Pediatric Sarcomas

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KEYWORDS

- Rhabdomyosarcoma • Osteosarcoma • Ewing's sarcoma
- Nonrhabdomyosarcoma soft tissue sarcoma

KEY POINTS

- Pediatric sarcomas are best treated with a multidisciplinary team to include surgery, radiation, and oncology.
- Rhabdomyosarcomas (RMS) often occur in young children, whereas nonrhabdomyosarcomas occur in infants and teenagers.
- All patients with RMS receive chemotherapy.
- Low-grade osteosarcomas and low risk nonrhabdomyosarcomas are treated with surgery alone.

Pediatric sarcomas are a heterogeneous group of tumors and account for approximately 10% of childhood solid tumors.[1] Treatment is focused on multimodality therapy, which has improved the prognosis over the past 2 decades. Current regimens focus on decreasing treatment for low-risk patients to decrease the long-term side effects of chemotherapy and radiation while maximizing therapy for patients with metastatic disease in an attempt to improve survival. Pediatric sarcomas can be divided into soft tissue sarcomas and osseous tumors. Soft tissue sarcomas are further delineated into rhabdomyosarcoma (RMS), which affect young children and nonrhabdomyosarcoma, which are most common in adolescents. The most common bone sarcomas are osteosarcoma (OS) and Ewing sarcoma (ES).

RHABDOMYOSARCOMA

Epidemiology

RMS is the most common soft tissue sarcoma in children and adolescents, accounting for nearly 250 cases of childhood cancer in the United States each year.[2] RMS is a

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malignant soft tissue tumor of mesenchymal origin, accounting for approximately 3.5% of cancers among children aged 0 to 14 years and 2% of the cases among adolescents aged 15 to 19 years.[3] The incidence of RMS is 4.5 per million children, with one-half of cases seen in the first decade of life.[4] During the course of 4 consecutive Intergroup Rhabdomyosarcoma Study Group clinical trials, our understanding of RMS tumor biology has advanced, and the outcome for children and adolescents with RMS has improved significantly.[5–8] Five-year survival for RMS has increased, from 53% to 67% for children younger than 15 years and from 30% to 51% for adolescents aged 15 to 19 years.[9]

The incidence of RMS varies depending on histologic subtype.[2] Embryonal RMS patients are predominantly male (male = 1.5 × female), with a peak incidence in the 0- to 4-year age group (approximately 4 cases per million). Adolescents have a lower incidence, with approximately 1.5 cases per million. The incidence of alveolar RMS is relatively constant through childhood (1 case per million) and does not show a gender predilection.[9] Undifferentiated sarcoma is more common in infants less than 1 year of age, with increased numbers found in the trunk and abdomen and fewer in the parameningeal site as compared with noninfants.[10]

The most common primary tumor sites for RMS are the head, the genitourinary (GU) tract, and the extremities.[11] Extremity tumors are more commonly found in the hand and foot of older patients, and are more likely to display alveolar histology and metastatic spread.[12] Less frequently seen primary tumor sites include the trunk, chest wall, perineal/anal region, and abdomen (including retroperitoneum and biliary tract).

The majority of RMS cases are sporadic, with no identifiable risk factors.[2] Embryonal RMS is associated with high birth weight and infants that are large for gestational age.[13] The Li-Fraumeni syndrome (germline *p53* mutations),[14] pleuropulmonary blastoma (*DICER1* mutations),[15] neurofibromatosis type I,[16] Costello syndrome (germline *HRAS* mutations),[17,18] Beckwith-Wiedemann syndrome,[19] and Noonan syndrome are all associated with RMS.[20]

Prognosis

The prognosis for children with RMS depends on age, primary tumor site, tumor size, resectability, presence or absence of metastases, number of metastatic sites, presence or absence of regional lymph node involvement, histopathologic subtype (alveolar vs embryonal), and, in some cases, delivery of radiation therapy.[5–8,11,21,22]

In children with localized disease who receive combined-modality therapy, there is greater than 70% survival at 3 years.[8] Relapses are uncommon after this point, with a less than 10% late event rate through 10 years. However, children with gross residual disease in unfavorable sites after initial surgery and those who have metastatic disease at diagnosis are more likely to experience relapse.[23]

Patient- and tumor-specific factors with prognostic implications include the following:

