Soft Tissue Sarcomas

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Introduction

Soft tissue sarcomas (STS) are a very heterogeneous group of non-epithelial extraskeletal malignancies that are classified on a histogenic basis according to the adult tissue they resemble. Overall, STS are rare: with an annual incidence around 2–3/100,000, they comprise for less than 1 % of all malignant tumors and account for 2 % of total cancer-related mortality [1]. However, in pediatric age STS are relatively more frequent, accounting for 8 % of tumors.

- Rhabdomyosarcoma (RMS) represents about 50 % of STS of childhood and adolescence:
  - It is one of the typical embryonal tumors of childhood, composed by cells resembling normal fetal skeletal muscle.
  - It is always characterized by high grade of malignancy, local invasiveness, and a marked propensity to metastasize, to the point that all RMS patients should be assumed to have micrometastatic disease at diagnosis.
  - It is generally characterized by good response to chemotherapy (90 % response rate) and radiotherapy.
- The remaining 50 % of pediatric STS are usually grouped under the definition of "non-rhabdomyosarcoma soft tissue sarcomas" (NRSTS); these tumors represent more than three fourths of all STS in patients ages 15–19 years:
  - They are very rare tumors, some of them being peculiar of infants and small children, but most of the entities being really tumors more common in adults than in children.
  - They have a very heterogeneous clinical behavior, related to the different subtypes, but also to the different grade of malignancy;
  - Like their adult counterparts, they tend to be seen as being relatively insensitive to chemotherapy, though treatment strategies have changed to some degree in recent years and multiple-modality treatments including systemic chemotherapy have increasingly been attempted.

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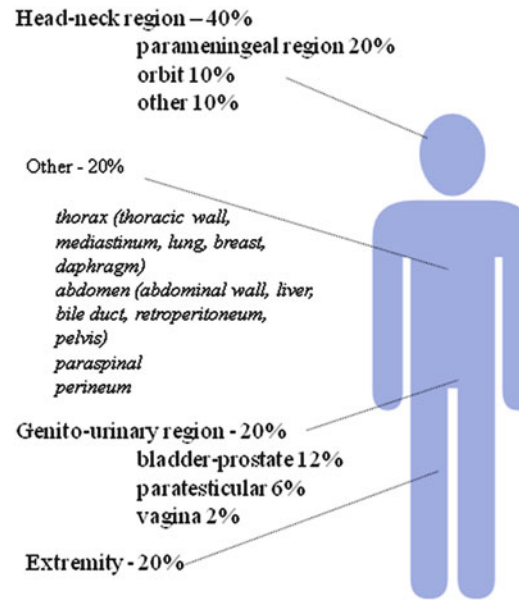
Rhabdomyosarcoma

RMS is a highly malignant mesenchymal tumor with a propensity to undergo myogenesis [2]. RMS can occur at any age, but its incidence declines significantly with increasing age (about three in four cases occur in children under 10 years old, with a first peak incidence in 3- to 5-year-olds and a second, smaller peak in adolescence) [3].

RMS is classically divided into the favorable histologic group of embryonal subtype (including the spindle cell and botryoid variants) and the unfavorable group of alveolar RMS [4]. Genetically, embryonal RMS is associated with loss of heterozygosity at 11p15, involving loss of maternal genetic information; the majority (80–85 %) of the alveolar RMS have the reciprocal chromosomal translocations t(2;13)(q35;q14) or t(1;13)(p36;q14). Recently, an European study demonstrated that fusion negative RMS, with histological aspects resembling alveolar RMS, are clinically and molecularly indistinguishable from embryonal tumors [5].

RMS is not usually associated with genetic syndromes; however, increased incidence has been reported with neurofibromatosis type 1, Li Fraumeni syndrome, Costello syndrome as well as genitourinary congenital anomalies [6].



5-year overall survival of RMS by site

Location	5-year OS
Paratesticular-vagina	90-95%
Orbit	85-90%
Bladder/prostate	75-80%
Parameningeal	70%
Other	60-65%
Extremities	55%

Fig. 21.1 Distribution of primary sites of rhabdomyosarcoma and survival according to tumor location

Clinical Presentation

RMS can arise anywhere in the body and it is generally characterized by local aggressiveness and a propensity to metastasize. The most common locations are the head-neck region (i.e., parameningeal and orbital sites) and the genitourinary tract (i.e., bladder and prostate, vagina, paratesticular region) (Fig. 21.1). The most common presentation is a painless mass. Other presenting symptoms depend on the site of origin: pain could arise at any location; proptosis, nasal obstruction, hemorrhagic discharge, and cranial nerve palsies are typical symptoms of head-neck RMS; hematuria, polypoid vaginal extrusion of a mass, and painless scrotal mass are typical presentation of genitourinary RMS; ascites and gastrointestinal, or urinary tract obstruction could be associated to intraabdominal RMS. Symptoms related to distant metastasis depend on the site and size or degree of involvement.

Different tumor sites may be associated to different RMS subtype: botryoid histology is seen commonly in the mucosa of the female genital tract and in the head and neck region of young children, while alveolar RMS is common in the extremities of adolescents.

Regional lymph node dissemination is present in around 20 % of cases (it is higher in alveolar RMS, in adolescents, and in tumor of the extremities). Distant metastasis is present in 15–25 % of newly diagnosed patients, lung being the most common site of hematogenous metastasis (40–50 %), followed by bone marrow (10–20 %) and bone (10 %).

Table 21.1 Approach to patients with rhabdomyosarcoma before initiating treatment

Collect data at diagnosis	*Patient*	*Physical exam*	*Imaging studies*
	Age	Lymph node (special sites: neurological exam to detect cranial nerve palsy in parameningeal RMS)	Local imaging (MRI/CT)
	Nutritional status		*Distant metastases stage*
	Tumor		Chest CT
	Size (< or ≥5 cm)		Bone scan
	Site (see below)		*Other studies*
			Bone marrow biopsies
Tumor site	Favorable	Orbit	
		Head-neck non-parameningeal	
		Genitourinary non-bladder/prostate	
	Unfavorable	Parameningeal	
		Extremities	
		Other sites: trunk, chest, abdominal wall, etc.	
TNM classification	*T1* and *T2* based on local invasiveness	*N0*/*N1* and *M0*/*M1*: absence or presence of nodal and distant involvement	
	A or *B*, i.e., less or more than 5 cm		
Assess regional lymph nodes	Physical exam	All tumors	
	CT/MRI	Important for pelvic and extremity tumors	
	Sentinel node biopsy	Consider for extremity tumors	
	Retroperitoneal sampling	Consider for paratesticular tumors	
Assess resectability	Resectable	Conservative complete excision with negative margins	
	Unresectable	Biopsy only	
Extent of resection	*IRS grouping*		
	Group I	Completely excised tumors with negative microscopic margins	
	Group II	Grossly resected tumors with microscopic residual disease and/or regional lymph nodal spread	
	Group III	Gross residual disease after incomplete resection or biopsy	
	Group IV	Metastases at onset	
Histology	Favorable	Embryonal, spindle cell, botryoid	
	Unfavorable	Alveolar	
Before proceeding to treatment, we should have the following information	1. Imaging of primary tumor (essential for radiotherapy planning)		
	2. Full surgical report		
	3. Pathology data (histology and margins)		
	4. Lymph node assessment if needed		
	5. Metastatic work-up done (chest CT, bone scan, bilateral bone marrow biopsies)		
	6. Stage		

