically osteoblastic. Therefore, it was traditionally not felt that this form of bone metastasis might respond to antiresorptive therapy. Meanwhile, histomorphometric analyses of bone biopsy specimens<sup>(53,54)</sup> and later studies on biochemical markers of bone turnover<sup>(54,55)</sup> showed that enhanced bone formation in osteoblastic lesions is accompanied by severe bone resorption. Levels of bone resorption markers could even be higher than for patients with breast cancer or other tumors with predominantly lytic bone metastases.<sup>(55)</sup>

In two studies where bone pain palliation was the primary endpoint and objective complications of bone metastases only secondary endpoints, neither oral clodronate nor intravenous pamidronate significantly reduced the need for radiotherapy<sup>(13,56)</sup> or the frequency of other SREs.<sup>(13)</sup> There is only one study whose primary objective was to show a reduction in the frequency of objective SREs after bisphosphonate therapy. Hormone-refractory prostate cancer patients with bone metas-

tases ( $n = 643$ ) were randomized to intravenous zoledronic acid 8 mg or 4 mg or placebo every 3–4 weeks.<sup>(14,15)</sup> As mentioned above, the group receiving 8 mg was switched during the trial to 4 mg because of renal toxicity. At the end of the core trial, there was an absolute reduction of 11% corresponding to a relative reduction of 25% in the number of patients presenting an objective bone complication. Although the number of patients was much smaller, this difference was maintained at 24 months, as shown by a higher percentage of patients taking placebo who had SREs compared with those treated with zoledronic acid 4 mg (49% versus 38%;  $p < 0.05$ ). In a multiple-event analysis, zoledronic acid 4 mg significantly decreased the risk of developing skeletal complications by 36% compared with placebo ( $p < 0.005$ ; Fig. 2, middle). Other secondary endpoints, including the time to the first SRE or the percentage of patients who presented a fracture, were also significantly reduced in the 4 mg zoledronic acid group. One can speculate that part of the favorable effects of zoledronic

acid, especially on the fracture rate, could be caused by effective therapy of castration-induced osteoporosis.

**Other Solid Tumors.** In a similar phase III study, patients with lung and other solid tumors ( $n = 773$ ) received intravenous zoledronic acid 4 or 8 mg or placebo every 3–4 weeks.<sup>(37,38)</sup> The results were less impressive than in other cancers, but, because of the short survival of lung cancer patients, the median duration of treatment was only 4 months. At 9 months, the primary endpoint (percentage of patients with an SRE) was not significantly lower with zoledronic acid 4 mg than with placebo, but a multiple-event analysis indicated a favorable effect (Fig. 2, middle). Retrospective subset analysis of patients with kidney cancer suggested a marked efficacy in that particular tumor.<sup>(38)</sup>

**Bisphosphonates as Adjuvant Therapy.** Another potential major role for bisphosphonates is the prevention or at least a delay in the development of bone metastases. Bisphosphonates have the potential to reduce tumor burden in bone, whether indirectly by decreasing bone turnover or directly by one or several antitumor effects.<sup>(57)</sup> Published trials have only used clodronate thus far. The results of the two open studies are conflicting.<sup>(58,59)</sup> The only double-blind placebo-controlled trial involving >1000 unselected breast cancer patients after surgery treated for 2 years with 1600 mg clodronate or placebo indicates that clodronate can indeed reduce the incidence of bone metastases (by 31% at 5 years,  $p = 0.043$ ) and may prolong survival ( $p = 0.048$ ).<sup>(60)</sup>

An ongoing trial is comparing clodronate with placebo in the adjuvant setting (National Surgical Adjuvant Breast Project [NSABP] B-34 trial;  $n = 3200$ ). The accrual is completed, and this study will prove to be the confirmatory trial for the effects of adjuvant clodronate. Newer aminobisphosphonates such as ibandronate and zoledronic acid are expected to inhibit bone metastases more effectively, and they are currently being tested in the adjuvant setting.

### Practical Recommendations for Possible Individualized Use, Safety Aspects, and Perspectives

**Breast Cancer.** The indications of bisphosphonate therapy in breast cancer patients nowadays go from the correction of tumor-induced hypercalcemia to the prevention of cancer treatment-induced bone loss. Their main use is currently the prevention of SREs in patients with tumor bone disease. The fact that the efficacy of monthly 8-mg zoledronic acid infusions is not superior to the 4-mg dose<sup>(44,46)</sup> suggests that we have reached some form of a ceiling effect, at least with classical therapeutic schemes. The efficacy of new generation bisphosphonates looks quite similar (e.g., the comparable effects of zoledronic acid and ibandronate on markers of bone turnover in a 3-month study),<sup>(61)</sup> although comparative trials with clinical endpoints are needed to confirm this statement. Increasing the dose in patients who seem to respond poorly to standard doses of zoledronic acid cannot be recommended because of possible renal toxicity, and caution is probably mandatory with all bisphosphonates on a long-term basis.

