CHAPTER

20 Malignant Bone Tumors

GENERAL CONSIDERATIONS

Incidence

Bone sarcomas constitute 0.2% of all cancers, with an incidence of 0.8/100,000 (Fletcher et al, 2013). In children, it contributes about 5.4% of all pediatric malignancy, ranking as the fifth most common tumor. The relative frequency of different histologic types is presented in (Table 20-1). Age incidence is outlined in (Fig 20-1). Osteosarcoma and Ewing sarcoma are common in prepubertal age. Giant cell tumor affects adults, whereas, solitary myeloma, lymphoma, chondrosarcoma and malignant fibrous histiocytoma (MFH) develop in old patients. There is a male predominance in most sarcomas, with a ratio of 2:1. But, females predominate in giant cell tumor and Ewing's sarcoma. There is equal affection of both sexes in: juxtacortical osteosarcoma.

Etiology

Bone sarcomas may arise de novo from normal bone (primary), or may be secondary to an underlying bone lesion, such as, Paget disease, irradiation, fibrous dysplasia, osteochondromas or enchondromas.

Pathogenesis

Bone sarcomas mostly arise from primitive mesenchymal cells (stem cells) which are committed to a specific tissue lineage e.g. osteogenic, chondrogenic or fibrogenic. In case of osteosarcoma, multiple cell differentiation may occur, thus explaining the diverse histology of this tumor. Also, the majority of bone sarcomas (about 40%) occur before puberty, a period of active bone growth. The site specificity of the different tumors is explained by the "field" theory, which postulates that the most active cells of a certain area in bone give rise to tumors which are characteristic of that area.

Like other malignant tumors, mutations are important pathogenetic mechanisms. Thus, inactivation of the tumor suppressor gene p53 is evident in many sporadic osteosarcomas. Germline mutation of retinoblastoma (Rb) gene predisposes patients to develop retinoblastoma in childhood and osteosarcoma in adolescence. A similar mechanism is operable in P53 germline mutation (Li-Fraumeni syndrome). Multiple gene rearrangement (chromothripsis) is common in osteosarcoma and chordoma resulting from chromosomal breaks and fusion (Fletcher et al, 2013).

Table 20-1 Histogenesis and Frequency of Primary Bone sarcomas

Mesenchymal
Osteogenic, Osteosarcoma (35%)
Chondrogenic, Chondrosarcoma (30%)
Neuroectodermal, Ewing's sarcoma (10%)
Fibrogenic, Fibrosarcoma and MFH* (3%)
Unknown Origin, Giant cell tumor (8%)
B-lymphocytes, Lymphoma, NHL (7%) and Solitary myeloma (5%)
Notochordal, Chordoma (2%)
Epithelial inclusions, Adamantinoma (<1%)
Vascular, Angiosarcoma (<1%) and Hemangioendothelioma (<1%)

(10,165 Patients, Dahlin, 2009)
*MFH= Malignant Fibrous Histiocytoma

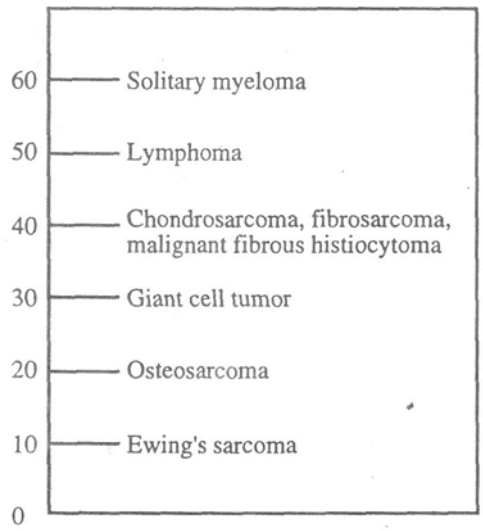

Fig 20-1 *Age incidence of Primary Bone Cancer*

Other bone sarcomas have different histogenetic origin (Table 20-1). Thus, Ewing sarcoma is of neuroectodermal origin, arising from neural crest cells which migrate to the bone during early embryonic life. Plasmacytoma and bone lymphoma (NHL) are of B lymphocyte origin. Chordoma arises from notochordal remnants in the vertebral column and adamantinoma arises from epithelial inclusions in the tibia from the overlying epidermis or skin adnexal structures.

The pathogenesis of giant cell tumor is still unknown. Current opinion suggests that mononuclear stromal cells are the neoplastic cells, whereas, the giant cells are likely a reactive cell population derived from macrophages.

Radiography

Plain radiography is the most important diagnostic imaging. Although MRI and computed tomography (CT) are very useful in evaluating invasive extension (staging), they contribute little to diagnosis. The importance of cooperation among orthopedic surgeons, radiologists, and pathologists has always been emphasized. A biopsy may not be necessary in certain benign lesions such as metaphyseal fibrous defect and osteochondroma, which can be diagnosed by combining clinical and radiological findings. A bone tumor is evaluated by six radiographic parameters, including: anatomic site, borders, bone destruction, matrix formation, periosteal reaction and soft tissue extension.

Bone sarcomas develop at different anatomic sites in long bones (Fig 20-2). Giant cell tumor develops in the epiphysis, whereas, chondrosarcoma develops in the diaphysis. In the vertebral column, malignant tumors commonly affect the vertebral body, whereas, benign tumors affect the vertebral arch.

