Ewing Sarcoma Family of Tumors

Abstract

The Ewing sarcoma family of tumors (ESFT) consists of a group of tumors characterized by morphologically similar round-cell neoplasm and by the presence of a common chromosomal translocation. Although rare, such tumors constitute the third most frequent primary sarcoma of bone after osteosarcoma and chondrosarcoma. ESFT most commonly affects young children and adolescents. Because most patients with clinically apparent localized disease at diagnosis may also have occult metastatic (ie, systemic) disease, multidrug chemotherapy as well as local disease control with surgery and/or radiation therapy are indicated for all patients. Despite marked improvements in survival during the past 40 years for patients with localized disease, lesser improvements have been seen in patients with metastatic or recurrent disease. A better understanding of the complex biology of ESFT may lead to the successful development of biologically targeted therapies. As the regulatory pathways responsible for transformation, growth, and metastasis of ESFT become more refined, the number of potential therapeutic targets will expand.

Tumors of the Ewing sarcoma family of tumors (ESFT) are characterized by morphologically similar round-cell neoplasms as well as by the presence of common chromosomal translocation. In 1918, Stout described a case of an ulnar nerve tumor composed of undifferentiated round cells that formed rosettes; this lesion was subsequently defined as primitive neuroectodermal tumor (PNET) of soft tissue. In 1921, Ewing reported a case of round-cell tumor in the radius of a 14-year-old girl as a “diffuse endothelioma of bone,” proposing an endothelial derivation (Ewing sarcoma [ES]). Angervall and Enzinger reported the first case of an ES arising in soft tissue. In 1979, Askin et al reported a “malignant small-cell tumor of the thoracopulmonary region” (ie, Askin tumor) with histologic features similar to those in PNET. In 1984, Jaffe et al described a neuroectodermal tumor of bone, calling it a PNET of bone.

Initially, ESFT were believed to be biologically distinct. However, based on their wide spectrum of neural differentiation (PNET being the most differentiated); their immunohistochemical, cytogenetic, and molecular uniformity; and their identical response to Ewing-based chemotherapy regimens, it was determined that these sarcomas are related and that they originate from unique mesenchymal stem cells capable of multilinage differentiation. A common chromosomal translocation that results in EWS-ETS fusion (between the EWS gene on chromosome 22 and an ETS-type gene, most commonly the FLI1 gene on chromosome 11) has been implicated in 80% to 95% of cases of ES, PNET, and Askin tumor. Thus, these le-
sions have been grouped as the same entity, called ESFT. Treatment principles are the same regardless of anatomic location. Herein we have chosen to focus on ES of the bone.

**Epidemiology**

Currently, it is believed that ES most likely can be ascribed to spontaneous genetic translocations rather than to exposure to environmental factors or drugs, mendelian inheritance, disease, or traumatic events.4\(^6\)\(^8\) The incidence of secondary ES after radiotherapy (RT) has been reported to be <3%.9 The histogenesis of these tumors remains unknown, and debate continues regarding the neuroectodermal or mesenchymal lineage.

Although rare, ES is the third most frequent primary sarcoma of bone, after osteosarcoma and chondrosarcoma.10 It is the second most common bone tumor (after osteosarcoma) occurring in children and adolescents, accounting for approximately 3% of all pediatric malignancies and approximately 10% of all primary malignant bone tumors.10,11

ES is reported in all age groups, from infancy to advanced age, but the condition is most commonly diagnosed in persons in the second decade of life.12\(^17\) The annual incidence is low (0.6 per million) in patients aged <5 years but rises in concordance with the arrival of puberty to approach a peak rate of 5 per million.11 The median age of patients with ES is 15 years, and >50% of patients are adolescents. In the European Intergroup Cooperative Ewing’s Sarcoma Study 86 trial, only 10% of cases were diagnosed in patients aged >20 years.18\(^\)\(^20\) Patient age has significance. In patients aged >30 years who present with primary lung disease, small-cell carcinoma should be excluded. In younger patients, alternative diagnoses must be considered, such as lymphoma/leukemia, rhabdomyosarcoma, medulloblastoma, and neuroblastoma. ES is more common in males than in females, with a reported ratio of 1.3 to 1.5:1.12\(^\)\(^17\) Caucasians are much more frequently affected than Asian persons; African and African-American persons rarely suffer from ES.16\(^\)\(^17\)

Esiashvili et al17 searched the Surveillance, Epidemiology, and End Results (SEER) database for information on ES in patients aged 1 through 19 years. Based on data reported from 1973 through 2004, the mean annual incidence of ES is 2.9 cases per 1,000,000 population. Of the 906 patients with ES, 830 were Caucasians and 18 were African American (91.6% versus 2%, respectively). There was a male preponderance (553 patients [61%]), and 212 cases were reported in children aged <10 years (23%).