RMS rhabdomyosarcoma, *MRI* magnetic resonance imaging, *CT* computed tomography scan, *TNM* tumor node metastases, *IRS* Intergroup Rhabdomyosarcoma Study

Diagnosis, Risk Stratification, and Prognosis

Table 21.1 describes initial diagnostic work-up and information needed before proceeding to treatment. Ultrasonogram is often the first instrumental assessment to be used. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the primary site is mandatory for the local extension assessment before any treatment (MRI could be considered superior in defining soft tissue extension). Distant assessment requires chest CT scan,

Table 21.2 Children Oncology Group (COG) risk stratification

Risk	Estimated 5-year EFS (%)	Description	Current treatment
Low risk	90	Nonmetastatic embryonal tumors	Subset 1: VAC × 4 cycles followed by VA for a total of 24 weeks
		Except intermediate risk	Subset 2: VAC
Intermediate risk	65–73	Nonmetastatic embryonal tumors in unfavorable locations (stage 2 or 3) with incomplete resection (clinical group III) *and* All nonmetastatic alveolar	VAC
			ARST0531 study randomizes patients between VAC and VAC + VI
High risk	<30	All metastatic	ARST0431 backbone (benefit with multiagent chemotherapy with interval compression—dose-density: VAC + VDC + VI + IE)

VAC vincristine + actinomycin-D + cyclophosphamide, *VI* vincristine + irinotecan, *VDC* vincristine + doxorubicin + cyclophosphamide, *IE* ifosfamide + etoposide

Technetium bone scan, abdominal ultrasound, and bone marrow aspiration plus trephine biopsy, to identify lung, bone, abdominal, and bone marrow dissemination, respectively. Special sites may require particular evaluations, i.e., cerebrospinal fluid cytology in parameningeal RMS, to assess meningeal dissemination; regional lymph node biopsy in extremity RMS; retroperitoneal lymph node sampling in paratesticular RMS older than 10 years [7–9].

The initial biopsy (incisional biopsy or trucut) has the aim to define the histological diagnosis and should be the initial surgical procedure in all patients, also when a subsequent primary excision is planned. Initial biopsy must be carefully planned by experienced surgeons, taking into account the possible subsequent definitive surgery, which must include the scar and the biopsy tract (for example, in RMS of the extremities, the incision must be longitudinal to the limb and not traverse multiple compartment; very careful hemostasis must be ensured to avoid post-surgical hematoma and drains).

The prognosis of RMS depends on multiple factors, including age, primary tumor site and size, lymph node involvement, histology, surgical resection, and distant metastasis. In the past 30 years, the cure rates for RMS have improved dramatically from 25 to 30 % (before the modern chemotherapy-era) to approximately 70 %, due to the development of multidisciplinary and risk-adapted treatment approaches conducted by International cooperative groups. Of course, not all patients with RMS fare well with modern therapies. Patients with alveolar histology continue to have less than optimal outcome. Most patients with distant metastasis do not achieve long-term cure and may benefit of more intensive treatment and are candidates for experimental treatment with novel agents [10].

With the identification of different prognostic factors [11–16], risk assessment has now become more complex, but also more accurate. The approaches of Children Oncology Group (COG) (Table 21.2) and European pediatric Soft Tissue Sarcoma Study Group (EpSSG) (Table 21.3) for risk stratification use similar principles but with different approaches. The EpSSG, for example, identifies low, standard, high, and very high-risk groups (with eight subgroups) for localized RMS, plus the group of metastatic RMS cases; the EpSSG high-risk group grossly corresponds to the COG intermediate-risk group.

Table 21.3 European pediatric Soft Tissue Sarcoma Study Group (EpSSG) RMS 2005 risk stratification

Risk group	Subgroup	Pathology	Postsurgical stage	Site	Node stage	Size and age	therapy
Low risk	*A*	Favorable	I	Any	N0	Favorable	VA
standard risk	*B*	Favorable	I	Any	N0	Unfavorable	IVA + VA or IVA ± XRT
	C	Favorable	II, III	Favorable	N0	Any	
	D	Favorable	II, III	Unfavorable	N0	Favorable	
High risk	*E*	Favorable	II, III	Unfavorable	N0	Unfavorable	*First random*: IVA + XRT vs. IVADo + XRT
	F	Favorable	II, III	Any	N1	Any	*Second random*: maintenance[a] vs. stop therapy
	G	Unfavorable	I, II, III	Any	N0	Any	
Very high risk	*H*	Unfavorable	I, II, III	Any	N1	Any	IVADo + XRT + maintenance

VA vincristine + actinomycin-D, *IVA* ifosfamide + vincristine + actinomycin-D, *IVADo* ifosfamide + vincristine + actinomycin-D + doxorubicin, *XRT* radiotherapy

[a]Maintenance chemotherapy: vinorelbine and low-dose oral cyclophosphamide

Treatment

RMS is a rare tumor and its treatment is necessarily multidisciplinary and complex. The overall multimodality treatment strategy involves surgery, radiotherapy, and chemotherapy, and it is important that the optimal intensity and timing of these treatment modalities should be planned with regard to the patients' risk stratification and late effects of treatment. In particular, radiotherapy needs to be used with caution in children, given the important sequelae of these treatments. For example, survivors after parameningeal RMS (requiring full doses and large volume of radiotherapy) have a high risk of facial growth retardation (bone and soft tissue hypoplasia, facial asymmetry), but also dental abnormalities, neuroendocrine dysfunctions (growth hormone deficiency, hypothyroidism), visual problems, hearing loss.

Chemotherapy

The VAC regimen (vincristine, actinomycin-D, cyclophosphamide, given at 1.2 mg/m^2/cycle) is the gold standard for chemotherapy for RMS in North America. On the other hand, the standard in Europe is considered the IVA regimen (ifosfamide, given at 6 g/m^2/cycle, vincristine, actinomycin-D), which differs only in the choice of alkylating agent—probably producing a slightly different pattern of hematological, renal, and gonadal toxicity. The Intergroup Rhabdomyosarcoma Study (IRS)-IV study found no differences in survival rates in a randomized comparison between VAC and IVA [17]. The duration of treatment is currently 6–12 months according to different protocols.