Benign bone tumors also have characteristic locations. Thus, chondroblastoma is epiphyseal, whereas, chondromyxoid fibroma and nonossifying fibroma are metaphyseal. The latter is commonly eccentric (subcortical)

Radiologically, bone tumors manifest 3 patterns of bone destruction: geographic, moth-eaten and permeative. The geographic pattern, observed in benign tumors, is homogeneous with well-demarcated margin surrounded by a rim of sclerosis. The moth-eaten pattern, observed in moderately aggressive malignant tumors, appears as multiple large defects. The permeative pattern indicates a highly-aggressive tumor, and appears as small confluent defects in the cortex, as well as, the medullary cavity. Matrix formation, in the form of calcification or new bone formation, produces areas of increased density within the tumor. The opacities are mottled (popcorn) in chondrosarcoma and illdefined in osteosarcoma.

Radiologic parameters of benign and malignant tumors are quite different (Fig 20-3). Benign tumors have a rounded geographic defect, with smooth well-circumscribed borders, no cortical destruction and continuous periosteal reaction. Conversely, malignant tumors produce irregular defects with evidence of bone destruction, interrupted periosteal reaction and soft tissue mass.

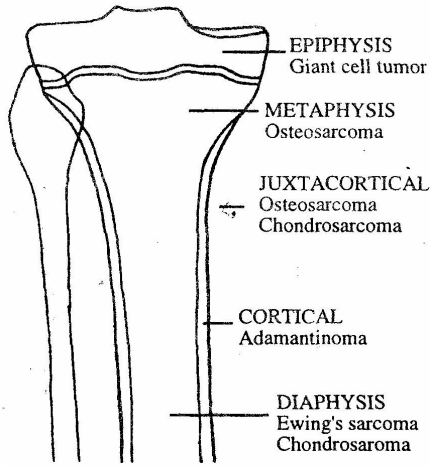

Fig 20-2 *Anatomic locations of malignant bone tumors*

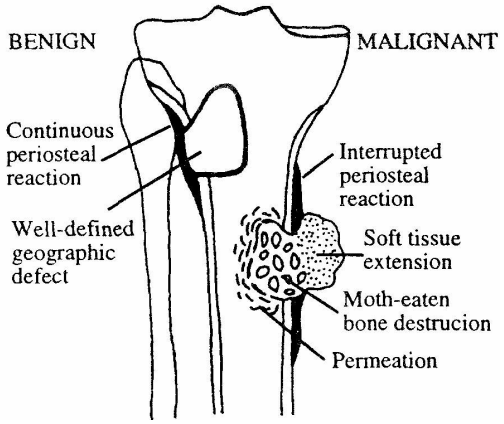

Fig 20-3 *Radiologic features of benign and malignant bone tumors compared.*

Tumor angiography is also valuable to assess the response to chemotherapy. Thus, osteosarcoma is a hypervascular lesion. A good response to chemotherapy is associated with disappearance of tumor neovascularity.

Spread

Bone sarcomas are initially confined within the bone of origin (intra-compartmental), then invade soft tissue or joint (extra-compartmental). The three modes of spread are: local, lymphatic and hematogenous.

(1) *Local spread:* The epiphyseal plate has been shown to be a relatively poor barrier to tumor invasion. Thus, in metaphyseal osteosarcoma, 59% of cases have gross or microscopic evidence of extension to the epiphysis. Invasion of soft tissue is common with juxtacortical, as well as central tumors. The joint may be invaded by 4 mechanisms, namely: extension through articular cartilage, pericapsular structures, intra-articular structures and pathologic fracture (Fig 20-4).

(2) *Lymphatic spread:* Since bone lacks a lymphatic system, lymph node metastases only occur after invasion of soft tissue. The frequency of lymph node metastases in osteosarcoma is only 3%.

(3) *Hematogenous spread:* In osteosarcoma the incidence of pulmonary metastases is high (80%) and occurs at an early stage of the disease. Second in frequency is distant metastases in other bones. A skip metastasis, however, is a tumor nodule located within the same bone of the main tumor but not in continuity with it. A skip lesion develops through angioinvasion and embolization of tumor cells within the marrow sinusoids.

Staging

Mesenchymal sarcomas of bone behave similarly, regardless of histologic type, hence, they have a common staging system. The surgical staging system of Enneking (1980) is based on the GTM classification, or (G) grade, (T) tumor site and (M) metastases. The histological grade may be low (Gl) or high (G2). The tumor site may be Tl (or intra-compartmental) if confined within the bone or T2 (or extra-compartmental) if there is invasion of soft tissue or articular structures. Ml denotes lymph node spread, skip tumors or distant metastases. In general, low-grade bone sarcomas are commonly (Tl), whereas, high grade ones are (T2). Bone sarcomas that are designated as grade 3 include Ewing sarcoma/ PNET, malignant giant cell tumor, angiosarcoma, and dedifferentiated chondrosarcoma. According to this system three stages are recognized (Table 20-2), namely: low grade (stage I), high grade (stage II) and metastatic (stage III).

The updated TNM staging of bone sarcomas includes tumor size and nodal status in staging criteria (Table 20-3 and Fig 20-5). A tumor less than or equal to 8 cm is T1 while a tumor more than 8 cm is T2. A discontiguous tumor (skip lesions) of any size is T3 . Nodal metastasis is N1 while distant metastasis is M1.