**Clinical Features**

**Site**

ES occurs most often in bone. Soft-tissue involvement is rare. Almost any bone can be affected, and the sites of origin are roughly split anatomically between the central and peripheral skeleton.3\(^\)\(^15\)\(^\)\(^21\)\(^\)\(^24\) Osteosarcoma typically involves long bones; however, in ES, flat and long bones are nearly equally represented, with pelvic involvement in 23% to 27% of cases.8\(^\)\(^15\)\(^\)\(^\)\(^21\)\(^\)\(^\)\(^24\) Older patients have a higher proportion of pelvic tumors as well as of large tumors. Pathologic fracture may be present in up to 15% of patients.25

**Signs and Symptoms**

The most common presenting symptoms of ES are pain, swelling, and a mass, especially in an extremity.26 The patient with a large pelvic tumor may present with signs of bowel or bladder disturbances in addition to pain. Paraspinal tumors are generally associated with back pain, with or without neurologic impairment. Children with Askin tumor may present with respiratory symptoms, including cough, shortness of breath, and, in some cases, chest pain and pleural effusion.

Patients may also present with systemic signs and symptoms, and approximately 20% to 28% present with a fever.10,26 Laboratory studies are nonspecific but may reveal anemia, leukocytosis, or an increased erythrocyte sedimentation rate. Although the differential diagnosis includes osteomyelitis, distinguishing features usually help avoid delay in the management of either condition. Patients with osteomyelitis often present with systemic illness and usually do not have the large exosaceous solid mass that is common with ES. However, because necrotic tumor can look like purulence, it is vital to culture all suspected tumors and biopsy all sites with suspected osteomyelitis.

Delay between symptom onset and diagnosis is common. In one study, 50% of patients had symptoms for >6 months before the tumor was diagnosed.27 Delayed diagnosis of pelvic tumors is particularly common because a mass in that area is not palpable until it becomes quite large. In another study, 26% of patients with ES related the onset of symptoms to minor injury.28 Thirty-four percent of patients with ES had a palpable mass at initial presentation. The most frequent initial misdiagnoses in older patients with ES were tendinitis (21%) and sciatica (11%) and, in younger patients, coxitis simplex (9%) and osteomyelitis (6%). The mean delay in diagnosis from the first medical visit was 19 weeks (range, 1 to 72 weeks). A high index of suspicion, along with persistent follow-up and early diagnostic imag-
ing, is helpful in obtaining an earlier diagnosis.

Several factors have been associated with metastatic disease: the presence of constitutional symptoms, a shorter interval between the onset of symptoms and diagnosis, pelvic location, older age, larger tumors, and a high level of serum lactic dehydrogenase.29

**Imaging Features**

**Plain Radiography**

Unlike osteosarcoma, which usually originates in the metaphysis, ES of the long bones tends to arise from the diaphysis or metadiaphysis. Of the 206 patients in the Intergroup Ewing’s Sarcoma Study 7299 group, 121 (58.7%) presented with lesions located in the metadiaphysis, 73 (35.4%) with lesions in the diaphysis, 11 (5.3%) with lesions in the metaphysis, and only 1 with a lesion in the epiphysis (0.5%).25

Typically, ES appears as an ill-defined, permeative, mottled, or focally moth-eaten, destructive intramedullary lesion. Periosteal reaction, with a laminated or “onion skin” appearance (a prominent multilayered reaction), is common in ES, but it is not pathognomonic. Periosteal reactions may be seen, such as a sunburst or stipulated pattern (the latter displaying as a perpendicular reaction), as well as the Codman triangle (ie, triangular lifting of the periosteum from the bone at the site of detachment). However, these presentations are less common in ES than in osteosarcoma. An ill-defined soft-tissue mass adjacent to the primary bone lesion is very common in ES. Of the 373 patients in the Intergroup Ewing’s Sarcoma Study 7299, common radiographic findings (present in >30% of evaluated cases) included poor margination (ie, indistinct lesion borders; 96%), soft-tissue component (80.4%), permeative component (76.1%), laminated periosteal reaction (56.6%), and sclerotic component (39.7%).25 The major radiographic differential diagnoses included osteosarcoma, osteomyelitis, and eosinophilic granuloma.

