Soft Tissue Sarcoma

74

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74.1 Introduction Including Definition and Incidence

74.1.1 Definition

The term sarcoma etymologically means a tumour of the flesh. Any malignancy arising from the muscle layer of the body integument is technically a sarcoma. The common term used, soft tissue sarcoma, is a misnomer as the tumour is rarely soft and it is a descriptive term with no scientific basis. The word sarcoma encompasses a wide variety of tumours of the integument, not just those arising from muscle but all structures that make up this mesoderm layer. In addition certain organs in the body have sarcomatous elements, e.g. the genitourinary system, the biliary tree, the gastrointestinal tract as well as the kidney can develop malignancies that are sarcomatous.

74.1.2 Incidence

Soft tissue sarcomas account for about 5–6% of all childhood malignancies. There is an increased incidence in males compared to females. They are divided into two groups. The rhabdomyosarcoma group (RMS), which originate from striated muscle and are by far the commoner and the second group are a heterogeneous collection of sarcomas referred to as non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). These tumours behave in a very different biological manner from those tumours arising from blastemal elements.

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74.2 Age of Presentation and Epidemiology

This is usually bimodal occurring early on between the ages of 2 and 5 years and a secondary peak occurring in the teenage years. However all ages are susceptible to develop these tumours and some may present in the neonatal period which makes them very difficult to treat (Fig. 74.1).

The clinical evaluation of the patients includes a careful history and a physical examination because by their very nature rhabdomyosarcomas may occur anywhere in the body. A family history may be significant since soft tissue sarcomas may occur in cancer families as a component of the Li-fraumeni syndrome as well as the Beckwith-Wiedemann syndrome. The genetics of these two syndromes are associated with soft tissue sarcomas.

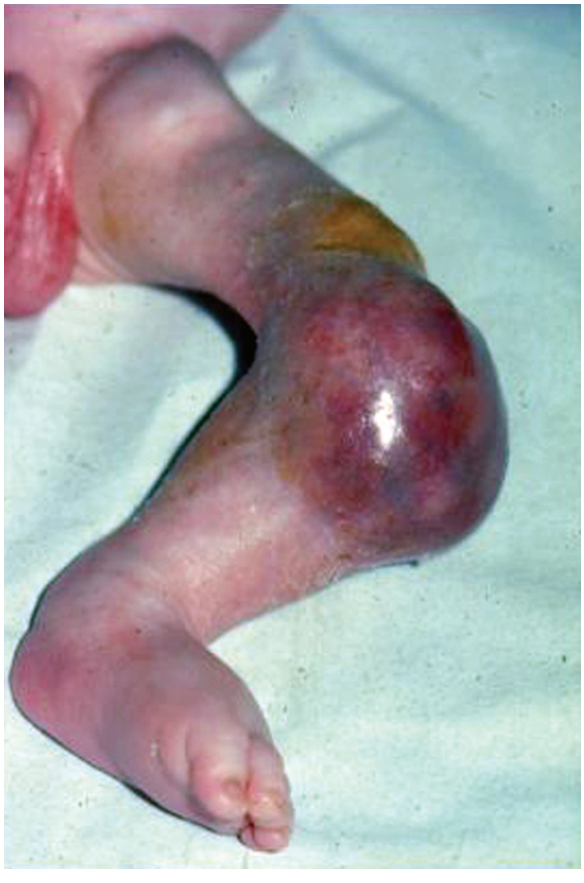

Fig. 74.1 RMS of the left leg in a neonate with enlarged inguinal lymph nodes

The Beckwith-Wiedemann syndrome has a complex genetic makeup. It is often associated with several 11p15 chromosomal changes. It is an overgrowth syndrome often associated with hypoglycaemia. Other tumours associated are Wilms' tumour and liver tumours.

The Li-fraumeni syndrome is an autosomal dominant disorder where soft tissue sarcoma occurs at an early age in a cancer family. Other tumours associated are brain lesions, breast cancer and leukaemia.

Rhabdomyosarcoma has also been associated with neurofibrosarcoma.

