6 Current Approaches to Therapy: Soft Tissue Sarcomas Other than Rhabdomyosarcoma in Children and Adolescents

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6.1 Introduction

Sarcomas in children and adolescents under 18 years of age are rare diseases and include various different histiotypes that include soft tissue sarcomas of "pediatric-type" (i.e., rhabdomyosarcoma), "adult-type" (i.e., liposarcoma and leiomyosarcoma tumor), or special entities (infantile fibrosarcoma, desmoid tumor, etc.). The group of "non-rhabdomyosarcoma soft tissue sarcomas" (NRSTS) includes all soft tissue sarcomas, except rhabdomyosarcoma and Ewing sarcoma, occurring during childhood and adolescence (Ferrari and Casanova 2005). The incidence varies with age, but NRSTS are more frequent during adolescence and in early adulthood (Fig. 6.1). Because treatment decisions are complex, management of these sarcomas in patients under 18 years is best overseen by a multidisciplinary team, preferably starting before any biopsy. The onset of these sarcomas in growing patients makes the local treatment and subsequent reconstruction more complex, requiring broad expertise in pediatrics, oncology, surgery, radiotherapy, and psychosocial disciplines. Sensitivity to medical therapies depends on the type of disease but must also be adapted to the age of the patient, the tumor extent, and the potential resectability of the primary tumor. The evolution of the treatment philosophy has historically differed between pediatric oncology where primary chemotherapy is frequently used prior to surgery and medical oncology where local treatment is often the first step in the therapeutic strategy. However, collaboration between pediatric and medical oncology is increasingly frequent, particularly in sarcomas occurring in adolescents and young adults who may be treated by either pediatric or medical oncologists (van der Graaf et al. 2017). International collaboration in studying pediatric soft tissue sarcomas, as well as engagement of both pediatric and medical oncologists, has facilitated our understanding of the clinical and therapeutic issues and optimized the care of these patients. The survival of most of these sarcomas is good, although lower in adolescents than in younger patients and in certain histologies and in metastatic presentations that are difficult to cure with current treatments. In these cases, patients should be included in biology-driven protocols as much as possible.

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C. A. S. Arndt (ed.), *Sarcomas of Bone and Soft Tissues in Children and Adolescents*, Pediatric Oncology, https://doi.org/10.1007/978-3-030-51160-9_6

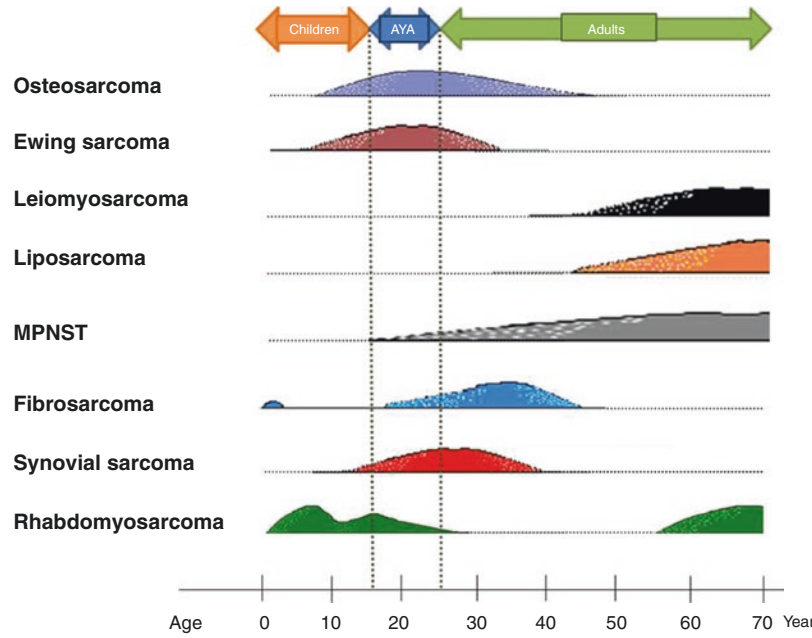

Fig. 6.1 Age distribution of the most frequent soft part sarcomas. *AYA* adolescents and young adults, *MPNST* malignant peripheral nerve shealth tumor

6.2 Local Therapy

6.2.1 Surgery

Surgery is the mainstay of therapy in NRSTS. The quality of the surgical operation is so important that children and adolescents with deep, large (>3–5 cm) soft tissue lesions suspected of being sarcomas should be referred to centers of excellence, preferably before undergoing biopsy. Surgery aims to obtain negative margins with no or minimal long-term sequelae. A resection with negative margin is defined as complete tumor removal with a surrounding rim of normal tissue, with no macroscopic tumor visible and no microscopic tumor cells present at the edge of the resected specimen. The crucial issue is the quality and quantity of the resected tissue surrounding the tumor mass or in other words the definition of the "safety distance" between the tumor and the resection margins. As for adult STS, the surgical guidelines for NRSTS should be based on the concept of compartmentalization in the extremities as popularized by Enneking (Enneking et al. 2003). Local management of extremity STS historically necessitated entire "compartmental resection" (en bloc removal of the tumor with the entire anatomical compartment, covered by intact deep fascia). With better local imaging which improves the definition of local tumor extent and with the introduction of combined multimodal treatment, more conservative and function-preserving surgery has been utilized. Compartmentalization is based on fascial boundaries, which generally act as barriers to tumor growth: sarcoma originating within a muscular compartment may grow longitudinally along fascial planes but typically cannot grow in a radial pattern beyond the fascia which acts as a barrier to local growth. Though fascial compartments do not exist in some anatomic sites, the concept of fascia and compartments has been traditionally utilized to define different types of resection. The so-called "wide" resection according to Enneking is a resection with either an intact fascial boundary (even within a few millimeters of the tumor) or an adequate surrounding layer of tissues indicating that the tumor was removed with an intact pseudocapsule (the first surrounding tissues compressed by the tumor), reactive zone (both the pseudocapsule and the reactive zone may contain microscopic disease),

and some additional normal tissue. A metric definition of this "additional normal tissue" is somewhat arbitrary and challenging: 1–2 cm of healthy tissue (when the tissue is a muscle) around the tumor has been selected as a cut-off in some studies, but it is important to realize that the margin can be minimal (>1 mm) when the tissue is a resistant anatomical barrier, such as muscular fasciae, periosteum, and perineurium (O'Donnell et al. 2014). Since 1–2 cm margins may be difficult to achieve in small patients, some studies have utilized a 0.5 cm margin based on studies in adults suggesting that this smaller margin may be adequate. However, inadequate surgical margins adversely affect local outcome and consequently also overall survival (Gronchi et al. 2010).

In children IRSG staging (Intergroup Rhabdomyosarcoma Staging (IRS) grouping system) is frequently used, and in adults the UICC "R system" is used to define surgical margins. Surgical resection margins are currently defined as:

- R0, which corresponds to IRS I (negative margin), includes both the "compartmental" and the "wide" resection as defined by Enneking but potentially also resection with close but negative margins (associated therefore with a higher risk of local relapse).
- R1/IRS II (microscopically positive margin), the so called "marginal resection," the dissection extends into or through the reactive zone that surrounds the tumor, with microscopic tumor extension at the margin of resection (without evidence of macroscopic disease residue).
- R2/IRS III (grossly positive margin), the Enneking intralesional resection that occurs if the tumor is entered at any point during surgery or if macroscopic tumor residue is left in situ. R2 also includes patients with only a biopsy at diagnosis.

6.2.2 Radiotherapy

Radiotherapy is an important component of local tumor control for pediatric patients with NRSTS, where it has a role in facilitating tumor resection in those with unresectable tumors and preventing local tumor recurrence in those who have undergone resection. Radiotherapy produces considerable long-term toxicity including growth impairment, organ dysfunction, and secondary neoplasia and must be used cautiously in children. Conformal techniques and proton radiotherapy may spare normal tissues, although these approaches have undergone limited study in pediatric NRSTS (Krasin et al. 2010; Merchant 2009). Nevertheless, brachytherapy and proton radiotherapy may be beneficial in selected anatomic sites where sparing of radiotherapy dose to normal structures can be achieved. In considering whether or not radiotherapy should be administered, the likelihood of local tumor control must be assessed. The factors that most influence local tumor control include tumor size, tumor histologic grade, and extent of surgical resection (Spunt et al. 1999; Ferrari et al. 2005a). Patients with high-grade tumors >5 cm and those with unresectable disease are at the greatest risk for local disease progression or recurrence. Aggressive surgical resection and radiotherapy may not be warranted in the patient with widely disseminated disease who has a short life expectancy.