**Advanced Imaging Studies**

Initial plain radiographs, particularly of the pelvis, may appear to be normal, and advanced imaging studies are needed for tumor localization. MRI provides the most precise definition of the local extent of bone tumor, including the degree of expansion into the intramedullary region, extent of soft-tissue involvement, and the relationship of the lesion to adjacent neurovascular structures. MRI may also be used to assess responses to neoadjuvant chemotherapy and irradiation. CT is useful for staging the disease and detecting macrometastasis. As an adjunct to MRI, CT may also be helpful in target planning for radiation. A technetium Tc-99m whole-body bone scan is important in detecting skip or distant metastases; these occur in 10% of patients.10 False-negative bone scans occasionally occur. In conjunction with the aforementioned studies, fluorodeoxyglucose positron emission tomography, thallium-201 scintigraphy, and dynamic MRI also may be used to assess responses after neoadjuvant therapy.30

**Pathology**

Grossly, ESFT presents as a gray-white tumor with a variable amount of necrosis, hemorrhage, or cyst formation. Morphologically, ESFT are composed of sheets of small round cells with a high nuclear-to-cytoplasmic ratio. They are often classified into a group of small, blue, round-cell tumors that include neuroblastoma, alveolar rhabdomyosarcoma, and lymphoblastic lymphoma. The cells typically have scant, weakly eosinophilic cytoplasm that usually contains glycogen (making them positive on periodic acid-Schiff [PAS] stain), diastase degradable granules, and round nuclei with evenly distributed chromatin and little mitotic activity (Figure 1). Tumor histology may range from undifferentiated (ES) to more differentiated (PNET). The PNET type may exhibit neural differentiation under light microscopy (ie, Homer Wright rosettes in >20% of tumor tissue). In addition, neuroen-
Endocrine differentiation can be observed on ultrastructural studies, which visualize the presence of neurosecretory granules.

Immunohistochemical findings are helpful in distinguishing ESFT from other neoplasms. However, they should be interpreted alongside cytogenetic and molecular studies to be most definitive. CD99 is nearly universally expressed at high levels by ESFT cells (95%) (Figure 2), even in the absence of the characteristic 11;22 translocation, but is not specific for this tumor type. Depending on their neural differentiation, ESFT can also express neuron-specific enolase (NSE), S-100 protein, Leu-7 (ie, CD57), and protein gene product 9.5, as well as neurofilaments and synaptophysin. ESFT cells are reactive with antivimentin antibodies and, in fewer than one quarter of cases with anticytokeratin antibodies. In addition, ESFT neoplasms are often PAS-positive, because of the presence of intracellular glycogen, and reticulin-negative. In contrast, lymphomas are PAS-negative and reticulin-positive. Lymphocyte-derived tumors also stain positive for leukocyte common antigen and other T and B cell markers (eg, CD45, TdT, or both). Neuroblastoma cells are NSE-positive and reticulin-negative. Embryonal rhabdomyosarcoma may express CD99, but it also expresses desmin, myoglobin, and muscle-specific actins (eg, MyoD1, myogenin, or both).

Genetic studies, along with histopathology and immunochemistry, are essential for diagnosis. At the genetic level, ESFT is defined by the presence of these EWS-ETS fusion gene arrangements (Table 1). The rearrangements of EWS with FLI1 or FLI1-related genes make up >95% of all ESFT; t(11;22)(q24;q12) translocation, a chromosomal abnormality specific to ESFT, is detected in approximately 80% to 95% of cases. Recently, the EWS gene has been found to be rearranged with still other ETS-like genes in other cancers, such as clear cell sarcoma (ie, melanoma of soft parts [EWS-ATF1]) and desmoplastic small round-cell tumor of the abdomen (EWS-WT1). Fluorescence in situ hybridization has been reported to be a more sensitive and reliable ancillary technique than reverse-transcription polymerase chain reaction for the diagnosis of ESFT in formalin-fixed paraffin-embedded tissue; however, the latter provides additional information regarding fusion transcript subtype and prognosis. These methods are particularly helpful in differentiating synovial sarcoma from ESFT because synovial sarcoma usually harbors a well-characterized t(X;18) translocation. However, one must be careful, because although the occurrence is rare, other tumors (eg, polyphenotypic tumors, rhabdomyosarcomas) have been found to have the EWS-FLI1 transcript.

