

Pediatric Nonrhabdomyosarcoma Soft Tissue Sarcomas

SHERI L. SPUNT,^{a,b} STEPHEN X. SKAPEK,^{a,b} CHERYL M. COFFIN^c

^aDepartment of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; ^bDepartment of Pediatrics, University of Tennessee College of Medicine, Memphis, Tennessee, USA; ^cDepartment of Pathology, University of Utah, Salt Lake City, Utah, USA

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LEARNING OBJECTIVES

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

1. Evaluate the clinical features of NRSTS in pediatric patients.
2. Identify the factors that influence the selection of treatment and the clinical outcomes of pediatric patients with NRSTS.
3. Select an appropriate treatment strategy for pediatric patients with NRSTS.

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ABSTRACT

The nonrhabdomyosarcoma soft tissue sarcomas (NRSTSs) are a heterogeneous group of mesenchymal cell neoplasms that account for about 4% of childhood cancers. Because each histologic subtype of NRSTS is rare, they have been poorly studied and little is known about their biology, natural history, or optimal treatment. Data from adults with soft tissue sarcomas provide some helpful insight, but adult and childhood NRSTSs differ considerably in the distribution of their

histologic subtypes, and certain entities are known to behave differently in young children. The greater risks posed to children by treatment, particularly by radiotherapy, also must be considered in treatment planning for children. This article summarizes what is known to date about childhood NRSTS, including the epidemiology, pathogenesis, and clinical approach to diagnosis and treatment of these tumors. *The Oncologist* 2008;13:668–678

INTRODUCTION

The nonrhabdomyosarcoma soft tissue sarcomas (NRSTSs) are a heterogeneous group of mesenchymal cell neoplasms, most of which are named for the mature

tissue that the tumor most resembles. For example, synovial sarcoma is named for its histologic similarity to synovium, although it may arise far from joints. Ewing sarcoma may occur in soft tissues, but is widely consid-

Correspondence: Sheri L. Spunt, M.D., St. Jude Children's Research Hospital, Department of Oncology, 332 N. Lauderdale Street, ALSAC-6032, Memphis, Tennessee 38105-2794, USA. Telephone: 901-495-3984; Fax: 901-521-9005; e-mail: sheri.spunt@stjude.org Received October 1, 2007; accepted for publication April 8, 2008. ©AlphaMed Press 1083-7159/2008/\$30.00/0 doi: 10.1634/theoncologist.2007-0182

ered a subtype of the Ewing sarcoma family of tumors rather than NRSTS.

Childhood NRSTSs are rare and not well studied. Little is known about their biology, natural history, or optimal treatment. Data from adults provide some helpful insight, but adult and childhood NRSTSs differ considerably in the distribution of their histologic subtypes [1], and certain entities (e.g., fibrosarcoma, hemangiopericytoma) are known to behave differently in young children [2, 3]. The greater risks posed to children by treatment, particularly by radiotherapy, also must be considered in treatment planning for children. Here, we summarize what is known to date about childhood NRSTSs.

EPIDEMIOLOGY

NRSTSs (about 4% of childhood cancers) occur in 500–550 children <20 years of age each year in the U.S. [4]. The incidence is marginally higher in males, and blacks are affected slightly more often than whites. In childhood, NRSTSs have a bimodal age distribution, occurring most often in infancy and adolescence. The most common pediatric NRSTSs are dermatofibrosarcoma protuberans, malignant fibrous histiocytoma, synovial sarcoma, malignant peripheral nerve sheath tumor (MPNST), and fibrosarcoma [4, 5]. Unique to pediatrics are infantile fibrosarcoma, infantile rhabdomyofibrosarcoma, infantile hemangiopericytoma, malignant rhabdoid tumor, and ectomesenchymoma, although rare cases of the latter two have been reported in adults.