Rendering an unresectable tumor amenable to gross resection is among the clearest indications for radiotherapy in pediatric NRSTS since unresected disease is rarely curable. Retrospective studies suggest that neoadjuvant radiotherapy combined with chemotherapy produces a better tumor response than either modality alone, but there has been no prospective evaluation of this hypothesis (Spunt et al. 2002). A recently completed clinical trial in NRSTS patients under 30 years of age showed that combined neoadjuvant chemotherapy and radiotherapy was feasible and produced a 15% estimated 5-year cumulative incidence of local failure when combined with delayed surgery when feasible (Tinkle et al. 2017). Neoadjuvant radiotherapy alone is used infrequently in pediatric patients, although this approach has been used successfully in adults for whom chemotherapy is not warranted (Tsagozis et al. 2018).

A second indication for radiotherapy is adjuvant use for microscopic residual disease following maximal resection of high-grade NRSTS. In this setting, local tumor control can be achieved in about 85% of cases (Tinkle et al. 2017). When microscopic residual disease is anticipated after resection of a high-grade tumor, preoperative radiotherapy should be considered. Preoperative irradiation may allow a 10–15% reduction in dose, and the volume irradiated may be smaller, thereby potentially producing fewer long-term effects on normal tissues.

Recent studies suggest that radiotherapy may not be required for all widely excised high-grade NRSTS (Ferrari et al. 2017). In a retrospective series of 100 IRS group I patients for a high-grade tumor, the estimated cumulative incidence of local failure was 14% at 5 years (Ferrari et al. 2005b). It is unknown whether widely resected >5 cm, high-grade tumors require radiotherapy, although there is some retrospective evidence in adults that these patients may also be safely treated with surgery alone even though a small pediatric retrospective analysis showed a better outcome with adjuvant radiotherapy in IRS group I > 5 cm adult-type sarcomas (overall survival 90% vs. 54%; $p = 0.02$) (Ferrari et al. 2005b; Baldini et al. 1999).

Radiotherapy is rarely indicated for treatment of resected low-grade NRSTS in pediatric patients. Those with widely excised tumors have excellent local tumor control rates exceeding 95% without radiotherapy (Spunt et al. 2020). Historically, patients with marginally resected low-grade NRSTS received radiotherapy. Although a lower local failure rate might be expected with radiotherapy, it appears that about 85% of patients can be cured without radiotherapy. Given the potentially serious toxicities of radiation, it seems prudent to restrict radiotherapy for low-grade tumors to settings where a local recurrence would be highly problematic or where the tumor has recurred after surgery alone. In a recent published large COG study, patients with nonmetastatic low-grade tumors or high-grade tumors up to 5 cm who have undergone negative (R0) or microscopically positive (R1) tumor resection were treated with conservative approach of omitting adjuvant radiotherapy (Spunt et al. 2020). Despite limited retrospective data showed that omission of adjuvant radiotherapy for R1 low-grade tumors produced a local recurrence rate of only 25% without any effect on disease-specific survival (Brennan 1997), authors adopted a surgery-only strategy for patients with low-grade tumors even with R1 margins following maximal surgery, aiming to avoid the majority of these patients receiving radiotherapy while recognizing that a small subset would require further treatment for local recurrence. Overall, 205 low-risk patients were treated with exclusive surgery and reached a 5-year event-free survival of 88.9% (95% CI 84.0–93.8) and an overall survival of 96.2% (93.2–99.2). Main tumor events were isolated local recurrence or progression (15/26 cases, 58%).

Radiotherapy has a palliative role in patients with NRSTS whose disease cannot be cured. Treatment of unresectable metastases must be individualized based on the number of sites, their locations, and whether disease control at each site is likely to produce meaningful clinical benefit. Radiotherapy may be helpful in relieving focal bone pain or pain from nerve compression since small changes in tumor volume may have a significant impact on symptoms. Conformal techniques such as stereotactic radiosurgery are an ideal way to limit normal tissue damage when delivering high radiotherapy doses over a short timeframe, as in a palliative setting. Whole lung, liver, or abdominal-pelvic radiotherapy are not recommended for diffuse metastases.

6.3 Conventional Chemotherapy

The role of chemotherapy in NRSTS is still controversial. Like their adult counterparts, NRSTS are generally considered minimally sensitive to chemotherapy. However, more than 50 different subtypes of soft tissue sarcomas are indeed heterogeneous not only in their biology and clinical behavior but also in their therapeutic sensitivity, e.g., synovial sarcoma is far more sensitive to standard chemotherapy compared to more resistant subtypes like alveolar soft part sarcoma or clear cell sarcoma (Orbach et al. 2013; Reichardt et al. 2003). In addition, treatment strategies for

these tumors have changed to some degree in recent years, and multiple-modality treatments that also include chemotherapy have increasingly been attempted. In fact, though approximately 70% of patients with localized NRSTS can currently be cured, the outcome depends on various prognostic factors; prognosis may be unsatisfactory for patients with high-grade, large, invasive tumors if the treatment is limited to local therapies alone, because these neoplasms have a marked tendency to spread. It is therefore essential to identify patients who are at high risk of metastatic failure and consequently in need of systemic treatment to try and improve their outcome.

In addition, certain histological characteristics make NRSTS more likely to respond to chemotherapy, e.g., in general, high-grade sarcomas may have greater benefit from chemotherapy than low-grade tumors (Spunt et al. 2019). The chemosensitivity of synovial sarcoma is intermediate between that of typical adult sarcomas (with fewer than 40% of tumors responding to chemotherapy) and that of pediatric small round cell tumors, such as rhabdomyosarcoma (with up to 80% of responders). The intensive ifosfamide (9 g/m^2 cycle) and doxorubicin (75 mg/m^2 cycle) regimen is currently considered to be the best front-line systemic therapy for most NRSTS (Ferrari et al. 2005b).

Apart from patients with metastatic disease (for whom chemotherapy, although rarely curative, may lengthen survival and possibly quality of life), the best indication for chemotherapy may be in NRSTS patients with unresectable advanced disease (Spunt et al. 2019; Ferrari et al. 2011). Chemotherapy may achieve tumor shrinkage and facilitate complete resection, as well as helping to treat any micrometastases promptly, since these patients have a high risk of distant dissemination. A study pooling series from various international research groups on initially unresected NRSTS showed a 41% response rate (in terms of major response), but the figure rose to 57% when minor responses were included (Ferrari et al. 2011). The study reported an overall survival of 51% at 10 years, with better outcome for patients whose tumors responded to chemotherapy.

The role of adjuvant chemotherapy in preventing distant recurrences after initial surgery in NRSTS remains uncertain (Ferrari et al. 2005a). This has long been a point of controversy in clinical studies on adult soft tissue sarcomas, where trials have suffered from the heterogeneity of patients with different histiotypes and clinical factors, the relatively small sample size, and the use of different chemotherapy regimens. The historic Sarcoma Meta-analysis Collaboration (pooling together data from 14 trials of anthracycline-based adjuvant chemotherapy conducted between 1973 and 1990 showed only a small benefit of chemotherapy (Sarcoma Meta-analysis Collaboration 1997). A significant benefit for adjuvant chemotherapy was documented in the Italian randomized trial that strictly selected high-risk patients (with high-grade, large, deep-seated tumors) and delivered a regimen of full-dose ifosfamide plus anthracyclines (Frustaci et al. 2001). The contribution of pediatric oncologists to this debate has been limited. The only randomized trial of adjuvant chemotherapy in pediatric patients was conducted by the Pediatric Oncology Group (POG) (1986–1992) and failed to adequately assess the role of adjuvant chemotherapy because the majority of patients refused randomization (Pratt et al. 1999). This study demonstrated how difficult it is to conduct prospective randomized studies in pediatric patients with such rare tumors, for which no standard therapy has been established. A potential role for chemotherapy in high-risk NRSTS has been suggested by pediatric retrospective analyses (Spunt et al. 1999; Ferrari et al. 2005a, 2011).

