Soft Tissue Sarcoma

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Abbreviations

AIEOP	Associazione Italiana di Ematologiae Oncologia Pedaitrica
AJCC	American Joint Commission on Cancer
ASPS	Alveolar soft part sarcoma
ATFS	"Adult type" fibrosarcoma
BSA	Body surface area
COG	Children's Oncology Group
COG-STS	Children's Oncology Group Soft Tissue Sarcoma Committee
COL1A1	Collagen type 1, alpha 1 gene
CT	Computerized tomography
DFSP	Dermatofibrosarcoma protuberans
Dox	Doxorubicin
DSRCT	Desmoplastic small round cell tumor
E	Etoposide
EFS	Event free survival
EWS	Ewing sarcoma gene
FDG	Fluorine-18-fluorodeoxyglucose
FDG-PET	Fluorodeoxyglucose positron emission tomography
FHT	Fibrohistiocytic tumors
FISH	Fluorescent in situ hybridization
FNCLCC	French Federation of Cancer Centers Sarcoma Group
FSRT	Fractionated stereotactic radiotherapy
HART	Hyperfractionated accelerated radiotherapy
HIPEC	Hyperthermic intraperitoneal chemotherapy
I	Ifosfamide
IFS	Infantile fibrosarcoma
IGF-II	Insulin-like growth factor-2
IGF-IR	Insulin-like growth factor-1 receptor
IMRT	Intensity-modulated radiation therapy
IRS	Intergroup Rhabdomyosarcoma Group
IRSG	Intergroup Rhabdomyosarcoma Study Group
LOH	Loss of heterozygosity
MFH	Malignant fibrous histiocytoma
MMS	Mohs micrographic surgery
MPNST	Malignant peripheral nerve sheath tumor
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF1	Neurofibromatosis type 1
NOS	Not otherwise specified
NRSTS	Nonrhabdomyosarcoma soft tissue sarcomas
OS	Overall Survival
PCR	Polymerase chain reaction
PDGF	Platelet-derived growth factor
PDGFB	Platelet-derived growth factor beta
PET	Positron emission tomography
PFS	Progression-free survival
POG	Pediatric Oncology Group
PRE	Pre-treatment re-excision
RMS	Rhabdomyosarcoma
RT	Radiation therapy
SEER	Surveillance Epidemiology and End Results
STS	Soft tissue sarcomas
STSC	Soft Tissue Sarcoma Committee
VA	Vincristine (V) actinomycin D (A)
VAC	Vincristine (V) actinomycin D (A), and cyclophosphamide (C)
WHO	World Health Organization
WLE	Wide local excision
WT1	Wilms' tumor gene 1

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Introduction

Pediatric sarcomas are typically divided into soft tissue sarcomas and bone sarcomas. The original distinction of soft tissue sarcomas and bone sarcomas from epithelial and hematopoietic tumors is attributed to Virchow who, in the middle 1850s, propounded his theory of "cellular pathology" ascribing the origin of tumors to specific types of cells [1]. The soft-tissue sarcomas (STS) of childhood are a relatively rare and heterogeneous group of tumors that arise primarily from connective tissue and may develop in any site of the body. In the US, 850–900 children less than 20 years of age are diagnosed with STS which accounts for 7.4 % of all cancers in this population of patients [2].

STS are extra skeletal malignant tumors of mesenchymal cell origin. They are classified according to the normal tissue they resemble – for example, rhabdomyosarcoma (skeletal muscle), leiomyosarcoma (smooth muscle), fibrosarcoma and malignant fibrous histiocytoma (connective tissue), neurofibrosarcoma or malignant peripheral nerve sheath tumor (MPNST) (nervous tissue), liposarcoma (adipose), synovial sarcoma (synovium), and angiosarcoma (blood and/or lymphatic vessels). Other sarcomas include rare entities such as alveolar soft-part sarcoma, clear cell sarcoma, desmoid tumor, desmoplastic small round cell tumor, epithelioid sarcoma, extraosseous Ewing's sarcoma, mesenchymal chondrosarcoma, perivascular epithelioid cell neoplasms (PEComas), plexiform histiocytic tumor and undifferentiated soft tissue sarcomas.

Rhabdomyosarcoma (Greek for rhabdos, "rod", mys "muscle", sarkos "flesh") (RMS) is the most common STS among children and adolescents accounting for 40 % of tumors in persons <20 years old [3]. RMS arises from embryonic mesenchyme with the potential to differentiate into skeletal muscle. STS differ widely in their response to therapy, and in children, STS are generally classified as either RMS or Nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) with the NRSTS further divided into multiple histologic subtypes as listed above. RMS are the only STS that are found more commonly in children than adults [3] and therefore, much of our knowledge regarding these tumors is based on findings from pediatric studies. NRSTS are much more common in adults and thus most of the information on the natural history and treatment of these tumors is based on findings from adult studies. The information provided in this chapter is based on the most up-to-date management approaches for each disease entity. However, it remains unclear whether the clinical behavior of a given STS is independent of age and thus whether or not children and adults should be managed similarly. An international trial of pediatric soft tissue sarcomas conducted by the Children's Oncology Group was the first to examine the outcome of pediatric adolescent and young adult patients with NRSTS treated with an adult protocol. Results are pending.

Nonrhabdomyosarcoma Soft Tissue Sarcomas

Epidemiology

In the US, 500–550 children <20 years old are diagnosed with NRSTS each year accounting for approximately 4 % of all childhood cancers [4]. In children, NRSTS have a bimodal age distribution with peaks in infancy and adolescence. However, the distribution of patient age at diagnosis and gender varies among the histologic subtypes. For example, fibrosarcoma is more common in infants, whereas synovial sarcoma and MPNST are more frequently encountered in older children and adults [2, 5]. Black children have a slightly higher incidence than white children [2]. There is a slight male predominance (1.5:1) for all types of STS except alveolar soft part sarcoma and leiomyosarcoma which are seen more frequently in females [3]. The incidence of NRSTS in children and adolescents in the US is 6.6 per million person years and represents 4.5 % of all childhood malignancies [6]. There is no evidence that the incidence of NRSTS is increasing [6]. However, the 5- and 10-year overall survival of children and adolescents with NRSTS is also unchanged at 78 % and 74 %, respectively [6].

Although the majority of patients with NRSTS have no identifiable etiology, a few genetic and environmental factors have been associated with the development of NRSTS. Genetic conditions associated with NRSTS include LiFraumeni syndrome [7], hereditary retinoblastoma [8], neurofibromatosis type 1 [9], Gorlin syndrome [10], and Werner syndrome [11]. Patients with Li-Fraumeni syndrome, a rare autosomal dominant disease characterized by germ line p53 mutations, have an increased risk for development of soft tissue tumors, bone sarcomas, breast cancer, brain tumors and acute leukemia [12, 13]. Approximately half of all patients with MPNST are diagnosed in patients with neurofibromatosis Type 1, (NF-1, VonRecklinghausen's disease) [14] and 2–13 % of patients with NF-1 will develop a MPNST [14–18]. Desmoid tumors occur in 4–20 % of all patients with familial Gardner syndrome [19–21]. Leiomyosarcomas have been linked to Epstein-Barr virus infection in patients with AIDS [22]. Chronic lymphedema is a risk factor for the development of lymphangiosarcoma [23]. Therapeutic radiation doses result in a cumulative incidence of in-field sarcomas in 1–2 % of long-term cancer survivors 10–15 years after therapy [24, 25], with malignant fibrous histiocytoma being the most common.

Clinical Presentation

NRSTS usually present as a painless, enlarging mass in the extremities, back, flank or abdominal wall. Although NRSTS may arise anywhere in the body, intra-abdominal NRSTS are quite rare. Systemic symptoms such as fever and weight loss are rare. Symptoms usually develop due to invasion or compression of adjacent neurovascular structures [26]. In a review of 575 patients age <21 years with STS including 212 patients with NRSTS, the extremities were the most common site of presentation and swelling was the main presenting sign or symptom [27]. In this study, the symptom interval ranged between 1 and 60 months with a longer symptom interval occurring in older patients with larger tumors, extremity primaries, and NRSTS histology [27]. In addition, the risk of death increased significantly the longer the symptom [27]. Approximately 15 % of patients present with metastatic disease most commonly in the lungs [28]. Bone, liver, brain and subcutaneous metastases have been reported; however, bone marrow involvement is exceedingly rare [28]. Thus, as with most malignancies, early and accurate diagnosis is key.

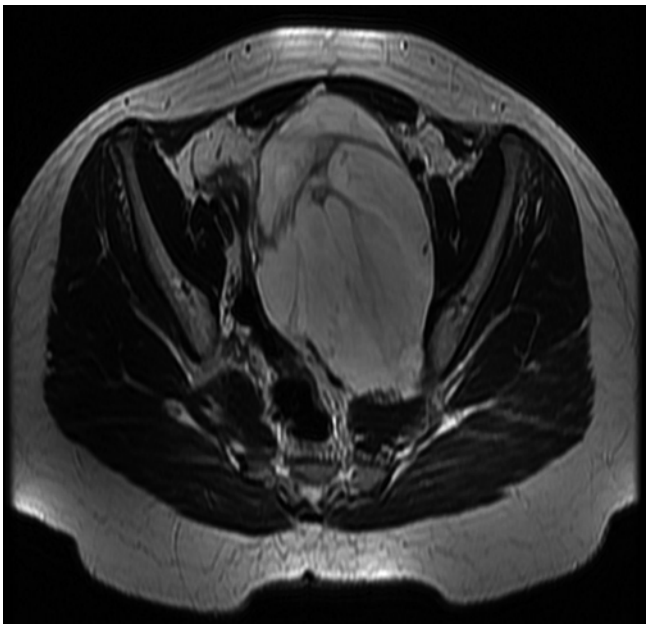

Fig. 20.1 A 17 year-old girl presented with pain in her left thigh. MRI abdomen showed a large pelvic mass. She underwent incomplete resection of a myxoid liposarcoma with pleomorphic elements followed by second look operation and resection of metastatic disease with hyperthermic intraperitoneal chemotherapy (HIPEC)

Diagnosis

NRSTS are a large, heterogenous group of malignancies composed of cells similar to mesenchymal cells. Although NRSTS are easily distinguished from RMS, type classification of these tumors is often difficult. For a suspicious lesion, an adequate tumor specimen must be obtained to identify the histologic subtype and grade of NRSTS. Incisional biopsy is preferred but multiple core needle biopsies may be sufficient [29]. The biopsy should not compromise subsequent wide local excision. For example, longitudinal incisions are preferred in the extremity to allow for excision of the biopsy tract at the time of definitive resection. Inappropriately placed incisions at any location make resection or rotational or advancement flap closure more difficult. Image guidance using ultrasound, computed tomography scan or magnetic resonance imaging (MRI) may be necessary [30].

The pathologist plays a key role in the diagnosis and thus future management of the patient with NRSTS. The initial approach to the fresh pathology specimen is crucial and appropriate specimen handling includes triage for diagnostic and prognostic studies including routine histopathology and immunohistochemistry, cytogenetic and molecular studies, flow cytometry, and electron microscopy. Reverse transcriptase polymerase chain reaction (RT-PCR), biochemical, and microarray gene product analyses may aid in diagnosis. Cytogenetic imprints allow for fluorescent in situ hybridization (FISH) evaluation of mutated genes, tumor defining translocations, and other cytogenetic abnormalities.

Many NRSTS are characterized by chromosomal abnormalities. Despite their complexity, NRSTS may be divided into two groups: those with histology-specific chromosomal rearrangements and those with evidence of widespread genomic instability [26]. The tumors with histology-specific chromosomal rearrangements usually consist of balanced translocations which may lead to fusion of two disparate genes. The resulting fusion transcript is easily detected using polymerase chain reaction-based techniques which facilitates diagnosis of these tumors. Table 20.1 summarizes the genetic aberrations in NRSTS.

If possible, it is preferred to perform diagnostic imaging prior to any surgical intervention. Imaging studies are a valuable tool in staging and preoperative planning and provide baseline measurements for assessment of the response to therapy. Magnetic resonance imaging is the modality of choice as it provides excellent soft tissue definition and provides clear visualization of regional lymph node enlargement if present (Fig. 20.1). Gadolinium-enhanced MRI improves the signal intensity on T1 weighted images and may help distinguish cystic versus necrotic areas as well as highlight the vascularity of the tumor and its relationship to nearby neurovascular structures [31]. Computed tomography may be more useful for tumors within the chest and abdomen/pelvis or in evaluating for lung metastases. Although Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) has not been used routinely in pediatric NRSTS, it may prove to be a useful tool in evaluating tumor response to adjuvant therapy.

Table 20.1 Genetic aberrations in NRSTS

Histology	Genetic aberration
Alveolar soft part sarcoma	der (17)t(x;17)(p11.2;q25) with *ASPL-TFE3* fusion
Clear cell sarcoma	t(12;22)(q13;q12) with *EWS-ATF1* fusion
Dermatofibrosarcoma	t(17;22)(q21;q13) with *COL1A1-PDGFB* fusion
Desmoplastic small round cell tumor	t(11;22)(p13;q12) with *EWS-WT1* fusion
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) with *EWS-CHN* fusion
Infantile fibrosarcoma	t(12;15)(p13;q25) with *ETV6-NTRK3* fusion; trisomy 8, 11, 17, 20
Inflammatory myofibroblastic tumor	2p23 rearrangement with *ALK* fusion to *TPM3*, *TPM4*, clathrin, and other genes
Leiomyosarcoma	Complex abnormalities
Low-grade fibromyxoid sarcoma	t(7;16)(q34;p11) with *FUS-BBF2H7* fusion
Malignant fibrous histiocytoma	Complex abnormalities
Malignant peripheral nerve sheath tumor	Complex abnormalities
Myxoid liposarcoma	t(12:16)(q13;p11) with *DDIT2*(*CHOP*)-*FUS* fusion; t(12;22)(q13;q12) with *DDIT3-EWS* fusion
Rhabdoid tumor	Deletion of 22q with *HSNF5*(*INI1* deletion or mutation
Synovial sarcoma	T(X;18)(p11;q11) with *SYT-SSX* fusion; *MYCN* overexpression

Prognostic Factors

There are few prospective studies on NRSTS in children and adolescents [32–34], and therefore, most of our understanding of the factors that influence prognosis are based on retrospective case series and adult studies. Factors shown to impact survival in pediatric NRSTS patients include the extent of disease (metastatic versus non-metastatic), histologic grade, size of the primary tumor, and extent of resection [26]. Tumor resectability and the presence or absence of metastases are the most important prognostic factors. The clinical outcome for completely resected NRSTS's is quite good but more than 20 % of these patients eventually develop disease recurrence and ultimately die due to their disease [34–36]. Risk factors for recurrence are important in determining prognosis, therapy and intensity of therapy. Tumor size and grade predict early relapse, whereas surgical margin status predicts late relapse [37].