- Age: Children aged 1 to 9 years have improved prognosis, whereas those less than 1 year and greater than 9 years have worse prognosis (5-year survival is 76% for patients <1 year, 87% for patients 1–9 years, and 76% for patients >10 years).[10] It is unclear if infants have poorer outcomes because of disease-specific factors or owing to adjustments that are made to therapy owing to their small size (eg, less chemotherapy because of intolerant bone marrow, less use of radiation therapy).[8,24] Additionally, adolescent patients seem to present with unfavorable tumor-specific factors, such as alveolar histology, regional lymph node involvement, and metastatic disease.[25] Finally, 5-year survival rates for adults are markedly worse than those for children.[26]

- Primary tumor site: Sites with favorable prognosis include the orbit and nonparameningeal head and neck, paratesticular, vulva, vagina, uterus (nonbladder, nonprostate GU tract), and biliary tract.[5,7]
- Tumor size: Smaller tumors ($\leq$5 cm) have improved survival; however, it is unclear if this relationship is true across all ages, because tumor volume versus body surface area may be of importance.[7]
- Metastatic disease: Children who present with metastatic disease have a worse prognosis and outcome, although this varies by primary tumor histology and site/number of metastases.[27] Additionally, regional lymph node involvement portends a worse prognosis.[28]
- Tumor resectability: The extent of remaining disease after the primary surgical resection correlates with outcome. In the Intergroup Rhabdomyosarcoma Study III (IRS-III) study, patients without residual tumor after surgery (group I) experienced greater than 90% survival at 5 years, those with microscopic disease (group II) had approximately 80% survival at 5 years, and those with gross residual disease (localized, group III) had approximately 70% survival at 5 years.[7]
- Tumor histology: Alveolar histology is associated with a worse outcome than embryonal histology. Alveolar histology is more common amongst patients with other unfavorable features, including age less than 1 year, age greater than 10 years, extremity primary tumor site, and metastatic disease. Alveolar histology has been associated with a less favorable outcome even in patients whose primary tumor was completely resected.[5] In the IRS-III study, the outcome for patients with completely resected alveolar tumors was similar to that for other group I tumors, but patients with alveolar histology received more intensive therapy.[7]

Classification

RMS is divided into 3 histologic subtypes: embryonal, alveolar, and pleomorphic. Embryonal RMS has embryonal, botryoid, and spindle cell subtypes.[2] Additionally, embryonal and alveolar histologies have distinct molecular profiles that are used in diagnosis and treatment planning.[29–31]

Embryonal RMS is the most frequently observed subtype in children, accounting for approximately 60% to 70% of cases.[2] These tumors may occur in any location, although the typically arise in the head and neck region or in the GU tract. Embryonal tumors often show loss of heterozygosity at 11p15 and gains on chromosome 8. One-third of cases show mutations of genes in the RAS signaling pathway (*NRAS*, *KRAS*, *HRAS*, and *NF1*). Less frequently observed mutations include *FGFR4*, *PIK3CA*, *CTNNB1*, *FBXW7*, and *BCOR*.[18,32]

Botryoid tumors are embryonal tumors that arise under the mucosal surface of body orifices such as the vagina, bladder, nasopharynx, and biliary tract, accounting for approximately 10% of all RMS cases. The spindle cell variant of embryonal RMS is most frequently observed at the paratesticular site.[2] Botryoid and spindle cell subtypes are associated with very favorable outcomes.[2]

Alveolar RMS accounts for approximately 20% of pediatric cases, with a higher frequency seen in children greater than 10 years and in extremities, trunk, and perineum/perianal primary sites.[2] To be designated as alveolar, the tumor must have greater than 50% alveolar elements. The majority (approximately 75%) of alveolar tumors carry a *PAX-FOXO1* fusion between the *FOXO1* gene (chromosome 13) and either *PAX3* (chromosome 2, approximately 60%) (t(2;13) (q35;q14)) or *PAX7* (chromosome 1, approximately 20%) (t(1;13) (p36;q14)).[33] Less frequently, other fusions involving

PAX3 are seen. Cases associated with the *PAX7* fusion tend to occur in younger patients and may be associated with longer event-free survival versus *PAX3* fusions.[18,33]

Pleomorphic RMS occurs predominantly in adults over age 30 and is rarely seen in children.[26] In children, these tumors are referred to as anaplastic and may not carry a worse prognosis.[34]

Staging and Risk Stratification

Once the diagnosis of RMS is established, evaluation then focuses on determining the extent of disease for treatment planning. Evaluation includes chest radiography, computed tomography (CT) scan of the chest, bilateral bone marrow aspirates and biopsies, and bone scan. For lower extremity or GU tract tumors, a CT scan of the abdomen and pelvis is included. For parameningeal tumors, MRI of the base of the skull and brain and lumbar puncture are included. In general, cross-sectional imaging (CT or MRI) of regional lymph node basins should be considered and concerning lymph nodes biopsied. Two modalities that are under investigation for metastatic evaluation include sentinel lymph node biopsy and fluorodeoxyglucose-PET imaging.[35,36]

Tumors are segregated into those occurring in favorable sites (orbit, nonparameningeal head/neck, GU tract other than bladder/prostate, biliary tract) versus unfavorable sites (all others). After this, TNM (tumor/node/metastasis) classification is determined (**Table 1**). Together, these determine the pretreatment tumor stage (**Table 2**). Next, the surgical–pathologic group is assigned based on surgical findings (**Table 3**). Finally, these factors are combined with histology to determine the risk group (**Table 4**), which determines treatment.

