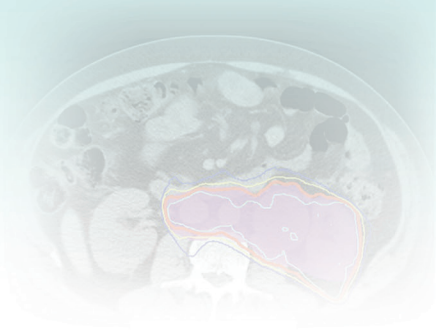
CHAPTER

69 Pediatric Sarcomas of Bone



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INCIDENCE
The pediatric sarcomas of bone are osteosarcoma (5.6 cases per million children per year) and Ewing's sarcoma (2.8 cases per million children per year).

BIOLOGIC CHARACTERISTICS
Osteosarcoma is associated with inactivation of the retinoblastoma gene. Ewing's sarcoma is characterized by a reciprocal translocation involving breakpoints on the *EWSR1* gene on chromosome 22q12A. The most common chromosomal translocation, t11:22 (q24;q12), is present in 85% to 90% of Ewing's sarcoma.

STAGING EVALUATION
Staging involves determining whether disease is localized or metastatic.

PRIMARY THERAPY
The primary therapy for osteosarcoma is surgical resection and multiagent chemotherapy. The 5-year survival rate is 60% to 70%. Ewing's sarcoma is treated with surgery or radiation therapy, or both, and neoadjuvant and adjuvant multiagent chemotherapy. The 5-year survival rate is 70%.

ADJUVANT THERAPY
For both osteosarcoma and Ewing's sarcoma, neoadjuvant and adjuvant multiagent chemotherapy are used.

ADVANCED DISEASE
Advanced osteosarcoma requires multiagent neoadjuvant and adjuvant chemotherapy, as well as surgical resection of the primary tumor and limited metastatic disease. The 5-year overall survival (OS) rate is 20% to 30%.

Ewing's sarcoma requires multiagent neoadjuvant and adjuvant chemotherapy, radiation therapy, or surgery, or a combination of these treatments for the primary tumor. Metastatic sites require definitive local therapy, most often with radiotherapy. The 5-year OS rate is 10% to 30%.

PALLIATION
Chemotherapy, surgery, or radiation therapy is used for palliation.

Osteosarcoma and Ewing's sarcoma are the two most-common malignant bone tumors in the pediatric and adolescent age-groups. Although osteosarcoma is more common than Ewing's sarcoma, radiotherapy is only used in rare situations. This section, therefore, is devoted largely to the discussion of Ewing's sarcoma. As with all other pediatric malignant diseases, patients should be treated on protocols and in institutions familiar with, and experienced in, the treatment of childhood tumors.

ETIOLOGY AND EPIDEMIOLOGY

In the United States, 650 to 700 children and adolescents younger than 20 years old are diagnosed with bone tumors every year. Ewing sarcoma family of tumors (ESFT) is the rarer of the two with approximately only 200 cases diagnosed each year. The incidence of Ewing's sarcoma is approximately 2.8 cases per million in children younger than 15 years of age.[1] Generally, the disease occurs in the teenage years during the adolescent growth spurt (ages 10 years to 15 years). However, approximately 30% of cases occur in the first decade of life and 30% occur in the third decade. There is a slight male predominance (1.6:1). Genome wide analysis suggests ethnic variations in susceptibility genes associated with Ewing's sarcoma but the strong Caucasian predominance is not completely understood.[2]

The cause of Ewing's sarcoma is unknown, and it does not appear to be induced by any known agents.

Osteosarcoma also is primarily a disease of adolescents and young adults; a different type of osteosarcoma linked to Paget's disease occurs in older adults. This section focuses on osteosarcoma in the younger age-group. Similar to Ewing's sarcoma, the peak incidence coincides with a period of rapid bone growth. Osteosarcoma is known to be associated with retinoblastoma gene mutations as well prior radiation therapy, particularly in children with retinoblastoma or other genetic abnormalities.[3]

PREVENTION AND EARLY DETECTION

The rate of secondary osteosarcomas has decreased with the declining use of radiotherapy in retinoblastoma patients. Some evidence suggests that limiting dose to <60 Gy can reduce risk of secondary osteosarcoma in patients receiving radiotherapy for Ewing's sarcoma. Early detection is possible with careful evaluation of persistent swelling or pain.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The histogenesis of Ewing sarcoma is controversial. The tumor was first described as an endothelioma of bone. Another hypothesis suggests Ewing is a primitive cell of neural origin, specifically from postganglionic, parasympathetic, and primordial cells.[4] Most recently, an alternative hypothesis suggests Ewing cells arise from mesenchymal progenitor or mesenchymal stem cells (MSC), which are found in bone marrow.[5] Previously, extraosseous Ewing's sarcoma and malignant peripheral neuroectodermal tumor (PNET) were considered separate entities from Ewing's sarcoma of bone and were treated differently; genetic studies now confirm they

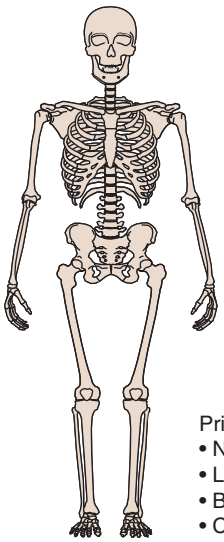

Figure 69-1 Distribution of primary sites and sites of metastases in Ewing's sarcoma.

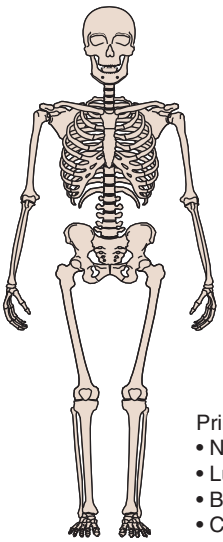

Figure 69-2 Distribution of primary sites and sites of metastases in osteosarcoma.

are from the same family of tumors, and together are termed *Ewing sarcoma family of tumors* (ESFT).[4] All exhibit identical chromosomal translocations, t11:22 (q24;q12), and more than 85% of patients share a common surface antigen, MIC2.[6-8] Ewing's sarcoma, atypical Ewing's sarcoma, and PNET of bone exist in the spectrum within this family, from the most undifferentiated tumors to those with neural differentiation. PNET can be differentiated from Ewing's sarcoma by the presence of a globular growth pattern, neuron-specific enolase (NSE) positivity, and Homer Wright rosettes.

