Malignant Soft Tissue Tumors

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Contents

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107.1 Introduction

The soft tissues of the body have their origin in embryonic mesoderm and include fat, bone and cartilage tissue, fibrous tissue, muscles, nerves, blood and lymphatic vessels, tendon, and synovial tissues around joints.

In children, tumors of these soft tissues (STS) are mostly benign or reactive lesions of connective tissue and usually present as an asymptomatic mass in an extremity. Malignant tumors are less common with less than 1000 new soft tissue sarcomas being reported in children each year in the United States.

However, a number of malignant tumors arising from these tissues are aggressive and require multimodal approach including surgical management. These malignant tumors are usually tissue specific, indicating the tissue of origin, but a number of undifferentiated tumor types occur. Malignant soft tissue tumors that occur in the connective tissue of the body, such as muscle, fat, and fibrous tissue, are usually referred to as sarcomas.

The most common sarcomas in children are rhabdomyosarcoma (muscle), osteosarcoma (bones), and Ewing's sarcoma (inside or outside the bone).

107.1.1 Epidemiology of Soft Tissue Tumors

107.1.2 Demographics

Malignant soft tissue sarcomas (STSs) are relatively rare in childhood, contributing approximately 5–8% of childhood malignancies (approximately 850–900 children and adolescents diagnosed in the United States each year) [1].

In general, STS tumors are slightly more common in boys than girls. In a retrospective study of 91 children conducted in Nigeria, the male/female ratio was 1.5:1 with a mean age of 6.2 years (range 1–14 years) [2].

The prevalence of STS appears to vary among population groups worldwide. In ethnic groups representing mainly Caucasian populations, an age-standardized STS annual incidence rate of 5–9 per million can be expected, but this rate has recently been observed to be increasing in Europe. In the United Kingdom, about 60 children develop a soft tissue sarcoma each year. In Asia, the age-standardized STS annual incidence rate is less than 6 per million. Due to the paucity of data, the age-standardized STS annual incidence rates for Africa remain uncertain, but there is a widely held view that they are more common—if not more frequent—in black African children and adolescents than in Western population groups. A Nigerian study has reported STS as making up as much as 11.3% of all childhood cancers.

Rhabdomyosarcoma (RMS) predominates as the most common malignant tumor of soft tissues presenting during childhood, the most common being in the head and neck, the bladder, and paratesticular sites.

Fibrosarcomas have been reported as being more prevalent in black African Americans than in Caucasians (both males and females) in the United States [3]. A similar spectrum is thought to exist in Africa.

107.1.3 Etiology and Pathophysiology

Sarcomas are malignant tumors of mesenchymal origin and derive from a variety of cell types. Their pathology usually relates to their site and cell of origin. Although they represent only 1% of tumors seen in an adult oncology clinic, their prevalence in childhood appears higher.

The most commonly occurring malignant STS tumor is rhabdomyosarcoma which makes up 50–60% of all STS in childhood. It is thus the most common sarcoma in children with approximately 66% occurring under 6 years of age. Other soft tissue sarcomas include synovial sarcoma, infantile fibrosarcoma, malignant peripheral nerve sheath tumors, and malignant fibrous histiocytoma among others.

There is a noted interethnic variation between rhabdomyosarcoma and fibrosarcoma occurrence in children versus adults. This, together with the established genetic and inheritable associations, suggests that genetic dysfunction is important in the pathophysiology. In addition, viral exposure may also play a role, and Kaposi sarcoma (KS) rates are peaking in African children, mostly from Eastern and Southern Africa in association with the acquired immune deficiency syndrome (AIDS) epidemic.

Although the etiology of sarcomas remains obscure, however, a possible genetic origin is proposed, because of the associations of known genetic syndromes and other genetic associations such as the translocated fusion genes associated with the alveolar subtype and Ewing's tumor groups. Germline mutations could account for familial transmissibility in conditions like the complex cancer predisposition associated with the Li-Fraumeni association (Germline TP53 (tumor protein 53) mutation) [4]. Impaired differentiation of myoblasts in RMS is associated with a tumor suppressor-like action due to reconstitution of miR-29, which promotes cellular differentiation and inhibits tumor growth in animals [5], as there is an association with the alternative lengthening of telomeres (ALT) mechanism in about half of the osteosarcomas, STSs, and glioblastomas.

107.1.4 Diagnosis

STS falls into a large and heterogeneous group of lesions which include both neoplastic (benign and malignant) and nonneoplastic lesions. Soft tissue masses may

represent a diagnostic dilemma to the clinician; the differential diagnosis is extremely wide. Clinical assessment of the local and regional involvement as well as the relationship with other neighboring structures may prove difficult to assess.

107.1.4.1 Clinical Presentation

The diagnosis of soft tissue sarcoma (STS) is a complex assessment involving an initial careful history and physical examination. All clinicians should be able to identify the unique characteristics of malignant soft tissue tumors and assist patients with obtaining care from a specialist. This is followed by diagnostic imaging studies and surgical biopsy where indicated.

STSs occur in numerous sites, including the trunk, retroperitoneum, or the head and neck, in addition to the extremities. No etiologic factors have been identified in the majority, even though a variety of predisposing or associated factors have been identified.

From a clinical point of view, at least three separate clinical groups of malignant STSs are encountered in childhood:

- Congenital fibrosarcoma (CFS).
- Rhabdomyosarcoma (RMS).
- Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS).

Fibrosarcoma may also warrant a separate group in the classification, but fibrosarcomas that occur in childhood have a very different biological behavior, despite their malignant histological appearance. In contrast to the situation in adults, where fibrosarcoma was the most frequent STS, rhabdomyosarcoma predominates in children in Africa as well as worldwide.

107.1.4.2 Differential Diagnosis

Because of its origin in soft tissue, the differential diagnosis of STS is extremely wide, being that of any soft tissue mass that is growing. Findings on physical examination depend on the type and site of the tumor.

107.1.4.3 Special Investigations

Imaging of Soft Tissue Tumors

For the most part, special investigations are presented in this chapter under the specific type of STS.

In Western countries, computed tomography (CT) and particularly magnetic resonance imaging (MRI) are considered essential for the staging of STS. With the excellent tissue contrast, multi-planar capability, and lack of ionizing radiation, MRI has rapidly become the modality of choice in the evaluation of deep and large soft tissue tumors in children.

Histological Grading

Histological grading of STS is often difficult, with more than 70 histologic types currently being identified, including RMS, KS, and vascular tumors, predominantly in the pediatric and adolescent age groups. RMSs and undifferentiated sarcomas are the most frequent types, making up more than 50% of STSs in most series of childhood tumors, with the remainder falling into the heterogeneous NRSTS group.

107.1.5 Management of STS

107.1.5.1 Priorities in Management

The main aim of STS management is initial accurate diagnosis and classification. An assessment of staging of the disease remains an important prognostic parameter.

Treatment aims at improved local control, disease-free survival, and outcome with quality of life. The role of systemic chemotherapy for soft tissue sarcoma is still evolving, but at present there are overall survival benefits for specific histological types, especially in children. Novel therapies, which are based on disease mechanisms at the molecular level, show promise for future advances.

107.1.5.2 Surgical Management

The role of the surgeon in STS is to

- Establish a diagnosis.
- Perform timely and adequate removal (often following chemotherapy).
- Assess spread with a view toward staging.
- Provide supportive care (e.g., long-term venous access, feeding, etc.)

107.1.6 Outcomes and Prognosis

The outcome of most STS has shown a marked improvement over the past 30 years, with a decrease in radical surgical procedures, improved 5-year survival, and a decrease in morbidity. This improvement can largely be attributed to teamwork within national and international study groups and the establishment of clear treatment protocols.

The age at diagnosis of STS appears to be a fairly major predictor of survival. Up to 77% of tumors occurring before the age of 1 year are surgically resectable, having the lowest occurrence of invasive or high-grade tumors. As a result, a 5-year survival of 93% has been reported in this age group [6]. The good prognosis of this group drops significantly with increasing age, and is probably below 50% event-free survival for children aged 5 years, and less than one-third for older children (>11 years of age).

107.2 Specific Malignant Soft Tissue Tumors

107.2.1 Fibrosarcoma in Childhood

The age-standardized STS annual incidence rate for malignant fibromatous tumors is 1–2 per million in the United States. Fibrosarcoma is the most common NRSTS in the <1 year age group.

Congenital fibrosarcoma usually occurs in the extremities or trunk, (■ Fig. 107.1) and although histologically it appears malignant, it behaves benignly and rarely metastasizes. In children older than 4 years of age, the natural history of fibrosarcomas approximates that of the adult tumor, and the treatment is more radical than for younger children.

In U.S. population groups, a higher incidence of fibrosarcoma has been reported among black people compared to white people for both sexes, suggesting that fibrosarcoma may be more prevalent in African populations.

Malignant fibrous histiocytoma (MFH) also occurs in children.

Inactivation of the RB1 gene has been shown to be involved in tumors such as fibrosarcoma, osteogenic sarcomas, and melanomas in early adult life. Of interest is the association of this gene with infantile fibrosarcoma via the ETV6-NTRK fusion protein [7].