Treatment

Multimodality therapy, consisting of systemic chemotherapy and either surgery or radiation therapy (or both) for local control, is employed in all children with RMS.[37]

Surgical resection consists of wide and complete resection of the primary tumor with a surrounding envelope of normal tissue.[38] This is performed at diagnosis (prechemotherapy), unless it involves sacrifice of normal tissue that either cannot be resected or would result in an unacceptable loss of function, or is not technically feasible.

Table 1
TNM staging of RMS

Tumor (T)	Definition
T1a	Confined to anatomic site of origin, ≤5 cm diameter
T1b	Confined to anatomic site of origin, >5 cm diameter
T2a	Extension or fixation to surrounding tissue, ≤5 cm diameter
T2b	Extension or fixation to surrounding tissue, >5 cm diameter
Nodal Status (N)	**Definition**
N0	No clinical regional lymph node involvement
N1	Clinical regional lymph node involvement
Nx	Unknown
Metastasis (M)	**Definition**
M0	No metastatic disease
M1	Metastatic disease

From National Institutes of Health. National Cancer Institute Physician Data Query. Available at: http://www.cancer.gov/publications/pdq.

Table 2
Pretreatment tumor stage of rhabdomyosarcoma

Stage	Primary Site	T	Tumor Size	N	M
1	Favorable	T1 or T2	Any	Any	M0
2	Unfavorable	T1 or T2	a	N0 or Nx	M0
3	Unfavorable	T1 or T2	a	N1	M0
			b	Any	
4	Any	T1 or T2	Any	Any	M1

From National Institutes of Health. National Cancer Institute Physician Data Query. Available at: http://www.cancer.gov/publications/pdq.

Exceptions to the operative approach include primaries in the orbit and possibly some GU sites. Resection of RMS that arises from muscle (particularly in the extremities) does not require excision of the entire muscle of origin or the entire compartment. However, adequate margins of normal tissue are preferable to leaving gross or microscopic tumor. Reexcision for positive margins may limit adjuvant therapy and decrease long-term side effects from therapy. Surgical guidelines vary by specific primary sites (eg, head/neck, extremity, trunk, GU) and are beyond the scope of this review.[39]

In the majority of cases, upfront surgical resection is not feasible, and a biopsy is performed. The majority of patients have group III (gross residual) disease and receive definitive radiation therapy for control of the primary tumor after chemotherapy. Selected patients may undergo delayed primary excision to remove residual tumor if the delayed excision is deemed feasible with acceptable functional/cosmetic outcome and if a dose reduction in radiation therapy is expected to reduce significantly the risk of long-term adverse effects. Radiation therapy is given to clinically or radiologically suspicious lymph nodes unless the suspicious lymph nodes are biopsied and shown to be histologically tumor free. Retroperitoneal lymph node dissection is limited to children greater than 10 years of age with paratesticular RMS owing to the high rate of lymph node involvement and decreased survival when these patients are understaged.[40]

The intensity and duration of chemotherapy for RMS is dependent on Risk Group (see **Table 4**). Currently, low-risk patients are treated with triple drug chemotherapy consisting of vincristine, dactinomycin, and low-dose cyclophosphamide. Intermediate risk patients receive similar therapy with higher doses of cyclophosphamide,

Table 3
Surgical–Pathological Group of rhabdomyosarcoma

Group	Definition
I	Localized disease, completely resected, no lymph node involvement
II	Total gross resection with evidence of regional spread: grossly resected tumor with microscopic residual disease; regional disease with involved nodes, completely resected with no microscopic residual; regional disease with involved nodes, grossly resected but with evidence of microscopic residual disease or histologic involvement of most distal lymph node from the primary site
III	Incomplete resection with gross residual disease: localized tumor, incompletely removed with gross residual disease (biopsy of primary tumor only or resection of primary tumor >50%)
IV	Distant metastasis at diagnosis

From National Institutes of Health. National Cancer Institute Physician Data Query. Available at: http://www.cancer.gov/publications/pdq.