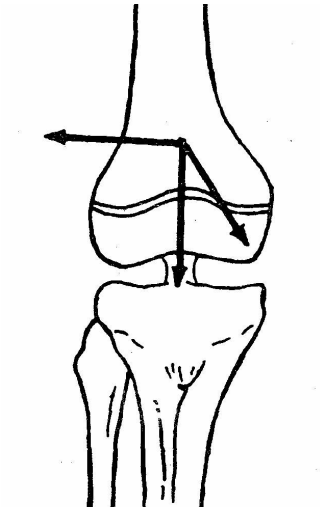

Fig 20-4 *Local spread of bone sarcomas to epiphysis, joint or soft tissue*

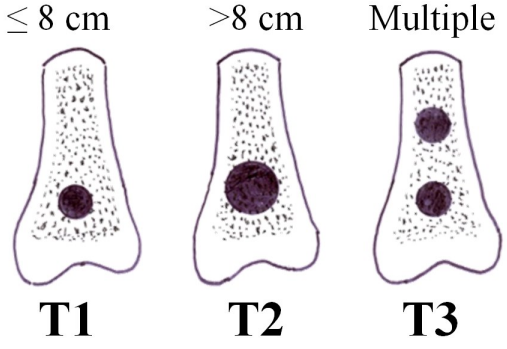

Fig 20-5 *The T categories of primary bone sarcomas (Edge et al, 2009)*

Table 20-2 Enneking Staging of Bone Sarcomas

Stage	Grade	Site	M
IA	G1	T1	M0
IB	G1	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
III	any G		M1

G1 = low histologic grade
G2 = high histologic grade
T1 = intra-compartmental
T2 = extraompartmental
M1 = regional or distant metastases
This system does not include tumor size and nodal status

(Enneking, 1980)

Table 20-3 Updated TNM Staging of Bone Sarcomas

Stage	Grade	Tumor	Metastases
I	Low	Solitary (T1 or T2)	N0
II	High	Solitary (T1 or T2)	N0
III	any	Multiple (T3)	N0
IV	any	any T	N1 or M1

(Edge et. al, 2010)

OSTEOSARCOMA

Incidence

Osteosarcoma is the most common bone sarcoma constituting 35% of cases, followed by chondrosarcoma and Ewing sarcoma. The age distribution is bimodal, with the first peak during the second decade and the second peak among older patients (over 40 years). During adolescence, osteosarcoma arises in areas of rapid growth e.g. lower end of femur, and upper ends of tibia, humerus and femur. Whereas, in older patients, osteosarcoma develops most frequently in areas of prior bone disease or in previously irradiated sites. The male predominance is 2:1.

Radiography

There is irregular bone destruction, both metaphyseal and cortical. Tumor ossification may be slight, moderate or densely sclerotic. Periosteal reaction is interrupted by soft tissue extension of tumor. The subperiosteal new bone formation takes the form of Codman triangle and/or sun-ray appearance. MRI gives additional information on spread into the medullary cavity or overlying soft tissue (extracompartmental extension).

Histopathology

The diagnostic criterion is direct formation of immature osteoid by tumor cells, not preceded by a stage of cartilage. The osteoid is thin (micro-trabecular), curved or lace-like, with anasto-mosing pattern, lacking lacunae, as well as, lamellae or osteoblastic rimming (it is directly lined by tumor cells). Malignant osteoblasts are characteristically stellate in shape.

The recently revised WHO classification of bone tumors recognizes the intrinsic biologic diversity within osteosarcoma, and is based on etiology, site and histopathology of tumors (Table 20-4). Conventional osteo-sarcoma is the most common (80%) and may be subclassified into: osteoblastic, chondroblastic, and fibroblastic according to the presence of any additional differentiation. Juxtacortical or pa-rosteal osteosarcoma has a benign-like histology with fibrocytic stroma and relatively mature trabecular bone. Patients with this tumor variant are about a decade older than patients with conventional osteosarcoma, and sexes are equally affected. Periosteal osteosarcoma is frequently chondrogenic. High-grade surface osteosarcomas are high grade variants of peripheral tumors. Dedifferentiated parosteal osteosarcoma behaves similarly as high grade surface osteosarcoma.

Differential Diagnosis

1. Aggressive osteoblastoma (P 20-13) lacks an infiltrative growth pattern, lace-like osteoid, atypical mitosis, and necrosis while showing evidence of osteoblastic rimming.

2. Myositis ossificans (P 20-14, P 20-15) can be confused with juxtacortical osteosarcoma, however osteosarcoma lacks the zonal process of maturation evident in myositis ossificans, where hypercellular zone is at the inner side of the lesion and mature bone is at the outer side.

Table 20-4 Osteosarcoma Clinicopathologic Entities, their Frequency, Grades, and Prognosis

Entity	Picture	Frequency (%)	10-year Survival (%)
Conventional	P20-1 to P20-3	80	70
Telangiectatic	P20-4	3	60
Small cell	P20-5	2	Undetermined
Low grade central	P20-6 to P20-8	2	85
Surface			
Parosteal	P20-9, P20-10	4	95
Periosteal	P20-11	2	75
High grade surface		1	70
Secondary		6	10-30
Postradiation sarcoma			
Paget sarcoma	P20-12		

(Folpe and Inwards, 2010 and/Fletcher et al, 2013)

3. *Callus* (P 20-16), although hypercellular, the presence of cartilage with orderly maturation of bone and rimming of osteoblasts are helpful in differential diagnosis.

4. *Osteoid osteoma* (P 20-17), the presence of the nidus composed of woven bone rimmed by osteoblasts, combined with the clinical and radiologic features (cortical location) are diagnostic.

5. *Fibrous dysplasia* (P 20-18) can be confused with well-differentiated osteosarcoma because of the presence of immature bone with no osteoblastic rimming. It can be monostotic or polyostotic, affecting mostly craniofacial bones, femur, and ribs. Lack of radiological features of an invasive tumor, no lace-like osteoid, and the presence of characteristic curvilinear pattern of bone are usually helpful in the differential diagnosis

6. *Osteofibrous* dysplasia of long bones and maxillofacial ossifying fibroma can be confused with well-differentiated osteosarcoma. In both of the above mentioned lesions, there is evident osteoblastic rimming and absence of lace-like osteoid features.