These factors may be used to classify tumors as high, intermediate or low risk. Children with metastatic disease are high risk and overall survival is approximately 15 %. Intermediate risk includes patients with unresectable tumors or tumors that are both high grade and >5 cm in maximal diameter. The survival for intermediate risk patients is approximately 50 %. Low-risk tumors are resectable tumors that are either high grade and <5 cm in maximal diameter or low grade and any size. Survival for low risk patients is approximately 90 %. Other factors that may influence survival include microscopic surgical margin, primary site with visceral tumors associated with a worse prognosis, and age with age >10 years as an adverse factor in patients with unresectable tumors [26]. It was based on this risk classification by Spunt and colleagues, the first prospective international trial of pediatric adolescent and young adult NRSTS was conducted by the Children's Oncology group. Long term results from this study are pending.

The most important factor related to local control is extent of resection rather than tumor grade or size. A negative microscopic margin is associated with the lowest risk for local recurrence followed by microscopic residual disease. Patients with gross residual disease are unlikely to achieve local control. Radiotherapy has been shown to decrease local recurrence in patients with microscopic residual disease.

Metastatic disease at the time of initial presentation occurs in approximately 15 % of children with NRSTS [28]. The lung is the most common site of distant metastases, although metastases to bone, liver, and mesentery have also been reported. Regional lymph node spread is rare with most histologic subtypes; however, it may occur in high-grade lesions, synovial sarcoma, angiosarcoma, and epithelioid sarcoma. The prognosis of patients with lymphatic metastases is similar to patients with metastatic disease at other sites.

Staging

Despite the importance of clinical staging in predicting outcome and determining the most effective therapy, there is no validated pediatric NRSTS staging system. In the past, the Intergroup Rhabdomyosarcoma Study Group's surgicopathologic staging system for rhabdomyosarcoma has been used [38]. This staging system will be described in greater detail in the RMS section of this chapter. However, this system fails to account for tumor grade and size which are known to be important prognostic factors in NSRTS.

Although the American Joint Commission on Cancer (AJCC) staging system that is used in adults has not been validated in pediatric studies, the current Children's Oncology Group (COG) trial is using the AJCC staging sys-

Table 20.2 NRSTS pathologic grading system

Grade 1
Angiomatoid malignant fibrous histiocytoma
Deep-seated dermatofibrosarcoma protuberans
Myxoid chondrosarcoma
Myxoid and well-differentiated liposarcoma
Well-differentiated or infantile (≤4 years old) fibrosarcoma
Well-differentiated or infantile (≤4 years old) hemangiopericytoma
Well-differentiated malignant peripheral nerve sheat tumor
Grade 2
Less than 15 % of the surface area shows necrosis
Mitotic count <5 mitotic figures per 10 high-power fields using a ×40 objective
Nuclear atypia is not marked
Tumor is not markedly cellular
Grade 3
Alveolar soft part sarcoma
Clear cell sarcoma
Desmoplastic small round cell tumor
Epithelioid sarcoma
Extraskeletal osteogenic sarcoma
Malignant triton tumor
Mesenchymal chondrosarcoma
Malignant triton tumor
Pleomorphic or round cell liposarcoma
Synovial sarcoma
Undifferentiated sarcoma
Any other sarcoma not in grade 1 with >15 % necrosis and/or ≥5 mitotic figures per 10 high-power fields using a ×40 objective

tem [39]. The AJCC system designates stage based on four criteria including tumor size (< or >5 cm in greatest diameter and superficial or deep), nodal status, metastasis, and tumor grade (well-differentiated, moderately differentiated, or poorly differentiated). Other staging systems commonly used in adult soft tissue sarcomas include those developed by the Memorial Sloan-Kettering Cancer Center [40] and the Musculoskeletal Tumor Society [41]. The system most useful for pediatric NRSTS is not yet determined as none of the adult systems include the unique pediatric histologic subtypes.

In 1986, the Pediatric Oncology Group (POG) conducted a prospective study to evaluate a pediatric NRSTS grading system based primarily on the National Cancer Institute (NCI) system [42, 43]. The NCI system stratifies STS into three different grades based on histologic subtype and a composite of histopathologic parameters that includes tumor necrosis, cellularity, pleomorphism, and mitotic activity [42]. The POG study identified three different tumor grades based on histopathologic subtype, amount of necrosis, number of mitoses, and cellular pleomorphism [43]. Table 20.2 describes the POG grading system.

The grading system used by the French Federation of Cancer Centers Sarcoma Group (FNCLCC) is based on tumor differentiation, mitotic count and necrosis. Although early evidence suggested that the FNCLCC grading system better predicted risk of metastases and mortality when compared to the NCI grading system [44, 45], a more recent study showed both systems to provide an adequate prognostic measure of outcome for pediatric NRSTS [46]. A subset of cases with intermediate prognosis was graded differently by the two systems and included the following histologic subtypes: synovial sarcoma, sarcoma not otherwise specified, alveolar soft part sarcoma, and MPNST [46]. In this study, mitotic index appeared to be the key parameter in grading pediatric NRSTS [46].

Treatment

Given the rarity of the disease, all children, adolescents and young adults with NRSTS should be treated using a multidisciplinary approach that includes pediatric oncologists, surgeons and radiotherapists. In addition, these patients should be considered for entry into institutional or national treatment protocols. Multimodality therapy offers the best chance for a successful outcome. Although the evaluation and treatment of NRSTS is similar in children and adults, several important differences need to be considered. In some young patients, the biology of the tumor seems to be less aggressive, while

the complications of adjuvant therapy may be greater (i.e., radiation induced injury). The long-term effects on growth and second malignancies need to be weighed against the potential benefits of the treatment [47–54]. In general, NSRTS are relatively resistant to chemotherapy and radiotherapy, and therefore, complete surgical resection remains the mainstay of therapy and should be attempted whenever feasible without causing undue loss of tissue or function.

Surgery

Complete surgical resection is the cornerstone to curative therapy in pediatric NRSTS, and therefore, every effort should be made to resect the primary tumor with negative margins before or after chemotherapy. Surgical approach is site specific and tumor size is also important in determining the surgical approach as well as the timing of surgery. Tumor size is a known prognostic variable in NRSTS [55], and therefore, the size of the mass partially determines the surgical approach. Although the AJCC staging system uses a tumor diameter of 5 cm as the cut off between T1 and T2 lesions, this size cut off may not be applicable in children of all ages. Ferrari and colleagues developed a formula to estimate the equivalent size tumor in a child using actual tumor size and adjusting for body surface area (BSA) [55]. The formula is applicable to infants and young children (age < 5 years) with tumors less than 5 cm in size [55]. If a tumor is suspicious for malignancy and either >5 cm in greatest diameter or > infant/toddler equivalent to 5 cm, the tumor should be biopsied to determine the histology prior to proceeding with definitive resection [56].

Although wide local excision is the optimal approach, the amount of tumor free margin necessary is not precisely known and controversy remains in defining an adequate margin. Historically, the standard margin in adults was 2 cm with local recurrence rates of 10–15 % [57]. However, in young children and patients with tumors in locations such as the head and neck, mediastinum, or retroperitoneum, a 2 cm margin may lead to excessively mutilating surgical procedures. The 2 cm margin may not be feasible in locations limited by neurovascular bundles such as tumors arising in the popliteal or antecubital fossa, groin or posterior thigh. In a small series of pediatric patients with NRSTS, Blakely and colleagues found that a pathological resection margin of >1 cm reduced local recurrence in patients with both low- and high-grade tumors [58]. In a similar retrospective review, it was shown that the presence of positive or negative margins is more important than the depth of the margins [35].

In general, close margins are preferred near neurovascular bundles and other vital structures rather than primarily resecting these structures. For extremity tumors, limb salvage by intracompartmental resection has evolved along with improved multimodality therapy. Mutilating resections should only be considered after poor response to radiation other treatment. An adequate wide resection includes the tumor, its pseudocapsule, and a margin of normal tissue removed in all directions enbloc. Since there have been no prospective randomized studies on margin size in NRSTS, a negative margin of at least a centimeter is recommended. Complete R0 resections will not require radiation. Whereas unresectable tumors receive preoperative radiation. R1 resections require post-operative radiation.

It is important to be aware that some tumors, such as synovial sarcoma, have a pseudocapsule and if the operating surgeon fails to recognize it, he/she may inappropriately shell out the tumor leaving behind a positive microscopic margin. Local recurrence rates are extremely high in these circumstances. Patients who present following an unplanned initial resection should be considered for pretreatment re-excision [59]. In these patients, the incidence of residual tumor is high and a negative margin may be achieved with pretreatment re-excision [59]. Pathologic examination or post-operative imaging suggestive of residual tumor should prompt the surgeon to recommend pretreatment re-excision of the primary site to ensure local control.

Lymph Node Dissection

In general, regional lymph node metastases at diagnosis are rare in NRSTS. However, several histologic subtypes require lymph node for staging and include RMS, synovial sarcoma, epithelioid sarcoma and clear cell sarcoma. In synovial sarcoma, regional disease is noted in 20 % of pediatric patients registered in the Surveillance, Epidemiology and End Results (SEER) dataset [60]. Another study suggests lymph node involvement is more common in patients with epithelioid sarcoma and clear cell sarcoma compared to other histologic subtypes [61]. If lymph nodes are clinically enlarged as determined by physical exam or imaging studies, fine needle aspiration or open biopsy may be performed. For clinically negative lymph nodes in patients with extremity primaries, sentinel lymph node biopsy is the preferred method to evaluate the lymphatic basin [56]. Several studies describe sentinel lymph node mapping in pediatric sarcoma patients [62–64]. Sentinel lymph node biopsy is often performed at the time of wide local excision. The primary tumor is injected with a technetium-labeled sulfur colloid and isosulfan blue dye (Lymphazurin). Intraoperatively, a radioisotope detector is used to localize the sentinel node and a small skin incision is made overlying the area of maximal signal. The radioisotope detector in combination with the blue dye is used to identify the sentinel lymph node(s) within the lymphatic

basin. The sentinel lymph node(s) is/are excised and submitted for pathologic review.

Although the identification of positive lymph nodes contributes to staging, it remains unclear as to whether completion lymph node dissection improves survival. Few studies evaluate the role of therapeutic regional lymph node dissection for patients with NRSTS [65, 66]. Riad and colleagues demonstrated a modest improvement in 5-year survival in patients with extremity STS who had resection of involved lymph nodes versus those treated without surgery [66]. Thus, in the setting of a positive sentinel lymph node(s) or clinically positive nodal disease, a formal lymph node dissection may be considered for extremity STS.

Resection of Metastatic Disease

Depending on the histologic subtype, 2–33 % of pediatric patients with NRSTS develop distant disease with most metastases occurring in the lungs [67]. Most studies evaluating the effectiveness of pulmonary metastatectomy in STS include only adult patients. With complete resection of all pulmonary metastases, the 3-year survival is 46–54 % in adults with metastatic STS [68–70]. A recent review suggests that selected patients with a maximum of two pulmonary nodules may benefit from a thoracoscopic versus an open approach for pulmonary metastatectomy [71]. In addition, Weiser and colleagues showed survival benefit with repeat resection of pulmonary metastases in those patients with completely resectable disease [72]. In this study, other prognostic factors associated with a poor outcome included ≥ nodules, largest metastases >2 cm in size, and high-grade primary tumor histology [72]. To date, few studies have evaluated the benefit of pulmonary metastatectomy in pediatric patients with STS [73, 74]. However, a small proportion of patients with metastatic disease may be cured if all distant metastases are completely resected. This is primarily true for patients with low grade NRSTS. In pediatric patients with low grade tumors and metastasis, effort should be made to resect any metastatic disease. Thus, pulmonary mestatectomy is advocated as an adjunct to multimodality therapy in children and adolescents with NRSTS.

NRSTS Pediatric Histologies

The most common NRSTS in the pediatric and adolescent population is synovial sarcoma, followed by undifferentiated, or unclassified sarcoma. These as well as more rare NRSTS will be discussed.

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) is a rare sarcoma accounting for 5 % of pediatric NRSTS with an age-adjusted incidence rate of 0.1 per million [1]. The median age at diagnosis is 25 years (range 0–84 years) and it occurs more commonly in females than males (1.6:1) [3]. ASPS is considered to be a tumor of uncertain differentiation with no specific cell lineage identified to date [75]. However, ASPS is characterized by an unbalanced recurrent translocation t(X;17)(p11;q25) which juxtaposes the *ASPSCR1* gene with the *TFE3* gene [76, 77].

In children and adolescents, the tumor most commonly arises in the extremities (55 %) followed by the head and neck (28 %), and trunk (15 %) [3]. However, it may present in any region of the body including sites such as the tongue, orbit, heart, and lung [78–81]. The clinical course is often indolent and the primary tumor may grow for years prior to definitive diagnosis. Approximately 23 % of pediatric patients present with distant metastases [3]. The most common metastatic site is the lung, followed by brain, bone, and lymph nodes [82].

Complete resection with negative microscopic margins of localized ASPS is key to achieving long term survival [83]. Thus, it is imperative that patients undergo preoperative imaging, usually MRI, with consideration of fine-needle aspiration or core biopsy prior to definitive surgery. Unlike other NRSTS, ASPS may be diagnosed by fine-needle aspiration due to the presence of intracellular crystals [84–88]. Approximately 17 % of patients present with regional disease [3], and there are a few reports of the use of sentinel lymph node biopsy in these patients [62, 89]. If complete excision of the primary tumor is not feasible, radiation therapy should be considered. Although ASPS is considered chemoresistent, there are reports of benefit with neoadjuvant chemotherapy to induce tumor shrinkage and improve resectability in patients who initially present with unresectable tumors [83]. The value of adjuvant chemotherapy in completely resected ASPS is not proven. There are a few reports of objective responses to biologic agents including interferon-alpha, bevacizumab, and sunitinib [90–94]. Radiotherapy may improve local control in patients with incompletely resected primary and/or metastatic tumors [83, 95]. ASPS is associated with an indolent clinical course and metastases may occur after prolonged disease-free intervals.

Pediatric ASPS is associated with a better prognosis compared to adults. In a population-based study using SEER data, the 5-year relative survival for patients age 0–9 years and 10–19 years was 100 % and 91 %, respectively [3]. In a pediatric series with a median follow-up of 74 months, the 5-year overall was 80 % for the entire cohort and 91 % for patients with localized disease [83]. In this series, tumor size

significantly impacted survival [83]. All patients with tumors ≤5 cm were alive at 5 years compared to only 31 % of patients with tumors >5 cm [83]. Other series have also shown tumor size to be the most important factor related to survival and the likelihood of metastases [95–97].

