Bone tumors: osteosarcoma and Ewing's sarcoma

Travis Heare[a,b,c], Mary A. Hensley[a,b,c] and Shelley Dell'Orfano[a,b,c]

[a]Musculoskeletal Tumor Program, [b]The Department of Orthopaedic Surgery, University of Colorado and [c]The Children's Hospital, Denver, Colorado, USA

Correspondence to Dr Travis Heare, MD, Associate Professor, The Children's Hospital Department of Orthopedics, 13123 East 16th Avenue, B060 Aurora, CO 80045, USA
Tel: +1 720 777 6682; fax: +1 720 777 7268; e-mail: heare.travis@tchden.org

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Purpose of review

Osteosarcoma and Ewing's sarcoma are the two most common primary malignant bone tumors in children and account for approximately 6% of all childhood malignancies. Treatment methods have seen significant advancements, particularly in regard to chemotherapy and limb-sparing surgery. These advancements have led to increased survival rate. With many long-term survivors, it is important to evaluate long-term patient outcomes following treatment, including function and health-related quality of life. We will review the current trends in treatment of these diseases, different reconstructive options available, and the methods and results for evaluating the long-term results.

Recent findings

There have been many improvements in the medical treatment of these tumors leading to increasing long-term survival. There have also been improvements in reconstructive techniques for the maintenance of functional extremities in these patients. Newer evaluation methods for both functional outcome and health-related quality of life measures that are more specific to children and adolescents are being developed and in use.

Summary

This report will provide an overview of the current treatment options and long-term complications in primary malignant bone tumors for the pediatrician caring for a child with these problems.

Keywords

Ewing's sarcoma, function, health-related quality of life, limb salvage, osteosarcoma

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Introduction

Primary malignant bone tumors account for approximately 6% of all childhood malignancies. Of these, osteosarcoma and Ewing's sarcoma are the most common and have an annual incidence of 8.7 per million under the age of 20 years. With the use of multiagent chemotherapy, there have been significant improvements in the overall survival in these patients. This summary will review the current techniques in the evaluation, diagnosis, and treatment of these tumors. Indications and alternatives for limb-salvage surgery versus amputation and their functional outcome and the health-related quality of life will be discussed.