7. *Aneurysmal bone cyst* (P 20-19) differs from telangiectatic osteosarcoma by the absence of cytologically malignant cells within the cyst walls.

Prognosis

A biologic classification (grading) of osteosarcoma into favorable and unfavorable groups is presented in (Table 20-4 and 20-5). Parosteal osteosarcoma is the most favorable, whereas, radiation-induced and Paget-associated osteosarcomas are particularly most aggressive. Maxillofacial osteosarcoma has a relatively good prognosis than extremity osteosarcoma with less liability to metastasis. It affects relatively older age groups with less response to chemotherapy.

In the past, about 80% of patients with osteosarcoma died of pulmonary metastases within two years of amputation. However, recent chemotherapy regimens given as preoperative (neoadjuvant) and/or postoperative settings (adjuvant) has dramatically improved the survival and allowed limb- salvage procedures in the majority of patients. Disease-free survival has increased from 20% to 60 to 95%.

Evaluation of Chemotherapy

The most powerful prognostic indicator in osteosarcoma is tumor necrosis following neoadjuvant chemotherapy. This provides an in vivo chemosensitivity test, and the observed tumor response helps to guide the selection of

Table 20-5 Grading of Osteosarcoma

Grade	Subtype
I	Perosteal osteosarcoma
	Low-grade central
II	Periosteal osteosarcoma
III	Conventional
	High-grade surface
	Telangiectatic
	Paget or irradiation related

(Folpe and Inwards, 2010)

drugs for postoperative chemotherapy. Tumor necrosis is classified into 4 grades (Huvos, 1977), namely: Grade I no necrosis, Grade II minimal necrosis, Grade III extensive necrosis, and Grade IV complete necrosis. In the Huvos system, a favorable response (Grade III and IV) indicates 90% or greater tumor necrosis, whereas, unfavorable histologic response (Grade I and II) imply less than 90% tumor necrosis. Patients with a favorable response have a 85% long-term survival, but those with unfavorable response have a poor prognosis (5-year survival of 25%).

In another grading system (Picci, 1985), tumor necrosis is divided into three grades: good, fair and poor. Good indicates diffuse necrosis greater than 80%, fair signifies 50% to 80% necrosis, and poor indicates a necrosis less than 50%. The latter was based on the probability that a 50% necrosis might be encountered in osteosarcoma even without any chemotherapy. This study also demonstrated the existence of preferential sites where viable tumor was likely to persist after chemotherapy. Thus, residual viable tumor is commonly observed in peripheral locations as: invaded soft tissue, cortical or subcortical sites, zones in contact with the epiphyseal plate, articular cartilage and ligaments (Fig 20-6). In contrast, necrosis appears most concentrated in the central regions of the tumor.

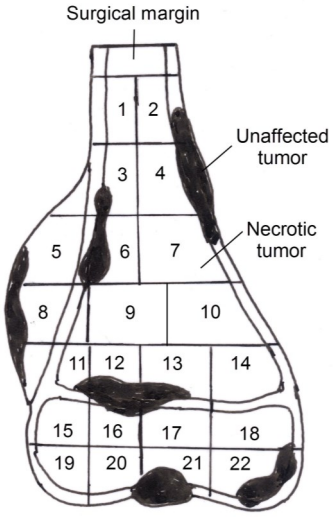

Fig 20-6 *Osteosarcoma after chemotherapy, sites of viable tumor (black areas). A total of 22 tissue blocks and surgical margins are taken for pathologic evaluation of therapy effect.*

CHONDROSARCOMA

Incidence

Chondrosarcoma is the second most common bone sarcoma, accounting for 30% of cases (Dahlin, 2009). It commonly affects the central skeleton, and the most frequent sites are: the pelvis, proximal femur, scapula, humerus and ribs. The age incidence varies between 40 to 60 years with predominance of the male sex.

Radiography

Affection of flat bones, and metadiaphyseal regions of long bones are characteristic. Central chondrosarcomas show typical mottled or popcorn-like calcification. Peripheral tumors, on the other hand, tend to have long, lightly calcified spicules radiating from the cortex to a flattened outer surface, with little evidence of cortical or medullary involvement.

Histopathology

The microscopic appearance of conventional chondrosarcoma is characterized by the formation of cartilage with malignant chondrocytes (P 20-20 to P 20-25). Low grade chondrosarcoma may simulate chondroma, but differences include: (1) axial or flat bone affection, (2) osteochondroma with cap more than 3 cm, (3) central lesion larger than 6 cm, (4) permeation inbetween bone trabeculae in the medullary cavity, and (5) frequent multinucleation and multiple cells in lacunae.

The biologic diversity of chondrosarcoma is also recognized in the recent WHO classification (Table 20-6). Four variants are recognized based on location and histology, namely: dedifferentiated, clear cell type, mesenchymal and juxtacortical.

1. Dedifferentiated chondrosarcoma (P 20-26) is characterized by the presence of areas of low-grade, as well as, areas of high-grade tumor (spindle and MFH cell components) indicating tumor progression, and hence, a worse prognosis. It affects old patients (age 60 years).

2. The clear cell variant (P 20-27) occurs in the femoral head or humeral head of adult men. The histology is characterized by clear cells, focal ossification and giant cells, with a tendency to lobulated pattern. There is a risk of marked local recurrence and eventual late development of metastases.