Since the 1980s the identification of balanced translocations in STSs has changed the face of histopathological identification to a combination of histopathological and molecular genetic identification. Sarcomas that are known to have identifiable gene fusions include synovial sarcomas (SYT-SSX), Ewing's sarcomas (EWS-Fli1), clear cell sarcomas (EWS-ATF1), and myxoid liposarcomas (FUS-CHOP), among others [7]. The ETV6-NTRK fusion associated with infantile fibrosarcoma may link it to mesoblastic nephroma. Considered to be disease-specific, the identification of sarcoma translocations and their fusion is possible, but limited by the availability of specific resources. Fibrosarcomas of bone may also occur.

Prognosis for infantile fibrosarcomas is excellent following surgical excision. The survival rate drops to 60% in the older child, however.

107.2.2 Rhabdomyosarcoma in Children

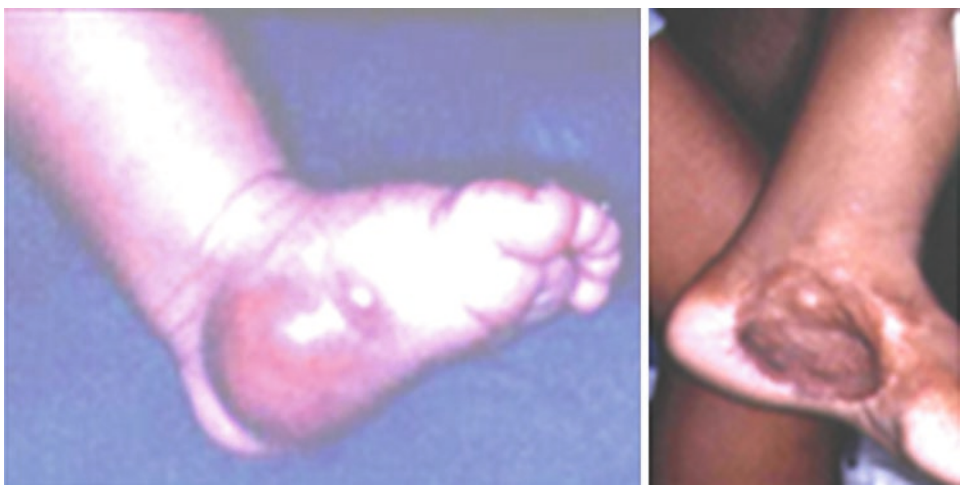
Rhabdomyosarcoma is a malignant tumor of striated muscle, which usually displays early local invasiveness and may later metastasize via lymphatic and hematogenous pathways. It is derived from mesenchymal cells that differentiate along rhabdomyoblastic lines, often displaying cross-striations on histopathological examination. It is the most common STS encountered in childhood, occurring even in the perinatal period [8] (10% of neonatal malignancies [9]). RMS may arise from any site during childhood but the commonest sites include the head/neck (25.6%), leg/foot (26.7%), and thigh 50 (19%) in an African series.[10] Rhabdomyosarcoma can occur anywhere in the body: with the Head and neck: accounting for ±39% and parameningeal sites (near the meninges) 24%. The orbit accounts for ±8% and other head and neck sites 7%.

It is also not uncommon in genitourinary sites (29%) as well as other sites in 17%. These include the trunk and other intrathoracic sites, the biliary tract, and other retroperitoneal, pelvic, or perineal sites (mostly in proximity to the anus, vagina, etc.)

107.2.2.1 Rhabdomyosarcoma Etiology

Although the etiology of RMS is still unclear, certain families have an increased susceptibility to multiple primary neoplasms. This is particularly true of certain syndromic associations (e.g., the Li-Fraumeni syndrome). In this context, RMS may be associated with a number of genetically related syndromes which include:

- Beckwith-Wiedemann syndrome.
- Li-Fraumeni syndrome.



■ **Fig. 107.1** Congenital fibrosarcoma of the foot in an infant (left) and the result of wide excision at 7 years of age (right)

- WAGR association (Wilms' tumor, Aniridia, Genitourinary malformations, mental Retardation) syndromes.
- Neurofibromatosis (type 1).
- Basal cell nevus syndrome.

The Beckwith-Wiedemann syndrome is often associated with changes in regions of DNA on chromosome 11 BWS and is caused by various epigenetic and/or genetic alterations that dysregulate the imprinted genes on chromosome 11p15.5.

In addition to changes in the structure of chromosome 11, genetic variations in the *CDKN1C*, *H19*, *IGF2*, and *KCNQ1OT1* genes are also associated. Some of these chromosomal abnormalities are inherited from a parent, while others occur as random events during the formation of reproductive cells (eggs and sperm) or in the earliest stages of development before birth. An additional association is the Li-Fraumeni syndrome which is related to variation in the p53 tumor suppressor gene.

Whereas the majority of the alveolar RMS subtypes show reciprocal chromosomal translocations ['t(2;13)(q35;q14) or t(1;13)(p36;q14).t(2;13). Embryonal subtypes show a loss of heterozygosity (LOH) on the short arm of chromosome 11 [11p15.5]. The latter shows the suppression of the tumor-suppressor gene H19 on 11p15.5, which results in insulin growth factor II (IGFII) gene overexpression. In keeping with this observation, rhabdomyosarcoma (as well as retinoblastoma), has been shown to be positively associated with increased intrauterine growth, suggesting a possible role of fetal growth factors in its pathogenesis [10]. Rhabdomyosarcomas are also associated with a number of other genetic variations (e.g., mutations in the p53 and adverse outcome, as well as the loss of 1p36, which corresponds to the locus for PAX 7, a paired home box characteristically altered in alveolar RMS tumors).

The PAX/FKHR fusion gene is found in as many as 60% of alveolar RMS cases, but a further 10% of patients with particularly poor prognosis histological types may carry the Ewing's sarcoma fusion gene EWS/ETS (occasionally with the PAX/FKHR gene).

107.2.2.2 RMS Prevalence and Demographics

In Western countries, STSs have an annual prevalence of 8.4 per million in Caucasian populations, and the American Cancer Society estimates about 8680 new cases per year [11]. This would give RMSs an occurrence between 10% and 15% of pediatric solid malignancies. A male predilection (male-to-female ratio of 3:2) has been reported, and the peak age group is 2–5 years with a second peak occurring in adolescence. Ethnic differences have been reported, with RMS in the United States being more frequent in Caucasian than in black patients. Although it is possible that RMS is underreported worldwide in black communities, a suggestion that there is an increased preponderance in black African children is not supported by US data; one study showed that out of 5623 cases of STS reported in whites and blacks living in the United States, only 574 cases (10.2%) were reported in blacks. This appears to be mainly in females, as RMS prevalence has been found to be only half of the Caucasian rate in black girls in the United States, as opposed to a similar rate in both black and white boys. Furthermore, certain studies have shown no striking differences between blacks and whites concerning anatomic sites, histologic types, histologic grades, or clinical stages. This has led to the conclusion that there are no really significant differences in occurrence or survival between white and black STS patients. The prevalence in mixed races in Africa is unknown.

In a retrospective study of 91 children conducted in Nigeria, the pattern of rhabdomyosarcoma was similar to that reported in the United States and Europe, apart from a decreased prevalence of parameningeal sites and extremities [2]. In a South African series of 33 patients, pain was the presenting symptom in 9%, and more than half presented with a mass at varying sites. Almost 25% presented with urinary symptoms resulting from bladder tumors. In this series, the primary site was the head and neck (45%) and the pelvis (42%). The most common histological subtype was embryonal rhabdomyosarcoma (45%) [12].

107.2.2.3 Rhabdomyosarcoma: Clinical Presentation

RMS tumors occur in numerous sites, including the trunk, the retroperitoneum, or the head and neck in addition to the extremities (◘ Fig. 107.2). The most common clinical presentation is that of an asymptomatic mass (often noted by the parents). The precise signs and symptoms usually vary, depending on the anatomical site of the primary tumor..

Head and Neck Tumors

Head and neck RMS tumors are classified as those occurring in the orbit and in the parameningeal and nonparameningeal sites [13].

Orbit

Primary RMS of the orbit presents with proptosis, loss of vision, chemosis, and swelling. Opthalmoplegia may occur in advanced disease. A mass may be present on the eyelid or subconjunctivally. This site usually demonstrates embryonal histological features and has the best prognosis, given appropriate management.

