CHAPTER 106
Malignant Soft Tissue Tumours

Sam Moore
Hugo Heij

Introduction

Tumours of soft tissue are mostly benign lesions of connective tissue in children. A number of aggressive malignant tumours that require multimodal therapy do occur, however, usually including surgical management. These malignant soft tissue sarcomas (STSs) are relatively rare in childhood, contributing approximately 5–8% of childhood malignancies (approximately 850–900 children and adolescents are diagnosed in the United States each year).[1] STSs arise predominantly from the embryonic mesoderm and mostly present as an asymptomatic mass in an extremity in older children or adults.

Demographics

The prevalence of STS appears to vary among population groups worldwide. In ethnic groups representing mainly caucasian populations, an age-standardised 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 Asia, the age-standardised STS annual incidence rate is less than 6 per million. Due to the paucity of data, the age-standardised STS annual incidence rates for Africa remain uncertain, but there is a widely held view that they are as 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.

Rhabdomyosarcomas (RMSs) and fibrosarcomas predominate; fibrosarcomas were found to be more prevalent in black African Americans than in caucasians (both males and females) in the United States.[2] A similar spectrum is thought to exist in Africa. This interethnic variation in rhabdomyosarcoma and fibrosarcoma occurrence, together with their genetic and inheritable associations, suggest that genetic dysfunction is important in the pathophysiology. Viral exposure may also play a role, and Kaposi sarcoma (KS) rates are peaking in African children, mostly those from eastern and southern Africa in association with the acquired immune deficiency syndrome (AIDS) epidemic.

Aetiology and Pathophysiology

Sarcomas are malignant tumours 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 tumours seen in an adult oncology clinic, their prevalence in childhood appears higher.

Although the aetiology of sarcomas remains obscure, a possible genetic origin is proposed, as there is an association with the alternative lengthening of telomeres (ALT) mechanism in about half of the osteosarcomas, STSs, and glioblastomas. Familial transmissability is a possibility, an example of which is the complex cancer predisposition Li-Fraumeni association (the molecular basis of which is a germline TP53 (tumour protein 53) mutation).[3] Impaired differentiation of myoblasts in RMS is associated with a tumour suppressor-like action due to reconstitution of miR-29, which promotes cellular differentiation and inhibits tumour growth in animals,[4]

Clinical Presentation

STSs occur in numerous sites, including the trunk, retroperitoneum, or the head and neck, in addition to the extremities. No aetiologic 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); and
- nonrhabdomyosarcoma soft tissue sarcoma (NRSTS).

Fibrosarcoma may 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.

Findings on physical examination depend on the type and site of the tumour.

Investigations

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

Histological grading of STS is often difficult, with more than 70 histologic types currently being identified, including RMS, KS, and vascular tumours predominantly in the paediatric 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 tumours, with the remainder falling into the heterogeneous NRSTS group.

Management

The role of the surgeon is to

- establish a diagnosis;
- perform timely and adequate removal (often following chemotherapy);
- assess spread with a view towards staging; and
- provide supportive care (e.g., long-term venous access, feeding, etc.).

Prognosis

The outcome of 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 tumours occurring before the age of 1 year are surgically resectable, having the lowest occurrence of invasive or high-grade tumours. As a result, a 5-year survival of 93% has been reported in this age group.[5] 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).

Fibrosarcoma

The age-standardised STS annual incidence rate for malignant fibromatous tumours 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 (Figure 106.1) or trunk, and although histologically it appears malignant, it behaves benignly and rarely metastasizes.

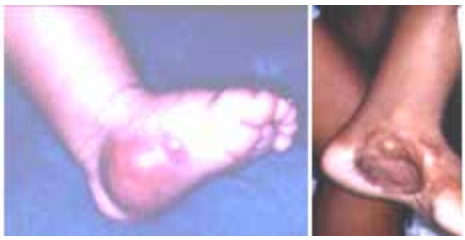


Figure 106.1: Congenital fibrosarcoma of the foot in an infant (left) and the result of wide excision at 7 years of age (right).

In children older than 4 years of age, the natural history of fibrosarcomas approximates that of the adult tumour, and the treatment is more radical than for younger children.

In US 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 tumours 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.[6]

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 availability of specific resources. Fibrosarcomas of bone may also occur.