Table 4
Risk group classification of rhabdomyosarcoma

Risk Group	Stage	Group	Histology
Low	1	I, II, III	Embryonal
	2, 3	I, II	Embryonal
Intermediate	2, 3	III	Embryonal
	1, 2, 3	I, II, III	Alveolar
High	4	IV	Any

with additional agents (additional courses) being tested for efficacy in prolonging event-free and overall survival. High-risk patients also receive vincristine, dactinomycin, and low-dose cyclophosphamide therapy plus irinotecan, etoposide, and doxorubicin, with studies to date failing to demonstrate increased efficacy with additional or alternative agents. Biologic agents are currently being studied in high-risk patients.

Summary

RMS is the most common soft tissue sarcoma in children. Before the use of multimodal therapy including surgery, chemotherapy, and radiotherapy, fewer than one-third of children with RMS survived. The use of intensive combination chemotherapy, better staging, more effective local therapy with surgery and radiation, and improved supportive care have resulted in marked advances. Currently, more than 70% of children with localized RMS and more than 50% of selected children with metastatic disease (those who are younger than 10 years and have embryonal histology) can be cured of their disease. After completion of therapy, patients should have radiographic imaging every 3 months looking for recurrence. Imaging is spread out over time with follow-up imaging ending 5 years after completion of therapy. The diversity of primary tumor sites, the unique surgical and radiation therapy considerations for these primary sites, and the need for ongoing trials to improve outcomes, particularly intermediate- and high-risk disease, underscore the importance of treating children with RMS in medical centers with appropriate experience in all diagnostic and therapeutic modalities.

NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMAS

Epidemiology

Nonrhabodmyosarcoma soft tissue sarcomas (NRSTS) are a heterogeneous group of tumors that are most common in adolescents and young adults. They comprise 60% of soft tissue sarcomas over all ages in the Surveillance, Epidemiology and End Results database from 1975 to 2012.[41] The most common subtypes only account for 10% of pediatric soft tissue sarcomas. A small proportion occur in infants such as infantile fibrosarcoma (**Fig. 1**), hemangiopericytoma, and malignant rhabdoid tumors.

Most NRSTS are owing to sporadic mutations but a few can be associated with genetic syndromes, such as Li–Fraumeni syndrome, hereditary retinoblastoma, neurofibromatosis type 1, Gorlin syndrome, and Werner syndrome.[42]

Histology

NRSTS derive from cells similar to mesenchymal cells (fibroblasts, smooth muscle cells and perineural cells). They are classified into 4 groups by the International Classification of Childhood Cancers: (1) fibrosarcomas, (2) Kaposi's sarcoma, (3) the "other specified" soft tissue sarcomas (synovial sarcoma, angiosarcoma, hemangiopericytoma, leiomyosarcoma, liposarcoma, and extraosseous Ewing sarcoma [ES]), and

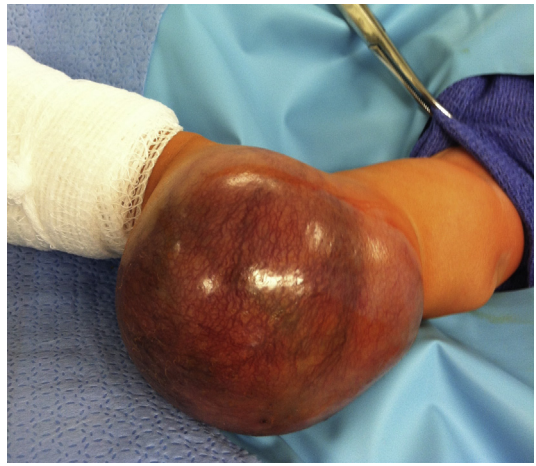

Fig. 1. Infantile fibrosarcoma in a 4-month-old boy.

(4) unspecified soft tissue sarcomas.[41] These classifications have no bearing on treatment and prognosis, which is mostly based on risk assessment. Most have characteristic chromosomal translocations that aid in diagnosis (**Table 5**).

Grading of tumors is based on adult systems, the National Cancer Institute-based Pediatric Oncology group system and the Federation Nationale des Centers de lute Contre le Cancer system. Both systems have been shown to predict prognosis in children.[43]

Prognostic Factors

Several studies have demonstrated common themes with regard to prognosis of patients with NRSTS: extent of disease (local vs metastatic), extent of tumor resection (resectable vs unresectable), maximal tumor diameter (<5 vs >5 cm), and tumor grade (low vs high).[44–46] Using these factors, 3 distinct risk groups were proposed (**Table 6**):

- Low risk
  - Patients with grossly resected nonmetastatic tumors except those patients with high grade and greater than 5 cm in maximal diameter tumors.
  - A 5-year survival estimate of 90%.
  - Comprise about 50% of the population of NRSTS.