There are few evidence-based medicine criteria for when bisphosphonate treatment should be started and stopped.<sup>(62)</sup> In an analysis of the subset of patients with breast cancer in the phase III comparative trial between zoledronic acid and pamidronate, patients who had experienced at least one SRE (68% of the total) had almost a 2-fold higher risk for the development of a subsequent SRE compared with patients who had no prior SREs (58% versus 32%, respectively). These high-risk patients seemed to benefit more from zoledronic acid than from pam-

idronate.<sup>(63)</sup> More importantly, this suggests that giving bisphosphonates early in patients with metastases from breast cancer might help to reduce skeletal complications. Current guidelines from ASCO recommend the routine use of intravenous pamidronate or zoledronic acid in patients with breast cancer and radiographic evidence of bone destruction, with additional consideration for patients who have an abnormal bone scan and localized bone pain.<sup>(30)</sup> However, the impact of an early treatment on quality of life has rarely been studied, and only ibandronate has shown a significant effect in phase III trials.<sup>(34,35)</sup> Oral bisphosphonates could be a preferred alternative for many patients on endocrine therapy to avoid the inconvenience of monthly infusions that may reduce quality of life, whereas the intravenous route will evidently be preferred for patients receiving chemotherapy.<sup>(62)</sup>

Based on the available data, it is thus reasonable to begin bisphosphonates immediately when there is lytic or mixed metastatic bone disease in weight-bearing bones or vertebrae, when painful site(s) correspond to areas of bone destruction as shown by imaging techniques, or when bone disease is multifocal on presentation. However, when starting therapy, clinicians might also need to consider the risk of an excessive anti-osteolytic therapy, in order not to induce “frozen bone” after prolonged bisphosphonate use in an asymptomatic patient with minimal bone disease and a good chance to respond to a first regimen of antineoplastic therapy. Animal data indicate that high-dose bisphosphonates for 1 year significantly increase microdamage accumulation and reduce bone toughness (i.e., its ability to absorb energy or sustain deformation without breaking). Both factors are significantly related to the suppression of bone turnover.<sup>(64)</sup> Although the clinical relevance of these data are unproven, cases of osteonecrosis of the jaw after prolonged bisphosphonate therapy<sup>(65)</sup> might, at least in part, be a symptom of excessive bone turnover inhibition and/or excessive suppression of angiogenesis.

ASCO guidelines recommend that, once initiated, intravenous bisphosphonates should be continued until there is a substantial decline in the patient's general performance status.<sup>(30)</sup> However, criteria are lacking to determine if and how long an individual patient benefits from their administration. Promoting lifelong therapy is somewhat in contradiction with the extreme paucity of data regarding the usefulness and the safety of treatment durations beyond 2 years. Biochemical markers of bone resorption might help identify patients who continue to benefit, particularly as a high rate of bone resorption is one of the factors indicating resistance to bisphosphonates.<sup>(66,67)</sup> Using bone markers to guide clinical decisions is not currently recommended by ASCO for the individual patient. However, with the growing number of studies indicating their value in predicting disease outcome and bisphosphonate efficacy, there may soon be enough evidence for clinicians to use bone markers to individualize and optimize therapeutic schemes.<sup>(67)</sup> For example, if bone turnover markers are suppressed in a patient whose bone disease is well controlled by antineoplastic therapy, it might be reasonable to consider a temporary arrest of bisphosphonates or a switch to intermittent infusions after prolonged administration. The benefits of such an approach are currently being tested. There is also a need for prospective cost-effectiveness assessments of bisphosphonates that take into account multiple endpoints such as SREs, bone pain, and quality of life.

Despite quite encouraging results with clodronate, the use of bisphosphonates in the adjuvant setting still has to be viewed as experimental and several randomized trials are ongoing. This should be one of the most promising avenues for the future, but it will be essential to select the patients at high risk of devel-



oping bone metastases before recommending a general primary preventive use of bisphosphonates.

**Other Neoplasms.** Myeloma patients should be treated with bisphosphonates when they present with lytic disease on plain X-rays, and it is reasonable to also treat osteopenic patients without lytic disease. The optimal duration of therapy is unknown, but patients should certainly be treated as long as the disease is active given the intimate relationship between bone cells and myeloma cells. However, it is unknown if bisphosphonates have to be continued when a complete remission has been obtained.

Although skeletal metastases from prostate cancer are typically osteoblastic, prolonged administration of zoledronic acid can significantly reduce the incidence of skeletal complications, particularly the need for radiation therapy and the occurrence of pathological fractures.<sup>(14,15)</sup> Bisphosphonates should probably be recommended for all patients with hormone-refractory prostate cancer and bone metastases, especially when they are symptomatic, even if part of the benefit is probably caused by effective prevention of cancer treatment-induced bone loss.

In other tumor types, it is reasonable to start bisphosphonates if the skeleton is one of (or the) predominant symptomatic metastatic site(s) and expected survival time is at least 4–6 months.

**Safety Aspects.** Although generally well tolerated, bisphosphonates are occasionally associated with adverse events. Hypocalcemia is a side effect that may occur with all bisphosphonates, regardless of administration method. It is advisable to administer calcium and vitamin D to all patients on prolonged bisphosphonate therapy to avoid hypocalcemia and the deleterious effects of chronic secondary hyperparathyroidism. Characteristic adverse events with oral bisphosphonates are gastrointestinal, such as epigastric pain and esophagitis, although oral clodronate and ibandronate have been shown to be well tolerated in controlled phase III trials.<sup>(25,39)</sup> Intravenous infusions can be associated with renal safety issues, injection site reactions, and flu-like syndromes.<sup>(68)</sup> Osteonecrosis of the jaw was more recently reported with some bisphosphonates.<sup>(65)</sup> Although sometimes devastating, it is a rare complication (probably around 1%), typically seen after dental extraction and/or concomitant corticosteroid therapy. The relationship with bisphosphonates is likely but needs further study.

