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Pediatric Soft Tissue Sarcomas

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Overview

A malignant tumor of mesenchymal cell origin is called a sarcoma. Mesenchymal cells normally mature into skeletal muscle, smooth muscle, fat, fibrous tissue, bone, and cartilage. Soft tissue sarcomas of children are thought to arise from mesenchymal cells committed to a specific tissue lineage, for example, skeletal muscle (rhabdomyosarcoma [RMS]), smooth muscle (leiomyosarcoma), fat (liposarcoma), fibrous or connective tissue (fibrosarcoma, malignant fibrous histiocytoma [MFH], synovial sarcoma), or peripheral neuronal tissue (malignant peripheral nerve sheath tumors). Other soft tissue sarcomas committed to a specific tissue lineage include hemangiopericytoma, alveolar soft-part sarcoma, and soft tissue clear cell sarcoma. Soft tissue sarcomas, however, may also display multilineage markers, as is seen in ectomesenchymoma (tumors with evidence of both skeletal muscle and neuronal lineage) and malignant Triton tumor (malignant peripheral nerve sheath tumors [schwannomas] with evidence of rhabdomyoblastic elements).

Soft tissue sarcomas are the sixth most common cancer in children.[1] Collectively, these tumors account for about seven percent of all pediatric cancers, with an annual incidence of about eight to nine per million children younger than 19 years of age.[2] The incidence of RMS is equal to or greater than that of all other forms of nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) combined. Important differences in epidemiology, biology, and treatment exist both within the family of RMS and between RMS and NRSTS. Although RMS has traditionally been staged by a unique surgicopathologic staging system (the Clinical Grouping System), there has recently been a move to adopt a more uniform tumor-nodes-metastases (TNM)-based staging system comparable to what has been used for adult NRSTS.

The development of increasingly intensive, multimodality treatment protocols for these tumors, particularly RMS, tested in large-scale, international studies has led to a steady increase in the cure rate for these neoplasms, especially for the group of patients with locally extensive, unresectable tumors. Along with the improvements in outcome, however, has come an increase in both the short- and long-term sequelae of therapy.

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Rhabdomyosarcoma

Epidemiology

The annual incidence of RMS in children younger than 19 years of age is about four to five cases per million children, and slightly more than 200 new cases are diagnosed each year in the United States. Among the extracranial solid tumors of childhood, RMS is the third most com-

mon neoplasm after neuroblastoma and Wilms' tumor.[2] Nearly 50 percent of cases of RMS are diagnosed in children aged five years or younger, with a smaller incidence peak in midadolescence. The tumor is slightly more common in males than in females (about 1.3 to 1.4 times more common). There are no known significant differences in the incidence of these tumors between different races or ethnic groups, although they do appear to be somewhat more common in whites than in blacks in the United States. These tumors may arise virtually anywhere in the body, even in sites where skeletal muscle is not normally found. There are certain distinctive features that appear to cluster around the site of the primary tumor, the age at diagnosis, and histology. For example, head and neck tumors are more common in children younger than eight years of age and when arising in the orbit are almost always of the embryonal variety, while extremity tumors are more common in adolescents and are typically of the alveolar subtype. A unique form of RMS arising from the bladder or vagina, the botryoid variant (so named because of its resemblance to a protruding cluster of grapes), is almost exclusively seen in infants.

Soft tissue sarcomas are the sixth most common cancer in children.

While the overwhelming majority of RMS cases occur sporadically in a population, the now well-defined family cancer syndrome known as the Li-Fraumeni syndrome includes RMS and other soft tissue sarcomas.[3,4] Recently, this syndrome has been associated with germline mutations of the p53 gene.[5] In a study of 151 children with soft tissue sarcoma, a genetic predisposition to cancer was thought to be present in seven to 33 percent of patients based on the patterns of cancer in their families.[6] These included other syndromes that appeared to not include p53 abnormalities. Of further interest, RMS has been observed in association with Beckwith-Wiedemann syndrome, a fetal overgrowth syndrome associated with abnormalities on 11p15, where the gene for insulin-like growth factor II (IGFII) is located. Some of the factors that may play a role in these phenomena are discussed below.

Biology

While the cause of RMS remains unknown, much has been learned in the past decade regarding molecular genetic alterations that are associated with the development of this tumor. In this section, we will review the known genetic alterations that are seen in these tumors.

The two major histologic subtypes of RMS, embryonal and alveolar, have indeed been found to have characteristic but distinct genetic alterations that are presumed to play a role in the pathogenesis of these tumors. Alveolar RMS has been demonstrated to have a characteristic translocation between the long arm of chromosome 2 and the long arm of chromosome 13, referred to in cytogenetic notation as t(2;13)(q35;q14).[7,8] Recently, this translocation has been molecularly cloned and has been shown to involve the juxtaposition of the *PAX3* gene, believed to regulate transcription during early neuromuscular development, and the *ALV* gene, a member of the forkhead family of transcription factors.[9,10] While the precise consequence of this tumor-specific translocation remains to be elucidated, polymerase-chain-reaction (PCR) assays are now available that allow for precise confirmation of the diagnosis of alveolar RMS.[10]

The other major histologic subtype, embryonal RMS, is now known to have loss of heterozygosity (LOH) at the 11p15 locus.[11,12] Furthermore, it has been

shown that this LOH involves loss of maternal genetic information with duplication of paternal genetic material at this locus.[13] This region is of particular interest because it is where the *IGFII* gene resides, a growth factor believed to play a role in the pathogenesis of RMS (see below). Of further note, *IGFII* has now been demonstrated to be imprinted with only the paternal allele being transcriptionally active.[14,15] It is therefore conceivable that in this tumor, LOH with paternal disomy may lead to overexpression of *IGFII*. However, it is also possible that LOH at 11p15 may also reflect the loss of a tumor suppressor activity that has not been identified yet, or activation of *IGFII* and loss of tumor suppressor activity may both result from LOH at 11p15 in embryonal RMS.[16]

Change in DNA content or ploidy of a cell is another genetic abnormality that may be useful in prognosis, especially for embryonal RMS tumors. Ploidy is measured using flow cytometry, with normal cells having a diploid content of DNA (46 chromosomes). Many tumors have abnormal DNA content related to abnormal chromosomal number. Embryonal RMS tumors have been found to have DNA contents ranging between diploid and hyperdiploid (1.1 to 1.8 times the normal amount of DNA). It is noteworthy that diploid tumors appear to have a worse prognosis than hyperdiploid tumors, and this appears to be an independent prognostic factor.[17,18] It is unknown why diploid DNA content would carry a worse prognosis, but it is important to remember that a diploid DNA content does not mean normal chromosomal composition. Prospective studies are currently underway to further determine the prognostic significance of DNA content.

Both alveolar and embryonal RMS appear to overproduce IGFII, a growth factor that has been shown to stimulate the growth of these tumor cells.[19] Of further note, blockade of the receptor for IGFII (type I IGF receptor) with monoclonal antibodies has been demonstrated to inhibit growth of RMS both in vitro and in vivo.[19,20] It therefore appears likely that IGFII plays an important role in the growth of these tumors. The mechanism that leads to overproduction of IGFII in these tumors is unclear, although loss of imprinting of this locus has recently been implicated as one potential mechanism of IGFII overexpression.[21] That is, while normal tissue, including fetal muscle, normally only expresses IGFII from the paternal allele, several cases of both alveolar and embryonal RMS have shown expression from both parental alleles, a phenomenon referred to as loss of imprinting. The mechanisms involved in normal imprinting and the abnormalities that lead to loss of imprinting are currently the subject of much investigation.

Nearly 50 percent of cases of rhabdomyosarcoma are diagnosed in children aged five years or younger.

The p53 tumor suppressor gene has also been implicated in RMS. A substantial percentage of tumors evaluated have had a p53 mutation resulting in a loss of function of that gene, with a diversity of types of mutations observed.[22] The finding of a codon 248 mutation in one RMS cell line is of interest because a mutation at this codon has also been observed as a germline mutation in the Li-Fraumeni syndrome, where the index case was noted to be a RMS. However, it is not known whether alterations in p53 function are primary events in the pathogenesis of these tumors or whether these alterations are more often associated with progression events.

The most frequently observed oncogene abnormalities seen in RMS are *RAS* mutations. Activated forms of both

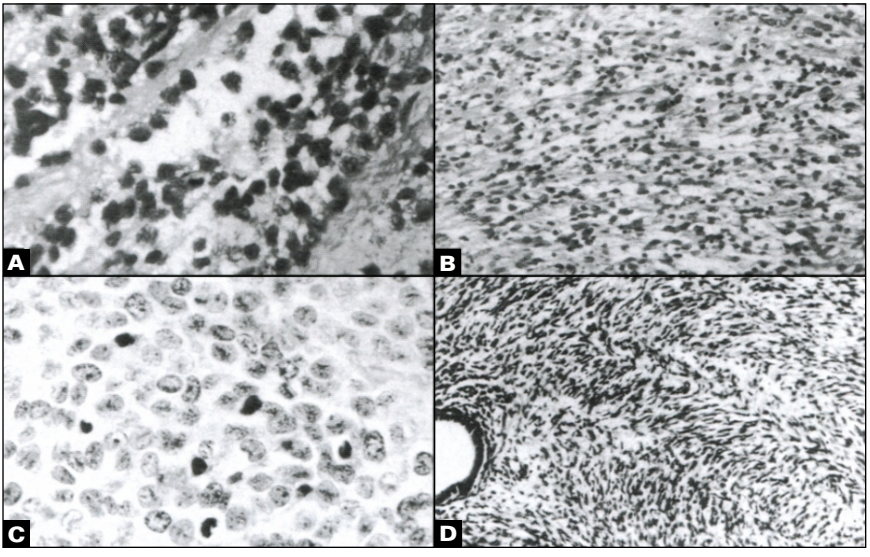

Fig. 1. Light microscopic appearance of the histologic variants of rhabdomyosarcoma (RMS). (A) Alveolar RMS: typical small, round cells with dense appearance, lined up along spaces resembling pulmonary alveoli. These tumors are characteristically associated with a translocation between the long arms of chromosomes 2 and 13. (B) Embryonal RMS: typical spiral-shaped cells, less densely cellular, with stroma-rich appearance. These tumors are associated with a characteristic chromosomal abnormality on the short arm of chromosome 11. (C) Solid alveolar RMS: variant form of alveolar RMS, contains the same genetic abnormality and has similar clinical features. Cells are small and round but lack the typical architecture of "septations" seen in alveolar RMS. (D) Leiomyomatous (spindle cell) RMS: variant form of embryonal RMS with particularly favorable prognosis and predominantly paratesticular origin.

NRAS and *HRAS* have been isolated from RMS cell lines as well as from tumor specimens.[23,24] Thirty-five percent of embryonal RMS tumor specimens assayed by Stratton et al contained either activated *NRAS* or *KRAS*.[25] As with the alterations observed in the p53 tumor suppressor gene, it is not known whether these alterations are primarily involved in the pathogenesis of these tumors or reflect secondary abnormalities that occur during progression events.

