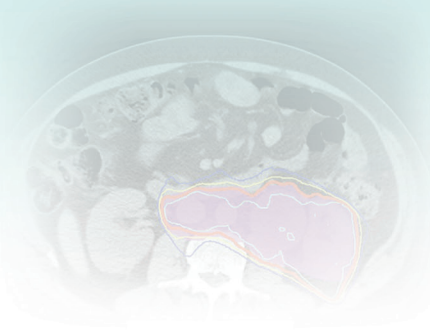
CHAPTER

68 Pediatric Soft-Tissue Sarcomas



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INCIDENCE

There are 350 cases annually in the United States of rhabdomyosarcoma (RMS).
- Of those, embryonal rhabdomyosarcoma (ERMS) comprises 75% (260 cases), botryoid subtype (35 cases), and alveolar rhabdomyosarcoma (ARMS) comprises 25% (90 cases).

There are 500 cases annually of non-rhabdomyosarcoma soft-tissue sarcoma (NR-STS) in the United States. These are divided into high grade (Pediatric Oncology Group [POG] grade III), 67% (335 cases), and low and intermediate grade (POG grade I/II), 33% (165 cases).

BIOLOGIC CHARACTERISTICS

RMS
- With EMRS, there is a loss of heterozygosity chromosome 11p and RAS/NF1 pathway mutations.
- In alveolar rhabdomyosarcoma, t(2;13) or t(1;13) translocations result in *PAX-FKHR* fusion protein (80%)

There are diverse histologies in NR-STS with mixture of distinct genetic events. Examples include:
- Synovial cell sarcoma: t(X;18) and resulting fusion product *SYT-SSX*
- Alveolar soft-part sarcoma: der(17)t(X;17) and resulting fusion *TFE3-ASPL*
- Diverse genetic signatures (e.g., malignant fibrous histiocytoma)

STAGING EVALUATION

RMS
- There is the Intergroup Rhabdomyosarcoma Study Group (IRSG) clinical grouping system based on the degree of surgery, nodal involvement, and metastatic disease.
- In the TNM pretreatment staging classification, stages are based on location of primary tumor, size, invasiveness, nodal involvement, and metastatic disease.

NR-STS uses the American Joint Committee on Cancer staging system, which is based on grade, size, invasiveness, nodal involvement, and metastatic disease.

PRIMARY THERAPY

For RMS, nonmorbid "upfront" surgery is the first line of therapy.
- Radiation therapy (RT) is used for primary and metastatic sites of disease. The following are recommended doses:
  - microscopic disease: 36 Gy; microscopic nodal disease: 41.4 Gy; and gross disease: 50.4 Gy
- Local failure rates are 10% for Group I/II and 13% for Group III.

For NR-STS, the recommended course is surgical resection with or without adjuvant RT (55.8 Gy to 63 Gy) or brachytherapy (34 Gy at 3.4 Gy twice daily, high-dose rate).
- In some cases, preoperative chemoradiation (conventionally fractionated external beam RT, 45 Gy to 50.4 Gy) followed by surgery is needed.
- Local failure rates are 4% for resected and range from 40% to 80% for unresected disease.

ADJUVANT THERAPY

For RMS, vincristine, dactinomycin (Actinomycin D), cyclophosphamide (VAC)–based chemotherapy is the standard. For high-risk disease, vincristine, irinotecan, dactinomycin, cyclophosphamide, doxorubicin, ifosfamide, etoposide, or experimental agent(s) is used. With these treatments, there is a 5-year event-free survival:
- low risk (group I/II embryonal RMS): 90%;
- intermediate risk (alveolar RMS groups I-III, embryonal RMS group III): 70% to 73%; and high risk (metastatic embryonal or alveolar RMS): <30%.

In NR-STS,
- neoadjuvant chemoradiation or adjuvant chemotherapy (ifosfamide/doxorubicin) is used. There is a 5-year event-free survival:
  - Localized, resected: 75%; localized, unresectable: 45%; and metastatic: 10%.

EPIDEMIOLOGY

Soft-tissue sarcomas (STS) account for approximately 7% of all pediatric cancers. RMS comprises 40% of STS, and the other NR-STS comprise 60%.[1,2] This results in 350 patients with RMS and 500 with NR-STS (divided about 2:1 between high and low grade) available for participation in clinical trials in the United States annually. Based on prior clinical trials, 75% of children with RMS have required RT, and based on the presence of high-grade disease only, approximately two thirds of children with NR-STS receive irradiation. This yields 600 sarcoma cases annually for the study of radiation-specific clinical trial questions, training of young radiation oncologists, and study of radiation-specific long-term sequelae.

Patients with RMS have benefited from the Children's Oncology Group (COG) sarcoma studies (formerly the IRSG). The trials conducted by these groups have defined the combined modality management of children with RMS in North America and allowed the randomized comparisons of new chemotherapeutics as well as RT strategies that would not be possible without the cooperative group structure. These approaches, as well as the specifics of modern RT, are discussed in this chapter.

