Current Approach to Pediatric Soft Tissue Sarcomas

MELINDA S. MERCHANT, CRYSTAL L. MACKALL

Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Key Words. Sarcoma • Soft tissue • Pediatric malignancy • Chemotherapy • Ewing’s sarcoma • Synovial sarcoma

Disclosures
Melinda S. Merchant: None; Crystal L. Mackall: None.

Section editors Laurence Baker and Jaap Verweij have disclosed no financial relationships relevant to the content of this article.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias.

LEARNING OBJECTIVES
After completing this course, the reader will be able to:

1. Describe the heterogeneous histologies of soft tissue sarcomas that may occur in pediatric and young adult patients.
2. Explain biology, risk classification, prognosis, and rational clinical management of pediatric type and adult type soft tissue sarcomas.
3. Discuss the ways in which the histology and stage of cancer are currently used to devise treatment plans and how monitoring subsets (such as subtype of sarcoma, adequacy of resection, age of patient, and duration of therapy) and trying novel agents may improve results in pediatric STS.

ABSTRACT
The development of a new soft tissue lesion in an otherwise healthy child, adolescent, or young adult can present many challenges for pediatric or medical oncology teams. Although uncommon, the diagnosis of a soft tissue malignancy should always be considered in the differential diagnosis of persistent pain, even if no mass is palpable. The definitive diagnosis and treatment of a soft tissue mass is aided by timely scans, appropriate biopsy for anatomic and molecular pathology, and a treatment approach guided by the specific diagnosis. Because pediatric soft tissue sarcomas are rare, cooperative groups play a crucial role in defining the standard of care through retrospective series and well-designed prospective clinical trials. Enrollment of newly diagnosed patients in clinical studies should be encouraged in order to continue to improve outcomes and understanding of these rare tumors. This review focuses on the current recommendations for management of sarcomas that typically occur in the soft tissues of pediatric and young adult patients. The Oncologist 2009;14:1139–1153

Correspondence: Melinda Merchant, M.D., Ph.D., Pediatric Oncology Branch/NCI, 10 Center Drive, Building 10, Room 1W-3940, Bethesda, Maryland 20892, USA. Telephone: 301-443-7955; Fax: 301-451-7052; e-mail: merchamm@mail.nih.gov Received July 17, 2009; accepted for publication October 6, 2009; first published online in The Oncologist Express on November 6, 2009. ©AlphaMed Press 1083-7159/2009/$30.00/0 doi: 10.1634/theoncologist.2009-0160

The Oncologist 2009;14:1139–1153 www.TheOncologist.com
INTRODUCTION

Soft tissue sarcomas (STSs) are a heterogeneous group of malignant tumors arising from the mesoderm. Accounting for 5% of adult solid tumors and approximately 8%–10% of pediatric or young adult cancers [1], many STSs have characteristics of differentiation stages seen during maturation from mesenchymal stem cells (MSCs) to mesoderm-derived structures such as muscle (rhabdomyosarcoma [RMS]), fibrous tissue (fibrosarcoma), fat (liposarcoma), Schwann cells (malignant peripheral nerve sheath tumors [MPNSTs]), stromal cells (fibrosarcoma), and blood vessels (angiosarcoma, hemangiopericytoma). In some STS histologies, the exact lineage remains unclear (e.g., malignant fibrous histiocytoma, alveolar soft part sarcoma [ASPS]). In other cases (Ewing sarcoma, undifferentiated sarcomas), very immature mesenchymal cells or the MSCs themselves have been postulated to be the target of oncogenesis.

This review focuses on current recommendations for the management of STSs that typically occur in pediatric and young adult patients. RMSs comprise approximately half of the STSs in children, and many have “lumped” the other half of childhood STSs into a heterogeneous group of nonrhabdomyosarcoma STS (NRSTS). Alternatively, some have emphasized the importance of age in contributing to histology, grouping STSs with a median incidence in the first two decades of life as pediatric-type STSs, compared with adult-type STSs, which occur most often beyond the third decade of life (Fig. 1). This division has some biologic basis because pediatric-type STSs are commonly small round blue cell tumors with a

Figure 1. Schema for multimodality treatment of pediatric-type and adult-type soft tissue sarcomas based on histology. Solid boxes represent standard of care whereas dotted lines may not apply to all or are still in clinical trials. Dotted lines represent possible recurrence. DSRCT and synovial sarcoma are represented with a gradient because they have features of both pediatric-type and adult-type sarcomas. In addition, the mean incidence for both is higher than for the other pediatric-type sarcomas. Peak incidence occurs in the second and third decades of life for DSRCT and at 25–35 years old for synovial sarcomas.

Abbreviations: ARMS, alveolar rhabdomyosarcoma; ASPS, alveolar soft part sarcoma; DFSP, dermatofibrosarcoma protuberans; DSRCT, desmoplastic small round cell tumor; ERMS, embryonal RMS; ESFT, Ewing’s sarcoma family tumors; Ifos/Dox, ifosfamide and doxorubicin; IRS, Intergroup Rhabdomyosarcoma Study; IVA, ifosfamide, vincristine, and actinomycin; IVADo, IVA plus doxorubicin; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor; RMS, rhabdomyosarcoma; RT, radiotherapy; STS, soft tissue sarcoma; VAC, vincristine, actinomycin-D, and cyclophosphamide; VDC/H11001, vincristine, doxorubicin, and cyclophosphamide plus ifosfamide and etoposide; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide.
high propensity for metastases and excellent response rates to chemotherapy, whereas adult-type STSs tend to be locally aggressive spindle cell tumors with poor responses to chemotherapy.

