# Cancer of bone in children

**Norman Jaffe, MD, DSc**

## Abstract

*Bone cancer in children is extremely rare. The two most common malignant bone tumors are Ewing's sarcoma and osteosarcoma, which is more common. An outline of the incidence, biological behavior, treatment tactics and strategies of both tumors is presented. In historical controls, the cure rate for both tumors was usually less than 20%. With current treatment methods, cure rates in the vicinity of 65% may be anticipated. In many instances, amputation has been replaced by limb salvage procedures, particularly in osteosarcoma. (Pediatr Dent 17:263–67, 1995)*

Malignant tumors of the skeleton are extremely rare in the pediatric population. The annual incidence for black and white children younger than 15 years old combined, is approximately 5.5 per million; younger than 4, it is 1.5; between 5 and 9, 3.8; and between 10 and 14, 12.2.[1] The two most common malignant bone tumors are Ewing's sarcoma and osteosarcoma; osteosarcoma is more common (the eponym "osteosarcoma" as opposed to "osteogenic sarcoma" is preferred by the World Health Organization). There is a slight preponderance of both tumors in males. The etiology of malignant bone tumors is unknown, but certain associations have been identified. This article will compare and contrast characteristics and current approaches to treating both tumors.

### Ewing's sarcoma

The annual incidence of Ewing's sarcoma in the United States is two to three cases per million children.[2] There is a very low incidence of Ewing's sarcoma in blacks and Asians and there are no known associated congenital syndromes. There is also no known pattern of hereditary transmission and no constitutional karyotypic abnormality. Recently, however, a t(11;22)(q24;q12) chromosomal translocation was discovered in tumor cells in the tissue culture of Ewing's sarcoma.[3] The tumor has a predilection for the diaphyseal portion of bones.

### Osteosarcoma

The annual incidence of osteosarcoma is approximately 3.5 cases per million in children younger than 15 years. It accounts for approximately 60% of malignant bone tumors in the first two decades of life.[4] (Ewing's sarcoma is more common than osteosarcoma in children younger than 10 years.) The peak incidence of osteosarcoma occurs in the second decade during the adolescent growth spurt, which is younger in females than in males.[5] The increased incidence later in males may be a consequence of the larger volume of bone in the male.

Patients with osteosarcoma usually are taller than their peers.[6] Large breeds of dogs (e.g., the Great Dane and the St. Bernard) also have been reported to have an increased incidence of osteosarcoma compared with smaller breeds.[7] The tumor has a predilection for the metaphyseal portions of bone. These are the most rapidly growing regions: distal femur, proximal tibia, and proximal humerus.

A viral etiology for osteosarcoma in animals has been suggested.[8,9] Thus, C-type virus particles in human osteosarcomas have been noted but a definite cause has not been established.[10,11] Immunologic studies with antisarcoma-specific antibodies also have been found in patients and in close relatives of patients with sarcomas.[11,12] Lymphocytes cytotoxic to osteosarcoma cells also have been reported in the peripheral blood of patients with osteosarcoma and in their parents.[13]

There is no evidence to suggest that antecedent trauma may be responsible for osteosarcoma development. Ionizing radiation has been implicated in approximately 3% of cases.[14] Radiation in these circumstances was administered to treat benign and malignant bone and soft tissue tumors. The average interval between radiation and the (later) diagnosis of sarcoma was 13.4 years.[14] In the older patient, osteosarcoma has been reported as a complication of Paget's disease of bone.[15] Lesions predisposed to malignant (osteosarcoma) degeneration include solitary or multiple osteochondroma, solitary enchondroma, enchondromatosis (Ollier's disease), multiple hereditary exostosis, and fibrodysplasia.[15,16]

Several families have been described in which members have developed osteosarcoma.[17,18] A genetic predisposition has been demonstrated in patients with hereditary retinoblastoma.[19,20] The actuarial risk for

developing second tumors among patients with bilateral retinoblastoma is 90% at 30 years.[21] This specific locus involved in generating retinoblastoma has been mapped to chromosome 13 and also has been implicated in osteosarcoma development.[22]

## Pathology

### Ewing's sarcoma

Ewing's sarcoma originally was considered to be an endothelioma. The cell of origin has not yet been firmly established. Early investigations suggested a mesenchymal, osteoblastic, and myelogenous origin.[23-25] More recent evidence suggests that it constitutes a family of tumors of parasympathetic nerve origin with a spectrum of differentiation. Askin's tumor (probably a type of Ewing's sarcoma) and peripheral primitive neuroectodermal tumors (PPNET), also called peripheral neuroepithelioma, share an identical reciprocal translocation (11; 22) with Ewing's sarcoma.[26] Thus, the tumor may possibly also be of neural origin.