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

Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant tumour of striated muscle, which usually displays early local invasiveness and may later metastasize via lymphatic and haematogenous 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 most common sites include the head/neck (25.6%), leg/foot (26.7%), and thigh (19%) in an African series.[10]

Although the aetiology of RMS is still unclear, familial STSs do occur, and RMS may be associated with a number of syndromes (e.g., Beckwith-Wiedeman, Li-Fraumeni, and WAGR (Wilms' tumour, Aniridia, Genito-urinary malformations, mental Retardation)) as well as neurofibromatosis (type 1) and the basal cell naevus syndrome. 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 tumour-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 foetal growth factors in its pathogenesis.[11] Rhabdomyosarcomas are also associated with a number of other genetic variations (e.g., mutations in the p53 tumour suppressor gene 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 tumours).

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 EWS/ETS fusion genes (occasionally along with the PAX/FKHR gene).

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 8,680 new cases per year.[12] This would give RMSs an occurrence between 10% and 15% of paediatric 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 5,623 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.

Clinical Presentation

RMS tumours occur in numerous sites, including the trunk, retroperitoneum, or the head and neck in addition to the extremities (Figure 106.2).

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 tumour.

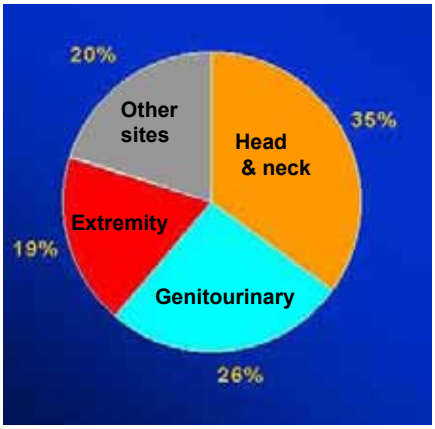


Figure 106.2: Approximately 35% of primary RMS occurs in the head and neck region, 19% in the genitourinary region, and the same in the extremities. Other sites are approximately 20% of the total.

Head and Neck Tumours

Head and neck RMS tumours 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. Ophthalmoplegia 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.

Parameningeal sites

Parameningeal sites 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 tumours not infrequently require radiotherapy. Parameningeal tumours 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.

Genitourinary Tumours

Genitourinary tumours include primary sites from the vulva, vagina, uterus, or bladder/prostate. Patients may present with a mass or may present with haematuria and/or bladder outlet obstruction (Figure 106.3).

Patients also may have an abdominal or pelvic mass. These masses may be large, making identification of the primary site difficult.

Paratesticular RMS

Paratesticular RMS tumours present with nontender scrotal masses but may present with a large abdominal mass of retroperitoneal lymph nodes. These tumours 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 retropertitoneal nodes was required, these patients may present with lung metastases (see Figure 106.4).

Sarcoma botryoides

Sarcoma botryoides is a particular form of genitourinary RMS that presents with grape-like structures (Figure 106.5) protruding from the vulva or causing bladder neck obstruction in a child younger than 4 years of age. The histopathology is usually embryonal and the prognosis usually good due to chemosensitivity of the tumour.

Tumours of the Body Wall

Tumours of the body wall occur either in the chest wall or paraspinally. Tumours of the chest wall are of considerable interest due to the possibility of an extra-osseous Ewing's tumour of soft tissue or a primitive neuroectodermal tumour (PNET; the so-called Askin tumour) in the differential diagnosis (Figure 106.6).

Tumours of the abdominal wall are rare. They have a high rate of local (as opposed to lymph node) recurrence and are often chemoresistant.

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

Imaging

In Western countries, computed tomography (CT) and magnetic resonance imaging (MRI) are considered essential for the staging of RMS as it often affects deep organs, and clinical assessment of the local and regional involvement as well as the relationship to other neighbouring structures may prove difficult. 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

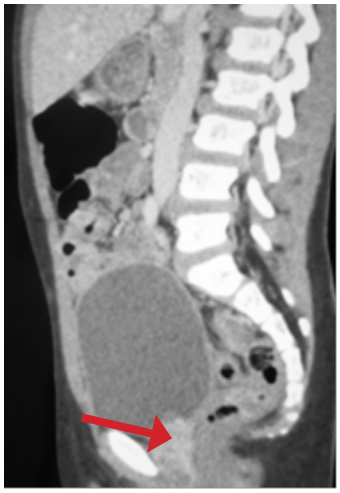


Figure 106.3: RMS of bladder neck presenting with bladder outlet obstruction.