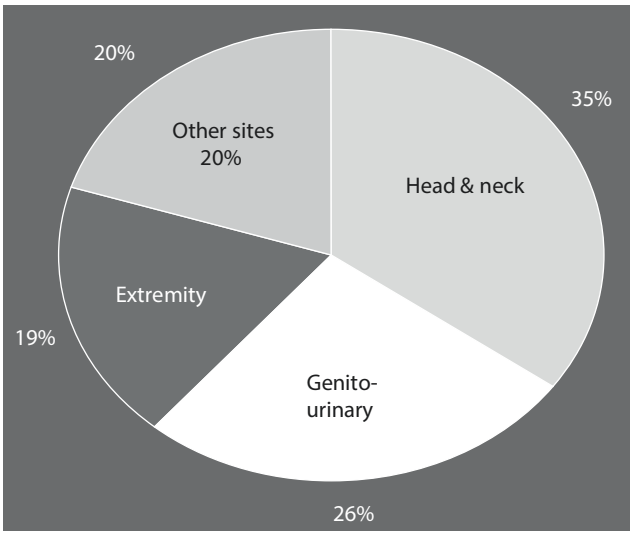


Fig. 107.2 Approximately 35% of primary RMS occurs in the head and neck region, 19% in the genitourinary region, and the same in the extremities. Other sites make up approximately 20% of the total

Parameningeal Sites

Parameningeal sites in the head and neck include the external auditory meatus, the middle ear, the nasopharynx, and other sites around the pharynx and larynx where erosion of bone is a feature. RMS may present with a bleeding mass and/or meningeal symptoms with possible cranial nerve involvement. Complete surgical extirpation may be difficult, so these tumors not infrequently require radiotherapy. Parameningeal tumors mostly have a poor outcome because their deep situation leads to delay in presentation and hence extensive local infiltration as well as early distant metastases (15%) due to the rich lymphatic and blood networks in these areas.

Nonparameningeal Sites

Nonparameningeal sites include the cheeks, oral cavity, and oropharynx, scalp, and thyroid, among others.

107.2.2.4 Pelvic Rhabdomyosarcoma

Rhabdomyosarcoma of the genitourinary tract may present with pain or have difficulty in voiding the bladder or passing stool. As a result, acute urine retention can be the first clinical sign of a rhabdomyosarcoma (RMS) of bladder and prostate and may present as an emergency with intestinal or urinary obstruction.

Genitourinary RMS Tumors

Genitourinary tumors include primary sites from the vulva, vagina, uterus, or bladder/prostate. Patients may present with a mass or may present with hematuria and/or bladder outlet obstruction (Fig. 107.3). Patients also may have an abdominal or pelvic mass. These masses may be large, making identification of the primary site difficult.

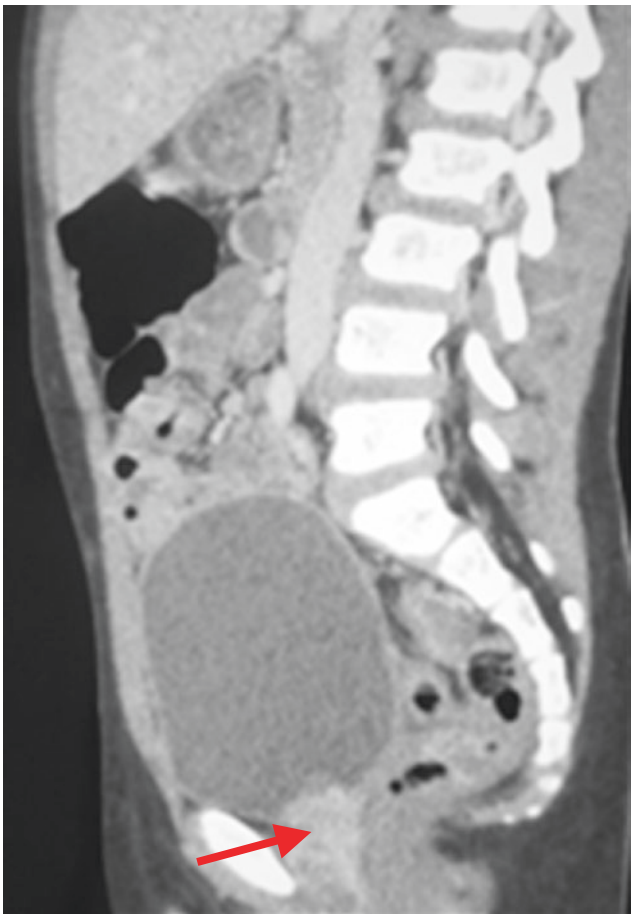


Fig. 107.3 RMS of bladder neck presenting with bladder outlet obstruction

Emergency management may involve temporary urinary diversion (nephrostomies). As many of these pelvic tumors are embryonal subtype and respond fairly rapidly, intestinal obstruction may be treated expectantly with gentle washouts.

Paratesticular RMS

Paratesticular RMS tumors present with non-tender scrotal masses but may present with a large abdominal mass of retroperitoneal lymph nodes. These tumors may be spindle-shaped, being embryonal in 93% [14], and having a good prognosis on the whole. Whereas, in the past, an extensive dissection of the retroperitoneal nodes was required, these patients may present with lung metastases (see Fig. 107.4).

Sarcoma Botryoides

Sarcoma botryoides is a particular form of genitourinary RMS that presents with grape-like structures (Fig. 107.5) protruding from the vulva or causing bladder neck obstruction in a child younger than 4 years of age.

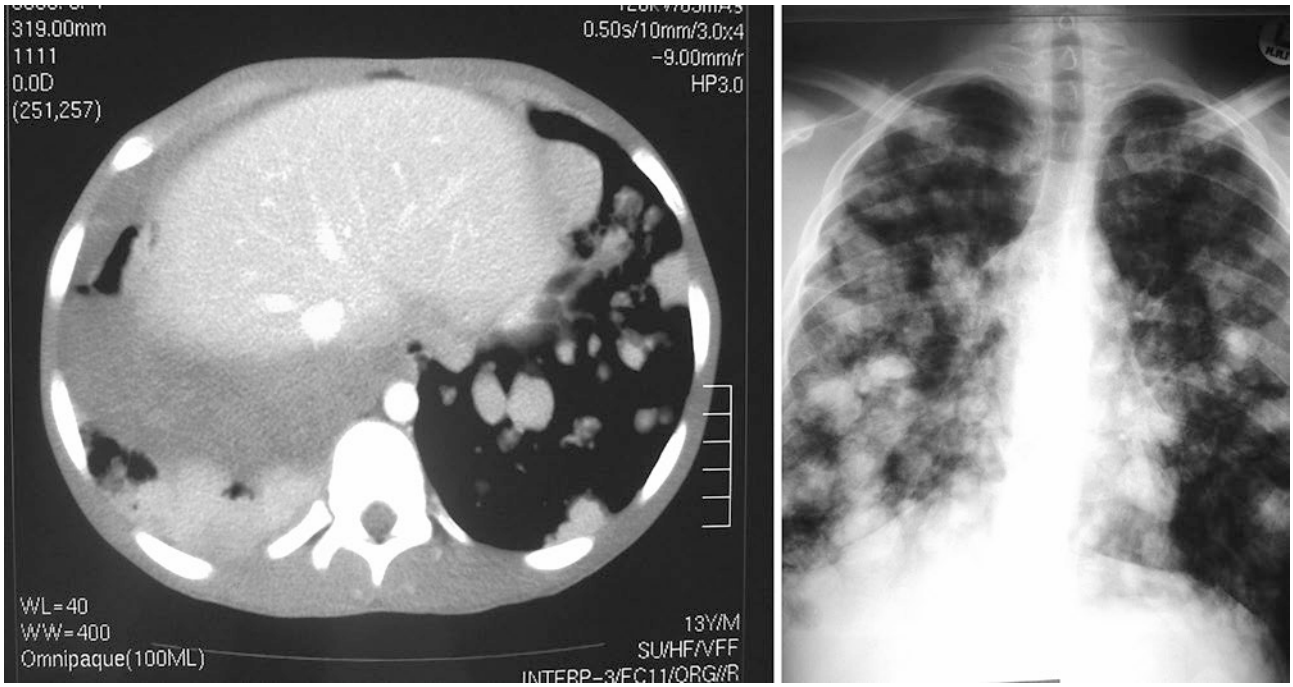


Fig. 107.4 Chest X-ray and CT scan of pulmonary metastases from a 12-year-old boy with a paratesticular RMS tumor

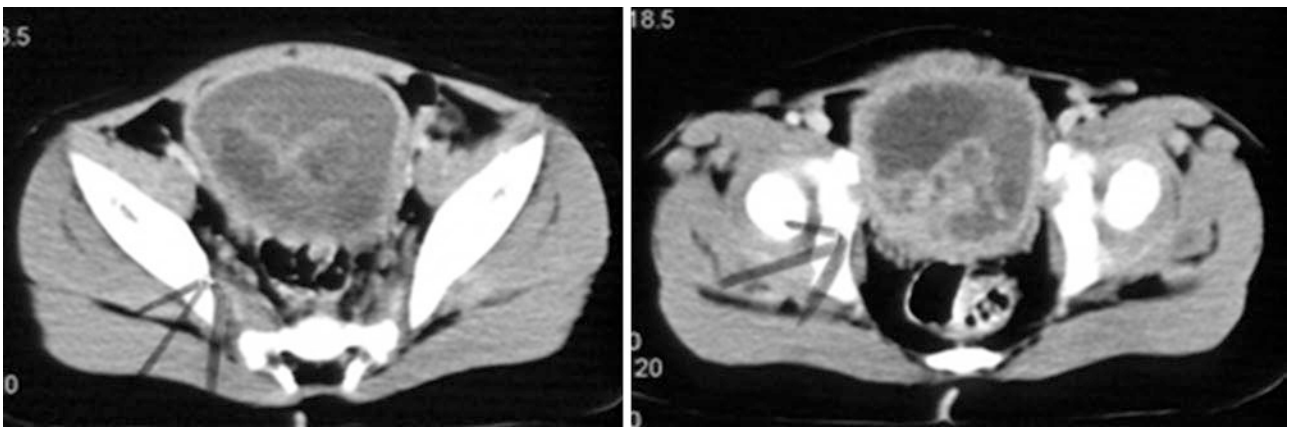


Fig. 107.5 Sarcoma botryoides of the bladder. Note the grape-like structures in the lumen

The histopathology is usually embryonal and the prognosis usually good due to chemo-sensitivity of the tumor.

