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Pediatric Soft Tissue Sarcomas

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Abstract

Soft tissue sarcomas in children are relatively rare. Approximately 850 to 900 children and adolescents are diagnosed each year with rhabdomyosarcoma (RMS) or one of the non-RMS soft tissue sarcomas (NRSTS). Of these, 350 are cases of RMS. RMS is the most common soft tissue sarcoma in children 14 years old and younger, and NRSTS is more common in adolescents and young adults. Infants also get NRSTS, but their tumors constitute a distinctive set of histologies, including infantile fibrosarcoma and malignant hemangiopericytoma, not seen in adolescents. Surgery is a major therapeutic modality for all pediatric soft tissue sarcomas, and radiation can play a role in the local therapy for these tumors. RMS is always treated with adjuvant chemotherapy, whereas chemotherapy is reserved for the subset of NRSTS that are high grade or unresectable. This review discusses the etiology, biology, and treatment of pediatric soft tissue sarcomas, including new approaches to therapy aimed at improving the dismal prognosis of patients who have recurrent and metastatic disease.

Rhabdomyosarcoma

Epidemiology

RMS is the most common soft tissue sarcoma among children less than 15 years old, with an incidence of 4.6 per million per year [1]. This represents 50% of all soft tissue sarcomas in this age range. It is slightly more common in boys than in girls, with a ratio of 1.1:1. RMS is

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slightly more common in white children than in black children less than 5 years old (1.1:1) but is more common in black children than in white children 5 years of age or older (1.2:1). Over the past 30 years, the incidence of RMS in the pediatric age group has been constant [1].

Etiology

Little is known about the etiology of RMS. A few cases are associated with Li-Fraumeni syndrome (caused by germline mutations in p53) [2] or with neurofibromatosis (caused by mutations in NF1) [3]. There also is a weak association with congenital anomalies, especially in boys [4]. These tumors sometimes are seen as second malignant neoplasms after radiation therapy.

Molecular and cellular biology

There are two major histologic variants of RMS—embryonal and alveolar. Other, minor, histologic types include spindle cell, botryoid, and pleomorphic. Embryonal RMS is named for its resemblance to immature skeletal muscle, accounts for 60% of RMS cases in patients less than 20 years of age, and tends to arise in the head and neck region, orbits, and genitourinary region (including bladder and prostate). Alveolar RMS, named for its resemblance to normal lung parenchyma, arises predominantly in the head and neck region and the extremities [3]. Histologically, RMS is a small round blue cell tumor, characterized by expression of muscle-specific antigens, such as desmin and MyoD, and by the presence of eosinophilic rhabdomyoblasts on standard pathologic staining.

Alveolar RMS is characterized by the presence of one of two recurrent chromosomal translocations: t(2;13)(q35;q14), seen in 55% of cases, or t(1;13)(p36;q14), seen in 22% of cases [5]. These fuse the FKHR gene on chromosome 13 with PAX 3 (chromosome 2) or PAX 7 (chromosome 1). In each case, the DNA-binding domain of the PAX gene is fused to the transactivation domain of the FKHR gene. Disruption of PAX genes leads to abnormal muscle development [6], suggesting a causal relationship between the translocation and the development of malignancy. The PAX3-FKHR translocation seems to carry a poorer prognosis than PAX7-FKHR [7].

Recurrent translocations have not been identified in cases of embyronal RMS. As the age of molecular medicine is begun, there is a movement toward redefining the subtypes of RMS as “translocation associated” and “non–translocation associated,” allowing a disease classification based on objective molecular data rather than on subjective histologic appearance.

Clinical description

Signs and symptoms at the time of diagnosis depend on the location of the primary tumor. In general, patients present with a painless mass, although involvement of cortical bone causes pain, orbital tumors may present with proptosis, and genitourinary tumors often present with hematuria. Head and neck primaries account for 29% of cases of embryonal RMS and for 22% of alveolar RMS. Extremity primaries account for 39% of cases of alveolar RMS but

only 6% of embryonal cases. In contrast, 28% of cases of embryonal RMS arise in the genitals, bladder, and prostate whereas only 3% of alveolar cases arise in these areas [5].