Treatment of children with NR-STS is less well defined. Local therapy approaches have evolved from adult paradigms, incorporating limb salvage over amputation, adjuvant irradiation, and subsequently, preoperative RT approaches.[3-6] Despite an adult parallel to draw from, little prospective

research has been conducted in the pediatric NR-STS population. A recently closed trial through COG (ARST0332) sought to address some of these deficiencies delivering both preoperative and postoperative RT in conjunction with surgery and chemotherapy to define the role of local and systemic approaches in a comprehensive clinical trial; preliminary data from this recently closed study suggests that a risk-based approach may be used with lower dose RT or RT avoidance in select patients.[7]

BIOLOGIC CHARACTERISTICS AND PATHOLOGY

Rhabdomyosarcoma

RMS is broadly classified as one of the small, round, blue cell malignancies of childhood.[8] The histologic subtypes, in order by worsening prognosis, include ERMS, the most common form (with spindle cell and botryoid comprising two favorable variants); ARMS; and undifferentiated sarcoma. Patients with undifferentiated sarcoma were previously enrolled in IRSG clinical trials in a fashion similar to ARMS. More recently, these patients have received systemic therapy similar to patients with Ewing's sarcoma and have also been included in the COG ARST0332 trial. Light microscopy often describes ERMS with spindle-shaped cells and ARMS with small, round, blue cells forming alveolar-like spaces, although tumor biopsy specimens may also look like collections of poorly differentiated cells complicating definitive diagnosis by hematoxylin and eosin staining alone. Immunohistochemical staining can include positivity for MyoD1.[9] Cytogenetic events occur in ERMS with a loss of heterozygosity on chromosome 11p and frequent mutations of the RAS/NF1 pathway,[10,11] and in 80% of ARMS with translocations between chromosomes 2 and 13 or 1 and 13. These represent loci of *PAX3* and *PAX7* (chromosomes 2 and 1) and their fusion with *FKHR* on chromosome 13. These fusion proteins act as transcription factors and are diagnostic of ARMS.[8] Other genetic abnormalities and syndromes associated with RMS include neurofibromatosis type 1 (with a prevalence of 1:200 noted on IRSG-IV), Li-Fraumeni syndrome, and Beckwith-Wiedemann syndrome.[12-14]

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The pediatric NR-STS comprise a heterogeneous group of tumors managed homogeneously largely because of the limitations in patient numbers and effective chemotherapy. The most common histologies include synovial cell sarcoma and malignant peripheral nerve sheath tumor (MPNST), although several rarer variants including rhabdoid tumor and infantile fibrosarcoma are almost exclusive to the pediatric age group.[15,16] Although many NR-STSs have no genetic signature, several histologic variants do have specific translocations or deletions[15,17] (Table 68-1).

CLINICAL MANIFESTATIONS

Rhabdomyosarcoma

The presentation of children with RMS is diverse, characterized by the site of involvement and extent of disease. The median age for children presenting with RMS is younger than 5, although a second incidence peak occurs in the mid-teens. The head and neck region is the most frequent site of involvement and is divided into favorable and unfavorable (parameningeal) sites.[18,19] This site comprised 42% of localized presentations in patients enrolled in IRSG III and IRSG IV and serves as an example of the important nature of primary tumor location.[20] Metastatic disease occurs 20% of the time at presentation, and nodal involvement is rare (<5%) except for paratesticular (25%) and extremity (24%) sites of disease, which warrant computed tomography ([CT] including paratesticular sites at <10 years of age), nodal sampling (paratesticular sites for ≥10 years of age), or sentinel node biopsy (extremity sites).[21-25]

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The presentation of NR-STS is often as a painless mass, whereas other symptoms are site specific. Approximately half of the cases arise in the extremity, and the incidence increases throughout the adolescent years and into adulthood.[26,27] Although the vast majority of soft-tissue "masses" are either not real or benign, consideration should be given to malignancy because an ill-chosen surgical approach may compromise future local therapy (Figure 68-1).

Fifteen to 22 percent of patients present with metastatic disease at diagnosis, with the lungs being the predominant

TABLE 68-1 Genetic Abnormalities: Nonrhabdomyosarcoma Soft-Tissue Sarcomas

Histology	Genetic Abnormality
Synovial cell sarcoma	t(X;18); fusion *SYT-SSX*
Clear cell sarcoma	t(12;22); fusion *EWS-ATF1*
Desmoplastic small round cell tumor	t(11;22); fusion *EWS-WT1*
Infantile fibrosarcoma	t(12;15); fusion *ETV6-NTRK3*
Alveolar soft-part sarcoma	der(17)t(X;17); fusion *TFE3-ASPL*
Low-grade fibromyxoid sarcoma	t(7;16); fusion *FUS-CREB3L2*
Myxoid and round cell liposarcoma	t(12;16); fusion *FUS-DDIT3*

Figure 68-1 Rhabdomyosarcoma of the pinna of the ear presenting as a painless soft-tissue mass.

site of metastatic involvement.[16,28] Clear cell sarcoma and epithelioid sarcoma carry a risk of regional nodal involvement and warrant evaluation of the draining nodal bed(s) with sentinel node sampling.[29]

STAGING

Rhabdomyosarcoma

Staging workup is similar for most patients with RMS (Table 68-2). A site-specific history and physical examination should be performed by the treating radiation oncologist at the time of presentation to define the site of primary disease, its extent, and symptoms possibly related to potential metastatic sites of involvement. Attention to cranial nerve involvement for head and neck primary sites as well as attending the examination under anesthesia for genitourinary sites (vaginal, cervix, uterus, bladder, and prostate) will assist in the multidisciplinary discussions regarding staging and local therapy approaches.

Laboratory studies include a complete blood cell count and chemistry panel, which may be suggestive of bone marrow disease (anemia) or other organ-specific dysfunction related to metastatic involvement.

