Rhabdomyosarcoma

What is a Rhabdomyosarcoma?[1]

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and represents a high-grade neoplasm of skeletal myoblast-like cells. There are 2 major subtypes:

- Alveolar rhabdomyosarcoma (ARMS).
- Embryonal rhabdomyosarcoma (ERMS).

Both subtypes pose substantial clinical challenges because achieving a cure requires controlling the primary tumour (which may arise in a wide variety of anatomical sites) by surgical resection and/or ionising radiation and eradicating systemic metastatic disease using intensive chemotherapy.

The World Health Organization (WHO) also recognises two rarer RMS subtypes:

- Pleomorphic RMS is a morphological variant of RMS that typically occurs in adults.
- In children, a spindle cell/sclerosing RMS variant is seen. Those tumours arising in the head/neck region seem to be more likely to carry specific somatic mutations and have a poorer prognosis.

Other types of sarcomas are liposarcomas, fibrosarcomas and mesenchymomas.

Rhabdomyosarcomas can occur anywhere in the body but occur more commonly near muscular structures - eg, around the intestines, around the ocular muscles and in the cardiac muscle in tuberous sclerosis.[2] The most common locations of rhabdomyosarcomas are:

- Head and neck (35-40%).
- Bladder (20%).
- Muscles, limbs, chest and abdominal wall (15-20%).
- Other sites - eg, testes.

Rhabdomyosarcomas are highly malignant and grow rapidly. They are, however, potentially curable.

How common is Rhabdomyosarcoma? (Epidemiology)

- Rhabdomyosarcomas are rare but are the most common soft tissue sarcoma in children.[3]
- Rhabdomyosarcomas is diagnosed in children and adolescents with an annual incidence of 4.3 cases per one million people younger than 20 years of age.[4]
- Rhabdomyosarcomas can occur at any age but approximately 87% of patients are younger than 15 years. Rhabdomyosarcoma rarely affects adults.[5]

Types

Rhabdomyosarcomas arise from rhabdomyoblasts - a primitive muscle cell. There are four types:[6]

- **Embryonal rhabdomyosarcoma** - the cells have a similar appearance to embryo cells aged 6-8 weeks. This is the most common type and has a predilection for the head, neck and the genitourinary tract. **Sarcoma botryoides** is a variant of the embryonal type and presents as a grape-like lesion, particularly in the vagina or bladder.
- **Alveolar rhabdomyosarcoma** - the cells have a similar appearance to embryo cells aged 10-12 weeks. This tends to affect older children and teenagers and has a more aggressive nature. It is associated with muscles of the trunk and limbs.
- **Pleomorphic rhabdomyosarcoma** - this entity is more common in adults and has a tendency to affect muscles of the extremities.

- **Spindle cell/sclerosing RMS** - seen in children.

Aetiology[1] [7]

- Most cases are sporadic in nature.
- Genetic risk factors: certain genetic disorders develop RMS more frequently, including Li-Fraumeni syndrome, Neurofibromatosis type I, Costello syndrome, Noonan syndrome, Beckwith-Wiedemann syndrome and DICER1 syndrome. However, only about 5% with RMS are thought to have co-morbid germline susceptibility syndromes.
- Environmental factors which may increase the risk of rhabdomyosarcoma include:
    - Parental use of marijuana and cocaine.
    - Intrauterine exposure to X-rays.[8]
    - Vaginal bleeding during pregnancy.
    - Premature birth.

Rhabdomyosarcoma symptoms (presentation)[1]

RMS can arise in virtually any anatomical site. The most common sites depend on the histological subtype:

- ERMS most commonly arises in the head and neck, including the eye socket, or in genitourinary sites.
- ARMS typically arises at extremity sites, with a smaller fraction arising in the head and/or neck or torso.

Radiographic or clinical evidence for distant metastatic disease is present in about 20% of children at diagnosis. Metastases arise by both lymphatic and haematogenous routes, and spread to lung, bone, and bone marrow are relatively common.

Signs and symptoms are typically associated with soft tissue mass and are often described as painless masses found in the extremities, or head and/or neck region.

They can also be associated with signs and symptoms due to mass effect on adjacent organs or neurovascular tissues, or associated with a visible mass protruding from an orifice, eg, a 'grape-like' mass in botryoid RMS of the vagina.

Orbital primary sites typically present as a unilateral, space occupying lesion with proptosis.

Other features depend upon the area of the body affected. Examples include:

- Nose - nasal obstruction and discharge.
- Abdomen - pain and change in bowel habit.
- Bladder - haematuria.

