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Soft Tissue Sarcomas in Children

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Abstract Pediatric soft tissue sarcomas (STS) are a heterogeneous group of malignant tumors constituting about 7% of all cancer cases. Rhabdomyosarcomas (RMS) constitute about half of all soft tissue sarcomas in children, the rest being constituted by non- rhabdomyosarcoma soft tissue sarcomas (NRSTS). Most RMS present in young children <6 y of age while the NRSTS occur in adolescents and young adults. The latter constitute a diverse group of tumors and are rare in children. The STS generally present as painless enlarging mass or with symptoms of compression/infiltration of adjacent organs or structures. Staging, risk stratification and multidisciplinary approach are needed for the treatment of STS and outcome depends on stage, site and histological type. Treatment of RMS has evolved systematically through various clinical trials. Chemotherapy remains the backbone of treatment for RMS and local control is achieved either with surgery or radiotherapy or both. Management of NRSTS is still a challenge as it is generally chemotherapy-resistant and surgery remains the mainstay of treatment. Outcome therefore depends on whether wide local excision with negative margins is possible. Local radiotherapy is reserved for recurrent, residual and large high grade NRST. The prognosis of metastatic as well as recurrent STS remains dismal.

Keywords Rhabdomyosarcoma · Pediatric · Soft tissue sarcoma · Non-rhabdomyosarcoma soft tissue · Sarcoma

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Introduction

Pediatric soft tissue sarcomas (STS) are a heterogeneous group of malignant tumors that originate from primitive mesenchymal tissue and account for 7% of all childhood tumors. Among children these neoplasms are broadly classified into two groups, the rhabdomyosarcomas (RMS) comprising about half of all cases of pediatric STS and the non rhabdomyosarcomatous soft tissue sarcomas (NRSTS) that account for approximately 3% of all childhood tumors. The latter constitute a diverse group of tumors and are rare in children. These include fibrosarcoma, neurofibrosarcoma, leiomyosarcoma, dermatofibrosarcoma protruberans, liposarcoma, synovial sarcoma, hemangiopericytoma, alveolar soft part sarcoma, epitheloid sarcoma, and malignant fibrous histiocytoma; of which the synovial sarcomas, fibrosarcomas, and malignant peripheral nerve sheath tumors predominate in pediatric patients.

Epidemiology

The STS constitute 4–8% of all cancers in children 0–14y of age in Europe, Asia and America, which is similar to that reported by the Indian cancer registry (ICMR) [1, 2]. US Cancer statistics reveal that in 2008 about 10,390 new cases of STS were diagnosed, of which about 10% were in the age group of <20 y [3]. In addition, about 350 new cases of RMS occur each year in the US in the same age group. Nearly 2/3rd cases of RMS occur in children ≤6 y with a small mid-adolescent peak [4]. In contrast, the NRSTS account for >75% of STS in the 15–19 y age group [5].

Etiopathogenesis

There are no known definitive environmental factors that cause rhabdomyosarcoma in children. Some genetic and environmental factors have been associated with the development of NRSTS and rarely with RMS: Li-Fraumeni syndrome and Neurofibromatosis type 1 (NF1). Members of the Li-Fraumeni families have an increased risk of developing soft tissue tumors, bone sarcomas, breast cancer, brain tumors, and acute leukemia and have heritable mutations in the*p53*tumor suppressor gene. Approximately 4% of patients with neurofibromatosis type 1 develop malignant peripheral nerve sheath tumors. Patients with familial adenomatous polyposis are at increased risk for developing desmoid tumors; while those with malignant fibrous histiocytoma can develop within a previously irradiated site; others (*e.g.*, leiomyosarcoma) have been linked to Epstein-Barr virus infection in patients with Acquired Immune-Deficiency Syndrome (Kaposi sarcoma) [6].

Pathology

Rhabdomyosarcoma is a malignant round cell tumor, and can appear very similar to other childhood cancers at the microscopic level, and immunohistochemistry (IHC) and molecular genetic tests are often required to confirm the diagnosis. The immunohistochemistry for muscle and muscle specific protein and genes include muscle specific actin, desmin, myosin, myoglobin, myo D and Z band protein.