As mentioned above, the risk stratification as adopted by the collaborative groups directs the treatment direction. In the COG most recent low-risk RMS trial (ARST0331), patients with subset I (Table 21.2) had an excellent outcome (2 year EFS, 88 %; OS, 98 %) with short therapy duration (22 weeks) and a low cumulative dose (4.8 g/m^2) of cyclophosphamide. On the other hand, subset 2 had a 3-year EFS of 66 % using low dose of cyclophosphamide [18]. This group had better outcome on the previous protocols with standard doses of cyclophosphamide.

The COG intermediate-risk/EpSSG high-risk RMS category is currently treated with the standard VAC or IVA regimen. Adding other agents to these regimens by collaborative groups did not result in significant impact to survival, so far. Among other drugs that were tested, camptothecin derivatives (topoisomerase I inhibitors) showed the best outlook. Addition of topotecan to the standard VAC regimen for intermediate-risk

RMS failed to show benefit [19]. Nevertheless, the more promising drug, irinotecan, combined with vincristine is being evaluated in combination with the VAC regimen in the same population of patients.

Doxorubicin is an effective drug in RMS, but the role of anthracyclines as part of a multidrug regimen remains somewhat controversial. For that reason doxorubicin is being evaluated in the current EpSSG trial (Table 21.3). It was also added to the COG high-risk RMS trial ARST0431 which is currently used as a backbone for future trials in high-risk patients [10]. Of note, this regimen incorporated irinotecan/vincristine and ifosfamide/etoposide and used an approach of "dose-compression"—increase of chemotherapy dose intensity and dose density by administering chemotherapy cycles at 2-week interval instead of the usual 3-week interval—similar to that used successfully for Ewing sarcoma [20]. In fact, the prognosis of metastatic RMS remains poor and their management is the subject of ongoing trials. The limited pool of these patients makes it difficult to conduct randomized trials to answer critical questions, but it is agreed that treatment intensification is warranted for this group of patients. High-dose, myeloablative chemotherapy, followed by autologous stem cell rescue, has been variously attempted in metastatic RMS patients. Weigel et al. reviewed 389 patients reported in the literature who underwent myeloablative chemotherapy for metastatic or recurrent RMS [21] and found the outcome much the same as in reports on metastatic patients given conventional therapy [22, 23]. This approach remains experimental and should not be considered as a standard approach for patients with high-risk RMS.

Finally, a potentially interesting option is that of maintenance therapy (metronomic therapy, i.e., regular, frequent administration of low doses of drug with the aim to achieve an antiangiogenic effect). Currently, the approach of a 6-month maintenance therapy comprising a combination of vinorelbine and low-dose oral cyclophosphamide is under investigation in the EpSSG RMS trial for high-risk patients [24] (Table 21.3).

Possible complications of chemotherapy should be always taken into account. The VAC regimen has serious toxicity that might be exploited in malnourished and very young population. Some of these toxicities are tolerable, including neuropathy that is commonly observed after weekly administration of vincristine. Neutropenia is often observed but is less expected if lower doses of cyclophosphamide are used [25]. A very serious complication is hepatopathy, in the form of veno-occlusive disease (VOD) [26]. This potentially fatal complication is observed mainly in children less than 3 years of age and warrants careful dosing of vincristine and actinomycin-D in this group. Acute and late cardiotoxicity is a known complication of doxorubicin.

Radiotherapy

Radiotherapy is the mainstay of treatment in RMS, since local progression or relapse continues to represent the major cause of treatment failure. Radiotherapy is generally delivered to the pretreatment tumor volume with doses generally ranging between 40 and 55 Gy [17, 27–35]. Three-dimensional conformal radiotherapy—if available—may reduce the long-term toxicity by avoiding unnecessary exposure to vital structures. Similarly, intensity-modulated radiotherapy (IMRT), proton radiotherapy, and interstitial brachytherapy may provide adequate local control with better delineation of the treatment area, and hence, decreased toxicity.

Various issues on radiotherapy in RMS remain to be clarified: should all patients with RMS receive radiotherapy? Can the dose of treatment be modified based on response to treatment and delayed surgical resection? Is it possible to reduce the volume of radiotherapy based on new tumor volume following treatment with chemotherapy and/or surgery?

As for the first question, there is a general consensus that radiotherapy may be omitted in IRS group I patients (initial complete resection) with favorable histology, whereas it must be always required for alveolar histotypes. COG protocols suggest radiotherapy for all RMS patients except

for IRS group I embryonal RMS [30], while in European groups it is more debated the indication of radiotherapy in IRS group III patients (patients with initially unresected tumor) after delayed complete surgery or after complete remission to initial chemotherapy, for those tumors arising in particularly favorable sites (i.e., orbit or vagina), especially for young children.

As for the second question, COG recently published its experience with dose reduction (up to 36 Gy) in patients with low-risk embryonal RMS, based on completeness of surgical resection of the primary tumor. Local control was adequate when cyclophosphamide was given (patients treated with VAC regimen), but the analysis suggested that radiotherapy dose reduction should be avoided in patients treated with two drugs only (VA) [34].

The third question remains unanswered: it has been suggested that volume reduction (from the pre-chemotherapy to the post-chemotherapy volume) may be potentially safe (but not for parameningeal cases) [35], but to date the standard treatment volume should remain the pre-chemotherapy one, except for very selected situations (e.g., large pelvic or chest wall tumors where pretreatment volume radiation exposes normal structures to untolerable doses of radiation).

Surgery

Surgery for RMS has evolved over the years from the primary treatment modality (prior to the introduction of effective antineoplastic agents) to one component of a multidisciplinary approach, and from an aggressive surgery to a more conservative organ-sparing procedures, to the point that chemotherapy and radiotherapy may permit in some cases to cure the disease without any surgery (i.e., patients with parameningeal RMS).

Surgery with risk of anatomic or functional impairment is not recommended as first surgical approach and should be considered only as salvage treatment, after the failure of other procedures (special circumstances must be considered, however, e.g., a lower extremity RMS in a toddler, the choice between amputation and radiotherapy, with its long-term effects on limb growth, may pose a difficult dilemma). Tumors considered unresectable at diagnosis can be conservatively and completely resected in a large percentage of cases after tumor shrinkage achieved by primary chemotherapy. Wide resections are generally considered adequate to obtain local control, differently from adult STS that in general should require compartmental resection. In case of primary marginal resection, primary re-operation (prior to any other treatment) is recommended when feasible, hoping to achieve clear margins and proving the absence of microscopic residue in order to avoid radiotherapy [36].