Table 5
Cytogenetics in nonrhabdomyosarcoma soft tissue sarcomas

Diagnosis	Translocation
Alveolar soft part sarcoma	t(X;17)
Dermatofibrosarcoma protuberans	t(17;22)
Infantile fibrosarcoma	t(12;15)
Liposarcoma	t(12;16)
Myxoid chondrosarcoma	t(9;22)
Synovial Sarcoma	t(X;18)

Table 6
Risk classification for nonrhabdomyosarcoma soft tissue sarcomas

Level	Description
Low risk	Grossly resected nonmetastatic tumors except high grade or >5 cm in diameter
Intermediate risk	High grade and/or tumors >5 cm Initially unresectable tumors
High risk	Metastatic tumors

- Intermediate risk
  - Patients with both high-grade and greater than 5-cm tumors.
  - Patients with initially unresectable nonmetastatic tumors, regardless of grade or size.
  - A 5-year survival estimate of 50%.
  - Comprise approximately 35% of NRSTS patients.
- High risk
  - Patients with metastatic tumors, including those with regional lymph node metastasis.
  - A 5-year survival estimate of 15%.
  - Comprise 15% of NRSTS tumors.

These risk groups were validated using Surveillance, Epidemiology and End Results data from 1988 to 2007 and were used in the most recent Children's Oncology Group protocol, which recently closed for accrual.[47] On multivariate analysis, malignant peripheral nerve sheath histology, chemotherapy-resistant histology, and higher risk group were significantly poor prognostic factors for overall and cancer-specific survival. Chemoresistant histologies include fibrohistiocytic tumors, fibroblastic/myofibroblastic tumors, tumors of uncertain differentiation, extraskeletal OS, pericyte tumor, nerve sheath tumors, and undifferentiated sarcomas.

Staging

Diagnosis is made with imaging and confirmed with biopsy. Imaging modalities depend on the location of the tumor and include ultrasonography, CT, and MRI. The most common site of metastasis is the lung and all workups should chest imaging.[48] Lymph nodes should be investigated in patient with lymphadenopathy and tumors with propensity for nodal metastasis (epithelioid, synovial, clear cell and vascular sarcomas).[49,50] Brain and bone imaging are reserved for patients with symptoms.

Treatment

Treatment for NRSTS includes surgical excision with 1-cm margins if possible, radiation for positive margins or unresectable disease, and adjuvant chemotherapy for high-risk tumors. These modalities vary depending on the risk classification and are now focused on adaptive therapy, which limits adjuvant therapy in low-risk patients to decrease long-term side effects and increases therapy in high-risk patients to improve survival.

Low risk

Patients with low-risk tumors can be classified into 4 cohorts.

1. Low-grade tumor completely excised with negative microscopic margins. These patients do not require radiation or chemotherapy. Close observation occurs after surgical resection and relapse is usually salvaged with multimodality therapy.
2. Small (<5 cm), high-grade tumor completely excised with negative microscopic margins. Recent adult trials have shown these patients can be managed safely without radiotherapy.[51–53] Close observation is necessary to allow for rescue therapy if local recurrence occurs.
3. Low-grade tumor excised with positive microscopic margins. These patients only require surgical excision with close follow-up for recurrence.
4. Small (<5 cm), high-grade tumor excised with positive microscopic margins. Owing to the high grade of the tumor, these patients do need adjuvant radiotherapy for adequate local control.

Intermediate risk

1. Large (>5 cm), high-grade tumors completely excised. These patients have significant risk for local recurrence and metastatic disease; therefore, they should receive radiation for local control[54] and chemotherapy for systemic control. Doxorubicin and ifosfamide are common chemotherapeutic agents, which have shown effectiveness, particularly in adult studies.[55]
2. Unresectable tumors. These patients need both radiation and chemotherapy before attempt at resection.

High risk

1. These patients should receive intensive combined chemoradiotherapy before resection of the primary tumor.
2. After completion of therapy, all metastatic sites should be excised if possible.
3. Bone marrow transplant after intensive chemotherapy has been conducted as part of a clinical trial and did not show a benefit to traditional chemotherapy.[56]

Summary

Nonrhabdomyosarcoma soft tissue sarcomas are a diverse group of tumors with variable and the prognosis depends on the extent of disease, size and grade of tumor, and extent of resection. Children with NRSTS have a good prognosis if tumor resection is possible. Lymph node or distant metastasis portends a dismal survival (<15%) warranting aggressive multimodality therapy to improve overall survival.