DIAGNOSTIC EVALUATION FOR PEDIATRIC STSS
The diagnostic evaluation of a STS should include computed tomography (CT) and magnetic resonance (MR) imaging of the primary site to determine the extent of disease and a plan for surgery. Adequate tissue should be obtained to test for diagnostic pathology as well as molecular testing by either fluorescence in situ hybridization or reverse transcription-polymerase chain reaction for specific translocations. This may be accomplished by open biopsy or core biopsies. Fine-needle aspirates are discouraged because they rarely yield sufficient tissue for the histology, cytogenetics, and molecular testing required for a full diagnostic and prognostic evaluation. Regardless of the approach, the orthopedic or oncologic surgeon who will be performing the definitive surgery should direct the site of the biopsy so that the entire biopsy tract or scar may be removed at the time of definitive surgery. Sarcomas classically metastasize via the bloodstream, and therefore CT scans of the chest are needed to rule out metastases to the lungs, and a radioisotope bone scan or fluorodeoxyglucose positron emission tomography (FDG-PET) is needed to rule out metastases to bone. Ewing’s sarcoma and RMS can also metastasize to bone marrow, which can be evaluated by MR, FDG-PET, or bilateral bone marrow aspirate plus biopsy. Nodal spread occurs most commonly in RMS and synovial sarcoma (SS), whereas liver metastases are more common in desmoplastic small round cell tumor (DSRCT). FDG-PET can be helpful in the management of several STSs, especially Ewing’s sarcoma, MPNST, and DSRCT [2]. Parameningeal RMS tumors require imaging of the brain and spine to determine any intracranial extension as well as to analyze cerebrospinal fluid for the presence of cells. Many STSs are high-risk tumors that are best treated at tertiary care centers, because optimal treatment requires experienced multidisciplinary teams to provide surgery, chemotherapy, and/or radiation therapy. Collaborative groups such as the Children’s Oncology Group (COG) and the European Pediatric Soft Tissue Sarcoma Group (EPSSG) have ongoing STS trials, and enrollment should be considered in all patients with these rare tumors so as to continue to improve care while decreasing unnecessary long-term side effects.

Figure 2. Alveolar rhabdomyosarcoma of the calf. (A): A soft tissue sarcoma lesion is not always visible on x-ray, but a subtle finding of greater fullness is noted in the deep soft tissue of the left calf without evidence of bony involvement. (B, D): Heterogeneous mass on short T1 inversion recovery image. (C): Lymph node spread—3 cm inguinal lymph node.
RMS

RMS is one of the most common extracranial solid tumors of childhood, accounting for approximately 5% of pediatric cancers and half of pediatric STSs. With a bimodal peak, the mean age at diagnosis is approximately 6–8 years. Head and neck RMSs account for 35%–40% of cases and can present with exophthalmoses, diplopia, headache, congestion, nasal discharge, or cranial nerve palsies. Genitourinary RMSs account for approximately 20% of cases and can cause urinary tract obstruction or constipation. Extremity tumors can present with pain and may not be visible on plain films (Fig. 2). Approximately 15% of patients have distant metastatic disease [3]. Complete familial cancer histories should be recorded, because RMS may be associated with the Li-Fraumeni, neurofibromatosis type 1 (NF-1), Beckwith-Wiedemann, and Costello cancer predisposition syndromes.

RMS is a small round blue cell tumor with two main histologic subtypes that arise commonly in pediatrics: (a) embryonal RMS (ERMS), containing dense spindle areas and loose myxoid stroma, is diagnosed in approximately 60% of cases and (b) alveolar RMS (ARMS), containing nests with dense stroma and pseudoalveolar spaces, occurs in 20%–25% of pediatric cases [4]. Pleomorphic RMS is diagnosed in 1% of pediatric RMS cases but approximately 20% of adult RMS cases. Desmin stains are positive in most RMSs and evidence for myoblastic differentiation may be identified by nuclear positivity of MyoD1 or myogenin. Compared with ERMS, ARMS is more common in adolescents and presents with primary tumors of the extremities, trunk, or perineum. Approximately 70% of ARMS have specific translocation of a PAX gene family member with the C-terminal transactivation domain of FOXOA1 (Table 1) [5, 6]. The resultant fusion protein is a potent oncogenic transcription factor [7, 8].

The majority of pediatric RMSs are chemosensitive at initial presentation, with response rates up to 85%. Radiation therapy plays a key role in the local control of most RMSs. Surgical dissection or radiation of regional lymph nodes should be undertaken if imaging suggests regional spread of disease (Fig. 3C). Risk categorization and appropriate treatment rely on disease site, tumor–node–metastasis classification, and postsurgical clinical grouping [3, 9, 10]. Aided by the early cooperative work of the Intergroup Rhabdomyosarcoma studies (IRS I-IV), stepwise increases in long-term survival have occurred in the low- and intermediate-risk categories of RMS. Review of data from IRS-II and IRS-IV estimate an 88% failure-free survival.