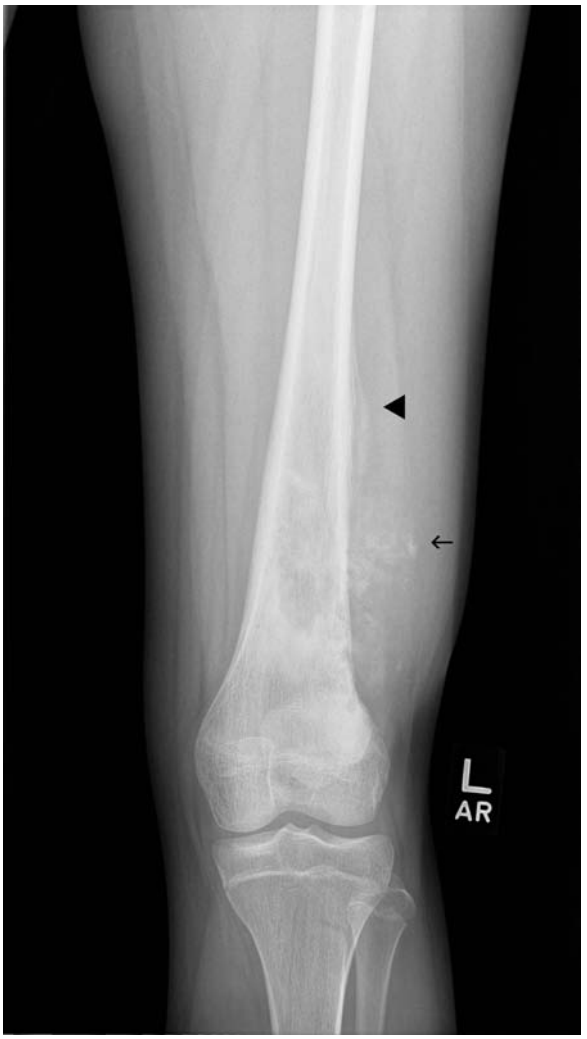
Osteosarcoma

The most common malignant bone tumor in childhood and adolescence is osteosarcoma. It represents 15% of all primary bone tumors and 0.2% of all malignant tumors in children. There are slightly more boys affected than girls (1.5 : 1). The peak incidence is in the second decade of life [1,2•,3]. About 80% of osteosarcomas occur in the extremities, with the most common sites being the distal femur, the proximal tibia, and the proximal humerus. About 80% of cases have localized tumor at presentation whereas the remainder present most commonly with pulmonary metastasis. In children with osteosarcoma, about 3% carry a germ line mutation in p53, with the majority of these having a family history suggesting Li-Fraumeni syndrome [1]. The incidence of osteosarcoma has been increasing by about 1.4% per year for the past 25 years [2•].

Clinical presentation

The most common clinical symptom at presentation is pain, generally described as dull or aching. Pain occurring at night or pain that is not related to activity should alert the physician to the possibility of an underlying problem. Other common complaints are swelling or a palpable mass. Systemic symptoms such as weight loss, fever, or loss of appetite are rare. A pathologic fracture can be seen in 10–15% of pediatric patients [1]. In these patients, there is a history of sudden onset of pain, often with a preceding history of some dull pain. Laboratory exams are usually normal with the exception of an occasional elevation of serum lactate dehydrogenase (LDH) or alkaline phosphatase or both.

Figure 1 Distal femoral osteosarcoma showing a destructive lesion with mixed lytic and sclerotic lesion with a Codman's triangle (◀) and ossification in the soft tissue mass (←)



Radiology

The first diagnostic study should be a plain radiograph, which will show a destructive lesion, most typically in the metaphysis of a long bone. The lesions most frequently are mixed radiolucent and radiodense and usually have an associated soft tissue mass at presentation. There is often a Codman's triangle of periosteal bone formation, and the soft tissue mass is often described as 'sunburst' in appearance (Fig. 1). The plain radiographic appearance is typically highly suggestive of a malignant process. The amount of ossification in the lesion on radiograph varies and therefore can be difficult to distinguish from Ewing's sarcoma or infection.

MRI of the primary site is usually the next radiographic study performed. MRI is optimal for evaluation of intramedullary and extraosseous extent of the tumor and its relationship to the neurovascular structures. These relationships are important in planning a biopsy and potential limb-salvage surgery. A computed tomography (CT) scan of the lungs is an important study to evaluate for pulmonary metastasis, the most common site of metastasis, found in 20–25% of patients at presentation [4•]. A radionucleotide whole body bone scan will show the primary tumor site and is valuable in screening for skeletal metastasis, the second most common site of metastasis. [^{18}F]Fluorodeoxyglucose positron emission tomography (PET) scans are being evaluated both for treatment response and in follow-up of suspected recurrence [5••].

Biopsy

The definitive diagnosis and treatment plans must always be based on a tissue diagnosis. Biopsy may be done either with a needle or as an incisional biopsy. It is important that the biopsy plan be carried out by a surgeon with expertise in musculoskeletal oncology to avoid compromising potential limb-salvage surgical options. The biopsy tract should be placed such that it can be excised en bloc with the ultimate surgical resection [6,7•,8,9].

Treatment

The treatment of osteosarcoma after biopsy begins with chemotherapy. Initial chemotherapeutic agents include methotrexate, Adriamycin (doxorubicin), and cisplatin, with or without ifosfamide. There have been multiple trials of intra-arterial chemotherapy; however, this approach has not to date been shown to be more effective than intravenous [2•,10]. Preoperative or neoadjuvant chemotherapy is given for 2–3 months followed by management of the primary tumor with surgery. When present, metastatic disease should also be resected at the same time or in a staged surgical procedure [4•].