Table 20-6 Chondrosarcoma, WHO Classification

Primary (85%)
A. Central
Conventional (75%)
Dedifferentiated
Clear cell type
Mesenchymal
B. Peripheral
Juxtacortical
Secondary (15%)
A. Central
Paget
Enchondroma
Fibrous dysplasia
B. Peripheral
Osteochondroma
Exostosis

(Fletcher et al, 2013)

*3. Mesenchymal chondrosarcoma (*P 20-28) affects adolescents in the second decade and develops preferentially at ribs, jaw, skull and extra-skeletal sites. Histologically, it shows in addition to the usual cartilaginous areas, small round cell component simulating the histology of Ewing sarcoma.

4. Juxtacortical chondrosarcoma differs, from parosteal osteosarcoma by the lack of direct bone formation by tumor cells. In chondro-sarcomas, bone is only formed through a stage of cartilage (endochondral ossification).

Differential Diagnosis

1. Enchondroma (P 20-29) is differentiated from low grade chondrosarcoma by the absence of myxoid change and lack of an infiltrative growth pattern.

2. Osteochondroma (P 20-30) has a thin cartilage cap (less than 2 cm) which differentiates it from secondary chondrosarcoma that usually invades into surrounding tissues.

3. Chondroblastoma (P 20-31) shows chondroid differentiation; however hyaline cartilage is rarely seen. Significant nuclear atypia is not present

4. Chondromyxoid fibroma (P 20-32) tends to be well-circumscribed by radiology, is more cellular at the periphery of the lesion. No invasion of surrounding tissues.

Prognosis

The 5-year survival is 98%, 53%, and 22% according to Evan grade. A Prognostic classification of chondrosarcomas into favorable and unfavorable groups is presented in (Table 20-7 and Table 20-8). In secondary chondro-sarcomas, the tumors that develop in patients with multiple enchondromas (Ollier) are generally low-grade, whereas, those associated with soft tissue hemangiomas (Maffucci) are more frequently high-grade tumors. Chondrosarcoma, contrary to osteosarcoma, is not affected by current chemotherapy regimens. Recently, chon-drosarcoma is graded into 3 grades, with 5-year survival of 83% in grade 1 and 53% in the com-bined grades 1 and 2 (Fletcher et al, 2013) the low-est survival was observed in dedifferentiated sub-type (7-24%).

Table 20-7 Evan Grading of Chondrosarcoma

Grade	Ana-plasia	Mitosis	Biology
1	Non	Non	Borderline
2A	+	Non	Borderline
2B	+	1/10 HPF	Malignant
3	++	2/10 HPF	Malignant

(Evan, 1976)

Table 20-8 Prognostic Classification of Chondrosarcoma

Favorable (80%)*	Unfavorable (<50%)
Evan grade I and IIA	Evan grade IIB and III
Myxoid Chondrosarcoma	Dedifferentiated
Clear cell chondrosarcoma	Mesenchymal

(Fletcher et al, 2013) * 5 year survival

EWING SARCOMA

Incidence

Ewing sarcoma accounts for about 10% of primary malignant bone tumors (Dahlin, 2009). Its incidence peaks between the ages 10 and 25 years (mean age 11 years); with a male to female ratio of 2:1. Both Ewing sarcoma and osteosarcoma occur primarily in the prepubertal age group, but can be distinguished from each other by several clinicopathological features.

Pathogenesis

Recently, Ewing sarcoma proved to be of neuroectodermal origin. This is supported by finding pseudorosettes in some tumors, NSE positivity, presence of neurosecretory granules by EM, presence of characteristic t(11;22) of PNET and neurite differentiation in tissue culture.

Practically 85% of Ewing sarcoma/PNET show the reciprocal translocation 11;22 (q24; ql2), resulting in the fusion of the EWS (Ewing sarcoma) and FLI-1 genes (Fig 20-7). This translocation can be detected by fluorescence in situ hybridization (FISH) and reverse transcriptase PCR reaction. In the remaining 15% of cases, evidence of other translocations involving EWS on chromosome 22 can be identified. Common to all EWS fusion partners in Ewing sarcoma is that they encode for members of the ETS transcription factor family.

CD99 is a cell membrane protein coded by a gene located on the short arms of X and Y chromosomes that is consistently expressed by the cells of Ewing sarcoma/PNET but not pathognomonic of this group as it is occasionally expressed in other tumors (e.g. embryonal rhabdomyosarcoma). FLI1 nuclear protein is positive in Ewing sarcoma but is also non-specific.

Radiography

Ewing sarcoma occurs most often in the diaphysis of long bones and in bones of pelvis, ribs, vertebrae, mandible and clavicle. It generally arises from medullary canals of shafts. The typical radiological changes are cortical thickening, widening of the medullary canal, permeative invasion and a prominent soft tissue component (P 20-33). With progression of lesion, reactive periosteal bone may give an onion-skin appearance.

Histopathology

This group of tumors is formed of solid sheets of small rounded uniform blue cells separated by fibrous strands into irregular masses (P 20-34). Nuclear characteristics are those of primitive uncommitted cells, namely a finely dispersed chromatin and indistinct nucleoli. Pseudorosettes may be seen. Necrosis is common and may dominate the picture. Tumor cells are usually rich in cytoplasmic glycogen which can be demonstrated by PAS.

Immunohistochemically, the most consistent positivity is for vimentin and CD99. In ideally processed tissue, positivity for NSE, FLI1, low-molecular weight keratin and neurofilaments may be found.