### Table 1. Characteristics of translocation-positive soft tissue tumors with a peak incidence in the pediatric and young adult populations

<table>
<thead>
<tr>
<th>Estimated incidence (in AYA)*</th>
<th>Chromosome translocation</th>
<th>Fusion protein</th>
<th>IHC commonly positive stains</th>
<th>Systemic therapy</th>
<th>Potential targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial sarcoma 500–600 (120)</td>
<td>t(X;18)(p11;q11)</td>
<td>SSX-SYT</td>
<td>Cytokeratin, EMA, Bcl-2</td>
<td>Ifos/Dox</td>
<td>NY-ESO-1</td>
</tr>
<tr>
<td>Extraosseus ESFT 170 (80)</td>
<td>t(11;22)(q24;q12) or t(21,22)(q22;q12)</td>
<td>EWSR1-FLI1 EWSR1-ERG other EWSR1-ETS</td>
<td>CD99</td>
<td>VDC+IE or VIDE</td>
<td>IGF1R</td>
</tr>
<tr>
<td>ARMS 100 (30–40)</td>
<td>t(3;13)(q35;q14) or t(3;13)(p36;q14)</td>
<td>PAX3-FOXOA1 PAX7-FOXOA1</td>
<td>Desmin, MyoD, myogenin</td>
<td>Depends on clinical group—VAC, IVA, or VDC+IE</td>
<td>IGF1R</td>
</tr>
<tr>
<td>ASPS 90 (40)</td>
<td>t(X;17)(p11.2;q25)</td>
<td>ASPL-TFE3</td>
<td>CD147, TFE3</td>
<td>Targeted therapy</td>
<td>VEGFR</td>
</tr>
<tr>
<td>DSRCT</td>
<td>t(11;22)(p13;q12)</td>
<td>EWSR1-WT1</td>
<td>Vimentin, cytokeratin CD99</td>
<td>VDC+IE</td>
<td>WT1?, VEGFR</td>
</tr>
<tr>
<td>IFS b</td>
<td>T(12;15)(p13;q25)</td>
<td>ETV6-NTRK3</td>
<td>Vimentin</td>
<td>Targeted therapy</td>
<td>PDGFR</td>
</tr>
<tr>
<td>DFSP b</td>
<td>t(17;22)(q13;q13)</td>
<td>COL1A1-PDGFB</td>
<td>CD34, vimentin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*As estimated by Herzog [44] based on 2004 Surveillance Epidemiology and End Results data for the U.S.

Abbreviations: ARMS, alveolar rhabdomyosarcoma; ASPS, alveolar soft part sarcoma; AYA, adolescents and young adults; DFSP, dermatofibrosarcoma protuberans; DSRCT, desmoplastic small round cell tumor; EMA, epithelial membrane antigen; ESFT, Ewing’s sarcoma family tumors; Ifos/Dox, ifosfamide and doxorubicin; IFS, infantile fibrosarcoma; IGF1R, insulin-like growth factor 1 receptor; IHC, immunohistochemistry; IVA, ifosfamide, vincristine, and actinomycin; PDGFR, platelet-derived growth factor receptor; VAC, vincristine, actinomycin-D, and cyclophosphamide; VDC+IE, vincristine, doxorubicin, and cyclophosphamide plus ifosfamide and etoposide; VEGFR, vascular endothelial growth factor receptor; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide.
rate at 3 years for low-risk, nonmetastatic ERMS patients who received vincristine and actinomycin-D (VA) or VA plus cyclophosphamide (VAC) with radiation to any residual tumor [11]. In an effort to improve the outcomes of intermediate- and high-risk RMS patients, several regimes are currently under study. The COG study ARST0531 is comparing the efficacy of VAC with that of VAC alternating with irinotecan plus vincristine over a 42-week period of therapy in the intermediate-risk cohort of patients with localized ARMS or ERMS with gross residual disease.

Intermediate risk patients have a 5-year overall survival rate of approximately 65%, with some subgroups as high as 85%, following VAC or vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC+IE) chemotherapy [12]. Adverse risk factors include site, size, older age, IRS group III (macroscopic residual disease), and progression on initial chemotherapy [9, 13]. Patients with metastatic RMS (IRS group IV) continue to have very poor overall survival rates of approximately 20% [3]. Several studies, ongoing or recently completed, are addressing the question of how to improve the outcomes for patients with metastatic disease. High-risk patients with metastatic disease enrolled in COG protocol ARST0431 receive vincristine, irinotecan, and dose compression of VAC over a 54-week treatment schema. The role of doxorubicin in RMS chemotherapy regimens has not been fully established, but evidence of activity in select groups of previous studies has led to the inclusion of doxorubicin in several current trials [12, 14]. The EPSSG clinical trial is testing ifosfamide, vincristine, and actinomycin (IVA) versus IVA plus doxorubicin (IVADo) based on positive results in a pilot study [15]. The role of maintenance therapy will be addressed by this EPSSG study as well, in that high-risk patients who achieve a complete response (CR) after nine courses of IVA or IVADo will be randomized to complete therapy or receive 6 months of vinorelbine and low-dose cyclophosphamide in the high-risk group (EPSSG RMS2005). The question of maintenance therapy is also being addressed by an ongoing pilot phase II study using irinotecan plus carboplatin in addition to the backbone of VDC+IE for patients with intermediate- or high-risk RMS (ClinicalTrials.gov identifier, NCT00077285).