Pathology

RMS falls into the broader category of the small, round, blue-cell tumors of childhood. Thus, the role of the pathologist is to identify characteristic features, both by conventional light microscopic techniques and by newer immunohistochemical, electron microscopic, and molecular genetic techniques. The characteristic feature that permits a tumor to be classified as RMS is the identification of myogenic lineage. Typically, this consists of the light microscopic identification of cross-striations characteristic of skeletal muscle or characteristic rhabdomyoblasts. Immunohistochemical staining is a useful and reliable adjunctive means of identifying skeletal muscle and muscle-specific proteins or genes. Muscle-specific proteins include α-actin, myosin, desmin,

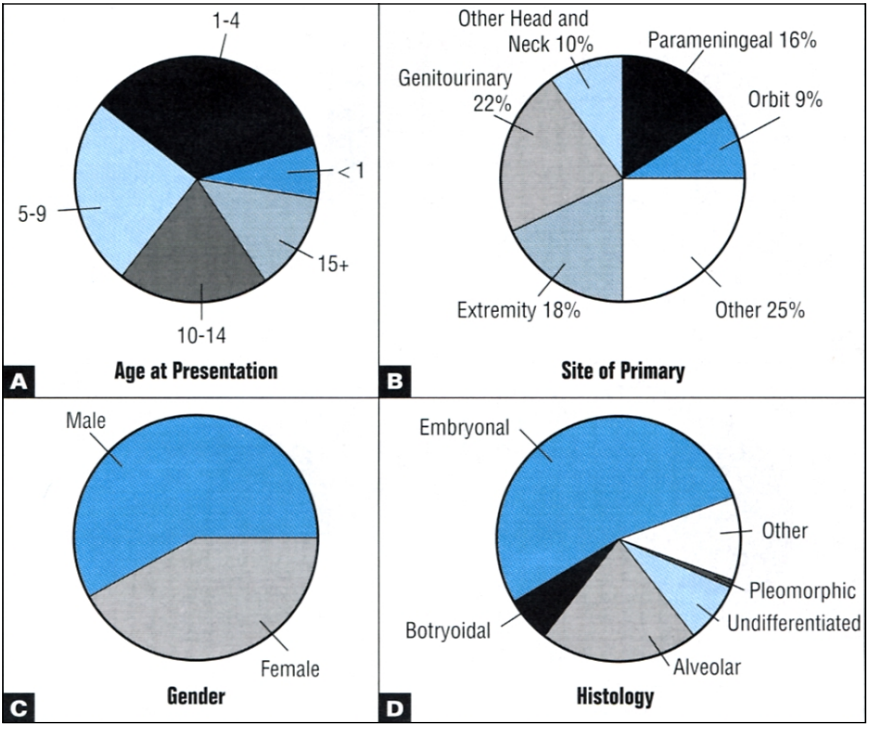

Fig. 2. Clinical features of rhabdomyosarcoma. (A) More than 50 percent of cases are diagnosed in children younger than nine years of age. (B) About 35 percent of tumors arise in the head and neck region, followed by tumors arising in the genitourinary tract or an extremity. (C) The male to female ratio is about 1.4. (D) More than 50 percent of all cases (in IRS-I and IRS-II) were of the embryonal variety.

myoglobin, Z-band protein, and MYO-D.[26,27,28]

The two major subtypes of RMS, embryonal and alveolar, each have a relatively characteristic histologic appearance and also have specific and distinctive molecular genetic abnormalities (see above). The histologic appearance of the two subtypes, which is based on the identification of typical cytologic and architectural features, is generally sufficiently distinctive to permit their straightforward categorization (Fig. 1). However, there are times when the specific diagnosis is more difficult to establish. Moreover, the importance of establishing a histologic subtype is the subject of considerable debate because of conflicting evidence concerning the prognostic significance of histology.[29,30]

The controversy over the prognostic significance of histologic subtype is complicated by differences among pathologists on how to establish the subtype and the evolution that has occurred in the criteria by which these diagnoses are made. In the first two Intergroup Rhabdomyosarcoma Studies (IRS-I and IRS-II), the diagnosis of alveolar RMS was made only if an overt alveolar appear-

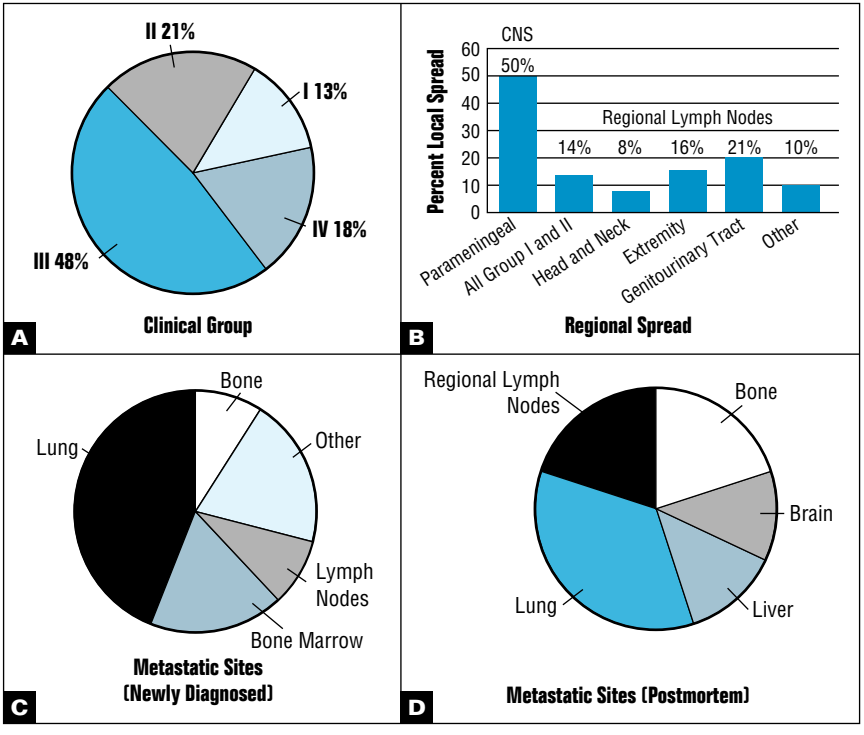

Fig. 3. Clinical features of rhabdomyosarcoma: extent of tumor at diagnosis. (A) About two thirds of patients have unresectable tumors or metastatic tumors at diagnosis. (B) The likelihood of "local" extension varies by primary site: up to 50 percent of parameningeal tumors will be regionally invasive; the incidence of regional lymph node metastases is relatively uncommon in head and neck tumors but more common in extremity lesions. (C) Among patients with metastases at diagnosis (Clinical Group IV), the lung is the most common site. (D) At autopsy, a higher incidence of visceral and central nervous system metastases is seen.

ance was seen in 50 percent or more of the sampled tumor, whereas in IRS-III and IRS-IV, the diagnosis is made if any alveolar component is seen. To develop a more uniform system for establishing the histologic subtype, new classification schemes have been proposed: one by investigators from the National Cancer Institute (NCI) and St. Jude Children's Research Hospital and one by a collaborative group of international pathologists.[29,30]

Under these new schemes, embryonal tumors are diagnosed when the tumor has a stroma-rich, less dense, spindle-cell appearance, and there is no evidence of an alveolar pattern. Variant forms of embryonal RMS, including botryoid and leiomyomatous (spindle cell), have been identified. These variants, which are histologically related to the conventional embryonal form, have characteristic clinical and pathologic features.[31] The botryoid tumors tend to arise almost exclusively from the bladder or vagina in infants and young children or

from the nasopharynx in slightly older children. The spindle-cell variants tend to arise disproportionately in the paratesticular region, but may also be seen in the head and neck, especially the orbit, and the extremities.[32] They are almost always associated with limited disease and appear to have a less aggressive pattern of behavior than the classic embryonal tumors and an extremely good prognosis. About two thirds of newly diagnosed cases of RMS are of the embryonal subtype (Fig. 2).

The presence of any alveolar pattern has been proposed as sufficient to categorize the tumor as an alveolar subtype.[29] Typically, these tumors are composed of densely packed, small, round cells that line a septation that appears histologically reminiscent of a pulmonary alveolus. A variant form of the alveolar subtype, known as solid alveolar RMS, has been identified in tumors that lack the characteristic architectural appearance (i.e., the alveolar septations), but whose cells are small, round, and densely packed.[29] Pleomorphic RMS is only rarely diagnosed and when anaplastic cells are present in large aggregates or diffuse sheets also appears to have a poor prognosis.[33]

Different investigators have attributed more or less prognostic significance to histologic subtype.[34,35] The current IRS-IV study does not include histology as an independent prognostic variable. This is due to previous analyses of large numbers of patients indicating that site (which is associated with histologic subtype) is an independent prognostic factor, and histology is only a prognostic factor because of its association with site (see below).[36-40] More recently, investigators from the NCI and St. Jude Children's Research Hospital evaluated a group of 159 patients with RMS treated at the two institutions over a 15-year period.[29] Among patients with nonmetastatic tumors, histology was found to be an independent prognostic variable, with embryonal tumors having a better outcome than the identically behaving alveolar or solid alveolar tumor variants (six-year survival of 60 percent versus 25 percent, p=0.001).

Clinical Features

The spectrum of presenting signs and symptoms of RMS can vary greatly depending on the site of origin of the primary tumor, the age of the patient, and the presence or absence of metastatic disease. The most common site of origin is the head and neck (Fig. 2). In IRS-II, 34 percent of all tumors arose from a site in the head or neck, including 18 percent from the parameningeal sites (middle ear, nasal cavity and paranasal sinuses [maxillary, ethmoid, and sphenoid], nasopharynx, and infratemporal fossa or pterygopalatine and peripharyngeal areas), eight percent in the orbit, and eight percent from one of the other sites in the head and neck (including the scalp, parotid gland, oral cavity, larynx, oropharynx, cheek, hypopharynx, thyroid and parathyroid glands, and neck).[41] These head and neck tumors are most commonly of the embryonal subtype and rarely spread to regional lymph nodes (Fig. 3).[42,43] They are commonly seen in younger patients, particularly the orbital tumors, and may present as orbital swelling with or without associated nasal congestion (Fig. 4).

The two major subtypes of rhabdomyosarcoma have been found to have characteristic genetic alterations.