The reported incidence of renal function deterioration in clinical trials of zoledronic acid was 10.7% in patients with multiple myeloma or breast cancer, not significantly different than the pamidronate figures in that trial.<sup>(44)</sup> Although most cases of renal deterioration were mild and reversible, the FDA subsequently reported 72 cases of renal failure with zoledronic acid observed in clinical practice.<sup>(69)</sup> Serum creatinine monitoring is thus recommended before each infusion of zoledronic acid, and recent updates to the product label advocate stepwise dose reductions when baseline creatinine clearance is 30–60 ml/minute. Zoledronic acid is not recommended in patients with severe renal deterioration or those taking nephrotoxic medications. Prolonged use of intravenous ibandronate in patients with breast cancer has shown a low incidence of renal adverse events that is comparable with placebo.<sup>(7)</sup> No cases of renal failure have been reported at the time of this writing, but the renal safety of ibandronate has also to be confirmed in routine clinical practice outside of clinical trials.

## Other Short-Term Therapeutic Perspectives

**Treatment of Severe Bone Pain.** Patients with metastatic bone disease can present with very severe treatment-resistant bone pain, a cause of significant disability. First-line treatment tends to focus on opioids and/or radiotherapy to bone but many patients continue to experience bone pain despite these therapies.<sup>(70)</sup> Monitoring pain levels regularly in the clinic is likely to be an important step toward tailoring treatment to individual needs. Ibandronate renal safety could possibly allow the administration of higher doses in selected patients. While standard doses of bisphosphonates are typically associated with moderate bone pain-relief benefit, open trials suggest that loading doses of intravenous ibandronate could relieve severe or refractory metastatic bone pain in patients with various tumor types.<sup>(28,29)</sup> This suggests that we are yet to reach the limit of what can be achieved in terms of bone pain reduction with bisphosphonate use.

**Inhibition of RANKL.** Initial data indicate that blocking the RANK/RANKL system by osteoprotegerin (OPG) or an antiserum against RANKL could inhibit bone resorption for a longer period than pamidronate.<sup>(71,72)</sup> The antiserum against RANKL seems to be particularly promising because of its potency, the ease of its administration (subcutaneous route), and the apparent lack of toxicity.

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## Chapter 70. Skeletal Complications of Breast and Prostate Cancer Therapies

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### INTRODUCTION

Cancers of the breast and prostate are extremely common, with breast cancer accounting worldwide for 23% of cancer cases in women and prostate cancer accounting for 12% of cases in men. While advances in nonsurgical treatment options such as chemotherapy, hormonal therapy, and radiation are improving survival rates in patients with these diseases, these therapies also carry significant side effects. This chapter focuses on one such category of side effects—cancer treatment-induced skeletal complications such as bone loss, osteoporosis, and fractures, a growing cause of morbidity in this patient population.

### SKELETAL COMPLICATIONS OF BREAST CANCER TREATMENT

#### Adjuvant Hormonal Therapy

In adults, the skeleton undergoes complete turnover every 10 years. Bone mass maintenance is a balance between the activity

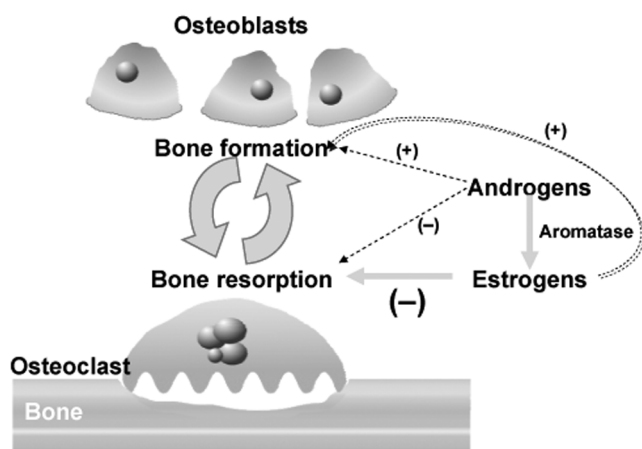
of osteoblasts, which form bone, and osteoclasts, which resorb it. Estrogen plays a key regulatory role in this cycle of bone remodeling by mediating effects through the estrogen receptor (ER), present on several cell types in the bone (Fig. 1). Estrogen stimulates osteoblasts to produce osteoprotegerin (OPG), a decoy receptor for RANK.<sup>(1)</sup> OPG blocks the binding of RANKL to RANK on osteoclasts, leading to impaired osteoclast activity and decreased bone resorption. Additionally, estrogen is believed to directly induce apoptosis of bone-resorbing osteoclasts.<sup>(2)</sup> Thus, in premenopausal women, estrogen both inhibits bone remodeling and suppresses bone resorption, contributing to bone strength. As estrogen levels decline in postmenopausal women, this regulation diminishes and bone resorption increases out of proportion to bone formation, leading to a net loss in bone and weakened bony microarchitecture. Despite the persistence of low levels of circulating estrogen in the postmenopausal state (produced by the conversion of peripheral tissue androgens to estrogen by the aromatase enzyme), bone mass can decrease by as much as 3% per year in the first 5 years after menopause.<sup>(3)</sup>

The ER is expressed by 70% of breast tumors,<sup>(4)</sup> and circulating estrogen promotes the growth of ER-positive tumors.