BONE SARCOMAS

Osteosarcoma

Epidemiology

OS is the most common primary malignant bone tumor in children and adolescents, with an estimate of 4.8 per million new cases each year in children younger 20 years in the United States. This results in an incidence of roughly 450 cases per year in this age group, accounting for approximately 3% to 5% of childhood tumors.[57] OS is more common in males and African Americans. Children younger than 5 years are rarely affected; after age 5, the incidence increases with a peak at age 15 years. A second peak occurs in the sixth to seventh decade. This second peak has been associated with Paget disease and prior radiation therapy, although one-half of older OS patients have neither condition. The adolescent peak occurs at a younger age in girls (13 years) compared with boys (15–17 years), and this corresponds with the age of greatest bone growth. More than 50% of these tumors

arise from the long bones around the knee and distal femur, followed by the proximal tibia.[58]

Chemotherapy has played a role in the increased overall survival obtained through different clinical trials over the last decades leading to dramatic prognostic improvements in young patients with localized extremity disease, with relapse-free survival rates of approximately 50% to 80%; before 1970, the estimated overall survival for patients treated with surgery alone was approximately 20%.[59]

Clinical presentation

The most common clinical presentation of OS is pain that becomes continuous and severe with time. This pain is often attributed to recent trauma or bone growth. In some patients, a mass may be palpable and the progressive swelling will affect adjacent joints. Pathologic fractures may occur in OS patients either spontaneously or as a result of minimal trauma. Respiratory symptoms from metastatic lung involvement is rare and require extensive bilateral lung disease.

Systemic symptoms such as fever and malaise are uncommon.[60] The time between onset of symptoms and diagnosis ranges from 2 to 4 months in developed countries.[61] Some genetic conditions, including Rothmund–Thomson syndrome, Li–Fraumeni syndrome, Paget disease, and some tumors such as retinoblastoma, predispose to develop OS.[62]

Prognostic factors

Several prognostic factors affecting overall survival have been identified in patients with OS, but these have not been helpful in identifying patients who might benefit from treatment intensification.[63] Some of these prognostic factors include tumor location, tumor size, localized versus metastatic disease, surgical resectability, and degree of tumor necrosis after neoadjuvant chemotherapy. Other possible prognostic factors identified in localized high-grade OS include age at diagnosis, serum lactate dehydrogenase level at diagnosis, alkaline phosphatase level, histologic subtype, and body mass index at initial presentation. Older patients are considered to do worse secondary to the increased proportion of unfavorable axial lesions with increasing age.

Tumor location Axial skeleton primary tumors (particularly the pelvis or the spine) are associated with a worse prognosis related to the inability to achieve a complete surgical resection and maintain local control. This tumor location is more likely to present with metastatic disease at diagnosis, which could be secondary to a prolonged latency period before obtaining the diagnosis. Within an extremity, a distal tumor location has a more favorable prognosis than a proximal location, secondary to the ability to completely remove the tumor with negative margins. A better prognosis has been documented in patients with head and neck OS when compared with extremity tumors, and this may be related to the relatively smaller size of tumors in this anatomic area and a higher proportion of low-grade tumors. Extraskeletal OS is rare in childhood and the outcomes seem to be similar to that for patients with primary bone tumors. The proximal tibia is considered to be a prognostically favorable site when compared with the distal femur, but conclusions are not consistent. An earlier growth spurt of the humerus has been associated with an earlier development of OS at this site, but this is also controversial.[60,64]

Tumor size Larger tumors have been associated with a worse prognosis, although no correlation between tumor size and response to chemotherapy has been documented. The worse overall survival in patients with large primary bone tumors must be associated with an increased macrometastatic and micrometastatic burden.

Interestingly, the proportion of large tumors is higher in proximity to the trunk. The reason proximal site represents an independent risk factor remains to be determined.[63,64]

Localized versus metastatic disease at diagnosis Radiographically detectable metastases at diagnosis are seen in 20% to 25% of patients with OS, with the lung being the most common site. Among patients with nonmetastatic disease at diagnosis, 20% to 25% will relapse, usually in the lungs. For patients with localized tumors, prognosis is better, with an overall event-free survival of 60% to 70%. This survival remains at about 20% to 30% for patients with metastatic disease at diagnosis. In this group, the prognosis seems to be determined by the site, the number of metastases, and their surgical resectability. Factors that predict a better outcome in patients with pulmonary metastatic disease include fewer pulmonary nodules, unilateral pulmonary metastases, and longer intervals between primary tumor resection and metastases.[65] Patients with skip metastases ($\geq$2 discontinuous neoplastic lesions in the same affected bone) have been reported to have a worse prognosis. Analysis of the German Cooperative Osteosarcoma Study experience, however, suggests that skip lesions in the same bone do not confer a worse prognosis if they are included in the definitive surgical resection. Skip lesions across a joint have a worse prognosis. Bone metastases in a bone other than the primary bone should be considered systemic disease.[66]