74.3 Symptoms and Signs

Over 80% of the patients have localised disease at the time of presentation. The symptoms at presentation often depend on the primary site. In general there are three main areas that can be affected. These are the head and neck, the trunk and limbs and the genitourinary system.

74.3.1 Clinical Presentation of Rms in the Head and Neck

These tumours often present early with a swelling or bleeding from an orifice, which might be the ear or the nose or even proptosis of the eye. Such tumours may mimic parotitis or even cause neurological dysfunction secondary to extension of parameningeal lesions affecting the central nervous system. These tumours may be confused with commoner lesions initially but gradually the progression of tumour growth is relentless and it soon becomes obvious that this is not an infective condition when they do not respond to standard regimes of antibiotic chemotherapy. These tumours are aggressive and gradually erode bony margins and can infiltrate from one space in the head and neck to another. Regional lymph nodes are often involved and can initially present as an enlarged lymph node in the neck region (Fig. 74.2).

Head and neck tumours may arise in the orbit at parameningeal or nonparameningeal sites. Orbital rhabdomyosarcomas may present with proptosis, chemosis or a conjunctival mass. This may lead to blindness and ophthalmoplegia later on. Tumours that arise from parameningeal sites are associated with erosion of the cranial

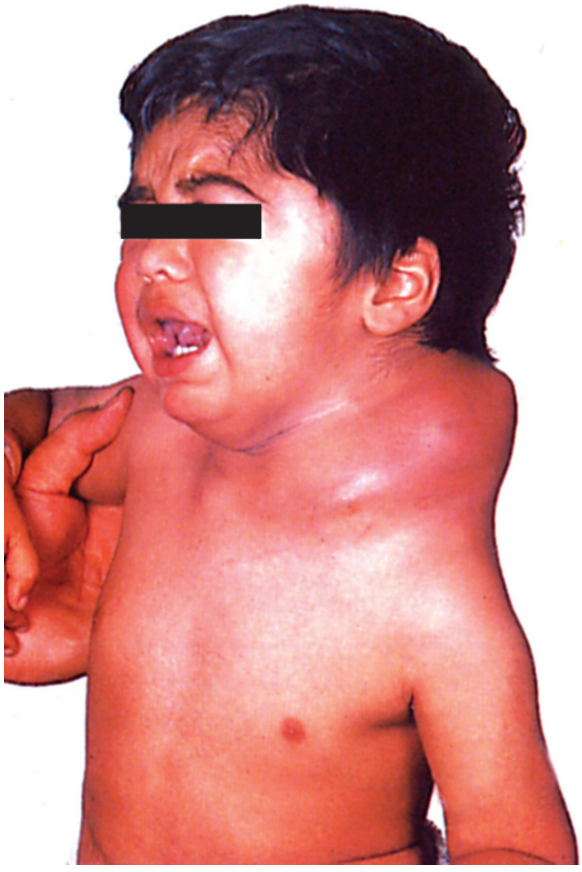

Fig. 74.2 RMS of the neck presenting as a lump

bones, which can present with meningeal symptoms and cranial nerve manifestations. A tumour arising in the nasopharynx may cause airway obstruction and bleeding. Those arising in the paranasal sinus present with pain and nasal discharge. A tumour in the middle ear or mastoid region may present as a polypoidal tumour with obvious facial nerve palsy. The commonest histology in this group of tumours is embryonal. Thus a clinical presentation may at first present to the general practitioner, to the ear, nose and throat surgeon or even to the ophthalmologist.

74.3.2 Clinical Presentation of RMS of the Trunk and Limbs

Truncal RMS can present as a nodule or a mass occasionally going into the chest wall causing respiratory symptoms or neurological ones if cord compression results from a paraspinal tumour.