Slightly less than one fourth of all cases arise in the genitourinary tract. In IRS-II 12 percent of the genitourinary tumors arose from a nonbladder, nonprostate site (including paratesticular,

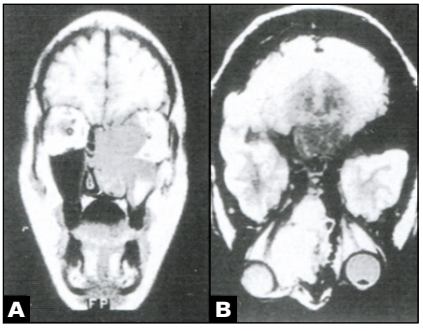

Fig. 4. Radiographic appearance of rhabdomyosarcoma. (A) Large tumor involving left orbit and ethmoid sinus and eroding through base of skull. This patient was treated for sinusitis for one month before the correct diagnosis was made. (B) The tumor caused significant proptosis and nasal congestion. In cases like this, it may be difficult to distinguish the primary site of origin.

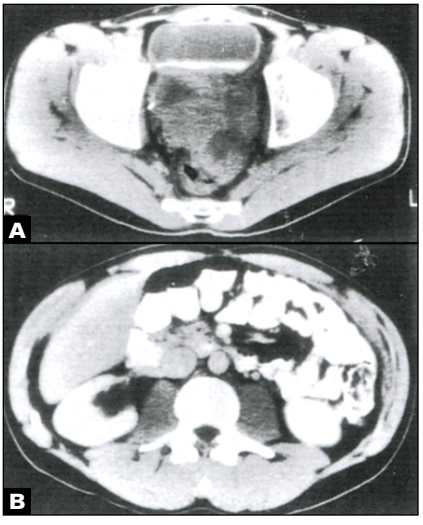

Fig. 5. Radiographic appearance of rhabdomyosarcoma. (A) Large tumor arising from the bladder-prostate region. This patient presented with obstipation and a palpable mass on rectal exam. (B) These tumors can grow quite large before they are diagnosed, often leading to obstruction of the ureters and hydronephrosis (seen in the right kidney). Cystectomy or pelvic exenteration is rarely indicated in the primary management of these tumors.

perineal, vulvar, vaginal, or uterine primaries), while 11 percent of tumors arose from either the urinary bladder or the prostate (often in males it is difficult to distinguish the precise site of origin).[41-44] As with primary tumors of the head and neck, most tumors tend to be the embryonal variety, with the special subcategory of botryoid tumors seen almost exclusively in infants. They may present as a painless, firm swelling or lump in the scrotum or vulvovaginal region, or if arising in the bladder region, they may present with urinary frequency or constipation if the mass significantly compresses the bladder or intestinal tract (Fig. 5).

The third most common site of origin is the extremities. These tumors typically develop in adolescents and tend to behave relatively aggressively, with a high incidence of nodal spread and distant metastases. They typically present as a painful lump (or lumps, if nodal metastases are present) (Fig. 6). The single most important prognostic factor—independent of any other feature—is the presence or absence of distant metastatic disease. Factors associated with better prognosis include smaller tumor size and noninvasiveness, orbital or paratesticular primary site, embryonal histology (particularly botryoid and spindle-cell), the absence of regional lymph-node metastases, complete resectability, and younger age (2 to 10 years).[37,38,41,44-47]

Diagnostic Evaluation

The diagnostic work-up of patients suspected to have RMS should be directed toward defining two complementary issues: the nature and extent of the primary tumor and the presence or absence of locoregional or metastatic disease. Fre-

quently, much of this information can be obtained quite simply, even in the absence of sophisticated and expensive radiologic studies, with a well-performed history and physical examination. The most critical part of the staging evaluation is the procurement of sufficient material to permit a definitive diagnosis to be established.

In IRS-I, IRS-II, and IRS-III, a surgicopathologic staging system was employed to determine subsequent treatment decisions. This system, known as the Clinical Grouping System, was based on the premise that lesions that could be completely resected had a better prognosis, even with less-intensive therapy, than tumors that could not be completely resected. Thus, in the first Intergroup Study (1972-1978), aggressive and often mutilating procedures, such as orbital or pelvic exenteration, were often performed to accomplish complete surgical resection.[48] Table 1 summarizes the criteria employed in the Clinical Grouping System. Today, however, with the adoption of a new, nonsurgically based staging system (Table 2), it is rarely (if ever) necessary to perform the diagnostic biopsy or definitive surgical procedure before most of the radiologic work-up has been completed. This is particularly important in circumstances where a complicated and potentially morbid surgical intervention is planned, as a less aggressive procedure would be warranted if distant metastatic disease is identified. It is especially crucial that adequate imaging studies of the primary site be obtained before surgical resection is attempted because, in the event that a complete resection cannot be accomplished, lack of this preoperative information will severely compromise the likelihood of achieving local control with subsequent radiation therapy.

When the biopsy is performed (generally by an open, incisional biopsy; less frequently by excisional biopsy or complete resection; and increasingly by percutaneous core-needle biopsy or fine-needle aspiration), adequate tissue should be procured to permit routine pathologic studies—including immunohistochemistry and electron microscopy—and, where available, karyotypic, cytogenetic, and molecular-genetic studies as well.

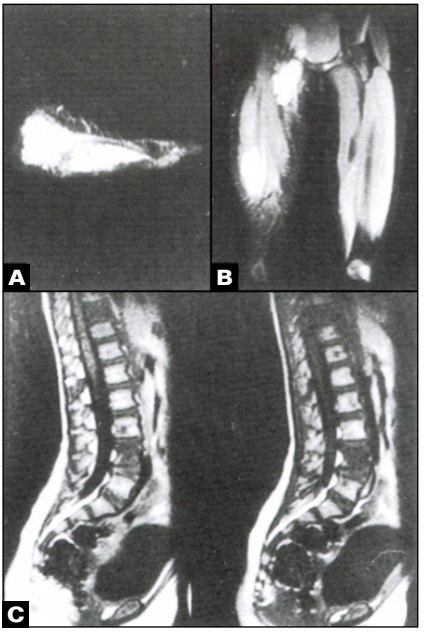

Fig. 6. Radiographic appearance of rhabdomyosarcoma. (A) Alveolar rhabdomyosarcoma arising from the plantar surface of the foot. These tumors typically develop in adolescents and are associated with aggressive clinical behavior. (B) Soft tissue metastases in the anterior thigh and inguinal/pelvic region. (C) This patient also had osseous metastases involving numerous vertebral bodies.

The minimum radiologic evaluation of the primary tumor site should consist of a computed tomography (CT) scan of the suspected site of origin and the immediately adjacent tissues. In certain instances where questions arise about the involvement of contiguous structures, magnetic resonance imaging (MRI) of the head and neck region (particularly in

Table 1
Clinical Group Stage System for Rhabdomyosarcoma

Clinical Group	Extent of Disease/Surgical Result
I	A. Localized tumor, confined to site of origin, completely resected
	B. Localized tumor, infiltrating beyond site of origin, completely resected
II	A. Localized tumor, gross total resection, but with microscopic residual disease
	B. Locally extensive tumor (spread to regional lymph nodes), completely resected
	C. Locally extensive tumor (spread to regional lymph nodes), gross total resection, but microscopic residual disease
III	A. Localized or locally extensive tumor, gross residual disease after biopsy only
	B. Localized or locally extensive tumor, gross residual disease after major resection (≥ 50 percent debulking)
IV	Any size primary tumor, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor

parameningeal primaries) or ultrasonography of the pelvic region may be useful. Because the most common sites of metastatic spread are the lungs, bone, and bone marrow, distant metastatic disease should be evaluated with a CT scan of the chest, a ^{99m}Tc-diphosphonate bone scan, bilateral aspiration and biopsy of iliac bone marrow, and plain films of any sites that appear abnormal on bone scan (this includes hyperintense as well as hypointense lesions).[49] Certain tumor sites have a propensity to spread to specific sites, and appropriate imaging studies should be performed to rule out the presence of tumor in those locations. For example, parameningeal primaries may directly extend to the meninges so the work-up of tumors arising in that site should include a lumbar puncture to evaluate cerebrospinal fluid cytology. Similarly, an abdominal CT scan to rule out the presence of retroperitoneal adenopathy is warranted in any patient with a paratesticular primary tumor. Finally, given the disproportionately high incidence of alveolar histology in extremity tumors and the greater propensity of these tumors for nodal spread, it is important that draining lymph-node regions be included in the CT and/or MRI evaluation of the primary tumor site.

Although Clinical Group was quickly established as an important prognostic

Table 2
TNM Staging of Rhabdomyosarcoma*

Stage	Sites	T-invasiveness	T-size	N	M
I	Orbit	T_1 or T_2	a or b	N_0 N_1 or N_x	M_0
	Head & neck[1]	T_1 or T_2	a or b	N_0 N_1 or N_x	M_0
	Genitourinary[2]	T_1 or T_2	a or b	N_0 N_1 or N_x	M_0
II	Bladder/prostate	T_1 or T_2	a	N_0 or N_x	M_0
	Extremity	T_1 or T_2	a	N_0 or N_x	M_0
	Cranial parameningeal	T_1 or T_2	a	N_0 or N_x	M_0
	Other[3]	T_1 or T_2	a	N_0 or N_x	M_0
III	Bladder/prostate	T_1 or T_2	a	N_1	M_0
	Extremity	T_1 or T_2	b	N_0 N_1 or N_x	M_0
	Cranial parameningeal	T_1 or T_2	b	N_0 N_1 or N_x	M_0
	Other[3]	T_1 or T_2	b	N_0 N_1 or N_x	M_0
IV	All	T_1 or T_2	a or b	N_0 or N_1	M_1

T = Tumor
- T_1 Confined to anatomic site of origin
- T_2 Extension
- a ≤5 cm in diameter
- b >5 cm in diameter

N = Regional Nodes
- N_0 Not clinically involved
- N_1 Clinically involved
- N_x Clinical status unknown

M = Metastases
- M_0 No distant metastasis
- M_1 Distant metastasis present

[1]excluding parameningeal

[2]nonbladder/nonprostate

[3]includes trunk, retroperitoneum, etc.

*TNM pretreatment staging classification for the Intergroup Rhabdomyosarcoma Study-IV

variable, a growing sense of discomfort arose about the validity of a staging system that, to a large degree, relied primarily on the skill and aggressiveness of the surgeon rather than the intrinsic biology of the tumor. Consequently, in the current Intergroup Study (IRS-IV), which opened in 1992, a site-based TNM staging system is being prospectively evaluated as a potentially more objective (and, it is hoped, clinically valid) prognostic staging system (Table 2). This system has been retrospectively evaluated by numerous investigators and shown to be highly predictive of outcome.[36,38-40] The Clinical Grouping System has been retained,

however, for planning radiation therapy. It is likely that in the future, as newer insights are gained into the basic biology of RMS, new staging systems will be developed based on such intrinsic tumor properties as chromosomal content, the presence or absence of specific genetic abnormalities such as translocations, or the overexpression of autocrine growth factors.