Review of the pretreatment imaging is critical to ensure adequate imaging of the primary tumor as well as understanding the extent of disease. Often, standard diagnostic imaging protocols (particularly magnetic resonance imaging [MRI]) will not encompass the entire tumor, because the studies were designed for evaluation of joint or intracranial disease. Repeating these studies will facilitate better local therapy decisions and delivery. Standard diagnostic imaging should include MRI of the primary site of disease, CT of the chest (and abdomen for infradiaphragmatic presentations), bone scintigraphy, and site-specific imaging related to potential metastatic disease.[19] F-Fluorodeoxyglucose–labeled positron emission tomography (FDG-PET) may be useful in the evaluation of distal metastases, especially lymph nodes, and may eventually replace bone scintigraphy.

Bone marrow aspiration and biopsy should be performed for all patients, as well as cerebrospinal fluid cytology for patients with parameningeal, orbital, and paraspinal primary sites of disease. Lymph node sampling should be performed for patients 10 years of age or older with paratesticular primary tumors, and sentinel node mapping and sampling should be done for patients with disease of an extremity.

After staging evaluation, a clinical stage should be assigned (outlined in Table 68-3). If surgery has been performed (or

TABLE 68-2 Staging Workup and Follow-Up Evaluations for Patients with Rhabdomyosarcoma and Nonrhabdomyosarcoma Soft-Tissue Sarcomas

	Rhabdomyosarcoma	Nonrhabdomyosarcoma Soft-Tissue Sarcomas
Staging		
Clinical	Site-directed history and physical examination	Site-directed history and physical examination
Imaging	MRI of primary tumor CT of chest CT of abdomen (infradiaphragmatic tumors) Bone scintigraphy	MRI of primary tumor CT of chest
Procedures	Biopsy: primary tumor/metastasis Extremity: sentinel lymph node biopsy Paratesticular (>10 years): ipsilateral retroperitoneal lymph node dissection Head and neck: cerebrospinal fluid cytology Genitourinary: examination under anesthesia	Biopsy: primary tumor/metastasis Histology: specific sentinel lymph node biopsy
Follow-up		
Year 1	History and physical examination every 3 months, laboratory studies, MRI of primary tumor area CT of chest and other metastatic imaging every 3 months	History and physical examination, laboratory studies every 3 months, MRI of primary tumor area CT of chest every 6 months
Years 2 to 3	Every 4 months: history and physical examination, laboratory studies, MRI of primary area Every 4 months: CT of chest and other metastatic imaging	Every 6 months: history and physical, laboratory studies, MRI of primary tumor region, CT of chest
Years 4 to 5	Every 6 months: history and physical, MRI of primary area, chest radiograph	Annual history and physical laboratory studies, MRI of primary area, CT of chest

CT, *Computed tomography;* MRI, *magnetic resonance imaging.*

TABLE 68-3 Clinical Staging System for Rhabdomyosarcoma

Stage	Sites	Tumor	Size	Node	Metastasis
1	Favorable site: Orbit, head and neck (excluding parameningeal), genitourinary (excluding bladder/prostate), biliary tract	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Unfavorable site: Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, etc.)	T1 or T2	a	N0 or Nx	M0
3	Unfavorable site: Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, etc.)	T1 or T2	a b	N1 N0 or N1 or Nx	M0
4	All	T1 or T2	a or b	N0 or N1	M1

TABLE 68-4 Clinical Grouping System for Rhabdomyosarcoma

I	Completely resected localized disease
Ia	Confined to muscle of origin
Ib	Involvement outside of muscle of origin (contiguously)
II	Microscopic residual disease and regional nodal involvement
IIa	Microscopic residual disease (after gross resection, N0)
IIb	Regional nodal involvement (without microscopic residual disease)
IIc	Regional nodal involvement (with microscopic residual disease)
III	Gross residual disease
IIIa	After biopsy
IIIb	After gross major resection (>50% of disease)
IV	Distant metastasis

after a planned surgical resection or biopsy), a grouping should be defined (Table 68-4). These two factors plus the patient's histology are combined into a risk classification to assign patients to protocol therapy.

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The workup for patients with NR-STS is similar to that for RMS (see Table 68-2). A site-specific history and physical examination should be performed by the treating radiation oncologist at the time of presentation to define the site of primary disease, its extent, as well as symptoms related to potential metastatic sites of involvement.

Laboratory studies include a complete blood cell count and chemistry panel, the findings from which may be suggestive of organ-specific dysfunction related to metastatic involvement.

Diagnostic imaging studies include MRI of the primary site, CT of the chest, and other metastatic imaging, including bone scintigraphy, as indicated by symptoms and laboratory studies. FDG-PET may be useful in the workup of patients

EVALUATION AND DEFINITION OF RISK CLASSIFICATION

Rhabdomyosarcoma

Favorable and unfavorable sites of disease are defined as part of the staging system and are noted in Table 68-3. In addition, histology affects outcome and is related to site of disease; favorable sites of disease in the orbit and genitourinary region are four and five times as likely to be of an embryonal histology as opposed to alveolar or undifferentiated histology. This yields higher disease control rates for localized ERMS compared with ARMS (failure-free survival [FFS], 82% versus 65%).[20] Clinical group (see Table 68-4) is also prognostic of FFS in both ERMS and ARMS. Because of the strong interaction of site, histology, group, and stage, a risk classification system was devised to stratify patients for therapeutic decisions. This resulted in three strata[20,30,31]:

1. Patients with low-risk disease (ERMS, stage 1, groups I to III and ERMS, stage 2 to 3, groups I to II) whose tumor is treated by upfront with or without nodal resection at any site as well as patients with group III orbital site of disease. Patients with nonorbital group III ERMS are also considered low risk in the context of current research protocols. The FFS for this group is approximately 90%.
2. Patients with intermediate-risk disease (ERMS, stage 3, group II to III and ARMS stage 1 to 3, group I to III) are the remaining localized tumors and have variable outcomes, ranging from 30% to 85% FFS.
3. Patients with high-risk disease are those with metastatic disease and have FFS rates of 26% to 40%.