Recently, a possible role for debulking procedure has been suggested for huge retroperitoneal and pelvic RMS [37]. This issue remains, however, controversial, particularly when these surgeries necessitate mutilation. What to do in cases of masses that remain after finishing treatment is debatable; biopsy may cause difficulty in interpreting results, in particular when mature rhabdomyoblasts are detected [38, 39].

Finally, surgery of positive regional lymph nodes is generally considered a diagnostic procedure: any involved lymph nodes warrant radiotherapy, so initial radical lymphadenectomy (which carries a high risk of morbidity) is unnecessary.

Special Situations

Orbital RMS

Orbital RMS carries an excellent outcome, probably reflecting favorable biological behavior combined with early diagnosis because of the location. Embryonal histology is present in approximately 90 % of these cases [40]. The surgical approach to these patients is limited to initial biopsy. Complete resection or exenteration is limited to patients who have local failure following radiotherapy. In a review of pooled data from different studies conducted in Europe and North America, the 10-year EFS and OS were 77 % and 87 %, respectively. Eighty percent of patients received radiotherapy as part of primary therapy. Although more patients who did not receive radiotherapy had local relapse, OS was excellent

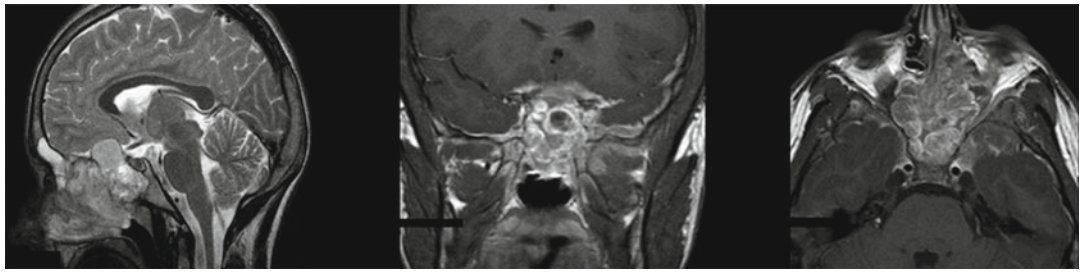


Fig. 21.2 Magnetic resonance imaging of a 13-year-old patient with a huge alveolar rhabdomyosarcoma arising from nasopharynx/nasal cavity and sphenoidal region, with cranial base bone erosion, intracranial extension, and meningeal diffusion

regardless of the use of radiotherapy, since many relapsing cases were salvaged with radiation and more systemic chemotherapy [40]. The current recommendation in COG protocols is to treat these patients with radiotherapy (reduced dose of 45 Gy), while in Europe the use of radiotherapy is left to the discretion of the treating institution (recommended in Italy and not in France).

Parameningeal RMS

This group of tumors arising in middle ear/mastoid, nasopharynx/nasal cavity, parapharyngeal space, paranasal sinuses, pterygopalatine, and infratemporal fossa region represents a special challenge (Fig. 21.2). Complete resection is rarely feasible even after chemotherapy (difficult accessibility parameningeal sites, risk of mutilation) and radiation therapy must imply high-doses and wide fields, with risk of serious sequelae, in particular in young children. Initial attempts to improve survival by cranial radiotherapy or intrathecal chemotherapy were of no proven value [41]. The cornerstone of local control remains well-planned conformal radiotherapy, though recently, IMRT and proton radiotherapy emerged as viable choices for better delivery of radiation without compromising outcome [42, 43]. COG recommend early radiotherapy (<2 weeks after initiating systemic treatment) in patients with meningeal impingement (defined as cranial nerve palsy, cranial base bone erosion with or without intracranial extension). Despite increased long-term morbidity in infants and toddlers, radiotherapy remains necessary to achieve local control [44].

Paratesticular RMS

Paratesticular RMS generally have a good prognosis, in the range of 90 % survival [7]. This is probably due to the peculiar superficial location that allows early diagnosis and complete surgery in most cases, but perhaps also due to a general favorable biology (the adverse prognostic role of alveolar subtype would be counterbalanced by the favorable site, for example) [45].

Paratesticular RMS should be resected, associated to orchidectomy, via an inguinal excision. European groups do not require surgical evaluation of retroperitoneal lymph nodes as routine staging procedure in paratesticular RMS [7], while biopsy is recommended in COG study in patients over 10 years old, considered at major risk to nodal involvement.

Bladder/Prostate RMS

These tumors are typically seen in young patients. Bladder tumors tend to grow intraluminally (Fig. 21.3), in or near the trigon. Prostate tumors usually produce large pelvic masses. Historically, the best approach for local control was believed to be complete excision with margin clearance, which was often pelvic exenteration or aggressive resection with serious complications. However, whether this approach should be always required remains debatable [46], and in some cases a less aggressive surgery with organ preservation may be considered a better option. Brachytherapy may be indicated, providing adequate local control with least morbidity [47].

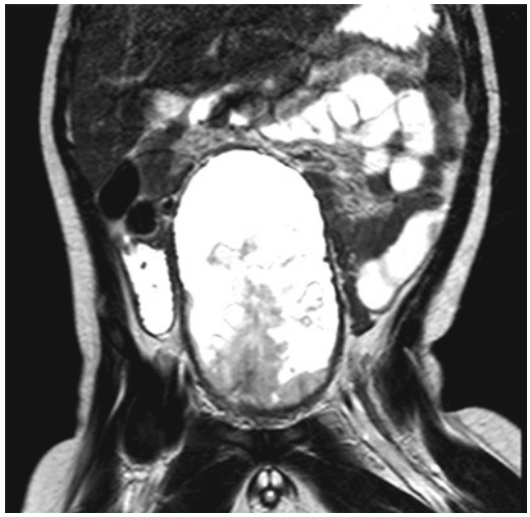


Fig. 21.3 Magnetic resonance imaging of a 2-year-old patient with an embryonal rhabdomyosarcoma of the bladder: the tumor grew intraluminally to completely fill the organ

Young Patients

Patients less than 1 year old at diagnosis continue to have worse prognosis in comparison to older children (1–10 years old). Whether this is the result of different biology of the tumor or treatment modifications that are practiced (e.g., reduction of chemotherapy does, omission of radiotherapy) is not clear yet [48, 49]. Practical general roles in the management of infants with RMS may be the following:

- Careful dosing of chemotherapeutic agents to avoid hepatotoxicity (e.g., VOD).
- In case of initial reduction of chemotherapy doses, these should be increased in subsequent cycles if therapy has been well tolerated.
- Maximum surgical resection to compensate for the high complication related to radiotherapy: amputation may be considered for extremity unresectable tumors since the long-term functional outcome of an irradiated limb may be much worse than amputation.
- Careful planning of radiotherapy; although decreasing treatment volume is not well established based on available data, the decision to decrease volume should lean toward reducing toxicity in this age group.
- When decisions are made to decrease treatment, survival should remain as the main target of treatment. This was shown by the International Society of Pediatric Oncology—Malignant Mesenchymal Tumour Committee (SIOP-MMT) approach to young children with parameningeal tumors, where treatment reduction resulted in unacceptable low survival [44].