Once the preoperative radiologic assessment has been completed, a decision must be made about the surgical approach to the primary tumor. In the current Intergroup Study, the extent of surgical resection only influences radiation-therapy treatment decisions and is not the critical factor in determining the stage of the disease. Thus, to avoid the potential long-term toxicities of radiation therapy, an attempt at complete surgical excision is a reasonable approach to most localized tumors (assuming that major functional or cosmetic deficits are not likely), except orbital/parameningeal and bladder/prostate primaries. Lymph-node dissection is not recommended to look for the presence of nodal disease. However, lymph nodes that appear suspicious on physical exam, CT, or MRI should be removed for pathologic evaluation.

After determining the site of origin, size, invasiveness of the primary tumor, and presence or absence of regional lymph node or distant metastatic disease and completing the surgical procedure with confirmation of the diagnosis, one of several chemotherapy regimens (with or without the addition of radiation therapy) can be employed to reduce the residual primary tumor mass (if any) and eradicate micrometastatic (or overt) disease.

Treatment

In addition to the clinically apparent primary tumor, the overwhelming majority of patients with RMS are presumed to have, at a minimum, microscopic amounts of metastatic disease. Thus, the primary aim of therapy must focus on both achieving local control and eradicating metastases. Over the past 20 years, an effective multimodality strategy has been developed that has cured over half of all patients with newly diagnosed RMS and as many as 90 percent of patients with localized orbital and paratesticular tumors.[50] In large part this has been possible because of the enrollment of virtually all eligible patients in either an IRS or one of several smaller, institutional protocols. The multimodal approach uses a combination of surgery, "risk-based" chemotherapy, and radiation therapy. It reflects an evolutionary change in the management of these tumors, developed as a result of studies that conclusively demonstrated that therapies of varying intensities are necessary to cure different categories of patients.

The most frequently observed oncogene abnormalities seen in rhabdomyosarcoma are RAS mutations.

Surgery

A major conclusion of IRS-I was that complete resection of tumors had a major influence on overall survival.[44,51] One major difficulty in interpreting these data is that many of these patients were treated prior to the advent of CT scan-guided treatment planning for radiation therapy. It is quite possible that most of the benefit that appeared to result from the more aggressive surgical approach advocated in the earlier studies was due to the inability of then state-of-the-art radiation therapy

to adequately achieve optimal local control. In one multivariate analysis of the risk of local failure in children with RMS, "inadequate" radiation therapy (either inappropriately low dose [1,000 to 3,500 cGy, median 2,600 cGy] or adequate dose but inadequate margins) was identified as the most significant predictor of subsequent local failure.[52] Presently, for patients with nonmetastatic tumors—except for orbital and bladder/prostate primary tumors—it is reasonable to attempt complete surgical resection of the primary tumor. The guiding principle of the approach, however, should be that mutilating and cosmetically damaging procedures are inappropriate given the effectiveness of chemotherapy and radiation therapy at eradicating residual disease.

Chemotherapy

The chemotherapeutic approach to RMS is guided by the initial extent of disease and the site of origin of the primary tumor. It has become clear that certain patients, such as those with primary orbital tumors, will do quite well with relatively nonintensive, two- or three-drug therapy, while other patients, such as those with metastatic disease, will do poorly regardless of how intensive their therapy—despite the achievement of significant objective antitumor responses in more than 75 percent of cases.[53]

Patients with Localized Disease

Over the past two decades, the two-drug regimen of vincristine and actinomycin D (VA), without radiation therapy, became recognized as the "gold standard" for cure of patients with nonalveolar Clinical Group I tumors, and it was adopted as the standard therapeutic approach for such patients in IRS-III. In IRS-IV, where no distinction is made between alveolar and embryonal histology, only Clinical Group I patients with paratesticular or orbital tumors are being treated with VA, while all other Clinical Group I patients are being randomized between three triple-drug combinations: VAC (vincristine, actinomycin D, cyclophosphamide), VAI (vincristine, actinomycin D, ifosfamide), and VIE (vincristine, ifosfamide, etoposide).

For Clinical Group II patients with nonalveolar tumors, IRS-I and IRS-II showed that outcome was excellent with VA alone, and no benefit was seen with the addition of cyclophosphamide.[41,44] A subset analysis of this group of patients, however, showed that outcome appeared to be strongly influenced by the site of the primary tumor. Thus, in IRS-III, patients with "favorable-histology" Clinical Group II tumors arising in either the paratesticular region or any nonparameningeal head and neck site received cyclic-sequential VA (plus radiation therapy); patients with favorable-histology tumors arising in other sites were randomized to receive either one year of cyclic-sequential VA or one year of cyclic-sequential VA plus doxorubicin. In IRS-IV, the standard VA regimen is reserved only for patients with nonmetastatic Clinical Group II orbital tumors; all other patients (again, independent of histology, but predicated on primary site) are randomized to one of the three, three-drug regimens (VAC versus VAI versus VIE). Conventional radiation therapy continues to be given to all patients with microscopic residual disease.

In both IRS-II and IRS-III, patients with Clinical Group I or II alveolar tumors arising in the extremities were nonrandomly assigned to receive more intensive therapies. In IRS-II this consisted of repetitive pulse VAC for one to two years (with or without conventional radiation therapy as appropriate to the clinical group). In IRS-III, these patients received pulse VAC plus additional chemotherapy agents (doxorubicin and cisplatin). In IRS-IV, no distinction is made for histologic subtype in assigning

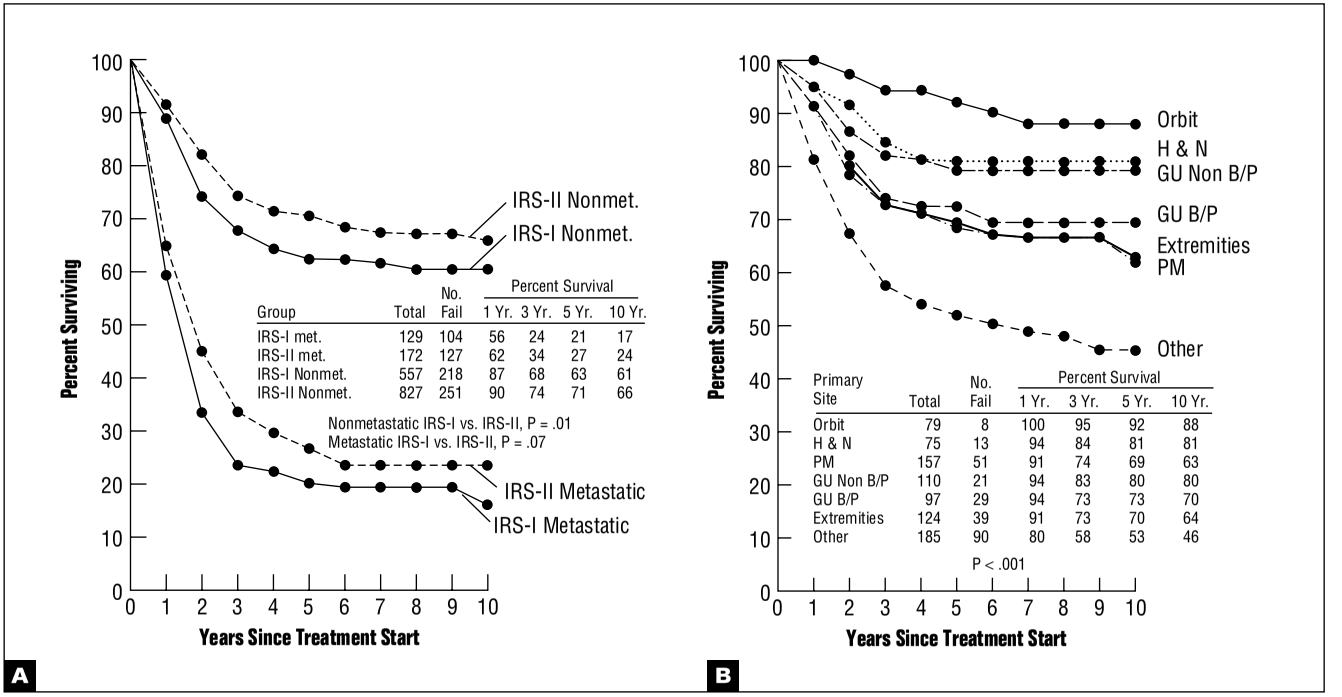

Fig. 7. Outcome of patients on Intergroup Rhabdomyosarcoma Study (IRS)-I versus IRS-II. (A) Overall five-year survival on IRS-II was significantly improved for patients with nonmetastatic tumors (71 percent versus 63 percent, p=0.01), with a trend towards improved outcome for patients with metastatic disease (27 percent versus 21 percent, p=0.07). (B) IRS-II confirmed the excellent outcome seen on IRS-I among patients with nonmetastatic orbital tumors (five-year survival rate of 92 percent), head and neck tumors (five-year survival rate of 81 percent), and genitourinary/nonbladder, nonprostate tumors (five-year survival of 80 percent). The major improvement in outcome was seen in patients with nonmetastatic parameningeal tumors (five-year, disease-free survival rate of 69 percent on IRS-II versus 45 percent on IRS-I, p<0.001). Reprinted with permission from Maurer et al.[41]

chemotherapy treatment. Patients are being randomized to one of the three, three-drug chemotherapy regimens, regardless of histology.

Patients with Locally Extensive, Nonmetastatic Tumors

IRS-I studies showed a five-year survival rate of about 50 percent for patients with locally extensive, nonmetastatic tumors, with no difference seen between VAC and VACA (VAC alternating with vincristine, doxorubicin, cyclophosphamide).[44] IRS-II compared VACA with VAC alone and found no difference between treatment arms with a five-year survival of 64 percent for both.

Overall, IRS-II showed an improvement in the five-year survival rate for nonmetastatic disease compared with IRS-I (Fig. 7).[41] Although this overall improvement in outcome was attributed to the development of more effective therapies, several other explanations have been raised that call this conclusion into question, including the following: the improvement in supportive-care techniques, which may have reduced the number of deaths from therapy-related complications; the increase in postrelapse survival rates seen in IRS-II compared with IRS-I; the more routine availability of CT scans for radiation-therapy treatment planning during the period of IRS-II (particularly for patients with parameningeal primary tumors); and the inclusion of a larger number of "favorable-prognosis" patients in Clinical Group III in IRS-II (where Clinical Group III made up 53 percent of all patients), most of whom would likely have been Clinical Group I or II patients in IRS-I (where Clinical Group III patients made up only 41 percent of patients). Finally, although the IRS-II analysis concluded that doxorubicin was not an effective agent in RMS (that is, despite its activity in patients with recurrent tumors, it did not improve the results that could be obtained with the standard VAC regimen alone), this conclusion is somewhat suspect because of the low dose-intensity with which doxorubicin was administered. As has been suggested for other pediatric solid tumors, it is quite possible that had this agent been used more intensively, a significant advantage would have been detected.[54]

In IRS-III, therapy for Clinical Group III patients was based on the extent of the disease as well as the site of origin and histology. Patients with favorable-histology, nonparameningeal head and neck tumors received cyclic-sequential VA for one year, while patients with favorable-histology, "special" pelvic tumors received pulse VAdriaC (vincristine, doxorubicin, cyclophosphamide)-VAC plus cisplatin. Patients with favorable-histology tumors arising in all other sites and patients with unfavorable-histology tumors arising from any site were randomized to one of three multiagent chemotherapy regimens (pulse VAC for two years, pulse VAdriaC-VAC plus cisplatin for two years, pulse VAdriaC-VAC plus cisplatin and etoposide for two years. Although the final results of IRS-III have not yet been published, preliminary results suggest a significant improvement in outcome at three years (overall survival of 80 percent) compared with the first two Intergroup studies.[55] In

The characteristic feature that permits a tumor to be classified as rhabdomyosarcoma is the identification of myogenic lineage.