Osteosarcoma is associated with inactivation of the retinoblastoma tumor suppressor gene (13q14), which occurs in approximately one third of cases.[9] Other genetic abnormalities include translocations, gene amplification, and abnormal *TP53* function.[10,11]

PATHOLOGY AND PATHWAY OF SPREAD

Ewing's sarcoma is an undifferentiated blue round cell tumor usually of the bone. Its pathologic appearance is a monomorphic pattern of densely packed, small, round, malignant cells with hyperchromatic nuclei and varying amounts of cytoplasm.[12] Immunohistochemical studies reveal cell-surface glycoprotein p30/32 MIC2 (CD 99) and vimentin, HBA-71, and β_2-microglobulin positivity. Occasionally, cytokeratin and NSE are positive. These studies can help differentiate ESFT from other small round cell malignant tumors of childhood. Approximately 87% of cases within the ESFT are Ewing's sarcoma of bone.[13] The remainder is PNETs or extraosseous Ewing's sarcoma.

About 75 % percent of patients with Ewing's sarcoma present with localized disease at diagnosis (Figure 69-1). Approximately 80% of children experience distant metastases if treated with only local therapy. This suggests that in the majority of cases, there are unidentifiable micrometastases present at diagnosis. The most common site of metastasis is the lung, followed by bone. Other distant sites include bone marrow, soft tissues, and rarely, the liver or central nervous system (Figure 69-1).

Osteosarcoma is derived from bone-forming mesenchyme and is described as a malignant sarcomatous stroma associated with the production of osteoid bone, its defining histopathologic feature.[12] The most common types in the pediatric population are the conventional osteosarcomas, including osteoblastic, chondroblastic, and fibroblastic types. Each type has varying amounts of osteoid formation and a different predominant component. There is no difference in outcome or treatment recommendations among these different types. Other types of less common osteosarcomas include telangiectatic, small cell, juxtacortical, periosteal, and high-grade surface sarcomas.

Approximately 90% of children with osteosarcoma present with localized disease at diagnosis (Figure 69-2). However, if only the primary tumor is treated, about 90% will experience metastatic disease.[12]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Patients with Ewing's sarcoma present in general with localized pain, swelling, and a palpable mass. The most common primary tumor sites are illustrated in Figure 69-1. In Ewing's sarcoma, plain radiographs show a lytic, destructive lesion, most typically of the diaphysis, with or without a soft-tissue mass. Codman's triangle may form from the elevated periosteal reaction. An "onion skin" effect, derived from the development of parallel, multilaminar, periosteal reactions, is typically seen.

Patients with osteosarcoma present with similar signs and symptoms, in general, localized pain, swelling, and a palpable mass. The frequency with which osteosarcoma occurs within the different regions of the body is illustrated in Figure 69-2. Plain radiographs of patients with osteosarcoma typically show sclerotic or lytic lesions of the metaphysis. The elevated periosteal reaction may cause Codman's triangle to form. In osteosarcoma, periosteal new bone formation may be present, with the blastic component showing a bony sunburst pattern.

The evaluation for patients with Ewing's sarcoma and osteosarcoma is similar. A complete history and physical examination are performed, with particular attention to the duration of symptoms, the presence of pain, difficulty of function, neurologic symptoms, and the location and size of the mass. Studies commonly obtained to evaluate the extent of disease include routine blood work, urine analysis, bone scanning, plain radiographs, and computed tomography (CT) scanning or magnetic

TABLE 69-1 Staging Investigations at Diagnosis in Osteosarcoma and Ewing's Sarcoma

Investigation	Diagnosis	Follow-up
Radiograph in two planes, whole bone with adjacent joints	+	+
MRI or CT, affected bone(s) and adjacent joints	+	+
Biopsy: material for histologic and molecular biologic testing	+	
Thoracic CT (lung window)	+	+
Bone marrow biopsy and aspirates (in Ewing's sarcoma): microscopy (molecular biology still investigational)	+	
Whole-body technetium-99 m bone scan	+	+
FDG-PET scan	++	++

CT, *Computed tomography;* FDG-PET, *fluorine-18 fluorodeoxyglucose-positron emission tomography;* MRI, *magnetic resonance imaging; +, mandatory; ++, indicated, if available.*

resonance imaging (MRI) of the primary region. A chest CT scan should be obtained to rule out lung metastases. If the chest radiograph is negative and the CT scan is positive for subtle anomalies, an excision may be needed for accurate staging and treatment recommendations. Single-institution and small multiinstitutional studies suggest fluorodeoxyglucose-positron emission tomography (FDG-PET) has improved sensitivity to bone and lymph node metastases compared to bone scan and CT.[14] An electrocardiogram and echocardiogram are included in the evaluation before chemotherapy is initiated. In the case of Ewing's sarcoma, a bone marrow biopsy is obtained. A summary of staging and follow up investigations is given in Table 69-1.

A biopsy of the primary lesion should be obtained after complete evaluation, ideally by the surgeon who will perform the definitive resection. The biopsy should be placed carefully to avoid contamination of uninvolved areas, vital structures, and hematoma development. It must not increase the extent of surgery or preclude a limb-sparing procedure or sparing of a strip of skin outside the radiation port.

Currently, there is no staging system for Ewing's sarcoma. Patients are classified as having either localized disease or metastatic disease and are treated accordingly.