**Figure 1**

Ewing sarcoma family of tumors present as small round uniform cells with high nucleus-to-cytoplasmic ratio and grow in dense, solid sheets (hematoxylin-eosin, original magnification ×600). (Courtesy of J. Carlos Manivel, MD, and Michelle Dolan, MD, Minneapolis, MN.)

**Figure 2**

Strong immunoreactivity for CD99 is seen in all tumor cells (immunoperoxidase stain, original magnification ×600). (Courtesy of J. Carlos Manivel, MD, and Michelle Dolan, MD, Minneapolis, MN.)

**Table 1**

<table>
<thead>
<tr>
<th>Chromosomal Translocations in Ewing Sarcoma Family of Tumors</th>
<th>Gene Fusion</th>
<th>Incidence (%)</th>
</tr>
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<tbody>
<tr>
<td>t(11;22)(q24;q12)</td>
<td>EWS-FLI1</td>
<td>80-95</td>
</tr>
<tr>
<td>t(21;22)(q22;q12)</td>
<td>EWS-ERG</td>
<td>5-10</td>
</tr>
<tr>
<td>t(7;22)(p22;q12)</td>
<td>EWS-ETV1</td>
<td>Rare</td>
</tr>
<tr>
<td>t(17;22)(q12;q12)</td>
<td>EWS-EIAF</td>
<td>Rare</td>
</tr>
<tr>
<td>t(2;22)(q33;q12)</td>
<td>EWS-FEV</td>
<td>Rare</td>
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It is important to identify the patient at high risk for ESFT and calculate the prognostic stratification because different subgroups may require different treatment strategies.

**Prognosis and Prognostic Risk Factors**

It is important to identify the patient at high risk for ESFT and calculate the prognostic stratification because different subgroups may require different treatment strategies.
ferent treatment intensities. Although the literature differs on the exact impact of individual prognostic factors, clinically evident metastatic disease remains the most important independent prognostic indicator in ESFT. The relative importance of tumor site and size as a prognostic factor is diminishing with the use of modern treatment protocols. Recently, analysis of risk factors has come to include the amount of tumor load (ie, volume, macrometastasis pattern, amount of bone marrow disease by polymerase chain reaction) and the biologic factors (ie, histologic response, gene expression, type of fusion transcript) (Table 2).

**Figure 3**

G-banded karyotype demonstrating a balanced 11;22 translocation (arrows): 46,XX,t(11;22)(q24;q12). (Courtesy of J. Carlos Manivel, MD, and Michelle Dolan, MD, Minneapolis, MN.)

**Treatment**

Most patients with apparently localized disease at diagnosis have subclinical micrometastatic (ie, systemic) disease; thus, systemic therapy using multidrug chemotherapy as well as local disease control via surgery and/or RT is indicated in the treatment of all patients (Figure 4). Regardless of tumor extent, most patients receive four to eight cycles of neoadjuvant chemotherapy. Thereafter, treatment varies based on the eventual resectability of the tumor. With these protocols, event-free survival and overall survival have increased to 65% to 82% at 5 years in patients with localized disease and to 25% to 39% in those with detectable metastatic disease at diagnosis. The corresponding 10-year survival rate has been reported to be 63% for localized disease and 32% for metastatic disease.

**Chemotherapy**

Despite various local control measures, chemotherapy is usually provided both before (ie, neoadjuvant) and after (ie, adjuvant) definitive local control therapy. The clinical trials performed in the past 15 years have been undertaken in an attempt to improve survival by maximizing the chemotherapy dose per cycle, increasing the total number of cycles provided, or decreasing the interval between cycles (“dose-dense” or “dose intensification” therapies) with the addition of granulocyte colony-stimulating factor. In the United States, current standard chemotherapeutic agents used include vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide. The mode of administration and dose intensity within courses differs markedly between protocols. The duration of primary chemotherapy ranges from 6 months to approximately 1 year.