Spread

Metastatic spread is to lungs, pleura, bones (particularly the skull), central nervous system and rarely regional lymph nodes. About 25% of patients have multiple bone and/or visceral lesions at the time of presentation. Bone marrow metastasis, microscopically detectable in about 10% of patients, is associated with poor prognosis.

Prognosis

The new combination of high-dose irradiation and multidrug chemotherapy without amputation have dramatically led to over 85% local control and 5-year disease-free survival of 75%. More recently, improvements in orthopedic surgery have allowed preservation of function without compromising survival rates. Prognostic

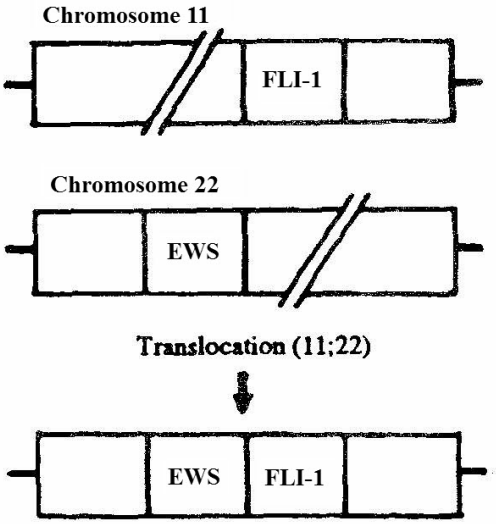

Fig 20-7 *Genetic recombination in Ewing sarcoma with creation of a novel fusion product.*

factors include the age, site and stage of the disease. Thus, 70% of patients under the age of 10 years survive, as compared with 46% in older patients. Tumors located in the pelvis are more unfavorable than those of extremities. Extension of tumor to soft tissues is associated with poor prognosis. However, about 25% of patients with distant metastases can be cured with recent therapy.

FIBROSARCOMA AND MALIGNANT FIBROUS HISTIOCYTOMA (MFH)

Primary fibrosarcoma of bone and malignant fibrous histiocytoma (MFH) are histogenetically closely related tumors in view of the interconversion of fibroblast and histiocyte. Fibrosarcoma and MFH account for 3% of malignant primary bone tumors. They are common in adults (age 40-60 years) usually affecting the metaphyses of knee region.

Radiologically it is characterized by bone destructtion without new bone formation or calcification. Extension through the cortex to the soft tissue is common.

Histologically, fibrosarcoma should be differentiated from *desmoplastic fibroma of bone* (P 20-35). It is composed of atypical fibroblasts only (P20-36), whereas, in MFH histiocytic giant cells are present in addition (P20-37). Both tumors show hypercellularity, anaplasia and mitotic activity. The 5-year survival varies between 34-53%.

GIANT CELL TUMOR

This is a tumor of borderline malignancy of unknown histogenesis with high tendency to recur locally after curette (50% of cases) but without producing distant metastases. It constitutes about 8% of malignant primary bone tumors (Dahlin, 2009). The median age is 30 years (range 20-40 years) with slight female predominance (1.2:1). About 50% of giant cell tumors affect the epiphyses of the knee region. Other common sites are the upper end of humerus and lower end of the radius.

Radiography of the tumor reveals an eccentric epiphyseal lesion, with partial spread to the metaphysis since the barrier effect of the epiphyseal cartilage is absent. The lytic expansile lesion is usually without peripheral bone reaction, except in case of pathologic fracture (P 20-38).

Histologically, it is composed of two elements: oval to spindle stromal cells (neoplastic cells proper positive for p63) and osteoclast-like multinucleated giant cells which are uniformly-distributed in the tumor (P 20-39). Mitosis may occur in stromal cells, but not giant cells, and is always of normal type. Immunohistochemically, both giant cells and stromal cells are positive for alpha-1-antitrypsin. Brown tumor of hyperparathyroidism (P 20-40) should be excluded before the diagnosis of giant cell tumor.

Malignant giant cell tumor (giant cell sarcoma) accounts for 6% of giant cell tumors and 0.6% of primary bone sarcomas. It may be malignant on first presentation or complicate about 30% of giant cell tumors. Sarcomatous transformation develops an average of 9 years after initial treatment, and may be related to repeated recurrences or prior radiotherapy. Histologically, a predominance of stromal cells, abnormal mitosis and diminished number of giant cells, are suggestive of malignancy. Contrary to classic giant cell tumor, giant cell sarcoma usually produces distant metastases, commonly in the lungs.

NON-HODGKIN LYMPHOMA

It contributes 7% of all primary bone sarcomas. It affects patients after the age of 40 years with male predominance of 1.6:1. It is most common in peripheral bones and is multifocal in 11-38%.

Radiologically, it shows an osteolytic permeative pattern, with soft tissue component lacking bone formation, but, sclerotic bone may occur within the medullary cavity (P 20-41). *Histologically,* the tumors are B-cell lymphomas of diffuse large or mixed cell types. The differential diagnosis from other small round cell tumors of bone is outlined in (Table 20-9). The 5-year survival of primary lymphoma localized to the bone varies between 30% to 50%.

SOLITARY MYELOMA

Multiple myeloma (page 427) is not discussed in this chapter, since it is not a primary bone tumor. However, solitary myeloma of bone (plasma-cytoma) presents in its initial course as a localized primary bone tumor (P 20-42). It accounts for about 5% of primary bone sarcomas. The median age is 55 years and men are affected in

Table 20-9 Round Cell Tumors of Bone Compared

Feature	Ewing	Osteosarcoma (round cell type)	Lymphoma (NHL)	Langerhans cell disease	Solitary plasmacytoma
Age (years)	5-20	30-40	30-60	5-15	50-60
Site	Diaphysis	Metaphysis	Metaphysis	Metaphysis and diaphysis	Metaphysis and diaphysis
Histology	Uniform round cells, clear cytoplasm, PAS+	Round and stellate cells, osteoid	Mixed large and small lymphoid cells	Histiocytes, eosinophils and lymphocytes	Atypical plasma cells
Markers	MIC2 (CD99), FLI1	Osteonectin	LCA, CD20	S-100, CD1a Langerin (CD207)	CD38, CD79a, CD138,
Response to irradiation	Sensitive	Resistant	Sensitive	Sensitive	Sensitive

70% of cases. In most patients (85%) the disease eventually progresses to multiple myeloma.