Evaluation and management

The initial evaluation of patients who have RMS involves determining a patient's stage and clinical group. A biopsy is required for diagnosis, and because clinical grouping of RMS is based in part on the extent of surgery, an excisional biopsy is preferred. When complete excision of the tumor is not feasible, an incisional biopsy is still necessary to confirm the diagnosis. Staging usually consists of a CT scan of the chest, abdomen, and pelvis; a bone scan; and bone marrow aspirates and biopsies (Fig. 1). The role of positron emission tomographic (PET) scanning in the evaluation of RMS patients remains controversial. A retrospective study of the usefulness of PET scans in the staging of patients who had RMS from Memorial Sloan-Kettering Cancer Center showed that a negative PET excluded disease in 21 of 23 cases where a CT or MRI was equivocal, but PET failed to show disease in 10 other sites where it was clearly visualized by CT, MRI, or bone scan (and confirmed clinically) [8]. Thus, a prospective study is necessary to definitively determine the value of PET in the evaluation of patients who have RMS.

RMS is staged using a disease-specific TNM staging system (Table 1). Unique to this system is the recognition that some sites of disease (orbit, head and neck, and biliary tract, for example) carry an inherent more favorable prognosis [9]. In addition to staging, a clinical group is assigned to each patient (Table 2), based on the extent of initial resection, margin status, lymph node involvement, and distant spread. Intergroup Rhabdomyosarcoma Study Group (IRSG) studies have demonstrated that clinical group is one of the most important predictors of treatment failure [10], further emphasizing the important role the initial surgery plays in overall patient outcome. After assignment of a stage and clinical group, this information is combined to categorize patients as low, intermediate, or high risk (Table 3), which determines the specific treatment course.

Because of the importance of clinical group in determining treatment and prognosis, and because of the dependence of clinical grouping on the initial surgery, adherence to appropriate surgical principles is critical. The basic principle of wide and complete resection with a surrounding envelope of normal tissue should be followed whenever and wherever possible, as long as sacrifice of surrounding normal tissue does not result in unacceptable loss of function or is not feasible.

Pathologic confirmation of clinically positive lymph nodes is essential, because this has a direct impact on the extent of radiotherapy. There is little literature available on the role of sentinel lymph node identification and biopsy in patients who have RMS, but this approach may be helpful in RMS of the extremities [11], where the current Children's Oncology Group (COG) recommendation is for aggressive regional lymph node sampling. Prophylactic regional node dissection is not recommended, but staging ipsilateral retroperitoneal lymph node dissection is required for all boys 10 years of age or older who have paratesticular RMS or patients less than 10 years old who have radiographically positive nodes.

If the initial surgical procedure is a biopsy or an excision designed for a benign tumor, the question of pretreatment re-excision often arises. Wide re-excision is the current recommendation in such cases, unless this results in unacceptable loss of function or an unacceptable cosmetic result. If this re-excision is performed before administration of chemotherapy, it results in a lower clinical group and a more favorable prognosis. In patients for whom local radiotherapy is the primary local treatment modality, a residual persistent mass is common and is not associated with patient outcome [12]. For that reason, second-look surgeries are not routinely recommended.

The treatment of RMS has evolved over time, driven primarily by national cooperative group studies under the auspices of the IRSG. The success of this approach is evident from comparing survival of patients who have had RMS treated in successive IRSG studies. From IRS-I through IRS-IV there has been steady improvement in patient outcomes (Fig. 2).

Guidelines for the use of local radiotherapy depend on clinical group. Analysis of clinical group I patients treated in the first four IRSG studies showed a significant benefit to the use of radiotherapy for patients who had alveolar histology in local control and overall survival [13]. Radiotherapy for clinical group II patients has been used routinely in the IRS studies with local and regional failure rates of 8% and 4% at 5 years [14]. Good local control has been reported historically with radiotherapy for clinical group III patients also, with a local failure rate of only 13% at 5 years on IRS-IV [15]. Some cooperative groups have attempted to minimize the impact of local therapy by withholding radiotherapy in clinical group III patients who had favorable response to chemotherapy or patients whose disease is resected after induction chemotherapy, but this approach is associated with unfavorable local control and decreased survival [16,17].

As with other high-grade solid tumors, successful treatment of RMS requires systemic chemotherapy, which is used to treat distant metastases or prevent the progression of micrometastases to overt disease. The specifics of systemic chemotherapy vary depending on risk stratification. For low-risk patients, current standard therapy consists of four cycles of vincristine, actinomycin, and cyclophosphamide (VAC) followed by four cycles of vincristine and actinomycin for the lowest-risk patients and 12 cycles of vincristine and actinomycin for the patients who have slightly higher-risk tumors. For intermediate-risk patients, standard treatment consists of 14 cycles of VAC. Currently, the COG is conducting a clinical trial comparing this with 14 cycles of alternating VAC and vincristine and irinotecan. For high-risk patients, the current COG protocol treats patients with an admixture of chemotherapy cycles including vincristine and irinotecan; vincristine, doxorubicin, and cyclophosphamide; and ifosfamide and etoposide, with a total of 20 cycles of therapy. Because of the dismal prognosis for patients presenting with metastatic RMS, autologous peripheral blood stem cell transplant has been used; however, its role is not established and its use should be reserved for clinical trials.