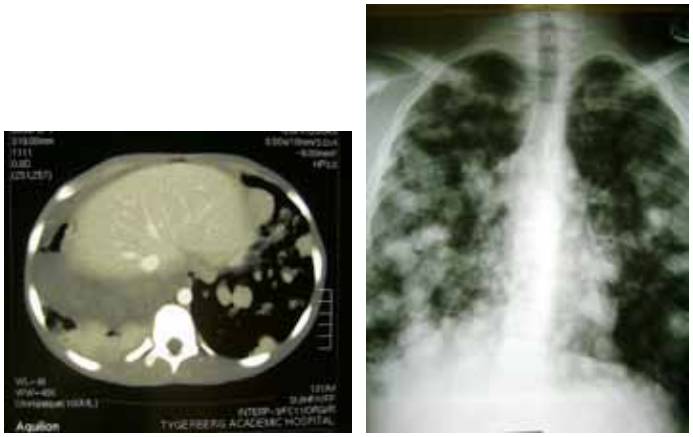


Figure 106.4: Chest x-ray and CT scan of pulmonary metastases from a 12 year-old-boy with a para-testicular RMS tumour.

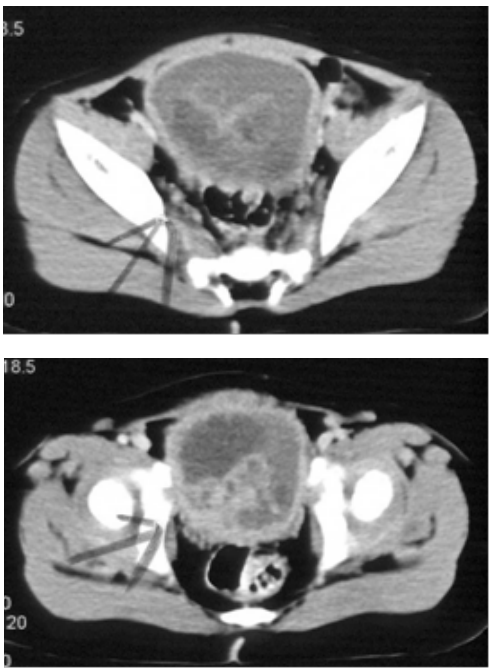


Figure 106.5: Sarcoma botryoides of the bladder. Note the grape-like structures in the lumen.

available. Where they are available, however, they should be used to evaluate these tumours.

Clinical procedures such as cystoscopy, examination under anaesthesia, and lumbar puncture for tumours affecting the spinal canal gain importance as alternatives in many African centres. 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 centres due to its good definition of regional anatomy and the absence of artifacts on CT scanning. For example, MRI holds the added benefit of special signal characteristics in certain tumours 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 whether imaging per se can identify malignant as opposed to benign tumours.

Histopathology

Arising from immature striated muscle, RMS is one of the small blue round cell tumours of childhood, along with neuroblastoma, Ewing's family of tumours, and lymphoma. Histopathology may be difficult, and many subtypes exist. Cross-striations may be visualised even on light microscopy to indicate the myogenic origin of the tumour. 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.

Embryonal RMS

Embryonal RMS is the most common RMS, making up about 66% of all childhood RMS, virtually all in the <8 year age group. Embryonal RMS makes up at least 80% of genitourinary RMS and 60% of head and neck tumours in the younger child. Two very favourable subtypes have been identified: (1) the spindle cell embryonal variant seen in paratesticular RMS, and (2) some head and neck tumours and sarcoma botryoides of the genitourinary tract.

Sarcoma botryoides, discussed previously (see Figure 106.5), 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 tumours, 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 tumours is currently 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.

Pretreatment Investigation

Pretreatment investigation includes, but is not limited to

- *blood tests:* full blood count, platelet count, urea and electrolytes, liver function tests, and urinanalysis;
- *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); and
- *lumbar puncture:* cerebrospinal fluid (CSF) cytology if parameningeal.