Relapsed RMS

Relapsing patients remain one of the greatest challenges in the management of RMS. Approximately, one third of these patients can be expected to be alive at 3 years. Actual long-term cure remains to be possible in a minority of patients, in particular, those who relapse locally and did not receive radiotherapy as part of their initial therapy fare better [50]. Aggressive surgery and second-line drugs should be considered; however, it may be said that in countries with limited resources, treating patients with recurrent metastatic disease may be generally of little value, unless it is directed to proper palliative care.

Challenges in Developing Countries

It is generally considered that the therapeutic standards achieved in developed countries in RMS are unlikely to be reproduced in low-income countries, due to the differences in health infrastructures and training, the limited availability of some active drugs and supportive care to face life-threatening toxicities of modern chemotherapy, and the poor treatment compliance by patients. Nevertheless, the quality of care in developing countries is rapidly increasing.

A limited number of RMS series in developing countries has been published [25, 51–55] (Table 21.4).

Multiple factors seem to have a role in affecting RMS patient outcomes in developing countries. In addition to the general socio-economic factors that adversely affect the care of children with cancer in countries with limited resources, negative factors that may be more specific for RMS include:

Table 21.4 Published rhabdomyosarcoma series by developing countries

Study	Country	Number of pts	Results	Comments
Al-Jumaily et al. [25]	Jordan	45 pts	4-year PFS = 61 % 4-year OS = 72 %	Improved outcome in more recent years with
Badr et al. [54]	East Egypt	41 pts	FFS = 68 % OS = 57 %	Metastatic disease = 39 %
Wood et al. [51]	South Africa	49 pts with genitourinary RMS	OS = 65 % Better in pts treated after 1992 (80 %)	More advanced tumors compared to the literature
Friedrich et al. [53]	Central America	240 RMS among 785 pts with sarcoma	4-year EFS = 33 % 4-year OS = 44 %	High rate of metastatic disease at diagnosis; treatment abandonment = 25 %
Hessissen L et al. [52]	Morocco	100 pts	10-year EFS = 39 % 10-year OS = 70 %	Treatment abandonment = 37 %
Antillon F et al. [55]	Guatemala	47 pts	3-year EFS = 26 % 3-year OS = 43 %	Difficulties in local control; abandonment = 30 %
Shouman et al. [56]	Egypt	190 pts	5-year FFS = 40 % 5-year OS = 50 %	No standardized protocols

RMS rhabdomyosarcoma, *PFS* progression-free survival, *OS* overall survival, *FFS* failure-free survival, *EFS* event-free survival *pts* patients

1. The problem of delayed diagnosis and advanced stage of disease at diagnosis, related to the difficulty in referral to specialized centers and the poor access to healthcare in general; delay in diagnosis in RMS has been demonstrated to be a significant prognostic factor [57].
2. The high percentage of abandonment of treatment prior to its completion (particularly when transportation is a challenge), probably due to refusal to radical local control and the need for long treatment plan.
3. Intensive chemotherapy toxicity; patients with malnutrition are at particular risk, and the lack of supportive care including the lack of well-equipped intensive care units and the cost of growth factors make it difficult to provide treatment for high-risk patients.
4. The poor quality of local control, potentially related, in principle, to the quality of radiotherapy techniques, the personal experience of radiotherapists and surgeons, the nonoptimal multimodal interaction between radiotherapists, surgeons, and pediatric oncologists in defining local procedures.

Many initiatives and intervention programs are considered in order to improve early diagnosis and decrease abandonment rates, i.e., public information and education programs to improve awareness at various levels (patient, community, healthcare system) and facilitating early referrals to medical care, social worker program to strongly support the families, including financial assistance, the development of satellite pediatric oncology units to facilitate treatment of patients in rural areas.

The current programs of partnership with groups of healthcare providers in the developed countries may prospectively improve quality of care in countries with limited resources. Establishing a continuous cooperation with international experts to discuss difficult cases may be of great importance. Programs involving telemedicine, in particular tele-pathology, may be

considered and can potentially have a major impact on outcome.

Concerning more specifically the management of RMS patients, possible suggestions may be as follow:

- Establish multidisciplinary teams that meet regularly to discuss these patients. Particular attention should be given for the best planning of local treatments. Involve surgeons and radiotherapists in the programs. All RMS cases should be considered as "difficult" case and discussed accordingly.
- Simplify stratification. Use the standard therapy for most cases. Avoid reduction of therapy (e.g., VA chemotherapy in low-risk cases) because of the risk of inadequate staging accuracy.
- Use shorter duration of treatment when possible (e.g., 6 months instead of 12 months) and lower doses of cyclophosphamide (1.2 g/m^2) to prevent unnecessary exposure to higher dose.
- Try to provide definitive therapy in first-line therapies. For example, protocols that try to minimize radiation in upfront treatment rely heavily on close surveillance to identify early local relapses; this might not be practical in places where patients might be lose for follow-up.
- Establish palliative care programs that handle patients with poor outcome, e.g., relapsed patients.

Non-rhabdomyosarcoma Soft Tissue Sarcoma

The term NRSTS describes a group of very heterogeneous malignant tumors with different biology and clinical history, classified on the basis of their differentiation according to the adult tissue they resemble [58]. Whether these tumors originate from a mesenchymal stem cell or from a less primitive precursor committed to a differentiative lineage is still unknown. However, the current WHO classification (WHO 2002) [59] describes soft part tumors as adipocytic tumors (e.g., liposarcoma), fibroblastic/myofibroblastic tumors (e.g., fibrosarcoma), fibrohistiocytic tumors (e.g., pleomorphic sarcoma), smooth muscle tumors (e.g., leiomyosarcoma), perivascular tumors (e.g., the so-called PEComa, perivascular epithelioid cell tumors), skeletal muscle tumors (e.g., rhabdomyosarcoma), vascular tumors (e.g., epithelioid hemangioendothelioma, angiosarcoma), chondro-osseous tumors (e.g., mesenchymal condrosarcoma), and the vast group of tumors of uncertain differentiation (including synovial sarcoma, epithelioid sarcoma, alveolar soft part sarcoma, and many other subtypes). The WHO classification also recognizes three prognostic categories: benign tumors, malignant tumors, and tumors with intermediate prognosis (locally aggressive and rarely metastasizing). NRSTS are malignant tumors by definition. There are often clinical and histologic overlaps between these forms, making their diagnosis particularly challenging and complex. Although the diagnosis is based on morphology, the widespread use of immunohistochemistry with specific lineage markers and the identification of cytogenetic and molecular genetic abnormalities have contributed to a more precise classification and to a better understanding of the mechanisms involved in tumor development and prognosis. A modern view divides STS according to their genomic and expression: (a) sarcomas with specific translocation, (b) sarcomas with specific activating or inactivating mutations, (c) sarcomas with 12q13-15 amplification, and (d) sarcomas with a complex genomic profile [60].