In osteosarcoma, available staging systems are those of the Musculoskeletal Tumor Society and, lately, of the International Union Against Cancer and American Joint Committee on Cancer (UICC/AJCC).[15,16]

The prognosis for patients with Ewing's sarcoma is dependent on a number of factors, the most important of which is the presence or absence of metastatic disease. Data from European studies suggest histologic response to chemotherapy is the primary predictor of outcome in patients undergoing surgery.[17] This has yet to be confirmed in North American regimens although single-institution reports suggest response correlates with improved survival (Ahmed). Historically, other prognostic factors include the site of the lesion and its size and age and gender of the patient. In more recent studies, data is conflicting with no association of outcome with site or size reported in INT-154, a Children's Oncology Group (COG) study evaluating dose-intense multiagent chemotherapy.[18] However, on the recently reported COG AEWS0031 evaluating interval-compressed multiagent chemotherapy, pelvic site was associated with inferior event-free survival (EFS) and OS.[19] The French study EW93 reported poorer outcomes in axial and pelvic tumor as well as large tumor volumes, however, prognostic factors varied by type of local therapy. For surgical patients, location and histologic response correlated with survival. For radiotherapy patients, tumor volume remained significant but site did not.[17] Historically, older patients and male gender was also associated with poor survival. When accounting for histologic response in more recent studies, age and gender have not remained significant.[17] Age older than 18 was associated with poorer survival in the most recent COG study reported (AEWS0031) but histologic response was not assessed in this study.[19] Multiple retrospective studies suggest molecular biomarkers such as *p53* and *p16* may correlate with outcomes, however, prospective validation has not confirmed these findings.[20]

The prognostic features of osteosarcoma are similar, namely, the presence or absence of metastatic disease, the tumor location and size, whether complete resection of the primary tumor was possible, and the response to adjuvant chemotherapy.[21] No molecular markers have been validated in osteosarcoma.

TREATMENT OF EWING'S SARCOMA

Primary Therapy

Historically, patients with Ewing's sarcoma received treatment to the primary lesion only; cure rates were less than 20%. In the early 1960s, single-institution studies began to show an improved outcome with the addition of adjuvant chemotherapy.[22-24] Today, the standard treatment consists of local therapy and neoadjuvant and adjuvant polychemotherapy. Local therapy consists of surgery or radiotherapy or a combination of both. Concerning systemic therapy, a number of randomized trials have been performed to assess the value of different drug combinations.

The first Intergroup Ewing Sarcoma Study (IESS) investigated the use of polychemotherapy from 1973 until 1978. Patients received radiation therapy to the primary lesion and were randomized among three adjuvant chemotherapy treatment arms: vincristine, actinomycin D, and cyclophosphamide (VAC); VAC plus doxorubicin (trade name Adriamycin, so the regimen is known as VACA); or VAC plus bilateral pulmonary radiation therapy.[25] This study showed a significant improvement in all parameters with the addition of doxorubicin. Furthermore, VAC plus bilateral lung irradiation, although less effective than VACA, showed superior results to VAC alone. As a consequence of these results, doxorubicin was considered to be an essential drug in further trials.[26]

The third large intergoup study, INT-0091, investigated the addition of etoposide and ifosfamide to VACA; at 5 years, data showed a statistically significant benefit from the addition of these two drugs. In addition, local control was also significantly improved in patients on the experimental arm.[27] In the European Cooperative Intergroup Ewing Sarcoma Study EICESS-92, the value of the single agents was evaluated. In standard-risk patients (localized disease and tumor volume of <100 mL), VACA was randomized against VAIA (ifosfamide instead of cyclophosphamide). There was no significant difference in EFS rates between the groups. In high-risk patients (larger tumors or metastatic disease), VAIA was randomized

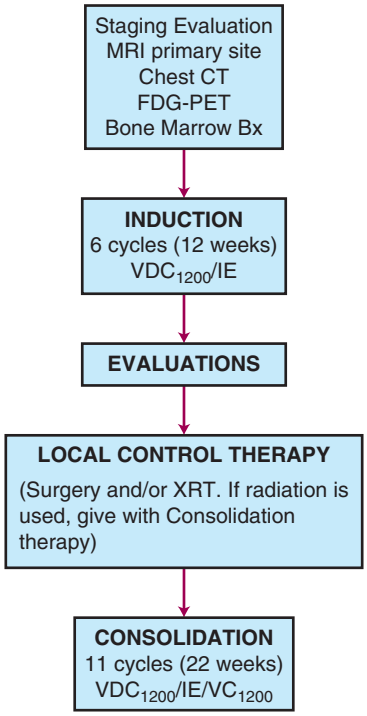

Figure 69-3 Treatment schema. *CT*, Computed tomography; *FDG-PET*, fluorodeoxyglucose-positron emission tomography; *IE*, ifosfamide-etoposide; *MRI*, magnetic resonance imaging; VC1200, vincristine-cyclophosphamide 1200 mg; VDC1200, vincristine-doxorubicin-cyclophosphamide 1200 mg; *XRT*, radiation therapy.

against VAIA plus etoposide; again, no significant difference in EFS rates was observed, but a marginal benefit was demonstrated for patients with large localized disease with the use of etoposide.[28] The most recently reported COG trial, AEWS0031, comparing vincristine, doxorubicin, cyclophosphamide, ifosfamide-etoposide (VDC-IE) dosed every 3 weeks versus every 2 weeks showed an 8% 5-year EFS benefit for interval compressed chemotherapy. This regimen remains the current standard in the United States.[19] Figure 69-3 depicts the most common treatment schema in North America. An alternative for treatment intensification used more commonly in European studies has been high-dose chemotherapy with stem cell rescue.[29] Because of its toxicity, this treatment is mainly used for very high-risk patients. In the Euro-EWING 99 trial, patients with poor pathologic response were randomized to either high-dose chemotherapy with busulfan or conventional therapy with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) give every 3 weeks. For patients with lung metastases only, high-dose chemotherapy with busulfan was compared to conventional chemotherapy and whole-lung irradiation with 15 Gy or 18 Gy, depending on the age of the patient. Results of this trial are still pending for localized patients. The results for patients with metastatic disease are discussed in this chapter.

A summary of results of different Phase III trials is given in Table 69-2.