Future classification systems may adjust certain subsets of patients with low-risk disease into the intermediate group where treatment reduction yielded poorer outcomes.[32,33] The presence or absence of PAX/FKHR fusion protein has been shown to be more closely associated with outcome than histologic classification and will likely be included in future risk stratifications.[34]

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

Stratification for patients with NR-STS is based on retrospective data being tested in a prospective clinical trial.[23,24] Patients with low-risk disease are those with low-grade tumors (POG grade I or II) as well as high-grade tumors (POG grade III) that are less than or equal to 5 cm in maximal diameter, with an expected overall survival (OS) above 90%. Patients with intermediate-risk disease with large (>5 cm) high-grade tumors have a 5-year OS of 56%, and patients with high-risk disease with metastatic disease fare poorly, with a 5-year OS of 15%.[26,27]

PRIMARY THERAPY

Rhabdomyosarcoma

All patients with RMS are managed in a combined modality fashion. Participation by a pediatric oncologist, pediatric surgeon, radiation oncologist, and orthopedic or otolaryngologic oncologist (if indicated) at the outset ensures optimal planning for the many therapeutic decisions necessary for this diverse and complicated disease. This multimodal approach has been the hallmark of the studies of the IRSG performed in North America. Since 1972, these trials have enrolled thousands of patients, unified the therapeutic approach across the United States, and improved OS for this disease.

IRSG I (1972-1978) and IRSG II (1978-1984) answered several important questions. Patients in group I (without RT) and group II (with RT at doses of 40 Gy to 45 Gy) were noted to fare well with a regimen of vincristine and dactinomycin [Actinomycin], VA (and omitting cyclophosphamide).[18,35] Patients in group III did not benefit from the addition of doxorubicin, whereas patients treated in the CT era (IRS-II) with parameningeal disease and specific meningeal RT guidelines fared significantly better (OS, 67% versus 45%).[18] Unfortunately, 75% of patients in group IV continued to experience progressive disease.

IRSG III (1984-1991) went on to confirm that the VA regimen is equivalent to therapy with VAC for patients in group I and resulted in a progression-free survival of 83% without RT. The addition of doxorubicin to VA did not improve outcome for group II disease, and patients with groups III/IV disease did not benefit from the addition of cisplatin or etoposide, with progression-free survival for the latter group remaining at 27%.[36]

IRSG IV (1991-1997) was the first trial to employ presurgical staging in addition to the grouping system. A randomized question was asked about systemic therapy (now standard VAC versus VAI [ifosfamide] versus VIE [ifosfamide/etoposide]) for patients with stages 1 to 3 disease. Despite the hope for improvement in overall outcomes, no benefit was seen, and VAC remains the standard of care.[37] Patients with group III disease also underwent a randomization between

standard RT (50.4 Gy/1.8 Gy daily fraction) and hyperfractionated RT (59.4 Gy/1.1 Gy twice daily fractions). Hyperfractionated RT yielded the same FFS (73%) as conventional RT, and local failure was equivalent (15% versus 12%).[38] IRSG IV, in a retrospective fashion compared with IRSG III, also clarified the management of patients with group I paratesticular disease. Patients younger than age 10 years could be evaluated by CT for retroperitoneal lymphatic involvement (without retroperitoneal lymph node dissection [RPLND]), maintaining a 90% FFS. Those 10 years old or older benefited from RPLND (100% FFS with RPLND compared with 63% with CT alone) to define nodal involvement and the need for subsequent lymphatic RT.[22,37]

IRSG V is the last of the intergroup named trials, now named with the COG nomenclature ARST. Patients with group II disease had a reduction in RT dose from 41.4 Gy to 36 Gy for positive microscopic surgical margins. Orbital primary tumors were also irradiated using a reduced dose of 45 Gy. Outcome on this low-risk trial appears equivalent to previous studies, suggesting this is a safe and effective approach, particularly when cyclophosphamide is included in chemotherapy regimens.[39,40] Another randomized question was tested for patients with intermediate-risk disease comparing VAC against VAC alternated with VTC (substituting topotecan). This did not improve outcome, with a 4-year FFS of 73% and 68%, respectively.[41] Patients with high-risk disease during this era underwent several Phase II window therapy trials incorporating new agents. The combination of vincristine and irinotecan demonstrated a 70% response rate. Although FFS remained poor (26% at 2 years), its activity was sufficient to incorporate VI into further trials for patients with intermediate- and high-risk disease.[30]

The most recent round of trials in low-risk RMS (ARST0331) further tailored and reduced therapy for patients with ERMS resected upfront (groups I/II), stage 1 to 3, and unresected (group III), stage 1 disease. The RT dose remained 36 Gy for microscopic disease and 41.4 Gy for nodal disease. Group III vaginal tumors were treated with intent to avoid or delay radiation therapy, but a 2 year FFS of 42% in this subset demonstrated the importance of RT for local control.[33] Patients with intermediate-risk disease (ERMS stages 2/3, group III and alveolar RMS stage 1 to 3, groups I to III) were randomized between VAC and VAC/VI (ARST0531), incorporating irinotecan from the prior high-risk pilot trials. Patients with high-risk disease received multiple-agent systemic therapy (ARST0431) that was later used as a backbone to incorporate new agents such as an insulin-like growth factor-1 receptor inhibitor or temozolomide (ARST08P1), seeking improvement in FFS in this poor prognosis population.

