Rhabdomyosarcoma

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Abstract

Rhabdomyosarcoma (RMS) is the commonest soft tissue sarcoma (STS) in children. Most cases occur in young children and although the majority are sporadic, RMS can be a manifestation of certain cancer predisposition syndromes. Treatment for RMS involves a multimodality approach including chemotherapy, surgery and radiotherapy with attendant risks of long term treatment related morbidities. Whilst outcomes in localised RMS have improved steadily, those for metastatic and relapsed disease remain poor and there is a pressing need for novel therapeutic approaches. This review outlines the key points related to the diagnosis and management of children with RMS with a focus on current and future practice within the UK and Europe.

Keywords children; diagnosis; rhabdomyosarcoma; teenage; treatment; young adult

Epidemiology

A malignancy resembling striated-muscle, RMS accounts for about 5% of all childhood cancers and over 50% of all STS in children and is the most frequently occurring STS in children and teenage/young adult (TYA) patients. Slightly more frequent in males, these tumours may be found at any anatomic site. The mean UK annual incidence is 5.2 per million children under 15 years of age (National Registry of Childhood Tumours), amounting to approximately 60 newly diagnosed paediatric cases per year. Incidence has a bimodal distribution peaking at age 3 in the UK with a smaller peak occurring in the TYA age group. Over half of RMS cases are diagnosed within the first decade of life and the majority within the first 6 years, making it a significant contributor to cancer morbidity and mortality in this age group.

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Clinical presentation

The clinical presentation of RMS is variable. When children present with a visible tumour mass, RMS is usually considered in the differential diagnosis (Figure 1). The commonest sites of disease in children are the head and neck (H&N; orbital, parameningeal or non parameningeal; 36% of cases) and the genitourinary (GU) tract (23%) with 20% of cases occurring in the extremities (Figure 2). Between 15% and 25% of patients have distant metastases at presentation, most commonly in bone, bone marrow, lung or lymph nodes.

Making a diagnosis of RMS can be challenging as the differential diagnosis of a mass arising in virtually any anatomic site of the body is wide. Table 1 lists the most common presenting signs and symptoms of the tumour mass by site: most symptoms are a direct result of compression or invasion of surrounding structures, sometimes associated with pain, and are not specific to RMS. Definitive diagnosis is made from tumour tissue.

Although the majority of paediatric/TYA RMS cases arise sporadically, in some patients they may be part of a genetic syndrome, most frequently Li-Fraumeni syndrome. Most children aged <5 years with RMS are offered a genetics referral, irrespective of family history, owing to this strong association. Other syndromes should also be considered, particularly if the patient presents with additional associated findings (Table 2).

Clinical investigations

The investigation of patients with suspected or confirmed RMS involves accurate assessment of the size, position and invasiveness of the primary tumour. Cross-sectional imaging of the primary site is with magnetic resonance imaging (MRI), the preferred modality, or with computerised tomography (CT) although paratesticular tumours are best assessed with ultrasound scan. Regional lymph node groups must also be assessed using appropriate imaging (usually CT or MRI) as lymph node involvement impacts on local control treatment options. In limb RMS, imaging should include the entire limb, to include both regional and in-transit lymph node sites, and regional lymph node sampling is recommended.

All potential metastatic sites should be examined also to assess extent of disease. Whereas historically bone scan was used to assess bony metastases, whole body fluorodeoxyglucose positron emission tomography (FDG PET)- CT or whole body MRI are now the modalities of choice for assessing disease in bone and lymph nodes as well as other distant sites. A CT scan of the chest should be obtained looking for pulmonary metastases and a bone marrow biopsy is usually done for all but the lowest risk patients to assess medullary involvement. If the primary tumour is located in a parameningeal site, neurologic imaging and cerebrospinal fluid (CSF) cytology should be obtained to detect central nervous system (CNS) extension.

Safely obtaining adequate tissue for histologic diagnosis and molecular testing is critical to confirm diagnosis and initiate treatment. This may be done via an open incisional biopsy under general anaesthesia although increasingly percutaneous tru-cut biopsy is utilised provided adequate tissue can be obtained. With the newly established need for molecular analysis of biopsy specimens for diagnostic and potentially for treatment assignment purposes, this step is critical. The specialist team can ascertain the