Advanced Disease and Palliation

Children with metastatic Ewing's sarcoma at diagnosis continue to have a poor outcome despite the use of aggressive multiagent chemotherapy. The European approach in these patients is to intensify adjuvant and neoadjuvant chemotherapy using high-dose chemotherapy with busulfan or etoposide or treosulfan, and melphalan with autologous stem-cell rescue for patients with bone metastases. EuroEwing99 results using six cycles of VIDE followed by one cycle VID then local therapy. Patients then went onto high-dose busulfan and melphalan followed by stem cell rescue. Overall 3-year EFS and OS were 27% and 34%, respectively.[29] Patients with lung metastases only appear to be a more favorable subset of metastatic patients. European studies have used risk adapted strategies that are intermediate intensity compared to localized and bone metastases patients. Standard chemotherapy with whole-lung radiation has shown favorable results in the Cooperative Ewing Sarcoma Studies (CESS) and European Intergroup Cooperative Ewing Sarcoma Studies (EICESS) trials in comparison to patient with lung metastases only who did not receive whole lung radiation (5-year EFS 40% and 19%, respectively).[30] The EuroEwing99 pulmonary metastases arm evaluated the use of standard chemotherapy with whole-lung irradiation compared to high-dose chemotherapy with stem-cell rescue. The results are still pending. In the United States, metastatic patients were included on the intergroup study INT-0091 evaluating the addition of Ifosphamide/Etoposide (IE). The addition of IE did not result in and improvement in survival (5-year EFS 22%) for metastatic patients.[27] Interval compression was not evaluated in metastatic Ewing's sarcoma, however, because of the favorable results in localized patients it has been adopted for use in metastatic disease as well. In the upcoming COG study, AEWS1221, which will include all metastatic sites, interval compressed VDC-IE chemotherapy with whole lung radiation for lung metastasis patients will be the standard arm reflecting current clinical practice in the United States. Definitive treatment of metastatic sites appears to improve outcomes in metastatic Ewing's sarcoma. Definitive local treatment with surgery or radiotherapy is recommended on the upcoming COG AEWS1221 trial that is also evaluating the role of stereotactic body radiotherapy (SBRT) for bone lesions to improve feasibility of treatment. Even in patients in whom definitive local treatment of all metastatic sites is not feasible, radiation therapy can be used as a palliative local measure.

Local Therapy

Local therapy is an essential modality in the treatment of Ewing's sarcoma. With systemic therapy alone, cure cannot be obtained. Local control on modern COG studies is close to 90%. The modality of local therapy with best local control rates and functional outcome has been a matter of debate for some time. Retrospective analyses of cooperative group studies suggest that local control is improved when surgery is performed although a selection bias for more favorable tumor likely exists confounding these analyses.[31-34] Regardless of differences in efficacy, because of the risk of secondary malignancy associated with radiation, surgery is generally the recommended treatment when an oncologic resection can be obtained with acceptable morbidity. However, because Ewing's sarcoma is radiosensitive and radiotherapy is curative, radiotherapy is recommended for tumors that cannot be resected without significant morbidity. In United States, 60% to 65% of patients are treated with surgery alone, 20% to 25% are treated with radiation alone, and the remainder receives a combination of both. European studies report slightly higher rates of radiation and surgery and lower rates of surgery alone reflective of the risk-adapted approach used for higher risk tumors.[35-38] Patients on EuroEwing99 received preoperative radiation when margins were expected to be close with surgical resection and received postoperative radiation for poor histologic response.

TABLE 69-2 Treatment Results in Selected Clinical Studies of Localized Ewing's Sarcoma Family Tumors

Study	Reference	Schedule	No. Patients	5-year Event-Free Survival
COG				
IESS-I (1973-1978)	Nesbit, J Clin Oncol 8:1664, 1990	VAC VAC + WLI VACD	342	24% 44% 60%
IESS-II (1978-1982)	Burgert, J Clin Oncol 8:1514, 1990	VACD-HD VACD-MD	214	68% 48%
First POG-CCG (INT-0091) (1988-1993)	Grier, N Engl J Med 348:694, 2003	VACD VACD + IE VACD ± IE (metastatic)	200 198 120	54% 69% ($p = 0.005$) 22% ($p = 0.81$)
Second POG-CCG (1995-1998)	Granowetter, J Clin Oncol 27:2536, 2009	VCD + IE 48 wk VCD + IE 30 wk	247 231	70% 72% ($p = 0.57$)
AEWS 0031	Womer, J Clin Oncol 30:4148, 2012	VDC + IE 3/wk VDC + IE 3/wk	284 284	65% 73% ($p = 0.048$)
MEMORIAL SLOAN-KETTERING CANCER CENTER				
T2 (1970-1978)	Rosen, Cancer 41:888, 1978	VACD (adjuvant)	20	75%
P6 (1990-1995)	Kushner, J Clin Oncol 13:2796, 1995	HD-CVD + IE	36	77% (2 year)
P6 (1991-2001)	Kolb, J Clin Oncol 21:3423, 2003	HD-CVD + IE	68	Localized: 81% (4 year) Metastatic: 12% (4 year)
ST. JUDE CHILDREN'S RESEARCH HOSPITAL				
ES-79 (1978-1986)	Hayes, J Clin Oncol 7:208, 1989	VACD	52	82% < 8 cm (3 year) 64% ≥ 8 cm (3 year)
ES-87 (1987-1991)	Meyer, J Clin Oncol 10:1737, 1992	Therapeutic window with IE	26	Clinical responses in 96%
EW-92 (1992-1996)	Marina, J Clin Oncol 17:180, 1999	VCD-IE × 3	34	78% (3 year)
UKCCSG/MRC				
ET-1 (1978-1986)	Craft, Eur J Cancer 33:1061, 1997	VACD	120	41%
ET-2 (1987-1993)	Craft, J Clin Oncol 16:3628, 1998	VAID	201	62%
CESS				
CESS-81 (1981-1985)	Jürgens, Cancer 61:23, 1988	VACD	93	<100 mL 80% ≥100 mL 31% (both 3 year) Viable tumor < 10%: 79% >10%: 31% (both 3 year)
CESS-86 (1986-1991)	Paulussen, J Clin Oncol 19:1818, 2001	<100 mL (SR): VACD ≥100 mL (HR): VAID	301	52% (10 year) 51% (10 year)
EICESS (CESS PLUS UKCCSG)				
EICESS-92 (1992-1999)	Paulussen, J Clin Oncol 6:4385, 2008	SR: VAID/VACD HR: VAID/EVAID	155 492	68%/67% ($p = 0.72$) 44%/52% ($p = 0.12$)
ROI/BOLOGNA, ITALY				
REN-3 (1991-1997)	Bacci, Eur J Cancer 38:2243, 2002	VDC + VIA + IE	157	71%
SFOP/FRANCE				
EW-88 (1988-1991)	Oberlin, Br J Cancer 85:1646, 2001	VD + VD/VA	141	58%
EW-93 (1993-1999)	Gaspar, Eur J Cancer 48:1376, 2012	<100 mL >95% response (SR): VD + VD/VA >100 mL, 70-95% response, <50% size response (IR): VD + VD/VA + IE >100 mL, <70% response, <50% size response (HR): VD + VD/VA + IE + HD	116 46 48	70% 54% 48%
SSG/SCANDINAVIA				
SSG IX (1990-1999)	Elomaa, Eur J Cancer 36:875, 2000	VID + PID	88	58% (metastases-free survival)
EUROEWING (EICESS + SFOP)				
EuroEwing99 (1999-2005)	Ladenstein, J Clin Onc 28:3284 2010	R3 (multiple metastases): VIDE + VAI + HD	281	27% (3 year)