The authors have reported no conflicts of interest.



## Control of Bone Remodeling: Androgens and Estrogens



**FIG. 1.** Contribution of estrogens and androgens to bone remodeling. Estrogen and androgens help to maintain a balance between bone formation and bone resorption. Estrogen inhibits osteoclast activity and contributes to osteoclast apoptosis; androgens are converted to estrogen by aromatization and may also directly affect osteoblast differentiation. As such, a decrease in estrogen and/or androgens leads to increased bone resorption and an imbalance in bone remodeling, which ultimately manifests as bone loss.<sup>(2,50)</sup> Printed with the permission of Postgraduate Institute for Medicine and Interlink Healthcare Communications, joint sponsors of the CME Lecture Series titled *Skeletal Complications Across the Cancer Continuum Slide/Lecture Kit*. Released June 2005.

Current breast cancer therapies exploit this relationship either by decreasing circulating estrogen levels or by blocking or downregulating the receptor itself. While some of the estrogen-mimicking agents seem to be bone-sparing, others that disrupt the estrogen-skeleton axis cause adverse effects on bone remodeling, leading to decreased BMD and an increased risk of osteoporosis and fracture (Fig. 2).

**Selective Estrogen Receptor Modulators.** Tamoxifen is a selective estrogen receptor modulator (SERM) that binds to the estrogen receptor and acts as an estrogen antagonist in breast tissue. Tamoxifen is routinely used as adjuvant therapy in patients with ER-positive breast cancers as well as a preventative in high-risk patients because of its anti-estrogen effects in the breast. In bone, tamoxifen has both positive and negative effects depending on the menopausal state; premenopausal women taking tamoxifen may experience bone loss, whereas the drug seems to have agonistic effects in postmenopausal women.<sup>(5,6)</sup>

Two placebo-controlled trials in postmenopausal women with breast cancer showed statistically significant increases in BMD in the groups receiving tamoxifen versus placebo.<sup>(3)</sup> The National Surgical Adjuvant Breast and Bowel Project P-1 study (NSABP-1) showed 21% decrease in fracture risk in patients >50 years of age taking tamoxifen versus placebo for primary prevention of breast cancer, but this was not found to be statistically significant (hazard ratio = 0.79; 95% CI = 0.60–1.05).<sup>(7)</sup> The International Breast Cancer Intervention Study (IBIS-1), a randomized breast cancer prevention trial including both premenopausal and postmenopausal women, showed no difference in fracture incidence in the tamoxifen group versus placebo.<sup>(8)</sup>

Another SERM, the “fixed-ring” benzothioephene derivative raloxifene, is currently being studied as a potential breast

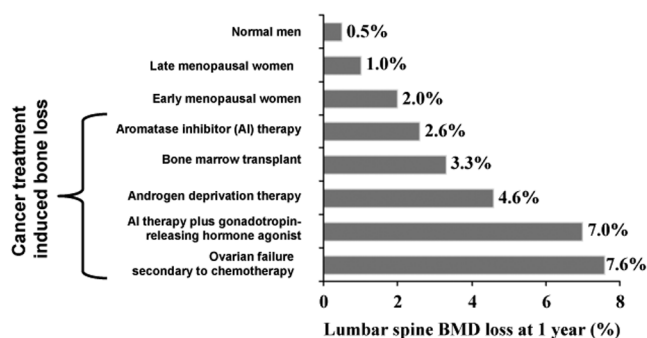
cancer preventative in The Study of Tamoxifen and Raloxifene (STAR) trial. This compound, approved for the prevention of osteoporosis in postmenopausal women in 1997, would likely also promote enhanced bone health in this patient population. In sum, SERMs do not seem to contribute to skeletal complications in postmenopausal women with breast cancer.

**Aromatase Inhibitors.** Postmenopausal women maintain a low level of circulating estrogen because of the aromatization of androgens to estrogen in tissues such as fat and muscle by the cytochrome P450 aromatase (P450arom) enzyme. Inhibitors of this enzyme are now commonly used for adjuvant endocrine therapy in postmenopausal women with breast cancer. There are two major classes of aromatase inhibitors: the nonsteroidal reversible inhibitors such as anastrozole and letrozole and the steroidal irreversible inhibitors such as exemestane.<sup>(9)</sup> Randomized clinical trials evaluating each of these aromatase inhibitors in the adjuvant therapy of breast cancer have shown decreased cancer recurrences and improved disease free survival in women who received aromatase inhibitors compared with tamoxifen, although no differences in overall survival have been reported to date.<sup>(3,10)</sup> Consequently, aromatase inhibitors are being commonly administered to postmenopausal women with ER<sup>+</sup> breast cancer.