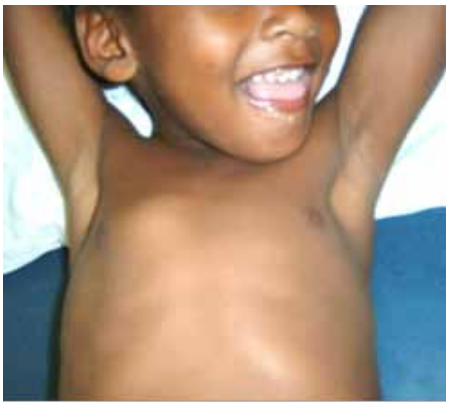


Figure 106.6: Anterior chest wall tumour.

Table 106.1: 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 tumour 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 presence of macroscopic disease
Group IV	Distant metastases

Staging

Staging depends on such factors as the primary site and the extent of disease as determined by one of a number of staging systems. These include the International Society of Pediatric Oncology (SIOP), the tumour, nodes, metastases (TNM), or the Intergroup Rhabdomyosarcoma Study Group (IRSG) staging systems (see Table 106.1).

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

IRSG classification

The current staging system used in the United States is the IRSG system. Table 106.1 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 by SIOP/IRS (IRS is the Intergroup Rhabdomyosarcoma Study Group), based on studies of clinical outcomes in order to direct treatment protocols.[16]

- *Low-risk tumours* include stage 1, groups I and II (N0) (and orbit

eyelid up to group III) as well as stage 2 of group I tumours.

- *Intermediate-risk tumours* include the rest of stage 1 (group II (N1) and group III (nonorbit)), and stages 2 and 3.
- *High-risk tumours* consist mainly of group IV.

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 tumours. On the African continent, this mostly applies to the few patients who are not in advanced stages on presentation.

The correct pathologic diagnosis as well as the correct histologic subtype will determine much of the treatment, so they are important in RMS management. 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.

Chemotherapy

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

A 5-year survival rate of about 72% can be achieved on this regime. Large variations in the 5-year survival, however, depend on patient age and tumour characteristics. Children who survived the first 5 years after diagnosis have an excellent long-term prognosis.[15] 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%.

Surgical aspects of RMS management

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, tumours rely on surgery to achieve local control; and
- support in terms of vascular access, etc.

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 unresectable. 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 tumours.

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 tumour at surgery.

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

Diagnostic

Tumours 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 tumours with a good biological response to chemotherapy, the residual tumour 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, as survival is bound to a disease-free outcome. It is of limited value in stage IV disease.

Management of recurrence

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

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

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

Radiotherapy

Although radiation therapy is of considerable use in controlling local recurrence, its use 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 MMT89 (Malignant Mesenchymal Tumour 1989) protocol study,[17] this applied to only 23% who required local therapy to achieve complete control.

Radiotherapy is particularly used where either 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.

Prognosis

The prognosis of STS is largely determined by the degree of spread at the time of diagnosis, the biology of the tumour, the histological features, the site of origin, and the treatment given. Because much of the management of paediatric soft tissue sarcomas (NRSTS) is extrapolated from adult studies, the treatment is debated, due to their varying chemosensitivity.

Nevertheless, a 5-year survival rate greater than 70% has been reported in recent trials of localised 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 (Figure 106.7).

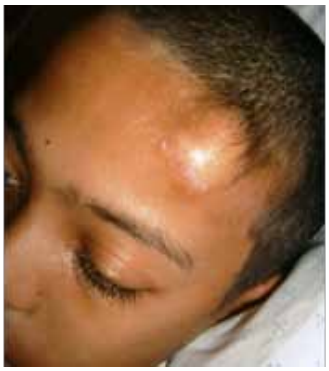
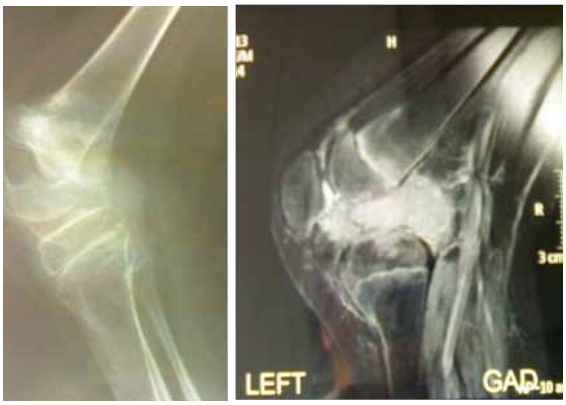


Figure 106.7: Metastatic RMS lesion on forehead from an extremity primary.