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a rare aggressive malignancy that occurs in children, adolescents and young adults. The majority of patients are Caucasian (85 %) with a strong predication for males (10:1) [98]. Although rare, increasing numbers of patients have been diagnosed with DSRCT following the discovery of its specific chromosomal translocation t(11;22)(p13;q12) involving fusion of the Ewing sarcoma gene (EWS) and the Wilms' tumor gene (WT1) [99, 100].

Most commonly, patients present with crampy abdominal pain associated with an abdominal mass [98]. Other symptoms include constipation, weight loss, abdominal distension, jaundice and ascites [98]. DSRCT has a propensity for serosal surfaces, most notably the peritoneal cavity. At diagnosis, patients often present with diffuse abdominal metastatic disease with tumor sizes ranging from 1 mm to confluent sheets and nodules up to 20 cm or greater [101]. DSRCT may spread to the lymph nodes as well as metastasize to distant sites including the liver, intrathoracic cavity, mediastinum, pleura, paratesticular and soft tissues.

The diagnostic evaluation includes CT or MRI of the abdomen and pelvis which often shows multiple nodules studding the peritoneal cavity. Percutaneous or open biopsy is indicated and the specimen should be submitted for immunohistochemistry and cytogenetics. The characteristic translocation is diagnostic of DSRCT. Additional imaging should include chest CT and whole body PET to be performed as part of the staging workup [102].

Complete surgical resection is rarely possible but if achieved, it improves survival in this disease with an otherwise dismal prognosis. Lal and colleagues showed significant survival benefit for patients receiving gross surgical resection compared to patients without resection (3-year survival of 58 % versus 0, respectively) [98]. In this study, 3-year survival was also significantly improved in patients who underwent multimodal therapy including induction chemotherapy, surgical debulking and radiotherapy, compared to patients who did not receive all three modalities [98]. The overall response of DSRCT to conventional chemotherapy is poor and durable remissions are rare. However, agents with known activity in DSRCT are similar to those used in Ewing's sarcoma and should include an alkylator-based regimen with either cyclophosphamide or ifosfamide. A recently described approach includes neoadjuvant chemotherapy followed by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) using cisplatin followed by adjuvant chemotherapy and abdominal radiation [103]. In this study, the 3-year survival was greatest for patients who received HIPEC (71 %) [103]. In addition, disease free survival at 12 months was 53 % for patients who received HIPEC and cytoreductive surgery compared to only 14 % in the patients who underwent surgical debulking without HIPEC [103].

Despite multimodal aggressive treatment strategies including chemotherapy regimens active in Ewing's sarcoma, aggressive debulking surgery, whole abdominal radiation, myeloablative and chemotherapy with autologous stem cell transplant, DSRCT survival remains poor. Many present with lymph node involvement and/or distant parenchymal disease at diagnosis [98]. Overall, 3- and 5- year survival is 44 % and 15 %, respectively [98].

Infantile Fibrosarcoma

Fibrosarcoma is a rare STS that represents approximately 10 % of pediatric STS [3]. However, it is the most common NRSTS in children less than 1 year of age accounting for approximately 25 % of cases [104]. Fibrosarcoma has two peaks of incidence in the pediatric population: infants and young children (infantile fibrosarcoma, IFS) and older children usually between ages 10 and 15 years ("adult type" fibrosarcoma, ATFS). IF is histologically indistinguishable from ATFS. However, IF is characterized by a specific translocation t(12;15)(p13;q25) resulting in *ETV6-NTRK3* fusion gene which differentiates it from other spincle cell neoplasms of childhood [105].

Despite the histologic similarity, the IF and ATFS behave quite differently. IF occurs almost exclusively in children younger than 2 years with the majority diagnosed either antenatally or during the first 3 months of life [106]. IF most commonly presents as an enlarging soft tissue mass involving the extremities with approximately one-third of patients presenting with a tumor >5 cm [106]. Tumor growth may be rapid and the tumor is often highly vascularized and may mimic benign vascular lesions. ATFS is most often diagnosed in patients 10–15 years old and more often presents in axial sites [107].

The goal of treatment for both IF and ATFS is complete non-mutilating excision of the tumor. In IF, the benefit of chemotherapy is not clear. However, initial non-mutilating resection is feasible in less than 25 % of infants. In the majority of infants, neoadjuvant chemotherapy may allow for a more conservative surgical approach [108]. Orbach and colleagues reported a 75 % response rate to chemotherapy in patients with IF [106]. In ATFS, aggressive surgical resection is also the treatment of choice. However, neoadjuvant is

indicated in patients who present with inoperable tumors and adjuvant chemotherapy should be given in all cases due to the frequent occurrence of micro metastases [107]. Radiation therapy is also indicated in ATFS for patients with microscopic or macroscopic residual disease after resection [107]. For both IF and ATFS, mutilating surgery is recommended only for patients with a poor response after neoadjuvant chemotherapy or in the case of local relapse.

Despite a reported local recurrence rate up to 50 %, IF rarely metastasizes (<10 % cases). It is associated with an excellent prognosis and a 5-year overall survival of 80–90 % [104, 106]. Spontaneous regression of incompletely resection IF have been reported. ATFS is more aggressive and often presents with distant metastases most commonly to the lungs. Survival is similar to adults with fibrosarcoma with a 10-year overall survival of 51 [107].

Fibrohistiocytic Tumors

Fibrohistiocytic tumors (FHT) in children and adolescents are a heterogeneous group of tumors that vary in malignant potential from benign (fibrous histiocytoma or dermatofibroma) to intermediate (dermatofibrosarcoma protruberans) to high grade (undifferentiated pleomorphic sarcoma or malignant fibrous histocytoma). These tumors consist of fibroblasts, myofibroblasts, and histiocytes-dendritic cells with a variable inflammatory component of lymphocytes and eosinophils [109]. They more commonly present in adults with a median age of 57 years [3]. Only 3.7 % occur in pediatric and adolescent patients [3].

Dermatofibrosarcoma protuberans (DFSP) is a FHT with low-grade malignant potential. It most commonly occurs in adults with a peak incidence in the second to fifth decade of life [110]. It is relatively rare in children with age-adjusted incidence of 1 per million in persons less than 20 years of age [2]. DFSP may present in infancy as a congenital lesion, and these tumors are often initially misdiagnosed as a vascular malformation. The clinical appearance of DFSP is heterogeneous and lesions may appear as sclerotic, atrophic, macular or nodular with variation in color from bluish, violaceous, and erythematous to flesh-colored, gray or black. Although the majority of DFSP in children occur on the trunk and proximal extremities, they may occur anywhere and the diagnosis should not be excluded based on anatomic location of the tumor.

Due to the infiltrating growth pattern and potential for extension into deeper tissues including fascia and bone, preoperative imaging with MRI is recommended [111]. The current standard treatment for DFSP recommended by the National Comprehensive Cancer Network (NCCN) is wide local excision (WLE) with 2- to 4-cm margins or Mohs micrographic surgery (MMS) [112]. Several studies have compared the two techniques. In a retrospective review of 79 patients who underwent WLE or modified MMS, Paradisi and colleagues found a significantly lower local recurrence rate associated with MMS compared to WLE (1.3 % versus 20.7 %) [113]. The disadvantage of MMS is the need for specialized equipment and technicians as well as the longer procedure time.

DFSP is associated with a translocation between platelet-derived growth factor beta (*PDGFB*, 22q13.1) and type 1 collagen (*COL1A1*, 17q21 ~ 22) leading to a fusion protein (PDGFB) which stimulates the PDGF receptor [114]. Imatinib mesylate is a tyrosine kinase inhibitor that exhibits activity against many proteins including PDGF receptors. Recently, Gooskens and colleagues reported efficacy of imatinib mesylate in children with DFSP [115]. The current NCCN guidelines recommend radiation therapy or imatinib for patients without clear surgical margins, local recurrence or concern for metastases [112].

DFSP may be locally aggressive and is likely to recur if incompletely excised. Fibrosarcomatous change occurs in 4.7 % of cases and increases the likelihood of metastases [116]. Although metastases occur in approximately 5 % of patients, the relative 5- and 15-year survivals for DFSP are excellent (99.2 % and 97.2 %, respectively) [110].

MFH was first described in the 1960's as a pleomorphic spindle cell neoplasm with fibroblastic and histiocytic differentiation. It eventually became the most common STS in adults; however, in recent years, both its histogenesis and validity as a clinicopathologic entity have been questioned. The World Health Organization (WHO) now includes MFH as a subtype of undifferentiated pleomorphic sarcoma. The WHO also reclassified both the plexiform and angiomatoid subtypes as fibrohistiocytic tumors of intermediate malignancy termed plexiform histiocytic tumor and angiomatoid fibrous histiocytoma, respectively. These tumors are quite rare in children and described only in a few case series in the literature [117–121]. The most common primary sites of disease are the head and neck and extremities; however, these tumors may originate from other locations including the orbit, cranial cavity, kidney and retroperitoneum [117, 118, 120, 122]. For MFH, clinical group III (macroscopic residual disease) or IV (distant metastases), tumor invasion and size >5 cm were associated with a worse prognosis [117]. The 5-year survival and event free survival (EFS) estimates for patients with MFH is 76.5 % ± 11.2 % and 70.6 % ± 12.1 %, respectively. The 5-year survival and EFS estimates were both 100 % ± 0 % for patients with plexiform histiocytic tumor and angiomatoid fibrous histiocytoma [117]. Significant prognostic factors included the ability to resect with adequate margins, tumor size, and recurrence. The use of chemotherapy and radiation was not found to improve survival although this may be affected by patient selection with larger and more aggressive lesions receiving chemotherapy

and radiation. Prospective trials of preoperative and post operation radiation as well as adjunctive chemotherapy for high-grade lesions are ongoing.

Leiomyosarcoma

Malignant smooth muscle tumors are uncommon and are particularly rare in childhood. In a recent review of 1,175 extremity soft tissue sarcomas in children and young adults, only 25 cases of leiomyosarcoma were identified) [67]. Only 0.9 % of leiomyosarcoma cases occur in patients less than 20 years old [3], and the incidence is 0.3 per 1 million persons age less than 20 years in the United States [2].

In children and young adults, the most common site of presentation is intra-abdominal followed by extremities, trunk and head and neck [3]. However, there are reports of tumors occurring in the oral cavity [123], parotid gland [124], esophagus [125], heart [126, 127], lung [128–130], pancreas [131], and mesentery [132]. There are several reports of a link between EBV and leiomyosarcoma in children with acquired immunodeficiency syndrome [133–135]. It is also known to occur as a second malignancy, most commonly occurring in a prior radiation field [136]. Hereditary retinoblastoma is a known risk factor for the development of secondary neoplasms [137]. Although the most common soft tissue secondary malignancy in patients with a history of hereditary retinoblastoma is osteosarcoma, there are several reports of leiomyosarcoma developing both within and outside the field of prior radiation [136, 138]. These include several cases of patients with leiomyosarcoma of the urinary bladder [139, 140].

Complete surgical resection is the mainstay of treatment for leiomyosarcoma, and the role of adjuvant chemotherapy and radiation therapy is not well established [141, 142]. The Soft Tissue Sarcoma Italian Cooperative Group reported a 5-year EFS and OS of 56 % and 73 %, respectively, in 16 pediatric patients with leiomyosarcoma [142]. Late recurrences are known to occur and often lead to death [141]. Thus, long-term follow-up and surveillance is mandatory.

Liposarcoma

Although liposarcoma is one of the most common malignant soft tissue tumors in adults, it is exceedingly rare in the pediatric population accounting for less than 3 % of all pediatric sarcomas. The incidence in the United States is 0.1 per 1 million persons less than 20 years old [2]. Alaggio and colleagues published one of the largest case series in a review of 82 less than 22 years old diagnosed with liposarcoma between 1997 and 2007 [143].

Liposarcomas may occur in any location but most commonly present on the extremities and trunk (Fig. 20.1) [3]. They may be divided into the following histologic subtypes: conventional myxoid and round cell liposarcoma, spindle cell myxoid liposarcoma, pleomorphic myxoid liposarcoma, atypical lipomatous neoplasm and dedifferentiated liposarcoma, and conventional pleomorphic liposarcoma [143]. Liposarcoma is rare in children. The conventional myxoid and round cell, spindle cell myxoid and pleomorphic myxoid liposarcomas account for more than 90 % of cases in children and young adults [143]. Pure myxoid liposarcomas are characterized by a t(12;16)(q13;p11) translocation [2]. The most common sites are the lower extremity and trunk including the retroperitoneum, and most present with localized disease [3]. Metastases are present in less than 5 % of cases [3].

Complete surgical resection is the standard treatment for liposarcoma. In a multi-institutional review of 33 pediatric and young adult patients, complete surgical resection was the sole treatment modality for 13 patients (39 %) including 11 patients with myxoid tumors [144]. Surgical resection followed by adjuvant radiation therapy was used in 8 cases (24 %) and adjuvant chemotherapy in addition to surgery and radiation was used in 7 cases (21 %). The estimated 5- and 10-year OS for the entire cohort was 89 % and 64 %, respectively; however, patients with myxoid or well-differentiated histology fared better with 5-year OS 100 % versus 54 % for those patients with pleomorphic histology [144]. Alaggio and colleagues found similar excellent survival in patients with myxoid liposarcoma [143].

Malignant Peripheral Nerve Sheath Tumor (MPNST)

MPNST's primarily occur in adults and only 10 % of cases are diagnosed in the first two decades of life [3]. They account for 5 % of STS's in children and occur more commonly in children with neurofibromatosis type 1 (NF1) [3, 145]. They most commonly present with an enlarging soft tissue mass in the trunk, extremities or head and neck region, with or without pain and dysesthesia. A nerve of origin may be identified in 70 % of cases [146]. The most common primary site is the extremities followed by the trunk and head and neck [3, 146].

Approximately 40 % of MPNST's develop in a preexisting neurofibroma, most often occurring in patients with NF1 [146]. The association between MPNST and NF1 is well established [9, 147, 148]. NF1 is present in more than 40 % of pediatric patients with MSPNT, and the lifelong risk of patients with NF1 developing MPNST is estimated at 8–13 % [145, 149]. NF1, also called von Recklinghausen or peripheral neurofibromatosis, is a relatively common autosomal dominant disorder with an incidence of approximately

1 in 3,000 live births [9]. The syndrome is characterized by learning disabilities, multiple café-au-lait spots, axillary or inguinal freckling, neurofibromas, iris hamartomas, and bony lesions [145, 150]. MPNST's usually occur at an earlier age in patients with NF1 than in patients without the syndrome. In a recent study, the median age at diagnosis was 27 years for patients with NF1 compared to 40 years in patients without NF1 [151].