The required diagnostic criteria include: (1) solitary bone lesion, (2) monoclonal plasma cell infiltrate in the biopsy, (3) negative plasma cell infiltrate in the bone marrow, (4) lack of anemia, hypercalcemia or renal involvement.

CHORDOMA

This is not an uncommon bone tumor (2%) originating from remnants of notochord. It affects the midline of vertebral column, 50% sacrococcygeal, 37% sphenooccipital region, and 13 % the cervical, lumbar and thoracic regions in descending order of frequency. Cranial chordomas presents as a nasopharyngeal mass with destruction of base of skull. The median age is 55 years, but, sacral lesions generally occurs in older patients, with a median age of 56 years, as compared with 47 year for cervical lesions. Male predominance is 1.8:1.

Histologically, it is characterized by giant cells with multiple cytoplasmic vacuoles (physaliferous or bubble cells) and myxoid stroma (P 20-43). Tumor markers are characterized by positivity to cytokeratin, vimentin and S-100. The tumor is locally-malignant (considered as low-grade sarcoma), rarely producing distant metastases. The median survival is about 6 years. A histologically related tumor *(parachordoma)* may occur in ectopic peripheral locations (bone cortex and soft tissue), but carries a more favorable prognosis than classic chordoma.

ADAMANTINOMA

A rare low-grade sarcoma (P 20-44) with epithelial and mesenchymal elements. Classically involves the tibia, usually shaft in young adults. Histogenesis is not clear, but it is suggested that the epithelial component derives directly from mesenchymal tissue or inclusion from skin.

Histologically, may be confused with metastatic carcinoma which is unusual below knee, occurs in older patients, has more malignant cytological features, with no osteofibrous dysplasia-like areas which may be encountered in adamantionoma. Cytokeratin is positive in the epithelial elements in both tumors.

HISTIOCYTOSIS OF BONE

1. Langerhans cell type (LCH) e.g. eosinophilic granuloma: Formerly called Histiocytosis X and represents less than 1% of bone tumors. It affects children between 5-15 years with a slight male predominance.

A neoplastic origin is proved by clonality studies. Usually present with solitary bone lesions where any bone may be affected but skull is more common. Patients with disseminated disease may have lymphadenopathy, skin lesions, or diabetes insipidus. The imaging features in these patients are usually characteristic.

Histologically, characterized by Langerhans cells (polygonal cells with eosinophilic cytoplasm, oval nuclei with longitudinal grooves resembling coffee

beans); also eosinophils, giant cells, neutrophils, foam cells, lymphocytes, plasma cells, fibrosis, necrosis; may have typical and atypical mitotic figures. CD1a, S100 and Langerin (CD207) may help along with the characteristic nuclear features of Langerhan's cells in differentiating LCH from osteomyelitis and lymphoma. The prognosis is much favorable and depends mostly on the stage of the disease.

2. Non-Langerhans cell type: Erdheim-Chester disease (polyostotic sclerosing histiocytosis). Is a very rare non-neoplastic disease affecting adults. Radiologically characterized by bilateral and symmetric osteosclerosis of long bones (diaphysis and metaphysis), usually lower extremities. Organs involvement may be seen.

BONE METASTASES

Skeletal metastases are more common than primary bone sarcomas. Metastatic carcinomas are more common (80%) than metastatic sarcomas, and the most common sites of primaries are thyroid, breast, lungs, kidney and prostate (Fig 20-8). Sarcomas with high metastatic potential *to* bones are embryonal rhabdomyosarcoma and neuroblastoma. About 70% of bone metastases affect the axial skeleton (skull, ribs, spine and sacrum). Exception to this rule are metastases of breast carcinoma and renal cell carcinoma which may affect peripheral bones distal to elbow and knee joint.

Radiography

From a radiologic point of view, bone metastases may be osteolytic, osteosclerotic or mixed (P 20-45 to P 20-48). (1) *Osteolytic* metastases are observed in thyroid carcinoma, melanoma and gastrointestinal cancer. (2) *Osteosclerotic* metastases develop in prostatic carcinoma, carcinoid, medulloblastoma and lymphoma. (3) *Combined* changes are seen in breast, lung metastases and mucinous adenocarcinoma. In difficult cases (sarcomatoid metastases), immunohistochemical staining for cytokeratin will reveal the epithelial nature of bone metastasis.

Metastases commonly occur in axial bone (skull, vertebral column and pelvis), However distal bones of extremities may be involved, particularly in breast and renal carcinomas.

Molecular Pathogenesis

Normally, osteoblasts are the bone-forming cells, whereas, osteoclasts are the bone resorptive cells. The osteolytic function of osteoclasts is under the control of osteoblasts through growth factors, hence a normal balance is achieved in bone remodeling and growth.

A molecular explanation of bony changes observed in metastasis was recently reported (Heymann, 2010). Metastatic cancer cells in bone produce various growth factors which may activate osteoclasts or osteoblasts resulting in lytic or sclerotic bony changes respectively (Fig 20-9).