**EXTRAOSSEOUS EWING’S SARCOMA AND PERIPHERAL NEUROECTODERMAL TUMOR**

The Ewing’s sarcoma family of tumors (ESFT) is a group of aggressive small round cell malignancies that occur primarily in the second decade of life. The second most common bone tumor of childhood, 20%–30% of Ewing’s sarcoma primary tumors can be fully extraosseous [16]. In addition,
two other groups of STS are included in the ESFT group: primitive neuroectodermal tumor of a peripheral nerve and Askin tumor of the thorax [17, 18]. The incidence of approximately three per million per year in the U.S. has not increased over the years of the Surveillance, Epidemiology, and End Results (SEER) evaluation [19].

A history of pain that waxes and wanes is common in the presentation of ESFT (Fig. 3). ESFT can be found almost anywhere in the body, with common presentation in the extremities, pelvis, chest wall, or paraspinal tissues, and one quarter of patients have metastases detected in the lungs, bone, or bone marrow. ESFT histology reveals a monotonous small round blue cell histology with limited stroma. Lacking specific morphologic features, diagnosis of ESFT is supported by CD99 glycoprotein staining, abundant cytoplasmic glycogen, and the lack of cytoplasmic filaments. CD99 is not a specific marker for ESFT and its presence alone does not confirm the diagnosis. ESFT tumors are distinguished from other small round blue cell tumors by a lack of differentiation markers such as S100, MyoD, and leukocyte common antigen.

In the original report, Askin et al. [18] noted that his 20 chest wall sarcomas could “represent the soft tissue equivalent of Ewing’s sarcoma.” The tools needed to prove this hypothesis came more than a decade later upon the identification of the t(11,22) chromosome rearrangement and molecular identification of EWSR1 gene on 22q12 translocation with an ETS oncogene [20] in all tumors now classified as ESFT. As a result of this chromosomal translocation, most commonly EWSR1-FLI1, a chimeric transcription factor is produced that is required for ESFT cell growth. The MSC has been implicated as a possible cell of origin [21–24].

Sequential studies have established a clear role for multiagent, dose-intensive chemotherapy including vincristine, doxorubicin, ifosfamide, and etoposide with or without cyclophosphamide (VDC/H11001 in the U.S. and VIDE in Europe), with a current survival rate of approximately 70%–80% for patients with nonmetastatic ESFT [16, 25]. For patients who...
present with metastatic ESFT, overall survival remains poor despite attempts to further increase dose intensity in the context of autologous stem cell transplantation [26–29].

Survival and response rates for soft tissue ESFT are not different than for bone ESFT [16]. Overall survival is better in patients with lung only metastases than for patients with bone or bone marrow metastases (~30%–40% versus <20%) [30, 31], and many studies have revealed a poorer outcome in patients >15 years old [30]. Tumor volumes >100 cm³ as commonly seen in pelvic disease, elevated lactate dehydrogenase, or an absolute lymphocyte count <500 cells/μl on cycle 1, day 15 are adverse prognostic factors [32, 33].

**Undifferentiated or Poorly Differentiated Sarcomas**

Careful histologic, immunophenotypic, and molecular pathology analysis is essential for accurate sarcoma diagnosis. Despite a comprehensive evaluation, however, some sarcomas remain unclassifiable. When cell markers are lacking and no translocation can be identified, the tumors are classified as undifferentiated or poorly differentiated sarcomas. These tumors often have some features that look like ESFT but do not meet all the criteria and lack a specific translocation (Fig. 4). Systemic therapy is recommended for patients with undifferentiated sarcomas, often per ESFT or RMS treatment protocols. Five of five patients with unresectable or metastatic undifferentiated sarcomas reported in a series of NRSTS had a CR (four patients) or partial response (one patient) to multimodality therapy including VDC+IE [34]. However, some groups prefer ifosfamide and doxorubicin, and no clearly superior regimen has been defined. Nonmetastatic undifferentiated sarcomas are eligible for the ARST0531 COG intermediate-risk trial to be treated with VAC. Given their rarity, sufficiently powered studies are not available to clearly establish a standard of care.

**DSRCT**

Described by Gerald and Rosai in 1989, DSRCT is a highly aggressive small cell malignancy with a peak incidence in the second and third decades of life [35]. The most common presentation is crampy abdominal pain and/or constipation in a male that prompts identification of an abdominal-pelvic mass identified by CT or MR (Fig. 5). FDG-PET imaging is useful to identify widespread intra-abdominal spread on mesothelial surfaces in the peritoneum, reminiscent of ovarian carcinomatosis. Macroscopic disease can often be found in the omentum, liver, lymph nodes, ascites, or pleural effusions [36]. Rarely, primary DSRCTs have been described outside the abdomen or metastatic to the central nervous system, lungs, or bone marrow. A diagnosis can be obtained by either biopsy of the tumor mass or molecular evaluation of cells from ascites. Histologically, DSRCT is a small round blue cell tumor with a desmoplastic reaction. It is often nodular with a nesting pattern of growth and immunohistochemistry (IHC) staining that can include epithelial, neural, or muscle markers. Molecular confirmation of the EWSR1-WT1 translocation should be obtained to confirm the diagnosis [37, 38].