Most NRSTSs appear to be sporadic, although some cases are associated with a known risk factor. Genetic conditions that predict a higher risk for NRSTS include Li-Fraumeni syndrome [6], hereditary retinoblastoma [7], neurofibromatosis type I (malignant peripheral nerve sheath tumor [MPNST]) [8], Gorlin syndrome (fibrosarcoma and leiomyosarcoma) [9], and Werner syndrome [10]. Survivors of childhood cancer are at a greater risk for soft tissue sarcoma than the general population. Factors with a potentially genetic basis (young age at primary diagnosis, primary diagnosis of sarcoma, and family history of cancer) and treatment exposures (radiation therapy, higher doses of anthracyclines and alkylating agents) appear to influence this risk [11]. Individuals with HIV are predisposed to leiomyosarcoma [12] that appears to be related to Epstein-Barr virus infection [13]. Chronic lymphedema is a risk factor for the development of lymphangiosarcoma [14], although it is more commonly seen in adults. A number of toxins have been implicated in the development of soft tissue sarcomas in adults but not in children [15, 16].

PATHOGENESIS

Cancer cells, including those of NRSTSs, display six attributes deemed essential to their complex biology [17]: self-sufficiency in proliferation signals, resistance to anti-mitogenic and proapoptotic signals, and the capacity for invasive growth, metastatic growth, angiogenesis, and limitless replication. Loss of two key tumor suppressors—*p53* and the retinoblastoma susceptibility gene *RB*—contributes to this phenotype [18]. *RB* encodes a protein that promotes cell cycle arrest and affects differentiation by influencing a variety of transcription factors and chromatin remodeling proteins. *RB* can be mutated in NRSTS or the protein can be functionally inactivated by cyclins and cyclin-dependent kinases (Cdks) or by mutation or repression of Cdk-inhibitory proteins (such as p16^{Ink4a}). Tumor suppression by *p53* reflects its ability to induce genes promoting either cell cycle arrest or apoptosis. Its activity can be disrupted by gene mutation or, functionally, by increased expression of the human homologue of murine double minute 2, which promotes *p53* degradation. NRSTSs have a variety of mechanisms that circumvent these tumor suppressors.

NRSTSs are a large, heterogeneous group of malignancies composed of cells similar to mesenchymal cells (e.g., fibroblasts, smooth muscle cells, and perineurial cells). Despite this complexity, they can be divided into two groups: those with histology-specific chromosomal rearrangements (usually balanced translocations) and those with evidence of widespread genomic instability (Table 1). In the former group, most of the translocations generate a chimeric (“fusion”) protein containing functional motifs from two different transcription factors. These proteins can drive sarcomagenesis, as established in mouse models [19, 20], but cooperating tumor-suppressor gene inactivation is also important. *ETV6-NTRK3* (in infantile fibrosarcoma [21]) and other translocations involving anaplastic lymphoma kinase (*ALK*) (in inflammatory myofibroblastic tumor [22]) create constitutively active kinases. Finally, the *COL1A1-PDGFB* fusion in dermatofibrosarcoma protuberans allows constitutive expression of platelet-derived growth factor B [23, 24]. In all these cases, the remarkable specificity of the chromosomal abnormalities to very limited NRSTS subtypes may reflect cell-type specific control and/or tolerance of expression of the involved genes. Alternatively, a particular histologic subtype may result from expression of a specific chimeric transcription factor. The more complex chromosomal abnormalities in other NRSTSs suggest fundamental DNA damage susceptibility and aberrant response capacity. Similar complexity is found in soft tissue sarcoma arising in mice lacking both DNA ligase IV and

Table 1. Key features of pediatric NRSTS according to predominant histomorphologic type