A, *Actinomycin D;* C, *cyclophosphamide;* D, *doxorubicin;* E, *etoposide;* HD, *high dose;* HR, *high risk;* I, *ifosfamide;* MD, *moderate dose;* P, *cisplatin;* SR, *standard risk;* V, *vincristine;* WLI, *whole-lung irradiation.*

Definitive Radiotherapy

Patients who receive radiotherapy as the only local therapy modality usually represent an unfavorably selected group of patients. They frequently present with large tumors or tumors in unfavorable locations (e.g., vertebral or pelvic tumors). In an analysis of 1058 patients with localized Ewing's sarcoma treated in the EICESS trials, 266 patients received radiotherapy alone for local treatment. Local or combined local and systemic failures in this subgroup occurred in 26% of patients, a recurrence rate that was worse than the rate following surgery with or without radiotherapy (4% to 10%).[33,34]

Bacci et al[39] performed a single-institution analysis of 512 patients treated in four consecutive trials. Treatment results in patients who received radiotherapy alone were worse than in patients who underwent surgery (local failure rates of 19% with radiotherapy alone, 11% with surgery and radiotherapy, and 9% with surgery alone). When analyzed by tumor site, radiotherapy alone was unfavorable in extremity sites but not in central tumor sites suggesting central tumor sites are problematic for surgical local control as well. Similar results were seen in a retrospective analysis of COG INT-0091 evaluating local control for pelvic tumors only. Overall local failure was 22% with no difference between surgery and radiation. Although not statistically significant, outcomes were improved in patients who received combination of surgery and radiotherapy as opposed to either surgery or radiotherapy alone (25% versus 10%, $p = 0.45$). Patients on the experimental arm (receiving IE chemotherapy) had improved local control with only 11% local failure rate for all patients.[38a]

Definitive radiotherapy is indicated is surgery is expected to leave gross disease (R2 resection). Debulking procedures do not improve local control rates and are associated with unnecessary morbidity. In the CESS and EICESS trials[33,34] and in the Bologna experience by Bacci et al,[39] patients who had intralesional resection followed by radiotherapy had the same local control rate as patients who had radiotherapy alone.

Postoperative Radiotherapy

Postoperative radiotherapy is always indicated following intralesional resections. These debulking procedures are not sufficient to obtain local control and should be avoided. Oncologic resection in Ewing's sarcoma has historically been defined by the Enneking classification.[15] Enneking et al reporting on outcomes in soft-tissue sarcoma described local failure rates of 50% for marginal resections (tumor was shelled out within the surrounding reactive zone), 25% after wide resection (resection passed through normal tissue outside the reactive zone but within the anatomical compartment), and 4% after radical excision (entire compartment resected). Although wide excisions are generally felt to ideal if possible with reasonable morbidity, with improvements in systemic chemotherapy modern surgeries are more accurately described as wide excisions. Historically COG trials recommend postoperative radiotherapy after close margins defined as margins <1 cm bone, <5 mm in muscle, and <2 mm along a fascial plane. Local control after surgery alone is approximately 90% on these studies.[18,19] In the CESS and EICESS trials, local control with surgery alone was excellent in all patients who had a wide resection according to the Enneking classification and showed a good response on histologic testing following initial chemotherapy (defined as <10% viable tumor cells in the resected specimen).[40] Only one local failure in 101 patients occurred in this subgroup. Patients with wide resection and a poor histologic testing response were at higher risk of local failure (12%). This local failure rate was improved with the use of postoperative radiotherapy (6%).[33] There was also a trend toward benefit with the use of postoperative irradiation in patients who had a marginal resection. Bacci et al[39] observed no improvement with postoperative radiotherapy following wide or marginal resection (local failure rate of 7% without postoperative radiotherapy and 6% with postoperative radiotherapy). Based on the importance of histologic response in local control reported in European studies, the current COG trial (AEWS1031) is evaluating the possibility of limiting postoperative radiotherapy after close margins (less than Enneking but still negative or R0 resections) to patients with poor histologic responses. Postoperative radiotherapy is still required for microscopic positive (R1 resection) margins.

Preoperative Radiotherapy

The systematic use of preoperative radiotherapy was incorporated into the EICESS-92 trial. The governing objective was to sterilize the tumor compartment before surgery and thereby potentially reduce the rate of dissemination during surgery. With growing experience with the use of preoperative radiotherapy, it was used in this trial when narrow resection margins were expected. More than 40% of the EICESS patients were treated with preoperative radiotherapy. In an analysis of the data from these 246 patients, however, a reduction in systemic failure could not be demonstrated.[33] On the other hand, the local control rate following preoperative radiotherapy was excellent, with only 5% of the patients experiencing local or combined local and systemic failures. However, preoperative irradiation may increase the infection rate postoperatively and may also interfere with bony union. In North America, preoperative radiotherapy remains fairly uncommon in Ewing's sarcoma for this reason.

Irradiation Techniques and Tolerance

Radiation Dose and Fractionation

The first Intergroup Ewing Sarcoma Study (IESS-I) evaluated the effect of dose on local control and showed no dose response between 30 Gy and 65 Gy. Single-institution report of the St. Jude experience showed higher rates of local recurrence in children treated with doses <40 Gy with no local failures using >40 Gy.[37] Although a clear dose-response correlation at doses above 40 Gy has not been established for definitive radiotherapy, doses between 55 Gy and 60 Gy are usually given. When surgery precedes or follows radiotherapy, the doses range between 45 Gy and 55 Gy, depending on the individual risk factors (e.g., resection margins and response). The current COG study (AEWS1031) recommends 45 Gy to prechemotherapy target volume, 55.8 Gy to postchemotherapy residual disease, and 50.4 Gy for microscopic positive margins postoperatively.

