Soft tissue sarcomas

Cynthia E. Herzog, MD

Soft tissue sarcomas (STS) make up 6–8% of pediatric cancer. About half of these are rhabdomyosarcoma (RMS), 15–25% undifferentiated sarcoma (UDS), and the remainder any of a diverse array of tumor types, with no single group predominating. Most STS present as painless, enlarging masses with other symptoms related to the specific site of the tumor.

Rhabdomyosarcoma and undifferentiated sarcoma

RMS is the most common STS, comprising about 50% of all STS with 250–300 new cases a year in the United States. The Intergroup Rhabdomyosarcoma Study I (IRS I) opened in 1972 and currently IRS IV is in progress with patients having either RMS or UDS being eligible for this study. The prognosis for RMS depends on a number of variables, including histology, site, and stage.[4-8]

Histology

The histologic diagnosis of RMS is based on light microscopic findings. Differentiation from other small, round blue-cell tumors is based on immunocytochemical studies using antibodies specific for muscle protein. Electron microscopy also is useful in confirming the diagnosis. The prognostic significance of the subtype of RMS, either embryonal or alveolar, as an independent variable has been called into question. However, when specific definitions are used for classification, histology seems to be a prognostic indicator. The botryoid subtype (8%), an embryonal variant occurring in very young children, has the best prognosis. Embryonal RMS (65%), with an intermediate prognosis, occurs in an intermediate age range. The alveolar subtype (25%) usually has the worst prognosis, and occurs in older children.

Site

Approximately 40% of RMS arise in the head and neck area, with another 20% occurring in the genitourinary region. These tumors usually are identified before regional spread or metastases, and most often display embryonal histology, so they generally have a better outcome. Extremity tumors account for about 20% and trunk tumors 10%, with the remaining 10% occurring in such sites as the retroperitoneum, perineal-perianal area, or biliary tract (Table 1).

Table 1. Primary site of rhabdomyosarcoma and undifferentiated sarcoma

	Relative Frequency (%)	
Primary Site	*IRS I*	*IRS II*
Head and neck total	37	34
Orbit	10	8
Parameningeal	14	18
Other	13	8
Genitourinary tract	21	23
Bladder-prostate		11
Other		12
Extremities	20	17
Trunk	7	—
Other	15	25

Stage

RMS metastasizes primarily to the lungs and bones. Although the extent of tumor is an important prognostic factor (with disseminated disease being an indicator of poor prognosis) the best staging system for RMS is not clear. This issue is being addressed in the current IRS IV Study. Previously, IRS has used a surgical-pathologic staging system (Table 2). This approach has the drawback of being

Table 2. Surgical-pathologic grouping for rhabdomyosarcoma

Clinical Group	*Definition*
I	A. Localized, completely resected, confined to site of origin
	B. Localized, completely resected, infiltrated beyond site of origin
II	A. Localized, grossly resected, microscopic residual
	B. Regional disease, involved lymph nodes, completely resected
	C. Regional disease, involved lymph nodes, grossly resected with microscopic residual
III	A. Local or regional grossly visible disease after biopsy only
	B. Grossly visible disease after ≥ 50% resection of primary tumor
IV	Distant metastases present at diagnosis

dependent on surgical options, which vary with site and surgeon. In IRS IV, this system is being compared to a TNM (tumor, nodes, metastases) system, which is based on evaluation prior to any treatment, including surgery (Table 3).

Current treatment per IRS IV

Surgery should be attempted when feasible — however, resulting function and cosmesis influence whether resection is attempted. Surgery often is not used for head and neck or bladder tumors.

Radiation therapy is indicated except in the case of localized, completely resectable tumors. In the current study, all group I, stage 3 and group II tumors will receive conventional therapy of 41.4 Gy. However, a comparison of conventional dose radiation therapy (50.4 Gy) or hyperfractionated radiotherapy to 59.4 Gy is being made in group III tumors. This is an attempt to improve outcome without the prohibitive toxicity seen with the higher dose of radiation therapy given by conventional means in earlier treatment of RMS.