An accurate risk-adapted stratification is essential to identify patients who are more likely to benefit from chemotherapy. In the Children's Oncology Group (COG) ARST0332 and the European Pediatric Soft tissue Sarcoma Group (EpSSG) NRSTS 2005 protocols, adjuvant ifosfamide-doxorubicin was only given to patients with initially resected high-grade and large (>5 cm) tumors.

In the recently completed Children's Oncology Group study ARST0332, patients were assigned to four treatment groups: A (surgery only), grossly excised low-grade and ≤5 cm widely

excised high-grade tumor; B (55.8 Gy radiotherapy [RT]), ≤5 cm marginally resected high-grade tumor; C (ifosfamide-doxorubicin chemotherapy + 55.8 Gy RT), >5 cm grossly resected tumor ± metastases; and D (neoadjuvant ifosfamide-doxorubicin chemotherapy and 45 Gy RT, then surgery and an RT boost based on margins), >5 cm unresected tumor ± metastases. The three risk groups defined were low (nonmetastatic R0 or R1 low-grade or ≤5 cm R1 high-grade tumor); intermediate (nonmetastatic R0 or R1 >5 cm high-grade or unresected tumor of any size or grade); or high (metastatic tumor). Risk group predicted event-free survival and overall survival ($p < 0.0001$) (Spunt et al. 2020). The most common subtype was synovial sarcoma followed by malignant peripheral nerve sheath tumor and undifferentiated sarcoma. Chemotherapy included six cycles of ifosfamide 3 g/m^2 per dose intravenously on days 1–3 and five cycles of doxorubicin 37.5 mg/m^2 per dose intravenously on days 1–2 every 3 weeks (Spunt et al. 2020). At a median follow-up of 6.5 years, 5-year event-free survival and overall survival were 88.9% (95% CI 84.0–93.8) and 96.2% (93.2–99.2) in the low-risk group. Patients in the intermediate-risk group (227 cases) had a 5-year EFS of 65.0% (95% CI 58.2–71.8) and OS of 79.2% (73.4–85.0). Metastatic recurrence or progression with or without local failure was the main tumor event (52/84 cases, 62%). In the high-risk group (80 cases), estimated 5-year EFS was 21.2% (95% CI 11.4–31.1) and OS 35.5% (23.6–47.4). Similarly, in this latter group, metastatic tumor relapse or progression was the main event (57/63, 90%). For this group, authors admitted that this treatment strategy was modestly efficacious.

6.4 Specific Therapy for Diseases

The recent development of new approaches targeted to specific molecular targets may overcome the limitations of systemic therapies in the near future, possibly identifying specific agents tailored to each histotype: imatinib for GIST and dermatofibrosarcoma and sunitinib for alveolar soft part sarcomas, for instance. While awaiting these developments, however, a more precise use of standard chemotherapy may prove important in improving the cure rate for these patients.

6.4.1 Synovial Sarcoma

Synovial sarcoma (SS) is a malignant mesenchymal tumor that occurs in both pediatric and adult patients and accounts for 8–10% of all soft tissue sarcomas (STS) in children (Fig. 6.1). SS tends to be locally invasive and has a propensity to metastasize. At diagnosis, fewer than 10% of patients present with metastases (mainly to the lung), but the disease subsequently spreads in 25–50% of cases. Lymph node metastases are rare. The biological hallmark of SS is the t(X;18)(p11.2;q11.2) chromosomal translocation which produces the SYT-SSX transcript. A 67-gene signature related to chromosome integrity and genome complexity named CINSARC (*complexity index in sarcoma*) and a genomic index (GI) analyzed using comparative genomic hybridization (CGH) have recently been developed and shown a high prognostic value in STS and in SS (Lagarde et al. 2013; Orbach et al. 2018). The molecular signatures identified (CINSARC and GI) may discriminate patients likely to benefit from chemotherapy from those for whom chemotherapy is not beneficial. The prognosis for SS patients depends on several variables and particularly on the tumor extension, the feasibility of the surgical resection, tumor size (±5 cm), and tumor site (worse prognosis for axial tumors vs. limbs).

The EpSSG NRSTS 2005 protocol included a prospective non-randomized trial of SS assessing the role of ifosfamide-doxorubicin chemotherapy in improving the response rates for patients with unresectable disease and elimination of adjuvant chemotherapy in low-risk cases. Patients were stratified by surgical stage, tumor size, nodal involvement, and tumor site as follows: (a) "low-risk," IRS group I and tumor size ≤5 cm; (b) "intermediate-risk," IRS group I, >5 cm in size, and all IRS group II; and (c) "high-risk," IRS group III tumors, nodal involvement (N1), or axial disease. "Low-risk" patients were treated

with surgery alone. "Intermediate-risk" patients received 3–6 courses of adjuvant ifosfamide-doxorubicin chemotherapy to prevent distant recurrences after initial local treatment, along with radiotherapy. "High-risk" patients had six courses of chemotherapy, delayed surgery (when feasible), and radiotherapy (local treatment was planned after three cycles of neoadjuvant chemotherapy). Neoadjuvant chemotherapy was considered the treatment of choice not only for patients with unresectable advanced disease but also whenever the surgeon was unsure whether a complete resection could be achieved at the first attempt. Ifosfamide + doxorubicin was given for a maximum of four cycles (maximum cumulative dose of doxorubicin: 300 mg/m^2). Two cycles of ifosfamide were given concomitantly with radiotherapy to patients in IRS group II, with tumors >5 cm in size, and to IRS group III patients. This trial (involving 138 patients <21 years old treated between 2005 and 2012) resulted in 5-year EFS and OS rates of 80.7% and 90.7%, respectively (Ferrari et al. 2014). In this series, 24 patients were classified as "low-risk" and were therefore treated with surgery alone; only two local relapses were observed in this cohort, with no metastatic relapses. Though the number of cases was relatively small and caution is needed, this finding suggests that adjuvant chemotherapy might be safely omitted for low-risk patients without jeopardizing their outcome (Ferrari et al. 2017).

6.4.2 Other "Adult-Type" Sarcomas (Fibrosarcoma, Liposarcoma, Mesenchymal Chondrosarcoma, PECOMA, Leiomyosarcoma, Epithelioid Sarcoma, Clear Cell Sarcoma, Angiosarcoma, Undifferentiated Sarcoma)

A formal definition of "adult-type NRSTS"—i.e., definitely malignant mesenchymal tumors, typical of adulthood, with morphological features resembling differentiated/mature tissues—was developed some years ago and has been utilized by the EpSSG to identify a more homogeneous subset of histiotypes within the large heterogeneous group of NRSTS (thus excluding from a common analysis, for instance, borderline tumors, infantile histiotypes, and small round cell tumors, which are biologically and clinically different entities that were sometimes studied together, giving rise to misleading results). However, this group still includes different entities whose biology and clinical history may be very different. For example, epithelioid sarcomas present typical features such as superficial distal location (i.e., hand, fingers), indolent growth along tendon sheaths, and a tendency for lymph node involvement (Spunt et al. 2019). Clear cell sarcoma mimics melanoma and is characterized by a prolonged clinical course with multiple local recurrences, late metastases, and a high rate of tumor deaths; chemotherapy is generally considered ineffective. Leiomyosarcomas may involve skin, superficial and deep soft tissues, and viscera and may arise as a second malignancy in patients treated with radiotherapy. Liposarcomas in children mainly occur in lower extremities, with the conventional myxoid liposarcoma being the most frequent histiotype. Undifferentiated high-grade pleomorphic sarcomas (in the past called malignant fibrous histiocytoma) are highly aggressive tumors and may be associated with a family history of cancer. The PEComa family of tumors (perivascular epithelioid cell tumors, including the classic benign angiomyolipomas, epithelioid angiomyolipomas of the kidney that may have malignant behavior, and clear cell myomelanocytic tumor that may be an aggressive disease) are generally treated with surgery alone, and neither radiotherapy nor chemotherapy is efficacious. Mesenchymal chondrosarcomas are high-grade sarcomas suggested to be closely related to Ewing sarcomas, for which multimodal regimens (as for Ewing sarcoma protocols) may be indicated. Acknowledging this heterogeneity, it is evident that the definition of "adult-type" sarcoma has been helpful for descriptive purposes, but for the future, these tumors should no longer be studied as a whole group. Rather, by concentrating separately on each histiotype, the hope is to have new targeted molecular therapies for each histology.