Clinical Presentation

Similarly to RMS, NRSTS can arise anywhere in the soft part of the body: the most common clinical presentation is that of a painless growing mass localized at lower extremities (Fig. 21.4); less frequent sites are the trunk or the head and neck region.

Their destructive local behavior and the propensity to local relapse, as well as their tendency to give distant metastases, may widely vary and are correlated to the different degree of malignancy along histotype and tumor grade. Some NRSTS can grow rapidly and present at diagnosis with

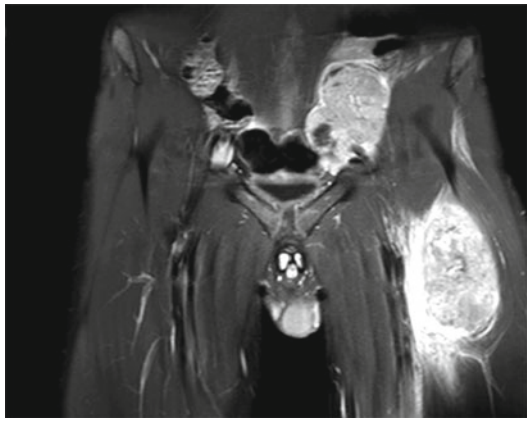


Fig. 21.4 Magnetic resonance imaging of a 16-year-old boy with a malignant peripheral nerve sheath tumor (MPNST) of the thigh, with regional lymph nodal involvement

lung metastases, other tumors may have an indolent course, being diagnosed after removing a small swelling that has existed for several years. Generally, low-grade tumors are often locally aggressive, but unlikely to metastasize, while high-grade tumors are more aggressive and have a strong propensity to metastasize, particularly to the lung [61–64]. The two most widely used grading systems for NRSTS in pediatric age are the POG (Pediatric Oncology Group) system [65] and the FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) system [66], which identify three grade of malignancy according to tumor resemblance to its normal counterpart, mitotic activity, and necrosis. However, some histotypes (i.e., synovial sarcoma, alveolar sarcoma, angiosarcoma) should be considered high-grade regardless of their morphological parameters, whereas in some cases (i.e., clear cell sarcoma, extraskeletal myxoid chondrosarcoma) the biological course seems impossible to predict from histological features.

In some cases, different histotypes with the same grade of malignancy may display the same clinical behavior. Other histotypes differ significantly for their natural history. As examples, malignant peripheral nerve sheath tumors (MPNST) occur most frequently at axial sites and are characterized by high local aggressiveness and poor prognosis, particularly when associated to neurofibromatosis type 1 (NF1) [67]; epithelioid sarcomas present typical features such as peculiar superficial distal location (i.e., hand, fingers), indolent growth, and tendency for lymph node involvement [68]; desmoplastic small round cell tumors (DSRCT) usually present as a large abdominal mass already disseminated to all the abdomen at the time of diagnosis, and the outcome is extremely poor [69]. Table 21.5 summarizes biological and clinical features of some NRSTS subtypes.

A particular group of mesenchymal tumors of infancy is represented by fibroblastic-myofibroblastic tumors of intermediate prognosis: desmoid-type fibromatoses, infantile fibrosarcoma, and inflammatory myofibroblastic tumor are locally aggressive tumors that rarely metastasize; they often appear as large, rapidly growing tumors infiltrating adjacent structures, but in some cases also spontaneous regressions have been described. They are potentially curable disease, but managing them is often a challenge in terms of their correct diagnosis and appropriate treatment [70]. In the last years, the treatment approach to these tumors has changed to some degree, taking into account the risk of severe iatrogenic anatomical and functional sequelae, i.e., from aggressive surgery to a multidisciplinary approach that involves a minimal-morbidity systemic treatment (e.g., mild chemotherapy containing no alkylating agents or anthracyclines for infantile fibrosarcoma) [71, 72] or also wait-and-see strategy for desmoid-type fibromatosis [73].

Diagnosis, Risk Stratification, and Prognosis

The diagnostic work-up for NRSTS is similar to that of RMS. Children presenting with an atypical soft tissue mass always require prompt attention and a multidisciplinary expert evaluation; the physician who first see the patient (sometimes pediatric dermatologist, vascular surgeon) should consider consulting a pediatric oncologist even before any precise diagnosis has been established. Benign lesions may mimic malignant diseases and vice versa and, for example, no