(A) **(B)**

Figure 106.8: (A) X-ray of left knee in a 13-year-old female with a synovial sarcoma. (B) MRI image demonstrates the extent of the tumour.

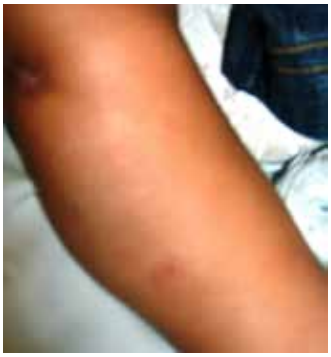


Figure 106.9: Malignant fibrous histiocytoma of the upper limb in a 6-year-old child.

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.

Nonrhabdomyosarcoma Soft Tissue Tumours

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 tumours (10%). Age appears to be important, as synovial sarcomas, peripheral nerve sheath tumours, 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 STS 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 paediatric STS, 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 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 centres. Where paediatric NRSTS patients have had an initial unplanned or incomplete resection, a wide re-excision should precede any further adjuvant treatment.

Synovial Sarcoma

Synovial sarcoma is an uncommon malignant soft tissue neoplasm that accounts for 7–8% of all malignant soft tissue tumours.[18] Approximately 30% of synovial sarcoma patients are younger than 20 years of age. Synovial sarcoma is the most common NRSTS in paediatric 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 (Figure 106.8). The upper extremity, trunk, abdomen, and head and neck regions may also be involved. It is also associated with a nonrandom chromosomal translocation t(X, 18)(p11; q11).

Initial biopsy should be incisional unless a very localized tumour is present, and should be longitudinal to allow for later wide excision. A wide surgical excision with clear 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.

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 tumour (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.

Leiomyosarcoma

Leiomyosarcoma arises from smooth muscle and is the most common retroperitoneal tumour STS in the paediatric 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.

Neurofibrosarcoma

Neurofibrosarcoma is a tumour 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.

Malignant Fibrous Histiocytoma

Like fibrosarcoma, malignant fibrous histiocytoma arises from fibroblasts, mostly occurring in the trunk and extremities (Figure 106.9). 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.

Liposarcoma

Liposarcoma is very rare in childhood, but has been described in the peripheries and retroperitoneally. It is sometimes difficult to distinguish from lipoblastoma, a benign condition; any fatty tumour with unusual features, such as poorly localized, invading fascia, should be evaluated.

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. Liposarcoma typically may be associated with a nonrandom gene translocation, t(12;16)(13;p11); it may be of myxoid lipoblastoma; or other genetic abnormalities may occur.

Liposarcoma tends to be locally invasive and rarely spreads to distant sites. Wide surgical excision is the treatment of choice.

Vascular Tumours and Kaposi Sarcoma

Kaposi sarcoma

Kaposi sarcoma in a child is usually regarded as a rare and unexplained condition. Essentially, KS is a multicentric neoplasia of microvascular origin arising in association with HIV-affected individuals. It 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 a similar male-to-female ratio, as opposed to the male predominance in adults.

Clinically, KS presents on the feet or ankles, thighs (Figure 106.10), 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 anaemia.

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 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.

Kaposi sarcoma is also associated with immunosuppression, and an increased KS-associated herpes virus (KSHV) seroprevalence, the risk being 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.

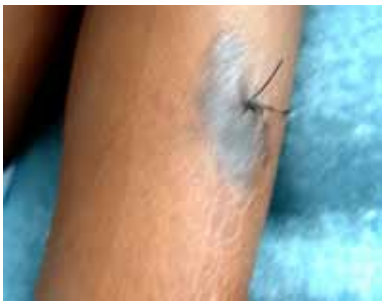


Figure 106.10: Kaposi sarcoma of leg with evidence of biopsy.