Diagnosis	Immunophenotype	Genetic alteration
Small round cell tumors		
Desmoplastic small round cell tumor	Polyphenotypic: cytokeratins, epithelial membrane antigen, vimentin, desmin, NSE, WT-1 (C-terminus)	t(11;22)(p13;q12) with <i>EWS-WT1</i> fusion
Clear cell sarcoma	HMB45, S100 protein, and other melanoma antigens; variable: NSE, synaptophysin, CD57, cytokeratin, actin	t(12;22)(q13;q12) with <i>EWS-ATF1</i> fusion
Extraskeletal myxoid chondrosarcoma	Vimentin; variable and focal S100 protein, cytokeratin, epithelial membrane antigen	
Malignant rhabdoid tumor	Polyphenotypic: vimentin cytokeratin, epithelial membrane antigen; variable: CD99, synaptophysin, NSE, S100 protein, muscle-specific actin	Deletion of 22q with <i>HSNF5 (INI1)</i> deletion or mutation
Spindle cell tumors		
Synovial sarcoma	Vimentin; cytokeratins, including 7 and 19; epithelial membrane antigen; Bcl-2; variable S100 protein, CD99, calponin, actin	t(X;18)(p11;q11) with <i>SYT-SSX</i> fusion; <i>MYCN</i> overexpression
Dermatofibrosarcoma protuberans	CD34, vimentin	t(17;22)(q21;q13) with <i>COL1A1-PDGFB</i> fusion
Infantile fibrosarcoma	Vimentin	t(12;15)(p13;q25) with <i>ETV6-NTRK3</i> fusion; trisomy 8, 11, 17, 20
Inflammatory myofibroblastic tumor	Vimentin; variable smooth muscle actin, muscle-specific actin, desmin, Alk-1	2p23 rearrangement with <i>ALK</i> fusion to <i>TPM3</i> , <i>TPM4</i> , clathrin, and other genes
Malignant peripheral nerve sheath tumor	Variable: S100 protein, Leu-7, neurofilaments, GFAP	Complex abnormalities
Leiomyosarcoma	Smooth muscle actin, muscle-specific actin, desmin, h-caldesmon	Complex abnormalities
Malignant fibrous histiocytoma	Vimentin	Complex abnormalities
Epithelioid tumors		
Alveolar soft part sarcoma	Reactive with antibody to TFE-3 carboxyl-terminus	der (17)t(X;17)(p11;q25) with <i>ASPL-TFE3</i> fusion
Epithelioid sarcoma	Vimentin, cytokeratins, epithelial membrane antigen; variable CD34	Incompletely defined
Myxoid tumors		
Lipoblastoma	Nonspecific	Rearrangement of 8q11-13; <i>PLAG1</i> gene rearrangements: <i>HAS2/PLAG1</i> , <i>COL1A2/PLAG1</i>
Myxoid liposarcoma	S100 protein	t(12;16)(q13;p11) with <i>DDIT2 (CHOP)-FUS</i> fusion; t(12;22)(q13;q12) with <i>DDIT3-EWS</i> fusion
Low-grade fibromyxoid sarcoma	Vimentin	t(7;16)(q34;p11) with <i>FUS-BBF2H7</i> fusion
Abbreviations: GFAP, glial fibrillary acidic protein; NRSTS, non-rhabdomyosarcoma soft tissue sarcoma; NSE, neuron-specific enolase.		

p53 [25] and in lymphoid tumors arising in telomerase-deficient mice also lacking *Atm* and p53 [26].

The cellular origin of specific types of NRSTS is be-

coming clearer. Histological similarities between tumor cells and their normal counterparts (e.g., leiomyosarcoma and smooth muscle cells) suggest that a particular NRSTS

may evolve from a mature mesenchymal cell that has “de-differentiated” or from a progenitor cell that is committed to or has begun to differentiate to a particular cellular lineage. This hypothesis is supported by the development of a MPNST within a plexiform neurofibroma in children with neurofibromatosis. Further, mutation of the mouse *Nf1* gene exclusively in Schwann cells causes MPNST [27]. This issue is less clear in other cases, such as synovial sarcoma, which does not always arise near pre-existing synovium. In fact, targeted expression of the *SYT-SSX2* fusion transcript in cells of skeletal muscle lineage causes a spindle-cell neoplasm reminiscent of synovial sarcoma [19]. While this finding suggests that human synovial sarcoma may arise from a cell committed to the skeletal muscle lineage, it may simply indicate that cells of this lineage can tolerate expression of the oncogenic fusion protein in an experimental context. Finally, cells with stem cell like properties have been found in several solid malignancies (breast [28] and prostate cancer [29] and brain tumors [30]). Recently, “side population” cells were found in a variety of bone and soft tissue sarcomas and shown to resemble tumor-initiating cells in a xenograft model [31]; hence, the cancer stem cell concept may also apply to NRSTS.