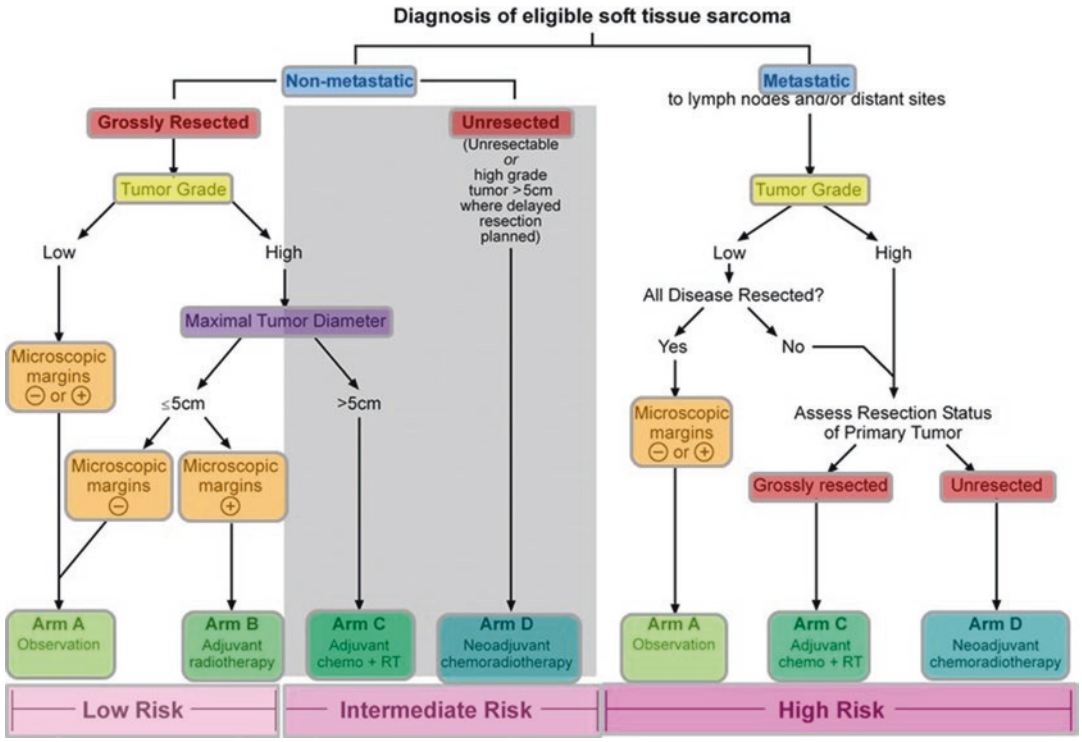

Fig. 6.2 Children's Oncology Group (ARST0332) treatment schema for adult-type soft tissue sarcomas

In addition, each of these tumors is very rare in the pediatric age group, and data on their natural history in children (and therefore on the best possible treatment) are limited. Extrapolating data from adult populations (where these tumors are more frequently observed) may be useful but must be performed cautiously, not only because the distribution of histologic subtypes differs considerably in adults and children but because certain histiotypes may behave differently in different age groups (e.g., in general, a less aggressively clinical course in children than in adults).

The COG ARST0332 study and the EpSSG NRSTS 2005 study stratified these patients according to histologic grade, size of primary tumor, extent of initial surgical resection, and presence or absence of metastatic disease. These variables have been shown to predict outcome in the few prospective and retrospective pediatric series, as well as in the large adult series (Spunt et al. 1999; Ferrari et al. 2011; Italiano et al. 2014). Surgery is the mainstay of treatment for these tumors. Radiotherapy and chemotherapy have been used in both protocols according to the risk stratification schema (Ferrari and Casanova 2005) (Fig. 6.2).

The successor study for NRSTS, ARST1321, Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS), A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib, was a combined effort of COG and NRG. The rationale for investigation of tyrosine kinase inhibitors (TKI) in NRSTS is based on the fact that tyrosine kinases are critical regulators of cellular growth, proliferation, and survival and TK dysregulation is felt to be a major contributor to tumorigenesis in a variety of cancer types (Krause and Van Etten 2005). Certain TKs have been found to be expressed in a range of NRSTS subtypes. Among these, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-Kit, and epidermal growth factor receptor (EGFR) have been the most prevalent and dysregulated across histologic subtypes

(Tamborini et al. 2004). Tumor growth and metastatic spread are critically dependent on tumor angiogenesis. VEGF and PDGFR are two of the main receptor proteins involved in this process (Potti et al. 2004; Holtkamp et al. 2006; Park et al. 2010). Further, their elevated expression has correlated with higher malignancy grade and worse outcome (Chao et al. 2001; Yudoh et al. 2001) Preclinical research demonstrated that the effect of simultaneous inhibition of VEGF and PDGFR on tumor angiogenesis and growth is additive suggesting that concurrent targeting of multiple signaling pathways may be more effective than targeting either pathway alone (Bergers et al. 2003; Erber et al. 2004) . The multi-targeted TKI pazopanib (GW786034) is a potent inhibitor of VEGFR, PDGFR, and c-Kit (Le Tourneau et al. 2008) . While VEGFR and PDGFR are critical regulators of tumor angiogenesis, c-Kit is associated with tumor progression (Masson and Ronnstrand 2009). A number of phase I and II pediatric and adult studies demonstrated activity of pazopanib in advanced soft tissue sarcomas, leading to its selection for study in ARST1321 (Hurwitz et al. 2009; Sleijfer et al. 2009; van der Graaf et al. 2012; Glade Bender et al. 2013). Patients in the chemotherapy cohort received the standard ifosfamide-doxorubicin backbone and were randomized to receive pazopanib. Patients in the non-chemotherapy cohort underwent radiotherapy and were randomized to receive pazopanib. The primary goal, after identifying the dose of pazopanib that was feasible when given in combination with radiation or chemoradiation, was to compare the rates of near complete pathologic response (> 90% necrosis) with the addition of pazopanib to preoperative chemoradiation (or radiation alone) versus preoperative chemoradiation (or radiation alone) alone for potentially resectable >5 cm, Grade 2 or 3 intermediate to high-risk NRSTS in the phase II portion of the study. The rate of near complete pathologic response was significantly greater with the addition of pazopanib to preoperative chemoradiation in children and adults with intermediate/high-risk NRSTS (Aaron et al. 2019) (58% vs. 22% >90% necrosis). The rate of wound complications was similar to that in current and historical literature. However, a longer follow-up seems necessary to analyze if these early results translate to an improvement on patients' outcome (Aaron et al. 2019).

6.4.3 Malignant Peripheral Nerve Sheath Tumor

Malignant peripheral nerve sheath tumor (MPNST) is a spindle cell sarcoma arising from or differentiating toward peripheral nerve sheath cells. The term *MPNST* is preferred to the "synonyms" *malignant schwannoma* or *neurofibrosarcoma*. There are no histologic markers predictive of clinical behavior and tumor grade does not appear to have prognostic significance (intermediate vs. high grade), but low-grade MPNST does have a less aggressive behavior. MPNST are rare (expected incidence being around 0.1/100,000 a year) and occur mainly in adults: only 10–20% are diagnosed in the first two decades. Nevertheless, they represent one of the most frequent subtypes among pediatric NRSTS (Fig. 6.1) (Ferrari and Casanova 2005; Carli et al. 2005). The clinical behavior of MPNST is generally that of an aggressive highly malignant tumor, often arising in axial sites (trunk or, less frequently, head and neck region). Association with a sizable nerve can be identified in more than 70% of cases. In approximately 40% of patients, MPNST develops in a preexisting neurofibroma, particularly in patients with neurofibromatosis type 1 (NF-1). In about 21–67% of cases, in fact, MPNST arises in patients affected by NF-1. The lifetime risk of developing MPNST in NF-1 patients has been estimated to be 8–13%, as compared to 0.001% in the general population. The molecular mechanisms responsible for malignant transformation of neurofibromas are still unclear. NF-1 is caused by mutation in the NF-1 suppressor gene, on chromosome band 17q11. This gene encodes neurofibromin, a protein inhibiting p21-RAS. NF-1 inactivation is not sufficient for malignant transformation, and further genetic alterations are needed. Several alterations in tumor suppressor genes playing a pivotal role in

cell cycle, such as mutations of TP53 and CDKN2A (p16INK4), have been reported in neurofibromas as they transform into MPNST.