Table 21.5 Distinctive clinical and biological features of some NRSTS subtypes

Histotypes	Molecular findings	Clinical characteristics and outcome
NRSTS subtypes typical of infants		
Infantile fibrosarcoma	t(12;15;)(p13;q25)	Rapid growth
	ETVG (TEL)-NTRK3 (*as mesoblastic nephroma*)	Relatively high chemosensitiveness (also to alkylating and anthracyclines-free regimens)
		Overall good prognosis (overall survival in the 90 % range)
Extracranial extrarenal rhabdoid tumor	Mutated hSNF5/INI 1 gene	Highly malignant tumor arising in kidney or soft part
		Poor prognosis
		Intensive multiagent chemotherapy
NRSTS subtypes typical of adolescents and young adults		
Synovial sarcoma	t(X;18)(p11;q11)	Most frequent NRSTS subtype in pediatric age
	SYT-SSX1, SYT-SSX2, SYT-SSX4	Extremity site (but it is the most frequent subtype in lung, pleura, and mediastinum)
		60 % Response rate to chemotherapy (ifosfamide-doxorubicin), halfway between adult STS (40 %) and pediatric small round cell sarcomas (RMS) (80 %)
Malignant peripheral nerve sheath tumor (MPNST)	Loss or rearrangement of 10p, 11q, 17q, and 22q	30 % Associated to neurofibromatosis type 1 (NF-1)
		Frequently located in the trunk
		Poor response to chemotherapy, poor prognosis
Dermatofibrosarcoma protuberans	t(17;22) t(2;17)(p23;q23)	Subcutaneous tumor, generally low-grade small lesion with indolent growth
	ALK-CLTC PDGFb-COL1A1	Excellent outcome with surgery
Desmoplastic small round cell tumor	t(11;22) (p13;q12)	Abdominal mass widely disseminated at onset, peritoneal seeding, metastases
	EWS-WT1	Extremely poor outcome
		Need for noval strategy and new drugs
Epithelioid sarcoma		Superficial distant site (fingers)
		Indolent course, but risk of lymph nodal spread
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	Head and neck and other unusual locations, high risk of metastases
	TFE3-ASPL	Poor response to chemotherapy, poor prognosis
Extra-osseous pPNET/ Ewing's sarcoma	t(11;22)(q24;q12)	Less frequent than bone Ewing's sarcoma, same biology, probably similar clinical history
	FLI1/EWS	High malignant tumors, strong propensity to give metastases
		Need for multimodality strategy including multiagent chemotherapy
Extraskeletal mesenchymal chondrosarcoma	Complex cytogenetic alteration	Head-neck region (orbit); highly aggressive tumor
	t(11;22) (q24;q12) (as Ewing family tumors)	Need for multimodality strategy including multiagent chemotherapy
NRSTS subtypes typical of older adults (very rare in children)		
Clear cell sarcoma	t(12;22)(q13;q12)	Extremity site, deep-seated
	t(9;22)(q22;q12)	Poor response to chemotherapy; poor prognosis
Adult-type fibrosarcoma	t(2,5) and t(7,22)	Tendency to metastatic spread according to tumor grade
Leiomyosarcoma		Retroperitoneum
		Immunocompromised patients

(continued)

Table 21.5 (continued)

Histotypes	Molecular findings	Clinical characteristics and outcome
Liposarcoma	Myxoid liposarcoma:	Different biology and clinical behavior according to the subtype, i.e., well-differentiated, dedifferentiated, or myxoid/round cell subtype
	t(12;16)(q13;p11)	Retroperitoneal location
	t(12;22)(q13;q12)	
	FUS-CHOP	
Angiosarcoma		High grade sarcoma, poor prognosis;
		Associated with lymphedema, after radiotherapy;
		Breast
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	Slow-growing tumor of extremity
	t(9;17)(q22;q11.2)	
	EWS-CHN	

NRSTS non-rhabdomyosarcoma soft tissue sarcoma, *STS* soft tissue sarcoma, *RMS* rhabdomyosarcoma, *pPNET* primitive peripheral neuroectodermal tumor

well-defined radiological criteria exist for the differential diagnosis between benign vascular tumors and sarcomas. Growing lesions that are already more than 3–5 cm in size and deeply seated beneath the deep fascia may warrant a biopsy. Needle core or incisional biopsy is indicated, while fine needle aspiration is rarely adequate to provide enough material to allow an adequate histological subtyping of the sarcoma. Excisional biopsy (or initial unplanned resection) should be avoided for the risk violation of tissue planes, resulting in dissemination of the tumor cells throughout the operative field.

MRI or CT scan of the primary site defines the local tumor extension. Since the risk of metastatic spread is definitely lower in NRSTS than in RMS (e.g., around 6 % for synovial sarcoma), and the majority of metastases occur in the lung (in 85 % of cases), some of the investigations generally suggested the distant assessment in RMS may be potentially omitted (e.g., technetium bone scan and bone marrow biopsy), at least for NRSTS other than high grade, to reduce both the burden of ionizing radiation received by pediatric patients and costs [74]. Similarly, chest CT scanning may improve the accuracy of pulmonary staging over X-ray, but requires different ionizing radiation exposures that might have carcinogenic potential. Recent studies showed that tumor diameter represented the major prognostic factor in STS [75], and in synovial sarcoma it may be used as a variable for identifying patients at greater risk of metastases (those with tumor size more than 5 cm) and warranting more accurate radiological investigations; in other words, the risk of metastases is very low in cases with tumor smaller than 5 cm, so CT scan can be omitted for them [74]. Similar considerations might suggest to reduce the indication for radiological investigations also in the patient follow-up.

In pediatric protocols, NRSTS are staged according to the same systems adopted for RMS, i.e., the clinical TNM system and the postsurgical IRS classification (Table 21.1).

The overall cure rate for NRSTS patients is around 70 %, but is strictly correlated to the risk group. Treatment must be planned according to the risk stratification, with the aim to give more intensive therapies to patients with less favorable prognostic factors, while avoiding overtreatment and side effects (without jeopardizing the outcome) in cases with more favorable clinical features.

Prognostic variables in NRSTS are the following [61–64, 67, 76–78]:

Disease extension at diagnosis: survival is very poor in children with metastatic disease (less than 20 % can be cured).

Initial surgery: 5-year overall survival is around 90 % in patients who underwent complete resection at diagnosis (IRS group I), 80 % in

those who had marginal resection (group II) and 50 % in initially unresected cases (group III).

Histology: among adult-type NRSTS, MPNST generally have worse prognosis.

Tumor grade: survival around 90 % for G1, 80 % for G2, and 65 % for G3.

Tumor site: survival around 80 % for extremity tumors and 60 % for axial location.

Tumor size: survival around 90 % for tumor < 5 cm, 55 % for size > 5 cm.

Patient's age: 5-year survival of 85 and 70 % for age less than and over than 10 years, respectively.

Tumor invasiveness (T-stage) and superficial/deep location are often associated to tumor size and site and are not commonly used in risk stratification in children. Most of these variables are inter-correlated, i.e., MPNST were often large and axial tumors, unresectable at diagnosis [67].

Treatment

While in the past children with NRSTS were often treated according to the guidelines defined for RMS, in the recent years both the COG and the EpSSG developed specific multimodal risk-adapted protocols focused on pediatric NRSTS (i.e., the COG ARST0332 and the EpSSG NRSTS 2005) [78]. The treatment management of NRSTS is complex and necessarily multidisciplinary. These tumor types are usually considered scarcely sensitive to chemotherapy (tumor response in the range of 40 % or less), and surgery thus remains the unquestionable keystone of treatment. The aim of surgery is that of obtaining adequate surgical margins with limited or no long-term sequelae. The definition of "adequate margins" depends on the quantity of healthy tissues surrounding the tumor (generally considered >1 cm), but also on its quality (periostium, vessel sheath, epineurium, or muscular fascia may act as barriers) [79]. The quality of the surgical operation is crucial since the chances of adjuvant therapies being able to compensate for inadequate surgery are still debatable. Demolitive surgery (e.g., amputation) is not generally considered as a standard procedure for patients at first onset; however, it is a justified option in particular situation, as locally relapsing patients [80] or in those cases with very large tumors presenting with long delay (as may often happen in developed countries).