PATHOLOGY

The World Health Organization’s 2002 revised classification of soft tissue and bone tumors [32] is the most up-to-date classification of soft tissue sarcomas available, and it emphasizes the relation between pathology and genetics. The histological characterization is based on resemblance to defined tumor types. Four categories of biological potential are included: benign, intermediate–locally aggressive, intermediate–rarely metastasizing, and malignant. This review emphasizes the sarcomas that occur predominantly or with significant frequency in children and adolescents. Other publications have recently described in detail the pathologic evaluation of pediatric soft tissue tumors [33, 34], the role of genetic testing in soft tissue sarcomas [35], and the evolving role of microarray technologies in soft tissue tumors [36].

The initial approach to the fresh pathology specimen is crucial for comprehensive evaluation of a pediatric soft-tissue tumor. Appropriate specimen handling includes triage for diagnostic and prognostic studies and collection of information with clinical, therapeutic, prognostic, and genetic importance. In addition to formalin-fixed, paraffin-embedded tissue for routine histopathology and immunohistochemistry, samples should be taken, when possible, from the fresh specimen for cytogenetic and molecular studies, DNA and RNA preparation, flow cytometry, electron microscopy, and research protocols, if

appropriate. Different types of specimens (needle biopsy, open incisional biopsy, and various resection specimens) differ in the information that can be obtained from them. When presented with a possible NRSTS specimen from a young patient, the pathologist considers the differential diagnosis, specimen handling, and optimal ways to gather the most information for diagnostic, prognostic, and therapeutic uses.

Although morphology remains the basis of NRSTS diagnosis, cytogenetic and molecular genetic abnormalities play an increasing role in diagnosis and prognosis [37–39]. Knowledgeable application of cytogenetic and molecular genetic tests in combination with histomorphology, immunohistochemistry, and electron microscopy is increasingly important in practice. Table 1 summarizes the key histologic features, immunohistochemical profile, and genetic aberrations of the more common pediatric NRSTSs.

Grading of sarcomas is based on the degree of malignancy and possibility of metastasis and is therefore an indicator of prognosis. The pathologist assesses tumor grade on the basis of the mitotic rate, necrosis, the extent of differentiation, the histologic type, and occasionally other features. The Pediatric Oncology Group (POG) grading system for pediatric NRSTS is based on the National Cancer Institute (NCI) sarcoma grading system [40]. The French Federation of Cancer Centers (FNCLCC) grading system for sarcomas is based on adult data. Its applicability to pediatric NRSTS has not been resolved.

Pediatric and adult NRSTSs can be pathologically challenging. Limited data from adult studies suggest diagnostic discrepancies in a significant proportion of cases [41, 42], but no data specific to pediatric sarcomas are available. Consultation is prudent when there is diagnostic uncertainty.

CLINICAL PRESENTATION

Because of its rarity, NRSTS may not be suspected by the pediatric primary care provider. In a retrospective study of children with soft tissue sarcomas, the median interval between the onset of symptoms and the diagnostic biopsy was 9.5 weeks [43]. Only epithelial and bone tumors had a longer lag time. In pediatrics, the differential diagnosis of NRSTS includes other solid cancers (rhabdomyosarcoma, Ewing sarcoma, neuroblastoma, and osteosarcoma), hematologic malignancies presenting with lymphadenopathy or chloroma, Langerhans’ cell histiocytosis, benign tumors such as neurofibroma and lipoma, and nonproliferative entities such as cysts and abscesses.

A painless mass is the most common presenting symptom of NRSTS, although impingement on normal structures may produce pain or other symptoms. Systemic

symptoms such as fever and weight loss are rare. About 15% of patients have metastatic disease (most commonly pulmonary) at the time of initial presentation [44]. Regional lymph node involvement is uncommon except in epithelioid sarcoma and clear cell sarcoma [45]. Bone, liver, brain, and subcutaneous metastases have been reported in a small proportion of children with metastatic disease [44]; bone marrow involvement is exceedingly rare.

DIAGNOSTIC EVALUATION

An adequate tumor specimen is required to identify the histologic subtype and grade of NRSTS. Although incisional biopsy is preferred, multiple core needle biopsies may be sufficient [46]. Fine-needle aspiration cytology is inadequate for the initial diagnosis, but may be useful at the time of suspected tumor recurrence [47].