MPNST is generally characterized by uncertain prognosis, in both adults and children. A large series on pediatric MPNST from the Italian and German cooperative groups included 167 cases treated over a 25-year period using a multimodality therapeutic approach (Carli et al. 2005). That series confirmed the aggressiveness of MPNST, for which complete surgical resection is the mainstay of successful treatment. Unfortunately, achieving a complete resection at the time of initial diagnosis is rarely feasible (Carli et al. 2005; Ferrari et al. 2007). In this experience, most of the patients had a large, invasive, and unresectable tumor at diagnosis. Progression-free and overall survival at 5 years were 37% and 51%, respectively, significantly lower than that generally reported for other pediatric soft tissue sarcoma subtypes. Local progression or relapse after therapy represented the main cause of failure. Outcome was only satisfactory for the small group of resected and small tumors. Survival rates look especially poor in patients with NF-1: 5-year PFS and OS were 19% and 32% in NF-1, versus 42% and 55% in non-NF-1 cases, but this is controversial (Kolberg et al. 2013).

Among NRSTS, MPNST is generally regarded as among the least chemosensitive (Ferrari et al. 2007). The Italian and German study reported a chemotherapy response rate of 28% in terms of major responses that rose to 45% when minor responses were considered too. However, response to chemotherapy was higher when considering patients who had received regimens containing ifosfamide (65%) and when analyzing the group of non-NF-1 patients (55%, versus 18% in NF1). In both the ongoing EpSSG NRSTS 2005 and the recently completed COG ARST0332 protocols dedicated to NRSTS, localized MPNST was treated according to risk stratification based on histologic tumor grade, tumor size, initial resectability, and extent of disease (Spunt et al. 2020; van Noesel et al. 2019). Surgery was the keystone of treatment; given its local aggressiveness, for MPNST the surgical approach may be more aggressive than for other pediatric NRSTS. The need for adjuvant therapies should be decided according to the risk of local and distant recurrence. Radiotherapy may improve local control after initial marginal resection, after wide resection of large tumors, and in large and invasive unresectable tumors. In NF-1 cases, the risk of second malignancies must always be borne in mind when considering the use of radiotherapy. The role of chemotherapy remains uncertain. Ifosfamide and doxorubicin may be considered as neoadjuvant therapy in locally advanced and metastatic disease. This approach may be debatable in completely resected MPNST (regarded as one of the NRSTS least likely to benefit from chemotherapy), particularly considering the serious toxicity of chemotherapy. For the future, there is a strong need for a new therapy specific for this histiotype. In the EpSSG risk-adapted strategy, 51 patients were stratified in four groups according these risk factors (van Noesel et al. 2019). Outcome for patients with resectable MPNST was excellent, but even if response rate to ifosfamide-doxorubicin regimen was 46%, outcome for patients with initially unresectable tumor was dismal (5 year EFS 29–42%). In this experience, the presence of NF1 was confirmed to be an independent poor prognosis factor for OS and EFS.

6.4.4 Desmoid Tumor

Desmoid fibromatosis, also known as *desmoid tumor* (DT), *deep fibromatosis*, or *aggressive fibromatosis*, is a locally aggressive soft tissue lesion arising from deep fascial or soft tissue structures (musculo-aponeurotic structures) (Kasper et al. 2017). Although surgery is the traditional treatment, it now appears that repeated stimulation of connective tissue by surgery is a risk factor for tumor recurrence (Orbach et al. 2017). Furthermore, complete resection (IRS I) in DT is rare even in small tumors (≈13%) (Oudot et al. 2012; Meazza et al. 2010). Moreover, DT can stabilize or even spontaneously resolve. This observation has led to a recommendation for a period of observation for tumors that are mini-

mally symptomatic and to restrict therapy to documented progressions. For unresectable or recurrent tumors, some nonsurgical approaches have been developed with conventional chemotherapy drugs, antiestrogens, nonsteroidal anti-inflammatory drugs, and targeted therapy (Orbach et al. 2017; Meazza et al. 2010; Sparber-Sauer et al. 2018a; Ferrari et al. 2019). The respective roles of these strategies remain to be specified in adults as well as in children. Furthermore, if the tumor appears to be unresectable, surveillance first is also recommended with complementary medical treatment only in the case of progression. There is no indication for partial resection in desmoid tumors. If the tumor has nevertheless been resected, simple surveillance is recommended in all cases (after complete or incomplete resection) with delayed treatments proposed only in the case of local progression. The duration of chemotherapy is arbitrary, but it is proposed to continue treatment for at least 6–9 months after stabilization of the tumor (often 12–18 months). The choice of treatment must take into account the "benign" nature of the lesion, the child's age and gender, the potential long-term effects of different therapies, the expected benefit of these treatments (overall expected partial response of about 30–40%, stabilization in 30%), and the expected local risks in the case of tumor progression (failure 20%) (Skapek et al. 2007). The goal of systemic therapy in AF should not be only tumor shrinkage to permit a subsequent resection but rather the induction of growth arrest and tumor stabilization. Due to the absence of long-term effects, one of the first-line treatment commonly used is methotrexate-vinblastine (Orbach et al. 2017). The efficacy of treatment is assessed on surveillance examinations, which must not be performed too frequently (every 3 months). Treatment should be continued in the case of stabilization of tumor volume. Only frank progression of tumor volume (>30%) should be considered to reflect treatment failure, and another second-line treatment should be considered (Fig. 6.3). Second-line treatments that may be considered include VAC/IVA alternating with VA (vincristine, actinomycin-D, cyclophosphamide or ifosfamide), tamoxifen with a nonsteroidal anti-inflammatory (NSAID) drug such as Sulindac-Arthrocine® or Celecoxib-Celebrex® [but the overall response rate to this last association (tamoxifen + NSAIDs) is estimated at only 8% in children] (Skapek et al. 2013), or a targeted therapy (imatinib, sorafenib®) (Kasper et al. 2017; Gounder et al. 2011). Furthermore, some recent limited data showed the efficacy of hydroxyurea in DT (Ferrari et al. 2019). In the rare case of emergency (huge mesenteric primary, rapidly growing tumor in a threatening site), liposomal doxorubicin can be considered (Constantinidou et al. 2009). As DT may have a hormonal sensitivity, oral contraceptive with estrogen treatments in adolescents may be avoided.

Finally, due to the benign condition, as far as possible radiotherapy should be avoided in children due to the expected long-term effects (cosmetic, functional morbidity, second malignancy), even if this therapy is efficient in DT. The current overall EpSSG strategy in DT is summarized in Fig. 6.3. Some new drugs showed promising effect in adults with DT and are under experimentation in children (Messersmith et al. 2015).

6.4.5 Rhabdoid Tumor

Extracranial rhabdoid tumors (RT) are rare and often present in infants or children at any anatomical site as a rapidly growing mass. The vast majority contain biallelic inactivating mutation of the *SMARCB1* gene, which is part of the chromatin remodeling complex SWI/SNF, which is important in cell cycle control and functions as a classic tumor suppressor gene. The primary tumor can be found in a variety of locations including the soft tissues of the trunk, extremities, head and neck, abdomen, pelvis, and retroperitoneum, as well as in a variety of organs such as the liver, heart, kidney, and bladder. Multifocal or metastatic disease is not uncommon and should be carefully checked at diagnosis. Early progressions are common in RT even during induction therapy. In the Bourdeaut et al. series of extrarenal non-cranial RT, the median time to progression was 5 months (0–44) (Bourdeaut