Rhabdomyosarcomas of the extremities are more common in the lower limbs and occur in the older age group. There is a higher incidence of nodal involvement in these cases. There is often a delay in presentation and occasionally may present with a metastasis in a groin node. Rhabdomyosarcomas of the trunk and the limbs usually present with a localised swelling, which can be confused with a haematoma following a minor injury. The lesion may be associated with bruising and may have an inflammatory component to it, which can be very confusing for the diagnostician. The tumour grows relentlessly and does not behave like a simple haematoma and metastise early to the regional glands. Another potential confusion is a sudden change in a congenital haemangioma/lymphangioma. If it suddenly changes in characteristics and becomes hard, it can be confused with the development of a rhabdomyosarcoma. Occasionally clinical presentation may be with metastatic disease to other parts of the body and especially to the lungs from a small primary in the periphery.

74.3.3 Clinical Presentation of RMS of the Genitourinary System

The sites that are generally affected include the bladder, prostate and paratesticular region in the male and the bladder, vagina, uterus and vulva in the female. The histopathology of this tumour is very often of the embryonal variety and carries a good prognosis. The poor sites include the rhabdomyosarcomas that arise in the base of the bladder and the prostate. Rhabdomyosarcoma of the genitourinary system can manifest with urinary frequency or retention or the presence of sarcoma botryoides, which are fleshy polyps that protrude from the vaginal orifice and may be found in the nappy of a child (Fig. 74.3a and b). Rhabdomyosarcoma of the genitourinary system usually present earlier because of the confined space within the pelvis causing an obstructive uropathy. During the examination of the child a full examination of the pelvic region and a digital rectal examination is mandatory in order to pick this up and avoid confusion with what maybe mistakenly diagnosed as a constipated child. In the genitourinary tract some of these masses may be very large and present as an abdominal mass. This can be a true tumour or can be due to an obstructed bladder, which may enhance the

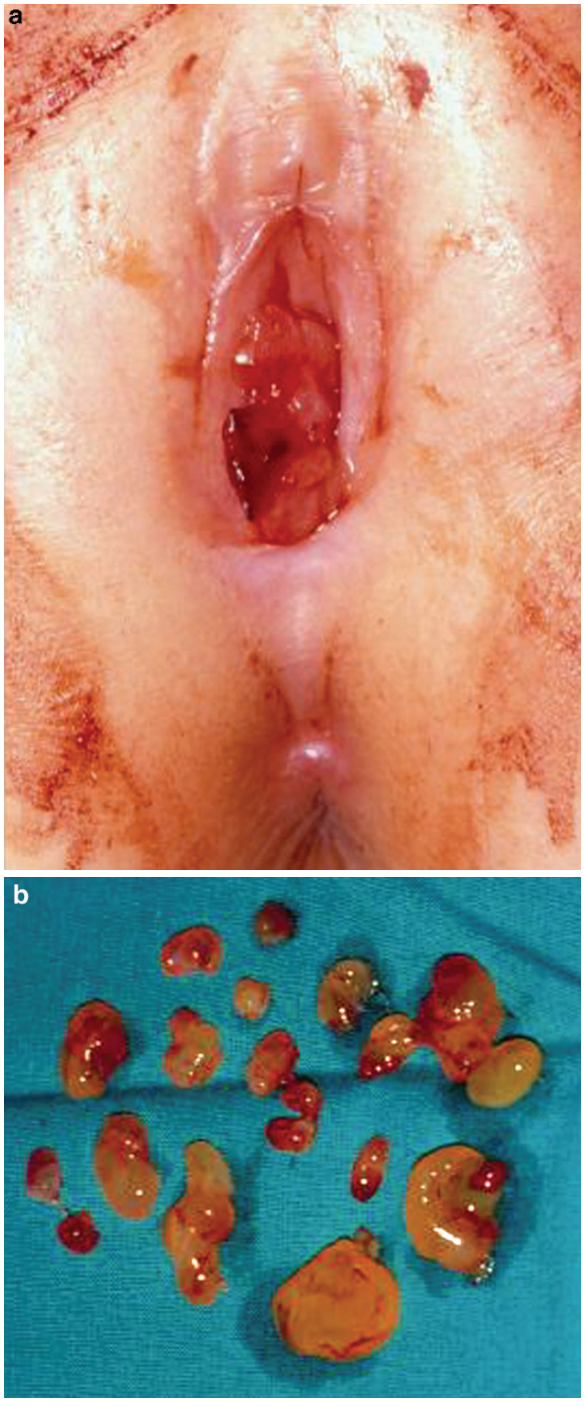

Fig. 74.3 (**a**) Sarcoma botryiodes protruding from the vagina, (**b**) Botryoid fleshy masses in nappy of the same patient

size of the mass. Paratesticular tumours are usually hard, painless scrotal swellings that can present with signs and symptoms secondary to a larger intraperitoneal mass and have a characteristic spindle cell on histology.