Tumors of the Body Wall

Tumors of the body wall occur either in the chest wall or paraspinally. Tumors of the chest wall are of considerable interest due to the possibility of an extraosseous Ewing's tumor of soft tissue or a primitive neuroectodermal tumor (PNET; the so-called Askin tumor) in the differential diagnosis (Fig. 107.6).

Tumors of the abdominal wall are rare. They have a high rate of local (as opposed to lymph node) recurrence and are often chemo-resistant.

Other sites where RMS can occur include the retroperitoneum (10%), and other, rarer sites such as the perineum, biliary tract, and GIT.

107.2.2.5 Imaging RMS Tumors

Because it often affects deep organs, imaging of RMS remains a problem in poorly resourced parts of the world, including Africa where many of the imaging modalities taken for granted in the West are often not available. Where they are available, however, they should be used to establish whether the clinically palpable lump represents a true mass and to help make a more specific etiologic diagnosis and finally to assess the extent of the lesion.

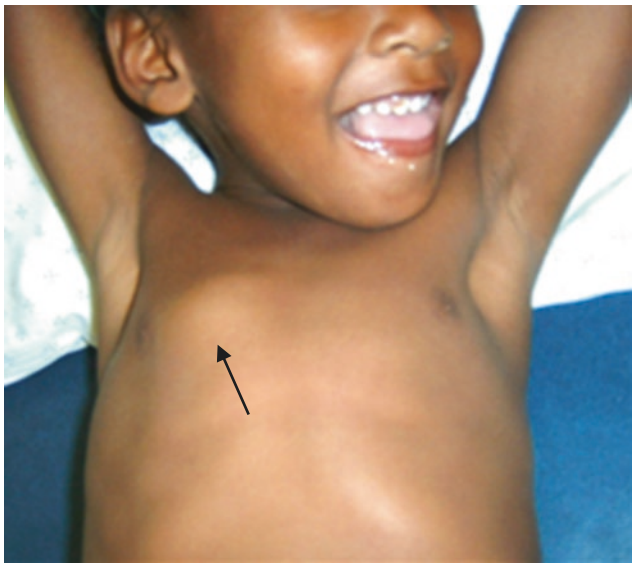


Fig. 107.6 Anterior chest wall tumor

Clinical procedures such as cystoscopy, examination under anesthesia, and lumbar puncture for tumors affecting the spinal canal have gained importance as alternatives in many African centers. When used in association with Doppler ultrasound (US) investigation, reasonable results can be obtained to guide the clinician in management decisions.

MRI is the preferred modality in many centers because of its good definition of regional anatomy and the absence of artifacts in CT scanning, for example. In certain tumors, MRI holds the added benefit of special signal characteristics that may assist in the diagnostic work-up of the patient. Examples of this are lipoma versus liposarcoma, vascular lesions, and fibromas. Nevertheless, it is highly debatable if imaging per se can identify malignant as opposed to benign tumors.

107.2.2.6 Rhabdomyosarcoma Histopathology

Arising from immature striated muscle, RMS is one of the small blue round cell tumors of childhood, along with neuroblastoma, Ewing's family of tumors, and lymphoma. Histopathology may be difficult, and many subtypes exist. Cross-striations may be visualized even on light microscopy to indicate the myogenic origin of the tumor. Subtypes may, however, be difficult to distinguish without highly sophisticated tools such as immunocytochemistry and even electron microscopy and genetic studies.

There are three main histological types of RMS: embryonal, alveolar, and pleomorphic. In a Nigerian study, the embryonal RMS subtype was the most common histological diagnosis made (61.5%). Other subtypes included the alveolar (13.2%), pleomorphic (4.4%), and rhabdomyosarcoma "not otherwise specified" (20.9%) subtypes [2].

Embryonal RMS

The head and neck are the most frequent (35–40%) sites of origin, followed by the genitourinary tract, extremities, trunk, retroperitoneum, and uncommon regions (e.g., intrathoracic, GI tract, perianal and anal regions). In the head and neck, the most common sites are parameningeal and orbital locations, which account for 16% and 9% of all cases of rhabdomyosarcoma, respectively. Over several decades, great progress has been made in the treatment of rhabdomyosarcoma. As a result, 5-year survival rates increased from 25% in 1970 to 73%, as shown in the Intergroup Rhabdomyosarcoma Study (IRS)-IV reported in 2001 [3].

Embryonal RMS is the most common histological type of RMS, making up about 66% of all childhood RMS and virtually all those <8 years of age at diagnosis. Embryonal RMS makes up at least 80% of genitourinary RMS and 60% of head and neck tumors in the younger child.

Embryonal RMS is identified histopathologically as a variable cell population consisting of small, round tumor cells with hyperchromatic nuclei and of large, polygonal-shaped tumor cells with abundant eosinophilic cytoplasm. Cross-striations are diagnostic.

Two very favorable subtypes have been identified:

- The spindle cell embryonal variant seen in paratesticular RMS.
- Also certain head and neck tumors and sarcoma botryoides of the genitourinary tract.

Sarcoma botryoides, discussed previously (see Fig. 107.5), is a specific embryonal subtype occurring in children younger than 4 years of age in muscular cavities such as the nasopharynx, vagina (appearing as grape-like lesions protruding from the vulva), and biliary tree. The histopathological picture includes small, round or possibly spindle-shaped cells surrounded by myxoid material. It has a very good prognosis, generally responding well to chemotherapy.

Alveolar RMS

The alveolar RMS type (20%) occurs mostly on the trunk or extremities and mostly has a poorer outcome [15]. The less well-defined histological subtypes include undifferentiated sarcomas and the pleomorphic (adult) type. There may be occasional difficulties in subtyping RMS tumors, which explains the origin of the term *sarcoma, type indeterminate* in the histopathological classification. Currently, the use of immunocytochemistry, electron microscopy, and cytogenetics for further subtyping of difficult tumors is in practice in the Western world due to the importance of correctly identifying subtypes on management stratification and prognosis.

Pleomorphic RMS

Pleomorphic RMS is virtually unknown in childhood, mostly presenting in adults.

107.2.2.7 Staging of RMS in Childhood

Staging depends on factors such as the primary site and the extent of disease as determined by a number of staging systems. Staging systems include those of the International Society of Pediatric Oncology (SIOP), TNM (tumor, node, metastasis) staging, or Intergroup Rhabdomyosarcoma Study Group (IRSG) (see ◘ Table 107.1).

In some respects, RMS staging must be site-specific due to individual aspects of local invasion, regional lymph node spread, and biologic tumor response.

▪ IRSG Classification

The current staging system used in the United States is the IRSG system. ◘ Table 107.1 refers to the IRSG postsurgical classification (in contrast to the presurgical classification, which depends on special investigations).

▪ SIOP Classification

More recently, patients have been classified into low-, intermediate-, and high-risk categories (SIOP/Intergroup *Rhabdomyosarcoma* Study Group (*IRSG*)), based on studies of clinical outcomes in order to direct treatment protocols [16].

- *Low-risk tumors* include stage 1, group I and II (N0) (and orbit eyelid up to group III), as well as stage 2 of group I tumors.
- *Intermediate-risk tumors* include the rest of stage 1 (group II (N1) and group III (nonorbital)) and stages 2 and 3.
- *High-risk tumors* consist mainly of those in group IV.

107.2.2.8 Management of RMS

Pretreatment Investigation

Pretreatment investigation includes but is not limited to

- *Blood tests:* full blood count, platelet count, urea and electrolytes, liver function tests, and urinalysis.
- *Bone marrow biopsy and aspirate:* usually bilateral.
- *Radiology*: chest *X*-ray, skeletal survey, CT chest (if available), MRI of primary site (with contrast).
- *Scintigraphy:* bone scan (if available).
- *Lumbar puncture:* cerebrospinal fluid (CSF) cytology if parameningeal.

RMS Treatment

The overall aim of treatment in patients with RMS is to optimize survival, minimize toxicity, and maximize the quality of life. The possibility of cure is a realistic goal in patients with localized early tumors. On the African continent, this mostly applies to the few patients who are not in advanced stages on presentation [12].