The mainstay of chemotherapy for RMS and UDS has long been VAC (vincristine sulfate, actinomycin-D, and cyclophosphamide). IRS IV is investigating whether ifosfamide is a more effective agent than cyclophosphamide. All patients with nonmetastatic disease are randomized to receive one of three treatment regimens: 1) VAC (at higher doses than in IRS III), 2) VIE (vincristine, ifosfamide, etoposide), 3) VAI (vincristine, actinomycin-D, ifosfamide). Exceptions to this are group I paratesticular tumors and group I and II orbit or eyelid tumors, which will be given only VA (without cyclophosphamide) because of their good prognosis.

The new study takes a different approach for metastatic tumors. Several drugs that have shown activity in relapsed patients are being used initially in an "up front window" phase II trial. This approach uses promising new therapies as the initial treatment in order to establish the effectiveness on chemotherapy-naive patients. Patients then receive conventional therapy. These patients are initially randomized to receive either VM (vincristine, melphalan) or IE (ifosfamide, etoposide), followed by alternating these combinations with VAC. These will be compared with patients who were treated with ID (ifosfamide, doxorubicin) up front in a pilot study.

The prognosis in IRS II was clearly dependent on clinical grouping and site. Patients with nonmetastatic disease had a 60% long-term progression-free survival, while in those with metastatic disease it was only 23%. Excluding those with alveolar histology, group I patients had a 70–80% disease-free survival (DFS) and group II a 69–74% DFS. Group III patients (excluding some pelvic tumors) had a 74–75% complete response (CR) rate, with 70% in continuous CR after 5 years. Group IV patients had only a 53% CR rate, with 40% continuous CR at 5 years. Likewise, the primary site of tumor was prognostic (Table 4).

TABLE 3. TNM STAGING SYSTEM FOR RHABDOMYOSARCOMA*

Stage	*Sites*	*T*	*Size*	*N*	*M*
1	Orbit Head and neck (excluding parameningeal) Genitourinary (non-bladder/nonprostate)	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_0
2	Bladder/prostate Extremity Cranial parameningeal Other (includes trunk, retroperitoneum, etc.)	T_1 or T_2	a	N_0 or N_x	M_0
3	Bladder/prostate	T_1 or T_2	a	N_1	M_0
	Extremity Cranial parameningeal Other (includes trunk, retroperitoneum, etc.)		b	N_0 or N_1 or N_x	M_0
4	All	T_1 or T_2	a or b	N_0 or N_1	M_1

* Definitions:

Tumor:	$T(site)_1$	Confined to anatomic site of origin
	(a)	≤ 5 cm diameter
	(b)	≥ 5 cm diameter
	$T(site)_2$	extension and/or fixation to surrounding tissue
	(a)	≤ 5 cm diameter
	(b)	≥ 5 cm diameter
Regional Nodes:	N_0	Regional nodes not clinically involved
	N_1	Regional nodes clinically involved by neoplasm
	N_x	Clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation)
Metastasis:	M_0	No distant metastasis
	M_1	Metastasis present

Nonrhabdomyosarcoma (NRS) soft tissue sarcomas

This group of tumors is made up of a number of different histologic subtypes with no one type occurring frequently enough to allow for good controlled studies (Table 5, Table 6).[1-3, 7, 9, 10] Because of this, the optimum treatment for these tumors is not clearly defined, although complete surgical excision should always be performed when possible. Age has been shown to be of prognostic importance in most NRS, with

younger age being associated with a much better prognosis. The role of radiation therapy and chemotherapy has not been adequately determined. Numerous chemotherapeutic agents, including Adriamycin™, vincristine, actinomycin D, cyclophosphamide, etoposide (VP-16), and ifosfamide have been shown to have an effect in many of these tumors. However, the best combination or even the role of chemotherapy has not been definitively determined.

Synovial sarcoma

Synovial sarcoma is the most common NRS-STS. Histologically it is composed of a spindle cell fibrous component and a glandular component with epithelial differentiation. A monophasic form also can occur, but the diagnosis can be made only in the presence of positive immunostaining for keratin. This tumor typically occurs in young adults with 30% of cases in patients younger than age 20. Most arise on extremities, with 15–20% in the head and neck area. Local recurrences are common, along with metastases to lung and bones, as well as lymph-node metastases with the biphasic type. Treatment is wide excision with radiation therapy for microscopic residual disease or close margins. Surgical resection of pulmonary metastasis also is indicated. Stage I and II tumors have a 45–70% 5-year survival, while stage III and IV have a poor survival rate.