Surgical resection is the mainstay of treatment for MSPNT and the role of adjuvant chemotherapy and radiation remains unclear. However, a recent international review of 167 pediatric patients with MSPNT assessed the value of chemotherapy and radiotherapy in the treatment of these patients [146]. In this study, chemotherapy was administered to 74 % of patients and radiotherapy to 38 %. The estimated 5-year OS and progression-free survival (PFS) was 51 % and 37 %, respectively. A multivariate analysis identified absence of NF1, tumors confined to the organ or tissue of origin, IRS groups I and II, and extremity primary as independent favorable predictors for OS. A trend toward benefit of radiation therapy after initial resection was observed, and the overall response rate to primary chemotherapy for group III patients was 45 %. However, the rate of response to chemotherapy was significantly lower in NF1 patients (17.6 % versus 55.3 %) [146].

Synovial Sarcoma

Although rare, synovial sarcomas are the most common NRSTS diagnosed in children and adolescents and account for 8 % of STSs in this population with an age-adjusted incidence of 0.7 per 1 million [2, 3]. It is exceedingly rare in young children with the majority of cases diagnosed in the second decade. It is slightly more common in males, and 75 % of patients present with an extremity primary [3].

Despite its name, synovial sarcoma does not arise from synovial tissues but may occur anywhere in the body (Fig. 20.2). They are malignant, high-grade, soft tissue neoplasms that may be subdivided into monophasic, biphasic and poorly differentiated subtypes. It is a clinically, morphologically, and genetically distinct sarcoma characterized by a specific chromosomal translocation t(x;18)(p11.2;q11.2) which is found in all morphologic subtypes [152, 153]. Approximately 10 % of patients present with distant disease [3], and the lung is the most common site of distant metastases. However, unlike most other NRSTS, synovial sarcoma may spread to regional lymph nodes [154] with 23 % presenting with regional disease [3].

The most important aspect of treatment is surgical resection with negative histological margins. In addition, sentinel lymph node biopsy should be considered given the incidence of nodal disease at presentation [155, 156]. Radiation therapy is indicated after incomplete surgical resection and may also be used preoperatively to facilitate complete surgical resection [157, 158]. In a pooled analysis of pediatric NRSTS from the United States and Europe, Ferrari and colleagues showed the use of radiotherapy to correlate with better survival after incomplete resection but it offered no benefit after complete resection [159]. In a retrospective review of 219 children and adolescents with synovial sarcoma, radiation therapy was independently associated with improved overall survival and event-free survival as well as decreased time to local recurrence [160]. However, it is important to consider the long-term effects of radiation therapy especially for young children. Several studies show minimal benefit of radiation therapy for patients with IRS group I and even IRS group II tumors with small tumor size [161, 162].

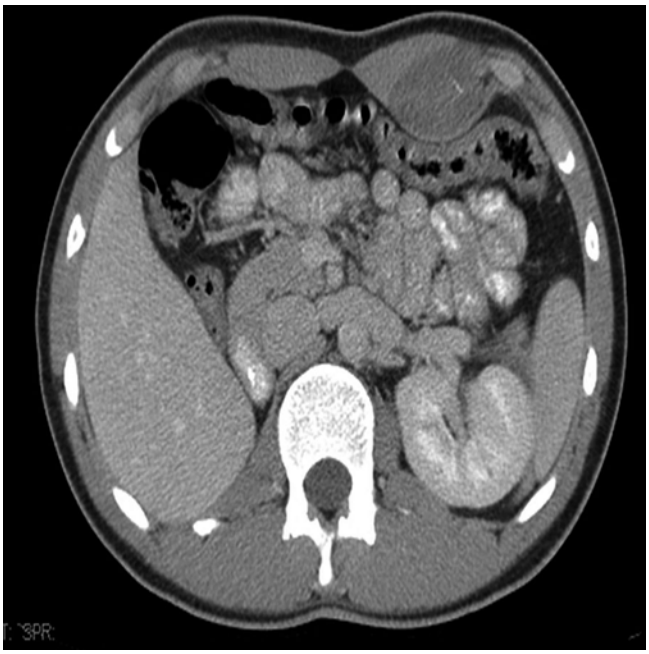

Fig. 20.2 A 16 year-old boy presented with a painless bump on his left abdominal wall. A CT abdomen (shown here) demonstrates a 5.1×3.2 cm anterior abdominal wall mass. He underwent incisional biopsy followed by complete resection for synovial sarcoma

Although synovial sarcoma is considered more chemo sensitive than many other NRSTS, the role of adjuvant chemotherapy remains controversial. In 1993, a German prospective trial suggested benefit of multi-agent chemotherapy and radiation therapy in the treatment of children and adolescents with synovial sarcoma [163]. However, Okcu and colleagues showed no significant differences in outcome between patients treated with or without chemotherapy for all patients with localized disease [160]. In the results of the pooled analysis from the US and Europe, major and minor responses to chemotherapy were seen in 40 % and 19 % of the 107 patients with synovial sarcoma, respectively [159]. In addition, survival was significantly better for patients who

had a major response to chemotherapy and/or received a complete tumor resection [159].

The estimated 5-year cancer-specific survival for children and adolescents with synovial sarcoma is 83 % compared to 62 % for adults [60]. Other important factors that influence overall and event-free survival include tumor size, invasiveness, IRS group, and primary site [60, 158, 160–162, 164]. Several studies show tumor size >5 cm to predict a worse event-free and overall survival [60, 158, 164]; however, other studies suggest tumor invasiveness is the more important factor predicting event-free and overall survival [160–162]. Axial sites, especially head and neck, are associated with a worse prognosis than extremity synovial sarcoma [160, 161, 164]. Ferrari and colleagues evaluated salvage rates and prognostic factors after relapse in 118 children and adolescents with initially localized synovial sarcoma [165]. Relapse occurred in 44 cases (37 %) with local relapse in 15 and metastatic in 29. Overall survival was 29.7 % and 21 % 5 and 10 years after relapsing, respectively, and was influenced by the timing and type of relapse as well as the chance of secondary remission [165]. Thus, it is important to consider surgical resection of locally recurrent and metastatic disease if complete resection is achievable. Late recurrences may occur and therefore, follow-up is recommended every 2 months for 1 year, then every 6 months for 2 years and every year thereafter.

Rhabdomyosarcoma

Epidemiology

Rhabdomyosarcoma (Greek for *rhabdos*, "rod"; mys, "muscle"; sarkos "flesh") is a primary malignancy in children and adolescents that arises from embryonic mesenchyme with the potential to differentiate into skeletal muscle. Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma accounting for approximately 60 % of soft tissues sarcomas in children and adolescents [3]. It is the third most common extra cranial solid tumor of childhood after neuroblastoma and Wilms' tumor. The annual incidence in children and adolescents (<20 years of age) is 4.4 per million children with approximately 350 new cases per year in the United States [166]. There is a slight male predominance (1.4:1), and it occurs more commonly in Caucasians than non-Caucasians (3.6:1) [166]. The median age at diagnosis is 7 years and most (62 %) are younger than 10 years of age [166].

Thirty percent of RMS patients have an associated congenital anomaly with genitourinary, central nervous system and gastrointestinal anomalies being the most common [167]. Although most cases of RMS occur sporadically, the disease is associated with familial syndromes. Neurofibromatosis-1 (NF-1), Rubinstein-Taybi syndrome, Beckwith-Wiedemann syndrome, Costello syndrome, Noonan syndrome, and Gorlin basal cell nevus syndrome have all been described in children with RMS [167–170]. Li-Fraumeni syndrome, a hereditary cancer syndrome first described in 1969, is an autosomal-dominant disorder usually associated with a germline mutation of p53 [13, 167, 171–173]. Li-Fraumeni syndrome is defined as the following: (1) a person diagnosed with sarcoma before the age of 45, and (2) a first degree relative diagnosed with any cancer before age 45, and (3) a first degree or second degree relative diagnosed with any cancer before age 45 or diagnosed with sarcoma at any age. Patients with this syndrome often present with RMS at an early age and have a family history of cancers including breast cancer, brain tumors, leukemia, adrenal cortical carcinoma, soft tissue and bone sarcomas.

Although no specific carcinogens have been identified that cause RMS, the use of marijuana or cocaine during pregnancy may be environmental factors that contribute to the pathogenesis of RMS. Other associations including fetal alcohol syndrome and maternal exposure to radiation have been suggested [174, 175]. A recent study examined the correlation between birth weight and the risk of RMS showing that high birth weight and large size for gestational age increased the risk of RMS [176].

Pathology

RMS is a highly malignant mesenchymal tumor classified as a small, round, blue cell tumor of childhood, a category that also includes neuroblastoma, Ewing's sarcoma, small cell osteogenic sarcoma, non-Hodgkin's lymphoma and leukemia. A combination of light microscopy, immunohistochemical techniques, electron microscopy, and molecular genetic techniques is useful in determining the tumor type. In RMS, light microscopy identifies cross-striations or characteristic rhabdomyoblasts [177, 178]. Immunohistochemical studies including staining for muscle-specific myosin and actin, desmin, myoglobin, z-band protein and Myo-D, may also support the diagnosis of RMS [179, 180].

Six major pathologic subtypes of RMS are outlined by the International Classification of RMS (presented in order of decreasing 5-year survival): (1) embryonal, botryoid; (2) embryonal, spindle cell; (3) embryonal, not otherwise specified (NOS); (4) alveolar, NOS or solid variant; (5) diffuse anaplasia and (6) undifferentiated sarcoma [181]. Although the prognostic value of specific histologic subtypes has varied between studies, each subtype is generally associated with a prognostic group as shown in Table 20.3. There is controversy as to whether the histologic subtype or the site of tumor most strongly influences prognosis.

Each of the two major subtypes of RMS, embryonal and alveolar, has a characteristic histological appearance. The

Table 20.3 International histopathologic classification for childhood rhabdomyosarcoma

Superior prognosis
Botryoid RMS
Spindle cell RMS
Intermediate prognosis
Embryonal RMS
Poor prognosis
Alveolar RMS
Diffuse anaplasia
Undifferentiated sarcoma

embryonal subtype is the most common subtype in children accounting for 68 % of all RMS in children and adolescents <20 years of age [166]. Although they may occur in any site, embryonal RMS typically arise in the head and neck region or genitourinary tract. The botryoid subtype represents 10 % of all RMS and is associated with an excellent 5-year survival rate (95 %). This subtype occurs in hollow organs arising under the mucosal surface of body orifices such as the vagina, bladder, nasopharynx and biliar tract. It is characterized on gross examination as resembling a "cluster of grapes." The spindle-cell subtype arises most often in the paratesticular region but may also occur in the head and neck, especially the orbit, and the extremities [181, 182].

The alveolar subtype accounts for 31 % of all RMS and most frequently arises in the extremities, trunk and perineum [166]. This subtype is seen more often in adolescents and is associated with a poor prognosis [183]. The alveolar variant is characterized by a prominent alveolar arrangement of stroma and dense, small, round tumor cells resembling lung tissue. To be designated as alveolar, the tumor must have greater than 50 % alveolar elements otherwise it is considered embryonal.

Pleomorphic RMS typically occurs in adults >45 years of age and is rarely seen in children. In adults, it is associated with a very poor prognosis. In children, pleomorphic RMS is often not pure and may be accompanied by embryonal type histologic foci [184]. In children, these tumors are most often classified as anaplastic [185]. These tumors account for only 1 % of RMS in children and adolescents [166]. Undifferentiated sarcoma is a poorly defined category of sarcomas whose cells show no evidence of myogenesis or other differentiation [181, 182].

Molecular Biology

The two histologic subtypes of RMS, embryonal and alveolar, have distinct genetic alterations that are useful in diagnosis and may play a role in the pathogenesis of these tumors. In approximately 80 % of cases, embryonal RMS is characterized by loss of heterozygosity (LOH) at the 11p15 locus. This is the location of the insulin-like growth factor-2 (IGF-II) gene and LOH results in overexpression of the gene [186]. IGF-II has been shown to stimulate the growth of rhabdomyosarcoma cells, whereas the blockade of this factor using monoclonal antibodies inhibits tumor growth both in vitro and in vivo [177]. Several other solid tumors are associated with genomic deletions on the short arm of chromosome 11, including Wilms' tumor, hepatoblastoma, and neuroblastoma.

In approximately 80 % of alveolar RMS, a unique translocation occurs between the *FKHR* gene (a member of the forkhead family of transcription factors) on chromosome 13 and either the *PAX3* gene on chromosome 2, t(2;13)(q35;q14), or the *PAX7* gene on chromosome 1, t(1;13)(p36;q14) [187]. *PAX3-FKHR* is more common than *PAX7-FKHR* fusion (59 % versus 19 %) and is associated with a worse overall survival [188]. *PAX3-FKHR* fusion occurs in older patients and is associated with a higher incidence of invasive tumor [189]. Polymerase chain reaction (PCR) assays are now available that allow confirmation of the diagnosis of alveolar RMS based on the presence of these fusion genes [187, 190–192]. However, approximately 20 % of alveolar RMS are translocation negative and by gene array analysis, these fusion negative tumors more closely resemble embryonal RMS with a similar prognosis [193, 194]. Thus, it has been proposed that RMS should be divided into *PAX-FKHR* fusion-positive and – negative tumors rather than alveolar and embryonal histologies. In future COG studies, RMS tumors will risk classify based on fusion status, instead of histologically.

Clinical Presentation

The clinical presentation of RMS is variable and depends on the tumor site, patient age and the presence or absence of metastases. Although adults most commonly present with extremity tumors, RMS may occur in any site in the body except bone. In children and adolescents, the most common sites are the head and neck and the genitourinary tract, with only 20 % of cases occurring in the extremities. Most symp-

toms are secondary to local mass affect and are specific to the primary tumor location. Thirty-five percent of RMS occurs in the head and neck region, 22 % in the genitourinary tract and 14 % in the extremities [166]. The presentation for each primary site will be discussed later in the chapter. There are no classic paraneoplastic syndromes associated with RMS. More than 60 % of patients present with advanced disease including 36 % with regional disease and 30 % with distant metastases [166]. Isolated lung metastases are unusual and should be biopsied to prove disease.

Neonatal presentation of RMS is extremely rare with only 14 cases (0.4 % of patients in IRS I-IV) reported in the literature [195]. They tend to be embryonal botryoid or undifferentiated histology. Children <1 year old accounted for only 6 % of cases in SEER registry data [166].