◘ **Table 107.1** IRSG staging of RMS, based on residual after surgical resection

Group	Description
Group I	Localized disease, completely resected Absence of regional lymphadenopathy (a) Confined to muscle of origin. (b) Infiltration outside muscle or organ of origin.
Group II	Total macroscopic resection, but evidence of regional spread (c) Grossly resected tumor with microscopic residual. (d) Regional disease with involved nodes—completely resected with no microscopic residual. (e) Regional disease with involved nodes—grossly resected but with microscopic residual and/or histologic involvement of the most distal node in the dissection .
Group III	Incomplete resection or biopsy with the presence of macroscopic disease
Group IV	Distant metastases

Site-specific issues, such as the specific patterns of local invasion, regional lymph node spread, and therapeutic response, as well as histopathological subtyping, require physicians to be familiar with site-specific staging and treatment details. They require clear protocols as well as attention to the significant acute toxicities and long-term effects that may occur in young children. The correct pathologic diagnosis as well as the correct histologic subtype will determine much of the treatment and so is important in RMS management.

Chemotherapy

All patients with RMS require chemotherapy. Generally speaking, embryonal RMS is more responsive to treatment than the alveolar subtype. A regimen of vincristine, actinomycin D, and cyclophosphamide (VAC) is generally administered.

A 5-year survival rate of about 72% can be achieved on this basic regime. Large variations in the 5-year survival, however, depend on patient age and tumor characteristics. Children who survived the first 5 years after diagnosis have an excellent long-term prognosis.[15] Chemotherapy, especially second line, may however have serious long-term complications and adverse effects so when patients with metastatic disease are removed from the analysis (i.e., localized disease) and more advanced chemotherapeutic regimes are used, the 5-year survival rate exceeds 80%.

The first new approval for the treatment of soft tissue sarcoma in 40 years [olaratumab, a monoclonal antibody

therapeutic directed against platelet-derived growth factor receptor alpha (PDGFR-alpha) which is increased in certain STS] is being licensed by the Food and Drug Administration (FDA) for certain patients with metastatic or surgically incurable soft tissue sarcoma. Recent randomized trials show that when used in combination with doxorubicin for metastatic STS, a significant improvement in overall survival can be achieved when compared to doxorubicin alone. Preclinical trials in pediatric patients currently show promising results for metastatic bone and other STS. Of course, it is very expensive and beyond the means of most centers in Africa.

Surgical Treatment

The surgeon is an integral part of the oncology team for three reasons:

- To establish a diagnosis and to obtain a pathological sample.
- Many, if not most, tumors rely on surgery to achieve local control.
- Support in terms of vascular access.

The surgical management of RMS has altered fairly dramatically over the past few decades from radical surgical treatment to preoperative chemotherapy followed by wide surgical excision. This is justified by the considerable improvement in 5-year survival and a marked decrease in morbidity.

RMS is treated with adjuvant chemotherapy, whereas chemotherapy is mostly reserved for NRSTS that is high-grade or non-resectable. Surgery appears to be a major therapeutic modality, although radiation may also play a role in certain circumstances. The possibility of NRSTS should be considered when resecting a soft tissue mass in children, and diagnostic incisional biopsy followed by wide local excision with negative microscopic margins should be the surgical goal for localized tumors.

Surgery is best suited to areas where both a good cosmetic result and wide excision can be achieved. It must be borne in mind that primary surgery is probably best reserved for easily resectable small lesions (e.g., extremity, trunk, anterior wall), where an excision biopsy can be achieved. In the IRSG trials, 64% of group III, who demonstrated more than a 50% response to the chemotherapy, were found to have no residual tumor at surgery.

In general, surgical treatment now rests on the principles of diagnosis (biopsy), neoadjuvant chemotherapy, and a primary re-excision of any remaining tumor. Second-look surgery may not be required, depending on post-therapy reassessment. It is generally true that younger patients have a significantly better response to chemotherapy and a longer survival than their older counterparts.

The results from International Society of Pediatric Oncology (SIOP) studies (MMT 84, 89, and 95) have shown that a conservative approach in localized rhabdomyosarcoma of the bladder and prostate is justifiable. Overall survival in these studies was comparable to that of other international groups, despite the lower use of radiotherapy and/or radical surgery in these trials. Jenney [16] states that the higher rate of adverse events must be evaluated against the long-term morbidity of the more radical approach.

Diagnostic Surgical Procedures

Tumors of the extremity lend themselves to initial biopsy. This procedure should be performed through a longitudinal incision so as not to compromise later surgical excision.

There is no place for debulking procedures, which usually result in an incomplete excision.

Primary Re-Excision

In tumors with a good biological response to chemotherapy, the residual tumor may be quite small, favoring conservative surgery with preservation of vital functions. Excision of the entire organ of origin is no longer the standard. Complete macroscopic and microscopic clearance gives rise to the best long-term results.

Second-Look Surgery

Some debate still exists about the value of second-look surgery in the presence of radiological clearance of disease. In patients with an incomplete chemotherapeutic response or doubt, second-look surgery still appears to have a role to play, as survival is bound to a disease-free outcome. Surgery is of limited value in advanced (Stage 1 V) disease.

Management of RMS Tumor Recurrence

Rhabdomyosarcoma (RMS) that does not respond and continues growing despite adequate treatment poses many therapeutic challenges. Management will depend on a number of factors, such as the site of recurrence (whether local or distant), the biology and histological subtype, as well as previous management.

The recurrence/relapse rate for RMS is as high as 30% [13] accounting for a mortality of 50–90% in these patients. These recurrences may be localized or widespread (Fig. 107.7).

Grade alone does not determine the rate of local recurrence. In both low- and high-grade tumors, a pathological margin of resection greater than 1 cm reduced local recurrence. The effect of margin of tumor resection and postoperative radiation therapy (RT) on local tumor recurrence is not yet clear in children.

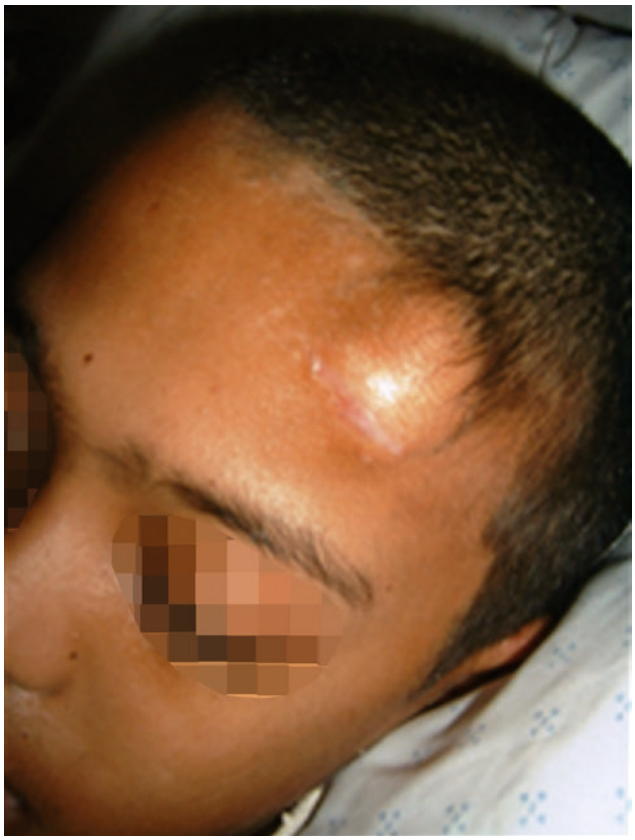


Fig. 107.7 Metastatic RMS lesion on forehead of extremity primary

Histology and tumor biology plays a major role in determining the outcome of these recurrences. Sarcoma botryoides recurrences have a 5-year survival of 64%, pleomorphic tumors 26%, and alveolar tumors only 5% (depending on IRSG).

Surgery may be appropriate for a local recurrence. However, chemotherapy is the best option for distant spread, whereas radiation may be appropriate if not part of the previous protocol.

Surgery may also be indicated in distant sites if localized.

Role of Radiotherapy

Although radiation therapy is of considerable use in controlling local recurrence, the use of radiation therapy varies considerably worldwide. Attempts to minimize side effects by avoiding radiation therapy have been very successful in the SIOP trials, where its use is limited to salvage therapy or local relapse. In the SIOP MMT89 study [17], this applied to only 23% who required local therapy to achieve complete control.

Radiotherapy is particularly used where microscopic disease remains after surgical resection or in areas where wide excision would result in a very poor cosmetic result (e.g., parameningeal, orbit, etc.).

Benefits of radiotherapy in preserving organs must be weighed against the long-term side effects which include secondary malignancies (e.g., thyroid) and features such as xerostomia, abnormal dental development, poor facial bone development, and neuroendocrine abnormalities, as well as hearing and visual loss in head and neck lesions. In the pelvic region, impaired gonadal function, poor pelvic bone development, and intestinal obstruction may ensue. Growth disturbance, bone and nerve damage, as well as limitation of function may result in the extremities.

107.2.2.9 Prognosis of RMS in Children

Prognosis of STS is largely determined by the degree of spread at the time of diagnosis, the biology of the tumor, the histological features, the site of origin, and the treatment given. Because much of the management of pediatric soft tissue sarcomas (NRSTS) is extrapolated from adult studies, the treatment is debated, due to their varying chemo-sensitivity.

Nevertheless, a 5-year survival rate greater than 70% has been reported in recent trials of localized rhabdomyosarcoma. Survival for group I is 93%; group II, 81%; group III, 73%; and group IV, 30%. Patients presenting with metastatic disease (20% of patients with newly diagnosed RMS) still have a poor outcome.