**Local Control**

Currently, treatment is centered on the use of neoadjuvant chemotherapy with the goal of eradicating micrometastases and reducing the size of the primary tumor so as to achieve better tumor demarcation and improve the success of subsequent local control measures. The precise indications for local control in the form of surgical resection and/or RT are controversial. The treatment plan should be individualized based on the stage and resectability of the tumor.

**Surgery**

The role of surgery continues to evolve in the treatment of patients with ESFT. Careful patient selection has led to local failure rates of <10%, although bias exists, in that smaller, more peripheral tumors tend to be selected for definitive surgical management and larger, more central tumors are managed with surgery and/or RT. The risk of secondary malignancy and the potential for growth retardation may be important considerations in the decision to select surgical treatment rather than RT. Surgery affords local control and may prevent late recurrence of chemoresistant cells. Another potential benefit with surgical resection of the primary tumor is in the opportunity to gather information concerning the amount of necrosis in the resected tumor. Patients with residual
viable tumor in the resected specimen have a worse outcome than patients with complete necrosis. In the third study of the French Society of Paediatric Oncology (EW88), event-free survival at 5 years for patients with <5% viable tumor, 5% to 30% viable tumor, and >30% viable tumor was 75%, 48%, and 20%, respectively.26

When surgery is selected, complete resection is required because there is a strong correlation between a positive surgical margin and local recurrence.20,22 Patients who are treated with adequate margins (ie, wide, radical) have been shown to have better 5-year event-free survival than those with inadequate margins (ie, intralesional, marginal) (58.2% versus 46.7%, respectively).22 Overall survival is also better with adequate margins than with inadequate ones (60.2% versus 40.1%). When positive margins are found, a repeat resection should be done, when possible. Although the addition of RT has also been recommended when resection margins are microscopically positive after an attempted wide excision, planned intralesional debulking procedures followed by RT do not improve local control rates and should be avoided.20,41

Limb salvage is now possible in most patients and should be performed in cases in which survival rates are anticipated to be the same regardless whether amputation is performed and in cases in which the salvaged limb is expected to provide satisfactory function with an accept-

<table>
<thead>
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<th>Table 2</th>
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| **Prognostic Factors for Ewing Sarcoma Family of Tumors**

<table>
<thead>
<tr>
<th>Pretreatment Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Ewing sarcoma family of tumors (ESFT) located in the distal extremities has the best prognosis, followed by the proximal extremities and then by central or pelvic sites. Cutaneous and subcutaneous lesions tend to have an indolent course associated with good outcome.</td>
</tr>
<tr>
<td><strong>Tumor size and volume</strong></td>
<td>Tumor size (&gt;8 cm) and volume (&gt;100-200 mL) are adverse prognostic factors. Larger tumors tend to occur in unfavorable sites (eg, pelvis).</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Patients aged ≤14 years have the best prognosis of any age group.</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Females have a better prognosis than males.</td>
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<tr>
<td><strong>Laboratory parameters</strong></td>
<td>Increased serum lactate dehydrogenase levels (LDH &gt;200 IU/L) pretreatment are associated with inferior prognosis. However, increased LDH levels are correlated with large primary tumors and metastatic disease. Anemia as well as elevated white blood cell counts and erythrocyte sedimentation rate (with constitutional symptoms) may indicate extensive disease and poorer prognosis.</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>Any metastatic disease is an adverse prognostic factor. Patients with metastatic disease confined to the lung have a better prognosis than do patients with extrapulmonary metastases (eg, bone, bone marrow). A skip metastasis in the same bone has a better clinical outcome than does metastasis to another site.</td>
</tr>
<tr>
<td><strong>Time to relapse</strong></td>
<td>The 5-year survival rate is considerably worse in patients who experience recurrence within 2 years of diagnosis.</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>Degree of neural differentiation has not been found to be a prognostic factor.</td>
</tr>
<tr>
<td><strong>Molecular pathology</strong></td>
<td>The EWS-FLI1 translocation associated with ESFT can occur at several potential breakpoints in each of the genes that join to form the novel segment of DNA. Some variants of the novel gene created by the translocation (type 1, EWS exon 7 fused to FLI1 exon 6) have been associated with a more favorable prognosis than other EWS-FLI1 fusion types independent of tumor size and location. Overexpression of tumor-suppressor gene p53, cell proliferation nuclear antigen Ki-67, and proto-oncogene HER-2/neu are associated with poor prognosis in some tumors. The prognosis is better when &lt;20% of cells express p53. Loss of 16q and increased telomerase activity may carry an adverse prognostic significance. In a recent study, the presence of p16(INK4a) alteration was a statistically significant predictor of prognosis for patients with Ewing sarcoma; however, its definite role remains to be determined.</td>
</tr>
<tr>
<td><strong>Detectable fusion transcripts in morphologically normal bone marrow</strong></td>
<td>Reverse-transcription-polymerase chain reaction can be used to detect fusion transcripts in bone marrow. In a single retrospective study of patients with normal marrow morphology and no other metastatic site, fusion transcript detection in marrow was associated with an increased risk of relapse.52</td>
</tr>
<tr>
<td><strong>Treatment response factors</strong></td>
<td>Patients with minimal or no residual viable tumor after preoperative chemotherapy (radiologic and/or pathologic) have significantly better event-free survival compared with patients with larger amounts of viable tumor. Contrary to the classic prognostic factors, treatment intensification may not have a major impact on patients with a favorable histologic response, likely because biologic factors influence the response to treatment. Decreased positron emission tomography uptake following chemotherapy was correlated with good histologic response in patients who received pre- and postinduction chemotherapy.53</td>
</tr>
</tbody>
</table>
Figure 4