Diagnostic imaging of the primary tumor before surgical resection delineates its boundaries for surgical planning and provides baseline measurements for assessment of the response to neoadjuvant therapy. Magnetic resonance imaging provides excellent soft tissue definition, and is therefore preferable for most anatomic sites. Computed tomography (CT) may be more useful for tumors within the chest and abdominal/pelvic cavities.

Assessment for metastasis depends on the histologic subtype and location of the tumor. Imaging of the draining nodal bed can define the extent of nodal involvement in tumors with a propensity for nodal metastasis (e.g., epithelioid sarcoma) [45] and when palpable adenopathy is present. Sentinel lymph node mapping may detect occult nodal disease [48] and should be considered in patients at high risk for lymph node metastasis. Because the lung is the most common site of distant metastasis, all patients with newly diagnosed NRSTS should have a chest x-ray or CT scan [49]. Liver imaging is needed only for intra-abdominal and retroperitoneal NRSTS and bone scintigraphy is needed only for patients with bone pain or other sites of metastasis [50]. Brain imaging is warranted only for symptoms referable to the brain and perhaps for those with widespread metastatic disease [51]. Bone marrow evaluation is not indicated.

PROGNOSTIC FACTORS

Few prospective studies have been conducted in children with NRSTS [52–54]. Our understanding of the factors that influence prognosis are derived largely from retrospective case series and studies in adults. The factors that most clearly influence survival outcomes in pediatric NRSTS are extent of disease (metastatic versus nonmetastatic), histologic grade, size of the primary tumor, and extent of resection, as in adult soft tissue sarcomas [1, 44, 52–57]. These

factors can be used to designate tumors as high, intermediate, and low risk. A high-risk category indicates metastatic disease; survival is approximately 15%, and most patients die of progressive metastatic disease. Intermediate risk indicates an unresectable tumor or a tumor that is both high grade and >5 cm in maximal diameter; survival is approximately 50%. Patients with unresectable tumors, regardless of histologic grade, usually succumb to local progression, whereas those with large, high-grade tumors typically die of metastatic disease. Low-risk tumors are resectable tumors that are either high-grade and <5 cm in diameter or low-grade (any size); survival is approximately 90%. Other factors that may influence survival but are not known to be independent predictors include the microscopic surgical margin (in resected tumors), primary site (visceral sites appear to have an inferior outcome), and age (age ≥ 10 years is an adverse factor in unresectable tumors) [56, 57]. Other factors correlated with survival in adult soft tissue sarcomas (upper versus lower extremity, superficial versus deep, histologic subtype) [58] have not been shown to be prognostically important in pediatric NRSTS.

The likelihood of local tumor control appears to depend more on the extent of resection than on tumor grade and size. Patients with negative microscopic margins fare best, those with microscopic residual disease fare less well, and those with gross residual disease fare worst. Radiotherapy also lowers the risk for local tumor recurrence.

CLINICAL STAGING

Despite the relatively high frequency of pediatric NRSTS, no pediatric NRSTS staging system has been validated. The Intergroup Rhabdomyosarcoma Study Group's surgicopathologic staging system for rhabdomyosarcoma has been used [59], but accounts only for the extent of disease and tumor resection. Other important predictors of outcome, such as tumor grade and size, are not included.

Staging systems commonly used for adult soft tissue sarcomas include those developed by the American Joint Committee on Cancer [60], the Memorial Sloan-Kettering Cancer Center (MSKCC) [61], and the Musculoskeletal Tumor Society (MTS) [62]. Each considers disease extent and grade, and all but the MTS system include tumor size. In adults with nonmetastatic extremity soft tissue sarcomas, the MSKCC system was superior in predicting metastatic recurrence [63]. The system most useful for pediatric NRSTS remains to be determined.

Tumor grade is a key component of the major staging systems. Of the various grading systems used for adult soft tissue sarcomas, however, none includes the unique pediatric histologic subtypes. The POG prospectively validated a pediatric NRSTS grading system [40] based largely on the

NCI system [64]. Although the POG system is commonly used, the FNCLCC grading system may be superior to the NCI system, on which the POG grading system is based; therefore, modification of the FNCLCC system for pediatric use may be warranted [65]. The ongoing Children's Oncology Group pediatric NRSTS study is addressing this issue.