In the future, risk-adapted classification of rhabdomyosarcoma will likely be based on biologic features, such as the presence of chromosomal translocations or specific gene expression profiles.

107.2.3 Non-rhabdomyosarcoma Soft Tissue Tumors

Whereas RMS predominates in children younger than 14 years of age, NRSTS occurs less commonly, making up less than 3% of childhood malignancies.[5] They are somewhat more common in boys than girls (ratio is 2.3:1) and occur mostly in adolescents (median age 12 years) and young adults. They may also present in infancy, usually occurring in the trunk or lower limbs. Pathologically, they make up a heterogeneous group, with the most common types being synovial sarcomas (42%), fibrosarcoma (13%), malignant fibrous histiocytoma (12%), and neurogenic tumors (10%). Age appears to be important, as synovial sarcomas, peripheral nerve sheath tumors, and malignant fibrous histiocytoma most frequently occur in patients aged 10–15 years as opposed to those younger than 1 year of age, who mostly had a congenital fibrosarcoma. The lower limb is the most common primary site of NRSTS in childhood, but the site does not appear to correlate with age. Prognosis is related to size, spread (stage), and biologic and histological features.

Complete surgical excision remains the mainstay of therapy in more than 70% of NRSTS, making it of considerable interest to surgeons. A multidisciplinary team approach with avoidance of mutilating procedures has become the standard for the treatment of soft tissue sarcomas in children and results in cure for many.

Postoperative adjuvant chemotherapy significantly improves the overall and disease-free survival for patients with large-size and high-grade sarcomas.

NRSTSs are less responsive to radiotherapy than the more common pediatric soft tissue sarcomas, RMS, and Ewing's sarcoma of soft tissue. However, radiation therapy does play an important role in the treatment of NRSTS, including synovial sarcoma. Limb preservation with adjuvant radiation thereby is the standard, and there is a greater incentive to reduce long-term complications of radiation in younger patients. Techniques such as using smaller margins, lower doses, and conformal techniques have changed the practice in many centers. Where pediatric NRSTS patients have had an initial unplanned or incomplete resection, a wide re-excision should precede any further adjuvant treatment.

107.2.3.1 Synovial Sarcoma

Synovial sarcoma is an uncommon malignant soft tissue neoplasm that accounts for 7–8% of all malignant soft tissue tumors [18]. Approximately 30% of synovial sarcoma patients are younger than 20 years of age. Synovial sarcoma is the most common NRSTS in pediatric patients. It is a high-grade malignancy and tends to spread to the lungs.

Clinically, synovial sarcoma classically arises from the knee or upper leg, closely related to joints, tendons, or bursae (Fig. 107.8). The upper extremity, trunk, abdomen, and head and neck regions may also be involved.

Synovial sarcoma is associated with a nonrandom chromosomal translocation where a section one chromosome translocates to another chromosome. This translocation occurs on the 18th and 11th chromosomes and the translocation (X18) (p11, q11) in the tumor cells confirms the diagnosis. Initial biopsy should be by incision unless the tumor is very localized. Incisional biopsy should be longitudinal to allow for later wide excision. Resection should be completed with clear, yet not necessarily large, margins. A wide surgical excision with clear

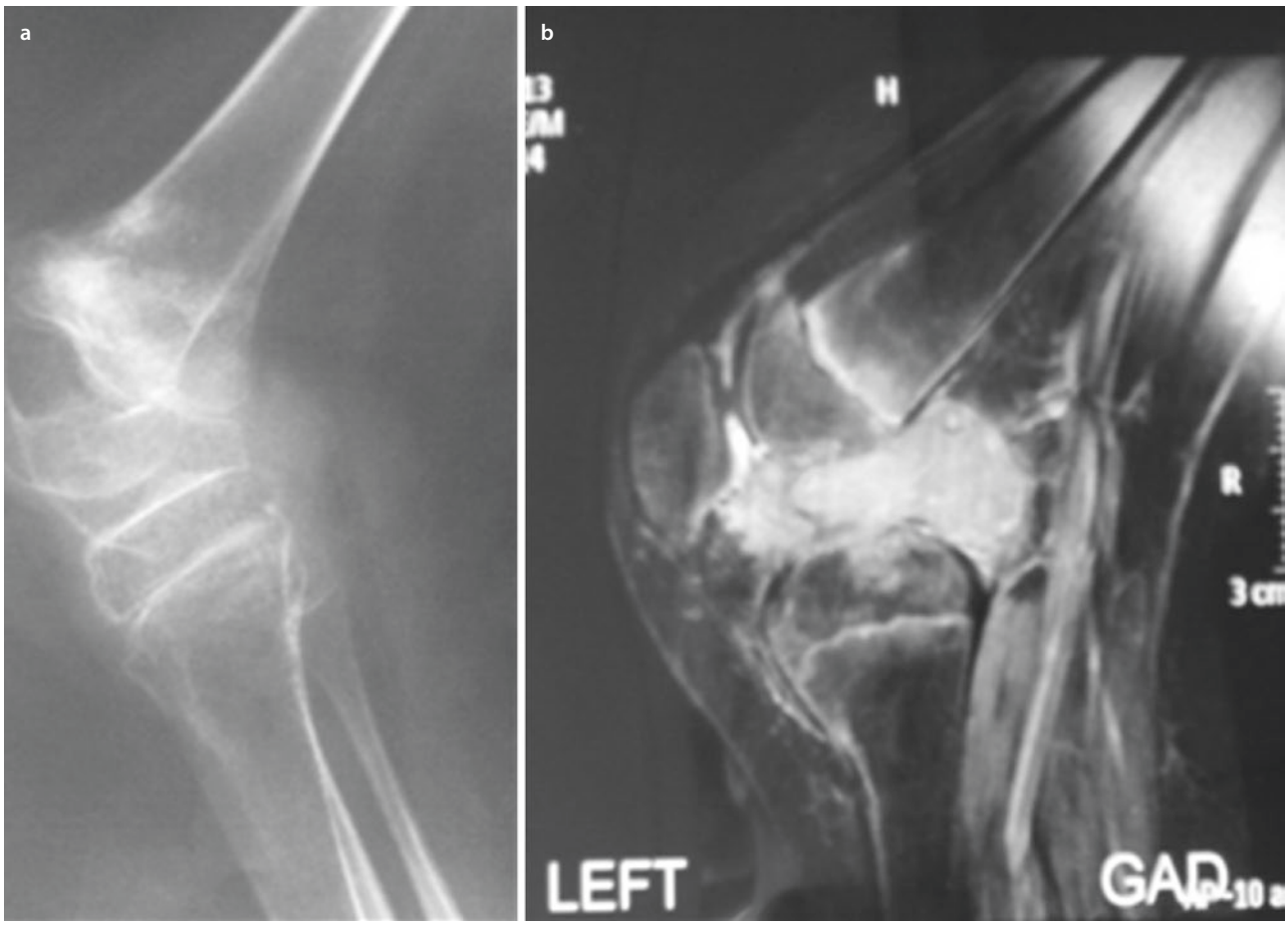


Fig. 107.8 (**a**) X-ray of the left knee in a 13-year-old female with a synovial sarcoma. (**b**) MR image demonstrates the extent of the tumor

margins remains the treatment of choice for synovial sarcoma in children, as microscopic residual has a major influence on local recurrence and survival. Amputation may be required in a limb to ensure adequate margins.

Regional lymphadenopathy may occur, and lymph nodes should be evaluated for local regional disease.

Big tumors have an increased risk of metastasizing, particularly to the lungs (>25% at diagnosis). Favorable outcomes have been reported for small tumors (<5 cm) and children <10 years of age. Adjuvant radiation therapy may assist in containing residual disease and should possibly be considered in patients with clear margins (IRSG group I) and in patients with microscopic residual tumor (IRSG group II). Overall, chemotherapy does not seem to improve the outcome, although chemotherapeutic drugs such as ifosfamide appear fairly effective in advanced disease. Survival of metastatic disease is rare.

107.2.3.2 Leiomyosarcoma

Leiomyosarcoma arises from smooth muscle and is the most common retroperitoneal tumor STS in the pediatric age group. It may arise from the GIT and is occasionally being seen in association with HIV infection and immunosuppression (e.g., renal transplantation). Leiomyosarcoma is associated with a t (12; 14) (q14; q23) translocation.

107.2.3.3 Neurofibrosarcoma in Childhood

Neurofibrosarcoma is a tumor of the nerve sheath with a strong association with neurofibromatosis, occurring in 16% of patients with an NF1 gene variation (up to 50% of cases with NF1). Other reported genetic variations include 22q11-q13, 17q11, and p53 mutations. It mostly occurs in the trunk or major plexuses (e.g., brachial plexus) in the periphery. It is locally invasive.