The histological classification of STS based on the International classification of childhood cancers is depicted in Table 1 [7]. Embyonal RMS (ERMS) (including botryord and spindle cell subtype) is associated with a very good prognosis, while the alveolar RMS (ARMS) is a resistant histological class. The alveolar RMS (ARMS) is associated with t (2;13) (q35, q14), and t (1;13) (p36, q14), while ERMS has LOH of 11q15.

The NRSTS have certain characteristic chromosomal aberrations for *e.g.*, synovial sarcoma t(x;18)(p11.2;q11.2) [SYT/SSX]; alveolar soft part sarcoma t(x;17)(p11.2;q25) [ASPL/TFE3]; dermatofibrosarcoma t(17;22)(q22;q13) [COL1A1/PDGFB]; desmoplastic small round cell tumors t(11;22)(p13;q12) [WT1/EWS] amongst others (Table 1).

Clinical Features

The most common presentation of childhood soft tissue sarcoma is a progressive painless lump or swelling which may occur anywhere in the body. There may be no other symptoms at first, however, as the sarcoma grows it may manifest with pressure symptoms on adjacent organs, nerves, muscles, or blood vessels, and also lead to pain or weakness.

As RMS may originate in different sites of the body, local features vary widely. About 40% of pediatric RMS originate in the head and neck region, with many (50%) having parameningeal involvement (base of skull- para-nasal sinuses and nasal cavity, pterygopalatine/infratempo-ral fossa, middle ear, nasopharynx). The remaining half are almost equally distributed among orbital and non-orbital non-parameningeal (scalp, face, larynx, oropharynx) RMS. They may present with headache, seizure, emesis, cranial nerve palsy, proptosis or polypoidal mass protruding from

Table 1 Classification of STS, according to histological type with corresponding chromo-somal aberration

Group	Histological type	Chromosomal aberration
Rhabdomyosarcomas	Pleomorphic RMS	
	Embryonal RMS	LOH of 11q15
	Alveolar RMS	t(2;13)(q35,q14), t(1;13)(p36,q14)
Non-Rhabdomyosarcomas soft tissue sarcomas	Fibrosarcoma	
	Neurofibrosarcoma	Deletion 17q 11.2
	Infantile Fibrosarcoma	t(12;15)(p13;q25)
	Malignant fibrous histiocytoma	(qp+, ring chromosome)
	Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)
	Kaposi's sarcoma	
	Hemangioendothelioma	
	Leiomyosarcoma	t(12;14)
	Liposarcoma	
	Angiosarcoma	
	Synovial sarcoma	t(x;18)(p11.2;q 11.2)
	Alveolar soft part sarcoma	t(x;17)(p11.2;q25)
	Epithelioid sarcoma	

Adapted and modified from Steliarova-Foucher E et al. [7]

nasal or aural cavity with or without sangiunous discharge. Most head and neck tumors occur in children under the age of eight, while those of the extremity are most commonly found in adolescents.

RMS arising from genitourinary tract may present with hematuria, stranguary or multiple polypoidal masses protruding from introitus (botryoid RMS of vagina). Paratesticular RMS generally present as painless, unilateral scrotal swelling reaching upto inguinal canal (thickened spermatic cord).

RMS arising from extremities usually presents as a painless lump, often of alveolar histology and 50% have lymph node involvement. RMS in body cavity (thorax, abdomen or pelvis) may produce mass effect like respiratory difficulty, intestinal obstruction and constipation. Rare sites include perianal, biliary, hepatic, cardiac and brain [8–10].

About 15–25% newly diagnosed RMS are found to have distant metastasis,lung being the most common site (50%); others being bone marrow (30–40%); bone (10%) and lymph node depending on site (5–50%). Systemic symptoms (*e.g.*, fever, weight loss, and night sweats) are however rare.

The NRSTSs arise most commonly in the trunk and extremities. These neoplasms can present initially as an asymptomatic solid mass, or they may be symptomatic because of local invasion of adjacent anatomical structures (*e.g.* nerve sheath or joint). Synovial sarcomas, the most common NRSTSs reported in children occur most commonly in the lower extremity followed by upper extremity, trunk, abdomen, and head and neck. Approximately 30% of patients with synovial sarcoma are younger than 20 y. The most common site of metastasis is the lung. Factors such as International Union Against Cancer/American Joint Committee on Cancer stage III/stage IVA, tumor necrosis, truncal locations, elevated mitotic rate, age, and histological grade have been associated with a worse prognosis in adults.