A general algorithm for the integration of chemotherapy, surgery, and RT is shown in Figure 68-2. As a first principle in nearly all North American RMS trials, only a nonmorbid surgical resection should be performed. Amputation, exenteration, or other extensive procedures are discouraged because RT will offer equivalent rates of local control with organ preservation. The timing of RT has varied across studies and disease stage. RT may be integrated after multiple weeks of chemotherapy, facilitating the time necessary to plan with modern radiotherapeutic techniques, allowing some reduction in tumor bulk, as well as potentially integrating a second-look surgical procedure. One exception to this variance is the consistent early introduction of RT in patients with parameningeal disease and intracranial extension.[42]

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The management of children with NR-STS, particularly the local therapy component, has paralleled that of adult

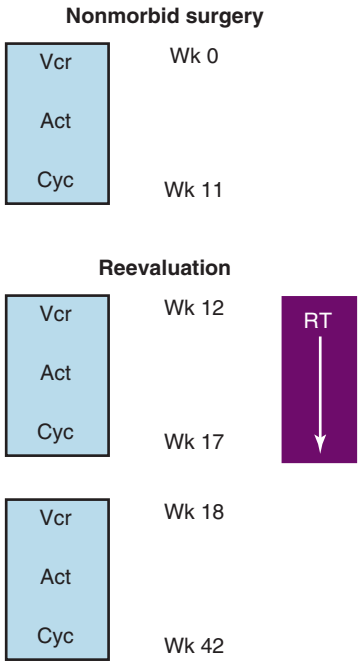

Figure 68-2 General algorithm for the delivery of multimodal therapy for rhabdomyosarcoma. *RT*, Radiation therapy; *Wk*, week; *Vcr*, vincristine; *Act*, actinomycin; *Cyc*, cyclophosphamide.

paradigms, including the move to wide local surgical excision (WLE) from amputation, the role of adjuvant RT, and most recently, the shift to preoperative chemoradiation. Compared with RMS, clinical trials in North America for children with NR-STS have been smaller, fewer, and have not resulted in well-defined prognostic groups from either a local disease control or overall outcome perspective.

The mainstay for management of children with NR-STS is surgery. Absent this modality, the outcome for patients is poor, with a fourfold higher risk of death.[43] The presence of metastatic disease predicts for subsequent disease recurrence in the majority of patients (10% EFS).[44] All patients, but particularly those with resectable primary site disease, benefit from multidisciplinary discussion before initiation of therapy. Planning the appropriate surgery in the context of tumor grade, size, location, probable surgical margin status, and the patient's age is the first critical step in the local management of patients with NR-STS. No prospective, completed clinical trials exist in the pediatric population to assist clinicians in selecting patients for specific aspects of local or systemic chemotherapy. The recent COG trial (ARST0332), stratified by risk group and local therapy approach, accrued more than 550 patients with the goal to determine the relative benefit of specific local and systemic therapeutic approaches. This multimodal approach to therapy incorporated standard-of-care approaches for NR-STS adapted for children and is outlined in Figure 68-3. More importantly, this trial provided a uniform, prospectively treated population of patients on which to evaluate prognostic factors, both clinical and biologic. The analysis of this study could lead to improved risk stratification of patients with NR-STS on future trials.

RADIATION THERAPY

Indications and Outcomes of Local Therapy

Rhabdomyosarcoma

The role of RT is to eradicate microscopic disease present after resection, treat gross disease, and consolidate visible sites of