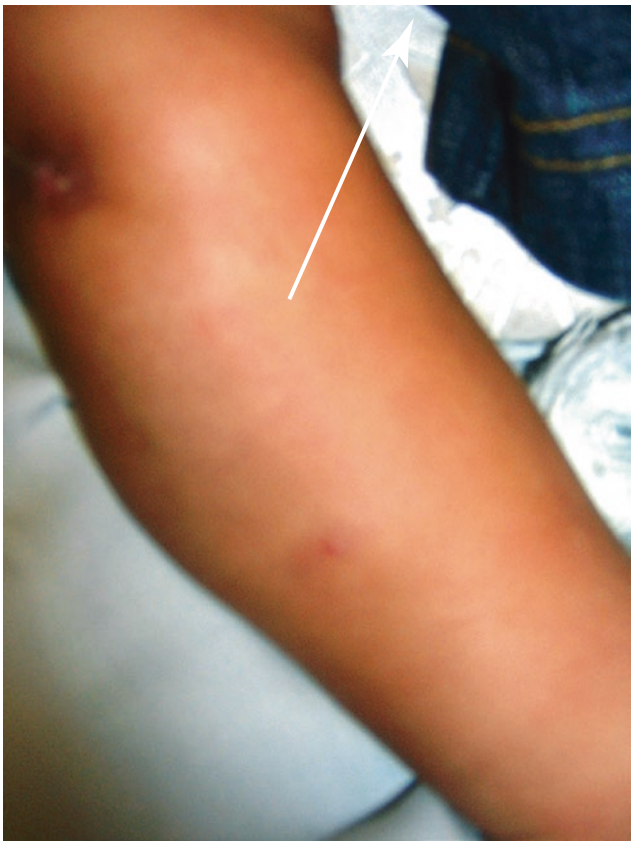
Surgical excision remains the mainstay of treatment, as it is largely chemo- and radio-resistant.

107.2.3.4 Malignant Fibrous Histiocytoma

Like fibrosarcoma, malignant fibrous histiocytoma arises from fibroblasts, mostly occurring in the trunk and extremities (◘ Fig. 107.9). Pathologically, it occurs deep in the subcutaneous layer, displaying a number of histopathological variants (giant cell, myxosis, storiform, and angiomatoid). The angiomatoid variant occurs in younger patients. Malignant fibrous histiocytoma is surgically curable by excision. A wide surgical excision is the treatment of choice. Chemotherapy may be required for advanced cases in the older child.

107.2.3.5 Liposarcoma

Liposarcoma, a tumor of fat cells which occurs rarely in childhood, has been reported both in the periphery and retroperitoneal regions in childhood. It is sometimes difficult to distinguish from lipoblastoma, a benign condition; any fatty tumor with unusual features, such as poorly localized, invading fascia, should be evaluated.



◘ **Fig. 107.9** Malignant fibrous histiocytoma of the upper limb in a 6-year-old child

It may be difficult to distinguish between lipoblastoma and liposarcoma on histopathology alone and may require karyotyping in order to make the distinction. Histological features are suggestive of malignancy with the formation of poorly defined larger lobules and/or nuclear pleomorphism, hyperchromasia, and atypical mitoses. Myxoid liposarcoma (low grade and responding to treatment) are the most common. Liposarcoma typically may be associated with a nonrandom gene translocation, t (12; 16) (13; p11); may be of myxoid lipoblastoma; or other genetic abnormalities may occur. The higher-grade pleomorphic liposarcoma responds less favorably.

Most liposarcomas in children and adolescents grow and metastasize slowly (low-grade malignancy). They tend to be locally invasive and spread to distant sites uncommon.

Wide surgical excision is the treatment of choice.

107.2.3.6 Vascular Tumors and Kaposi Sarcoma

Kaposi Sarcoma

Kaposi sarcoma in a child is usually regarded as a rare and unexplained condition. Essentially, Kaposi sarcoma is a multicentric neoplasia of microvascular origin arising in association with HIV-affected individuals. It

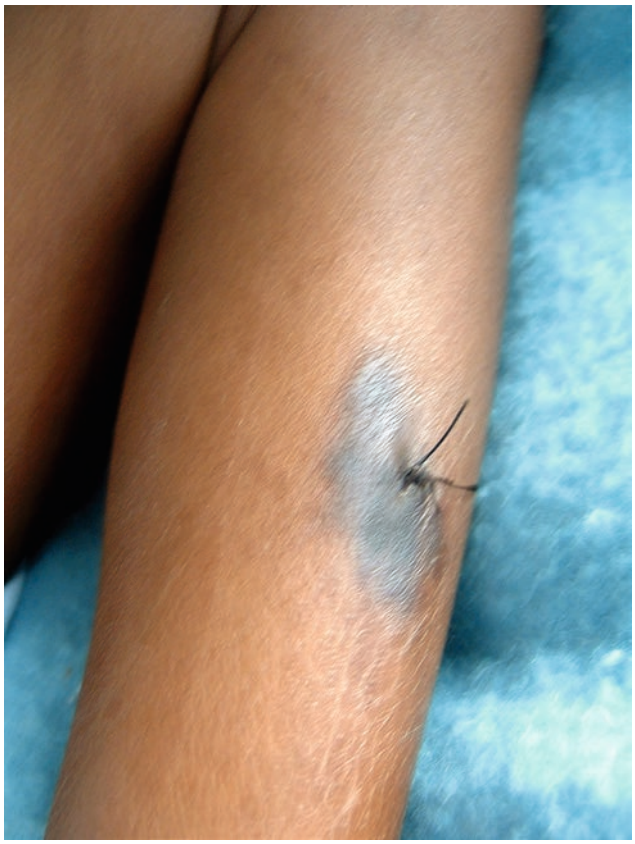


Fig. 107.10 Kaposi sarcoma of leg with evidence of biopsy

presents as brown, reddish, or purple cutaneous spots in HIV-positive patients.

The risk is known to be elevated in association with HIV-positive patients, immunosuppression, and human herpes virus 8 (HHV-8) infections [19]. Children are also at risk for KS following renal transplantation. Kaposi sarcoma rates are rapidly increasing in African children, mostly in association with the AIDS epidemic. In endemic regions, KS represents as much as 25–50% of STS in adult men and 2–10% of all childhood cancers [20]. A further difference in children is the male-to-female ratio (2.2:1 clinically); KS presents on the feet or ankles, thighs (Fig. 107.10), arms, hands, or face as a brown, reddish, or purple cutaneous spot but may involve any other part of the body. It can involve skin, mucous membranes, and lymph nodes, as well as viscera (e.g., liver). Apart from the skin lesions, KS often presents with lymphadenopathy in childhood as well as wasting and anemia. Although rare in most parts of the world, KS has become an increasing problem in areas of high HIV prevalence in Africa. This is particularly true of the highland areas of Zaire, Kenya, Tanzania, and Southern Africa. The incidence is increasing; for instance, in Zambia the incidence has risen from 2.63 per million in Zambia in 1982 to 19% 10 years later. Equally, in South Africa, a threefold increase in the incidence of KS has been reported from 1988 to 1996 and continues to increase as the HIV epidemic in this area continues [20]. African KS is fairly common in young adult males living near the equator. One form is also common in young African children. A study of 70 children with KS and HIV infection consecutively admitted to South African hospitals (January 1998 to December 2009) reported an average age at diagnosis of 73 months, and the male/female ratio was 1.59:1. Skin lesions were present in 57.14% and lymph node lesions in 44.44%. Antiretroviral therapy improved survival ($P = 0.001$) although only 20% were taking combined antiretrovirals at the time of diagnosis [21]. Kaposi sarcoma is also associated with immunosuppression and an increased KS-associated herpes virus (KSHV) sero-prevalence, the risk being the highest in children of KSHV-seropositive mothers.

The status of KS as a true soft tissue malignancy is still unclear and many still regard it as an opportunistic neoplasm rather than a genuine malignancy. Management decisions are governed by the extent and location of the lesions, as well as the symptoms and degree of immunosuppression. Diagnosis can be confirmed on skin biopsy.

The outlook depends on the immune status and patient's HIV viral load. Antiretroviral therapy can shrink the lesions, but the treatment of KS does not improve the outcome from HIV itself.

Radiotherapy or cryotherapy has been used for the local lesion. Chemotherapy also has to be used in certain circumstances.

Lesions may return after treatment, however.

Hemangiopericytoma

Hemangiopericytoma is an uncommon soft tissue tumor that arises from small pericapillary spindle-shaped cells (capillary pericytes). It may be benign or malignant, depending on the tumor biology, and it has a variable and unpredictable malignancy risk. Hemangiopericytoma is exceedingly rare in childhood. It mostly occurs in the lower limbs (Fig. 107.11) or retroperitoneally, but may also occur in the head and neck, particularly in older patients (but also is reported in childhood). It has been associated with certain chromosomal translocations (e.g., t (12; 19) (q13; q13) or t (13; 22) (q22; q11). Hemangiopericytoma may be difficult to diagnose clinically due to its rarity. It usually presents as a soft tissue mass but may have unusual clinical presentations as hypoglycemia or hypophosphatemic rickets.

Total surgical excision is the treatment of choice, and curative surgery is the most important predictor of survival. The role of chemotherapy in treatment is not well established.

Hemangioendothelioma

Hemangioendothelioma (congenital hemangioma) may occur in viscera (e.g., liver and lungs) or in soft tissue elsewhere.