Unlike many pediatric small round blue cell tumors, DSRCT has a poor response to standard chemotherapy. A multidisciplinary approach including aggressive surgical debulking is required to achieve any possibility of long-
term remission [39]. There is no single standard of care for newly diagnosed patients with DSRCT, but most are treated with the VDC+IE regimen used for ESFT. Despite this, outcomes remain poor, with a 5-year survival rate of 15% in the largest reported cohort to date [40]. Consolidation with whole-abdomen intensity-modulated radiation may play an adjunct role in disease control [41]. Irinotecan-based chemotherapy has shown activity against DSRCT in several case reports and its use in upfront trials or recurrent disease may be warranted [42]. Trials are ongoing to determine the efficacy of consolidation with hyperthermic peritoneal chemotherapy administration [43] or allogeneic transplant.

**STSs More Common in Adults**

**SS**

SSs account for approximately 6%–10% of all STSs, with a peak incidence at 26–35 years old and comprising approximately 16% of STSs diagnosed in young adults [44]. The most common primary site is the distal lower extremity (63%) or upper extremity (22%), but SS has also been reported in the head and neck, trunk, retroperitoneum, and mediastinum (Fig. 6). In a large Italian series, only 6% of patients with SS had metastases at presentation [45]. The lung is the most common site for metastatic disease. Clinically evident regional lymph node metastases occur in up to 14% of SS patients; however, routine sentinel node dissection has not been prospectively studied [46].

SS is a spindle cell tumor with variable epithelial differentiation and classified as biphasic, monophasic (spindle cell predominates), or poorly differentiated. Keratin and epithelial membrane antigen are strongly positive in the epithelial component in most cases (Table 1), although SS may be difficult to diagnose on histological stains alone if the tumor is poorly differentiated. The pathognomonic t(X;18) is found in virtually all cases of SS and involves the SYT gene at 18q11 and the SSXI, SSX2, or SSX4 gene at Xp11 [47–52]. The fusion transcript or protein is found in both the spindle cell and epithelial cells. Some reports have identified the SSXI, SSX2, or SSX4 fusion partner to be an independent predictor of outcome [53], but controversy remains regarding its prognostic value [54]. Fusion type does appear to make a clear impact on histology, however, because all SYT-SSX2+ tumors are monophasic [55]. In addition, there is an even male-to-female ratio for SYT-SSXI but a 1:2 ratio for SYT-SSX2, raising the potential of differences in X inactivation [53]. Haldar et al. [56, 57] modeled SS in mice by expressing the SYT-SSX translocation in myoblasts. The fusion protein was not oncogenic when expressed earlier or later in myogenesis, suggesting that the myoblast was uniquely suited for dysregulation by t(X;18) and may be the cell of origin [56–58]. Even in the mouse model, the majority of SSs occurred near a joint, leading investigators to speculate that the cartilaginous area near the joint provides prosurvival signals to the transformed SS cell.

Surgical excision with wide margins and preservation of function is recommended for SS because microscopic or macroscopic residual tumor is consistently an adverse prognostic factor [59–61]. Margins less than the preferred 3 cm should raise the consideration of second excision if possible without severe functional limitation. Adjuvant radiation therapy provides a benefit in terms of the local disease-free interval for patients with localized SS [62]. Radiation therapy to 50–70 Gy with margins should be administered for primary control of tumors that cannot be resected because of location or impact on function, and adjuvant radiation therapy is often recommended for all SSs >5 cm in maximal diameter [63]. Size of tumor (>5 cm), axial location, high grade (grade 3), invasiveness of tumor, and detection of distant metastases are consistently identified as poor prognostic factors [59, 64, 65].
There continues to be controversy regarding neoadjuvant or adjuvant chemotherapy for SS. Compared with other adult-type STSs, SS is more chemosensitive, with responses reported in 40%–60% of cases using multiagent chemotherapy [45, 66]. Based on this substantial response rate, most pediatric oncologists recommend adjuvant chemotherapy for high-risk SS as defined by high-grade histology, size >5 cm, axial primary, or metastatic disease. Prior to the initiation of the EPSSG NRSTS trials, all pediatric patients with SS enrolled in European trials received chemotherapy regardless of stage, with the same regimen used for RMS. A retrospective study of this cohort reported longer survival for children receiving adjuvant chemotherapy when tumors were >5 cm and high grade [45]. Although a clear impact on survival has not been definitively shown in randomized trials, a recent analysis of adult patients with SS >5 cm also reported a survival advantage for patients treated with an ifosfamide-containing regimen [67, 68]. In contrast, other reviews of SS in adults have not shown a positive effect of chemotherapy [69]. A multicenter, multivariate review of pediatric SS patients by Okcu et al. [59] revealed that chemotherapy responses resulted in longer survival in IRS group III patients. Prospective trials are still required, but these studies serve as the basis for recommending adjuvant chemotherapy in high-risk pediatric SS patients. COG study ARST0332 is attempting to determine if low-risk patients with <5 cm tumors can have good survival outcomes with surgery alone, as has been shown in adult studies of SS (ClinicalTrials.gov identifier, NCT00346164).