Animal studies suggest that while the steroidal inhibitor exemestane may have bone-sparing effects in ovariectomized rats, the nonsteroidal inhibitor letrozole does not. In two separate studies, Goss et al.<sup>(11,12)</sup> showed that exemestane treatment prevented the bone loss that normally occurs in animals after ovariectomy, yet this effect was not observed after letrozole treatment. Exemestane may mediate its protective effect through androgenic effects. Both exemestane and its metabolite, 17-hydroxyexemestane, are proposed to have androgenic properties,<sup>(12)</sup> and androgens have been previously shown to be important for maintenance of BMD independent of their conversion to estrogen.<sup>(2)</sup>

In contrast, clinical trials have indicated that both classes of aromatase inhibitors result in bone loss to some extent (Fig. 2). However, there are no trials that compare the extent of bone loss in women on steroidal versus nonsteroidal aromatase inhibitors. As such, it is not possible to definitively conclude which would have the best skeletal side effect profile.

## BMD Loss With Cancer Therapies



**FIG. 2.** Extent of bone loss caused by cancer therapy. Healthy men lose bone at a rate of 0.5% per year beginning at middle age, whereas menopausal women lose bone at a rate of 1–2% per year. Cancer treatments such as aromatase inhibitor therapy, androgen deprivation therapy, and chemotherapy accelerate this process, leading to significant bone loss and subsequent skeletal complications.<sup>(51–56)</sup> Printed with the permission of Postgraduate Institute for Medicine and Interlink Healthcare Communications, joint sponsors of the CME Lecture Series titled *Skeletal Complications Across the Cancer Continuum Slide/Lecture Kit*. Released June 2005.

A recent double-blind trial by Lonning et al.<sup>(13)</sup> compared the effects of exemestane versus placebo on BMD in 147 women after surgical resection of early breast cancer. They observed a slight increase in the annual rate of femoral neck BMD loss in the exemestane group (2.72% versus 1.48%,  $p = 0.024$ ). However, there was not a significant increase in BMD loss in the lumbar spine for the exemestane group. This suggests that exemestane causes a modest loss of BMD.

Recent updates in the ATAC trial (Arimidex, Tamoxifen, Alone or in Combination) have indicated that while anastrozole (Arimidex) may have a milder overall side effect profile compared with tamoxifen, the effects on BMD may be more severe. Data have indicated that there is a statistically significant increase in fracture rate for women on anastrozole compared with tamoxifen (22.6 compared with 15.6 fractures per woman-year,  $p < 0.0001$ ).<sup>(10)</sup>

A large ( $N = 5187$ ), randomized, placebo-controlled phase III trial evaluated the aromatase inhibitor (AI) letrozole in postmenopausal women with primary breast cancer who had completed 5 years of adjuvant tamoxifen therapy.<sup>(14)</sup> Compared with placebo, patients receiving letrozole (2.5 mg) experienced more cases of patient-reported osteoporosis (8% versus 6% for placebo:  $p = 0.003$ ).

In summary, clinical trials have indicated that aromatase inhibitors also lead to significant bone loss in women with breast cancer. As such, these women should be monitored carefully for changes in BMD and treated appropriately. Several multicenter randomized clinical trials are underway evaluating the role of bone targeted antiresorptive therapies to prevent bone loss associated with aromatase inhibitors.

**Selective Estrogen Receptor Downregulators.** Recently a new class of endocrine agent, the selective estrogen receptor downregulators (SERDs), has been introduced. SERDs downregulate cellular levels of the ER and act as pure ER antagonists without any agonist effects. SERDs represent a potential treatment option for patients unable to tolerate the agonist effects of SERMs or who have tamoxifen or AI-resistant disease. Fulvestrant is currently the only SERD used in the clinics and is approved for second-line treatment of advanced breast cancer in postmenopausal women. The effect of fulvestrant on bone is controversial. In animal studies, fulvestrant was shown to increase bone turnover; however, the opposite results were obtained when the rats were ovariectomized.<sup>(2)</sup> Currently BMD is not an endpoint in clinical trials testing the efficacy of fulvestrant.

## Chemotherapy

Chemotherapy is used as either neoadjuvant or adjuvant therapy in pre- and postmenopausal women diagnosed with breast cancer. Chemotherapy has both direct and indirect effects on the bone microenvironment, ultimately leading to decreased BMD.<sup>(15)</sup>

**Direct Effects.** Animal studies<sup>(15)</sup> showed that male rats treated with methotrexate had decreased cancellous bone volume and decreased mineralizing surface compared with saline injected controls. Additionally, cortical cross-sectional area and periosteal mineralization rates were lower in the methotrexate group. Another study<sup>(15)</sup> examined the effects of chemotherapy on BMD in postmenopausal women with early stage breast cancer. The for-age bone density scores of postmenopausal women who received adjuvant chemotherapy were  $\sim 0.5$  SD lower than women who had not received chemotherapy. These studies suggest that chemotherapy can have direct, nonhormonal effects on the skeleton.