At presentation, only small numbers of tumors are metastatic and lung is the most common site. Bone, bone marrow, liver and subcutaneous tissue metastasis are very rare. Lymph node involvement is noted with clear cell sarcoma and epitheloid sarcoma [11, 12]. Tumors (hemangiopericytoma, solitary fibrous tumor and leiomyosarcoma) may have paraneoplastic feature of hypoglycemia, while hemangiopericytoma may be associated with hypophosphotemic rickets [13, 14].

Diagnosis

The first step is to establish a confirmed histological diagnosis. Often an imaging (computed tomography (CT) scan or magnetic resonance imaging (MRI)) of the tumor is done followed by an FNAC prior to planning a biopsy. Obtaining adequate tissue for histology and immunohistochemistry is very important. The type of biopsy—trucut needle biopsy, incisional biopsy or excisional biopsy is determined based on the FNAC and imaging results. The genetic and molecular aberrations peculiar for the RMS and NRSTS are listed in Table 1 and help confirm the diagnosis. Parham et al. devised a grading system for NRSTS in children that has subsequently been verified by the Pediatric Oncology Group and is based on histological subtype, amount of necrosis, number of mitosis and cellular pleomorphism, grouping them as low, intermediate, and high grades [15].

Staging

Once histological diagnosis is confirmed further tests are done to determine the stage of the disease. Clinical staging has an important role in predicting the clinical outcome and determining the most effective therapy for pediatric soft tissue sarcomas. In RMS, staging work-up includes bone marrow aspiration and biopsy; CT chest and bone scan to look for metastatic disease. While for NRSTS only CT chest is done usually. Whole body PET scan may also be done as a single imaging to look for metastatic disease. The staging systems used for RMS are the CCG surgicopathological staging, IRSG (Intergroup Rhabdomyosarcoma Study Group) TNM (tumor, node, metastases) and the Children's Oncology Group (COG) Rhabdomyosarcoma Risk Group Classification for rhabdomyosarcoma (Tables 2, 3 and 4) [16–20]. There is no consensus over staging strategy for pediatric NRSTS although there are different proposals made by American Joint Committee on Cancer (AJCC), Memorial Sloan-Kettering Cancer centre (MSKCC) and Musculoskeletal tumor society [21–23].

Prognosis

The treatment outcome for pediatric RMS depends on anatomic site, patient age, stage and histology, on the basis of which they are risk stratified. The various unfavorable prognostic factors include older age, metastatic disease, large tumor, alveolar histology and primary in extremity, trunk or pelvis. Low-risk, intermediate-risk and high-risk patients have a 3-year failure free survival rate of 88%, 55–75% and<30% respectively (Table 4) [20].

Treatment

The treatment for childhood soft tissue sarcomas is coordinated by a multidisciplinary oncology team comprised of pediatric oncologists, surgeons, and radiotherapists in addition to the nutritionist, psychologist and physiotherapist.

Table 2 COG-STS pretreatment staging system [18, 19]

Stage	Sites of Primary Tumor	T Stage	Tumor Size	Regional Lymph Nodes	Distant Metastasis
I	Favorable sites	T1 or T2	Any size	N0 or N1 or NX	M0
	Orbit	T1 or T2			
	Head & Neck	T1 or T2			
	Genitourinary	T1 or T2			
II	Unfavorable sites	T1 or T2	a, ≤ 5 cm	N0 or NX	M0
	Bladder/Prostate	T1 or T2			
	Extremity	T1 or T2			
	Cranial parameningeal	T1 or T2			
	Other	T1 or T2			
III	Unfavorable sites	T1 or T2	a, ≤ 5 cm	N1	M0
	Bladder/Prostate	T1 or T2			
	Extremity	T1 or T2			
	Cranial parameningeal Other	T1 or T2	b, >5 cm	N0 or N1 or NX	
		T1 or T2			
IV	Any site	T1 or T2	Any size	N0 or N1 or NX	M1
	All	T1 or T2			

M0 absence of metastatic spread, *M1* presence of metastatic spread beyond the primary site, *N0* absence of nodal spread, *N1* presence of nodal spread beyond the primary site, *X* unknown N status

It is important to distinguish RMS from other soft tissue sarcomas that occur in children and adults, because RMS is generally a highly chemosensitive tumor. Although local control is essential for the successful treatment of RMS (because local progression or relapse is the main cause of treatment failure), surgery and radiotherapy need to be used with careful thought, given the important sequelae of these treatments in children.