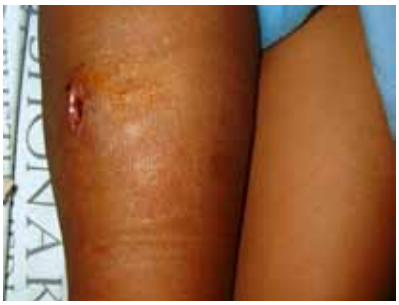


Figure 106.11: Poor healing in a biopsy wound of a haemangiopericytoma of the thigh.

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

Lesions may return after treatment, however.

Haemangiopericytoma

Haemangiopericytoma is an uncommon soft tissue tumour that arises from small pericapillary spindle-shaped cells (capillary pericytes). It may be benign or malignant, depending on the tumour biology, and it has a variable and unpredictable malignancy risk. Haemangiopericytoma is exceedingly rare in childhood. It mostly occurs in the lower limbs (Figure 106.11) 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)).

Haemangiopericytoma 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 hypoglycaemia or hypophosphataemic 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.

Haemangioendothelioma

Haemangioendothelioma (congenital haemangioma) may occur in viscera (e.g., liver, lung) or in soft tissue elsewhere.

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

Epithelioid haemangioendothelioma, in contrast, is a distinctive vascular soft tissue tumour that has been previously considered a tumour 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 tumours 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, tumours 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 tumour in childhood. At least one-third arise within the skin, and about 25% in soft tissue. Other sites (e.g., liver, breast, or bone) make up about 25% of occurrences. 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.

Miscellaneous Tumours

Alveolar Soft Part Sarcoma

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

Ewing's Sarcoma Family of Tumours

Long regarded as a tumour of the bone (Figure 106.12), the Ewing's sarcoma family of tumours (ESFT) remains a not 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.[21]

Although better known as Ewing's sarcoma of the bone, there is a distinct extra-osseous group of Ewing's sarcomas that originate from soft tissues (including PNET and the Askin tumour of the chest wall).

Prognostic factors used to stratify patients include

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

Ewing's sarcoma is treated successfully in many cases by a combination of chemotherapy, surgery, and radiotherapy.[22] Patients with small peripheral tumours without distant spread have been reported to have a high rate of cure (>70%) . Large, centrally located tumours and those with advanced stage disease have a very much less successful outcome (<33% 5-year survival).

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

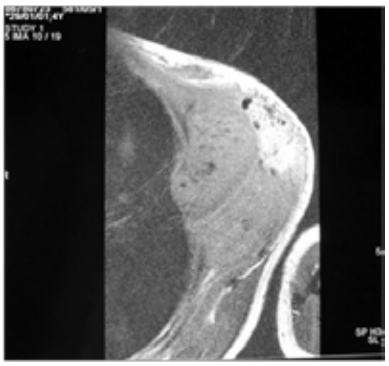


Figure 106.12: Ewing's sarcoma of the rib.

Evidence-Based Research

A number of aggressive malignant tumours occur that require multimodal therapy, usually including surgical management. Table 106.2 presents a review of management strategies for rhabdomyosarcoma in children.

Table 106.2: Evidence-based research.