Surgical resectability Complete resection of the primary tumor and metastatic disease is required for cure in patients with OS. This goal is more often missed in individuals with axial tumors or those with widespread metastatic disease. The ability to achieve a complete resection of recurrent disease is the most important prognostic factor at first relapse, with a 5-year survival rate of 20% to 45% after complete resection of metastatic pulmonary disease. For patients with axial skeletal tumors who are not candidates for surgery or who undergo surgery resulting in positive margins, radiation therapy may improve survival.[67]

Degree of tumor necrosis after neoadjuvant chemotherapy Tumor response after neoadjuvant chemotherapy in the resected tumor represents an important prognostic factor in primary, localized extremity OS. Patients with 90% or greater necrosis have a better prognosis than those with less necrosis who are at a higher risk for recurrence within the first 2 years. In general, male sex, long clinical history, and axial location confer a higher risk of poor degree of tumor necrosis.[68,69]

Staging

For the purposes of treatment, high-grade OS is divided in patients without clinically detectable metastatic disease (localized OS) and patients with detectable metastases at the time of initial presentation by routine clinical studies (metastatic OS). These studies include conventional radiography, MRI of the primary tumor, CT scan of the chest, bone scintigraphy, and PET scan. Patients with skip lesions confined to the bone that includes the primary tumor should be considered to have localized disease if the skip lesions can be included in the definitive surgical resection.[70]

Treatment

Procurement of adequate diagnostic pathologic specimens is key to determining the correct diagnosis, whether collected from the primary tumor or a suspected metastatic site (most commonly the lung), which avoids the violation of the primary tumor. Improperly performed biopsies may make definitive resections difficult to perform. A biopsy of the primary tumor carries a higher risk of postoperative hematoma and tumor seeding. For open biopsies, a small longitudinal incision, which allows access

to adequate tissue should be made. Once the diagnosis of high-grade OS is obtained, neoadjuvant multiagent chemotherapy based on cisplatin, methotrexate, doxorubicin, ifosfamide and etoposide is started.[71,72] Low-grade OS is treated with surgery alone. After the completion of neoadjuvant chemotherapy, local control with either a limb salvage procedure or an amputation is performed. If feasible, limb salvage surgery has become the standard of care with similar survival outcomes when properly performed. This procedure involves both the en bloc resection of the tumor and the reconstruction with synthetic materials, biologic materials, or a combination of both. Vascular and nerve reconstruction, muscle flaps, and skin grafts may be necessary. A multidisciplinary team that includes pediatric surgical oncologists, orthopedic surgeons, plastic surgeons, anesthesiologists with pain management skills, physical therapists, psychologists, occupational therapists, and wound care nurses should be involved in the care of the patients. Patients should receive radiographic follow-up every 3 months for the first year, every 6 months for the second year, and yearly thereafter for 5 years. After 5 years, the patients should be seen in a late effects clinic to monitor for toxicity from therapy.

Ewing Sarcoma

Epidemiology

The term "Ewing sarcoma" is the official World Health Organization term and includes ES of the bone, extraskeletal ES, Askin tumor of the thoracic wall, and peripheral primitive neuroectodermal tumor.[73] ES is the second most common primary malignant bone tumor in children and adolescents after OS, with an estimate of 2.9 per million new cases each year in younger than 20 years in the United States. ES is slightly more common in males and its incidence is 9 times greater in Caucasians than in African Americans. The median age at diagnosis is 15 years, and more than 50% of patients are adolescents. The most common osseous location is the lower extremity (41%), followed by pelvis (26%), chest wall (16%), upper extremity (9%), spine (6%), hand/foot (3%), and skull (2%). Extraosseous ES may be seen in the trunk, extremities, head/neck, and retroperitoneum. Patients with extraosseous ES are more likely to be older, female, nonwhite, and have axial primary tumors.[74,75] ES belongs to the group of neoplasms commonly referred to as small, round, blue cell tumors of childhood. A reciprocal chromosomal translocation involving the *EWSR1* gene between chromosome 11 and 22 [t(11;22) (q24;q12)] is present in about 85% of ES and represents the key feature in the diagnosis.[76] Before the era of chemotherapy, only 10% of ES patients treated with radiation alone survived. With multiagent chemotherapy regimens, surgery, and radiation, cure rates of greater than 60% can be achieved in patients with localized disease.