Diagnosis

The diagnosis of rhabdomyosarcoma usually is made by direct open biopsy. Initial biopsy is generally incisional except in small lesions in which case excisional biopsy is possible. It is important to recognize that the tumor may have a pseudocapsule and if the lesion is "shelled out," the surgeon may have a false notion that the tumor was completely excised. An incisional biopsy requires that the biopsy tract be excised at the time of resection. Therefore, it is imperative that careful thought be used in deciding the orientation of the biopsy incision. Extremity lesions should be biopsied through a longitudinal incision only (Fig. 20.3).

If an excisional biopsy is performed, surgical margins should be carefully marked to allow re-resection if the biopsy results reveal a positive margin. If biopsy margins are not carefully marked on the specimen and the resection bed (usually by sutures or clips), the ability of the surgeon to subsequently obtain negative margins at the time of re-resection is severely compromised. Several grams of tissue are required for histologic and cytologic diagnosis and classification, and therefore, open biopsy is preferred.

Prior to definitive surgery, a full evaluation including imaging, laboratory studies, and bone marrow evaluation should be performed (Table 20.4). Standard laboratory studies include complete blood counts, electrolytes, renal function tests, liver function tests and urinalysis. Imaging of the primary tumor should be performed with either Cat Scan (CT) or MRI depending on the primary tumor site. MRI is preferable for extremity, pelvic and paraspinal tumors whereas CT is valuable for the evaluation of bone erosion and abdominal lymphadenopathy [196].

Evaluation of regional and distant lymph nodes by clinical and radiographic studies (CT or MRI) should be performed. A CT of the abdomen and pelvis should be performed for all lower extremity and genitourinary primary tumors.

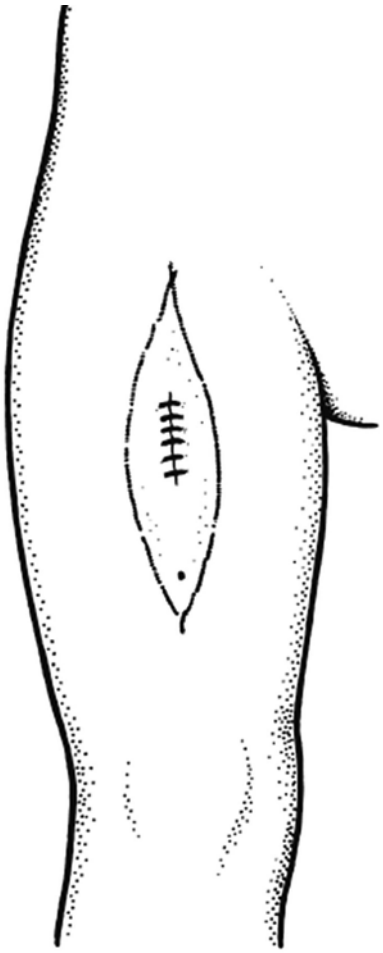

Fig. 20.3 Longitudinal biopsy incision with outline of WLE if necessary

Table 20.4 Diagnostic and preoperative evaluation

History and physical examination
Laboratory studies (cbc/differential, LFTs, electrolytes, creatinine, urinalysis)
CT or MRI of primary tumor
CT chest
Bone marrow biopsy and aspiration
Bone scan
CT abdomen and pelvis (for lower extremity and genitourinary tumors only)
MRI head (for parameningeal tumors only)
Lumbar puncture for CSF cytology (for parameningeal tumors only)
EKG or echocardiogram (selective)

The use of FDG-PET has been widely used in the adult population with sarcoma to determine extent of disease [197, 198]. However, the experience with FDG-PET in children is limited [199–201]. This modality may prove useful in the clinical determination of the extent of disease and improve pretreatment staging thus altering treatment for patients (Fig. 20.4) [196].

Evaluation for metastatic disease includes a bone marrow biopsy and aspirate, bone scan, CT chest, and lumbar puncture for cerebrospinal fluid collection (for parameningeal tumors only).

Pretreatment Staging, Clinical Grouping, and Risk Group Classification

RMS staging is determined by the site and size of the primary tumor, the degree of tumor invasion, nodal status, and the presence of absence of metastases. The staging of RMS is complex and requires three steps:

1. Assigning a pretreatment stage.
2. Assigning a local tumor surgical-pathologic group.
3. Assigning a risk group.

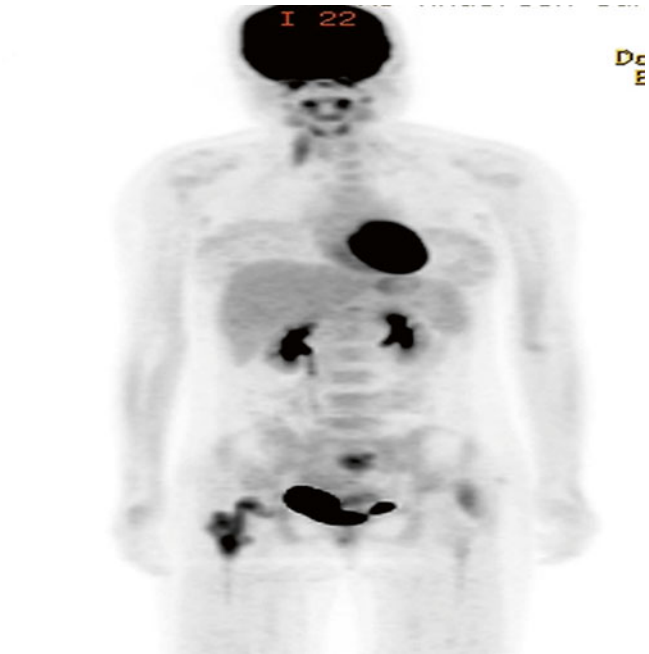

Fig. 20.4 A 18 year-old girl presented with metastatic alveolar RMS. PET CT showed multiple metabolically active sites of metastases including a metastasis in the right proximal femur with extension into the surrounding soft tissues

The Children's Oncology Group Soft Tissue Sarcoma Committee (COG-STS) protocols for RMS use a TNM-based pretreatment staging system that incorporates surgical-pathologic group, primary tumor site, tumor size, regional lymph node status, and the presence or absence of distant metastases (Table 20.5) [202, 203]. The genitourinary tract, biliary tract, nonparameningeal head and neck and orbit are considered favorable primary tumor sites. All other sites are considered unfavorable (Table 20.6). The pretreatment staging system is used to stratify the extent of the disease for different treatment regimens as well as compare outcomes for patients receiving protocol-based treatment.

The extent of residual disease after resection is an important prognostic factor for RMS. The surgical-pathologic or clinical group is based on the completeness of surgical resection and the presence or absence of lymphatic or distant spread after pathologic examination of the surgical specimens (Table 20.7). The clinical group was developed by the Intergroup Rhabdomyosarcoma Group (IRS), and used in the IRS-1, IRS-II and IRS-III studies as the basis for treatment assignment. This is a postsurgical staging system and provides an important adjunct to the pretreatment staging system. However, it does not take into account the biological nature or natural history of the tumor.

The COG-STS developed a risk-stratification system that incorporates pretreatment stage and clinical group in order to classify patients as low, intermediate or high risk (Table 20.8). The treatment assignment in current COG-STS protocols for RMS is based on risk group. This system reliably predicts

Table 20.5 TNM pretreatment staging classification for rhabdomyosarcoma

Stage	Sites	T	Size	N	M
1	Favorable sites	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_0
2	Unfavorable sites	T_1 or T_2	a	N_0 or N_x	M_0
3	Unfavorable sites	T_1 or T_2	a	N_1	M_0
–	–	–	b	N_0 or N_1 or N_x	M_0
4	Any site	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_1

T_1 Tumor confined to anatomic site of origin, T_2 Tumor extension and/or fixed to surrounding tissues, a ≤ 5 cm, b > 5 cm, N_0 Regional nodes not clinically involved, N_1 Regional nodes clinically involved by tumor, N_x Clinical status of regional nodes unknown, M_0 No distant metastases, M_1 Metastasis present

Table 20.6 Favorable and unfavorable anatomic sites for rhabdomyosarcoma

Favorable sites	Unfavorable sites
Orbit	Any site other than favorable
Nonparameningeal head and neck	–
Genitourinary (other than kidney, bladder and prostate)	–
Biliary tract	–

Table 20.7 Clinical grouping for patients with rhabdomyosarcoma

Clinical group	Definition
I	Localized disease, complete resection, negative margins, no regional lymph node involvement
II	Localized disease, grossly removed with microscopic disease at the margin and/or grossly removed but involved regional lymph nodes
III	Localized disease with gross residual disease after incomplete resection or biopsy only
IV	Distant metastasis present at diagnosis

Table 20.8 Rhabdomyosarcoma risk group classification

Risk group	Histology	Pretreatment stage	Clinical group
Low risk	Embryonal	1	I, II, III
–	Embryonal	2, 3	I, II
Intermediate risk	Embryonal	2, 3	III
–	Alveolar	1, 2, 3	I, II, III
High risk	Embryonal or Alveolar	4	IV

patient outcomes and allows correlation between intensity of therapy and outcome.

Treatment

Prior to the introduction of radiation and chemotherapy, surgical resection was the only treatment option for patients with RMS and radical, often mutilating, excision was the standard approach to these tumors. Survival rates were overall poor and ranged from 7 to 70 % depending on the site of disease [204]. In 1950, Stobbe and colleagues demonstrated improvement in outcome in head and neck sites when radiation therapy was added after incompletely resected RMS [205]. In 1961, Pinkel and Pinkren advocated adjuvant chemotherapy and radiation after complete surgical resection [206]. These early studies marked the beginning of the multimodal approach to solid tumors.

Recognizing the value of multimodality therapy and the rarity of these tumors, the first Intergroup Rhabdomyosarcoma Study Group (IRSG) was established in 1972 to investigate the therapy and biology of RMS and undifferentiated sarcoma in previously untreated patients less than 21 years of age. Since then, the IRSG conduced five successive clinical protocols involving almost 5000 patients between 1972 and 1997: IRS-I, 1972–1978; IRS-II, 1978–1984; IRS-III, 1984–1991, IRS-IV Pilot (for patients with advanced disease only), 1987–1991; IRS IV, 1991–1997 [1, 2, 12, 17, 24, 25, 207]. The results from these studies formed the foundation for IRS-V which opened in 1997 and used the concept of risk stratification to conduct separate studies based on clinical and biologic prognostic factors. In 2000, the Children's Oncology Group was established, and the work of the IRSG was continued by the COG Soft Tissue Sarcoma (COG-STS) committee [208].

The approach to the treatment of RMS has been multimodal for more than 30 years. The surgical treatment of the disease has been progressively less mutilating and less aggressive while maintaining excellent survival as seen in earlier studies.

Surgical Treatment

Primary Resection

The primary goal of surgical treatment for RMS is complete resection of the primary tumor with a surrounding rim of normal tissue. The prognosis for patients with RMS is closely linked to the amount of residual disease present after resection, and complete tumor resection, with no microscopic residual disease, offers the best chance for cure. The surgical approach depends on primary tumor site, size, presence or absence of lymph node involvement and distant metastases. The surgical treatment of RMS is site-specific; however, the general principles include complete wide excision of the primary tumor and surrounding uninvolved margins while preserving cosmesis and function. There is little data to support the minimal size of the circumferential margin but 0.5 cm is considered adequate [196]. Adequate margins of uninvolved tissue are required unless excision would compromise adjacent organs, result in loss of function, poor cosmesis, or are not technically feasible.

The margins should be marked and oriented at the operative field to allow precise evaluation by the pathologist. If a positive margin is suspected, intraoperative biopsies should be performed around the resection margin to establish a negative microscopic margin. Unresectable microscopic or gross residual disease should be marked with titanium clips in the tumor bed to direct radiotherapy and guide future re-excision.

A pre-treatment re-excision (PRE) is recommended in the following situations: (1) if only a biopsy was performed of a resectable tumor, (2) a non-oncologic operation was per-

formed, or (3) the status of the margins is unclear. A PRE consists of complete wide re-excision of the prior operative site with pathologically confirmed negative margins. PRE is performed prior to initiation of adjuvant therapy. Patients who undergo PRE with complete excision (clinical group 1) have a similar outcome to patients who are clinical group 1 after initial resection [209].

Lymph Node Evaluation

Lymph node status is an important prognostic factor in RMS and directly impacts risk-based treatment strategies. Approximately 1/3 of patients present with regional nodal disease [166], and positive lymph node status is an independently poor prognostic factor for both failure-free survival and overall survival [210, 211]. Thus, it is imperative that regional lymph nodes be assessed both clinically and radiographically. Any suspicious lymph node requires pathologic confirmation. In addition, RMS patients with extremity tumors, primary tumors of the perineum and paratesticular tumors in children>10 years old should undergo routine surgical evaluation of regional lymph nodes even if there is no clinically or radiographically suspicious disease [212–214]. These sites are associated with a high incidence of nodal disease and false-negative imaging and therefore, pathologic evaluation of the regional nodal basin is required. If the regional lymph nodes are involved, distal nodes must be sampled to determine metastatic disease. However, complete lymph node removal has no therapeutic benefit [215].

Sentinel lymph node biopsy allows adequate, and possibly superior, staging compared to traditional lymph node sampling while limiting operative morbidity [64, 213]. Sentinel lymph-node mapping uses a vital dye such as Lymphazurin® blue along with radio labeled technetium sulfur colloid to localize the regional node(s) most likely to contain metastatic foci [64]. The surgeon removes the sentinel node and the pathologist determines whether the sentinel node contains tumor cells. The sentinel node reflects the status of the nodal basin and therefore, if the sentinel node is positive, the nodal basin is irradiated. Sentinel lymph node biopsies are now part of the required evaluation for extremity RMS patients enrolled on COG studies.

Second Look Operation

It is common that the size, invasion and location of primary RMS tumors prohibit complete resection. Following initial adjuvant therapy with intensive multi-agent chemotherapy with or without radiation, repeat imaging with CT or MRI is performed. If residual tumor is present on imaging or the outcome of therapy is questionable, a second look operation should be considered [216, 217]. Similar to the initial resection, the primary goals of a second look operation is to remove any residual tumor and achieve a complete resection without compromising function or cosmesis. The use of second look operations was evaluated in IRS-III and found to be beneficial for clinical group II patients [218–221]. Second look operations resulted in reclassification of 75 % of partial responders to complete responders after excision of residual tumor, and 12 % of complete responders were found to harbor residual tumor. Thus, imaging studies are not always reliable in determining response to therapy. The survival rate of complete responders and those reclassified from partial responders to complete responders was similar [220, 221]. Second look operations were most effective in extremity and truncal tumors and least useful for head and neck tumors.