Differences in the 5-year survival curves for pediatric SS (60%–83%) versus adult SS (50%–70%) patients suggest that older age is an adverse risk factor [65, 69]. Because no studies have shown biologic differences in SS with age at diagnosis, the survival differences may reflect the different attitudes regarding the role of chemotherapy in these tumors. However, the SEER analysis showed that the 0- to 9-year-old age group had better outcomes than the 10- to 18-year-old age group, who would likely have been treated in a similar fashion [65]. The review from Milan by Ferrari et al. [45] also showed that chemotherapy could improve survival in SS, regardless of size, for younger patients (0–16 years old). In contrast, chemotherapy resulted in greater metastasis-free survival but not overall survival rates in patients >17 years old, suggesting that age may influence clinical behavior in SS [45]. Size of tumor, axial location, high grade (grade 3), invasiveness of tumor, and detection of distant metastases are consistently identified as poor prognostic factors [59, 64]. Without systemic treatment, approximately half of the patients diagnosed with a ≥5 cm extremity SS recur with distant metastases following primary resection [67]. The 5-year event-free survival rate was 66% in 86 patients with <5 cm sized SS treated in Milan, Italy, compared with a rate of 24% for SS >5 cm [45]. Other factors with potential prognostic importance include axial location, Ki-67, p53 overexpression, and older patient age [45, 65, 68].

**MPNST**

MPNST (previously named malignant schwannoma or neurofibrosarcoma) is a spindle cell sarcoma that occurs as a fusiform mass associated with a nerve and represents approximately 10% of all STSs. Half of all MPNSTs occur in patients with NF1, and there is a cumulative lifetime risk of 8%–13% for an NF1 patient to develop these tumors [70]. The common presentation is a painful mass, but it may be difficult to distinguish MPNST from a benign plexiform neurofibroma in the setting of NF-1. The mean age at presentation with MPNST is younger in NF1 patients than in the general population [71]. Histologically, there is marked pleomorphism, mitoses, and invasion of adjacent tissues. Differentiation can be seen, and rhabdomyoblastic components are seen in the malignant triton tumor. IHC for S100, CD34, p53, MIB-1, and topoisomerase IIα can aid in distinguishing MPNSTs from other STSs and from plexiform neurofibroma.

As in other spindle cell sarcomas, complete resection with wide margins is the mainstay of therapy. Radiation therapy is used when surgical resection is not possible or when margins are insufficient. MPNSTs are less sensitive to chemotherapy than pediatric-type STSs [70–72]. The largest reported series of MPNSTs in children and adults revealed that IRS group III patients with a response to chemotherapy had a better overall survival rate than nonresponders, but the rate is suboptimal. That retrospective analysis showed a response rate of 65% in patients who received ifosfamide-containing regimens [73]. Chemotherapy with ifosfamide and doxorubicin for MPNST is currently under study in a prospective multi-institutional trial (ClinicalTrials.gov identifier, NCT00304083).

Patients with NF-1–associated MPNSTs often present with more advanced disease, have a greater incidence of chemoresistant disease, and have poorer overall outcomes in several series [72–74]. Other prognostic factors are tumor size, grade, mitotic rate, and surgical margin [75].

**Other Adult-Type STSs**

Many other translocation-negative sarcomas can occur in the pediatric age group, including liposarcoma, epithelioid sarcoma, angiosarcoma, malignant fibrous histiocytoma,
leiomyosarcoma, clear cell sarcoma, and adult-type fibrosarcoma [44, 75]. More common in adults, this remaining group of adult-type STS accounts for <1%–2% of pediatric cancers. Other rare translocation-bearing sarcomas that involve the EWSR1 gene on chromosome 22 are included in this group, such as myxoid chondrosarcoma (as EWSR1-NR4A3), myxoid liposarcoma (EWSR1-CHOP), and clear cell sarcoma (EWSR1-ATF1).

Surgery is the mainstay of therapy for these adult-type STSs and complete resection can be curative. Patients with low-grade or small-sized adult-type STSs are unlikely to derive any benefit from chemotherapy, and therefore aggressive surgical resection is advised. A propensity to metastasize has been noted in patients with high-grade (grade 3) tumors that are >5 cm in size [76–78]. Administration of chemotherapy for such high-risk disease has been extensively evaluated in STS with no clear evidence for superior outcomes with adjuvant chemotherapy when all histologic subtypes are grouped together. A meta-analysis revealed a survival benefit from anthracycline-based adjuvant chemotherapy in patients following resection of a high-risk STS as defined by deep location, size >5 cm, or high histologic grade [79]. Overall response rates for NRSTS patients using doxorubicin and/or ifosfamide have been reported to be 19%–37%, with much of the activity reported in SS [80, 81]. There is some indication that these tumors may be more sensitive to chemotherapy in the pediatric setting than when they occur in adults, so that chemotherapy is often recommended in large, high-grade lesions [75, 82]. Multimodality treatment for patients with unresectable or metastatic NRSTS should be considered on an individual basis, depending on STS histotype, because CRs have been reported [34, 82].