Usually, conventional fractionation with daily fractions of 1.8 Gy to 2 Gy is given. In the CESS-86 and EICESS-92 trials, hyperfractionated radiotherapy with a twice-daily dose of 1.6 Gy was also applied; after a total of 22.4 Gy had been given, a 10-day break was scheduled to permit the administration of chemotherapy. There has been no difference in local control rates between the two different fractionation groups.[40]

Target Volume

In terms of volume, previous treatment recommendations were to include the entire bone. The Pediatric Oncology Group (POG) series and other series confirmed that local failures occur generally within the high-dose irradiation volume.[38] In a randomized trial, the treatment of the whole tumor-bearing compartment showed no better results than irradiation to the tumor and an additional safety margin.[41] With reliance on MRI for target volume delineation, margins have been reduced successfully on the most recent COG studies without increase in local failure.[18] Current COG recommendations include all

T1-gadolinium enhancing tumor, all T2 signal abnormality, and all bone abnormalities to be included in the prechemotherapy gross target volume (GTV). Prechemotherapy clinical target volume (CTV) is a 1-cm expansion of this volume. Prechemotherapy GTV and CTV can be modified for pushing, noninfiltrative, borders such as paraspinal tumors pushing into the abdominal cavity or lungs that have receded after induction chemotherapy and can be modified to be restricted to fascial planes if there is no evidence of infiltration. Postchemotherapy GTV includes residual soft-tissue mass after induction chemotherapy as well as all bone abnormality present prechemotherapy. Postchemotherapy CTV is a 1-cm expansion of GTV modified for anatomic pushing borders and limited to fascial planes if there is no evidence of infiltration. Planning target volumes (PTVs) are a 0.5-cm to 1-cm expansion on CTV depending on tumor location and daily image-guidance available at the institution. Surgically contaminated areas, scars, and drainage sites must be included in the radiation fields. Circumferential irradiation of extremities should be avoided to reduce the risk of lymphedema. In growing children, growth plates must be considered. They should either be fully included in the radiation field up to 30 Gy, or they should not be included at all. A dose gradient through the epiphysis results in asymmetric growth and may lead to functional deficits. Similarly, vertebral bodies should either be fully included or spared from the radiation field. Three-dimensional conformal radiotherapy should be given in patients with Ewing's sarcoma. In selected cases (i.e., in vertebral tumors), intensity-modulated radiotherapy (IMRT) or proton therapy may be beneficial. Figures 69-4 to 69-6 show an example of treatment planning.

Irradiation of Lung Metastases

The benefit of lung irradiation in Ewing's sarcoma tumors has been shown in the randomized IESS-I trial.[25] In patients without radiologic evidence of metastases (in the era before CT became available), the best results were observed with

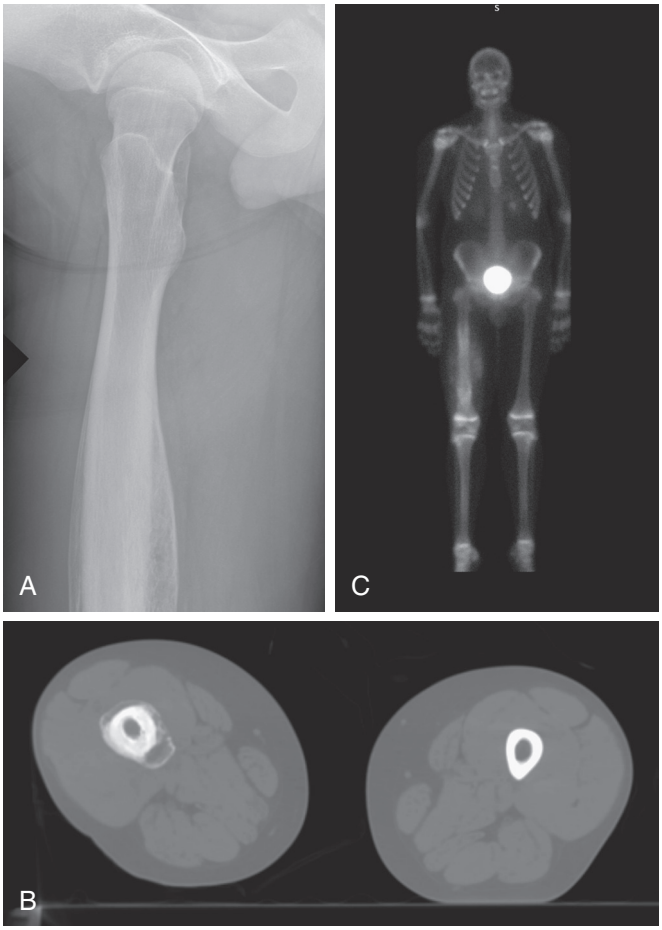

Figure 69-4 **A,** Plain radiograph; **B,** axial CT; and **C,** 99mTc bone scan of Ewing's sarcoma of right femur.