IRS-IV, Clinical Group III patients are randomized to the same three-drug chemotherapy regimens as patients with more limited disease.

Patients with Distant Metastatic Disease

There has not been significant improvement in the outcome of patients with distant metastatic disease despite the proliferation of ever more complicated and intensive multidrug chemotherapy regimens. Although most patients will respond to initial chemotherapy, these responses are rarely lasting and most patients will develop recurrent metastatic disease within 18 to 24 months of diagnosis. Currently, no more than 20 to 25 percent of patients with distant metastatic disease are curable with even the most aggressive chemotherapy regimens.[56] It is clear that new treatment strategies are needed to improve the outcome of this group of patients. Current efforts are aimed at identifying new active agents as well as substantially dose-intensifying regimens with the concurrent use of hematopoietic growth factors and/or autologous hematopoietic progenitor cells.

An effective multimodality strategy has been developed that has cured over half of all patients with newly diagnosed rhabdomyosarcoma.

Other novel approaches being developed to treat RMS include the use of differentiation agents such as low-dose cytosine arabinoside and the use of growth-factor "blocking" agents such as suramin. As new insights are gained into the basic biology of these tumors, it is hoped that other biologically-based therapies will be developed into clinically meaningful treatment strategies.

Radiation Therapy

The role of radiation therapy is to eradicate residual tumor cells at the primary site, or other sites of bulk disease, that have not been removed by surgery and have survived the initial exposure to chemotherapy. As with the recommendations for chemotherapy, guidelines for radiation dosages and radiation fields have evolved over the course of the IRS. Early treatment guidelines recommended doses as high as 5,500 to 6,000 cGy (with slightly lower doses for younger patients), independent of the amount of residual disease, for control of the primary tumor site.

Over the course of these studies, the following general principles have evolved. In cases of microscopic residual disease, lower doses of between 4,000 to 4,500 cGy are sufficient to achieve local control in the vast majority of patients. Slightly higher doses of between 4,500 to 5,000 cGy appear necessary for local control in patients with larger tumors (≥5 cm) and gross residual disease.[41] Prophylactic irradiation of clinically uninvolved regional lymph nodes was found to be unnecessary. There appeared to be a higher risk of local failure in patients with tumors larger than 5 cm.

The most dramatic increase in survival rate due to improved radiation-therapy management has occurred in patients with parameningeal tumors (five-year survival rate of 69 percent in IRS-II versus 45 percent in IRS-I, $p<0.001$).[41] Routine CT scanning to more adequately define tumor margins combined with the use of more extensive fields to doses between 4,500 to 5,500 cGy has been largely responsible for these gains. Whole brain (or craniospinal) irradiation plus intrathecal chemotherapy is not indicated in the absence of overt parenchymal, meningeal, or cerebrospinal-fluid in-

Table 3
American Joint Committee on Cancer Staging Protocol of Soft Tissue Sarcomas

Stage	Grade	Tumor	Nodes	Metastases
IA	1	1	0	0
IB	1	2	0	0
IIA	2	1	0	0
IIB	2	2	0	0
IIIA	3-4	1	0	0
IIIB	3-4	2	0	0
IVA	1-4	1-2	1	1
IVB	1-4	1-2	0-1	1

Histologic Grade (G)
- G_1 Well differentiated
- G_2 Moderately well differentiated
- G_{3-4} Poorly differentiated; undifferentiated

Primary Tumor (T)
- T_1 Tumor ≤5 cm in greatest diameter
- T_2 Tumor >5 cm in greatest diameter

Regional Lymph Nodes (N)
- N_0 No regional nodal involvement
- N_1 Regional nodes involved with tumor

Distant Metastases (M)
- M_0 No distant metastases
- M_1 Distant metastases

volvement.[57] The presence of extensive bony erosion (of the orbit or base of skull) appears to define a group of patients at high risk of local failure.[58]

In the current Intergroup Study (IRS-IV), guidelines for radiation therapy continue to be (primarily) based on Clinical Group, but are independent of age and histology. Except for patients with TNM Stage 3 tumors, patients with completely resected tumors (Clinical Group I) do not receive radiation therapy. Patients with incompletely resected tumors (Clinical Group II) all receive conventional fractionation radiation therapy to a total dose of 4,140 cGy, generally beginning about two months after the commencement of chemotherapy. The volume to be irradiated is the original extent of the tumor, prior to surgery and chemotherapy, plus a margin of at least 2 cm whenever possible. Draining lymph-node regions are not irradiated in the absence of tumor involvement. Except for patients with vulvar and vaginal tumors who receive conventional radiation therapy, patients with any TNM stage tumor and gross residual disease (Clinical Group III) are randomized to receive either conventional fractionation radiation therapy to a total dose of 5,040 cGy over $5^1/_2$ weeks or hyperfractionated radiation therapy to a total dose of 5,940 cGy (twice daily 110 cGy fractions) over the same time interval. This is being done to determine if hyperfractionation can

achieve comparable local control with less long-term morbidity. Patients with a primary tumor of the parameningeal region with intracranial meningeal extension in continuity with the primary tumor—but without positive cerebrospinal-fluid cytology—receive between 5,040 and 5,940 cGy to the primary tumor site plus base of skull; the portion of the tumor that extends intracranially should be treated with a 2-cm margin superiorly around the known extent of the disease.

Regionally positive lymph nodes should be treated to the full radiation-therapy dose (within the limits of normal tissue tolerance). The IRS-IV protocol recommends that sites of metastatic disease be irradiated, when feasible, but not all centers follow this practice because the major risk of failure in patients with metastatic disease is from distant dissemination—a risk that is not likely to be significantly impacted by the administration of radiation therapy to only the overtly involved metastatic loci. Currently, some important radiation-therapy questions that are being addressed include whether doses less than 4,000 cGy can eradicate microscopic residual disease and whether alternative radiation-therapy delivery methods, such as brachytherapy, can achieve local control in infants and young children without producing unacceptable damage of surrounding normal tissue and structures.[59,60]

Late Effects

As more patients survive for increasingly longer periods of time, it has become clear that serious and potentially life-threatening complications can develop many years after therapy has been completed. Patients with bladder or prostate primaries are at risk for bowel complications from either surgery (obstruction) or radiation therapy (enteritis) with unsatisfactory bladder function or hemorrhagic cystitis and sex-hormone deficiencies.[61] Patients with paratesticular tumors are at risk for a comparable spectrum of toxicities.[62,63] Patients receiving doxorubicin, even at seemingly "safe" cumulative doses, are at risk of developing a characteristic late cardiomyopathy, while the recent broad-scale introduction of ifosfamide may lead to an increased incidence of serious and irreversible damage to kidney function.[64,65]

The chemotherapeutic approach to rhabdomyosarcoma is guided by the initial extent of disease and the site of origin of the primary tumor.

The most devastating late complication of therapy is the development of a second malignant neoplasm (SMN). Twenty-two SMNs developed among 1,770 patients entered onto IRS-I and IRS-II, including eleven bone sarcomas (radiation related) and five cases of acute nonlymphoblastic leukemia, at a median of seven years posttherapy.[66] While the influence of genetic factors on the risk of developing an SMN is unknown, this problem, as well as the other late effects discussed above, clearly points to the need to develop less toxic, but equally efficacious treatment strategies—particularly for those patients with a high likelihood of cure.

Summary

The past twenty years have seen a slow but steady improvement in the prognosis for cure among patients with RMS, particularly for those with locally extensive, unresectable, nonmetastatic lesions. Be-

tween 60 and 70 percent of newly diagnosed patients can now be cured of their disease using modern chemotherapy and radiation therapy approaches. For the newly diagnosed patient with a low likelihood of cure (i.e, the patient with metastatic disease) and for the 25 to 30 percent of patients with favorable prognosis who ultimately relapse, the identification of active new drugs and the optimization of the use of known active agents are strategies that are being actively pursued. The development of a more uniform set of criteria for histologic diagnosis and the implementation of a nonsurgically based staging system should facilitate an improved understanding of the contribution to outcome of histologic subtype, tumor size, and location. Eventually, it is hoped that more sophisticated biologically based staging systems, such as ones based on chromosomal content or presence of specific genetic abnormalities within tumor cells, will lead to more accurate and prognostically informative, risk-based staging systems. Finally, these same insights into the basic biology of RMS are likely to lend themselves to the development of more tumor-specific, biologically based therapeutic approaches with fewer long-term side effects.

Nonrhabdomyosarcoma Soft Tissue Sarcomas

Background and General Principles of Treatment

Nonrhabdomyosarcoma soft tissue sarcomas of childhood comprise a large number of relatively uncommon tumors, including synovial sarcoma, fibrosarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumors (MPNST), hemangiopericytoma, alveolar soft-part sarcoma, leiomyosarcoma, and rarer tumors such as liposarcoma and soft tissue clear cell sarcoma (malignant melanoma of soft parts). Taken together, they have an annual incidence of about two to three cases per million children younger than 19 years of age.[2] Like RMS, they are associated with the Li-Fraumeni syndrome, which implies an association with p53 mutations.

The diagnostic approach for evaluating patients with a suspected NRSTS is essentially identical to that for patients with RMS, as it is impossible to determine on clinical grounds alone, in advance of the tissue diagnosis, whether the tumor will be an RMS or an NRSTS (and, if an NRSTS, whether it will be a high-, intermediate-, or low-grade tumor).[67] Although obtaining enough tissue to establish the correct diagnosis is critical, the diagnostic biopsy should be planned to avoid compromising a future complete excision.

The Clinical Grouping System used in the Intergroup Rhabdomyosarcoma Studies has been the most commonly used staging system for children with NRSTS (Table 1). More recent studies have attempted to evaluate the prognostic significance of stage for these tumors using a modified TNM staging system (based on the American Joint Committee on Cancer [AJCC] staging system for soft tissue sarcomas in adults, but using a different histologic grading system) (Tables 3 and 4).[67,68] In contrast to RMS, primary site is not a meaningful prognostic factor while histologic grade is. The rarity of these tumors makes it unlikely that one staging system will be found to be clearly superior to the other.