The histologic response to the preoperative chemotherapy is determined based on amount of 'tumor kill' in the resected specimen. Additional adjuvant chemotherapy is then continued after the definitive surgical management. Research trials are currently underway to evaluate the efficacy of changes in postoperative chemotherapy in order to improve long-term outcomes in patients found to be 'poor' responders (defined as <90% tumor necrosis) [2•].

Prognosis

Prior to the use of chemotherapy, the long-term cure rate of osteosarcoma that was nonmetastatic at presentation was 25%. Since the introduction of chemotherapy, the cure rate of nonmetastatic osteosarcoma has risen to 60–70%. Factors indicating an adverse prognosis are age less than 14 years, high serum alkaline phosphatase at presentation, tumor volume at presentation of more than 200 ml, inadequate surgical margins, and 'poor' responders to neoadjuvant chemotherapy [1,2•,11].

For patients with metastatic disease at presentation, the overall survival rate decreases to less than 20%. The lungs are the most common sites of metastatic disease at presentation, with bone being the second most common site. In these patients, complete surgical resection of both the primary tumor site and all metastatic sites is necessary for a chance at long-term survival [4•,12–14]. The prognosis for 5-year event-free survival (EFS) in patients with pulmonary metastasis at presentation improves significantly if the patient has unilateral versus bilateral lesions and less than three pulmonary nodules, and has complete surgical resection of all the lesions [4•]. Pulmonary nodule size is also prognostically significant. Nodules measuring less than 5 mm on CT scan have no prognostic significance. Nodules measuring 5–10 mm have a worse 3-year EFS and patients with nodules 10 mm or greater fare worse in terms of EFS [15].

Although many patients with osteosarcoma are cured with their initial treatment, approximately 30% will have a relapse, most commonly in the lungs. Other common sites of relapse include local recurrence and skeletal metastasis. The long-term survival after pulmonary recurrence is 25%. Important prognostic factors are number of lesions, unilateral disease, time since initial treatment, and, most importantly, the complete surgical resection of all disease. The role of second-line chemotherapy is controversial [16].

Ewing's sarcoma

Ewing's sarcoma is the second most common malignant bone tumor of childhood and adolescence. They comprise the 'small, round, blue-cell' tumors thought to arise from neural crest cells. Together with the malignant peripheral neuroectodermal tumors, they now make up the Ewing's Sarcoma Family of Tumors (ESFT). The annual incidence of ESFT in the United States is 2.1 cases per million children, and they account for approximately 2% of all cancers in children and young adults [17]. ESFT is more common in male than in female patients and has a greater incidence in white and Hispanic children than in black or Asian children [18,19]. The overall incidence of ESFT has remained stable over the past 25 years. ESFT is not felt to be inherited and is not associated with any cancer syndromes. In 95% of cases, a t(11;22)(q24;q12) translocation is detected. The skeletal distribution of ESFT is evenly distributed between the axial and appendicular skeleton, and, in the long bones, the diaphysis is the more typical location [2•]. ESFT may also occur in the extraosseous tissues.