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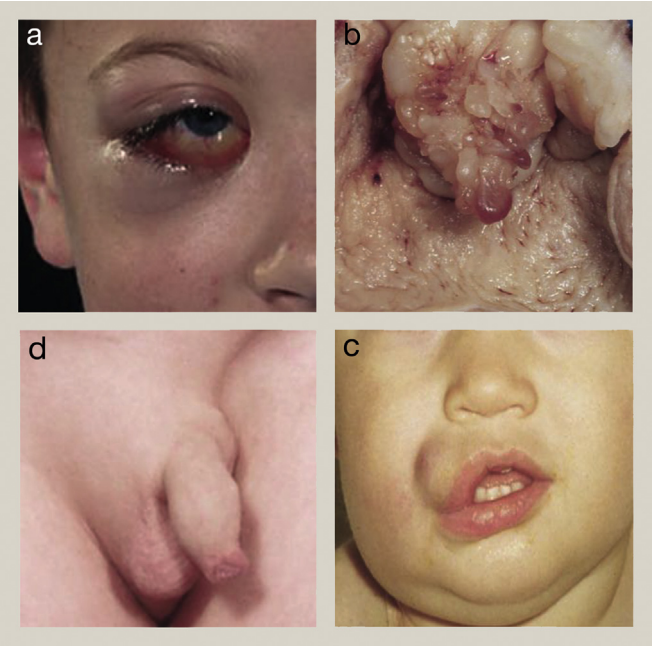

Figure 1 (**a**) Proptosis secondary to orbital RMS. (**b**) Embryonal/fusion negative RMS (botryoid type by histology) of the bladder. (**c**) RMS of the upper lip. (**d**) Paratesticular RMS in an infant.

Common presenting signs and symptoms of tumour mass by site

Site	Signs and symptoms
H&N	Proptosis
	Ophthalmoplegia
	Nasal/sinus congestion
	Nasal discharge
	Cranial nerve palsies
	Headache
	Vomiting
	Systemic hypertension
GU	Haematuria
	Urinary obstruction
	Extrusion of mucosanguineous tissue
	Mucosanguineous discharge Constipation
	Unilateral scrotal/inguinal swelling
Extremity	Swelling
	Pain
Abdomen/Pelvis	Palpable Mass
	Abdominal pain
	Intestinal obstruction
Biliary tract	Obstructive jaundice

Table 1

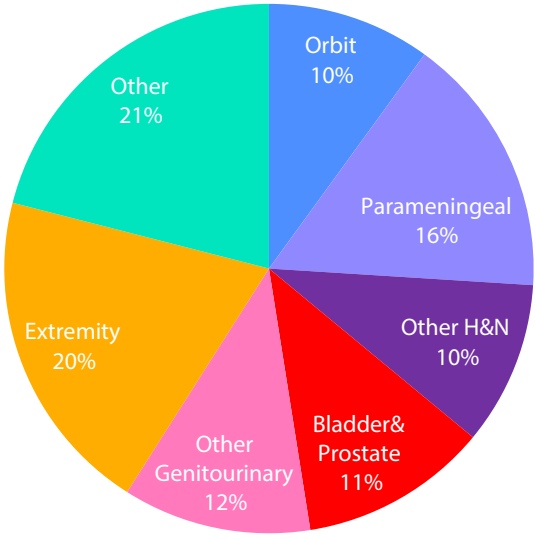

Figure 2 Proportion of Paediatric/TYA RMS cases by primary site. Figure modified from Principles and Practice of Pediatric Oncology (6th edition). H&N: head and neck. Parameningeal sites refer to base of skull, including middle ear/mastoid, paranasal sinuses, nasal cavity, parapharyngeal space and the pterygopalatine/infratemporal fossa region.

safest approach to biopsy, keeping in mind the potential need for subsequent surgery. Paratesticular tumours require orchiectomy via the inguinal approach with excision of the distal spermatic cord as the primary treatment; this establishes the diagnosis as well as providing surgical management. Of note, paratesticular tumours should never be removed through a scrotal approach owing to the risk of incomplete excision of tumour in the spermatic cord and contamination of the scrotal sac.

Pathology and molecular biology

RMS tumours are small round blue cell tumours of childhood whose origins are from mesenchymal precursor cells. They resemble developing skeletal muscle arrested in its ability to terminally differentiate. RMS can be classified into several histologic subtypes: embryonal RMS (ERMS) and alveolar RMS (ARMS) make up the majority, respectively accounting for approximately 70% and 25% of paediatric cases.

At a molecular level, the majority of ARMS tumours (80%) are defined by specific chromosomal translocations. The two key translocations are t (2; 13) (q35; q14) and t (1; 13) (q36; q14) leading to the fusion of *PAX3* or *PAX7* gene with *FOXO1*, respectively. These gene fusions lead to the expression of an aberrant transcription factor that inappropriately activates transcription of genes contributing to the transformed phenotype. While histology has historically deemed a particular tumour favourable (ERMS) or unfavourable (ARMS), based on inferior outcomes in ARMS, we now know that the 20% of ARMS which are "fusion negative" are molecularly and clinically more similar to ERMS than to fusion positive ARMS. This molecular distinction has recently led to fusion status replacing histological subtype in clinical risk stratification for RMS in European and North American studies.

Diagnostic testing in the pathology laboratory therefore includes several steps in addition to morphology. Immunohistochemical stains are typically positive for desmin, myogenin, MyoD1 and muscle-specific-actin, with higher levels of myogenin and MyoD1 seen in the alveolar subtype. Fluorescence in-situ hybridization (FISH) is performed to detect the presence of a translocation and reverse transcription polymerase chain

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