74.4 Imaging at Presentation

The commonest imaging used is a plain X-ray, which may demonstrate a soft tissue mass with calcification if haemorrhage has occurred into the tumour. In a tumour of the head and neck the bony structures may be eroded especially in orbital meningeal/parameningeal tumours. In a tumour arising from the neck, the mediastinum may be shifted and the trachea may be pushed away from its central position. In truncal lesions there may be bony erosions, metastases in the lung or pleural effusions.

Ultrasound is another modality that can be very helpful initially to define a solid from a cystic lesion. It is most helpful in genitourinary rhabdomyosarcomas to identify the origin of the tumour and detect any obstructive lesion causing an obstructive uropathy i.e. a large bladder and hydronephrosis (Fig. 74.4).

Computerised tomography (CT) and magnetic resonance imaging (MRI) are essential in the evaluation of the primary site and to detect any extension of the tumour and its relationship to other surrounding structures (Fig. 74.5). CT scans are very useful to confirm metastatic lung lesions in rhabdomyosarcoma. Similarly assessment of retroperitoneal lymphadenopathy in tumours that arise in the testis have replaced extensive retroperitoneal surgery to identify these lesions.

MRI scans are particularly useful in extremities, pelvic, head and neck regions and give very clear definition and differentiation between the different tissues and planes. There is still however a lot of doubt and debate whether MRI scans are able to differentiate between malignant soft tissue tumour from a benign condition.

74.5 Staging and Surgical Biopsy for Diagnosis

There is no place for needling a tumour, which could be a sarcoma whether it is to take a percutaneous biopsy or aspiration cytology. This approach compromises the care of the patient because it inevitably will seed tumour along the track and spread it resulting in upstaging of this type