TABLE 4. OVERALL 5-YEAR SURVIVAL FROM IRS II

Primary Site	*Total*	*Failures*	*Survival (%)*
Orbit	79	8	92
Head and neck	75	13	81
Parameningeal	157	51	69
Genitourinary (non b/p*)	110	21	80
Genitourinary (b/p*)	97	29	73
Extremities	124	39	70
Other	185	90	53

* b/p = bladder or prostate.

Fibrosarcoma

This is the most common type of STS in children younger than 1 year of age, and has two age peaks: < 5 and 10–15 years. Histologically, anaplastic spindle cells in a herringbone pattern are seen. Most of these tumors occur in the extremities, with 70% of congenital fibrosarcoma in this location. Axial lesions have a higher metastatic potential and greater mortality. The treatment for congenital fibrosarcoma is surgical excision. Since metastatic disease is rare and local recurrence does not worsen prognosis, conservative surgery can be used to preserve function. There is no clear role for adjuvant chemotherapy or radiation, however some have reported more conservative surgical approaches are possible after neoadjuvant chemotherapy. Congenital fibrosarcoma is associated with a much lower mortality than that occurring in adolescents, 11.5 versus 60%.

TABLE 5. HISTOLOGY OF NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMAS

	Number of Patients			
Histologic Type	*McCoy*[1]	*Dillon*[2]	*Horowitz*[3]	*Total*
Synovial sarcoma	4	32	18	54
Fibrosarcoma	3	10	4	17
Mali,qnant fibrous histiocytoma	3	9	5	17
Neurogenic sarcomas	4	8	12	24
Liposarcoma	6		4	10
Dermatofibrosarcoma	4		1	5
Desmoid fibroma	4			4
Epithelioid sarcoma	2			2
Extraosseous Ewing's sarcoma	2			2
Angiosarcoma	2			2
Hemangiopericytoma	1	4	5	10
Leiomyosarcoma		3	2	5
Alveolar soft parts sarcoma			6	6
Other		9	5	14
Total	35	75	62	172

TABLE 6. PRIMARY SITE OF NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMAS

	Number of Patients			
Anatomic Location	*McCoy*[1]	*Dillon*[2]	*Horowitz*[3]	*Total*
Head and neck	9	5	10	24
Extremity (upper/lower)	7/13	16/33	24	93
Trunk	5	21	28	54
Retroperitoneum	1			1
Total	35	75	62	172

Malignant fibrous histiocytoma (MFH)

Although common in adults, MFH is rare in children. Tumors reported as MFH in children may actually represent recurrent fibrosarcoma or fibromatosis. The only type of MFH presenting as a primary tumor in children is the angiomatoid type, which has low metastatic potential and may not be true MFH. These tumors typically present on the extremities, and may be radiation-induced. Treatment is surgical with a questionable role for chemotherapy.

Neurogenic sarcomas

Neurogenic sarcomas are also called neurofibrosarcoma, neurosarcoma, and malignant schwannoma. These tumors occur in association with Neurofibromatosis I. The histologic appearance is similar to fibrosarcoma, but without the herringbone pattern.

Complete surgical excision is the treatment of choice, with radiation to microscopic residual disease. There is no clear role for chemotherapy.

Hemangiopericytoma

This tumor is more common in adults, although an infantile form occurs in very young children. Histologically, a uniform staghorn vascular pattern is seen, with reticulin staining around each cell. Sites of occurrence are extremities, retroperitoneum, head and neck, and trunk. The infantile form is more likely to occur in the head and neck area and can be treated with surgery alone since it has a low metastatic potential. Adjuvant chemotherapy has been used for incompletely resected tumors. The adult form is more aggressive and is treated with a combination of surgery, chemotherapy, and radiation.

Alveolar soft part sarcoma

This is another rare tumor. The histology is uniform in appearance with an alveolar pattern. Periodic acid-Schiff stain is positive for intracellular crystals. The etiology of these crystals is unclear. These tumors more commonly present in the head and neck region in children, primarily the orbit and tongue. Although the prognosis is better in children, the tumor has an indolent course, and can metastasize to lungs, bones, liver, and brain. Treatment is primarily surgical, with radiation therapy and chemotherapy with recurrences.