All children diagnosed with rhabdomyosarcoma will require *surgery*, either to remove all or part of the primary tumor, or to perform an incisional/needle biopsy to reach a definitive diagnosis. Approximately 10% of newly diagnosed children have tumors that can be completely removed. Every attempt should be made to resect the primary tumor with negative margins before or after chemotherapy (second look surgery) and while causing minimum cosmetic and functional impairment.

Radiotherapy (RT) is an important local control measure for all children with rhabdomyosarcoma except those with completely resected stage I and II disease. Total radiation dose ranges from 4000 to 5500 cGy over a period of 4–6 wk. It is usually planned approximately 9 wk after chemotherapy has begun and earlier for those with parameningeal disease. With the use of both surgery and radiation therapy, local control of the primary tumor can be achieved in more than 80% of patients.

Chemotherapy is the backbone of treatment for rhabdomyosarcoma since it is believed to be a systemic disease with presence of micrometastasis from the time of diagnosis. It is a chemosensitive tumor as more than 80% cases of newly diagnosed cases of RMS respond to currently available chemotherapy regimens, and the role of multiagent chemotherapy in its treatment has been clearly demonstrated.

Table 3 COG-STS surgico-pathologic group system [16, 17]

Group	Definition
I (Approximately 13% of all patients are in this group)	A localized tumor that is completely removed with pathologically clear margins and no regional lymph node involvement
II (Approximately 20% of all patients are in this group)	A localized tumor that is grossly removed with (a) microscopic disease at the margin, (b) involved, grossly removed regional lymph nodes, or (c) both (a) and (b)
III (Approximately 48% of all patients are in this group)	A localized tumor with gross residual disease after incomplete removal or biopsy only
IV (Approximately 18% of all patients are in this group)	Distant metastases are present at diagnosis

Table 4 COG-STS rhabdomyosarcoma risk group classification [20]

Risk group prognosis(Event-free survival)	Histology	Stage	Group
Low risk excellent (70%–≥85%)	Embryonal	1	I, II, III
	Embryonal	2, 3	I, II
Intermediate risk good (50%–70%)	Embryonal	2, 3	III
	Alveolar	1, 2, 3	I, II, III
High risk poor (≤30%)	Embryonal or Alveolar	4	IV

Hence, all children with rhabdomyosarcoma receive chemotherapy, with the dose and duration dependent on risk stratification. Prior to combination therapy, surgery alone resulted in survival rates of less than 20%. The development of adjuvant and neoadjuvant therapy has increased survival in patients with localized disease to approximately 60%. Agents with known activity in the treatment of RMS include vincristine (V), actinomycin D (A), doxorubicin (Dox), cyclophosphamide (C), ifosfamide (I), and etoposide (E). The total duration of treatment ranges from 6 to 12 mo depending on risk group and treatment protocol selected.

The Intergroup Rhabdomyosarcoma Study Group (IRSG) was formed under the auspices of the National Cancer Institute in 1972 to investigate the therapy and biology of RMS and undifferentiated sarcoma (UDS) in previously untreated patients less than 21y of age. The patients were recruited from member institutions of the three cooperative pediatric cancer treatment groups existing at the time. Since then, five successive clinical protocols involving 4292 eligible patients have been completed: IRS-I, 1972±1978; IRS-II, 1978±1984; IRS-III, 1984±1991, IRS-IV Pilot (for patients with advanced disease only), 1987±1991; and IRS-IV, 1991±1997 [16, 24–26]. Some important lessons have been learnt from these trials. VAC has been the gold standard for combination chemotherapy in the treatment of most cases of RMS.