Clinical presentation

The most common presenting symptoms in patients with ES are a palpable mass or local pain, which can be intermittent and less severe at night. The pain is often mistaken for bone growth or from injuries.[77] Median duration of symptoms before diagnosis varies from 2 to 9 months.[78] Systemic symptoms are more common in patients with metastatic disease, which accounts for 25% of patients at diagnosis. Tumor location within the chest or pelvis may preclude an early diagnosis. Most malignant chest wall tumors in children are ES, although other histologies, including RMS, OS, and chondrosarcoma, can occur.

Prognostic factors

In addition to stage (localized vs metastatic), other prognostic factors including tumor location, tumor size, age, gender, serum lactate dehydrogenase level at diagnosis,

and others (complex karyotype, detectable fusion transcripts in morphologically normal marrow and biological factors) have been investigated.[79–81]

Localized versus metastatic disease The presence or absence of metastatic disease is the single most powerful prognostic factor of outcome in ES. Patients with metastatic disease confined to the lung have a better prognosis than patients with extrapulmonary metastatic disease. In general, patients with unilateral lung involvement do better than patients with bilateral lung involvement. Patients with metastasis to bone only seem to have a better outcome than patients with metastases to both bone and lung. Regional lymph node involvement is associated with an inferior overall outcome.[80,81]

Degree of response to neoadjuvant chemotherapy Minimal or no residual viable tumor after neoadjuvant chemotherapy have a significantly better event-free survival compared with patients with a large amount of residual viable tumor. Patients with poor response to neoadjuvant chemotherapy have an increased risk for local recurrence.[82]

Tumor location A better prognosis is seen in patients with ES in the distal part of the extremities, followed by patients with proximal extremity tumors. Patients with central or pelvic tumors have the worst prognosis.

Tumor size Larger tumors (>8 cm) have been associated with a worse prognosis and tend to occur in unfavorable sites.

Age Patients younger than 15 years have a better prognosis than adolescents aged 15 years or older, young adults, or adults.

Gender Girls with ES have a better prognosis than boys.

Lactate dehydrogenase Increased serum lactate dehydrogenase levels before treatment are associated with a poorer prognosis.

Staging

Pretreatment staging studies in patients with ES should include conventional radiography, MRI and/or CT scan of the primary tumor, bone scan or PET scan, CT scan of the chest, and bone marrow aspiration and biopsy, which differs from the OS metastatic pattern.[83] Tumors are considered localized when, by clinical and imaging techniques, there is no spread beyond the primary location or regional lymph node involvement. If there is a question of regional lymph node involvement, an excisional biopsy may be required. Microscopically detectable bone marrow metastases occur in fewer than 10% of patients and are associated with a poor prognosis.

Treatment

Cure for patients with ES requires systemic chemotherapy in conjunction with either surgery, radiation therapy, or both modalities for local tumor control.[84] The best approach for local control remains a matter of discussion. In general, radiation therapy has been associated with a higher rate of local recurrence and a significant risk for second radio-induced malignancies, whereas surgery has been associated with more functional defects.[85,86] For tumors located in the extremities, the same surgical principles applied to OS are valid, with the possibility of adding radiation therapy in case the resection margin is positive for tumor.[87] For tumors located in the pelvis or spine, radiation therapy plays an important role for local control. Patients who are selected to receive radiation therapy alone usually represent a group of patients

with an unfavorable prognosis.[88] For chest wall ES, an initial tumor biopsy followed by neoadjuvant chemotherapy and delayed surgical resection lead to high rates of cure and minimized morbidity. Complete surgical resection also avoids the need for adjuvant radiotherapy to the chest with its associated morbidities, such as scoliosis, second malignancies, and growth discrepancies.

Multiagent chemotherapy includes vincristine, cyclophosphamide, actinomycin-D, and doxorubicin with neoadjuvant therapy necessary for unresectable disease. For patients with metastatic disease at initial presentation, adjuvant radiation therapy to the metastatic sites is recommended. The use of whole lung irradiation in this group of patients have been shown to improve outcomes. Also, radiation therapy may be indicated for bone metastases if limited in number.[89]

SUMMARY

Pediatric sarcomas are a diverse group of tumors that are best managed with multidisciplinary care. The combination of chemotherapy, surgery and radiation has improved survival. Patients should be seen long term in a late effects clinic to monitor for signs and symptoms of toxicity or secondary malignancies.

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