Nonsarcomatous soft tissue tumors

Nonsarcomatous soft tissue tumors are all rare in the pediatric population, but since they occur in the head and neck area, and since treatment may involve radiation therapy, they deserve special mention in a presentation at a dental symposium.

Nasopharyngeal carcinoma

This tumor presents with several histologic patterns, undifferentiated (lymphoepithelioma), squamous carcinoma, and nonkeratinizing squamous carcinoma. These tumors are more common in Chinese and Southeast Asians. The undifferentiated form is most commonly seen in the pediatric population, presenting in adolescents and is associated with Epstein-Barr Virus. Conventionally these tumors are treated with radiation therapy, however they have been shown to be responsive to chemotherapy, although the role of chemotherapy and the best regimen is unclear. The 5-year DFS is about 60% after radiation therapy.

Juvenile nasopharyngeal angiofibroma

This is a histologically benign, but locally aggressive tumor that presents in adolescent males. The primary treatment is surgical, however with recurrence, radiation or chemotherapy may be used.

Conclusion

About 250 new cases of RMS are diagnosed in children each year, with another 250 cases of NRS-STS also diagnosed. Chemotherapy is always indicated in RMS and is often used in NRS-STS, therefore STS presents a challenge for dental care due to the complications of chemotherapy. Of even more concern for adequate dental care are the 40% of RMS and 10–30% of NRS-STS that occur in the head and neck region. Local therapy for these tumors with surgery and/or radiation therapy will add to the potential dental complications.

Dr. Herzog is assistant professor, Department of Pediatrics, University of Texas, M.D. Anderson Cancer Center, Houston.

1. McCoy DM, Levine EA, Ferrer K, Das Gupta TK: Pediatric soft tissue sarcomas of nonmyogenic origin. J Surg Oncol 53:149–53, 1993.
2. Dillon P, Maurer H, Jenkins J, Krummel T, Parham D, Webber B, Salzberg A: A prospective study of nonrhabdomyosarcoma soft tissue sarcomas in the pediatric age group. J Pediatr Surg 27:241–45, 1992.
3. Horowitz ME, Pratt CB, Webber BL, Huster HO, Etcubanas E, Miliauskas J, Rao BN, Fleming ID, Mabesh Kumer AP, Green AA: Therapy for childhood soft-tissue sarcomas other than rhabdomyosarcoma: a review of 62 cases treated at a single institution. J Clin Oncol 4:559–64, 1986.
4. Maurer HM, Beltangady M, Gehan E, Crist W, Hammond D, Hayes DM, Heyn R, Lawrence W, Newton W, Ortega : The intergroup rhabdomyosarcoma study—I: a final report. Cancer 61:209–20, 1988.
5. Maurer HM, Gehan EA, Beltangady M, Crist W, Dickman PS, Donaldson SS, Feyer C, Hannond D, Hays DM, Hermann J: The intergroup rhabdomyosarcoma study-II. Cancer 71:1904–22, 1993.
6. Raney RB Jr, Hays DM, Tefft M, Triche TJ: Rhabdomyosarcoma and the undifferentiated sarcomas. In: Principles and Practice of Pediatric Oncology, 2nd Ed. Pizzo PA, Poplack DG, Eds. Philadelphia: JB Lippincott Co, 1993, pp 769–94.
7. Miser JS, Pritchard DJ, Triche TJ, Kinsella, TJ: The other soft tissue sarcomas of childhood. In: Principles and Practice of Pediatric Oncology, 2nd Ed. Pizzo PA, Poplack DG, Eds. Philadelphia: JB Lippincott Co, 1993, pp 823–40.
8. Maurer HM, Ragab AH: Rhabdomyosarcoma. In: Clinical Pediatric Oncology, 4th Ed. Fernbach DJ, Vietti TJ, Eds. Mosby-Year Book, Inc, 1991, pp 491–515.
9. Kim TH, Bell BA, Maurer HM, Ragab AH: Sarcomas of the soft tissues and their benign counterparts. In: Clinical Pediatric Oncology, 4th Ed. Fernbach DJ, Vietti TJ, Eds. Mosby-Year Book, Inc, 1991, Chapter 27, pp 517–44.
10. Cangir A: Miscellaneous childhood tumors. In: Clinical Pediatric Oncology, 4th Ed. Fernbach DJ, Vietti TJ, Eds. Mosby-Year Book, Inc, 1991, pp 627–45.