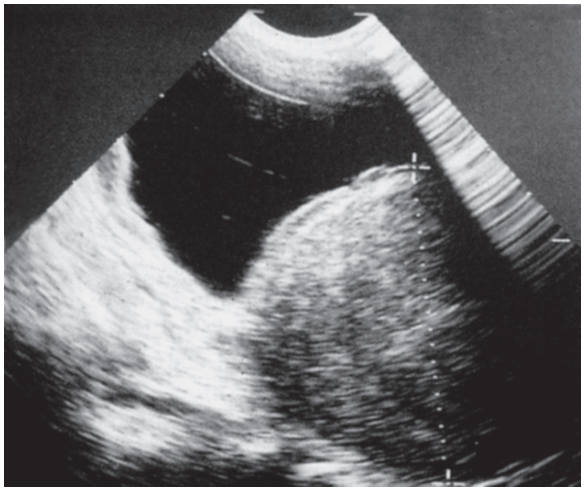

Fig. 74.4 Ultrasound of bladder with RMS of the base of the bladder

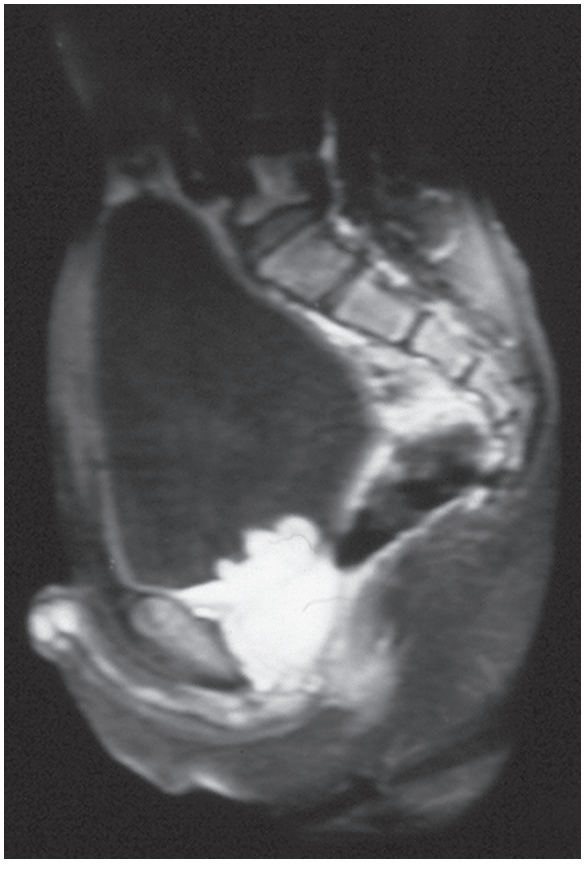

Fig. 74.5 CT scan of a extensive bladder neck RMS with outlet obstruction

of tumour. The role of the surgeon is to ensure that under a general anaesthetic an adequate open incision is made over the site of the tumour and a careful incision is made through the capsule of the tumour if there is one. This is in order to obtain a proper representation of the tumour. An adequate sample of the tumour will give an accurate diagnosis and allow proper staging as well as histological typing for the appropriate chemotherapy. The tumour must be sent fresh to the pathology department because of the variety of biological and histochemical tests that need to be carried out on this type of tissue. It is important that the pathologist is aware that this type of tumour surgery is being performed and can provide advice as to whether adequate amount of tissue has been obtained to be able to provide a diagnosis. The site where the incision is made has to be carefully planned so that this area is included in the eventual total resection of the tumour after chemotherapy has been instituted. All attempts at removal of the tumour en bloc at initial presentation should be resisted. The tumours are often gross at presentation and there is a real risk of compromising adjacent tissues, which may have been invaded by this tumour. Extirpative surgery and extensive surgery in these types of tumours should no longer be carried out at initial presentation. Trunk and extremity biopsies should be performed along the long axis of the tumour so that subsequent excisions are not compromised.

A clinical staging system has been developed to determine prognosis (Table 74.1). It has been demonstrated that the site of origin of the tumour, the size, the invasiveness as well as whether regional lymph nodes involvement is affected have a significant impact on the survival for non-metastatic rhabdomyosarcoma patients.

The diagnosis of Rhabdomyosarcoma depends on open surgical biopsies. These need to be open biopsies which should be generous so that full investigation of the tissue can take place which should include a chromosome analysis, surface markers and a whole range of histochemical testing and special stains which are available for these tumours. The detection of metastatic disease is very often included during the scanning of the chest by CT scans and MRI scans of the whole body. Regional lymph nodes should be sampled at the time of surgery for patients with lymph primaries. However the role of retroperitoneal lymph node sampling in patients with paratesticular tumours is still very controversial.

74.6 Histopathology

The histopathology of rhabdomyosarcoma falls into the small round blue cell tumours of childhood, which

Table 74.1 Pretreatment clinical staging[a] for rhabdomyosarcoma in IRS

Stage	Site	Size	Nodes	Distant mets
1	Favorable	≤ or > 5 cm	N_0 or N_1	None
2	Unfavorable	≤ 5 cm	N_0	None
3	Unfavorable	> 5 cm	N_0	None
4	Unfavorable	≤ or > 5 cm	N_1	None
	Either	≤ or > 5 cm	N_0 or N_1	Yes
Primary sites				
Favorable	**Unfavorable**			
Orbit	Parameningeal head and neck			
Superficial head and neck	Bladder prostate			
Paratesticular, vagina, uterus	Extremities			
	Other			

[a] Based on *clinical* evaluation *before* surgery, chemotherapy and/or radiation therapy begins.
IRS: Intergroup Rhabdomyosarcoma Study.