Ewing's sarcoma is a diagnosis of exclusion. Among the conditions to be considered are small cell osteosarcoma, undifferentiated primary sarcoma of bone, rhabdomyosarcoma, synovial sarcoma, primary lymphoma of bone, and neuroblastoma. The presence of glycogen in a round-cell tumor of bone initially was considered to be diagnostic of Ewing's sarcoma, but it is now known that Ewing's sarcoma may be glycogen negative.[27] Other round-cell tumors, for example rhabdomyosarcoma, also may be positive for glycogen. Immunocytochemistry may help differentiate the varieties of small round-cell tumors. A recent investigation demonstrated that the antigen HBA71 may be highly specific for Ewing's sarcoma.[28]

The light microscopic appearance of PPNET varies. Different types of rosette formation may be found, including a lobular or alveolar pattern or cells in sheet-like arrangements. Most tumors exhibit variable numbers of cells positive for neuron specific enolase (NSE) and cells positive for S-100 protein. Neurofilament triplet proteins (NFTP) sometimes are positive in PPNET but they also are present in rhabdomyosarcoma. The term "atypical Ewing's sarcoma" encompasses tumors that generally would not be classified as conventional Ewing's sarcoma due to cellular pleomorphism, high mitotic rate, and/or an inconsistent architectural pattern.

### Osteosarcoma

The histologic diagnosis of osteosarcoma derives from the presence of malignant stroma and the production of tumor osteoid and bone. The *sine qua non* for the diagnosis is malignant osteoid. The largest group of osteosarcomas is the conventional type in which the connective tissue stroma variably appears as a mixture of large, atypical, spindle-shaped cells with large, irregular nuclei and abnormal mitotic figures. The stroma may be highly anaplastic. Three categories of conventional osteosarcoma have been defined based upon the predominant differentiation of tumor cells: osteoblastic (50%), chondroblastic (25%), and fibroblastic.[4,14,16] In addition, a telangiectatic variety (3%), a predominantly lytic lesion with little calcification and bone formation, has been described.[4,15] Radiographically, it may resemble aneurysmal bone cyst or a giant-cell tumor. Small-cell osteosarcoma is a rare type that may be easily confused with Ewing's sarcoma.[29] Another extremely rare variant is the intraosseous well differentiated type.[30]

Certain varieties of osteosarcoma have been distinguished by their unique clinical, pathologic, and radiographic characteristics. Parosteal osteosarcoma (juxtacortical osteosarcoma) comprises less than 5% of osteosarcomas.[16] The posterior aspect of the distal femur is the bone most commonly involved. It generally occurs in females; intense ossification is typical, and histologically, the lesions appear low grade. Periosteal osteosarcoma arises on the surface of bone without involvement of marrow cavity.[31] The lesion has a propensity for the upper tibial metaphysis. Histologically it is a relatively high-grade, predominantly chondroblastic neoplasm. The prognosis is worse than for the parosteal type.

Several additional varieties of osteosarcoma may be encountered and are distinguished by differences in their biological behavior. Primary osteosarcoma of the jaw occurs most often in older patients, has a predominant chondroid differentiation, and is associated with a more indolent course. It also has a tendency to local recurrence rather than distant metastases. Extraosseous osteosarcoma is an uncommon variant that arises outside of bone and occurs most frequently in soft tissues. Finally, multifocal osteosarcoma is a rare entity in which multiple synchronous skeletal tumors are present at diagnosis and each lesion resembles a primary tumor radiologically.

## Clinical features

Pain is the presenting symptom in more than 90% of patients with malignant bone tumors. The majority have a palpable mass. Approximately one-fifth of patients with Ewing's sarcoma present with fever, which sometimes leads to a mistaken diagnosis of osteomyelitis.[32] In disseminated disease, a patient may present with a variety of symptoms, including pain in different bony sites and hemophysis. In Ewing's sarcoma, common sites for overt metastatic disease include the lungs, bone, bone marrow, lymph nodes, and liver.