**Indirect Effects.** Breast cancer chemotherapy frequently induces primary ovarian failure in premenopausal women, which leads to a sudden decrease in estrogen production and early menopause (Fig. 2).<sup>(15-17)</sup> This drop in estrogen is believed to stimulate increased osteoclast survival and activity.<sup>(2)</sup> As a result, these women often develop osteopenia and are placed at an increased risk for developing osteoporosis.<sup>(15,18)</sup>

Several studies have shown a correlation between adjuvant chemotherapy and decreased BMD in women with breast cancer. One study<sup>(16)</sup> examined BMD of the lumbar spine in women with breast cancer who received adjuvant chemotherapy compared with women with breast cancer who did not receive chemotherapy. They showed that 71% of women who received chemotherapy experienced amenorrhea (loss of menses) at the time of BMD measurements compared with 16% of the women who did not receive chemotherapy. In addition, the BMD measurements of women in the chemotherapy group were significantly lower than those in the non-chemotherapy group (1.17 compared with 1.29 g/cm<sup>2</sup>). Another study<sup>(16)</sup> also assessed BMD in women receiving adjuvant chemotherapy. They showed that women who became permanently amenorrheic as a result of chemotherapy had a BMD 14% lower than women who maintained menses after chemotherapy. These studies suggest that chemotherapy leads to an increased risk of entering early menopause and, subsequently, an increased risk of bone loss.

A more recent study<sup>(15)</sup> showed that chemotherapy-induced ovarian failure causes significant bone loss in the spine. This study examined 49 premenopausal women with stage I/II breast cancer receiving adjuvant chemotherapy. DXA scans and measurement of markers of skeletal turnover, namely osteocalcin and bone-specific alkaline phosphatase, were used to assess bone loss at baseline and 6, 12, and 24 months after initiation of chemotherapy. Thirty-five of these women were found to have ovarian failure, defined as a negative pregnancy test,  $>3$  months of amenorrhea, and follicle-stimulating hormone (FSH) levels  $>30$  MIU/ml at the 12-month evaluation. In turn, significant bone loss was observed by 6 months after initiation of chemotherapy. These women had an  $\sim 4\%$  decrease in BMD in the spine ( $p = 0.0001$ ) and increased serum levels of bone turnover markers. This bone loss continued at the 12-month interval.

Several groups have shown that bisphosphonates are able to reduce bone loss associated with breast cancer chemotherapy. One study<sup>(16)</sup> examined the effects of risedronate on BMD in 53 women who were postmenopausal because of chemotherapy or radiotherapy after breast cancer surgery. The annual rate of change in lumbar BMD in the risedronate group was  $0.3 \pm 0.5\%$  compared with  $-1.4 \pm 0.5\%$  in the placebo group ( $p = 0.018$ ). Another group<sup>(16)</sup> conducted a large double-blind randomized two-center trial to examine BMD in 311 women with primary breast cancer who had received chemotherapy and/or tamoxifen and who were given an osteoclast-inhibiting bisphosphonate (clodronate) or placebo for 2 years. They showed that the change in BMD for the lumbar spine was only  $-0.16\%$  at 2 years for the clodronate group compared with  $-1.88\%$  for the placebo group ( $p = 0.04$ ).

A more recent study<sup>(15)</sup> examined bone loss in 73 premenopausal women receiving the CMF regimen (cyclophosphamide, methotrexate, and 5-fluorouracil). The patients were randomized to oral clodronate daily for 3 years or to a control group. This study showed that women who lost menstrual function, indicative of ovarian failure, had increased bone loss compared with women who maintained menstrual function. Furthermore, the women in the clodronate group lost less lumbar BMD than the women in the control group ( $-3\%$  compared with  $-7.4\%$ ,  $p = 0.003$ ) at 3

years. Thus, adjuvant clodronate treatment significantly reduced bone loss.

In short, chemotherapy in the breast cancer setting has a negative impact on BMD in women undergoing treatment. This could be attributed to direct effects on the bone microenvironment as well as indirect effects caused by the decrease in estrogen that occurs after chemotherapy-induced primary ovarian failure.

## SKELETAL COMPLICATIONS OF PROSTATE CANCER TREATMENT

### Androgen Deprivation Therapy

Prostate cancer patients who are diagnosed with metastatic disease or whose other clinical features suggest a poor chance for cure often receive palliative therapy in the form of androgen deprivation therapy (ADT) as a first-line treatment. ADT includes surgical castration, pharmacologic castration with agents such as luteinizing hormone-releasing hormone agonists (LHRH-a), and antiandrogen therapy with agents such as flutamide, nilutamide, bicalutamide, or cyproterone.<sup>(19)</sup> One potential complication that can arise from surgical castration or gonadotropin-releasing hormone (GnRH) agonist therapy is a decrease in BMD<sup>(20,21)</sup> (Fig. 2). This is believed to be caused by a decrease in estrogen, because androgens can be converted to estrogen through aromatases, which is essential to maintain skeletal health.<sup>(22)</sup> A drop in estrogen is believed to lead to an increase in osteoclast survival and a subsequent increase in bone resorption as mentioned above.<sup>(23)</sup> In addition there may be a direct effect of androgens on osteoblast differentiation such that a decrease in androgens would lead to decreased bone formation.<sup>(24)</sup>