Nonrhabdomyosarcoma soft tissue sarcomas

Epidemiology

The incidence of soft tissue sarcomas in children younger than 20 years of age is 11.0 per million, representing 7.4% of cancer cases in this age group [1]. Approximately 60% of these are NRSTS. These tumors are rare in younger children and become more common with increasing patient age, and in older adolescents these tumors are more common than RMS, although no single histology accounts for more than 15% of all cases [1].

Etiology

There are no known causes, or even risk factors, for the development of NRSTS in children or adolescents.

Molecular and cellular biology

There is a wide variety of histologic tumor types grouped under the umbrella term, NRSTS. These correspond to the various normal cell types that develop from mesenchymal cells (Table 4). The International Classification of Childhood Cancer subdivides pediatric NRSTS into four categories: (1) the fibrosarcoma category, (2) Kaposi's sarcoma, (3) the "other specified" soft tissue sarcomas (including synovial sarcoma, angiosarcoma, and hemangiopericytoma; leiomyosarcoma; liposarcoma; and extraosseous Ewing's sarcoma), and (4) "unspecified" soft tissue sarcomas [1]. These categories are useful for epidemiology but ultimately have no bearing on treatment or prognosis.

Many of the NRSTS tumors have a characteristic chromosomal alteration that, along with distinctive histology, allows for definitive diagnosis (Table 5). In at least one such case, the t(17;22) found in dermatofibrosarcoma protuberans, the characteristic translocation provides a target for tumor-directed treatment. This translocation puts the platelet-derived growth factor (PDGF) β-chain under the control of the constitutively active collagen type Ia promoter, resulting in autocrine stimulation of the PDGF receptor. Inhibition of this receptor with imatinib mesylate resulted in an objective response in nine of nine patients in a recently published study from Australia [18]. It is hoped that future research will allow the development of additional therapies targeted at the molecular abnormalities that cause these cancers.

Clinical description

Typically, NRSTS presents with a painless mass that is found by a patient or a patient's parents. Usually, these masses are slow growing, and symptoms, if any, are the result of compression or invasion of normal structures and, therefore, vary by tumor location. Orbital tumors, for example, may cause proptosis, whereas intra-abdominal tumors may cause abdominal fullness, constipation, back pain, or early satiety.

Evaluation and management

The evaluation of a soft tissue mass in a child begins with careful imaging of the primary tumor, usually with an MRI. This provides superior anatomic definition, may be helpful in distinguishing benign from malignant tumors, and provides the necessary information

regarding proximity to surrounding neurovascular structures that allow appropriate surgical planning by an orthopedic or surgical oncologist. A CT scan of the chest, abdomen, and pelvis is an important part of the evaluation for metastatic disease. ^{18}Fluorodeoxyglucose-PET scan is gaining in importance for diagnostic purposes and for evaluating response to therapy [19,20].

A biopsy is necessary to establish the diagnosis. In most cases, a core needle biopsy is adequate to obtain diagnostic tissue, and the accuracy of core needle biopsies is excellent, with a high sensitivity and specificity [21–23]. Combined with low morbidity, this is the diagnostic procedure of choice. It is recommended that biopsies be obtained by a trained orthopedic surgical oncologist or radiologist and preferably at a multidisciplinary sarcoma treatment center. The biopsy site should be chosen so that the track lies in the field of future en bloc resection [24]. If a core needle biopsy does not provide a diagnosis, a surgical biopsy becomes necessary.

Surgery remains the mainstay of treatment for NRSTS. The goal of surgical excision is complete removal of the mass with a margin of surrounding normal tissue. In general, a 1-cm margin is considered acceptable, and closer margins should prompt consideration of re-excision. When tumors abut critical neurovascular structures, complete resection risks compromising the integrity of distal structures. Under these conditions, adequate resection may not be possible, and such patients require adjuvant chemotherapy or radiation therapy. Local control rates with limb-sparing surgery for extremity sarcomas, with judicious use of adjuvant radiation therapy, approach 95%, equivalent to what was once obtained with amputation [25,26]. Accordingly, amputation should be reserved for cases of major artery or nerve involvement, sufficiently extensive bone involvement such that removal of the entire bone is required, or recurrence after previous resection with adjuvant radiation therapy.