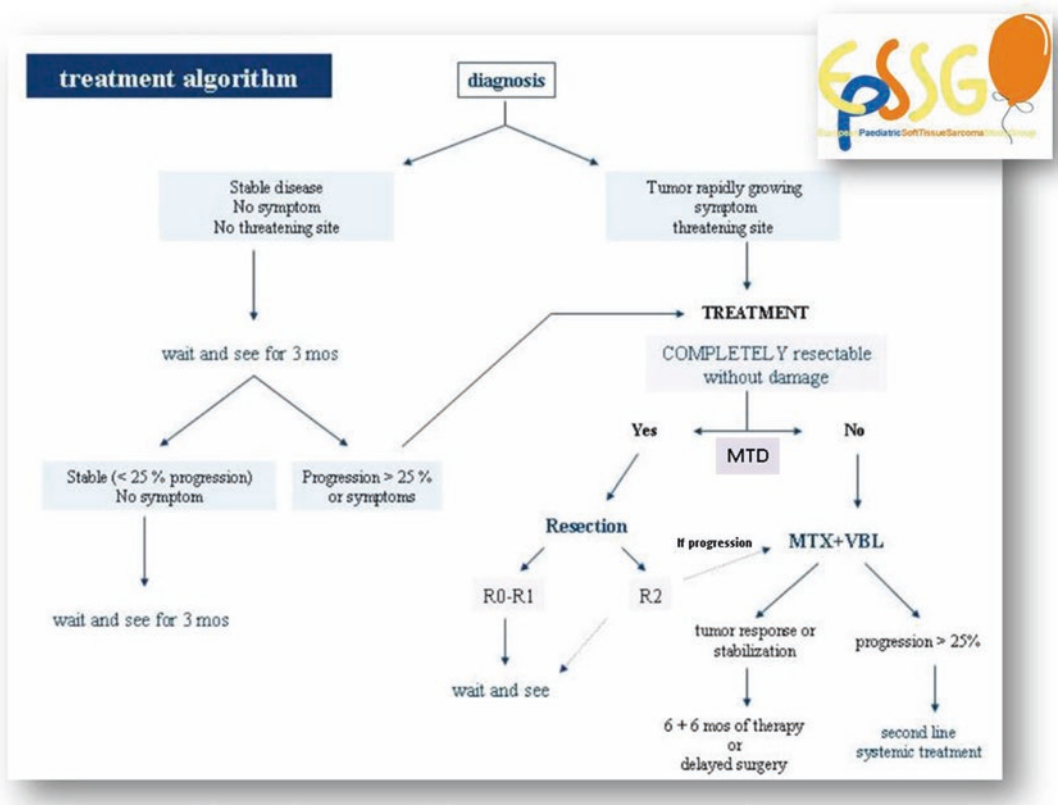

Fig. 6.3 E*pSSG* strategy for patients with desmoid tumors (protocol NRSTS 05). *R0* complete resection, *R1* marginal resection, *R2* gross residual disease, *MTX + VLB* methotrexate with vinblastine, *MTD* multidisciplinary team discussion

et al. 2008). Given the rarity of RT, there is no standard therapeutic pathway, and there have been no randomized trials examining the role of chemotherapy combinations or addition of new agents. The best therapeutic strategy in this tumor remains to be defined, but all decisions, especially radiotherapy, should take into account the young age of the patients with RT (median age: 28 months) and the aggressive nature of the disease (Fig. 6.4). RT are often described as rapidly lethal, with little evidence of improvement in survival in recent years (1-year survival <30%) (Bourdeaut et al. 2008; Brennan et al. 2016).

The general surgical principles apply to RT, i.e., complete surgical resection as early as possible, due to potential early progression. As soon as workup is completed, the tumor has been completely excised or biopsied, and the diagnosis of RT has been made; neoadjuvant or adjuvant chemotherapy should be given. Patients with initially unresectable or incompletely resected tumors should receive chemotherapy and undergo reassessment earlier in order to plan a delayed surgical resection to remove the primary tumor and any residual resectable metastases (Brennan et al. 2016).

Evidence for the role of chemotherapy, in particular ifosfamide, initially comes from a single historical institutional series from St Jude Children's Research Hospital. The inclusion of doxorubicin in chemotherapy combinations is suggested as important for survival in extracranial RT. Due to the absence of effective standard chemotherapy protocols, patients should be enrolled in prospective studies that contain sequential multidrug regimens for 6–12 months with mainly alkylating agents, anthracycline and platinum compounds. The current EpSSG strategy is interval-compressed chemotherapy with VDCy (vincristine, doxorubicin, cyclo-

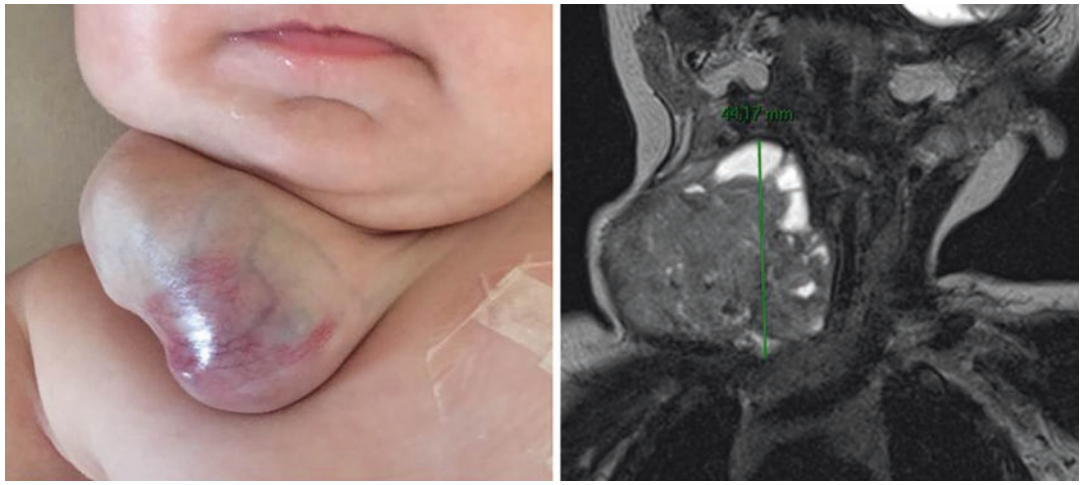

Fig. 6.4 Clinical and MRI presentation of localized cervical rhabdoid tumor (*SMARCB1* somatic mutation) in a 4-week-old female. The young age of the patient and the extent of local tumor invasion argue against the use of external beam radiotherapy

phosphamide) alternating with IE (ifosfamide, etoposide) in order to increase the dose intensity (Waldron et al. 1999). The value of intensification with high-dose chemotherapy or maintenance therapy after induction treatment is not known and should be explored. For the future, improved understanding of the biology and role of SMARCB1 in RT has enabled identification of new targets for small molecule inhibitors (EZH2 inhibitors, for instance) to combine with chemotherapy backbones that might be tested in future EpSSG and COG studies (Brennan et al. 2004).

Due to the aggressiveness of the tumor, local radiation should be considered early in all cases. The role of radiotherapy in local control of extracranial RT is suggested from small series (Bourdeaut et al. 2008). The real benefit of radiation is difficult to analyze in the literature because radiation tended to be given to those with a higher stage, without early progressive disease, and in older age groups. Furthermore, older patients were more likely to receive a higher radiation dose. Radiation dosages and fields are frequently limited by the tumor extent at diagnosis and the young age of the patients (Brennan et al. 2016) (Fig. 6.4).

6.4.6 Infantile Fibrosarcoma

Infantile fibrosarcoma (IFS) is a rare tumor, but it is the commonest soft tissue sarcoma in children less than 1 year of age (median age 1.43 months) and mainly arising in the extremity (54.0%) (Atallah et al. 2016; Sparber-Sauer et al. 2019). IFS is currently classified as a soft tissue tumor of intermediate malignancy characterized by a quite specific t(12;15)(p13;q25) translocation coding for an *ETV6-NTRK3* gene fusion. It often presents with initial rapid growth, sometimes with indolent evolution, and metastatic spread is uncommon (1–13%). Recent studies confirm the very good overall survival of children with IFS with a 5 year-OS >90% and emphasize the challenge of tumor resection without anatomic or functional damage (Atallah et al. 2016; Sparber-Sauer et al. 2019). Due to the very young age of patients, special attention should be paid to minimizing therapeutic late effects. Primary surgery should only be considered in small localized tumors that can easily be completely resected without any functional consequences. In case of complete surgery or microscopic residue (IRS I or II group) of a localized tumor, no further adjuvant treatment is needed. Since IFS is a chemo-

sensitive tumor, chemotherapy may play a role in the treatment strategy (Parida et al. 2013; Orbach et al. 2009; Surico et al. 2003). Recently, the VA regimen (vincristine-actinomycin-D) has been confirmed to be efficacious and may produce a response that facilitates surgery (Atallah et al. 2016; Orbach et al. 2009). The aim of neoadjuvant chemotherapy is to reduce the tumor size in order to allow delayed non-mutilating tumor resection. Response to chemotherapy can be slow (several months), and nonresponse to chemotherapy should only be considered in cases of tumor growth (>25% volume increase) or absence of tumor reduction after at least 3 months of therapy. If the tumor responds to VA and surgery could become feasible without anthracyclines and alkylating agents, VA is to be continued up to the surgery, and chemotherapy is discontinued after surgery. Other effective regimens include VAC (vincristine-actinomycin-D-cyclophophamide) and VAdriaC (vincristine-doxorubicin-cyclophophamide) but should be reserved for nonresponse to VA chemotherapy (Sparber-Sauer et al. 2019). The tumor shrinkage achieved in the majority of cases with initially unresected tumor will allow a conservative surgical approach in most cases (>95%). Radiotherapy should not be used due to its toxic consequences in infants. The EpSSG current treatment strategy is summarized in Fig. 6.5. Retrospective data of 66 infants (median age 1.7 months; range, 0–21.5) with IFS treated in