The second look operation will also determine the pathologic response to initial therapy prior to administering additional therapy. In IRS-IV, patients with viable tumor present at the second look operation had shorter event-free survival rates than those without viable tumor; however, there was no difference in overall survival [222]. Second look surgery is much less beneficial in children with metastatic disease.

Surgical Treatment of Recurrent and Metastatic Disease

Despite success in primary treatment of RMS, survival after relapse remains very poor. Approximately 30 % of RMS patients develop relapse, and 50–95 % of relapsed patients ultimately die of progressive disease [223]. There is little evidence that surgical resection contributes to improved survival in relapsed RMS. A report from MD Anderson Cancer Center suggests that resection of recurrent RMS confers a 5-year survival of 37 % compared to 8 % survival in patients without aggressive resection; however, the study is limited by a small sample size and the inherent biases associated with a retrospective study design [224]. It is recommended that treatment for locally recurrent disease be determined according to risk stratification. For relapsed patients with more favorable disease, intensive multi-agent chemotherapy followed by radiation and/or surgical resection is appropriate. For patients with less favorable disease, initial dose-intensified chemotherapy and maintenance chemotherapy or experimental therapies may be offered [223].

Metastatic disease most commonly involves the lung (58 %), bone (33 %), regional lymph nodes (33 %), liver (22 %), and brain (20 %) [225]. The role of surgery in the treatment of metastatic disease remains unclear [226]. Primary resection of metastatic disease at diagnosis is rarely indicated. In IRS-IV, 24 % of patients developed isolated lung metastases. A diagnostic biopsy followed by intensive salvage multimodality therapy was used for most of these patients. There was no survival advantage for biopsy confirmed versus radiographically diagnosed lung metastases [226]. The European multicenter, multinational, study group recently reviewed four consecutive trials to determine the impact of local control of pulmonary metastases in patients with metastatic embryonal RMS limited to the lungs [227].

The group reported a 38 % 5-year event-free survival for the entire cohort and did not identify any survival benefit for local control of pulmonary metastases [227].

Chemotherapy

Currently, all patients with RMS receive chemotherapy and the intensity and duration of chemotherapy are dependent on the risk group classification (Table 20.3). Standard therapeutic regimens consist of a combination of vincristine (V), actinomycin D (A), and cyclophosphamide (C) commonly referred to VAC. Other agents with known activity against RMS include doxorubicin (Dox), ifosfamide (I), and etoposide (E). Although significant advancement has been made in improving outcomes of patients with local and regional disease, little improvement has been seen in children with advanced RMS. This is primarily due to the failure of new chemotherapy agents and protocols to improve significantly upon the standard treatment regimens.

VAC has been the gold standard for combination chemotherapy in the treatment of most cases of RMS. Large randomized cooperative trials have allowed for modifications of this combination of agents tailored to specific subgroups according to clinical group and site of disease. A recent COG trial (COG-D9602) stratified patients with low risk embryonal RMS into two groups: subgroup A (Stage 1 Group I/IIA, Stage 2 Group I, and Stage 1 Group 3 orbit only) and subgroup B (Stage 1 Group IIB/C, Stage 1 Group III non-orbit, Stage 2 Group II, and Stage 3 Group I/II disease) [228]. Subgroup A patients received VA with or without radiation and subgroup B received VAC and a reduced dose of radiation. The 5-year overall failure free survival and overall survival were 88 % and 97 %, respectively, for subgroup A, and 85 % and 93 %, respectively, for subgroup B. Thus, two - or three-drug regiments (VA and VAC) with and without radiation therapy are considered standard treatment for specific subgroups of low-risk patients.

The standard chemotherapy combination for children with intermediate risk RMS is VAC. In IRS-IV, intermediate risk patients were randomized to receive either standard VAC or one of two other chemotherapy regimens with ifosfamide as the alkylating agent [229]. The outcomes for both groups were similar and standard VAC treatment was easier to administer [229]. Although cyclophosphamide and topotecan demonstrated substantial activity in patients with recurrent disease and newly diagnosed patients with metastatic RMS, there was no benefit for the addition of these drugs in patients with intermediate risk RMS [230, 231]. In certain intermediate risk patients, dose intensification using known active chemotherapeutic agents should be considered. A comparison of patients treated on IRS-IV with higher doses of cyclophosphamide compared to patients treated on IRS-III with lower doses of cyclosphosphamide suggested some benefit of higher doses in certain groups of intermediate risk patients [232]. These included patients with tumors at favorable sites and positive lymph nodes, patients with gross residual disease and patients with tumors at unfavorable sites with complete gross resection. Dose intensification was not beneficial for patients with unresected embryonal RMS at unfavorable sites [233]. Dose intensification of vincristine and actinomycin-D is not possible due to neurotoxic and hepatotoxic effects [196].

High risk patients have metastatic disease at presentation. These patients have a very poor prognosis despite aggressive therapy. The standard treatment for children with metastatic RMS is VAC. Despite many clinical trials attempting to improve outcome by the addition or substitution of new agents to the standard VAC regimen, no chemotherapy regimens have been more effective than VAC in the treatment of metastatic RMS [196, 234–239]. High-dose chemotherapy followed by autologous stem cell transplant for metastatic RMS fails to offer benefit [240, 241].

Radiotherapy

Radiotherapy is an important component of the multimodality treatment approach in RMS and has improved both local control and outcome for patients with the disease. It is an effective method for achieving local control in patients with microscopic or gross residual disease following biopsy, surgical resection or chemotherapy. In a recent review of patients with microscopic residual disease, local recurrence was due to noncompliance with guidelines or omission of radiation therapy (RT) in more than 50 % of group II patients [242].

RT is tailored for specific sites and extent of disease, but in general, all patients except those with group I embryonal tumors, receive RT. Several prior studies evaluated the radiation dose and method of administration necessary to achieve local control of the tumor [243–245]. Current radiation doses range from 36 to 50 Gy, and the dose depends primarily on the amount of residual disease following primary surgical resection. In patients with group II disease, low dose radiation (40 Gy) is associated with local control rates of ≥90 % [244]. For patients with gross residual disease (group III), radiation doses are usually higher (40–50 Gy). There is no benefit to hyperfractionated RT (59.4 Gy) compared to conventional, once-daily RT (50.4 Gy) [243].

The radiation treatment volume should be determined prior to surgical resection of the primary tumor and is based upon the extent of tumor at diagnosis. A margin of 2 cm is recommended and should include clinically involved regional lymph nodes [245]. In general, multiagent chemotherapy is given for 1–3 months prior to RT followed by 5–6 weeks of RT during which time chemotherapy is modified to avoid radio sensitizing agents such as doxorubicin and actinomycin-D.

RT in very young patients is especially challenging given the long-term sequela associated with RT [246]. The late effects are site-dependent. In the head and neck region, xerostomia, dental problems, facial growth retardation, neuroendocrine dysfunction, and vision and hearing loss may occur [247, 248]. For abdominal and pelvic sites, bowel obstruction and infertility as well as growth retardation are a concern [249]. Extremity RT is associated with fractures, growth retardation, fibrosis, atrophy and peripheral nerve damage [250]. However, the greatest long-term impact of RT may be its association with late secondary malignancies [251].

Thus, it is important to consider techniques that allow delivery of radiation specifically to the tumor while minimizing radiation to surrounding tissues. These techniques include conformal RT, intensity-modulated RD (IMRT), proton-beam RT, and brachytherapy. All of these techniques have been studied in the treatment of RMS. In conformal RT, a computer generates a 3-dimensional image of the tumor and allows the radiologist to administer higher doses of radiation to the tumor while sparing surrounding tissues [252]. IMRT uses computer-controlled linear accelerators to deliver precise radiation doses specifically to the tumor or areas within the tumor [253]. Proton-beam therapy targets tumor cell with streams of charged particles that have very little lateral dispersion and therefore significantly limit damage to surrounding tissues [254, 255]. Brachytherapy, using either intracavitary or interstitial implants, allows local delivery of RT and has been used in the treatment of head and neck, vaginal and vulvar, and select bladder and prostate RMS [256–259].

Management by Site

Head and Neck

Head and neck RMS accounts for 35 % of childhood RMS and the incidence is increasing with an annual percentage change of 1.16 % between 1973 and 2007 [260]. Head and neck RMS is divided into three subtypes: orbital, parameningeal (ear, mastoid, nasal cavity, paranasal sinuses, infratemporal fossa, and pterygopalatine fossa), and nonorbital nonparameningeal (oral cavity, larynx, parotid region, cheek, scalp and soft tissues of the neck). The orbit and nonparameningeal sites are considered favorable whereas nonparameningeal sites are unfavorable and associated with early recurrences and a poor prognosis.

Of head and neck RMS, 25 % occur in the orbit which is associated with a good prognosis [166, 260]. Orbital RMS usually presents in the first decade of life and boys are more commonly affected than girls [261]. The most common presenting symptoms are rapid onset and progression of proptosis and globe displacement [261]. However, the clinical presentation is dependent on the location of the tumor within the orbit and its rate of growth [261]. Although CT and MRI are important tools for preoperative planning and evaluating residual or recurrent disease, incisional biopsy is essential for definitive diagnosis. The majority of patients present with localized disease (61 %) with less than 10 % having metastatic disease [260]. Patients with localized orbital RMS have an excellent overall survival regardless of the extent of initial surgical resection with a 5-year overall survival rate of 89 % [251]. Thus, the mainstay of treatment for orbital RMS is a of combination chemotherapy and radiation therapy. Orbital exenteration is rarely performed and is confined to cases with recurrent disease [262].

While it is well established that complete surgical resection with negative margins offers the best chance for local control in patients with RMS, the multi-disciplinary approach to therapy has allowed less-aggressive surgical procedures while maintaining an excellent prognosis for most patients with head and neck RMS. When feasible, wide excision is indicated, however, it is often either not possible or would result in significant functional and/or cosmetic impairment. The possibility of achieving negative margins is usually restricted to small, superficial tumors [263]. After reviewing the literature, Gradoni and colleagues outlined an algorithm for the role of surgery in nonorbital head and neck RMS (Table 20.9) [264].

Table 20.9 The role of surgery in nonorbital head and neck RMS (Gradoni Surgical Oncology 2010)

Biopsy	All patients with suspected RMS
Primary surgical resection	For patients with alveolar RMS if Complete resection achievable No major functional or cosmetic consequences No high-risk features of meningeal involvement present
Surgical resection after primary chemoradiation	All patients with RMS in whom clinical and radiological re-staging shows resectable residual tumor.
Debulking surgery	Palliative and urgent situations only
Neck dissection	Alveolar RMS at the same time as surgical resection of primary tumor (not indicated for embryonal RMS)
Salvage surgery after locoregional relapse	Efficacy is limited but success reported for late relapses of embryonal RMS
Metastatectomy	Consider for limited pulmonary metastases

Parameningeal tumors account for 44 % of head and neck RMS and are associated with a poor prognosis compared to orbital and nonorbital, nonparameningeal head and neck RMS [260]. More than 50 % present with regional disease and 28 % present with metastases [260]. Paramenigeal tumors tend to recur locally and spread intracranially. High-risk features include intracranial extension, cranial base erosion, cranial nerve palsy and positive cerebrospinal fluid at cytology [265]. All patients with suspected parameningeal RMS should undergo MRI with contrast of the primary site followed by CT with contrast of the same region if skull erosion and/or transdural extension is equivocal on MRI (Fig. 20.5a, b). The cerebrosopinal fluid should be sent for cytology. For most parameningeal tumors, surgical resection is reserved for salvage for recurrent disease after chemoradiation or for tumors that fail to respond to chemoradiotherapy. Achieving negative margins is often difficult and possible in less than 50 % of cases [266]. Sentinel lymph node biopsy has been described as a useful tool in the staging of parameningeal RMS [267].

With intensive chemotherapy and hyperfractionated accelerated radiotherapy (HART), 5-year overall survival increased from 40 to 72 % in a series of 109 children with non-metastatic parameningeal RMS registered in the Associazione Italiana di Ematologiae Oncologia Pedaitrica (AIEOP) Soft Tissue Sarcoma Committee (STSC) protocols from 1975 to 2005 [268]. In this series, delayed surgery after initial chemoradiotherapy was associated with a better prognosis [268]. In a review of 611 patients with localized parameningeal RMS entered on IRS II-IV protocols, overall 5-year survival was 73 % and did not differ between protocol era [265]. Favorable prognostic factors included age <10 years, primary tumor in the nasopahrynx/nasal cavity, middle ear/mastoid or parpharyngeal areas ("better" sites) and no meningeal involvement [269]. Treatment was initial biopsy or surgical resection followed by multi-agent chemotherapy (vincristine, dactinomycin and cyclophosphamide) and radiation therapy [269]. Raney and colleagues also reviewed 91 patients with metastatic parameningeal RMS enrolled on IRS II-IV protocols [270]. They noted that tumors arising in "better" versus "worse" (infratemporal-pterygopalatine area) sites and embryonal versus other histology are associated with improved 10-year failure free survival [270]. In this series of patients with metastatic disease, estimated 10-year failure-free and overall survival was 32 % and 33 %, respectively [270].

Nonorbital, nonparameningeal sites include superficial and deep tumors that do not impinge on the meninges and account for approximately 30 % of head and neck RMS. The majority of patients present with either local (33 %) or regional disease (37 %) with only 20 % presenting with distant metastases [260]. If feasible, wide excision of the primary tumor and ipsilateral neck lymph node sampling of clinically involved lymph nodes is indicated [270]. Given anatomic constraints, narrow resection margins (<1 mm) are acceptable. Children and adolescents with localized nonorbital, nonparameningeal head and neck RMS entered on IRS III-IV protocols received a combination of vincristine and dactinomycin ± cyclophosphamide (VAC) with or without radiation therapy [32]. Five-year overall survival for these patients was 83 % [32].

In summary, modern protocols for head and neck RMS are comprised of chemotherapy and radiotherapy ± surgical resection depending on the primary site and extent of disease. Recently, a few reports have shown benefit with modern radiation therapy techniques including intensity modulated radiotherapy (IMRT), fractionated stereotactic radiotherapy (FSRT), and proton radiotherapy in the treatment of head and neck RMS [255, 271]. These modalities offer the advantage of delivery of high radiation doses to a defined target volume while sparing surrounding organs at risk. This may prove particularly beneficial in the pediatric population in whom conventional radiation therapy is often associated with long-term toxic effects.