The biochemical changes in blood observed in patients with bone metastasis (rise of blood calcium, alkaline phosphatase, and osteocalcin) are also related to osteoclastic or osteoblastic activity. Thus, hypercalcemia is the result of bone resorption by osteoclasts, whereas, elevated levels of alkaline phosphatase and osteocalcin are products of osteoblasts. The presence of these biochemical changes in the blood of cancer patients is helpful to detect bone metastasis early, even before their radiologic appearance.

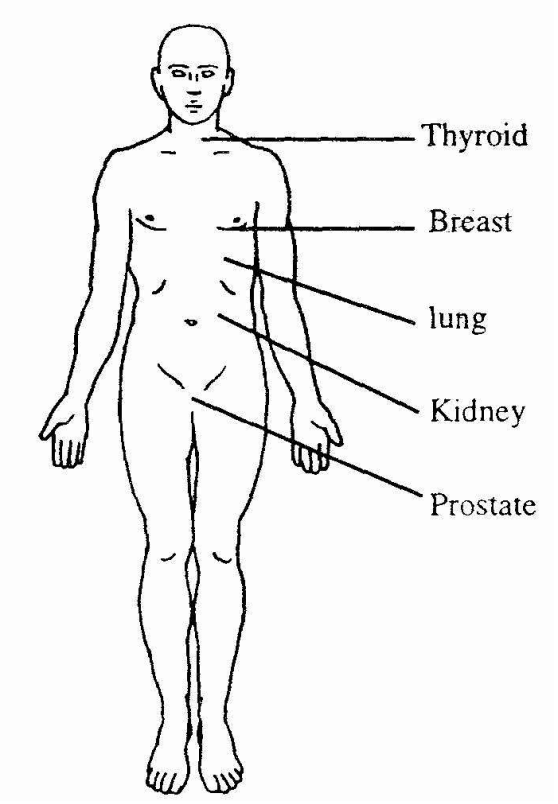

Fig 20-8 *Common primary sites of bone metastases*

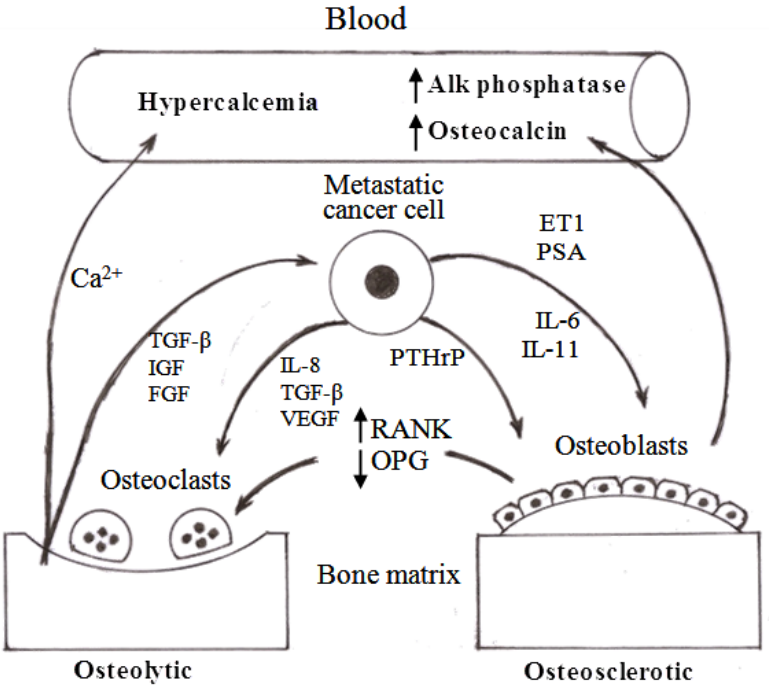

Fig 20-9 *Pathogenesis of osteolytic and osteosclerotic bone metastases and the associated biochemical changes in blood. Growth factors secreted by metastatic cells activate osteoclasts or osteoblasts resulting in osteolysis or osteosclerosis respectively. Moreover, osteoclasts are under the control of osteoblasts (RANK activating and OPG inhibiting). ET1, endothelin-1; PTHrp, parathyroid hormone-related protein; RANK, receptor activator of nuclear factor kappa-B(NF-κB); OPG, osteoprotegrin. Biochemical changes in blood help to detect metastases. (Adapted from Heymann, 2010).*

REFERENCES

Dahlin D: Bone Tumors, general aspects and data on 10,165 cases, 6th ed. Lippincott Williams and Wilkins, PA, 2009.

Enneking WF, Spanier SS, and Goodman MA: A System for the surgical staging of muscloskeledal sarcoma. Clinorthar 153:106,1980.

Edge SB, Byrd DR, Carducci MA, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.

Fletcher CD, Bridge IA, Hogendoorn PC and Mertens F: WHO Classification of Tumors of soft tissue and Bone. IARC, Lyon, 2013.

Folpe AL and Inwards CY : Bone and Soft Tissue Pathology, Foundations in Diagnastic Pathology, Saunders, ELsevier, Philadelphia, 2010.

Heymann D: Bone Cancer. Academic Press, Elsevier, London and New York, 2010.

Huvos AG, Rosen G and Marcove RC: Primary osteogenic sarcoma, Pathologic aspects in 20 patients after treatment with chemotherapy. Arch Pathol Lab Med, 101:14-18,1997.

Picci P, Bacci G and Campanacci: Histologic evaluation of necrosis in osteosarcoma induced by chemotherapy, regional mapping of viable and nonviable tumor. Cancer, 56:1515-1521,1985.