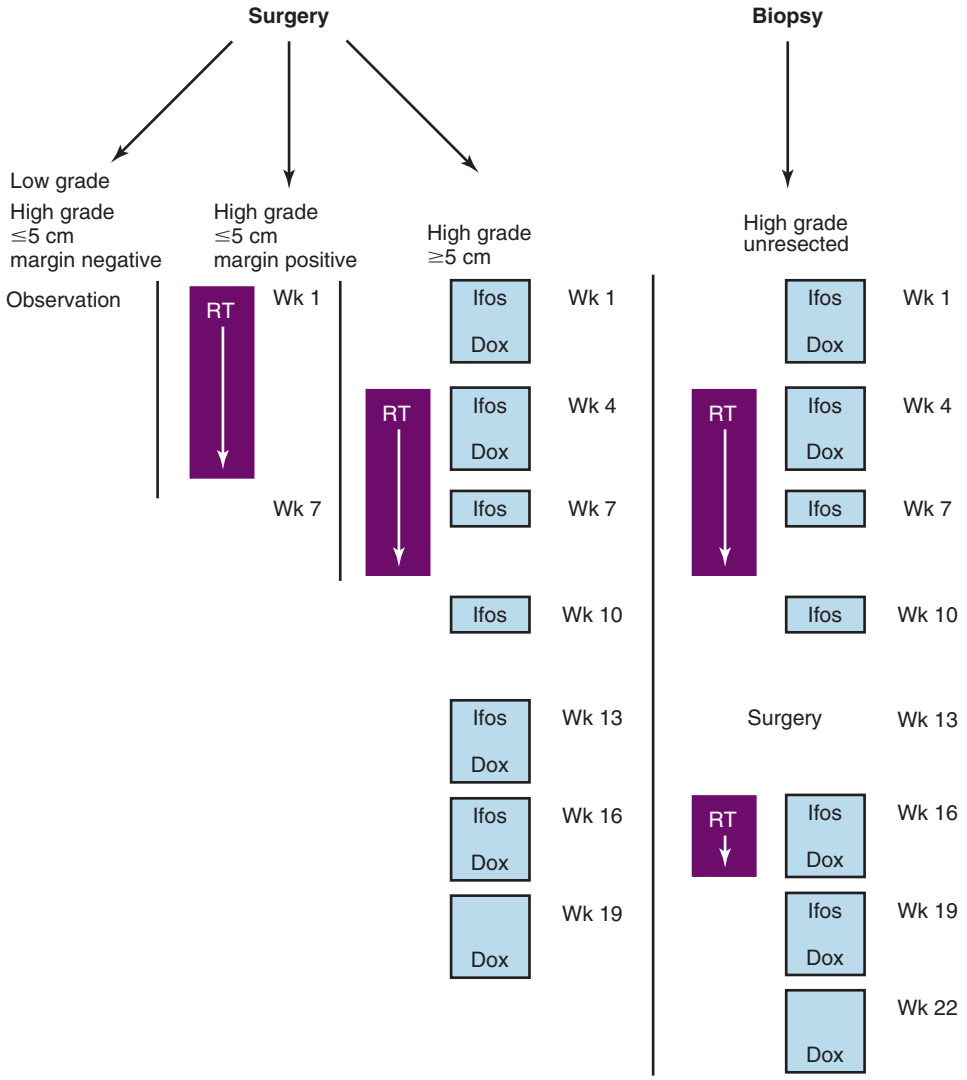

Figure 68-3 General algorithm for the delivery of multimodal therapy for nonrhabdomyosarcoma soft-tissue sarcomas. *RT*, Radiation therapy; *Wk*, week; *Ifos*, ifosfamide; *Dox*, doxorubicin.

TABLE 68-5 Indication for Radiation Therapy and Prescribed Doses for Patients with Rhabdomyosarcoma

Disease Status	Embryonal Histology	Alveolar Histology
Margin negative	No radiation	36.0 Gy
Margin positive	36.0 Gy	36.0 Gy
Node positive	41.4 Gy	41.4 Gy
Gross disease	50.4 Gy	50.4 Gy

metastatic involvement. The indications and doses, although complicated by site, can be generalized (Table 68-5). Doses are delivered at 1.8 Gy per fraction daily.

Data for the treatment of completely resected disease (group I) come from review of prior IRSG trials I to III demonstrating improvement in FFS and OS for patients with ARMS when RT is delivered (73% versus 44% and 82% versus 52%, respectively).[45] Patients with group II disease received adjuvant radiation, resulting in local failure rates of less than 10%.[46] Patients with group III disease have local failure rates of 11% to 16.5%, depending on site, size, and era of treatment.[38,41,47,48]

The parameningeal sites (middle ear, nasopharynx, paranasal sinuses, infratemporal and pterygopalatine fossae, and parapharyngeal region) require special attention to the skull base for adequate coverage of possible intracranial extension. If intracranial extension is present (Figure 68-4), then RT should be initiated within the first few weeks of the start of chemotherapy.

The orbit is a favorable site of disease involvement. Local management for this site with RT calls for delivery of 45 Gy at 1.8 Gy daily and yields excellent local control.[39,40] Despite the extremely thin and fragile nature of the bony orbit and the adjacent globe, these two structures are essentially never breached by orbital primary tumors and should be constrained out of the clinical target volume. If tumor does extend through these structures, consideration should be given that this may be parameningeal instead.

Female genitourinary tract (vulvar, vaginal, cervix, and uterus) tumors of ERMS (particularly the botryoid subtype) require adequate local therapy despite the often young age of the patients (frequently <2 years of age [Figure 68-5]). These patients should either undergo complete resection (group I) at

Figure 68-4 Coronal T1 contrast-enhanced magnetic resonance image obtained at presentation in a child with intracranial extension from a pterygopalatine fossa rhabdomyosarcoma.

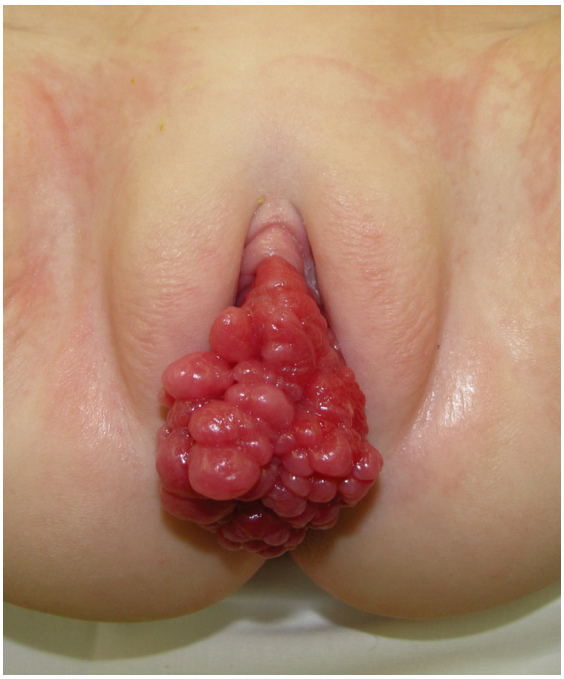

Figure 68-5 Botryoid embryonal rhabdomyosarcoma of the female urogenital tract in an infant.