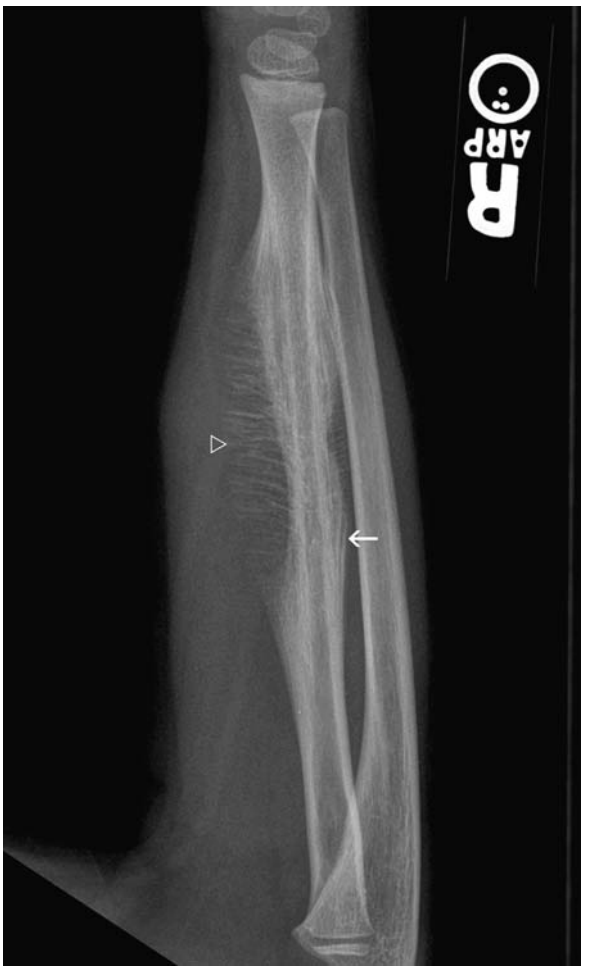
Clinical presentation

Similar to osteosarcoma, the most common presenting symptom is pain. Many patients also present with complaints of swelling or a palpable mass. Fever and weight loss can be seen in larger tumors, leading to the inclusion of osteomyelitis in the differential diagnosis. Although most patients have normal laboratory studies, some patients may have an elevated white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and/or LDH.

Radiology

Plain radiographs will show a mixed radiolucent and radiodense lesion with a permeative pattern of destruction. The lesions are frequently located in the diaphysis when they involve long bones and may show periosteal bone formation in an 'onion-skinning' or 'hair-on-end' pattern (Fig. 2). In lesions with metaphyseal involvement, the differential diagnosis will often include osteosarcoma and infection. MRI is typically the next study performed. It is the most sensitive test available for the evaluation of both the intramedullary and the soft tissue extent of the tumor. A CT scan of the lungs is used to screen for pulmonary metastasis, and a whole body bone scan is used to screen for skeletal metastasis. PET scans

Figure 2 Ewing's sarcoma of the radius – diaphyseal lesion with 'onion-skinning' (▷) and 'hair-on-end' (←) pattern of periosteal bone formation in a permeative destructive lesion



are being investigated as a staging study used to identify metastatic disease as well as for assessing response to therapy; therefore possessing prognostic significance [5••]. Distant lesions identified by bone scan or PET scan or both are usually evaluated with an MRI.

Biopsy

A definitive tissue diagnosis requires a biopsy, which may be accomplished with either a needle or an incisional biopsy, similarly to osteosarcoma. Because ESFT may also metastasize to the bone marrow, patients also require bilateral bone marrow aspirates and biopsies [2•]. Diagnosis can be established with light microscopy combined with appropriate stains or with additional studies to identify the chromosomal translocations found in ESFT. As in osteosarcoma, errors in placement of biopsy incision and tract may have an adverse effect on ultimate limb-sparing surgical options [6,7•,8,9].

Treatment

The treatment of ESFT typically begins with neoadjuvant chemotherapy. Local control is then addressed with surgery, radiation therapy, or a combination of the two modalities. Additional adjuvant chemotherapy is then used after local control. Chemotherapeutic agents known to be active in ESFT include doxorubicin, cyclophosphamide, ifosfamide, vincristine, etoposide, and dactinomycin [2•,20]. High-dose chemotherapy with or without autologous stem-cell rescue is under investigation for the treatment of patients with high-risk disease, metastatic disease, and recurrent disease [21,22].

Local control can be obtained in ESFT with surgery, radiation therapy, or a combination of the two. The same type of limb-salvage surgical techniques used in osteosarcoma may be employed in ESFT. However, unlike osteosarcoma, ESFT are also very responsive to radiation therapy. Recent trends toward surgical or combined surgery and radiation therapy have shown lower local recurrence rates than with radiation therapy alone. It is still unclear, however, if the overall survival has been improved by this approach [23•,24•]. Currently, most lesions that are resectable are treated surgically with or without adjuvant radiation therapy. Nonresectable tumors, which often involve the pelvis or spine, are more typically treated with chemotherapy and radiation therapy alone.