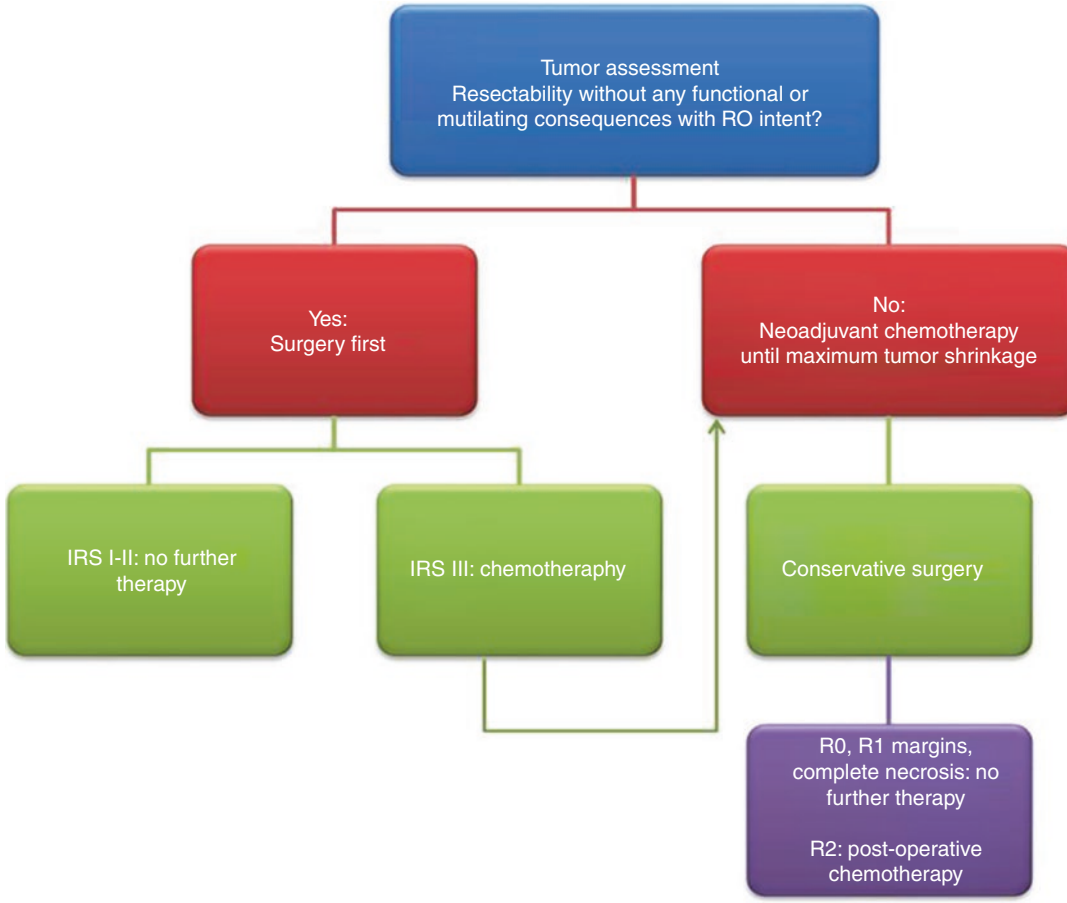

Fig. 6.5 Therapy summary for patients with infantile fibrosarcoma (EpSSG protocol). *IRS I* complete resection, *IRS II* microscopic residual disease, *IRS III* macroscopic residual disease, *R0* wide resection, *R1* marginal resection, *R2* gross residual disease after maximal surgery

the *Cooperative Weichteilsarkom Studiengruppe* (CWS) studies have been recently published (Sparber-Sauer et al. 2019). Main regimens used were vincristine, actinomycin-D, cyclophosphamide, Adriamycin (VACA) in CWS-81 and -86 and vincristine, actinomycin-D, cyclophosphamide (VAC) since the CWS-91 study (Ferrari et al. 2007). Since the CWS-96 study, a "wait and see" strategy was recommended after microscopically complete (R0, IRS group I) or microscopically incomplete (R1, IRS group II) resection. VAC was recommended for patients after macroscopically incomplete resection (R2 or biopsy, IRS group III) and in case of progressive disease (PD) (Sparber-Sauer et al. 2019). These regimens were followed by delayed surgery.

Since several decades, malignant tumors harboring a NTRK fusion transcript (Neurotrophic receptor tyrosine kinase) have been described. Initially, this fusion was highly associated to ETV6 (NTRK –ETV6) and mainly described in infantile fibrosarcoma (IFS). Progressively, this "specific" fusion transcript has also been discovered in other tumors as hypercellular mesoblastic nephroma, salivary gland carcinoma (Mammary analogue secretory carcinoma of salivary glands: MASC), or secretory breast carcinoma (Pavlick et al. 2017). In these tumors, the presence of this transcript is considered being frequent and remains an important tool for diagnosis (by FISH, RT-PCR, or RNA seq). Moreover, other partners (as, for instance, EML4-NTRK3 TMP3-NTRK1, LMNA-NTRK1, SCYL3-NTRK1) have been less frequently founded to be associated to NTRK gene in other malignant tumors (as other infantile mesenchymal tumors, colic carcinoma, lung carcinoma, inflammatory myofibroblastic tumor, brain tumor (low and high grade), or thyroid carcinoma, for instance) leading to consider that nowadays approximately the prevalence of the NTRK fusion transcript could be present in some more common tumors up to 1–2% (Wong et al. 2016). The recent clinical developments of a new class of compounds blocking the NTRK molecular pathway, which are still currently under early clinical investigation, give an important hope to find a specific new way to treat patients with these tumors. First results showed a real efficacy of these new drugs (larotrectinib, crizotinib, entrectinib) (DuBois et al. 2018). As an example, recently, Drilon et al. have tested a highly selective TRK inhibitor (larotrectinib) in adults and children who had tumors with these fusions and have found an overall response of 75% with a median time to response of 1.8 months (Drilon et al. 2018). Larotrectinib (LOXO-101) is the first highly selective pan-TRK inhibitor to enter clinical development with IC50 values in the low nanomolar range of inhibition for all the three TRK family members. Very encouraging efficacy results have been obtained in a phase I clinical trial (NCT02637687) (Laetsch et al. 2018). Larotrectinib is Food and Drug Administration (FDA)- and (European Medicines Agency) EMA-approved for the treatment of pediatric and adult patients with all solid tumors harboring *NTRK* gene fusions, and entrectinib is FDA and Japan approved.

6.4.7 Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT), seen mainly in adolescent and young adult males, usually presents as an abdominal or pelvic primary tumor with serosal dissemination and frequent invasion into other organs such as the liver, pancreas, and spleen. The tumor may also involve regional lymph nodes and frequently metastasize to the liver, kidney, lung, bone, and bone marrow (Philippe-Chomette et al. 2012).

Aggressive multimodality treatment with intensive chemotherapy may lengthen survival but usually is not curative. Although DSRCT is often responsive to sarcoma-directed chemotherapy, patients with this disease have an overall survival of only about 15% at 5 years. Tumor resection is critical for cure, as survival is vanishingly rare when the tumor is not grossly excised. Whole abdominal-pelvic radiotherapy has been used to treat serosal tumor dissemination. However, the dose that is feasible to deliver is usually insufficient for durable tumor control

even for microscopic residual disease. Hyperthermic peritoneal infusion with cisplatin chemotherapy has been shown to lengthen median survival in patients who have undergone a total or near total tumor resection but remains controversial in the literature, and some authors advise external beam radiotherapy instead (Atallah et al. 2016; Hayes-Jordan et al. 2014; Honore et al. 2017). Myeloablative chemotherapy with autologous stem cell transplant does not appear to significantly improve outcome and has fallen out of favor.