Table 74.2 Histologic variants of childhood rhabdomyosarcoma: International Rhabdomyo-sarcoma Pathologic Classification

I	Favourable prognosis
	(a) Botryoid
	(b) Spindle-cell
II	Intermediate prognosis
	(a) Embryonal
	(b) Pleomorphic (rare)
III	Poor prognosis
	(a) Alveolar
	(b) Undifferentiated

also include neuroblastoma, Ewing's sarcoma, small cell osteogenic sarcoma and lymphomas. It is possible for the histopathologist to differentiate between the different tumour types by a combination of microscopic appearance and immunohistochemical staining as well as the molecular genetic characteristics of these different types of tumours (Tables 74.2 and 74.3). The presence of rhabdomyoblasts or skeletal muscle and muscle-specific proteins can be identified by immunohistochemical staining. The commonest type of tumour encountered is the embryonal type of rhabdomyosarcoma, which consists of spindle shape rhabdomyoblasts and small round cells and longitudinal cytoplasmic striae. It is the commonest type of tumour in the younger age group and 80% of urinary tract tumours are made of the embryonal type whereas 60% of the head and neck tumours are embryonal and only half of the extremity ones fall into this category. The sarcoma botryoid a variant of the embryonal sarcoma can occur in the vagina, uterus, bladder. These are small round cells with a very mixed stroma and they are typical of this type of tumour. The prognosis in this age group is excellent. The alveolar type of tumour, which is second in frequency following the embryonal, most commonly occurs in the extremity and trunk.

The pleomorphic type of rhabdomyosarcoma is the least common in children and has large pleomorphic cells with large giant cells also present. This is seen in the extremity and trunk and carries a very poor prognosis. Thus the prognostic and therapeutic implications of biologic, immunologic and cytologic techniques makes it essential for the surgeon to obtain adequate quality and quantity of tissue to ensure proper transfer of the specimens to the laboratory while they are fresh. It has to be noted that the site where the open biopsy is carried out must be included in the planning for future so that when the final resection is carried out this site of biopsy is also included in the area of excision. The common sites for metastatic spread include the lungs, bones, bone marrow and these need to be evaluated by scans as well as bone marrow aspiration. In general patients with an alveolar histopathology have a poorer prognosis both for stage and site of disease. Histological grading in soft tissue sarcoma is dependent on the number of mitoses, the presence or absence of necrosis of tumour cells and the differentiation of the tumours. They are graded from I to III according to the scoring system. Table 74.4.

74.6.1 Cytogenetics

Specific chromosomal translocation is useful where light microscopy may be insufficient for a diagnosis,

Table 74.3 Examples of antibodies useful in pediatric tumor diagnosis

Antibody	Antisera/cell lineage marked	Tumor
CD45 Leukocyte common antigen	Leukocytes	Lymphomas
CD20 (L26)	B lymphocytes	Lymphomas
CD45RO (UCHL-1)	T lymphocytes	Lymphomas
CD30 (Ber H-2)	Activated lymphocytes/macrophages/ Anaplastic large cell lymphoma	Hodgkin's disease/Reed-Sternberg cells
CD15 (LeuM1)	Reed-Sternberg cells	Hodgkin's disease
CD68 (KP1)	Macrophages	Histocytic neoplasms
Kappa/Lambda proliferation	Ig light chains	Lymphoid clonal
Neuron-specific enolase (NSE)	Neuroectoderm	Neuroblastoma
S100	Glial/Schwann cells/others	Neurofibroma, etc. Langerhan's cells
b2-microglobulin	b2-microglobulin	PNET
Synaptophysin	Neuroectoderm/neuroendocrine	Ewing's/PNET
MIC-2 (CD99)	MIC-2 gene product (glycoprotein P30/32)	Ewing's/PNET
Vimentin	Intermediate filaments/mesenchyme	Ewing's/soft tissue
Sarcoma		
Actin (common, smooth muscle, sarcomeric)	Muscle filaments	Rhabdomyosarcoma
Desmin	Muscle (smooth/striated)	Rhabdomyosarcoma
Myoglobin	Striated muscle	Rhabdomyosarcoma
Myo D-1	Skeletal muscle	Rhabdomyosarcoma
Cytokeratins (AE1-AE3, CAM 5.2, etc.)		Epithelial
	Synovial sarcoma	
CD1a	Langerhan's cells	Langerhan's cell histiocytosis