Title	Optimal management strategies for rhabdomyosarcoma in children
Authors	Walterhouse D, Watson A
Institution	Division of Hematology/Oncology, Children's Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
Reference	Paediatr Drug 2007; 9(6):391–400
Problem	Rhabdomyosarcoma is the most common sarcoma of childhood. Fortunately, the goal of cure is realistic for the majority of patients with localized tumours. However, management of these patients remains challenging. The fact that the tumour arises in a wide variety of primary sites, some of which are associated with specific patterns of local invasion, regional lymph node spread, and therapeutic response, requires physicians to be familiar with site-specific staging and treatment details. In addition, rhabdomyosarcoma requires multimodality therapy that can be associated with significant acute toxicities and long-term effects, particularly when administered to young children. These factors sometimes present a dilemma as to the best approach to optimize the chance of cure, minimize toxicity, and respect quality of life.
Intervention	The purpose of this review is to discuss "optimal" management of this complicated tumour. Since the tumour is relatively rare and requires highly specialized care, and important management questions remain to be answered, optimal management of rhabdomyosarcoma includes enrollment in clinical trials whenever possible.
Comparison/ control (quality of evidence)	Appropriate management begins with establishing the correct pathologic diagnosis, histologic subtype, primary site, extent of disease (International Society of Pediatric Oncology (SIOP)-TNM-Union Internationale Contre le Cancer stage or Intergroup Rhabdomyosarcoma Study Group (IRSG) stage), and extent of resection (IRSG). Cooperative groups throughout North America and Europe have defined risk-adapted treatment based on these factors; this treatment requires a coordinated management plan that includes surgery, chemotherapy, and usually radiotherapy. The surgical approach for rhabdomyosarcoma is to excise the primary tumour, whenever possible, without causing major functional or cosmetic deficits. Wide excision is difficult in some primary sites and can be complicated by the fact that the tumour grows in a locally infiltrative manner so that complete resection is often neither possible nor medically indicated. Incompletely resected tumours are generally treated with radiotherapy. The cooperative groups reduce the dose of radiation based on the response of the tumour to chemotherapy and delay primary resection to differing degrees. Response-adjusted radiation administration may reduce the long-term effects of radiotherapy, such as bone growth arrest, muscle atrophy, bladder dysfunction, and induction of second malignant neoplasms; however, it may also be associated with an increased risk of tumour recurrence. All patients with rhabdomyosarcoma require chemotherapy. A backbone of vincristine and actinomycin D with either cyclophosphamide (VAC) or ifosfamide (IVA) has been established. Risk-adapted treatment involves reducing or eliminating the alklyating agent for patients with the most favourable disease characteristics.
Outcome/ effect	Clinical trials are ongoing to improve outcomes for higher risk patients; newer agents, such as topotecan or irinotecan, in combination with VAC or the use of agents in novel ways, are being investigated. Acute and long-term toxicities associated with these chemotherapy regimens include myelosuppression, febrile neutropaenia, hepatopathy, infertility, and second malignant neoplasms. A 5-year survival rate >70% has been achieved in recent trials for patients with localized rhabdomyosarcoma. However, the outcome for patients who present with metastatic disease remains poor.
Historical significance/ comments	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. It is hoped that newer therapies directed at specific molecular genetic defects will benefit all patients with rhabdomyosarcoma.

Key Summary Points

1. Tumours 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: congenital fibrosarcoma, rhabdomyosarcoma, and nonrhadomyosarcoma STS.
6. Nonrhabdomyosarcoma STS includes synovial sarcoma, liposarcoma, vascular tumours (e.g., Kaposi sarcoma, haemangiopericytoma, 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; assess metastatic spread; and provide supportive care (e.g., long-term venous access).
9. Although STSs are often highly malignant tumours, the prognosis has improved significantly over the last three decades. Up to 77% of tumours in children younger than 1 year of age are surgically resectable following neoadjuvant chemotherapy.