Genitourinary Sites

Rhabdomyosarcoma is the most common malignancy of the pelvic structures in children usually affecting children age 2–4 and 15–19 years old. Approximately 22 % of RMS cases arise from genitourinary sites [166]. These sites include the bladder, prostate, paratesticular areas, vulva, vagina, uterus, and rarely, the kidneys or ureter. Vulvar, vaginal, uterine and paratesticular tumors are considered favorable sites and account for approximately 60 % of genitourinary RMS. Less common, bladder, prostate and kidney are considered unfavorable sites [166]. Embryonal histology accounts for 90 % of genitourinary RMS and has a more favorable prognosis than alveolar pathology (82 % versus 65 % 5-year EFS) [210]. The diagnostic and therapeutic management of genitourinary RMS depends on the primary site of disease.

Bladder and Prostate

Bladder and prostate RMS account for 2 % and 4 % of RMS patients, respectively. These tumors usually presents with gross hematuria, urinary retention or urgency and ultrasound may be the initial imaging modality performed. CT or MRI of the abdomen and pelvis determines the extent of the primary tumor and provides visualization of retroperitoneal lymph nodes. The majority of bladder and prostate RMS are embryonal histology (71 %) followed by botryoid (20 %) and alveolar (2 %) histologies [182].

The initial surgical approach is usually limited to biopsy. Biopsy may be performed cystoscopically but care must be taken to obtain adequate tissue for diagnosis and minimize

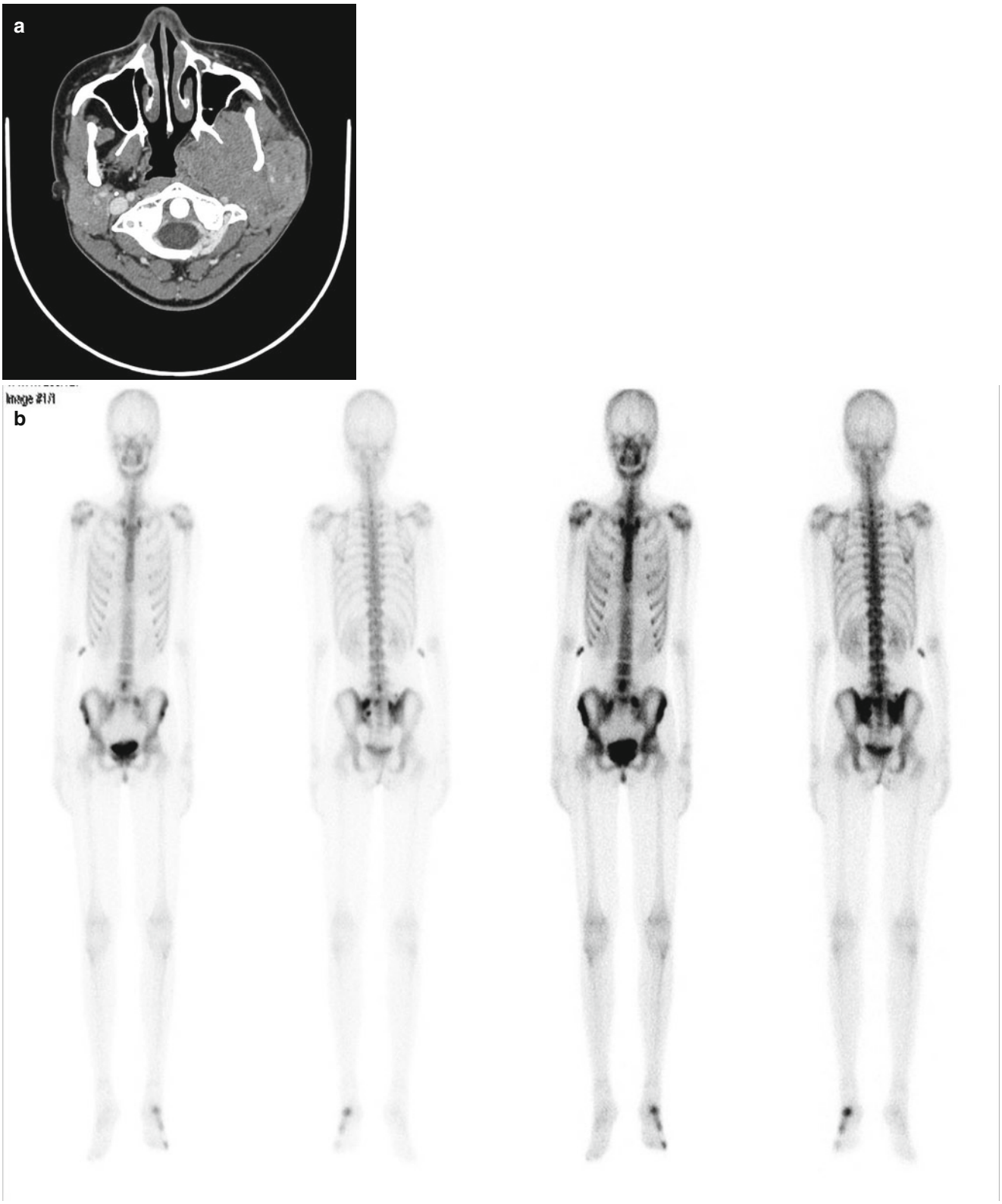

Fig. 20.5 (**a**) A 17 year-old girl presented with a enlarging left cheek mass. CT head and neck demonstrated 5.6×6.4 cm mass in the left masticular space. Biopsy confirmed embryonal RMS. (**b**) A bone scan performed at the time of diagnosis was remarkable for a L5 metastatic lesion

cautery artifact. Alternatively, open biopsy may be performed. In patients who present with ureteral obstruction, internal ureteral stents and/or percutaneous nephrostomy tubes may be necessary; however suprapubic catheters should be avoided due to the risk of seeding the tract with tumor [272]. The major goal of surgery is complete tumor resection with bladder salvage which is achieved in 50–65 % of patients [272–274]. In rare cases, the tumor is confined to the dome of the bladder and is amenable to complete resection with bladder preservation. Neoadjuvant chemotherapy and radiation have decreased the rate of exenterative cystectomy to approximately 30 % [275–277]. However, distal bladder tumors involving the trigone frequently require ureteral reimplantation and/or bladder augmentation. Conservative, delayed surgery performed after intensive chemotherapy with or without radiotherapy yields a better cure rate while maintaining a high rate of bladder salvage in children with prostatic RMS [278]. Pelvic exenteration is reserved for local control when residual viable tumor remains after chemotherapy and radiotherapy. Lymph nodes are involved in 20 % of cases. It is important to examine the retroperitoneum and remove any enlarged lymph nodes [279].

The timing of local control remains controversial and residual mass on imaging does not always represent viable tumor. The tumor may involute or differentiate into mature rhabdomyoblasts. In IRS III, 36 % of patients with no radiographic response were found to be in complete remission at the time of second-look surgery [280]. It has been suggested that bladder and prostate RMS <5 cm in size with embryonal histology may be successfully treated with chemotherapy alone [281].

Overall survival for bladder RMS is good - 82 % at 6 years in the IRS-IV study [229]. It is often difficult to differentiate between bladder and prostate RMS due to their anatomic proximity and tendency to present as large tumors. However, in patients in whom that differentiation is possible, it is clear that prostate RMS has a worse prognosis compared to bladder RMS [166]. Although bladder preservation is often achieved, half of patients will have reduced bladder capacity and only 55 % have normal bladder function [273, 282]. Sexual dysfunction may also be affected [283].

Paratesticular

Paratesticular RMS represents 7 % of all childhood RMS and 12 % of childhood scrotal tumors [213]. Most patients present with a painless scrotal mass. The standard of care is radical orchiectomy via an inguinal approach with resection of the spermatic cord to the level of the internal inguinal ring [196] (Fig. 20.6). The proximal spermatic cord should be evaluated and show no tumor on frozen section [279]. If tumor is present, a higher ligation is performed. When scrotal radiation therapy is planned, the contralateral testis may be temporarily transposed to the adjacent thigh to avoid the radiation field. In general, biopsy is unnecessary and should be avoided. If trans-scrotal biopsy or resection is performed, it may result in tumor seeding, and hemiscrotectomy or hemiscrotal radiation is required [284].

The incidence of nodal metastatic disease for paratesticular RMS is 26 % [285, 286]. Thus, all patients should undergo thin-cut (3.8 to 5.0 mm) abdominal and pelvic CT scans to evaluate nodal involvement. The incidence of lymph node metastases is higher in patients >10 years old and CT may not adequately predict lymph node involvement in these patients [212]. Therefore, a staging ipsilateral retroperitoneal lymph node dissection is required for all children >10 years old on IRSG and COG-STS studies. However, node dissection is not routine in Europe for adolescents with resected paratesticular RMS. All patients with enlarged lymph nodes on imaging irrespective of age should undergo retroperitoneal lymph node sampling and further therapy depends on lymph node status. For patients >10 years old and primary tumor >5 cm, ipsilateral retroperitoneal lymph node dissection up to the level of the renal hilum is recommended. This procedure may be performed laparoscopically by experienced surgeons [287]. Positive suprarenal lymph nodes are considered distant metastases and these patients are considered clinical group IV [196]. It is important to note that retroperitoneal lymph node dissection may be associated with significant morbidity including loss of ejaculatory function, lower extremity

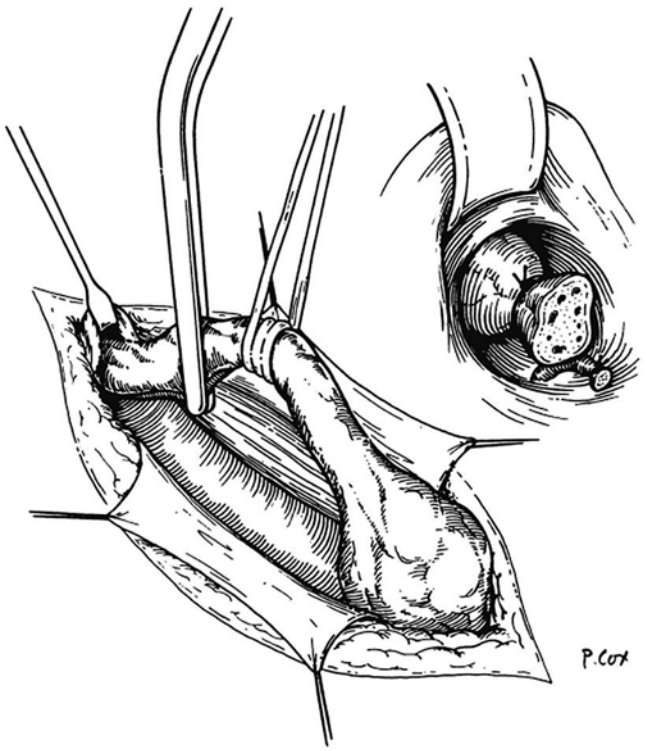

Fig. 20.6 Proximal control of the spermatic cord and orchiectomy through an inguinal incision

lymphedema, and intestinal obstruction [288]. Inguinal nodes are rarely involved and biopsy is performed only if the nodes are clinically positive or if the scrotum is invaded by tumor. Inguinal lymph node involvement is considered distant metastasis and thus, the patient is clinical group IV.

Most paratesticular RMS are embryonal, nonmetastatic, and highly curable with multimodal therapy including surgery, multiagent chemotherapy, and, for patients with retroperitoneal lymph node involvement or incompletely resected disease, radiation therapy [289]. The 3-year failure-free survival rate for paratesticular RMS is >81 % for all patients and >90 % for patients <10 years old [229]. Patients >10 years old and those with tumors >5 cm have significantly worse overall and event-free survival rates [290, 291].

Vulva, Vagina, and Uterus

Vulvo-vaginal and uterine RMS is the most common malignancy of the pediatric female genital system. Approximately half of all cases in the female genital tract arise in the vagina. This tumor generally presents in the first few years of life, with vaginal bleeding or blood-tinged discharge (66 %) and/or a vaginal mass (39 %) [292]. If the tumor arises from the vulva, it consists of a firm nodule embedded in the labial folds, or it may be periclitoric in location. On occasion, it may present as a labial hematoma related to trauma. Diagnosis is confirmed by vulvar or transvaginal incisional or excisional biopsy. Vaginal lesions usually have embryonal or botryoid embryonal histology and are associated with an excellent prognosis [178, 292–294]. Vulvar lesions may have alveolar histology, but most are localized and have a good prognosis. Thus, vulvar, vaginal and uterine RMS are considered favorable sites.

The management of these tumors has evolved from radical resection including pelvic exenteration in the 1970s and early 1980s to neoadjuvant chemotherapy followed by local control with surgery or radiotherapy in the past two decades [295]. The general management principles include biopsy and staging followed by chemotherapy as directed by pretreatment stage and clinical group. There is no role for initial management with radical surgery such as vaginectomy or hysterectomy [178]. Patients are followed with routine abdominal and pelvic MRI to determine tumor response and detect recurrence. Second look operations with biopsy and cystoscopy are common. Rhabdomyoblasts are evidence of chemotherapy response and should be treated with additional chemotherapy rather than surgical excision [178].

Vaginectomy and hysterectomy are performed only for persistent or recurrent disease, and vaginal and uterine salvage are achieved in greater than 40 % of cases [292]. If unresponsive to chemotherapy, primary uterine tumors require hysterectomy with preservation of the distal vagina and ovaries. Oophorectomy is only indicated for cases with direct tumor extension into the ovary. Lymph node involvement is very rare (5 %) and thus, pelvic lymph node dissection is not indicated [279, 296]. It is important to consider surgically relocating the ovaries to preserve fertility in girls who will receive radiation therapy to the lower abdomen and pelvis. In a recent COG-STS study, there was an unacceptably high rate of local relapse in patients with clinical group III vaginal tumors who did not receive radiation therapy, and therefore, it is recommended that all patients with residual, viable tumor receive radiation therapy [296, 297].

Prognosis for patients with loco-regional disease only is excellent with an estimated 5-year survival of 87 % [295]. However, more than half of women surviving treatment for pelvic RMS will have long-term endocrine, gastrointestinal, musculoskeletal, and urologic complications which commonly occur in the radiation field [298]. In addition, surgical complications may include rectovaginal fistula, vesicovaginal fistula, and urinary incontinence all of which are associated with significant morbidity [292].

Extremity

The most common extremity sarcoma in children is NRSTS accounting for 79 % of cases [67]. Only 21 % of extremity sarcomas in children and adolescents are RMS. The extremity is the primary site in 14 % of childhood RMS, and most are alveolar histology [3, 166]. The median age at presentation is 6 years, and it is evenly distributed between males and females [215]. Most children present with a painless mass or swelling but they may also present with a limp. The extremity is an unfavorable site, and therefore, all extremity RMS is at least a pretreatment stage 2 or greater. Approximately 30 % of patients present with nodal involvement and 35 % with distant metastases [67].