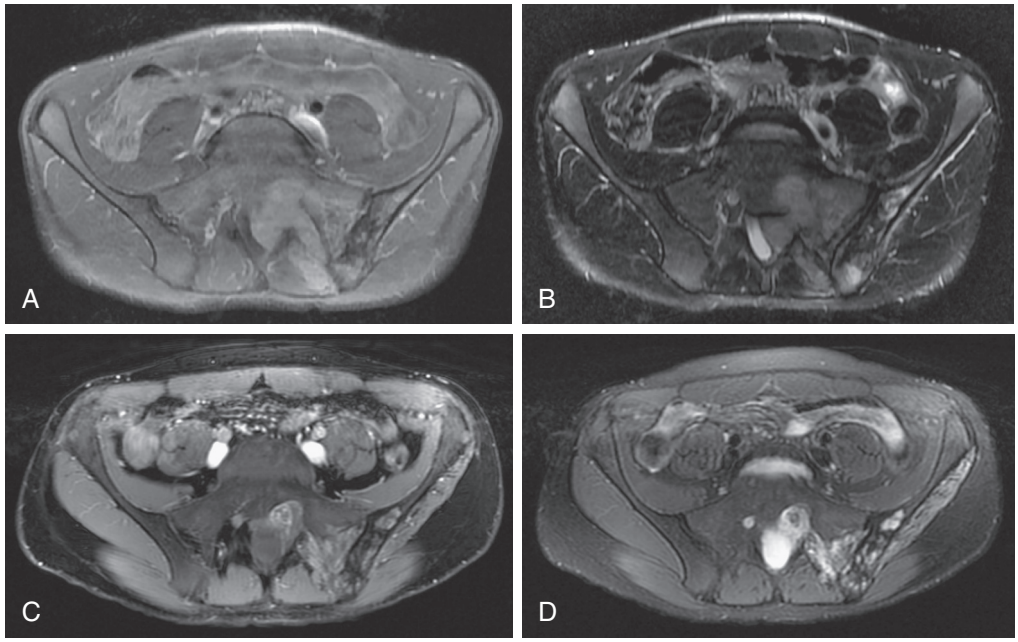

Figure 69-5 **A,** Pretreatment axial contrast-enhanced T1 MRI of a Ewing sarcoma located in the pelvis. **B,** Pretreatment axial T2 MRI of a Ewing's sarcoma located in the pelvis. **C,** Postinduction axial contrast-enhanced T1 MRI of a Ewing's sarcoma located in the pelvis. **D,** Postinduction axial T2 magnetic resonance imaging of a Ewing's sarcoma located in the pelvis.

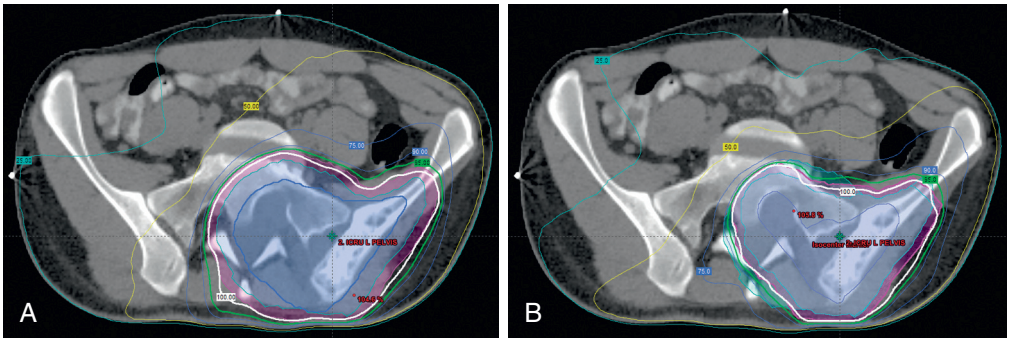

Figure 69-6 **A,** Dose distribution resulting from computed tomography (CT)-based intensity modulated radiotherapy treatment following induction chemotherapy for prechemotherapy planning target volume (PTV) receiving 45 Gy. **B,** Dose distribution resulting from CT-based intensity-modulated radiotherapy treatment following induction chemotherapy for postchemotherapy PTV receiving 10.8 Gy boost.

VACA, although VAC plus lung irradiation was significantly better than VAC alone. In an analysis of the EICESS-92 trial, patients with lung metastases alone showed a trend toward a better outcome with the use of radiotherapy.[42] The recommended dose is 15 Gy to 20 Gy in 1.5-Gy daily fractions. Opposing radiation portals should include both lungs down to the diaphragmatic recess. When possible, breath-hold treatment (treatment in deep inspiration) should be used to help to reduce the volume of irradiated liver, stomach, and upper kidneys. The inferior extent of the lung recesses is not well-seen on conventional or four-dimensional CT. If treatment cannot be performed with breath-hold technique, fluoroscopic evaluation or deep inspiration lateral chest x-ray should be used to define the inferior lung border. Doxorubicin and actinomycin D must not be given during whole-lung radiotherapy because of the increased risk of pneumonitis, and actinomycin D should also be avoided after lung irradiation because of the risk of recall pneumonitis. Lung radiotherapy is therefore best given after completion of conventional chemotherapy. Lung irradiation is not given in the context of a busulfan-containing regimen as a result of risk of significant lung toxicity.

Radiation Therapy of Bone Metastases

Radiotherapy is indicated in patients presenting with bone metastases. In an analysis of metastatic patients treated in the EURO-EWING 99 trial, there was a significant improvement in the 3-year EFS rate in patients who received local therapy to the primary tumor and to all metastatic sites compared with patients who received local therapy to the primary tumor only or no local therapy at all (39% versus 17% versus 14%).[43] In a multivariate analysis that considered patient age, volume of the primary tumor, number of bone metastases, type of therapy (i.e., high-dose chemotherapy and local therapy to the primary tumor or to extrapulmonary metastases), significant factors associated with a poor prognosis were no local therapy to the primary tumor or extrapulmonary metastases and no high-dose chemotherapy. When bone metastases are few, definitive radiotherapy can be given to all initially involved sites. Irradiation of more than 50% of the estimated bone marrow volume can result in significant myelosuppression may interfere with ability to administer the remaining chemotherapy. Therefore, in patients presenting with multiple bone metastases that preclude irradiation of all sites at the time of local therapy, radiotherapy can be either be administered at the end of therapy or may need to be selectively administered to bulky regions, lesions showing slow response to initial therapy (PET residual at the time of local therapy), or lesions with residual PET avidity at the end of therapy. Following high-dose busulfan therapy, two cases of myelopathy have been reported with the application of 50 Gy in conventional fractionation to vertebral sites. In this context, a dose reduction is necessary.