Several grading systems have also been used for the pathologic evaluation of these tumors. These grading systems evaluate such factors as the degree of necrosis, mitotic activity, cellularity, degree of matrix formation, and pleomorphism and are useful in predicting the biologic behavior of the tumors. As with RMS, it is likely that newer biologic assays, such as measurements of ploidy and proliferative fraction or the demonstration of certain cytogenetic and molecular genetic abnormalities, will assume greater importance in providing informa-

Table 4
Pediatric Oncology Group NRSTS Histologic Grading System*†

Grade 1	
	Myxoid and well-differentiated liposarcomas
	Deep-seated dermatofibroma protuberans
	Well-differentiated and infantile fibrosarcomas
	Well-differentiated and infantile hemangiopericytomas
	Well-differentiated malignant peripheral nerve sheath tumors
	Extraskeletal myxoid chondrosarcomas
	Angiomatous malignant fibrous histiocytomas
Grade 2	
	Sarcomas not specifically included in Grades 1 and 3, in which less than 15 percent of the surface area shows necrosis, the mitotic count is four or fewer per ten high power fields using a 40x objective, nuclear atypia is not marked, or the tumor is not markedly cellular
Grade 3	
	Pleomorphic or round cell liposarcomas
	Mesenchymal chondrosarcomas
	Extraskeletal osteosarcomas
	Malignant Triton tumors
	Alveolar soft-part sarcomas
	Sarcomas not included in Grade 1, with greater than 15 percent of the surface area with necrosis or with five or more mitoses per ten high-power fields using a 40x objective
	Marked atypia or cellularity are less predictive, but may assist in placing a tumor in this category

*NRSTS = nonrhabdomyosarcoma soft tissue sarcomas.
†Adapted from Rao et al.[70]

tion about a given tumor's likelihood of recurring locally or developing metastases.

The system currently employed by the Pediatric Oncology Group, a modification of the system developed by Costa et al, is summarized in Table 4.[69,70] Low-grade tumors (Grades 1 and 2) generally have an indolent course and are less likely to exhibit either aggressive local behav-

ior or dissemination. However, if inadequately treated, they can recur locally and may, in some cases, undergo histologic progression to a more aggressive phenotype. Conversely, high-grade tumors (Grade 3) are typically very aggressive and have a greater propensity for local invasiveness and a higher likelihood of distant spread.

Among the most important factors determining the likelihood of cure are the histologic grade of the tumor and, particularly for high-grade tumors, the ability to perform a complete surgical resection with pathologically confirmed negative margins.[71-74] High-grade tumors are frequently associated with other poor prognostic features—such as large size (>5 cm) and local invasiveness—that make complete surgical resection more difficult. Although some data suggest that high-grade tumors have a worse prognosis, it is unclear to what degree grade is prognostically significant independent of surgical resectability. The development of more uniform histologic grading and TNM-based staging of pediatric NRSTS represent important advances that will hopefully contribute to a better understanding of the behavior of these tumors and the relative contributions of histologic grade, invasiveness, and surgical resectability on outcome.

There have been very few large series on the treatment of pediatric patients with NRSTS, and most of those that have appeared are based on retrospective reviews of cases treated over two to three decades. In general, the most common NRSTS are synovial sarcomas (25 to 50 percent), fibrosarcomas (15 to 20 percent), malignant fibrous histiocytomas (10 to 20 percent), and malignant peripheral nerve sheath tumors (10 to 20 percent). The typical patient is a young (10 to 12 years of age), male patient who presents with a relatively slow-growing, occasionally painful mass. Between 30 and 50 percent of patients will have either unresectable disease or overt metastases at the time of diagnosis.

In the largest study of pediatric NRSTS to date, Rao analyzed outcome over a 30-year period in 154 children with NRSTS entered into IRS-I.[70] Consistent with other published reports, slightly more than half of the tumors (82 of 154) were invasive, and most of these were greater than 5 cm in maximum diameter (65 of 82) and high-grade (56 of 82). Death occurred in 52 (73 percent) of 71 patients with Grade 3 (high-grade) tumors and 41 (91 percent) of 45 patients with Clinical Group III (22/25) and IV (19/20) tumors. Two separate reports from St. Jude Children's Research Hospital and other smaller, single-institution, retrospective series generally confirm these epidemiologic and clinical observations as well as the finding of a consistent interrelationship between tumor size, invasiveness, grade, surgical resectability, and outcome.[71-74]

There has not been significant improvement in the outcome of patients with distant metastatic rhabdomyosarcoma despite the proliferation of intensive multidrug chemotherapy regimens.

In the only prospective series of pediatric NRSTS, 75 patients were seen at Pediatric Oncology Group institutions.[75] In this report, 63 percent of patients had either Stage III or Stage IV disease at diagnosis. Synovial sarcoma (42 percent) was the most common tumor in this series, followed by fibrosarcoma (13 percent), MFH (12 percent), and "malignant

neurogenic tumors" (10 percent). Patients with the two most common entities tended to have localized tumors (84 percent of synovial sarcomas, 80 percent of fibrosarcomas) arising primarily in an extremity (90 percent of synovial sarcomas, 60 percent of fibrosarcomas). No data on treatment or outcome were provided.

The basic approaches to treatment of pediatric NRSTS are largely based on the experience of adult patients with soft tissue sarcomas.[76] Because considerable controversy still exists about the indications for and benefit of preoperative and postoperative multimodality therapy in adult patients, it is not surprising that there are few definitive treatment guidelines for pediatric patients. Although 30 to 40 percent of patients with seemingly localized tumors will develop distant metastases, the achievement of local control is a critical first step in the attempt to cure the patient with an NRSTS. Complete surgical resection with microscopically negative margins, either at the time of diagnosis or following induction chemotherapy or chemoradiotherapy, remains the most important prognostic determinant for children with NRSTS. The critical importance of surgical resectability was clearly established in the report by Horowitz et al.[71] In this series of 62 pediatric patients with NRSTS, despite the fact that significant antitumor responses were seen, adjuvant chemotherapy and/or radiation therapy was not demonstrated to be of any obvious benefit, especially for the group of patients with gross residual or metastatic disease (one long-term survivor out of 26 patients with gross residual or metastatic disease versus 29 long-term survivors out of 36 patients with completely resected tumors or microscopic residual disease).

In adult patients with soft tissue sarcomas, excisional biopsy is a suboptimal surgical approach for high-grade tumors and is associated with near-universal local recurrence. Wide local excision (removal of the tumor in continuity with a margin of several centimeters of normal surrounding tissue) is sufficient to achieve local control in about 50 percent of patients.[77,78] Following radical local excision (removal of the tumor along with all tissue in the anatomic compartment occupied by the tumor), local recurrence will develop in 15 to 25 percent of adults.

The use of high doses of radiation (often greater than 6,500 cGy) is frequently necessary for control of soft tissue sarcomas when employed as the sole therapeutic modality. Local control rates in some adult series are reportedly as high as 90 percent for tumors less than 5 cm in maximal diameter, but substantially poorer for bigger tumors. Radiation therapy is a universal component of multimodality limb-sparing approaches.[79] Lower doses of radiation appear to be sufficient to control microscopic residual disease following conservative surgery. Local control rates of 75 to 95 percent have been reported with this approach. Randomized studies have demonstrated a significant decrease in local recurrence in adult patients with high-grade tumors who received postoperative radiation following nonradical surgery.[77] While large-scale, prospective, randomized studies of postoperative irradiation have not been conducted in pediatric patients, the results of nonrandomized single-institution studies have suggested that tumor size

As more patients diagnosed with rhabdomyosarcoma survive for longer periods of time, there has been an increase in sequelae of therapy.

greater than 5 cm and the presence of gross residual tumor are strongly predictive of local recurrence even following appropriate radiation therapy.[80] While a combined modality approach is feasible in children who have reached skeletal maturity, radical surgery may occasionally be the preferred approach in younger children who are at greater risk of long-term complications from full-dose irradiation.

Although a small percentage of adequately treated patients will recur locally, the major risk of treatment failure in patients with high-grade tumors is distant (primarily pulmonary) relapse. Chemotherapy has not been shown to be of any significant benefit to adult patients with metastatic soft tissue sarcomas, and the role of adjuvant chemotherapy for completely resected tumors is a much debated topic with most studies showing no clear long-term advantage with treatment.[77,81] Unlike the situation with RMS, the role of postoperative, adjuvant chemotherapy and radiation therapy for children with completely resected NRSTS remains to be determined. Again, based largely on the adult experience, doxorubicin (either alone or in some combination with vincristine, cyclophosphamide, dactinomycin, or dacarbazine) and ifosfamide appear to be among the most active agents, with some evidence that high-grade tumors are more likely to be chemoresponsive.[82-84]

To date, only a single prospective, multi-institutional, randomized study has been performed to assess the role of adjuvant chemotherapy and radiation therapy in pediatric patients with localized NRSTS. Following complete surgical resection and postoperative radiation for microscopic residual disease, patients were randomized to either observation or one year of alternating cycles of two chemotherapy regimens (VAC and VAdriaC) given every three weeks. Preliminary results in the first 83 patients eligible for this study have failed to show any benefit of adjuvant chemotherapy for patients with Clinical Group I or II low-grade (Grade 1 or 2) tumors or any benefit of postoperative radiation for Clinical Group II patients with low-grade tumors.[85] Patients with high-grade (Grade 3) tumors had a poorer disease-free survival than patients with low-grade tumors (61 percent versus 89 percent). This difference was not significant, and no obvious benefit could be attributed to the use of adjuvant chemotherapy in patients with high-grade tumors. Interpretation of these data is complicated because nearly two thirds of the eligible patients refused randomization. The small number of patients also precluded a multivariate analysis of the relative importance of tumor size, invasiveness, grade, and initial surgical resectability on outcome.