Treatment algorithm for Ewing sarcoma family of tumors.  

* Consider dose-dense therapy for children (q 2 weeks)
IGFR-1 = insulin-like growth factor-1, LDH = lactate dehydrogenase, PET = positron emission tomography
Pathologic fracture may not preclude surgical resection and is not necessarily associated with an adverse outcome. Conditions for which amputation is likely include extremely large tumors involving vital structures, an unmanageable or displaced pathologic fracture, and a lesion in the ankle or foot. Overall survival rates are similar whether amputation or limb salvage is performed; in general, functional outcomes and patient acceptance are better with limb salvage than with amputation, although complications are more common with limb salvage.

Many reconstruction options are available, including vascularized and nonvascularized autograft reconstruction (eg, fibula, scapula, iliac crest, rib, clavicle), allograft reconstruction, allograft-prosthetic composites, and endoprosthetic reconstruction, including expandable prosthesis, rotationplasty, and amputation. The technique selected should be tailored to each individual patient (Figures 5 and 6). Because it is usually more durable than prostheses, biologic reconstruction is preferable in younger patients. The use of allograft-prosthetic composites and endoprostheses is expected to increase with continued improvement in bioengineering and metallurgy.

Radiotherapy
RT traditionally has been used for local disease control in patients with ESFT. Radiation for local control is recommended for unresectable tumors and when there is a low likelihood that adequate surgical margins can be achieved. RT may also

A 27-year-old woman presented with pain and an enlarging mass in her right groin region. A, AP radiograph demonstrating a large soft-tissue shadow in the right lower pelvis with marked destruction of the superior and inferior pubic rami. B, Coronal MRI (TR 5220, TE 44) confirming the presence of a 14.6 × 12.1 × 11.0-cm heterogeneous mass with osseous destruction of the entire right superior and inferior pubic rami with involvement of the ischium and extension into the true pelvis and the adductor compartment. C, Coronal F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) CT scan showing the hypermetabolic mass with a standard uptake value of 8.8. Biopsy confirmed the diagnosis of Ewing sarcoma, and the patient underwent four cycles of neoadjuvant chemotherapy. D, Coronal MRI (TR 5910, TE 38) study demonstrating a substantial reduction in tumor volume. E, Coronal F-18 FDG-PET CT scan demonstrating minimal hypermetabolic activity. F, AP radiograph following wide local excision of the tumor and reconstruction using an allograft-prosthetic composite. The patient was disease-free at 30-month follow-up, after completing adjuvant chemotherapy.
have a role in improving local disease control in patients with poor chemotherapeutic response. The recommended doses in various clinical situations have been recently summarized in a retrospective review of large-group experiences. The irradiation treatment field should include the pretreatment tumor volume plus an adequate margin. A coned-down boost is then administered to the postinduction chemotherapy volume, also with an adequate margin. Most local treatment failures following RT alone are within the radiated field; thus, a 2- to 3-cm margin beyond the affected area is usually considered adequate. The dose for local control using radiation alone is 55.8 to 60.0 Gy. Typically, 45 Gy is administered, followed by a boost of 10.8 Gy. No adjuvant radiation is necessary in the setting of adequate margins and a good histologic response to prior chemotherapy. No difference has been found in overall survival regardless whether standard whole-bone radiation or RT of the involved field only is performed. Similarly, standard fractionation (180 to 200 cGy/d, 5 days a week) is as effective as hyperfractionation (120 to 160 cGy twice daily); however, hyperfractionation has been reported to cause less late toxicity.

