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Rhabdomyosarcoma

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ABSTRACT

A malignant tumor of striated muscle origin, rhabdomyosarcoma (RMS) is a childhood tumor that has benefited from nearly 30 years of multimodality therapy, culminating in a >70% overall 5-year survival. Prognosis for RMS is dependent on primary tumor site, age, completeness of resection, presence and number of metastatic sites, histology, and biology of the tumor cells. Multimodality treatment is based on risk stratification according to pre-treatment stage, postoperative group, histology, and site. Unique to RMS is the concept of postoperative clinical grouping that assesses the completeness of disease resection and takes into account lymph node evaluation at both the regional and metastatic basins. At all sites, if complete operative resection of disease is accomplished, including microscopic disease, survival is improved. Therefore, the surgeon plays a vital role in determining risk stratification for treatment, local control of the primary tumor and overall outcome for the patient with RMS.

Introduction

Rhabdomyosarcoma (RMS) is the most common form of soft tissue sarcoma accounting for 4.5% of all cases of childhood cancer. It is the third most common extracranial solid tumor of childhood after Wilms tumor and neuroblastoma. RMS is a malignant tumor of mesenchymal origin and is included in the group of small blue, round cell tumors of childhood along with neuroblastoma, lymphoma, and primitive neuroectodermal tumors (PNET). The aim of this article is to give an overview of treatment principles and outcome for RMS tumors in childhood, including the different treatment strategies in both North America and Europe.

Epidemiology

The incidence of RMS is approximately six cases per 1,000,000 population per year, which accounts for about 250 new cases in children each year. There is a bimodal distribution for the age at presentation with a peak between 2 and 6 years and then again between 10 and 18 years of age.[1] This reflects the occurrence of the two major histologic subtypes of RMS: embryonal (ERMS) for the younger patients, typically arising in head/neck and GU locations, and alveolar (ARMS) for older patients, typically developing in trunk and extremity locations.

Although most cases of RMS occur sporadically, the disease is also associated with familial syndromes, including Li Fraumeni and neurofibromatosis type I. Li Fraumeni is an autosomal dominant disorder usually associated with a germline mutation of p53.[2] Patients with this syndrome present with RMS at an early age and often have a family history of other carcinomas, especially pre-menopausal breast carcinoma.[1] Autopsy findings suggest that one-third of children with RMS have some sort of congenital developmental abnormality.[3]

Histology/pathogenesis

On histologic examination, desmin, myogenin, and MyoD1 and muscle-specific actin are the commonly used immunohistochemical stains to identify RMS. ERMS is present in approximately 75% of patients and has a high cytologic variability, which is thought to represent the progressive stages of muscle morphogenesis. ARMS is present in approximately 25% of patients and histologically appears similar to pulmonary parenchyma.

The pathogenesis of RMS remains unclear; however, it is thought that it arises due to the disruption of skeletal muscle progenitor cell growth and differentiation. Causal relationships have been suggested for the MET proto-oncogene and macrophage migration inhibitory factor (MIF), and P53 in oncogenic

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transformation and tumor progression.[4-6] Embryonal RMS is characterized by a loss of heterozygosity (LOH) at the 11p15 locus in up to 80% of patients. Within this locus lies the Insulin Growth Factor II (IGF-II) gene.[7,8] Other genetic aberrations noted in ERMS include FGFR1 and NRAS mutations and in ARMS include MYCN and CDK4.[9]

The FOXO transcription factor gene can fuse with either the PAX3 or PAX 7 transcription factor genes. These fusion proteins have been identified in patients with ARMS.[10] In these PAX/FOXO fusions, the DNA binding domain of PAX is combined with the regulatory domain of FOXO. This results in increased PAX activity, leading to de-differentiation and proliferation of myogenic cells.[11] PAX3-FOXO fusion is more common than the PAX7-FOXO fusion (55% vs 23%) and is associated with worse overall survival.[12] It has been demonstrated that approximately 25% of ARMS tumors are translocation negative. By gene array analysis these fusion negative ARMS tumors more closely resemble ERMS and also have a similar prognosis to patients with ERMS.[13] Fusion status will replace tumor histology in the classification and stratification of RMS tumors in future studies and treatment protocols.

Staging

The TNM staging of RMS is a pre-treatment staging system and is determined by the site and size of the primary tumor, degree of tumor invasion, nodal status, and the presence or absence of metastases, and is based solely on the preoperative workup of imaging and physical exam. Staging is the extent of tumor before any therapy (Table 1).

Clinical group

The extent of residual disease after the resection is an important prognostic factor in RMS and highlights the importance of adequate surgical resection. Patients are assigned to a clinical group based on the completeness of tumor excision and the evidence of tumor metastasis to the lymph nodes or distant organs after pathologic examination of surgical specimens. The clinical group is the pathologically determined extent of tumor after surgical resection of the primary tumor and nodal evaluation but prior to the initiation of chemotherapy (Table 2).

Risk group stratification

Risk stratification is used in an effort to tailor the intensity of therapy to optimize patient outcomes. The Children's Oncology Group (COG) risk stratification system incorporates pre-treatment staging [based on anatomic site and tumor-node-metastasis (TNM) status], the extent of disease after surgical resection (clinical group), primary tumor site, and histology/fusion status into a comprehensive risk-based system. This system has been shown to be an accurate predictor of patient outcome (Table 3). A risk grouping has also been established in the European Study groups [Société Internationale d'Oncologie Pédiatrique [SIOP] and Cooperative Weichteilsarkom Studiengruppe (CWS)], which depend on several prognostic factors (Tables 4 and 5). Finally, the risk stratification is divided into eight subgroups (Table 5), which are further separated into low, standard, high and very high-risk groups.

Presentation

RMS typically presents as an asymptomatic mass; however, the patient can present with signs and symptoms from growth of the mass and its impact on adjacent structures. The most common sites of primary disease are the head and neck region, the genitourinary tract, and the extremities.

Assessment

Patients with suspected RMS require a complete workup prior to treatment. A standard laboratory examination including complete blood count, electrolytes, renal function tests, liver function tests, and urinalysis should be performed. Imaging studies of the primary tumor with computed tomography (CT) or magnetic

Table 1
TNM pre-treatment staging classification.

Stage	Sites	T	Size	N	M
1	Orbit Head and neck (excluding parameningeal) GU—non-bladder/non-prostate Biliary tract/liver	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_0
2	Bladder/prostate Extremity, cranial Parameningeal, other (includes trunk, retroperitoneum, etc.) Except biliary tract/liver	T_1 or T_2	a	N_0 or N_x	M_0
3	Bladder/prostate	T_1 or T_2	a	N_1	M_0
	Extremity cranial		b	N_0 or N_1 or N_x	M_0
	Parameningeal, other (includes trunk, retroperitoneum, etc.) Except biliary tract/liver				
4	All	T_1 or T_2	a or b	N_0 or N_1	M_1

Tumor
- $T(site)_1$—confined to anatomic site of origin
- $T(site)_2$—extension and/or fixative to surrounding tissue
  - (a) ≤ 5 cm in diameter in size
  - (b) > 5 cm in diameter in size

Regional nodes
- N_0 regional nodes not clinically involved
- N_1 regional nodes clinically involved by neoplasm defined as > 1 cm by CT or MRI, or 2) 18-FDG avid
- N_x clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation

Metastasis
- M_0 no distant metastasis
- M_1 metastasis present