Table 74.4 Histological grading in soft tissue sarcoma

Feature		Score
Mitoses	0–9 (per 10 high power fields)	1
	10–19 (per 10 high power fields)	2
	>20 (per 10 high power fields)	3
Necrosis	None	1
	<50% of the tumor	2
	>50% of the tumor	3
Differentiation	Very highly differentiated	1
	Moderately differentiated but cell type easily recognizable	2
	Poorly differentiated or cell type uncertain	3
Grade is determined by aggregate score for all these features, i.e.		
Grade I	Score 3–4	
Grade II	Score 5–6	
Grade III	Score 7–9	

e.g. t(2:13) (q35:q14) in alveolar RMS and t(x:18) (p11.2:q11.2) in synovial sarcoma.

74.7 Management

In general once the diagnosis has been made the patient has a double lumen central line inserted and a regime of chemotherapy commenced.

74.7.1 Chemotherapy

The standard drugs used over the years has been a triple regimen of Vincristine, Actinomycin-D and Cyclophosphamide (VAC). Overall survival rate is above 70%. The site of origin as well as size of tumour and tumour spread determine the 5-year survival rate. It is best for localised lesions who can get a 95% rate. The patients with embryonal histology do well and

need less aggressive treatment than those with pleomorphic or alveolar histology who even with early stage disease and aggressive therapy do badly. Other drugs active in this disease include Doxorubicin, ifosphamide, etoposide, cisplatin, carboplatin, melphelan, topotecan, methotrexate, mitoycin C. In the majority of cases the chemotherapy is successful in shrinking tumours to allow surgical resection to take place.

74.7.2 Radiotherapy

Radiation therapy is used to mop up residual microscopic disease to achieve local control or gross residual disease that surgical removal was unable to excise because of dangers to the patient's life. It is very effective in reducing the mutilating surgery seen in days gone past. It may be delivered in the form of intracavitary brachytherapy in RMS of the vagina and uterus.

74.7.3 Surgery

The goal of the surgeon is to attempt a complete resection of the primary tumour with surrounding margins which are uninvolved but this must also be done to preserve organs and be cosmetically acceptable. There is no place for debulking operations in this type of tumour. Regional lymph nodes are often removed for pathological examination and evaluation at the time. If residual disease is present it is important to re-excise the area until there is microscopic clearance of the edges of the excised region. This may require raising of flaps to cover the area of the wound eventually. Second look surgery for patients who have had an incomplete response to therapy is important to determine how responsive the tumour was to the chemotherapy regime used and to have a second attempt at total excision of the tumour.

The resection margin in children is variable whereas in adults a 2 cm margin is usually adequate, in children this is at times not possible. This is especially so when one approaches a neurovascular bundle and at the risk of damaging this one may have to compromise on the amount of clear margin at the tumour edge. Another common pitfall in tumour surgery with these types of tumours – especially the synovial sarcoma – is that they develop a pseudocapsule which is thought to be the boundary of the tumour whereas the capsule itself is part of the tumour and may be left behind thus leaving behind residual disease. In these situations recurrence rates are extremely high and in high-grade tumours a need to adopt a more aggressive approach to extirpative surgery.

Lymph node dissection is not done routinely for the disease and one often depends on imaging techniques to decide if there is lymph node involvement. This of course is not always accurate since one knows that a large lymph node may be due to inflammation whereas a normal size lymph node may still contain metastatic tumour cells. Some centres still advocate the biopsy of the sentinel lymph node for a variety of these tumours and lymph node resection can be performed.

Patients who have a tumour close to organs i.e. the eye and the genitourinary system benefit from primary chemotherapy followed by radiation therapy. This may alter excision of a tumour as a result of shrinkage by chemotherapy with or without radiotherapy. Taking regional lymph node biopsies, especially sentinel lymph node biopsies has improved the outcome in some situation.