6.4.8 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive and rarely metastasizing neoplasm that is among the most common childhood soft tissue sarcomas. It usually arises in the trunk or extremities in superficial locations and is characterized by a t(17;22) translocation that produces the *COL1A1-PDGFB* fusion gene.

Wide local excision is curative in most cases, so primary re-excision should be considered after inadequate surgery. Mohs micrographic surgery may produce durable local tumor control while allowing smaller surgical margins than wide excision and should be considered in the appropriate clinical setting (Loghdey et al. 2014). In patients with unresectable, metastatic, or recurrent disease not amenable to surgery, systemic therapy is indicated. Imatinib, an inhibitor of the platelet-derived growth factor receptor tyrosine kinase, produces tumor responses in about half of patients with DFSP and can be curative in some cases. However, it is most often used in conjunction with surgical resection. Imatinib may also be considered in the adjuvant setting for patients with microscopic residual disease after maximal surgery. In adults whose tumor is resistant to imatinib, sunitinib also produces a high rate of disease control (Fu et al. 2015; Ugurel et al. 2014; Kerob et al. 2010). However, sunitinib has not been evaluated in pediatric patients for this indication. Although dermatofibrosarcoma protuberans is radiosensitive, radiotherapy is rarely used in pediatric patients since its toxicities are thought to exceed those of imatinib.

6.4.9 Gastrointestinal Stromal Tumor (GIST)

Although the most common adult soft tissue sarcoma of the gastrointestinal tract, gastrointestinal stromal tumor (GIST) is very rare in pediatric patients, where it disproportionally affects females. Unlike adult GISTs that are characterized by mutations causing constitutive activation of *KIT* or *PDGFRA*, most pediatric GISTs lack these mutations and are referred to as "wild-type." A substantial proportion of wild-type GIST have loss of function of the succinate dehydrogenase complex, which in some cases may be due to germline mutations that predispose to other types of cancer including paraganglioma (Miettinen et al. 2011).

Surgery is the mainstay of therapy for all GISTs. Those with tumors that can be removed with adequate margins and without significant functional consequences should undergo wide resection. Lymph node sampling should also be considered since nodal involvement is more common in young patients. Adjuvant therapy has not been studied in pediatric patients and is generally not recommended. The approach to treatment of pediatric GIST depends on the underlying tumor biology. If *KIT* or *PDGFRA* activating mutations are identified, treatment guidelines established for adults, such as those of the National Comprehensive Cancer Network, may be used. Because pediatric wild-type GIST may behave in an indolent fashion and there are no known effective treatments, patients with unresectable or metastatic disease who are asymptomatic may not require treatment. Symptomatic patients may be given tyrosine kinase inhibitors such as imatinib or rather sunitinib, although there are no published data yet comparing the efficacy of these two agents in pediatric GIST patients (Benesch et al. 2011).

6.4.10 Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is a rare soft tissue sarcoma that has a variable biologic behavior ranging from a benign course to aggressive disease dissemination. More than half have rearrangement of the *ALK* gene on chromosome 2p23; those without *ALK* rearrangement often have *ROS1*, *NTRK*, or *PDGFRB* fusions (Lovly et al. 2014).

The variable clinical behavior of IMT makes treatment selection challenging. When feasible, wide tumor resection is the treatment of choice. Cytotoxic chemotherapy has been used for unresectable or metastatic disease, but efficacy data are limited. Nonsteroidal anti-inflammatory drugs have also been used with some success; high VEGF and COX-2 expression in IMTs suggest that this may be due to disruption of angiogenic signaling. Steroids have also been used. *ALK* inhibitors such as crizotinib and *ROS1* or *NTRK* inhibitors (entrectinib, larotrectinib) may produce rapid and sustained tumor responses in *ALK/ROS/NTRK*-rearranged IMT, but acquired drug resistance can develop (Mosse et al. 2013; Rolfo et al. 2015).

6.4.11 Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) is a very rare sarcoma that can occur at any age but mainly affects adolescents and young adults, with a peak of incidence in the third decade. About one third of ASPS occur in children and adolescents (Orbach et al. 2013; Sparber-Sauer et al. 2018b). The critical role of surgery in localized disease is emphasized by all published studies. In case of incomplete initial resection, a second surgery before any other treatment (primary re-excision) is recommended to achieve clear margins and avoid the need for further treatment (Casanova et al. 2000). The possibility to obtain a complete tumor resection seems strictly related to the tumor dimensions and the absence of extension to nearby organs. This is little modified by the addition of chemotherapy and/or radiotherapy due to the unsatisfactory response of ASPS to neoadjuvant treatment.

Radiotherapy with doses ranging from 45 to 60 Gy has been administered to children with unresectable tumors. Although this seems a rational approach, there are no convincing data that irradiation may significantly change the natural history of the disease (Orbach et al. 2013; Casanova et al. 2000). Patients with complete tumor resection (IRS group I) likely do not need systematic adjuvant radiotherapy, unlike those who undergo marginal resection (IRS II) even if these latter case data are scarce (Orbach et al. 2013). In the literature, most patients with gross residual tumor (IRS group III) had delayed surgery after neoadjuvant medical therapy. Almost all received adjuvant radiotherapy even after complete secondary resection, preventing analysis of the precise benefit of radiotherapy in this situation.

ASPS is one of the less chemosensitive NRSTS. In different series of adult ASPS, no objective response to conventional chemotherapy has been reported. Recently, the European Cooperative Groups published a joint analysis on a large series of pediatric and adolescent patients with ASPS and reported a 17% response rate to conventional chemotherapy (Orbach et al. 2013). The better characterization of the biological features of ASPS has allowed testing of new molecules that can target the genetic alteration. In particular, gene expression profiling of ASPS specimens demonstrates an array of potentially therapeutically targetable, angiogenesis-related molecules. Reports about clinical use and efficacy of targeted therapies focus on sunitinib, cediranib, pazopanib, or bevacizumab or immunotherapy as immune checkpoint inhibitors (Bisogno et al. 2014). The systematic adoption of targeted agents as first-line chemotherapy for unresectable or metastatic ASPS should be considered given the low likelihood of response to standard chemotherapy. The response to tyrosine kinase inhibitors supports the inclusion of ASPS patients in specific trials testing the activity of these targeted therapies (Fig. 6.6). However, a recent publication showed that cediranib in a phase II study did not reach the targeted response

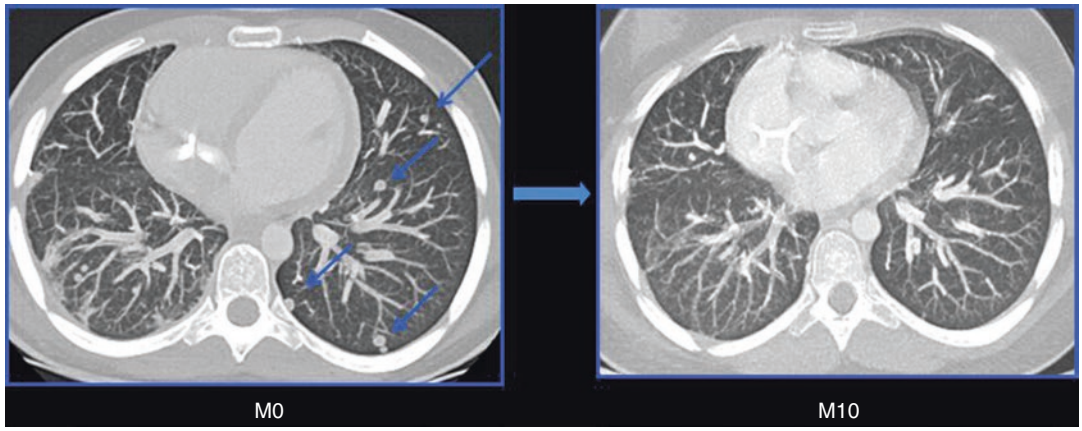

Fig. 6.6 Example of partial response of lung metastases to sunitinib in an 8-year-old female with stage IV thoracic wall alveolar soft part sarcoma (with ASPSTR1/TFE3 transcript). *M0* prior to initiation of therapy, *M10* after 10 months of therapy (sunitinib 25 mg/day, 4 weeks/6)

rate with no tumor response among seven children with ASPS and nevertheless prolonged stable disease (Cohen et al. 2019).

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