NCI Pediatric Branch Experience with Pediatric NRSTS

Over the past decade, the NCI Pediatric Branch has treated 20 patients with a variety of high-grade pediatric NRSTS. Table 5 summarizes the clinical features of these patients. Most of these patients had either unresectable or metastatic disease. All of the patients received chemotherapy with two or more agents, including VAdriaC: two patients; IE (ifosfamide and etoposide): one patient; doxorubicin plus IE (AIE): one patient; or VAdriaC plus IE: 16 patients. Objective responses (all partial responses) were observed in 10 of 16 patients with measurable disease; in seven cases, a subsequent complete response was achieved by either a complete surgical resection or a combination of surgery and radiation therapy of a previously inoperable tumor. One patient with metastatic fibrosarcoma (Case 4) has had stable pulmonary metastases (histologically confirmed) for more than four years following the completion of therapy, while another patient with metastatic gastric leiomyosarcoma (Case 5) has had resolution of her residual radi-

Table 5
Clinical Features of NCI-PB Patients with NRSTS

Patient's Number	Sex	Age on Study (Years)	Diagnosis	Primary Site	Primary Size (Maximum diameter [cm])	Metastases
1	Male	13	MPNST	Elbow	27	No
2	Male	15	Synovial sarcoma	Ankle	7	No
3	Male	15	Synovial sarcoma	Popliteal fossa	7	No
4	Male	12*	Fibrosarcoma	Ankle	6	Lungs
5	Female	20	Leiomyosarcoma	Stomach	9	Liver
6	Male	16	Hemangiopericytoma	Pubis	9	No
7	Female	15†	Clear cell sarcoma	Gluteus	5	Lungs
8	Male	18	Leiomyosarcoma	Pelvis	7	Lung, lymph node
9	Male	24	Leiomyosarcoma	Jejunum	10	Liver, omentum
10	Female	19	Epithelioid hemangioendothelioma	Pelvis	4	Bone, bone marrow lung, scalp
11	Male	14	Synovial sarcoma	Pelvis	13	Lung
12	Female	1	MPNST	Retroperitoneum	16	Omentum, ascites
13	Male	10	Fibrosarcoma	Paraspinal (cervical)	10	No

Patient's Number	Sex	Age on Study (Years)	Diagnosis	Primary Site	Primary Size (Maximum diameter [cm])	Metastases
14	Female	20	Stromal sarcoma	Retroperitoneum	20	Liver
15	Female	14	Alveolar soft-part sarcoma	Calf	6	Lung
16	Female	17	Clear cell sarcoma	Pelvis	10	Lung, pelvis
17	Male	15	Malignant mesenchymoma	Paranasal sinus	10	No
18	Female	19	Hemangiopericytoma	Forearm	12	No
19	Male	20	Undifferentiated sarcoma	Thigh	30	Lung
20	Male	28‡	Angiosarcoma	Foot	16	Pleura, bone
Median		15.5 years			10 cm	

*Patient was diagnosed at three years of age with congenital fibrosarcoma of the ankle and treated with surgery alone. Disease recurred at primary site and lungs at 12 years of age.

†Patient was diagnosed at 14 years of age with clear cell sarcoma of the gluteus and treated with surgery alone. Disease recurred in lungs at age 15.

‡Patient was diagnosed at 17 years of age with angiosarcoma of the foot and treated with surgery alone. Disease recurred at 28 years of age with rib metastasis and a soft tissue mass filling the hemithorax.

NCI-PB = National Cancer Institute-Pediatric Branch; NRSTS = nonrhabdomyosarcoma soft tissue sarcoma; MPNST = malignant peripheral nerve sheath tumor.

Table 6
Response to Treatment and Outcome of NCI-PB Patients with NRSTS

Patient's Number	Chemotherapy Regimen	Surgical Result (at entry onto study)	Best Chemotherapy Response	Best Combined Response (CT ± RT ± OR)*	Status
1	VAdriaC/IE-2†	Complete resection	Not evaluable	Not evaluable	Net at 75+ months
2	VAdriaC/IE-2	Complete resection	Not evaluable	Not evaluable	Relapsed at 58 months; DOD at 65 months
3	VAdriaC/IE-2	Complete resection	Not evaluable	Not evaluable	Relapsed at 49 months; NED at 72+ months
4	VAdriaC/IE-1	Gross residual disease	Stable disease	Stable disease	Progression free at 76+ months
5	VAdriaC/IE-1	Gross residual disease	Partial response	Complete response	NED at 59+ months
6	VAdriaC/IE-1	Gross residual disease	Partial response	Complete response	NED at 61+ months
7	VAdriaC/IE-1	Gross residual disease	Progressive disease	———————	PD at 2 months; DOD at 10 months
8	VAdriaC/IE-1	Gross residual disease	Partial response	Complete response	NED at 52+ months
9	VAdriaC/IE-1	Gross residual disease	Progressive disease	Complete response	PD at 3 months; AWD at 48+ months
10	VAdriaC/IE-1	Gross residual disease	Stable disease	Stable disease	PD at 16 months; DOD at 20 months
11	VAdriaC/IE-1	Gross residual disease	Partial response	Complete response	NED at 26+ months

Patient's Number	Chemotherapy Regimen	Surgical Result (at entry onto study)	Best Chemotherapy Response	Best Combined Response (CT ± RT ± OR)*	Status
12	VAdriaC/IE-1	Gross residual disease	Partial response	Partial response	DOD at 8 months
13	VAdriaC/IE-1	Gross residual disease	Stable disease	Stable disease	Progression free at 24+ months
14	VAdriaC/IE-1	Gross residual disease	Partial response	Partial response	Progression free/AWD at 8+ months‡
15	VAdriaC/IE-1	Complete resection	Progressive disease	Complete response	PD at 8 months; NED at 9+ months
16	VAdriaC/IE-1	Gross residual disease	Partial response	Complete response	PD at 7 months; DOD at 9 months
17	VAdriaC	Microscopic residual disease	Not evaluable	Not evaluable	NED at 107+ months
18	VAdriaC	Gross residual disease	Partial response	Complete response	NED at 112+ months
19	AIE	Gross residual disease	Partial response	Complete response	NED at 89+ months
20	IE	Gross residual disease	Partial response	Complete response	NED at 68+ months

*Best response to chemotherapy (CT) and/or radiation therapy (RT) and/or surgery (OR).

†VAdriaC/IE-2 is NCI protocol 87C10; VAdriaC/IE-1 is NCI Protocol 86C169; VAdriaC is NCI Protocol 83C73M; AIE is NCI Protocol 86C88; IE is NCI Protocol 85C154.

‡Patient on study with residual soft tissue mass.

NCI-PB = National Cancer Institute-Pediatric Branch; NRSTS = nonrhabdomyosarcoma soft tissue sarcoma; VAdriaC = vincristine, doxorubicin, cyclophosphamide; IE = ifosfamide, etoposide; AIE = doxorubicin, ifosfamide, etoposide;
NED = no evidence of disease; PD = progressive disease; DOD = dead of disease; AWD = alive with disease.

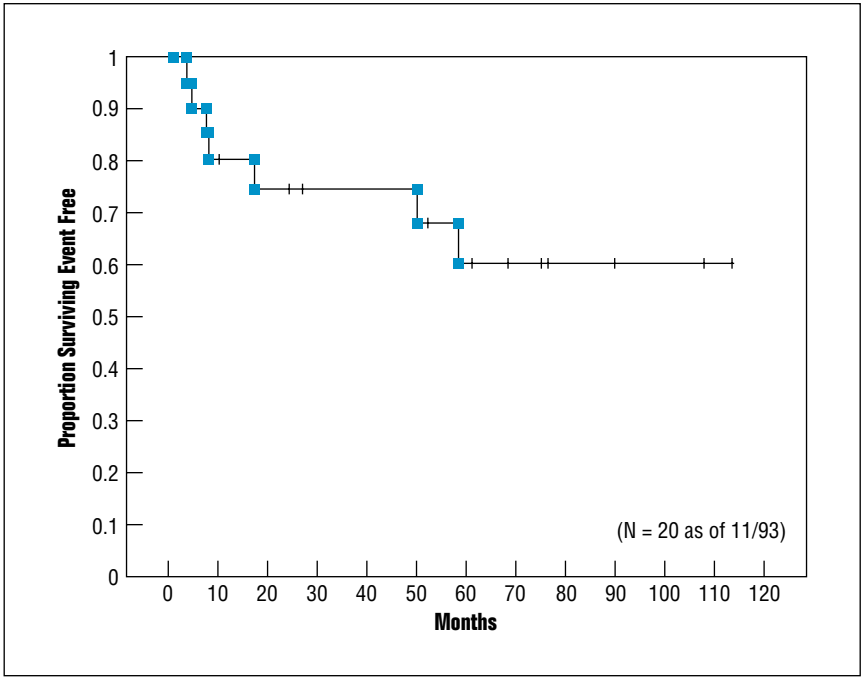

Fig. 8. Kaplan-Meier plot of event-free survival among 20 patients with nonrhabdomyosarcoma soft tissue sarcomas (primarily metastatic or unresectable high-grade tumors) treated at the National Cancer Institute Pediatric Branch. With a median duration of potential follow-up in excess of four years, event-free survival is 60 percent.

ologic abnormalities over the course of her off-treatment follow-up. Table 6 summarizes the responses to chemotherapy, subsequent management of the primary site, and eventual outcome in these patients. With a median duration of potential follow-up in excess of four years, event-free survival among this high-risk group of patients is 60 percent (Fig. 8). This experience clearly indicates that a substantial proportion of patients with unresectable or metastatic pediatric NRSTS can benefit from the use of appropriately intensive multiagent chemotherapy and/or radiation therapy. Whenever possible, such patients should be enrolled on clinical protocols to formally assess the chemoresponsiveness and long-term outcome of these tumors following the administration of appropriately intensive, modern, multimodality treatment regimens.

Given the paucity of published data in this area, the following general guidelines would appear reasonable given the current state of knowledge about these tumors. Patients with small, low-grade tumors that have been either completely or gross totally resected are likely to be cured without further radiation therapy or chemotherapy. Postoperative irradiation of grossly resected larger (greater than 5 cm) or locally invasive low-grade tumors is reasonable, but the use of adju-

vant chemotherapy appears to be of no benefit. The role of postoperative irradiation following wide local resection of high-grade tumors is unclear, but it would certainly be appropriate to administer radiation therapy to "marginally" resected tumors. The benefit of adjuvant chemotherapy in patients with completely and grossly resected high-grade tumors is still unproven, and, when possible, such patients are best managed by enrollment on a clinical research protocol that specifically addresses this question. Patients with tumors that are unresectable or metastatic at diagnosis (a disproportionate number of which will be high grade) should be treated with an aggressive chemotherapy or chemoradiotherapy induction regimen that may result in sufficient tumor shrinkage to make operative resection possible (assuming eradication of other sites of disease). The value of postoperative radiation therapy and chemotherapy following complete resection is uncertain; thus the results of ongoing Pediatric Cooperative Group studies are eagerly awaited. Our own experience, as well as smaller, single-institution reports, suggests that a significant proportion of patients with initially unresectable tumors may derive benefit from such an approach and can be rendered resectable. Whether reduction of bulk tumor will equate with eradication of occult micrometastases and translate into improvement in long-term survival remains to be seen. For patients with metastatic disease at diagnosis, aggressive treatment of the local tumor following eradication of metastatic foci (either with chemotherapy or surgery) offers the best chance at cure. Between 20 to 25 percent of patients with metastatic soft tissue sarcomas may be cured with the use of aggressive pulmonary metastectomy (unpublished results).

The basic approaches to treatment of pediatric NRSTS are largely based on the experience of adult patients with soft tissue sarcomas.