The initial workup includes a MRI of the primary tumor. CT is valuable to evaluate bone erosion and/or abdominal lymphadenopathy. Others suggest that ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) may improve pretreatment staging by evaluating for regional and distant metastases as well as detect viable disease or recurrence in a previously operated field [199–201, 299–302]. Incisional or excisional biopsy should be performed through a longitudinal or axial incision to allow for wide local excision of the primary tumor. The primary goal is wide and complete resection of the primary tumor with a surrounding rim of normal tissue while preserving form and function. There is no evidence that margins greater than 5 mm offer any advantage. In general, only pretreatment stage 2 (size <5 cm and no clinical evidence of nodal involvement) are amenable to primary surgical resection and even this is dependent on the location of the primary tumor. Amputation is rarely indicated except for bulky recurrent or persistent disease. Careful determination of margin status is extremely important, and re-resection

at initial or subsequent operation is warranted if a positive margin is present or suspected. Hays and colleagues demonstrated that patients with node negative extremity and trunk sarcomas who underwent re-excision for microscopic residual tumor had a significant survival advantage compared to patients who did not undergo re-excision or were reported to have no residual tumor after initial resection [209]. Thus, it is important to consider re-excision of the primary site after initial surgical resection for all node negative clinical group I and II patients.

For patients with tumors >5 cm or anatomic sites not amenable to primary surgical resection (hand, foot, groin, antecubital or popliteal fossa), an initial incisional biopsy is indicated. After diagnostic confirmation, the patient will receive multi-agent chemotherapy ± radiation therapy followed by a second-look procedure and resection of residual disease. Primary tumors of the hand and foot are especially challenging, and although current recommendations for local therapy include resection only if function can be preserved, some children still undergo amputation [303]. La and colleagues showed excellent local control using radiation therapy for patients with nonmetasatic RMS of the hand and feet [304]. They recommend either radiation therapy or definitive surgical resection that maintains form and function rather than amputation as primary local therapy in patients with hand or foot RMS [304].

Extremity RMS often has nodal involvement (30 %) which necessitates evaluation of the regional lymph nodes in staging of the tumor [166]. In a review of patients enrolled in IRS-IV, Neville and colleagues found that 50 % of biopsied lymph nodes were positive and that 17 % of patients with clinically negative lymph nodes were found to have microscopic nodal disease [215]. Nodal status is a significant predictor of failure-free and overall survival in patients with extremity RMS [215, 305]. Thus, it is imperative to adequately assess nodal involvement in extremity RMS as it will have significant prognostic and therapeutic implications. The COG-STS committee recommends evaluation of axillary nodes for patients with upper extremity tumors and inguinal and femoral triangle nodes for lower extremity tumors. If clinically positive nodes are present, biopsy of more proximal nodes is indicated. In-transit nodal disease may also play an important role. Failure to either sample or radiate the in-transit nodal site(s) is associated with an increase in in-transit failure (15 % versus 0 %) [304, 306]. Sentinel lymph node mapping has been used successfully to determine regional nodal involvement in children with extremity sarcomas [62, 63]. It offers a less invasive, but reliable alternative to aggressive or random lymph node sampling.

Despite intensive efforts of IRSG and now the COG-STS committee, outcome for children with extremity RMS remains suboptimal compared to children with RMS in more favorable sites. Overall 5-year survival is 56 % for all patients and 74 % for patients without metastatic disease [67, 307, 308]. Pretreatment stage and clinical group are highly predictive of failure-free survival in patients with extremity RMS [215]. Patients with complete resection or microscopic residual tumor have significantly better 3-year failure free survival compared to patients with advanced disease (clinical group I 3-year FFS 91 %, II 72 %, III 50 %, and IV 23 %) [215]. In a recent review of patients treated on IRS III and IV protocols, the 5-year failure-free survival was 31 % for patients with clinical group III alveolar or undifferentiated RMS at unfavorable sites and regional nodal involvement which is similar to patients with metastatic disease [210].

Other Sites

Trunk

RMS of the trunk comprises 27 % of childhood RMS cases and includes chest wall, intra-thoracic, paraspinal, and abdominal wall tumors [166]. Of truncal RMS, the chest wall is the most common primary site accounting for 61 % of cases [309]. These tumors usually present as asymptomatic, expanding soft tissue masses. The histology is more commonly alveolar and associated with a poor prognosis [310].

Although surgical excision is the mainstay of local disease control, it may not be feasible. In general, the surgical management of patients with truncal RMS should follow the guidelines used for extremity tumors which include wide local excision with negative margins and assessment of regional nodal status. Primary surgical resection is preferred in tumors <5 cm if negative microscopic margins are expected. It may be useful to perform preoperative lymphoscintigraphy and consider SLNB for patients with truncal RMS as the primary lymphatic drainage basin for truncal sites is often unclear. Very large truncal masses should undergo incisional biopsy followed by neoadjuvant chemotherapy prior to resection. For chest wall lesions, the biopsy should be performed longitudinal to the ribs.

For chest wall tumors, the resection includes the previous biopsy site (if present) and involved chest wall muscles, ribs, and underlying lung. On a review of COG data, the local recurrence of chest wall RMS is no different with an R0 compared to an R1 resection. Because of the efficacy of chemotherapy, microscopically positive margins did not affect outcome. Resection of rib periosteum instead of the entire rib, in select cases, should be considered [222]. Chest wall reconstruction often requires the use of prosthetic mesh, myocutaneous flaps and/or titanium ribs [214]. Thoracoscopy may be useful in determining the extent of pleural involvement and tumor extension to underlying lung [196]. Although RT may improve local control, it is associated with significant morbidity in this region including pulmonary fibrosis, decreased lung capacity, restrictive effects and scoliosis [311].

Paraspinal RMS is rare accounting for 3.3 % of cases entered on IRS I and II. These tumors present as an enlarging mass in the paravertebral muscle area and often invade the spinal extradural space [312]. They must be distinguished from extra-osseous Ewing's sarcoma which is more common in this area. Most patients present with tumors >5 cm and require neoadjuvant chemotherapy followed by surgical resection and postoperative RT.

Biliary Tract

Biliary RMS accounts for <1 % of all RMS. It usually presents at a young age (median 3.4 years) with jaundice and abdominal pain or swelling [313]. The histology is usually boytryoid which responds well to chemotherapy and RT without the need for aggressive surgical resection [314, 315]. Total resection is rarely feasible; however, the outcome is usually good despite residual disease after surgical resection. In a review of biliary RMS patients treated on IRS I-IV, Spunt and colleagues found that complete resection was rarely possible, external biliary drains significantly increased the risk of postoperative infectious complications and in general, the tumors responded well to multiagent chemotherapy and did not require aggressive surgical intervention [315].

Retroperitoneum and Pelvis

RMS of the retroperitoneum and pelvis are often unresectable at presentation due to the massive size of the tumor and extension into vital organs or vessels (Fig. 20.7a, b) [316]. More than 90 % of patients present with either clinical group III or IV disease [317]. Thus, initial biopsy is performed followed by neoadjuvant chemotherapy with or without RT then complete surgical resection. If possible, complete surgical resection offers a significant survival advantage compared to no surgical resection (73 % versus 34–44 %) [316]. In a review of IRS III-IV patients with group III retroperitoneal RMS, age <10 years at diagnosis and embryonal histology were favorable prognostic factors and in these patients, debulking prior to chemotherapy and RT proved beneficial [317]. Other studies have suggested that debulking of more than 50 % of tumor prior to the initiation of chemotherapy and RT is beneficial in patients with retroperitoneal and pelvic RMS [318]. The alternative is surgical resection following neoadjuvant chemotherapy.

Perineum and Perianal

Rhabdomyosarcoma (RMS) of the perineum or anus is a rare sarcoma of childhood that usually presents with advanced stage disease and a relatively poor prognosis. Although perineal and anal RMS is most often alveolar, histology does not affect overall survival for this site [196]. The majority (64 %) of patients present with clinical group III or IV disease and 50 % have lymph node involvement [319]. Late presentation can be due to unrecognized mass, or a perianal mass mistaken for an abscess or hemorrhoids. Resection is often challenging due to the proximity to the urethra and anorectum. It is important to preserve anal sphincter function and consider diversion for anorectal obstruction due to tumor. Regional lymph node evaluation with biopsy of clinically suspicious nodes or SLNB in cases without suspicious nodes is recommended. Age <10 years is an independent predictor of survival (71 % 5-year overall survival compared to 20 % for patients ≥10 years of age) [319].

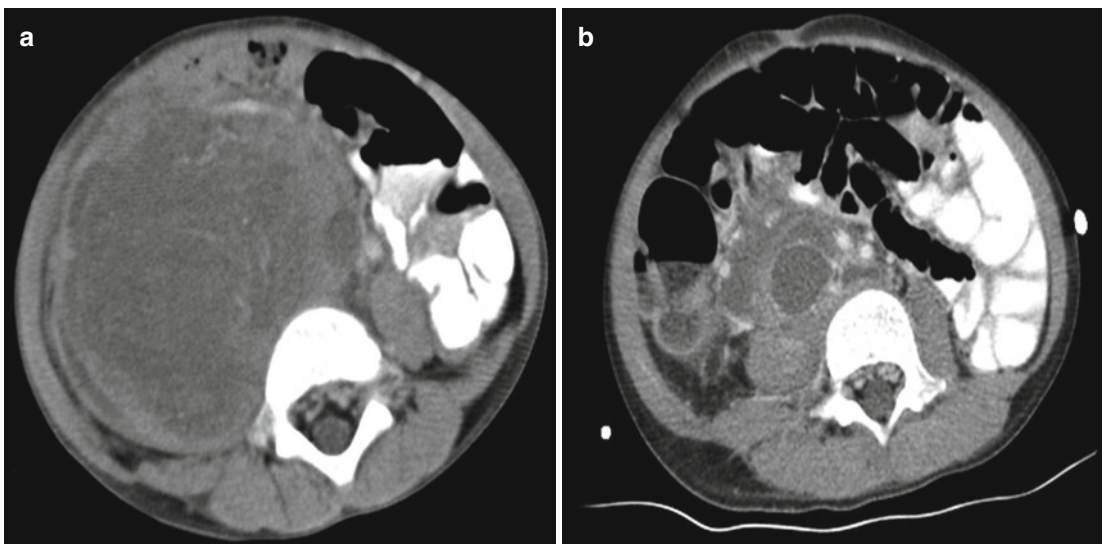

Fig. 20.7 (**a**) A 3 year-old girl presented with an enlarging, painless abdominal mass. CT abdomen and pelvis confirmed an 11.5×9.5×9.5 cm right retroperitoneal mass encasing the abdominal aorta. Open biopsy showed embryonal RMS, and she was started on VAC for stage 2, clinical group III, intermediate risk RMS. (**b**) Despite an initial response to chemotherapy and RT (shown in image), she developed progression intra-abdominal disease and later died

Outcome and Future Research

The overall 5-year survival for children and adolescents with RMS is 60 %; however, the prognosis for childhood RMS is multifactorial and cannot be summarized in a single survival statistic. Although metasatic disease is the single most important predictor of outcome, other factors play a significant role including patient age, tumor primary site and size, resectability, histopathologic subtype, and time to relapse [269, 320]. Biologic characteristics of the tumor cells, such as *PAX* gene rearrangements, are also important determinants of outcome [189]. Children ages 1–9 years have the best prognosis compared to infants and adolescents [229, 321, 322]. Tumor size is an integral prognostic indicator for RMS, and therefore, plays a major role in clinical grouping [55]. Patients with smaller tumors (≤5 cm) have improved survival compared to larger tumors; however, there is some evidence that the 5 cm cutoff used for adults may not be ideal for small children [55]. These factors are important in the designation of treatment groups for risk-based therapy.

Overall, FFS rates for the patients treated on IRS-IV did not differ from results in IRS-III (FFS rate 76 % versus 77 % for IRS-III and IV, respectively) [229]. FFS rates were improved for patients with embryonal rhabdomyosarcoma treated on IRS-IV compared to those of similar patients treated on IRS-III (3-year FFS rates, 83 % versus 74 %). The improvement seemed to be restricted to patients with stage II or stage II/III, clinical group I/II embryonal RMS. The sites of treatment failure were local in 93 patients (51 %), regional in 30 (17 %), and distant in 58 (32 %). Salvage therapy after relapse differed by group. Forty-one percent of the patients with group I/II tumors, compared with 22 % of those with group III tumors, were alive 3 years after relapse [229].

Overall survival for patients with low risk RMS is excellent. The results of IRS III-IV show that patients with non-metastatic tumors of embryonal histology arising from favorable sites (stage 1) and those with tumors in unfavorable sites (stages 2 and 3) that are grossly resected (clinical groups 1 and II) have very high 5-year failure-free survival (approximately 83 %) and overall survival (approximately 95 %) [229, 280, 320]. Thus, current research focuses on dose reduction in systemic therapy to hopefully decrease short- and long-term side effects while maintaining excellent survival for low risk RMS.

The overall survival for recurrent RMS is very poor. Approximately 30 % of patients with RMS will relapse, and 50–95 % of these patients die of progressive disease [280, 320, 323, 324]. In the IRS III, IV, and IV pilot, the 5-year survival for patients who experienced relapse after treatment was less than 20 %. Surgical resection did not impact survival in these patients. However, the results from other single-center studies support the use of aggressive surgical resection in select patients with relapsed RMS [318].

The overall trend has been an increase in survival for each subsequent IRS study; however very little if any progress has been made in the treatment of high risk RMS. Approximately 15 % of patients with RMS present with metastases at diagnosis [280]. Despite aggressive multimodality therapy, 3-year failure free survival is only 25 % in patients with metastatic disease [280, 324, 325]. Prognosis is slightly improved for patients with two or fewer metastatic sites and embryonal histology [226]. The current COG high risk protocol (ARST08P1) is evaluating the feasibility of using a fully human IgG1 monoclonal antibody targeting the Insulin-like Growth Factor-1 receptor (IGF-IR) as well as the addition of temozolamide, an alkylating agent, to the regimen with vincristine and irinotecan based on the synergistic effect of temozolamide plus irinotecan.

Multimodality therapy has improved outcomes for most children diagnosed with RMS. However, much work remains in the efforts to improve survival for patients with high risk disease. In the future, clinical trials will likely focus on the molecular biology that drives tumor behavior. All newly diagnosed patients with RMS should be considered for enrollment in ongoing biology and clinical trials. The surgeon plays a key role and must facilitate the collection and submission of fresh tissue for biology protocols. The success of these efforts will depend on the active participation of physicians from a multitude of disciplines including oncology, radiation therapy, and surgery. In the future, it may be possible to develop customized clinical therapies that improve survival in children and adolescents with RMS.

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