With the increase in long-term survival rates as a result of modern chemotherapy, the problems of late local recurrence, functional impairment secondary to radiation complications, and radiation-induced sarcomas have become more apparent. Radiation-related complications have been reported in up to 63% of patients and are most pronounced in skeletally immature patients. These complications include limb-length discrepancy, joint contracture, muscle atrophy, pathologic fracture, and secondary malignancies.

Surgery Versus Radiotherapy

Traditionally, ES has been treated with chemotherapy and radiation, with resection reserved for expendable bones. Advancements in imaging technology and technique have led to better planning for both resection and adjuvant radiation.
and RT. Many protocols have demonstrated superior local control and survival with surgery with or without RT compared with RT alone (5% to 10% versus 35% local recurrence). One possible explanation for the increased survival rate is that tumor resection eliminates residual clones of chemotherapy-resistant cells before they have a chance to recur locally or to metastasize. Selection bias for performing surgery on smaller and more surgically resectable tumors may explain these more favorable results. Conversely, other studies of modern chemotherapy protocols have noted no difference in survival or local failure on treatment protocol, radiation dose, or surgery.

Thus, the question whether to perform surgery or RT for local control cannot be answered with confidence. Only level III and IV evidence is available, and there is known selection bias in that resectable lesions tend to be operated on. A level I randomized trial comparing the two treatments is not feasible practically; thus, a level II individual comparative study will likely be the only and best evidence possible to answer this question. The trends, however, favor surgical resection in all cases in which the surgeon believes that the primary tumor can be removed completely, particularly in expendable or surgically reconstructible sites. RT is still used for tumors in anatomic sites in which wide resection cannot be done, when the functional deficit is unacceptable to the patient, when an attempted resection has unacceptable margins, and when the chemotherapeutic response has been poor.

High-dose Chemotherapy With Stem Cell Rescue

High-dose chemotherapy with hematopoietic stem cell transplant (HSCT) has been developed to treat patients at high risk of relapse following conventional treatment. However, the results with this therapy are difficult to evaluate in the absence of large randomized trials with heterogeneous patient groups. In one recent study, 33 patients with recurrent or progressive ES were treated with high-dose chemotherapy and HSCT with and without total-body irradiation. The 2- and 5-year event-free survival rates were 42.5% and 38.2%, respectively. In another study, Meyers et al reported 2-year event-free survival to be 20% and concluded that consolidation with total-body irradiation and high-dose chemotherapy with HSCT did not significantly improve survival in patients with ES metastasized to bone and bone marrow. Results are often superior for patients with isolated lung metastases than in those with bone and bone marrow disease and those with lung, bone, and bone marrow disease. Relapse and regimen-related toxicity remain the main obstacles to success.

Metastatic Ewing Sarcoma

ES has a strong potential to metastasize. In the SEER study, 26% to 28% of patients presented with distant macrometastasis. More than 10% of patients present with multiple bone metastases at initial diagnosis. Although metastases in the lungs, bone, bone marrow, or a combination thereof are detectable in approximately 25% of patients, metastases to lymph nodes, the liver, and the brain are rare. Despite advances in the treatment of localized ES, the prognosis for patients with detectable metastatic disease remains poorer than apparently localized disease. Standard chemotherapy combined with adequate local control measures applied to primary and metastatic sites may result in complete or partial responses; however, the 8-year event-free survival is approximately 20%, and the overall cure rate is 14% to 28%. A cure rate of 32% was reported for patients with lung/pleural metastases only. A worse outcome was reported without lung radiation than with it. Patients with only bone/bone marrow metastases were reported to have an approximate 20% to 25% cure rate. Patients with combined lung and bone/bone marrow metastases had a cure rate of <15%.