Specific Disease Entities

Synovial Sarcoma

The median age at diagnosis for a patient with synovial sarcoma is generally in the third decade of life, with about one third of cases arising in patients younger than 20 years of age. There is a slight male predominance in most large series, although in one large German series a female predominance (19 of 31 patients) was observed.[86] These tumors may arise from any site in the body, but most typically arise in an extremity, with about twice as many lower extremity cases (typically in the thigh or knee) as upper extremity cases. It is uncommon for these tumors to present with distant metastases, but when present, the lung is the most common site of distant spread. Synovial sarcomas are generally relatively slow-growing tumors, with a median time between onset of symptoms (swelling or mass with or without pain) and diagnosis of 12 months. A characteristic and specific chromosomal translocation between chromosome X and 18, t(X;18)(p11;q11), has been described in greater than 90 percent of these tumors, suggesting a likely role of this genetic alteration in the development of synovial sarcoma, although the gene or genes involved have yet to be identified.[87]

Synovial sarcomas are divided into one of two histologic subtypes, monophasic or biphasic, based on their light microscopic appearance. Monophasic tumors require the presence of a single, generally

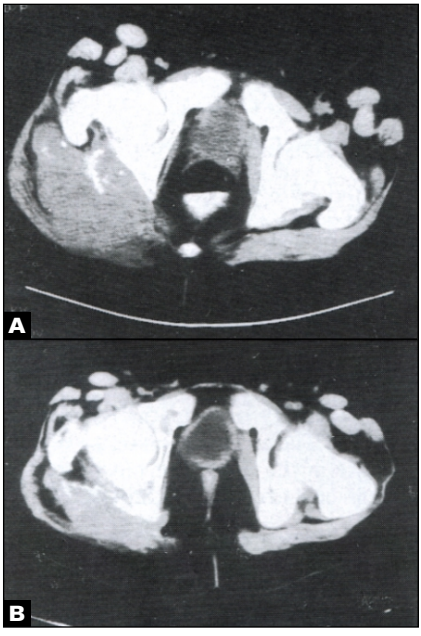

Fig. 9. Synovial sarcoma of the buttocks. (A) This 14-year-old boy presented with an unresectable tumor of the buttocks and pulmonary metastases (not shown). (B) Following four cycles of chemotherapy (2 VAdriaC, 2 IE), the buttock tumor underwent substantial regression permitting a gross total resection to be performed. Radiation therapy was administered for control of presumed microscopic residual disease. The pulmonary metastases resolved completely after four cycles of chemotherapy, and the patient is alive and without incidence of recurrent tumor more than two years after the completion of therapy.

spindle-cell fibrous stroma and may be difficult to distinguish from fibrosarcoma unless immunohistochemical evidence of keratin antibody reactivity can be demonstrated (a unique feature of synovial sarcoma). Biphasic tumors, in contrast, contain, in addition to the spindle-cell fibrous stroma, a distinct glandular component (indicative of epithelial differentiation). Biphasic tumors are generally considered more common than monophasic ones. In the past, synovial sarcoma was generally considered to be unresponsive to chemotherapy and radiation therapy, although more recent data suggest that significant antitumor responses can be achieved in a substantial number of patients with appropriately intensive chemotherapy (Fig. 9).[86,88]

Fibrosarcoma

Unlike synovial sarcoma, which is extremely rare in young children, fibrosarcoma may be seen in both infants and older children. A unique form of congenital fibrosarcoma is well described in newborn infants and is considered to be a histologically low-grade tumor.[89] These babies may have tumors that can be quite large, but the long-term outcome is generally quite good with conservative surgical management. These tumors are associated with trisomies of chromosome 8, 11, 17, and 20.[90,91] In infants with huge, unresectable tumors, there have been some reports that preoperative chemotherapy may permit eventual nonmutilating surgical resection.[92,93] Fibrosarcomas in older children, in contrast, must be treated with a more aggressive surgical approach. Fibrosarcomas are also common as secondary, radiation-induced neoplasms.

Malignant Fibrous Histiocytoma

Depending on the series, malignant fibrous histiocytoma is the second or third most common NRSTS, generally accounting for eight to 10 percent of cases. It can occur in children of any age and can arise from any site.[94] In patients who develop radiation-induced sarcomas, MFH is one of the more common diagnoses.[95] Cole et al reported their experience with nine pediatric patients seen at a single institution over a seven-year period.[96] There were seven male and two female patients; the average tumor diame-

ter was 8.9 cm (range, 1.5 to 20 cm); and the median age at diagnosis was five years (range, two to 13 years). Two of the nine cases occurred in the orbit following irradiation during the neonatal period for bilateral retinoblastoma. Other primary sites included extremity (three cases), trunk (two cases), scalp (one case), and kidney (one case). Six tumors had a storiform-pleomorphic pattern. Complete surgical resection was the primary approach in eight patients, and five patients received either neoadjuvant or adjuvant chemotherapy with one objective response noted. Six patients were recurrence free 20 months to eight years following the completion of therapy. Poor outcome was associated with large tumors, deep and proximal locations, and storiform-pleomorphic histologic pattern with atypical mitoses.

A rare form of MFH, the so-called low-grade "angiomatoid" variant, is seen primarily in children and young adults and has a characteristic clinical presentation as a painless nodular subcutaneous mass in the superficial soft tissues of an extremity. This variant has a distinctive microscopic appearance consisting primarily of solid arrays ("nests") of fibroblast- and histiocyte-like cells, occasionally containing variable amounts of intracellular hemosiderin or lipid; focal areas of varying size of hemorrhage or hemorrhagic cyst-like spaces; and aggregates of lymphocytes and plasmacytes. It has also been reported to have a unique pattern of immunohistochemical reactivity, possibly consistent with either a myogenic/myofibroblastic or histiocytic origin.[97]

In the original report of this entity, Enzinger studied 41 cases of angiomatoid MFH seen over a period of 22 years, with follow-up data available on 24 patients.[98] Two thirds of the tumors arose in patients aged 19 years or younger, and 85 percent of the tumors arose in one of the extremities (upper more common than lower). With a median follow-up of three years, 21 of 24 patients were alive, including 11 alive with disease (mostly local recurrence). Angiomatoid MFH is generally thought to be associated with less aggressive behavior and a more favorable outcome, though this is based on small numbers of patients.[99]

Malignant Peripheral Nerve Sheath Tumors

Malignant peripheral nerve sheath tumors are rare tumors that generally account for about 10 percent in most series of pediatric NRSTS. These tumors were previously referred to by a variety of terms including malignant schwannoma, neurogenic sarcoma, neurofibrosarcoma, and malignant neurilemmoma.[100] The finding of an extensive mass, occasionally encapsulated, arising as a fusiform enlargement of a nerve trunk suggests MPNST. These tumors tend to be high grade and locally invasive. About 25 percent to 35 percent of MPNST occur in association with von Recklinghausen's disease (neurofibromatosis), an autosomal dominant genetic disorder characterized by café-au-lait spots, axillary freckling, neurofibromas, skeletal dysplasias, and learning disabilities.[101,102] Recently, the *NF1* gene has been isolated and found to be related to a GTPase activating protein that may affect RAS signaling.[103,104] A molecular characterization of 32 cases of

The major risk of treatment failure for adequately treated patients with high-grade NRSTS is distant (primarily pulmonary) relapse.

acoustic and nonacoustic schwannomas suggested that partial loss of chromosome 22 is frequent in nonacoustic schwannomas and led to the hypothesis that a separate schwannoma-related tumor suppressor gene may be located on chromosome 22.[105]

Meis et al reported a total of 78 cases of MPNST (out of about 200) in children aged 15 years or younger seen from 1965 to 1985 for whom slides and patient records were available for review.[106] There were slightly more males than females (42:36), and the median age at diagnosis was 10 years (range, 8 days to 15 years). Nearly half of the cases (46 percent) arose in the extremities (especially the lower extremity and limb girdle), followed by the trunk (37 percent), and head and neck region (17 percent). Nearly one third of the patients either had a history of von Recklinghausen's disease or a family history of the disease. The most common presenting symptom was a mass (55 percent) followed by pain and sensory or motor disturbances due to nerve compression. The duration of symptoms ranged from three days to two years. Tumors ranged in size from 2 to 33 cm (median 7.5 cm) and were variegated in color, consistency, and appearance macroscopically. Most lesions (74 percent) were primarily composed of spindle cells arranged in fascicles, while in a smaller number either the predominant histologic component or smaller foci resembled a primitive neuroepithelial tumor (19 percent) or had a primarily epithelioid appearance (10 percent). Heterologous elements were seen in 11 cases, with a rhabdomyoblastic component (malignant Triton tumor) being most common.[107]

Virtually all patients were treated by surgical resection, while 53 patients received either chemotherapy (23), radiation therapy (18), or both (12). The median survival time for the 57 patients for whom follow-up information was available was 45 months; about one third of the patients were alive without evidence of disease from 7 months to 19-plus years following surgical resection. Factors that were found to be adversely associated with prognosis in a multivariate analysis included larger tumor size (≥6 cm), increased age (≥7 years), increased tumor necrosis (≥25 percent), and the presence of von Recklinghausen's disease. Primary site, cellularity, the presence of heterologous elements, and the average number of mitoses per 10 high-power fields were not found to be significantly associated with outcome.

The role of postoperative adjuvant chemotherapy and radiation therapy for children with completely resected NRSTS remains to be determined.

Less Common Pediatric NRSTS

Hemangiopericytoma and alveolar soft-part sarcoma each account for about three to six percent of pediatric NRSTS. Unlike hemangiopericytoma, which can be histologically benign or malignant, alveolar soft-part sarcoma is always considered a malignant tumor. Although quite rare, alveolar soft-part sarcoma is often seen in adolescents, particularly females, and despite its histologically aggressive appearance, it can often have an indolent course, even in children with distant metastases at diagnosis.[108-110] Both types of tumors tend to arise in an extremity, with hemangiopericytoma pre-

sumably arising from vascular pericytes and alveolar soft-part sarcoma from skeletal muscle tissue.

Leiomyosarcoma is an extremely uncommon tumor in children and accounts for less than two percent of cases of NRSTS, although there have recently been reports of leiomyomas arising with increasing frequency in children with the acquired immunodeficiency syndrome.[111,112] Of further interest, leiomyosarcomas have been noted to overexpress IGFII similar to what has been observed for RMS.[113] These tumors can arise in a variety of sites, including the retroperitoneum, vascular tissue, peripheral soft tissue, and gastrointestinal tract. A recent report has suggested that there may be a variant form of gastrointestinal leiomyosarcoma in adolescents (particularly females), which, despite the presence of metastases, may have an unusually favorable prognosis.[114]

Finally, soft tissue clear cell sarcomas are extremely rare tumors of childhood representing fewer than two percent of cases.[115] Although thought to arise from neuroectodermal tissue, these tumors are also known as malignant melanoma of soft parts, reflecting the confusion over their tissue of origin and the fact that they frequently produce melanin.[116,117] They tend to develop in sites of aponeuroses (tendon insertions) and most commonly arise in adolescents, particularly females, most often in an extremity. A recent report has suggested that these tumors may share a common genetic abnormality with Ewing's sarcoma and peripheral primitive neuroectodermal tumor at the breakpoint site on the long arm of chromosome 22.[118] CA

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