Diagnosis[6]

The diagnosis of RMS requires the direct analysis of tumor tissue from either an incisional or excisional biopsy or core needle biopsy and subjected to a series of histology and molecular pathology studies. The diagnosis of RMS has been traditionally based on recognising the features of skeletal myoblast-like tumour cells using light and, in some cases, electron microscopy, and the use of immunohistochemical (IHC) staining for skeletal muscle proteins.[1]

Evaluation typically includes the following:[9]

- Chest x-ray.
- Computed tomography (CT) scan of the chest.
- CT scan of the abdomen and pelvis (for lower extremity or genitourinary primary tumours).
- Magnetic resonance imaging (MRI) of the base of the skull and brain (for parameningeal primary tumours) and of the primary site of other non-parameningeal primary tumours, as appropriate.

- Regional lymph node evaluation: cross-sectional imaging (CT or MRI scan) of regional lymph nodes; enlarged lymph nodes should be biopsied when possible. Sentinel lymph node biopsy is more accurate than random lymph node sampling.
- Positron emission tomography (PET) with fluorine F 18-fludeoxyglucose scans can identify areas of possible metastatic disease not seen by other imaging modalities.
- Bilateral bone marrow aspirates and biopsies for selected patients.
- Bone scan for selected patients.

Non-resolving lumps in children should be investigated by a centre recognised by the United Kingdom Children's Cancer Study Group, as they will have better expertise in these rare tumours.

Staging

Soft Tissue Sarcoma Committee of the Children's Oncology Group: Pretreatment Staging System:[9]

- Stage 1: favourable sites; any tumour size; N0 or N1 or NX; no distant metastases.
- Stage 2: unfavourable sites; tumour less than or equal to 5 cm in longest diameter; N0 or NX; no distant metastases.
- Stage 3: Unfavourable sites;
    - Tumour less than or equal to 5 cm in longest diameter; N1; no distant metastases.
    - Tumour more than 5 cm in longest diameter; N0 or N1 or NX, no distant metastases.
- Stage 4: any site; any tumour size; N0 or N1 or NX; distant metastases present. The presence of positive cytology in pleural fluid, abdominal fluid, or CSF and the presence of pleural or peritoneal implants are considered evidence of metastases.

Favourable site: orbit; head and neck (excluding parameningeal); genitourinary tract (non-bladder/non-prostate). Unfavourable site is any site other than a favourable site.

- N0: regional nodes not clinically involved.
- N1: regional nodes clinically involved as defined as more than 1 cm measured in short axis on CT or MRI.
- NX: clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation).

Rhabdomyosarcoma treatment and management[9]

Eradication of the gross primary tumour, which is often accomplished using a combination of surgery and/or external beam ionising radiation.

Outcome is optimised with the use of multimodality therapy. All patients require chemotherapy and at least 85% also benefit from radiotherapy, with favourable outcome even for those patients with non-resectable disease.

Surgery

This is recommended for all lesions, provided it is feasible, and as much of the tumour should be removed as possible. However surgery is often not entirely successful in removing the tumour as it is often deeply embedded in surrounding tissue. If the rhabdomyosarcoma is in an extremity then amputation may be appropriate. Surgery may also be required to obtain a tissue biopsy.

Chemotherapy

The most active chemotherapy agents against rhabdomyosarcoma cells are vincristine, cyclophosphamide, actinomycin D, doxorubicin, isophosphamide and etoposide[6] .

Radiotherapy

This is given postoperatively, and occasionally pre-operatively to shrink tumour size, and commonly in head, neck and pelvic tumours.

Prognosis[1]

- The overall cure rates exceed 70%, with above 90% low-risk disease, 70% intermediate-risk disease, and less than 30% high-risk disease experiencing long-term survival.[10]

- High-risk individuals with rhabdomyosarcoma, include all those diagnosed as adults, those diagnosed with fusion-positive tumours during childhood (including metastatic and non-metastatic tumours), and those diagnosed with metastatic disease during childhood.[4]
- The embryonal type is the most treatable and has the most favourable prognosis.
- The ARMS subtype is characterised by PAX3–FOXO1 and PAX7–FOXO1 protein fusions:[10]
    - Fusion status has been found to be the most important prognostic factor for localised and metastatic disease. The 5-year event free survival rate is:
        - 52% for fusion-positive, localised disease.
        - 6% for fusion-positive, metastatic disease.
        - 78% for fusion-negative, localised disease.
        - 46% for fusion-negative metastatic disease.
    - The higher 5-year EFS rates for fusion-negative aRMS suggest that this group may unnecessarily receive therapies for high-risk disease, as these outcomes are similar to those of eRMS cases treated with intermediate-risk therapies.
- Location of the tumour also affects the prognosis, with orbital and genitourinary tract rhabdomyosarcomas having the most favourable prognosis.
- Recurrent RMS has a very poor prognosis.

Further reading

- Shern JF, Yohe ME, Khan J; Pediatric Rhabdomyosarcoma. Crit Rev Oncog. 2015;20(3-4):227-43. doi: 10.1615/critrevoncog.2015013800.

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