Prognosis

The most important prognostic factor in ESFT is the presence of metastatic disease at presentation. Nonmetastatic disease at presentation has a 5-year disease-free survival rate of 70% whereas patients with metastatic disease at presentation have a 5-year disease-free survival rate of 25% [2•]. Prognostically, patients with pulmonary metastases at presentation do better than patients with skeletal metastases. The prognosis is also worse with larger tumor volume and central versus peripheral location. Patients who suffer a relapse of ESFT have a very poor prognosis. Currently, there is interest in treating this group of patients with high-dose chemotherapy and autologous stem-cell rescue, but it is not yet clear whether this approach has improved the outcome in these patients [21,22].

Surgical management of osteosarcoma and Ewing's Sarcoma Family of Tumors

Historically, most bone sarcomas were managed with amputation. Over the past decades, however, there have been many advances in limb-salvage operations and considerable interest in utilization of these techniques. It has been shown that function is significantly improved by limb-sparing surgery when compared with amputations [25••]. Although the surgical strategies for addressing osteosarcoma and ESFT do not significantly differ, surgery in conjunction with radiation therapy is sometimes used in ESFT [23•,24•]. Limb-sparing surgery is possible in approximately 90% of patients with extremity tumors. Local recurrence risk is slightly higher in limb-sparing surgery; however, long-term survival rates are similar when compared with amputations. Long-term maintenance of limb-salvage has been shown to be approximately 85% at 20 years; however, this often involves multiple surgical revisions over time [26].

Biopsy by a physician unfamiliar with limb-sparing surgical techniques, or erroneous surgical procedures prior to the establishment of the diagnosis, has an adverse effect on local recurrence risk and the ability to perform limb-sparing surgery [6,7•,8,9]. Age of the patient and remaining skeletal growth are an important consideration in the patient under the age of 12 years, especially in the lower extremity.

Allograft reconstruction

Massive, or structural, allografts may be used to reconstruct bone defects after surgical resection. Used extensively in the past for joint reconstruction, structural allografts are now more commonly employed when a tumor is diaphyseal in location and the native joints can be preserved. Intercalary allograft reconstruction in that circumstance yields results with good function and excellent longevity [27,28]. Complications related to these procedures include prolonged time to healing of the allograft–host bone junction, allograft fractures with poor healing following fracture, and deep infections. All of these complications typically lead to repeat surgical procedures and may ultimately lead to amputation [29].

Prosthetic reconstruction

The early prosthetic reconstruction of extremities involved custom-made prostheses for individual patients.

Prostheses have now evolved to modular designs in which the appropriate 'off-the-shelf' parts can be assembled at the time of the limb-sparing surgery. Different prosthetic options are currently available for the proximal and distal humerus, proximal and distal femur, and the proximal tibia [30–34]. Prosthetic reconstruction typically involves the replacement of a segmental defect in an extremity bone as well as the adjacent joint. Complications associated with prostheses include deep infections and long-term prosthetic component wear or loosening. Many advances have been made to prostheses over the years, including fixation techniques to the bone and improved function of the prosthetic joint; however, they are still considered appropriate only for a walking, low-impact lifestyle.

Allograft prosthetic composite reconstruction

This reconstructive technique involves the use of a structural allograft in combination with a prosthetic joint and was originally employed to decrease the incidence of prosthetic loosening. The other advantage of this reconstruction has been the improved ability to reattach soft tissues to the allograft portion of the reconstruction with improved function as a result [35,36]. This is possible by suturing host structures to ligaments or tendons retained on the allograft for that purpose. The potential complications of this technique include deep infection and delayed or nonunion of the allograft–host junction, requiring repeat surgery. As this is still a prosthetic joint, it is appropriate for low-impact lifestyle as with prosthetic reconstructions.

Considerations in the young child

In the young child with significant remaining growth, special considerations must be made in order to avoid unacceptable limb length inequality. This is not only true for the lower extremity, but is also true for the upper extremity in the very young child. The majority of growth of the lower extremity occurs at the knee in the distal femur and proximal tibia, whereas the majority of growth of the upper extremity occurs in the proximal humerus and at the wrist. Upper extremity limb length inequality is tolerated much better than lower extremity inequality and thus is only a significant problem below the age of 6–8 years at the time of surgery.