diagnosis or receive adjuvant RT with either external beam or interstitial and intracavitary techniques. Absent adequate local control, high failure rates have been noted in the most recent low-risk clinical trials, prompting the call for improved local control.[33]

Paratesticular RMS is initially managed with radical inguinal orchiectomy with high ligation of the spermatic cord. RPLND, following a surgical template based on laterality, is conducted for all children 10 years of age or older.[22] Younger patients may still be managed with CT evaluation of their retroperitoneal lymphatics. Treatment of the lymphatic region is based on the discovery of microscopically or grossly involved lymph nodes.

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The best local tumor control rates are achieved in the context of microscopic disease and, as such, surgical resection—WLE or marginal—should be the goal for every patient presenting with NR-STS, including with metastatic disease. Clear surgical margins, defined as 5 mm or more of normal tissue beyond the tumor, are beneficial in cases in which RT may be avoided. Conversely, the operating surgeon should not proceed with a morbid or disfiguring resection to obtain clear surgical margins because there does not appear to be a significant reduction in local control when adjuvant radiation is delivered.[14] Preoperative RT may be employed in the context of larger (>5 cm) tumors or those deemed difficult to initially resect. This is most commonly combined with neoadjuvant doxorubicin and ifosfamide chemotherapy and given concurrently with ifosfamide chemotherapy to a cumulative dose of 45 Gy to 50.4 Gy at 1.8 Gy daily. Postoperative RT either in the form of external beam irradiation or interstitial brachytherapy may be delivered to the tumor bed after margin negative WLE (for high-grade tumors > 5 cm) or smaller high-grade tumors with involved surgical margins to doses of 55.8 Gy to 63 Gy at 1.8 Gy daily. Outcomes for either of these approaches have yielded excellent local control, with local failure occurring less than 5% of the time.[16]

Techniques

All treatment for pediatric patients with STS should be volumetric imaging based, require target volume and normal tissue delineation, and allow plan evaluation with dose-volume histograms. Conformal, intensity-modulated, and proton beam RT are all acceptable methods of radiation delivery backed by published outcome data from both cooperative group and institutional clinical trials. Patients treated on the D9803 trial with either three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiated therapy (IMRT) demonstrated similar rates of FFS despite superior target coverage by IMRT, and no differences in dose to critical adjacent structures.[49] Initial and postchemotherapy imaging studies are used to define the extent of disease. MRI is essential because CT provides poor soft-tissue definition for evaluating tumor extent. The definitions for gross tumor volume (GTV) and clinical target volume (CTV) are described in Table 68-6 for both RMS and NR-STS. It is important for the radiation oncologists to understand the point of origin or attachment of gross disease, which is often facilitated by examination of the patient and review of imaging at diagnosis. In tumors with an exophytic component such as bladder and prostate or female genitourinary rhabdomyosarcoma, this baseline evaluation will be valuable in helping define the GTV once significant response to chemotherapy occurs. Target volume delineation is anatomically constrained, meaning that the radiation oncologist determines the presumed infiltration of the gross tumor toward adjacent normal tissues when designing the shape of the clinical target volume. Planning volumes are institution, site, and treatment specific (e.g., photons compared to protons), but are typically 3 mm to 5 mm with some form of daily localization (cone-beam CT or fiducials) using photon techniques. Motion may be defined and managed through respiratory gating as necessary.

Treatment planners should consider adjacent normal tissues and weigh the relative risks of site-specific late effects

TABLE 68-6 Target Volume Delineation for Rhabdomyosarcoma and Nonrhabdomyosarcoma Soft-Tissue Sarcomas

	Rhabdomyosarcoma	Nonrhabdomyosarcoma Soft-Tissue Sarcomas
Gross Tumor Volume (GTV)		
Postoperative irradiation	The GTV (more appropriately defined as a CTV) will include the soft-tissue tumor bed and soft tissue contiguous with the tumor prior to surgical resection as defined by physical examination, imaging studies, operative notes, and pathology reports. The tumor bed may have "collapsed" in regions and may no longer have the same shape or extent as the presurgical, prechemotherapy volume. If bone was involved, the GTV includes the margin of bone initially involved with tumor.	Same as defined for rhabdomyosarcoma
Definitive irradiation/ preoperative irradiation	The GTV is defined as the initial tissues in contact with the tumor before therapy and the preirradiation extent of the visible mass, defined by examination and imaging studies before and after chemotherapy and physical examination. Bone involvement warrants targeting the pretherapy extent in bone. Gross residual disease (after an incomplete resection) will be targeted as a definitive irradiation case. Unresected, involved lymph nodes will be included as part of the GTV but may not form one contiguous gross tumor volume depending on tumor and nodal geometry.	Same as defined for rhabdomyosarcoma
Clinical Target Volume (CTV)	The CTV is the GTV with a 1.0-cm anatomically constrained margin of normal tissue accounting for probable pathways of microscopic disease spread. This margin may be reduced (constrained) at fascial planes, bony interfaces, or body cavities based on tumor biology. Nodal involvement is encompassed in the CTV, ideally in a contiguous volume with the GTV.	The CTV is the GTV with a 1.5-cm anatomically constrained margin of normal tissue accounting for probable pathways of microscopic disease spread. This margin may be reduced (constrained) at fascial planes, bony interfaces, or body cavities based on tumor biology. Nodal involvement is encompassed in the CTV, ideally in a contiguous volume with the GTV.