References

1. Loeb DM, Thornton K, Shokek O. Pediatric soft tissue sarcomas. Surg Clin North Am 2008; 88(3):615–627.
2. Gurney JG, Severson RK, Davis S, Robisin L. The incidence of cancer in children in the United States: sex, race and 1 year age-specific rates by histological type. Cancer 1995; 75:2186–2195.
3. Upton B, Chu Q, Li BD. Li-Fraumeni syndrome: the genetics and treatment considerations for the sarcoma and associated neoplasms. Surg Oncol Clin N Am 2009; 18(1):145–156.
4. Wang H, Garzon R, Sun H, Ladner KJ, Singh R, Dahlman J, et al. NF-kappaB-YY1-miR-29 regulatory circuitry in skeletal myogenesis and rhabdomyosarcoma. Cancer Cell 2008; 14(5):369–381.
5. Hayes-Jordan AA, Spunt SL, Poquette CA, Cain AM, Rao BN, Pappo AS, et al. Nonrhabdomyosarcoma soft tissue sarcomas in children: is age at diagnosis an important variable? J Pediatr Surg 2000; 35(6):948–953.
6. Minard-Colin V, Orbach D, Martelli H, Bodemer C, Oberlin O. Soft tissue tumors in neonates. Arch Pediatr 2009; 16(7):1039–1048.
7. Miettinen M. From morphological to molecular diagnosis of soft tissue tumors. Adv Exp Med Biol 2006; 587:99–113.
8. Plaschkes J. Epidemiology of neonatal tumours. In: Puri P, ed. Neonatal Tumours. Springer-Verlag, 1996, Pp 11–22.
9. Azizkhan RC. Neonatal tumours. In: Carachi R, Azmy A, Grosfeld JL, eds. The Surgery of Childhood Tumours, 1st ed. Arnold, 1999, Pp 107–123.
10. Mandong BM, Kidmas AT, Manasseh AN, Echejoh GO, Tanko MN, Madaki AJ. Epidemiology of soft tissue sarcomas in Jos, North Central Nigeria. Niger J Med 2007; 16(3):246–249.
11. Laurvick CL, Milne E, Blair E, de KN, Charles AK, Bower C. Fetal growth and the risk of childhood non-CNS solid tumours in Western Australia. Br J Cancer 2008; 99(1):179–181.
12. Gurney JG, Young JL, Roffers SD, et al. Soft tissue sarcomas. In: Gloeker Ries IA, Smith MA, Gurney JG, et al., eds. SEER Paediatric Monograph: Cancer Incidence and Survival among Children and Adolescents, United States SEER Program, 1975–1995. National Cancer Institute, 1999, Pp 111–124.
13. Paulino AC, Okcu MF. Rhabdomyosarcoma. Curr Probl Cancer 2008; 32(1):7–34.
14. Leuschner I, Newton WA, Jr, Schmidt D, Sachs N, Asmar L, Hamoudi A, et al. Spindle cell variants of embryonal rhabdomyosarcoma in the paratesticular region. A report of the Intergroup Rhabdomyosarcoma Study. Am J Surg Pathol 1993; 17(3):221–230.
15. Punyko JA, Mertens AC, Baker KS, Ness KK, Robison LL, Gurney JG. Long-term survival probabilities for childhood rhabdomyosarcoma. A population-based evaluation. Cancer 2005; 103(7):1475–1483.
16. Raney RB, Maurer HM, Anderson JR, Andrassy RJ, Donaldson SS, Qualman SJ, et al. The Intergroup Rhabdomyosarcoma Study Group (IRSG): Major lessons from the IRS-I through IRS-IV studies as background for the current IRS-V treatment protocols. Sarcoma 2001; 5(1):9–15.
17. Stevens MC, Rey A, Bouvet N, Ellershaw C, Flamant F, Habrand JL, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood and adolescence: third study of the International Society of Paediatric Oncology—SIOP Malignant Mesenchymal Tumor 89. J Clin Oncol 2005; 23(12):2618–2628.
18. Andrassy RJ, Okcu MF, Despa S, Raney RB. Synovial sarcoma in children: surgical lessons from a single institution and review of the literature. J Am Coll Surg 2001; 192(3):305–313.
19. Viejo-Borbolla A, Schulz TF. Kaposi's sarcoma-associated herpesvirus (KSHV/HHV8): key aspects of epidemiology and pathogenesis. AIDS Rev 2003; 5(4):222–229.
20. Sitas F, Newton R. Kaposi's sarcoma in South Africa. J Natl Cancer Inst Monogr 2001; 28:1–4.
21. Jawad MU, Cheung MC, Min ES, Schneiderbauer MM, Koniaris LG, Scully SP. Ewing sarcoma demonstrates racial disparities in incidence-related and sex-related differences in outcome: an analysis of 1631 cases from the SEER database, 1973–2005. Cancer 2009; 115(15):3526–3536.
22. Subbiah V, Anderson P, Lazar AJ, Burdett E, Raymond K, Ludwig JA. Ewing's sarcoma: standard and experimental treatment options. Curr Treat Options Oncol 2009; 10(1–2):126–140.

Further Reading

Carachi R, Grosfeld JL, Azmy AF, eds. The Surgery of Childhood Tumours. Springer, 2008.

Soliman H, Ferrari A, Thomas D. Sarcoma in young adult population: an international overview. Semin Oncol 2009; 36(3):227–236.

Walterhouse D, Watson A. Optimal management strategies for rhabdomyosarcoma in children. Paediatr Drugs 2007; 9(6):391–400.