Radiotherapy plays a well-defined role in local control, after incomplete resection and, according to adult experiences, also after wide excision, especially in case of large tumors. However, the indication for radiotherapy is usually stricter in children, given the higher risk of severe late effects (i.e., the risk of retardation or arrest of irradiated bone growth, the risk of functional impairment and that of second postirradiation tumor).

The role of chemotherapy in NRSTS remains a debated issue, in particular for the large group of adult-type STS histotypes (adult-type fibrosarcoma, MPNST, epithelioid sarcoma, leiomyosarcoma, clear cell sarcoma of soft part, liposarcoma, alveolar soft part sarcoma, undifferentiated polymorphous sarcomas, malignant solitary fibrous tumor/hemangiopericytoma, angiosarcoma, dermatofibrosarcoma). In this heterogenous group of tumors, chemotherapy response rate is generally in the range of 40 %. However, chemotherapy is necessary as front-line treatment in patients with advanced unresectable disease [62–64, 81, 82], with the aim of converting these cases into conservative complete resections, but also for treating any micrometastases promptly. Patients who respond to chemotherapy generally have better chances of survival, as well as those who may undergo complete delayed surgical resection and those treated with radiotherapy, suggesting that intensive multimodal treatment should be recommended in these patients [64].

The possible role of adjuvant chemotherapy in preventing distant recurrences after initial surgery is a further point of controversy. As a matter of fact, the outcome after initial tumor resection is reasonably good in patients with small and low-grade tumor (survival rate up to 90 %), while the prognosis for patients with high-grade and large invasive tumors may be unsatisfactory for the high risk of developing distant metastases (metastases-free survival around 40 %), particularly to the lung [64, 83, 84]. This would suggest,

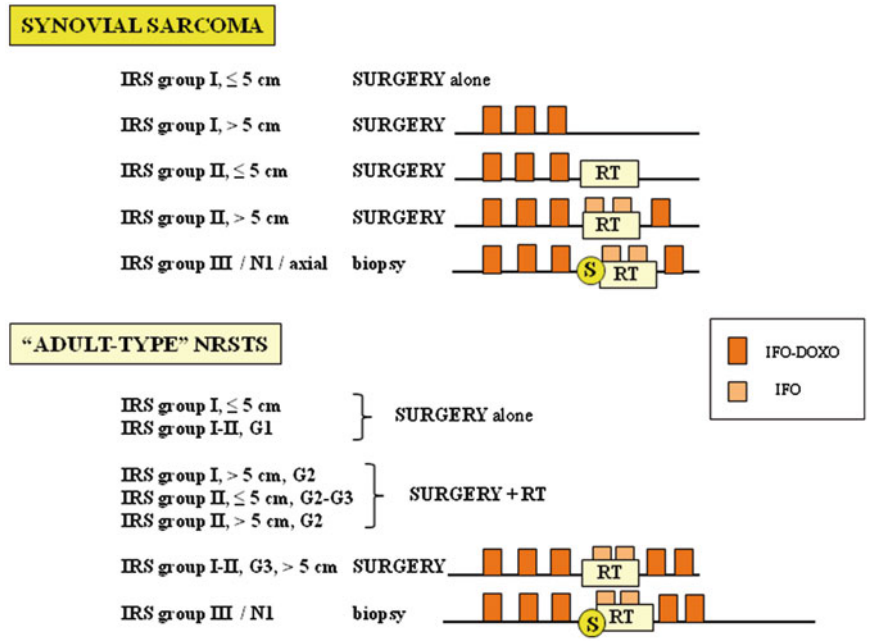


Fig. 21.5 Risk-adapted treatment plan for synovial sarcoma and adult-type soft tissue sarcoma in the European pediatric Soft Tissue Sarcoma Study Group (EpSSG) non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) 2005 protocol. *IRS* Intergroup Rhabdomyosarcoma Study, *N1* invasion of regional lymph nodes, *G* tumor grade, *IFO-DOXO* ifosfamide (9 g/m^2/cycle)—doxorubicin (75 mg/m^2/cycle) chemotherapy, *IFO* ifosfamide (6 g/m^2/cycle) chemotherapy, *RT* radiotherapy (50.4–54 Gy), *S* surgery

in principle, the use of systemic chemotherapy to try to improve survival. Moreover, some studies would advise an efficacy of adjuvant chemotherapy when targeting a selected group of high-risk patients (G3, size >5 cm) most likely to respond to chemotherapy, and when delivering the combinations of drugs currently recognized as the most effective in STS (full-dose ifosfamide plus anthracyclines) [83, 85, 86]. In the EpSSG NRSTS 2005 protocol, ifosfamide-doxorubicin adjuvant therapy is currently recommended in selected patients with high tumor grade and large tumor size (Fig. 21.5).

A tailored discussion should be dedicated to synovial sarcoma: this is the most common NRSTS in adolescents, an high-grade sarcoma crosswise between the pediatric and the adult age groups [87]. The chemosensitivity of synovial sarcoma probably stands midway between that of the most typical adult STS and that of pediatric small round cell tumors, such as RMS. This tumor has been historically treated, in Europe at least, as a "RMS-like" tumor by pediatric oncologists: all children with synovial sarcoma had received chemotherapy, even after the complete excision of very small tumors. An overall survival around 80 % has been reported in pediatric series [87–90]. Further analyses, however, permitted to identify a subset of patients—i.e., completely resected, with tumor smaller than 5 cm—with a very low risk of metastatic spread, for which adjuvant chemotherapy might be omitted, in principle, without jeopardizing the results [91]. The current management of pediatric synovial sarcoma patients has therefore changed to some degree, also taking suggestions from adult experiences and moved towards a treatment concept partially similar to that adopted in the adult setting: the full-dose ifosfamide-doxorubicin chemotherapy is currently adopted as standard regimen, and its indication is given according to the patient's risk stratification, based on tumor size and site and surgical stage (and is omitted in low-risk patients) [78] (Fig. 21.5).

Finally, it is worthwhile to report that in recent years various drugs other than the ifosfamide-doxorubicin combination have proved fairly active against particular STS histotypes, and the next steps of the treatment of NRSTS will go in the direction of histology-driven therapies (i.e., taxanes for angiosarcoma, gemcitabine ± docetaxel for leiomyosarcoma, trabectedine for myxoid/round cell liposarcoma) [92–94]. The improvement in our understanding of the biology of these tumors is paving the way towards the investigation of novel targeted drugs, the products of the specific chromosomal translocations occurring in NRSTS becoming the targets of new molecular agents specifically designed to influence the tumor's biology [95–97].

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