**ASPS**

ASPS is a rare and slow-growing, but highly metastatic, tumor of unknown origin. ASPS generally presents as a painless mass in the orbit or tongue in younger children or the thigh or trunk in adolescents [83]. The median age at diagnosis is in the second decade of life and there is a female predominance. CT and MR imaging reveal a poorly circumscribed, highly vascularized tumor. Distant metastases to the lung or brain are present in up to 30% of patients at presentation and late recurrences with metastatic disease occur in another 30% of patients who present initially with localized primary disease.

ASPS cells are uniform large round cells with abundant cytoplasm arranged in a characteristic nesting pattern [84], with a loss of cellular adhesion and necrosis that causes a pseudoalveolar pattern [85]. Mitotic figures are uncommon, and rod-shaped crystal inclusions can be seen variably. Local vascular invasion is often noted. The unbalanced tumor-specific translocation causes a der(17)t(X;17)(p11;q25) in ASPS. The resultant fusion protein contains the DNA-binding site of TFE3 and the ASPL protein that localizes to the nucleus and functions as a transcription factor [86]. Aberrant nuclear localization of TFE3 staining on IHC is a highly sensitive and specific marker for ASPS.

Surgical resection with wide margins is the mainstay of therapy for ASPS. The response rates to conventional chemotherapy and radiation therapy are poor, with no CRs reported with any chemotherapy regimen alone. However, a recent study by Gardner et al. [87] showed clinical responses to the vascular endothelial growth factor receptor inhibitor cedirinib, and further study of its use in phase II trials for this disease are under way.

Because of the indolent nature of ASPS, the 5-year overall survival rates are high at >80%; however, the 5-year progression-free survival rate is only ~20%. Successful resection provides 80%–100% survival rates in patients with IRS stage I disease [83, 88, 89]. Metastatic disease is again a poor prognostic factor, with the majority of patients demonstrating slowly progressive disease.

**INFANTILE OR CONGENITAL FIBROSARCOMA**

Fibrosarcoma is the most common STS in children <1 year of age and represents approximately 10% of pediatric STSs [90]. There are multiple subtypes of fibrosarcoma that arise in the pediatric setting. The majority of fibrosarcomas diagnosed in the first two decades of life are similar to the adult-type STSs discussed above in regard to histology, cytogenetics, slow growth, clinical course, and treatment. In contrast, infantile fibrosarcoma (IFS) has a markedly different clinical behavior and treatment strategies [91]. IFS commonly presents as a painless, quick-growing mass in a distal extremity in an infant or young child. The lesion can be soft, red, or ulcerated and can grow to quite a large size in these small patients. Benign fibromatoses and infantile hemangiopericytoma are in the differential diagnosis of IFS. Metastatic spread of IFS at diagnosis is uncommon even though lesions are locally infiltrative.

IFS and adult-type fibrosarcoma are histologically similar spindle cell tumors of fibroblastic origin. Cellular atypia and abnormal mitoses are found more often in adult-type fibrosarcoma, whereas a focal hemangiopericytomaticous pattern of blood vessels can be identified in IFS. Histologic grading has not been proven to be a prognostic factor in IFS. Identification of the t(12;15) translocation in 70%–90% of IFS cases and in congenital mesoblastic nephroma aids in distinguishing this rare en-
ity from adult fibrosarcoma or other benign infantile lesions [92, 93].

As with adult-type STSs, complete surgical excision is the primary treatment of choice. However, rapid growth and the location of IFS in young infants can sometimes make resection unfeasible. Unlike adult-type fibrosarcoma, IFS often responds to neoadjuvant chemotherapy, which can improve the ability to complete a full resection [91, 94–96]. Histologic grade may be high, but even tumor resection with microscopic residual disease can lead to long-term disease-free survival [97]. Following complete surgical resection, there does not appear to be a role for adjuvant chemotherapy or radiation. Patients <2 years old have a better prognosis, even following local recurrence [91]. Reportedly active chemotherapy regimens include VAC, I/E, and regimens containing doxorubicin.

NEW AGENTS AND OPTIONS FOR RELAPSED DISEASE

Depending upon stage, grade, and histology, 30%–50% of children and young adults with STS will develop recurrent or metastatic disease. Retrospective analyses as well as prospective multi-institutional studies have shown that the 5-year postrelapse survival rate is <25% in the setting of recurrent disease [98–102], regardless of the regimen used. A longer time to recurrent disease (>1–2 years) generally portends a better prognosis than early relapses.

The current regimens in use for relapsed pediatric sarcomas are based on phase II trials and retrospective studies. Irinotecan plus temozolomide, vinorelbine plus low-dose cyclophosphamide, cyclophosphamide plus topotecan, and gemcitabine plus docetaxel have all been shown to have activity, although none have substantial cure rates and therefore are not true salvage regimens [102–109]. These regimens are reasonably well tolerated in heavily pretreated patients as encountered in most relapsed STS cases.