RT to the primary tumor as well as to the sites of metastatic disease should be considered; however, this modality may interfere with delivery of chemotherapy if too much bone marrow is included in the field. All patients with pulmonary metastases should undergo whole-lung radiation, even when complete resolution of overt pulmonary metastatic disease has been achieved with chemotherapy. Radiation doses are modulated based on the amount of lung to be radiated and on pulmonary function. Doses between 12 and 15 Gy are generally used when the whole lung is treated.

More intensive therapies, many of which incorporate high-dose chemotherapy with or without total-body irradiation in conjunction with stem cell support, have not been found to demonstrate consistent improvement in event-free survival for patients with recurrent or metastatic disease.

Recurrent Ewing Sarcoma

The prognosis for patients with recurrent or progressive ES is poor; 5-year event-free survival and overall survival following recurrence often are <10%. Patients with both local and distant recurrence have a worse outcome than do those with either local or distant recurrence. Most relapses occur within 5 years of diagnosis, with 10% to 15% oc-
Ewing Sarcoma Family of Tumors

Second Malignant Neoplasms

Patients treated for ES show a trend toward a higher risk of developing second malignancies than do persons in the general population. Treatment-related acute myeloid leukemia and myelodysplastic syndrome have been reported to occur in 1% to 2% of survivors of ES, and some dose-intensive regimens appear to be associated with a higher risk of hematologic malignancy.²⁻⁶,²⁻⁹ Treatment-related acute myeloid leukemia and myelodysplastic syndrome arise most commonly at 2 to 5 years following diagnosis. The risk of developing solid tumors appears to be greatest in patients treated with RT, and sarcomas usually occur within the prior radiation field.²⁰,²² The cumulative risk of developing a bone sarcoma following treatment for ES is estimated to be 20% at 20 years.⁹ Of the 397 patients with ES treated at the Mayo Clinic during a 25-year period, 26 (6.5%) developed second malignancies: 12 sarcomas, 8 hematologic malignancies, and 9 carcinomas.⁷² The authors attributed sarcoma to RT and hematologic malignancy to chemotherapy. The mean latent period for the development of sarcoma was 10.9 years (range, 1.5 to 32.5 years) and for hematologic malignancy, 4.8 years (range, 1.7 to 12.9 years). The prognosis with carcinoma was better than with either sarcoma or hematologic malignancy. A similar prevalence has been reported by Kuttesch et al,⁷⁰ who found a 6.5% incidence of secondary sarcoma within the irradiated field in ES patients at 20-year follow-up. The incidence was dose-dependent; patients who received ≥60 Gy had a 20% incidence of second malignancy. Those who received a dose of 48 to 60 Gy had an incidence of 5%, and those who received a dose of <48 Gy did not develop a second malignancy.

Summary

ESFT is a rare malignancy of unknown origin that most often affects young children and adolescents. Because most patients with apparently localized disease at diagnosis have occult metastatic (systemic) disease, multidrug chemotherapy as well as local disease control with surgery and/or RT is currently indicated for all patients. Despite marked improvement in survival during the past 40 years for patients with localized disease, improvements have been relatively lesser in patients with metastatic or recurrent disease. The treatment plan must be individualized on the basis of tumor location, stage, and size. An improved understanding of the complex biology of...
ESFT may lead to the successful development of biologically targeted therapies. As our understanding of the regulatory pathway responsible for ESFT transformation, growth, and metastasis becomes more refined, the number of potential therapeutic targets will expand in parallel.

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References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 22 and 60 are level I studies. Level II studies include references 7, 12, 14-19, 23-25, 27, 29, 31-33, 38, 43, 44, 46, 48, 61, 66, and 68-74. Level III studies include references 9, 13, 34-46, 48, 61, 66, and 68-74. Level IV studies include references 5, 8, 10, 11, 21, 30, 45, 49, 50, 53, 59, and 67.

Citation numbers printed in bold type indicate references published within the past 5 years.

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