TREATMENT OF OSTEOSARCOMA

Primary Therapy

The overall current recommended approach to treatment of osteosarcoma is surgical resection of the primary tumor either by amputation or a limb-sparing procedure. Local treatment is preceded by neoadjuvant chemotherapy and followed by postoperative chemotherapy. Single-institution studies showed an improvement in OS rates among patients receiving adjuvant chemotherapy compared with historic controls.[20,44,45] Two prospective, randomized studies confirmed this, one at the University of California Los Angeles and one national multiinstitution study.[46,47] Currently, the initial chemotherapeutic agents used include methotrexate, cisplatin, doxorubicin, and ifosfamide. Pathologic response (tumor necrosis greater than 90%) is associated with improved survival in osteosarcoma.[19,20] If the primary tumor shows only minimal response to neoadjuvant chemotherapy, many believe the chemotherapy agents should be altered for the postoperative therapy, but this has not been proven. Currently, between 60% and 70% of patients with localized osteosarcoma are cured.

Because of the radioresistant nature of these tumors, radiotherapy has a limited role in osteosarcoma. Definitive irradiation is used in patients in whom complete surgical resection cannot be obtained as adjuvant therapy for close or positive margins and for palliation in patients with inoperable metastases.

Local Therapy

Surgery is the mainstay of local treatment of osteosarcoma. Surgical resection is performed either by amputation or a limb-sparing approach and has a 5% local failure rate. Although not well studied and rarely used, the addition of radiation therapy in limb-sparing approaches is a possibility and can be considered in special circumstances. Osteosarcoma is usually considered to be a radioresistant tumor. In vitro studies, however, show that it has a radiosensitivity similar to that of other human tumor cell lines.[48] Also, there have been case reports of patients with inoperable or residual tumor treated with radiation doses ranging between 50 Gy and 70 Gy who remained in continuous remission.[49] In an analysis of patients with osteosarcoma refusing surgery but receiving systemic therapy and local irradiation, the local progression-free survival rate at 5 years was 56%.[50] The survival rate was about

90% at 5 years in the subgroup of irradiated patients responding to chemotherapy. DeLaney et al reported on 41 patients with osteosarcoma who received radiotherapy with no surgery or close or positive resection margins. The respective local control rates at 5 years were 40%, 78%, and 78%, respectively.[51] Median dose was 66 Gy although doses as high as 80 Gy were used for gross disease. Because of the often unfavorable site of these tumors, 56% of patients received some or all of their treatment with proton radiotherapy. Recent reports suggest a benefit for heavier particle therapy in unresectable osteosarcoma. In a retrospective review of 78 patients with unresectable axial osteosarcoma treated with carbon ion radiotherapy, local control was 62% at 5 years and 88% for smaller tumors (<500 mL). Treatment was hypofractionated and patients received a median of 70.4 CGE in 16 fractions over 4 weeks. Although surgery is the local treatment of choice, cure can also be achieved with irradiation in inoperable tumors or patients refusing surgery.[52]

Advanced Disease and Palliation

The overall approach to metastatic disease with osteosarcoma is with multiagent chemotherapy. The overall prognosis depends on the location and number of metastases, whether complete surgical resection of all tumor tissue was possible, and the response to chemotherapy.[53,54] Patients with metastasis only in the lung or a limited number of metastases who can undergo complete surgical resection fare better; the 3-year survival rate is approximately 50%, compared with 20% to 30% for more advanced disease.

Radiation therapy to the lungs for metastases, when appropriate, can be given to a dose of 15 Gy to 20 Gy to the whole lung. The use of whole-lung radiation therapy in the setting of metastatic disease is controversial. Whole-lung radiation therapy as prophylaxis against metastatic disease is also controversial and is usually not recommended. Randomized trials of the European Organization for Research and Treatment of Cancer (EORTC) showed that prophylactic whole-lung radiation therapy compared well with chemotherapy.[55] However, no benefit was shown in the U.S. studies.[56]

Radiation therapy may be incorporated into the treatment of osseous metastatic sites not amenable to surgical resection. In an analysis of the prognosis of relapsing patients treated in the Cooperative Osteosarcoma Study Group (COSS) trials, results were best when metastases could be surgically removed. Radiotherapy of inoperable sites, though, was associated with an improved survival rate compared with that of patients who received no local therapy.[57]

The use of samarium-153 (^{153}Sm) ethylenediaminetetramethylene phosphonic acid (^{153}Sm-EDTMP) therapy has been investigated in unresectable osteosarcoma (for the primary tumor and metastases). This therapeutic beta-emitting isotope, which also emits a gamma photon to permit imaging and dosimetry, localizes to osteoblastic lesions with very high tumor to nontumor ratios.[58] Although it is not yet possible to make any definitive statements about the long-term efficacy of this treatment modality, a multimodal concept of high-activity ^{153}Sm-EDTMP in combination with external beam radiation therapy, polychemotherapy, and autologous hematopoietic progenitor cell support for unresectable osteosarcoma seems to be promising.[59,60]

It is therefore reasonable to offer radiation therapy in the treatment of osteosarcoma for (1) unresectable primary tumors or following incomplete resection, (2) patients who refuse surgery, and (3) unresectable metastatic tumors. The recommendation is to treat the tumor to the highest tolerable dose based on the surrounding structures, using a shrinking-field technique.

Treatment Planning Techniques

The treatment planning techniques used for osteosarcoma of the extremities and other sites are similar to those described for the treatment of Ewing's sarcoma.

FUTURE POSSIBILITIES AND CHALLENGES

Future challenges include maintaining a good outcome in patients with localized disease while decreasing treatment toxicity and increasing organ functionality. For patients with metastatic disease and for poor responders, the challenge is to improve the outcome. Pathologic response for patients who undergo surgery appears to be associated with survival outcomes but a reliable prognostic factor for nonsurgical patients is not available as yet. FDG^{18} PET-CT as a predictor of response is being evaluated on the currently open COG AEWS1031. Risk-adapted treatment based primarily on baseline characteristics and pathologic response when available is being evaluated in European studies but because of perceived lack of effective alternative treatment for poor responders has not been adopted in North America. Future possibilities include identifying new active agents based on molecular profiling of tumors and a better understanding of mechanism of oncogenesis.

New radiation therapy approaches to the treatment of pediatric bone sarcomas include the use of smaller margins and more conformal techniques such as intensity-modulation therapy and proton or heavy ion therapy.[51,52] Risk-adapted dose and volume constraints are being evaluated in the currently open COG AEWS1031 study for postoperative patients based on pathologic response. Risk-adapted dose and volume strategies for definitive radiotherapy patients also await validated results with noninvasive imaging such as FDG^{18}-PET.

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