relative to one another. Every effort should be made to deliver the recommended prescribed dose of radiation because doses used in many pediatric malignancies have already been lessened significantly because of concerns of late effects. Parallel-opposed fields should be avoided in nearly all cases to reduce normal tissue exposure to high radiation doses. Even in extremity sites, treatment with circumferential irradiation using an IMRT technique (resulting in low doses to the entire circumference of the extremity as opposed to sparing a strip of skin [Figure 68-6]) has not resulted in clinically documented lymphedema with moderate follow-up.[16]

Interstitial brachytherapy may be used for NR-STS and RMS (less frequently) at the time of surgical resection. Catheters are usually placed into the operative bed transcutaneously while the resection cavity is exposed after removal of the primary tumor. Catheters are spaced at 1-cm intervals and extend 1 cm to 2 cm beyond the known tumor bed. The tumor bed may be marked with surgical clips or other radiopaque markers to define the region to be treated at the time of planning. High-dose-rate brachytherapy is delivered to a dose of 34 Gy at 3.4 Gy twice daily for NR-STS and 21 Gy at 3 Gy twice daily for RMS.

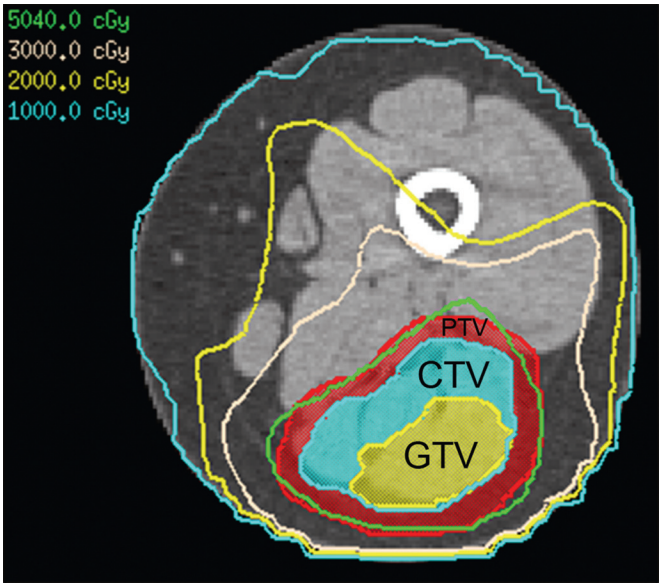

Figure 68-6 Cross-sectional image of an intensity-modulated radiation therapy plan for alveolar rhabdomyosarcoma of an extremity. *CTV,* Clinical target volume; *GTV,* gross target volume; *PTV,* planning target volume.

Timing

Rhabdomyosarcoma

The timing of delivery of radiation to the primary site of disease in patients with localized rhabdomyosarcoma has varied across the IRSG and COG clinical trials over time. Currently, for patients with low-risk disease, RT is performed after 12 weeks of every 3-weeks of chemotherapy. Patients with intermediate-risk disease also receive RT at week 12. Those with parameningeal tumors and evidence of intracranial extension receive RT near the start of treatment, primarily based on evidence of improved outcome for patients with parameningeal sites of disease irradiated earlier in the course of therapy.[42] Cranial nerve palsy and cranial base bony erosion are no longer considered high-risk features mandating early

RT.[50,51] Patients with high-risk disease (metastatic) require aggressive chemotherapy. Local control of the primary sites of disease is conducted at week 20, and metastatic sites of disease are irradiated with similar doses at the end of systemic therapy, unless symptomatic. Vincristine, cyclophosphamide, and irinotecan are given concurrently with RT whereas dactinomycin is held, owing to increased skin and mucosal toxicities.

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

Postoperative RT is delivered 2 weeks or more after resection, allowing for the initiation of wound healing and stabilization of the tumor bed. Adjuvant brachytherapy should be initiated on postoperative day 5 or later to allow for adequate healing. Preoperative chemoradiation on ARST0332 (the most recent COG NR-STS trial) is initiated at week 4 immediately after the second cycle of ifosfamide/doxorubicin chemotherapy.

FUTURE DIRECTIONS

The treatment of children with STS is now well centered in the modern conformal era. All of the benefits of focal, highly conformal, modern RT can be realized in this population when the treating radiation oncologist uses available means to ensure adequate tumor dose delivery and sparing of adjacent normal tissues. The increasing use of proton therapy in the treatment of pediatric cancers will yield further opportunities for research. Cooperative group trials will continue to select patients with low-risk disease for whom radiation can be decreased or eliminated, whereas RT remains a critical component of treatment for intermediate- and high-risk disease. Less favorable populations of patients will be managed with the incorporation of new therapeutic agents to improve overall outcome.

Pediatric radiation oncologists should focus on selection of patients for RT, better delineation of target volumes, including incorporation of functional imaging into the treatment paradigm, and leading the way in understanding radiation-related treatment effects that affect how we deliver RT.

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A full list of cited references is published online at www.expertconsult.com.

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