TREATMENT

Surgery

Because NRSTSs are relatively resistant to chemotherapy and radiotherapy, surgical resection of all gross disease is important. Unfortunately, wide resection may not be feasible or may cause unacceptable functional or cosmetic outcomes. Therefore, less aggressive marginal surgical resection may be appropriate. Amputation is generally reserved for patients whose tumor cannot otherwise be grossly resected or whose functional outcome after limb-sparing surgery may be poor. Pediatric patients appear to adapt well psychologically to amputation [66].

High-dose adjuvant radiotherapy is usually sufficient to control microscopic residual NRSTS. In adults with soft tissue sarcomas, amputation appeared to offer slightly better local tumor control than limb-sparing surgery with radiotherapy, although overall survival did not differ [67]. Therefore, the choice of wide resection versus limb-sparing surgery with radiotherapy depends on the likely side effects of each option.

The long-term risks of radiotherapy (impaired soft tissue and bone growth, mobility restriction, secondary sarcomas) must be considered in weighing wide resection versus marginal resection and adjuvant radiotherapy. Several retrospective adult studies suggest that radiotherapy is unnecessary after wide resection [68, 69]. The efficacy and safety of this approach are being confirmed in a prospective Children's Oncology Group trial.

Adjuvant radiotherapy may also reasonably be avoided for microscopic residual low-grade NRSTS. Although the risk for local recurrence is 25%–50% [56, 70], recurrent tumor may be adequately treated surgically, with or without radiotherapy. This approach may avert radiotherapy in a significant proportion of patients, although a small subset will require two operations.

A small proportion of patients with metastatic disease can be cured if all distant metastases are completely excised. Pulmonary metastasectomy is not advised for patients with widespread parenchymal metastases or for those with extensive mediastinal or chest wall involvement. Candidates for pulmonary metastasectomy should have adequately controlled primary tumor, no extrapulmonary

metastatic disease, and adequate pulmonary function. Complete resection of all pulmonary metastases is prognostically more important than the number of tumors removed; therefore, metastasectomy should be considered regardless of the number of nodules if complete resection is anticipated [71].

Radiation Therapy

Radiotherapy alone can control gross disease in patients with rhabdomyosarcoma and Ewing sarcoma, but is rarely successful in those with unresectable NRSTS [72]. Therefore, gross total resection should be performed if at all possible. Adjuvant radiotherapy significantly decreases the risk for local recurrence in patients with microscopic residual disease, whether the tumor is low or high grade [73]. As noted above, radiotherapy may be excluded for selected patients with grossly excised tumor.

Whole-lung radiotherapy is not recommended for patients with pulmonary metastatic NRSTS because the toxicity-to-efficacy ratio is too high. However, radiotherapy should be considered for the treatment of limited microscopic metastatic disease after metastasectomy.

Radiotherapy dosing and target volume recommendations for pediatric NRSTS are evolving. The radiotherapy doses typically used in adults with soft tissue sarcomas (63–70 Gy) may be reasonable for older adolescents but not for younger children. In the absence of data confirming the lowest adequate dose, factors such as patient age, tumor grade and site, and surgical margin should be considered.

The timing of radiotherapy depends on the diagnosis and tumor grade, primary site, extent of disease, and planned surgery and/or chemotherapy. Preoperative radiotherapy, with or without chemotherapy, may improve the quality of surgical resection in some cases. Theoretically, radiotherapy may be more effective against a well-oxygenated, intact tumor (i.e., preoperatively) than against a hypoxic tumor bed postoperatively. Preoperative radiotherapy may also decrease the risk for tumor spillage during surgery, and permit the use of smaller radiation doses and fields. In adult soft tissue sarcomas, 44 Gy of preoperative radiotherapy in combination with chemotherapy produced an approximately 90% local tumor control rate [74]. Adults receiving preoperative radiotherapy also appear to have better functional outcomes than those treated postoperatively [75, 76]. Potential disadvantages of preoperative radiotherapy include a delay in surgery, a higher risk for wound-healing complications, and less information about tumor pathology.