The role of adjuvant (or neoadjuvant) therapy in the management of NRSTS is still a matter of investigation. It generally is believed that the usefulness of chemotherapy and radiation therapy depends on a patient's risk for relapse and sarcoma-specific death. A nomogram for predicting 12-year sarcoma-specific death rates has been devised based on prospectively collected data from 2136 consecutive adult patients who had soft tissue sarcoma treated at Memorial Sloan-Kettering Cancer Center (Fig. 3) [27]. Prognostic variables, including patient age, tumor size, histologic grade, histologic subtype, and tumor location, were incorporated into the nomogram. The nomogram has been validated using an independent group of patients treated at University of California, Los Angeles and found to provide accurate prognostic information [28]. A study attempting to validate the nomogram for use in a pediatric population found that death rate was underestimated and that the majority of this effect was the result of an increased prognostic importance of tumor size in the pediatric population [29].

Retrospective studies of pediatric NRSTS have identified a similar group of important prognostic factors, including localized versus metastatic disease, extent of tumor resection, maximal tumor diameter, and tumor grade. A retrospective analysis of NRSTS patients treated at St. Jude Children's Research Hospital suggested three risk subgroups: (1) patients who had grossly resected localized tumors, with a predicted 5-year survival of 89%; (2)

patients who had initially unresected localized tumors, with a predicted 5-year survival of 56%; and (3) patients who had metastatic tumors, with a predicted 5-year survival of 15% [30]. This study, however, did not incorporate tumor grade or tumor size in its prognostic subgroups. The current COG NRSTS protocol is designed in part to test a similar risk stratification system that accounts for all of the identified prognostic variables: size, grade, metastatic status, extent of resection, and margin status.

For patients deemed at high risk for metastatic spread, systemic chemotherapy generally is administered. Two chemotherapy drugs have been reliably shown to have activity against a broad spectrum of NRSTS histologies as single agents: doxorubicin and ifosfamide [31,32]. Accordingly, current NRSTS chemotherapy regimens consist of combination therapy with these two drugs.

Because local control with radiotherapy alone is not achievable, radiation is used in combination with surgery. Radiotherapy can be administered as adjuvant or as neoadjuvant treatment to augment the efficacy of the surgery. It also can be given as adjuvant therapy for patients who have positive margins or incompletely resected tumors. The National Cancer Institute of Canada conducted a randomized trial of preoperative radiation compared with postoperative radiation in adults who had soft tissue sarcoma [33]. The preoperative dose was 5000 cGy and the postoperative dose was 6600 cGy. Patients who had positive surgical margins were given a postoperative boost of 1600 cGy. Local control was identical on the two arms, but toxicities were different: wound healing complications were more common on the preoperative radiotherapy arm, whereas late effects, such as fibrosis and joint stiffness, were increased among patients who received postoperative radiotherapy [34,35]. These radiation doses are typical of those used in standard practice. The treatment volume typically encompasses the preoperative tumor or postoperative tumor bed with 5-cm longitudinal margins and 2-cm radial margins. The longitudinal margins are reduced when boost doses are given.

Summary

Pediatric soft tissue sarcomas are rare, with fewer than 1000 new cases per year in the United States. These tumors are subdivided into RMS and the NRSTS. Surgery is a critical component of the treatment of all pediatric soft tissue sarcoma patients. There has been a series of cooperative group studies of RMS, dating back to 1972, which has continuously refined the diagnosis, risk stratification, and treatment of these patients. There is a well-established risk stratification scheme that accounts for tumor histology, location, extent of surgical resection, locoregional lymph node involvement, and the presence of distant metastases. The specifics of treatment depend on risk classification, but all patients who have RMS are treated with adjuvant chemotherapy and most also receive radiation therapy. Future work will aim at maintaining the excellent cure rate for patients who have low-risk disease while decreasing late effects of treatment and improving the outcome for high-risk patients.