Several retrospective studies have shown this link between androgen deprivation therapy and increased bone loss.<sup>(20,21,25)</sup> One study<sup>(21)</sup> showed an increased risk of osteoporotic fractures in men treated with orchiectomy. Information was gathered on men with prostate cancer diagnosed between 1983 and 1990. Of the 235 men in the study, 10 had osteoporotic fractures—8 in the treated group and 2 in the untreated group (13.6% versus 1.1%,  $p < 0.001$ ). Another retrospective study by Townsend et al. made use of chart reviews and phone interviews to assess the incidence of bone fractures in patients receiving LHRH-a for prostate cancer. They were able to show a 5% incidence of osteoporotic fractures in treated patients. Krupski et al.<sup>(20)</sup> used 1992–2001 claims data from a random sample of Medicare beneficiaries to investigate the link between ADT and bone complications in men with prostate cancer. They found that 45% of men who had received ADT for longer than the median duration (697 days) had sustained at least one fracture, whereas this was true for only 40% of men who received ADT for less than median treatment time of 697 days. This suggests that fracture risk may be related to the duration of ADT. Most recently, Shahinin et al.<sup>(25)</sup> performed a large retrospective study in which they examined records for 50,613 men diagnosed with prostate cancer between 1992 and 1997. They found that 19.4% of the men who received ADT suffered at least one fracture compared with 12.6% of men who did not receive ADT ( $p < 0.001$ ). All of these data strongly suggest that ADT is a risk factor for osteoporosis and fracture in men with prostate cancer.

A number of recent studies have suggested that bisphosphonate therapy can reduce this increased risk for bone loss and subsequent fracture in men receiving ADT. Maorabito et al.<sup>(26)</sup> randomized 48 osteoporotic prostate cancer patients to receive either calcium supplements alone or calcium in combination with the bisphosphonate neridronate. While the patients receive-

ing calcium alone had significant decreases in BMD as well as increased markers of bone turnover, the patients undergoing bisphosphonate treatment did not have any significant changes in BMD or markers of bone turnover. A double-blind randomized placebo controlled trial<sup>(27)</sup> was performed to assess the effect of the bisphosphonate zoledronic acid on BMD during ADT in 106 men with prostate cancer. While the men in the control group had a 2.2% decrease in BMD, the men in the zoledronic acid group had a 5.6% increase in BMD ( $p < 0.001$ ). Both of these studies suggest a strong benefit of bisphosphonate therapy on skeletal health for men undergoing ADT.

The use of SERMs, which have agonistic effects on bone in postmenopausal women, may also combat bone loss in men receiving ADT. An open-label randomized controlled trial conducted by Smith et al.<sup>(28)</sup> compared BMD scores in 48 men with nonmetastatic prostate cancer who received 12 months of raloxifene (60 mg/day) or no raloxifene during concurrent treatment with a GnRH agonist. The mean duration of GnRH agonist therapy in the raloxifene group was 31 months compared with 37 months in the no raloxifene group. Men receiving raloxifene showed an increase in total hip BMD of  $1.1 \pm 0.4\%$ , whereas the no raloxifene group showed a decrease in total hip BMD of  $2.6 \pm 0.7\%$  ( $p < 0.001$ ). Further studies investigating SERM use at the initiation of ADT and the effect of SERMs on fracture rates will further contribute to our understanding of skeletal benefits of this therapy.

Antiandrogen compounds, which competitively inhibit activation of the androgen receptor by testosterone, can be used as prostate cancer treatment alone or in combination with other forms of ADT. In men with nonmetastatic prostate cancer, monotherapy with the nonsteroidal antiandrogen bicalutamide provides similar survival rates to castration.<sup>(29)</sup> The observation that bicalutamide monotherapy significantly increases serum concentrations of testosterone and estradiol compared with baseline<sup>(30)</sup> suggests that bicalutamide monotherapy may have a bone-protective effect in men with nonmetastatic prostate cancer. Several studies support this assertion. One group<sup>(31)</sup> found an increase in biochemical markers of bone turnover in men undergoing medical castration but not in men receiving bicalutamide monotherapy. Another group<sup>(32)</sup> reported lower BMD in men with nonmetastatic, locally advanced prostate cancer treated with castration compared with those receiving bicalutamide monotherapy. Sieber et al.<sup>(33)</sup> measured BMD in men with localized or locally advanced prostate cancer ( $n = 103$ ) randomized to bicalutamide monotherapy or medical castration for 96 weeks; lumbar spine BMD was +2.42% and hip BMD was +1.13% in the bicalutamide group compared with lumbar spine BMD of -5.40% and hip BMD of -4.39% in the medical castration group (both  $p < 0.0001$ ). Finally, Smith et al.<sup>(34)</sup> found that BMD increased significantly from baseline in men with nonmetastatic prostate cancer randomized to 12 months bicalutamide therapy; in comparison, BMD decreased significantly from baseline in the group randomized to treatment with leuprolide, a GnRH agonist. In sum, it seems that bicalutamide monotherapy may offer skeleto-protective benefits in men with nonmetastatic prostate cancer. An important next step will be to evaluate its effect on fracture rate compared with other forms of ADT.