Brachytherapy and newer technologies such as intensity-modulated radiation therapy (IMRT) and proton beam therapy have an important place in the treatment of

pediatric NRSTS. The advantages of brachytherapy include sparing of surrounding normal tissues and the short duration of treatment. Intraoperative radiotherapy produces encouraging rates of local control when combined with external-beam radiotherapy for adult retroperitoneal sarcomas [77], although data in children are limited [78]. Interstitial brachytherapy has produced encouraging rates of local tumor control in children with soft tissue sarcomas [79]; however, documentation of its tissue-sparing effects compared with external-beam radiotherapy is limited. IMRT is another approach that may permit sufficient doses of radiotherapy to reach the tumor volume while simultaneously sparing critical surrounding structures. Small studies in children with rhabdomyosarcoma document adequate local tumor control with IMRT [80]. Again, though, there is limited information about radiotherapy-related late effects in patients treated with IMRT compared with those in patients treated with standard radiotherapy techniques. Proton beam radiotherapy has the potential to reduce the late side effects of radiation, which are of particular concern in children. To date, in pediatrics, proton beam radiotherapy has proven to be helpful mainly in the treatment of brain tumors [81, 82]. However, a small series of children treated with proton radiotherapy for orbital rhabdomyosarcoma demonstrated adequate local control with sparing of normal surrounding structures, compared with photon irradiation [83]. Studies evaluating these newer radiotherapy techniques in children with NRSTS are needed.

Chemotherapy

Chemotherapy for both childhood NRSTSs and adult soft tissue sarcomas is controversial. NRSTSs, unlike other pediatric sarcomas, are relatively chemoresistant. Limited prospective pediatric NRSTS studies suggest a response rate of 35%–40% [52, 53], similar to findings in adults. It is not known whether chemotherapy provides a survival benefit in children. In adults, chemotherapy appears to prolong survival but may not significantly increase the proportion of long-term survivors [84, 85].

Because chemotherapy has limited efficacy and causes both short- and long-term toxicity, treatment recommendations require caution. Chemotherapy is indicated most clearly for nonmetastatic but unresectable tumors, which may then become resectable and curable. Concomitant preoperative radiotherapy should be considered for these patients, because the response rate may be greater for combined chemotherapy and radiotherapy than for either modality alone [57]. Chemotherapy should also be considered for nonmetastatic tumors that are both high grade and >5 cm in diameter. These tumors

carry a significant risk for distant metastatic recurrence and only a 50% likelihood of long-term survival. Although chemotherapy is often used for metastatic disease, its efficacy is debatable; the only survivors are those whose disease can be completely resected.

The most active agents against adult soft tissue sarcomas are doxorubicin and ifosfamide [86], although it is unclear whether this combination is superior to doxorubicin alone. Dose-intensive regimens, which may be tolerated better by children than adults, appear to induce a higher response rate that may be of particular benefit to patients with unresectable tumors [87]. Gemcitabine and docetaxel have shown limited single-agent efficacy in adult phase II studies [88, 89]; the combination appears to be slightly more effective, particularly against leiomyosarcoma [90, 91]. The taxanes have shown promising activity against angiosarcoma [92]. Dose-intensive chemotherapy with stem cell rescue has not been studied in children, but adult studies have shown no significant benefit [93].

Given the limited efficacy and substantial toxicity of chemotherapy, novel therapeutic approaches, based on the rational application of “targeted” therapies, are being actively sought (Table 2). Unfortunately, many of these drugs have not yet undergone phase I or II testing in children. Because the efficacy of these targeted therapies will likely be histology specific, the small number of children with recurrent soft tissue sarcomas makes these clinical trials particularly challenging.

RECURRENT DISEASE

Little is known about the likelihood of survival when NRSTS recurs or progresses after frontline treatment. Among patients who undergo initial gross total tumor resection, those who experience local recurrence fare better than those who develop metastatic disease (5-year postrecurrence survival rate, 77% versus 36%) [56]. However, the situation is reversed when the tumor is initially unresectable; the outcome is worse after local tumor recurrence/progression than after distant metastasis (5-year postrecurrence survival rate, 9% versus 29%) [57]. The dismal outcome after local recurrence or progression is likely to reflect the unresectability of most locally recurrent tumors and the limitation of treatment options by prior radiotherapy.