## Radiographic characteristics

### Ewing's sarcoma

The tumor tends to be extensive, often involving the entire bone shaft. Osteolytic destruction generally is observed with occasional osteoblastic areas due to new bone formation. Endosteal scalloping is not uncom-

mon. The tumor often penetrates through the cortex and elevates the periosteum. Multiple layers of subperiosteal reactive new bone formation produce an onion skin appearance, which at one stage, was considered pathognomonic for Ewing's sarcoma. However, this feature may occur in other conditions as well. Extensive destruction in association with large extraosseous masses is not uncommon. "Saucerization" of the exterior surface of the cortex is an early and characteristic sign of subperiosteal tumors.

### Osteosarcoma

Variation in the roentgenographic findings may be observed. This depends on the amount of ossification and calcification. Tumors may be predominantly lytic or sclerotic or may exhibit a combination of both features. The older literature considered elevation of the periosteum (Codman's triangle) and spicules of new bone emerging at right angles to the shaft (sunburst appearance) as characteristic of osteosarcoma. These features, however, may also be seen in other bone lesions as well. Varying degrees of contiguous soft tissue involvement (generally less than in Ewing's sarcoma) are not uncommon. Osteoid substance does not produce radiopacity if it is not calcified. The roentgenographic diagnosis of osteosarcoma generally is suspected with a combination of bony destruction and proliferation of new bone, which usually has a streaky texture and ill-defined margins. Other radiographic findings may be more specific to the pathologic variety of osteosarcoma (vide supra).

## Biological behavior of malignant tumors

The biological behavior of Ewing's sarcoma and osteosarcoma indicates that pulmonary micrometastases are present in at least 80–90% of patients at diagnosis. These silent metastases are not visible on conventional radiographs but are surmised to be present if considered in the context of historical experience. Thus, after amputating the primary tumor, and in the absence of overt disease, pulmonary metastases invariably develop within 1 year in patients suspected to be free of this complication. These metastases usually are responsible for a patient's demise approximately 9–12 months later. Ewing's sarcoma and osteosarcoma, therefore, must be considered a systemic disease and systemic treatment must be administered in order to achieve cure.

## Diagnostic evaluation

At presentation, radiographs of the presenting lesion are obtained. These comprise an anterior-posterior, a lateral and two oblique views. In some centers, a skeletal survey is obtained to detect other coincidental lesions or metastases. The latter, however, are more appropriately identified by means of a bone scan. Examination of the presenting lesion usually is followed by a chest radiograph to detect the presence of overt metastatic disease.

After the initial radiographic studies are obtained, a biopsy of the lesion is requested. At the M.D. Anderson Cancer Center, this is usually accomplished with a fine needle aspirate or a core needle biopsy. Other centers may elect to obtain an open biopsy. Pathologic diagnosis of Ewing's sarcoma or osteosarcoma should be made only in conjunction with the radiographic studies.

After confirming the diagnosis of Ewing's sarcoma or osteosarcoma, additional radiographic studies will help establish the degree of disease involvement at the presenting site and in the lungs. This will also help assess the response to treatment. Thus, computerized axial tomography (CT scan) of primary lesion is utilized to determine the exact extent of tumor within the bone. A nuclear magnetic resonance study (MRI) is obtained for similar purposes. CT scan of the bone is also useful for assessing the degree of cortical involvement and MRI for the intramedullary extension and soft tissue component. A CT scan of the lungs is obtained to determine the presence of metastases, which may be undetected on a conventional radiograph. A bone marrow aspirate also is obtained in Ewing's sarcoma.

The tissue for biopsy is subjected to routine histologic evaluation, electron microscopy, immunochemistry, and cyto- and molecular genetics. In preparation for chemotherapy, a hemogram and liver and renal function are evaluated. A cardiac evaluation including echocardiogram may be obtained in anticipation of treatment with Adriamycin® (Adria Laboratories, Columbus, OH).

## Principles of treatment

Treatment comprises a rapid definitive attack upon the primary tumor and an attempt to destroy micro- or established metastases. Local therapy should not compromise delivery of effective systemic treatment since ultimately, disseminated disease is responsible for the patient's demise. Therapy should be implemented with curative intent unless the disease is widespread, in which circumstances palliation is a major consideration.