In contrast, the treatment of pediatric patients who have NRSTS is less standardized. A nomogram for the prediction of sarcoma-specific death has been developed and validated for

adults who have soft tissue sarcomas, but this algorithm may not be accurate for pediatric patients. A retrospective review of sarcoma patients treated at St. Jude Children's Research Hospital has led to the development of a pediatric soft tissue sarcoma risk stratification scheme, but this has not yet been validated in a national study. Although the importance of radiotherapy has been demonstrated, optimal dose and timing (pre- versus postoperative) has not been determined. Additionally, the role for chemotherapy in the treatment of children who have soft tissue sarcoma remains unclear. An ongoing cooperative group study will attempt to prospectively validate a pediatric soft tissue sarcoma risk stratification scheme and to optimize the use of chemotherapy and radiation therapy for these patients.

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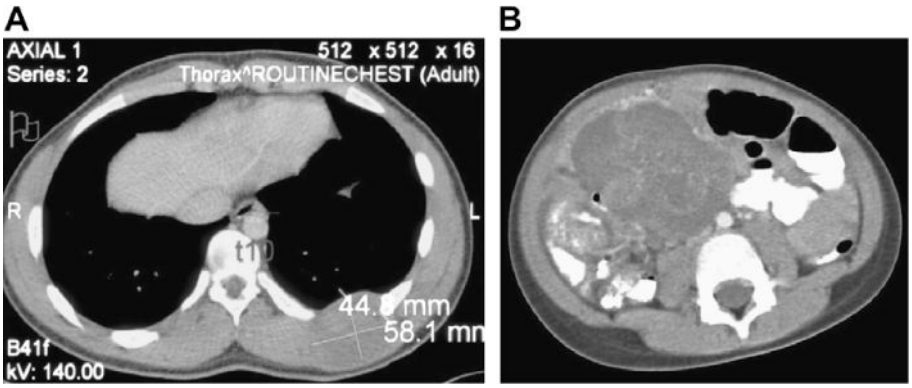

Fig. 1.

CT appearance of RMS. (*A*) Chest CT from a 16-year-old-boy who presented with a “lump on the back.” (*B*) Abdominal CT with intravenous and oral contrast from a 5-year-old girl who presented with abdominal pain and constipation.

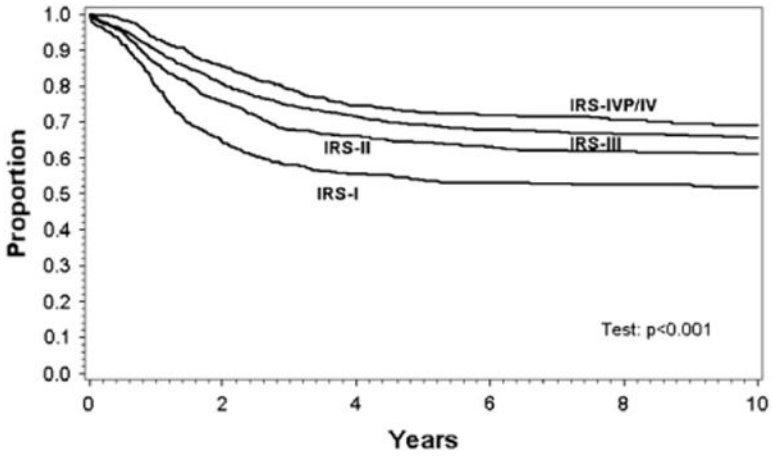

Fig. 2.

Survival IRS-I through IRS-IV. Improvement in survival with successive clinical trials. The overall survival curves for each IRS study are shown. (*Courtesy of* W. Meyer, University of Oklahoma, Oklahoma City, OK; with permission.)

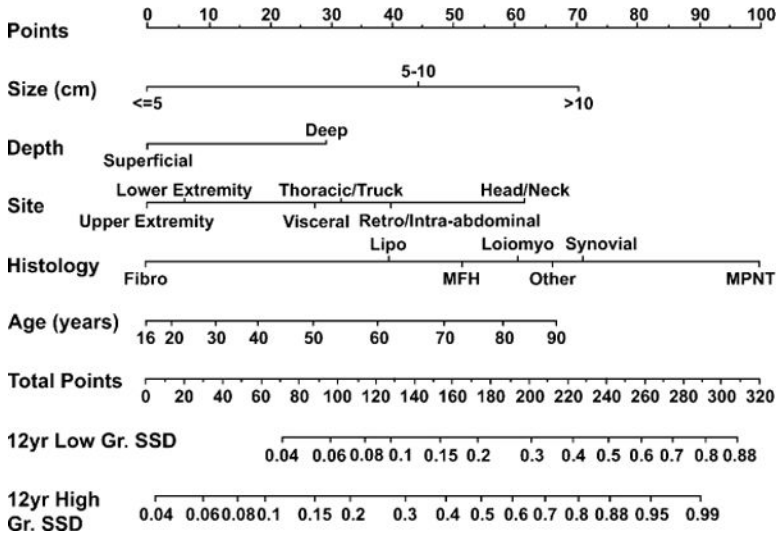

Fig. 3.