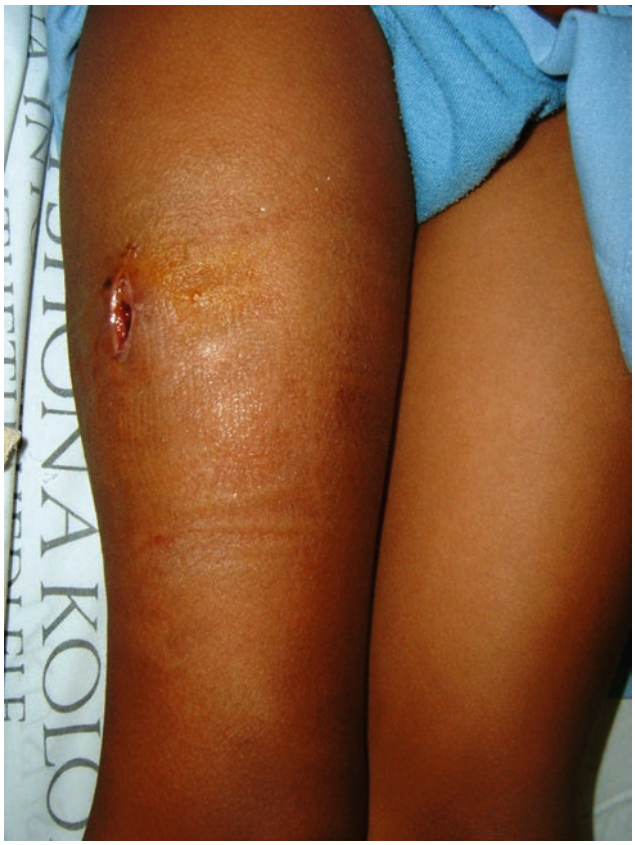


Fig. 107.11 Poor healing in a biopsy wound of a hemangiopericytoma of the thigh

Hepatic epithelioid hemangioendothelioma is an uncommon, low-grade vascular tumor with uncertainties about the best treatment. It usually has a favorable prognosis but may develop complications such as thrombocytopenia and cardiac failure, due to its size. This may lead to a poorer prognosis and may require liver transplantation.

Epithelioid hemangioendothelioma, in contrast, is a distinctive vascular soft tissue tumor that has been previously considered a tumor of borderline malignancy and low-grade angiosarcoma. It occurs in the extremities as well as the head and neck, mediastinum, trunk, genitals, and retroperitoneum. Most tumors occur in adults, affecting females predominantly, but some have been reported at 9 years of age. Although many run a benign clinical course and respond to wide local excision, tumors with more than 3 mitoses/50 high-power fields (HPF) and a size greater than 3.0 cm have a significantly worse prognosis.

Angiosarcoma

Angiosarcoma is an extremely rare tumor in childhood. It most commonly occurs in the skin (33%) and about 25% in soft tissue. Other sites (e.g., liver, breast, or bone) make up about 25% of occurrences.

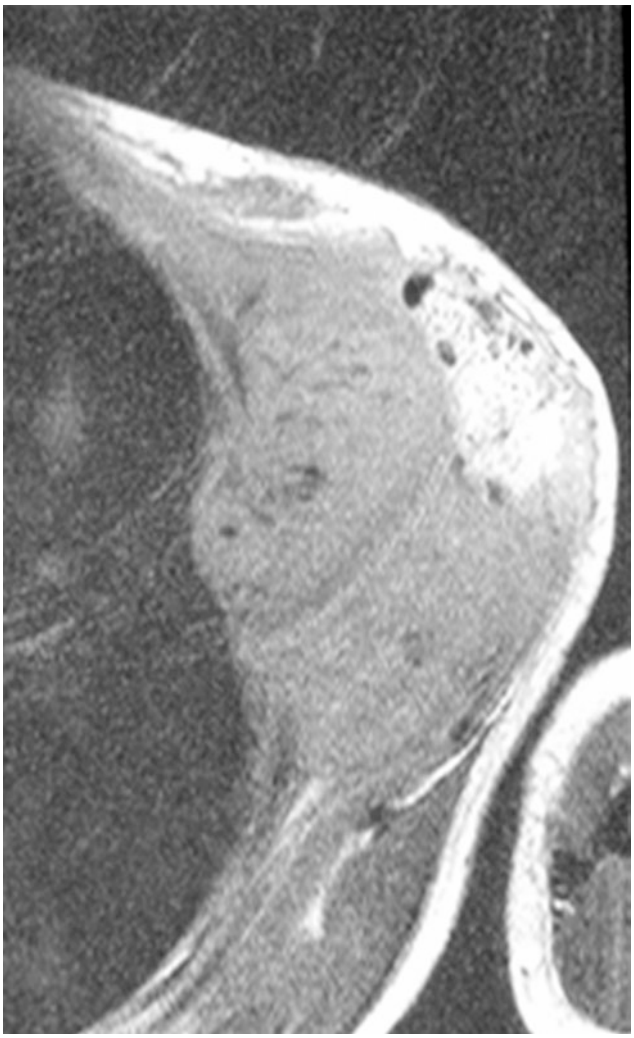


Fig. 107.12 Ewing's sarcoma of the rib

There is an association with the NF1 gene and neurofibromatosis, particularly with thoracic sites. Survival is generally poor, although long-term survival has been reported.

107.2.3.7 Miscellaneous Tumors

Ewing's Sarcoma Family Tumors

Long regarded as the second commonest bone tumor in children (Fig. 107.12). Although better known as Ewing's sarcoma of the bone, there is a distinct extraosseous group of Ewing's sarcomas that originate from soft tissues (including PNET and the Askin tumor of the chest wall) giving rise to the modern concept of Ewing's sarcoma family of tumors (ESFT). These are not an uncommon malignancy of children, adolescents, and adults younger than 25 years of age.

Ethnic disparities in incidence (more common in Caucasians) as well as sex-related differences in outcome (Caucasian females do better) have been reported [22].

Prognostic factors used to stratify ESFT patients include:

- Tumor-related stage (metastases), site, size, serum lactic dehydrogenase (LDH), chromosomal translocation (type and position), fusion transcripts (blood and bone marrow).
- Treatment (local surgical control, chemotherapy protocol, chemotherapeutic response (both histological and radiological)).
- Patient factors (e.g., gender and age).
- Early diagnosis and treatment.

Ewing's sarcoma is treated successfully in up to 50–75% of cases, particularly if diagnosed and treated early on, prior to widespread metastasis. Patients with small peripheral tumors without distant spread have been reported to have a high rate of cure (>70%). Large, centrally located tumors and those with advanced stage disease have a much less successful outcome (<33% 5-year survival). A combination of chemotherapy, surgery, and radiotherapy is used to treat these tumors [23].

Newer chemotherapeutic agents are currently being investigated, and there is now increasing interest in the identification of molecular targets in ESFT that could be exploited therapeutically, which include the mammalian target of rapamycin (mTOR) and insulin growth factor-1 (IGF-1) receptor pathways.

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma is a tumor that occurs in the head and neck or extremities and grows very slowly, tending to metastasize (to the lungs and brain) some years after diagnosis. It possibly arises from muscle. Complete surgical resection is the treatment of choice.

107.3 Evidence-Based Research

A number of aggressive malignant tumors occur that require multimodal therapy, usually including surgical management. ◘ Table 107.2 presents a review of management strategies for rhabdomyosarcoma in children.

107.4 Evidence-Based Surgery

Title	Childhood Rhabdomyosarcoma Treatment (PDQ®)
Authors	PDQ Pediatric Treatment Editorial Board
Institution	PDQ Cancer Information Summaries [Internet]
Reference	Bethesda (MD): National Cancer Institute (US); 0.2002–0.2015 PDQ Cancer Information Summaries [Internet] *Free download of entire booklet*
Comparison /control (quality of evidence)	Review
Outcome effect	Published online: August 5, 2015. This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of childhood Hodgkin lymphoma. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions. This summary is reviewed regularly and updated as necessary by the PDQ Pediatric Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI)
Historical significance/ comments	The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH)

Key Summary Points

1. Tumors of soft tissue are mostly benign lesions of connective tissue in childhood.
2. Malignant soft tissue sarcomas (STSs) arise predominantly from the embryonic mesoderm deriving from a variety of cell types.
3. STSs are relatively rare—approximately 5–8% of childhood malignancies per year.
4. STSs mostly present as an asymptomatic mass in an extremity in older children.
5. There are at least three clinically relevant groups in childhood, which are congenital fibrosarcoma, rhabdomyosarcoma, and non-rhabdomyosarcoma STS.
6. Non-rhabdomyosarcoma STS includes synovial sarcoma, liposarcoma, vascular tumors (e.g., Kaposi sarcoma, hemangiopericytoma, angiosarcoma), and alveolar soft part sarcoma.
7. Treatment is multimodal, usually involving neoadjuvant chemotherapy and conservative surgery. Radiotherapy is required only under certain circumstances.
8. The role of the surgeon is to establish a diagnosis, perform timely, adequate removal, and assess

metastatic spread and supportive care (e.g., long-term venous access).

9. Although often highly malignant tumors, the prognosis has improved significantly over the last three decades. Up to 77% of tumors in children younger than 1 year of age are surgically resectable following neoadjuvant chemotherapy.

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