Solitary lesions may be amenable to surgical resection and can produce long-term survival. This has been attempted by minimaly invasive surgery e.g. thoracoscopic approach for solitary lung lesion. However occurrence very often carries a poorer prognosis and these may relapse within the 1st years after treatment.

74.8 Genital Urinary Rhabdomyosarcoma

Patients with bladder and prostatic tumours may undergo radiation therapy and have a slightly higher survival rate and less recurrence. Attempts at intracavital or brachytherapy for tumours of the bladder and the prostate have been successfully treated with these conservative managements, however not without a price and in some instances tumour recurs and also complications of the radiation may result in necrosis and fistula formation. However with the increase in survival and with bladder preservation, which has been the main aim in recent years, it is certainly possible with tumours arising from the dome of the bladder where partial cystectomy can be performed. Prostatectomy

with preservation and urethra reconstruction is possible in some patients with bladder and prostatic rhabdo who do not respond to treatment. However, in some cases a total cystectomy is required in these patients and a urinary diversion would be necessary. Vulva, vaginal and uterine rhabdomyosarcoma carries a good prognosis with chemotherapy. It is possible to treat the majority of these tumours by conservative surgery.

74.9 Nonrhabdomyosarcoma Soft Tissue Sarcoma (NRSTS)

Although initially reported as an adult disease, more and more cases are reported in children and this group now form less than half of all the soft tissue sarcomas found in the paediatric age group. They may occur in association with neurofibromatosis. They occur most commonly in the lower limbs then the trunk followed by the chest and head and neck. Synovial cell sarcoma is the commonest of this group of tumours followed by the malignant fibrous histocytomas and fibrosarcoma.

This group of sarcomas is slightly less than half of the total number of sarcomas encountered in childhood and occasionally occur in older children and young adults. The clinical presentation is very often that of a localised mass and again presenting following a minor trauma and regional lymph nodes may be palpable in some instances. There is a slight preponderance of males and the most common type of tumour encountered in childhood is the synovial cell sarcoma which can be very misleading thinking it is a benign lesion. There are a whole variety of these tumours with their own histopathological pattern.

Imaging usually consists of CT scanning with contrast and MRI scans.

Synovial carcinomas are high-grade malignant neoplasms that account for the majority of the nonrhabdomyosarcoma soft tissue cell sarcoma. They occur in the teenage group and can present with metastases in the lung. Many of these tumours have got a pseudocapsule which gives a false impression during the time of surgery that the tumour has totally been excised. Many of these cases need to undergo re-excision for microscopic disease that might have been left behind at the time of the initial surgery. Chemotherapy is not of much value in this type of tumour, however radiation therapy may have some benefit (Table 74.5). Another type of tumour is infantile fibrosarcoma. Fibrosarcoma is one of the commonest NRSTS that occur in the paediatric population. It is histologically similar to the malignant adult counterpart. This tumour in infants is very often of a benign nature and does not metastasise although local recurrence may occur. Local excision of this tumour is adequate. The principles that have been learned from the past large studies from the United States indicated the following:

Table 74.5 Intergroup RMS Study Group Surgicopathological Staging System and Clinical Outcome According to Clinical Group

Group	Description	5-Year event-free survival %	5-Year survival %
I	Localised disease, completely resected	72–83	84–90
II	Microscopic residual, completely resected with nodes, nodes Involved with microscopic residual	65–72	84–88
III	Incomplete resection	—	35–54
IV	Distant metastases	15 (2 years)	34 (2 years)

1. Patients with localised completely resected disease have the best prognosis. Patients with metastasis at diagnosis have the worst prognosis thus in an attempt to remove all the visible tumour without excessive morbidity is an important consideration in these patients.
2. When a lesion has been incompletely resected, re-resection is important and any doubt about margin status should have a resection of that area.
3. It is desirable to preserve organ function and space structures such as the paraorbital region and the genitourinary system. These patients generally have a good prognosis.

The principles of management include adequate tissue biopsy, regional lymph node evaluation followed by chemotherapy. Eventually only radical surgery offers a cure.

Radiation therapy is particularly useful specially in limb involvement. The role of chemotherapy is unclear in NRSTS.

Further Reading

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