The addition of DOX and cisplatin with or without etoposide to the VAC regimen has not improved outcome for patients with advanced disease in IRS-III. Data from IRS-IV indicate that the current standard combination of VAC, with cyclophosphamide at 2.2 g/ml per dose with GCSF is equally efficacious with regard to failure-free and overall survival as are VAI and VIE [27]. The higher dose of cyclophosphamide was beneficial for patients with embryonal RMS and not alveolar subtype.

Low Risk Patients

Both North American and European studies have explored, the chances of reducing the intensity of chemotherapy, without jeopardizing the survival, in patients considered to be at low risk of failure. Currently, a 22-wk chemotherapy regimen lacking an alkylating agent and anthracyclines, the VA regimen (vincristine and actinomycin), is considered effective for low-risk patients.

Intermediate Risk Patients

The VAC regimen (combination of vincristine, actinomycin D and cyclophosphamide) is considered the mainstay of chemotherapy in IRS trials, whereas the IVA regimen (ifosfamide, vincristine, and actinomycin D), which differs in the alkylating agent selected is considered the gold standard in Europe [28–32]. The duration of treatment has progressively been reduced over the years, from the 2 y of the first IRS protocol, and it currently lasts 12 mo.

High Risk Patients

The prognosis for high-risk patients is still unsatisfactory, and effective drugs for new intensive regimens for these patients remain to be identified. These patients are currently treated with chemotherapy protocols that are similar to that for intermediate risk patients.

Management of *recurrent RMS* remains challenging with poor outcome. The optimal treatment is not well defined. While localized recurrence may be managed with complete surgical resection, adjuvant RT and chemotherapy with acceptable outcome, disseminated recurrence has very poor survival [33–35]. Various chemotherapeutic agents like vincristine, carboplatin, topotecan, irinotecan, cyclophosphamide and combinations like carboplatin/etoposide, cyclophosphamide/topotecan, irinotecan/vincristine have been tried in clinical trial settings with variable results [36–38]. High dose chemotherapy and autologous stem cell rescue has not been found to offer any survival benefit in these patients.

For *NRSTS, surgery* is the cornerstone of treatment. These tumors are generally radiosensitive but chemoresistent. The most important prognostic factor is the ability to completely remove the primary tumor mass with wide margins (portions of the surrounding tissue) to ensure that no microscopic disease remains.

Although NRSTS are *radiosensitive* tumors, they need higher doses of radiation. Extent of resection is determining factor for RT as it is not required for completely excised low grade or <5 cm tumor where negative margin is achieved. Adjuvant radiation therapy is indicated for patients with inadequate surgical margins (important in high-grade tumors with tumor margins less than 1 cm) or in cases with gross or microscopic residual tumor, or repeat

surgery. Although in low grade tumor even positive margins can be managed with observation or re-surgery without RT. A dose of 45–50 Gy is recommended for resected tumor and additional 10–20 Gy is given to margin positive tumors. Brachytherapy and intraoperative radiation may be applicable in selected situations.

The role of chemotherapy is not well established and its role remains controversial in adjuvant setting. It is sometimes used to shrink large tumors to make them operable. Some tumors like synovial sarcoma and desmoid fibromatosis are chemo-sensitive while majority are not [39]. The most effective agents are doxorubicin and ifosphamide [40–42]. Chemotherapy is often reserved for non resectable or overtly metastatic disease; however, their outcome remains unsatisfactory.

Late Effects

Improved outcomes with multimodality therapy, in children with soft tissue sarcomas, has caused increasing concern about the potential long-term side effects of therapy, especially when considering the expected longer life span of children. Late effects including consequences on growth and development, infertility, cardiac function, second malignancy *etc.* all need to be considered when planning treatment.

Key Messages

- Soft-tissue sarcomas comprise the fifth most common type of childhood solid tumor, of which rhabdomyosarcoma is the most common.
- They can arise at any site and in any tissue in the body except bone, hence may present as a mass or lump anywhere.
- Confirmation of histology and staging work-up are essential prior to starting therapy.
- The treatment for childhood soft tissue sarcomas is a coordinated multidisciplinary team effort comprising of pediatric oncologists, surgeons, and radiotherapists.
- Chemotherapy is an essential component of therapy for rhabdomyosarcoma along with surgery and/or RT for local control. Survival depends on risk group.
- For NRSTS surgery is the mainstay of treatment with or without RT.

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