Postoperative nomogram for 12-year sarcoma-specific death. Points are added up for size (second line), depth (third line), site (fourth line), histology (fifth line), and patient age (sixth line). A line drawn down from the point total to the low-grade or high-grade line reveals the likelihood of sarcoma-specific death in 12 years. Fibro, fibrosarcoma; GR, grade; Lipo, liposarcoma; leiomyo, leiomyosarcoma; MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral-nerve tumor; SSD, sarcoma-specific death. (*From* Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 2002;20(3):791–6; with permission.)

Table 1

TNM staging of rhabdomyosarcoma

Stage	Sites	T	Size	N	M
1	Orbit	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_0
	Head and neck				
	Genitourinary/not bladder or prostate				
	Biliary tract				
2	Bladder or prostate	T_1 or T_2	a	N_0 or N_x	M_0
	Extremity				
	Cranial parameningeal				
	Other				
3	Bladder or prostate	T_1 or T_2	a	N_1	M_0
	Extremity		b	N_0 or N_1 or N_x	M_0
	Cranial parameningeal				
	Other				
	All	T_1 or T_2	a or b	N_0 or N_1	M_1

Abbreviations: a, ≤5 cm in diameter; b, >5 cm in diameter, N_0, regional lymph nodes not involved; N_1, regional nodes clinically involved with neoplasm; N_X, clinical status of regional nodes unknown; M_0, no distant metastasis; T1, confined to anatomic site of origin; T2, extension or fixation to surrounding tissue.

Table 2

Rhabdomyosarcoma clinical group definitions

Group	Definition
Group I	Localized disease completely resected
Group IIa	Gross total resection with microscopic residual disease
Group IIb	Regionally involved lymph nodes, completely resected with the primary
Group IIc	Regional disease with involved nodes, totally resected with microscopic residual disease or histologic evidence of involvement of the most distant lymph node in the dissection
Group III	Incomplete resection
Group IV	Distant metastases

Table 3

Risk stratification in rhabdomyosarcoma

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

Table 4

Histologic subtypes of nonrhabdomyosarcoma soft tissue sarcomas in pediatric patients

Histology	Normal counterpart	Incidence
Fibrosarcoma	Fibroblast	0.6
Infantile fibrosarcoma	Fibroblast	0.2
Malignant fibrous histiocytoma	Fibroblast	0.8
Dermatofibrosarcoma protuberans	Fibroblast	1.0
Malignant peripheral nerve sheath tumor	Schwann cell	0.6
Kaposi's sarcoma	Blood vessels	0.1
Liposarcoma	Adipocyte	0.1
Leimyosarcoma	Smooth muscle	0.3
Synovial sarcoma	Synovial cells	0.7
Hemangiosarcoma	Blood vessels	0.2
Malignant hemangiopericytoma	Vessel pericytes	0.1
Alveolar soft part sarcoma		0.1
Chondrosarcoma	Chondrocytes	0.1

Incidence is age-adjusted rate per million for patients less than 20 years old.

From Gurney J, Young JL Jr, Roffers SD, et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. Vol NIH Pub. 99-4649. Bethesda (MD): National Cancer Institute, SEER Program; 1999.

Table 5

Cytogenetic abnormalities in soft tissue sarcomas

Diagnosis	Cytogenetic abnormality	Genes involved
Alveolar RMS	t(2;13) or t(1;13)	FKHR on chromosome 13 and PAX3 (chromosome 2) or PAX7 (chromosome 1)
Infantile fibrosarcoma	t(12;15)	TEL (ETV6) on chromosome 12 and NTRK3 (TRKC) on chromosome 15
Dermatofibrosarcoma Protuberans	t(17;22)	PDGF β-chain on chromosome 17 and collagen type Ia on chromosome 22
Synovial sarcoma	t(X;18)	SYT on chromosome 18 and SSX-1 or SSX-2 on the X chromosome
Liposarcoma	t(12;16)	FUS gene on chromosome 16 and CHOP gene on chromosome 12
Myxoid chondrosarcoma	t(9;22)	EWS on chromosome 22 and TEC gene on chromosome 9
Alveolar soft part sarcoma	t(X;17)	Unidentified genes, esp. at chromosome band 17q25