### Ewing's sarcoma

The following agents have been shown to be effective in treating Ewing's sarcoma: vincristine,[33] cyclophosphamide,[34] actinomycin D,[35] Adriamycin,[36] ifosfamide,[37] 5FU,[38] and bischloroethylnitrosourea (BCNU).[39] Several combination chemotherapeutic regimens have been devised incorporating most of these agents. The regimens were found to be effective against microscopic disease (pulmonary metastases) and the primary tumor.[40–42] Currently two major chemotherapeutic regimens are being investigated:

1. Vincristine, actinomycin D, cyclophosphamide, and Adriamycin
2. Vincristine, actinomycin D, cyclophosphamide, Adriamycin, etoposide, and ifosfamide.

These chemotherapeutic regimens are administered for approximately 3 months, after which treatment of the primary tumor is implemented. The objective is to

determine the efficacy of the regimen in treating the primary tumor (bulk disease), which hopefully will also reflect its impact upon micrometastases.

Local control for Ewing's sarcoma originally was attempted with surgery. Since the majority of patients succumbed to metastatic disease, investigations with radiation therapy were initiated in the hope of preventing mutilation in a patient destined to die. This was found to be highly successful in achieving good local control. Consequently, many regimens currently advocate treatment with 30–40 Gy to the whole bone with a boost to the primary tumor of 50–55 Gy. Adriamycin and actinomycin D potentiate the effects of radiation therapy and help increase the tumoricidal potential of radiation therapy.

With improvement in survival, the role of surgery as a means of achieving local control is now also being re-evaluated. Occasionally both surgery and radiation therapy are utilized. Radiation therapy is not suitable for treating long bones in children younger than 7 years of age.

### Osteosarcoma

The following chemotherapeutic agents have been found to be effective in osteosarcoma: Adriamycin,[43] cis-Diamminedichloroplatinum-II,[44] cyclophosphamide,[45] ifosfamide,[46] and high-dose methotrexate with leucovorin "rescue".[47] These agents initially proved active in eradicating overt disease (pulmonary metastases) and were then utilized as adjuvant therapy after removing the primary tumor. This strategy resulted in improved survival rates.[48]

Treating the primary tumor involves an immediate attempt at surgical ablation or the preoperative administration of chemotherapy. Many centers appear to favor the preoperative approach provided a response is achieved: chemotherapy is maintained for approximately 2 to 3 months at which stage a surgical procedure is performed.[49] In the past, this usually involved amputation.

With the demonstration that chemotherapy was effective, limb salvage received increasing recognition as a viable alternative to amputation.[50] Eligibility criteria for limb salvage include absence of major neurovascular involvement by tumor, the feasibility of performing wide resection of the affected bone, including potentially contaminated soft tissue, and an en bloc resection of the biopsy site if an open biopsy had previously been performed. The tumor-bearing bone should be sectioned at least 7 cm beyond the abnormal tumor uptake as determined by CT, MRI, and bone scan with removal of the adjacent joint and capsule. The resection is followed by motor reconstruction with possible regional muscle transfers and adequate soft tissue coverage. Other operative and reconstructive approaches also were devised, including an arthrodesis and a turnabout procedure*. Selecting which procedures to use depends on the site of the tumor and the eligibility criteria described earlier.

## Results

Utilizing current therapeutic approaches to treat Ewing's sarcoma and osteosarcoma, cure rates of 60–65% may be anticipated.[40-42,48-52] Approximately 10–30% of patients with osteosarcoma who present with or develop metastases while on therapy also may be cured.[53-55] In Ewing's sarcoma 25–30% patients with overt metastases at diagnosis also may be cured.[56] Current investigational strategies are aimed at improving survival not only in patients with metastases but also in those with seemingly localized tumor at diagnosis.

Dr. Jaffe is professor, Department of Pediatrics, University of Texas M.D. Anderson Cancer Center, Department of Pediatrics, Houston, Texas and W.W. Sutow Professor of Pediatrics.

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* The turnabout procedure involves excision of the femur with the tumor at the level of the lesser trochanter. The tibia then is excised distal to the proximal physis. The intervening skin and soft tissue also are excised with the exception of the neurovascular bundle. The tibia then is rotated 180° and the proximal tibia is fixed to the proximal femur with a blade plate, converting the ankle to a "knee". This transforms an above-knee amputation or hip disarticulation into a below-knee amputation with the potential for growth.

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