Modular tumor prostheses can undergo revision of the body of the prosthesis with a longer segment added to lengthen an extremity. This requires an open surgical procedure and typically can add only about 2 cm to a lower extremity at any one time to avoid undue loss of range of motion of adjacent joints or neurovascular compromise. The procedure can be repeated at intervals, and, in combination with reconstructing the extremity 1–2 cm longer at the time of original resection and allowing the nonoperated extremity to catch up over time, allows ultimate establishment of equal leg lengths in the majority of patients [36].

In recent years, several prosthetic designs have been employed that offer either minimally invasive or non-invasive lengthening [37–40]. These options offer the advantage of more frequent, smaller increment lengthening to accomplish ultimate limb length equality. An issue still under investigation, however, is loosening of the prosthesis due to increased growth in bone diameter and effects of chemotherapy on the skeleton [41–43]. Alternate methods for fixation of prostheses to bone are currently being investigated.

Rotationplasty

Rotationplasty has been used to reconstruct tumors in the distal femur, proximal tibia, and less frequently the proximal femur. This reconstruction technique involves the use of the ankle joint with the foot rotated 180 degrees to act as the knee joint (Fig. 3) [44–46]. This functions as a below-knee amputation and avoids problems of phantom pain seen with amputation. Although the reconstruction has been shown to have good function, it has been utilized less because of the unusual cosmetic

Figure 3 Clinical photo of rotationplasty without prosthesis showing patient bearing weight

Figure 4 Same patient playing soccer

appearance of the extremity [47]. For patients to choose this option, they must be educated on functional and activity-related advantages as well as have the chance to meet patients with functional rotationplasty. The patient desiring to remain active in sports will then often choose this alternative. The functional results as well as the psychological acceptance of the appearance of the limb have been shown to be equal to limb-sparing reconstruction and superior to above-knee amputation [47,48•]. Patients with this reconstruction are able to participate in all activities, including impact loading, while wearing their external prosthesis without the fear of reconstruction failure and the need for further surgery (Fig. 4).

Long-term effects of treatment and evaluation

Patients treated for osteosarcoma and ESFT must be followed at regular intervals to monitor for recurrent disease and late effects of treatment [5••]. Monitoring for local recurrence, distant metastasis, and status of the reconstruction are all performed. Cardiac function, hearing, bone mineral density and monitoring for a secondary malignancy are all important considerations as all can be affected by the treatment of the tumor. In patients with a prosthetic reconstruction, it is important to have life-long monitoring of the function and radiographic appearance of the reconstruction. Most limb-salvage reconstructive options involve serial surgical revisions over time to maintain a functional limb. There are times when earlier surgical intervention may involve smaller operative procedures with better results.

Functional and health-related quality of life evaluation

As the treatment of patients with osteosarcoma and ESFT has improved, with 5-year disease-free survival rates ranging from 50 to 70%, there are an increasing number of patients living with the long-term effects of their treatment. The functional effects of the treatment, both from a chemotherapy and a local control standpoint, have become more important. There is more research being done to evaluate both physical function and the health-related quality of life in these patients. It has been shown that many evaluation scales designed for adults are not appropriate for children and may also be inappropriate for adolescents. Newer methods to evaluate function in these age groups and this patient population are being developed and studies to critically look at the long-term effects of the medical, surgical, and radiation therapy management of these patients are necessary [49–56,57••].

Summary

The treatment of malignant bone tumors in the last decades has progressed dramatically, with more patients becoming long-term survivors and a much greater percentage having limb-sparing treatment. Challenges remain in the treatment of disease that is metastatic at presentation as well as recurrent disease. With greater numbers of long-term survivors, attention must be paid to the medical and surgical consequences of treatment. Treatment must consider long-term function and health-related quality of life as well as long-term survival. Objective measurements of function and health-related quality of life need to be specific to children and adolescents to ensure adequate comparison of the long-term consequences of treatment alternatives.

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This article reviews the quality-of-life assessment in pediatric patients with bone sarcomas and the difference with some different reconstructive techniques.