Repeat resection of recurrent pulmonary nodules after metastasectomy may be warranted in patients with few adverse risk factors. Adults with soft tissue sarcomas who had at most one adverse risk factor (high-grade tumor, more than three nodules, or any lesion >2 cm) had a significantly longer median disease-specific survival time than those

Table 2. Novel systemic therapeutic approaches for soft tissue sarcomas

Target	Example of drug	Tumor type	Specific target
Receptor tyrosine kinases	Imatinib [98]; sunitinib [99]	GIST	Kit, PDGFR-A
	Imatinib [100]	DFSP	PDGFR-B
	Sorafenib [101]	Angiosarcoma	Raf kinase
Heat shock proteins	IPI-504 [102, 103]	GIST, synovial sarcoma	Hsp-90
Cell cycle progression	Flavopiridol [104]	GIST	Multiple kinases, including Cdks
Cell growth and development	AP23573 [105, 106]	STS	mTOR
Angiogenesis	Bevacizumab [107]	STS	VEGF
Developmental signaling pathways	Triparanol [108]	Chondrosarcoma	Hedgehog
	FK228 [109]	Synovial sarcoma	Histone deacetylase
DNA repair, transcription factor modulation	ET-743 [110]	Liposarcoma, leiomyosarcoma	Nucleotide excision repair

Abbreviations: DFSP, dermatofibrosarcoma protuberans; GIST, gastrointestinal stromal tumor; Hsp-90, heat shock protein-90; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; STS, soft tissue sarcomas; VEGF, vascular endothelial growth factor.

with three adverse risk factors (65 months versus 10 months) [94].

LATE EFFECTS OF TREATMENT

Survivors of NRSTS face numerous long-term complications of therapy. Surgical interventions may impair organ function and may result in permanent disability or disfigurement. Radiotherapy may contribute to disability and disfigurement via its effects on tissue growth and development. Tissue fibrosis, growth arrest, joint dysfunction, and fracture are among the side effects seen. The likelihood of a radiation-induced second cancer after NRSTS has not been studied, although the risk is significantly increased after similar therapy for other childhood cancers [11]. The long-term sequelae of chemotherapy include cardiomyopathy [95] (doxorubicin), renal impairment [96] and gonadal hormonal failure/infertility [97] (ifosfamide), and second cancers (doxorubicin and ifosfamide).

CONCLUSIONS

The rarity of each histologic subtype of NRSTS and the absence of clinical trial data complicate the selection of treatment for children. Prospective pediatric clinical trials are needed to clarify predictors of outcome for risk-directed therapy. An appropriate histologic grading system and a staging system for pediatric NRSTS must be chosen. Among the most pressing therapeutic questions is which patients can safely be treated with surgery alone. For those who require radiotherapy, the minimum dose and field of

radiotherapy necessary for adequate local tumor control must be defined. Indications for chemotherapy must be clarified, and more effective and less toxic systemic treatment must be sought. For patients with unresectable disease, the optimal sequencing of chemotherapy and radiotherapy remains to be defined. As novel therapeutic targets are identified, the challenge will be to integrate targeted therapy into the multimodal approach to NRSTS. Finally, much work remains to be done to care for long-term NRSTS survivors. The risks faced by the growing survivor population remain poorly defined, as does optimal monitoring and intervention.

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AUTHOR CONTRIBUTIONS

Conception/design: Sheri L. Spunt
Administrative support: Sheri L. Spunt
Collection/assembly of data: Sheri L. Spunt, Stephen X. Skapek, Cheryl M. Coffin
Data analysis and interpretation: Sheri L. Spunt, Stephen X. Skapek, Cheryl M. Coffin
Manuscript writing: Sheri L. Spunt, Stephen X. Skapek, Cheryl M. Coffin
Final approval of manuscript: Sheri L. Spunt, Stephen X. Skapek, Cheryl M. Coffin

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