Trabectedin has reproducible activity in many sarcoma subtypes and has been approved in Europe for recurrent sarcoma based on activity in liposarcoma and leiomyosarcomas [110, 111]. Notably, trabectedin has significant activity in FUS(TLS)-CHOP translocation-positive myxoid liposarcoma and has potential clinical activity in SS and leiomyosarcoma. Inhibition of insulin-like growth factor 1 receptor (IGF1R)-mediated prosurvival signals resulted in decreased proliferation and tumor growth of ARMS, ESFT, and SS in preclinical studies, and several anti-IGF1R antibodies and small-molecule inhibitors have advanced to clinical trials in STS, with promising responses reported [112–114]. Preclinical evidence suggests that pediatric STSs may be sensitive to tumor necrosis factor receptor apoptosis-inducing ligand (TRAIL)-induced apoptosis, and agents that activate TRAIL receptors are currently in clinical trials.

Ultimately, inhibition of translocation proteins or their key downstream mediators of oncogenicity should, in theory, provide targeted therapy for translocation-positive STS, but clinical translation is dependent on overcoming delivery issues (such as nanodelivery of antisense or small interfering RNA constructs) or design of targeting agents. Few of the translocation products result directly in a constitutively activated tyrosine kinase, such as BCR–ABL in chronic myelogenous leukemia (CML) or platelet-derived growth factor receptor in dermatofibrosarcoma protuberans, so inhibition requires new approaches to blocking oncogenic transcription factors. A novel small-molecule inhibitor that disrupts EWSR1-FLI binding to RNA helicase A and is specifically cytotoxic to EWSR1-FLI1+ ESFT lines in vitro and in vivo was developed by Erkizan et al [114] and could provide a new paradigm for targeting oncogenic transcription factors.

Because CRs are achievable in the majority of patients with pediatric-type STS, the setting of minimal residual disease (MRD) following multimodality therapy provides an ideal period for targeted intervention. To this end, patients with metastatic disease at presentation fall into the highest risk group, and pilot trials are attempting to answer whether new agents and maintenance therapy (Memorial Sloan-Kettering Cancer Center; ClinicalTrials.gov identifier, NCT00077285), autologous stem cell transplant (University of Minnesota; ClinicalTrials.gov identifier, NCT00623077), or allogeneic stem cell transplant (National Cancer Institute [NCI]; ClinicalTrials.gov identifier, NCT0047372) administered during this time of MRD will lead to a higher disease-free survival rate. Immunotherapy also holds promise during this time. Vaccination against fusion peptides did not generate robust immune responses, but did show promising survival rates, perhaps as a result of administration of autologous T cells, which enhanced immune reconstitution after dose-intensive chemotherapy [116]. Currently, patients with newly diagnosed metastatic STS or relapsed disease with adequate T cells are eligible for a dendritic cell vaccine made with autologous tumor (NCI; ClinicalTrials.gov identifier, NCT00923351). Exciting progress is also under way using immunotherapy that targets the tumor-associated antigen NY-ESO-1 [118], which is expressed on >80% of SSs and has been found on some other sarcomas (NCI; ClinicalTrials.gov identifier, NCT00670748).
CONCLUSION
Treatement of pediatric or young adult patients with STS is a multidisciplinary effort that requires specialists familiar with these high-risk tumors. Radiologists, oncologists, surgeons, and radiation oncologists treating children and young adults with sarcomas ought to be aware of the national and international study options that will provide quality of care and also continue to move the field forward. Institutional pilot studies continue to be important in the translation of cutting edge science to the clinical care of these aggressive malignancies. Just as childhood acute lymphocytic leukemia trials informed chemotherapy treatment for all tumors and imatinib treatment for CML ushered in targeted therapeutics, targeting the transcription factors and growth pathways central to pediatric STS biology may ultimately be translatable to other tumors.

ACKNOWLEDGMENTS
We would like to express our sincere appreciation to Dr. Robert Maki at Memorial Sloan-Kettering Cancer Center for his helpful comments on this manuscript as well as his informative discussions regarding adult-type STS occurring in our pediatric patients. Thanks also to Joanne Derdak and Barb Wise, nurse practitioners at the Pediatric Oncology Branch, for their consistent care of sarcoma patients and assistance in obtaining representative images for the figures.

AUTHOR CONTRIBUTIONS
Conception/Design: Melinda Merchant, Crystal Mackall
Collection and/or assembly of data: Melinda Merchant, Crystal Mackall
Data analysis and interpretation: Melinda Merchant, Crystal Mackall
Manuscript writing: Melinda Merchant, Crystal Mackall
Final approval of manuscript: Melinda Merchant, Crystal Mackall

REFERENCES


48 Lu YJ, Birdsall S, Summersgill B et al. Dual colour fluorescence in situ hybridization to paraffin-embedded samples to deduce the presence of the der(X)t(X;18)(p11.2;q11.2) and involvement of either the SSX1 or SSX2 gene; A diagnostic and prognostic aid for synovial sarcoma. J Pathol 1999;187:490–496.


95 Russell H, Hicks MJ, Bertuch AA et al. Infantile fibrosarcoma: Clinical