### RADIATION-INDUCED FRACTURES

Breast conservation surgery combined with radiotherapy has become the standard of care for patients with early-stage breast cancer.<sup>(35)</sup> One potential complication of this treatment is rib fracture after X-ray exposure, although few studies have investigated this phenomenon. A retrospective study by Pierce et



al.<sup>(36)</sup> examined the incidence of various radiation-induced complications in 1624 patients with early stage breast cancer treated between 1968 and 1985. The median follow-up time for survivors was 79 months. They found that the incidence of rib fracture was between 0.4% and 2.2% depending on the type of linear accelerator used. Another retrospective study by Meric et al.<sup>(35)</sup> examined the incidence of radiation-induced complications in 294 women receiving surgery and radiotherapy treatment between 1990 and 1992. They found the risk of rib fractures to be 0.3%. These data suggest that radiotherapy for breast cancer may lead to a small risk of rib fracture.

Current recommendations for prostate cancer treatment suggest that brachytherapy (radiotherapy) is an option for non-metastatic patients with a long life expectancy (>5 years) or for patients for whom surgery is a contraindication.<sup>(37–39)</sup> While a possible side effect of brachytherapy could be pelvic fracture, there are no clinical studies examining this potential risk. There are, however, case reports documenting pelvic fracture in men who have received pelvic irradiation.<sup>(40)</sup>

### OSTEONECROSIS OF THE JAW

Bisphosphonates are osteoclast inhibitors that are now widely used in cancer therapy to inhibit bone loss resulting from treatment or bone metastases. There are three classes of bisphosphonates: (1) first-generation compounds, such as clodronate, (2) second-generation compounds, which are stronger and contain a single nitrogen atom, such as pamidronate, and finally (3) third-generation compounds, such as zoledronic acid, which contain one or two nitrogen atoms in a ring form and are the most potent.<sup>(41)</sup> The first-generation bisphosphonates are metabolized into cytotoxic analogs of ATP inducing osteoclast cell death. The nitrogen-containing bisphosphonates, on the other hand, function by inhibiting the activity of farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP). Because FPP and GGPP are required for post-translational lipid modification (prenylation) of small guanine triphosphatases (GTPases), bisphosphonates interfere with the function of GTPases such as Ras, Rac, and Rho. This leads to disruption of the actin cytoskeleton, altered tracking of intracellular components, and impaired integrin signaling within the osteoclast.<sup>(41)</sup> Second- and third-generation bisphosphonates do not have an effect on the osteoblast *in vivo*; thus, the bone formation is intact.<sup>(41)</sup> In addition, *in vitro* evidence suggests that bisphosphonates may have anti-angiogenic and antitumor properties, but these data have not been confirmed *in vivo*.<sup>(42,43)</sup>

In the last few years, zoledronic acid and pamidronate have been administered to >2.5 million cancer patients worldwide. In 2003, the first cases of osteonecrosis of the jaw (characterized by bone erosions and exposed bone) were reported in patients receiving chronic oral and intravenous bisphosphonate therapy for osteoporosis and bone metastases.<sup>(44,45)</sup> Osteonecrosis of the jaw is an extremely painful condition in which the mandible or the maxillary bones are exposed.<sup>(46,47)</sup> In addition to chronic bisphosphonate therapy, it is also associated with oral fungal infections, trauma, herpes zoster, and radiation therapy. In one study of 211 myeloma patients receiving zoledronic acid, 10% developed osteonecrosis of the jaw by 36 months, whereas 4% of 413 myeloma patients receiving pamidronate developed the disease by 36 months.<sup>(44)</sup>

Inhibition of the osteoclast by bisphosphonates is hypothesized to disrupt the critical balance between the osteoclast and the osteoblast. In a situation where healing of the bone is necessary, such as after chronic inflammation and infection associated with gum disease, the disruption of the dynamic and coupled processes of bone resorption and formation may contribute to the development of osteonecrosis of the jaw. The

anti-angiogenic effects of the bisphosphonates are also hypothesized to contribute to the process of necrosis.<sup>(48)</sup> This complication is thought to become more likely if the patient is undergoing any manipulations in the oral cavity, such as tooth extractions and placement of oral implants.<sup>(49)</sup>

Meticulous oral hygiene, antibiotics, and the discontinuation of bisphosphonates is currently recommended for therapy of osteonecrosis of the jaw. The diagnosis of osteonecrosis of the jaw is a clinical diagnosis made by physical examination. Biopsy of the affected bone can be associated with worsening of the situation. More studies must be initiated to determine the exact mechanisms and cause of this complication and how it can be prevented and treated.<sup>(46–48)</sup>

### CONCLUSION

Chemotherapy and hormonal therapies for breast and prostate cancer have the potential to lead to significant bone loss primarily through the disruption of estrogen's bone-enhancing properties. Current recommendations for avoiding the skeletal complications of cancer therapy include adequate intake of calcium and vitamin D, regular weight-bearing exercise, cessation of smoking, reduction in alcohol intake, and bisphosphonate therapy for osteoporotic patients.<sup>(16,31)</sup> Patients whose cancer is being treated with hormonal therapies are at increased risk for skeletal complications and should have regular BMD monitoring by DXA. The role of antiresorptive, osteoclast inhibitor therapy to prevent cancer therapy associated bone loss is under active study. It is recommended that patients who initiate bisphosphonate therapy receive a thorough oral examination and treatment for dental infections before initiating bisphosphonate therapy.<sup>(44,46–48)</sup> In addition to treating the cancer, careful monitoring of bone health is now an essential component of the treatment of both breast and prostate cancer.

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