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Rhabdomyosarcoma Update

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in infants and children representing about 5% of all cases of childhood cancer. The third most common extracranial solid tumor in children after Wilms tumor and neuroblastoma with 6 new cases per one million population per year. RMS has two age peak incidence, between 2 and 6 years, and a second surge during early adolescence (10-18 years). Head, neck and pelvic malignancies are more prevalent in infancy and early childhood, while trunk, extremity and paratesticular RMS is largely a disease of adolescents. RMS arises is a malignant tumor of mesenchymal tissue included in the group of small blue round cell tumors occurring at almost any body site (excluding brain & bone). RMS has two major histological subtypes: embryonal and alveolar. The predominant histologic type in infants and small children is embryonal affecting head, neck, and genitourinary location. Botryoid RMS is a subtype of the embryonal variety, which ordinarily extends into body cavities such as bladder, nasopharynx, vagina, or bile duct. The alveolar cell type, named for a superficial similarity to the pulmonary alveoli, is the most common form found on the muscle masses of the trunk and extremities, and is seen more frequently in older children. Most RMS are sporadic, while a few are associated with familial syndromes such as Li-Fraumeni, DICER1 syndrome and neurofibromatosis type 1. Histologically, embryonal RMS is found in 75% of patients and alveolar in 25%. Embryonal RMS is characterized by loss of heterozygosity at the 11p15 locus in 80% of patients, while the alveolar RMS is associated with the FOXO1 and PAX3/PAX7 transcription factor fusion of genes associated with worse overall survival in the case of the FOXO-PAX3 fusion. Approximately 80% of tumors that are alveolar RMS carry a FOXO1 fusion, while more than 95% of embryonal RMS have no FOXO1 fusion. The presence or absence of FOXO1 fusion gene drives the clinical behavior of RMS. PAX/FOXO1 fusion status is recognized as a more important prognostic factor compared to histological subtypes that will be utilized instead of histology for risk stratification. PAX fusion is so important that RMS is subdivided into 2 major subtypes, the commonest is PAX-fusion negative RMS (previously called embryonal), occurring in 70%, and the PAX fusion-positive RMS (previously called alveolar RMS). Spindle cell/sclerosing RMS is a third subtype, whereas pleomorphic RMS occurs only in adults. Initial pre-treatment staging uses the TNM system depending on site, size, degree of tumor invasion, nodal status, and metastasis. Extent of residual disease after resection is an important prognostic factor highlighting the importance of adequate surgical resection. Once resected patients are assigned to a clinical group prior of initiating chemotherapy. Risk stratification (low, intermediate, and high) is used to tailor the

intensity of adjuvant therapy and it incorporate TNM status pre-treatment, extent of disease after resection, primary tumor site and histology/fusion status into a system. For localized disease, fusion-positive patients had a 5-years survival of 52-65%, while fusion negative had survival of 78-88%.For metastatic disease, fusion-positive patients had a 5-year survival of 6-19% compared with a 46-58% fusion-negative survival. Postoperative clinical group classification is determined by extent of residual tumor, lymph nodes status and metastatic disease, and ranges from Group I (complete resection without regional node involvement), Group II (microscopic residual tumor, involved regional nodes or both), Group III (gross residual tumor after incomplete resection or biopsy), and Group IV (distant metastasis). Most RMS present as an asymptomatic mass. Standard labs, MRI and CT-scans are required including bone marrow aspirate, bone scan, CT of brain, lungs and liver and lumbar puncture of CSF collection (parameningeal tumors). PET/CT is useful in evaluation of regional adenopathy, occult metastasizes and persistent viable disease or recurrence. Determining lymph node involvement is essential as regional positive nodes are irradiated and positive distant nodes are metastatic disease. All patients with RMS receive chemotherapy based on risk group (vincristine, actinomycin-D, ifosfamide, irinotecan and cyclophosphamide). Ifosfamide has a lower gonadal toxicity when compared with cyclophosphamide but is more nephrotoxic. Low and intermediate risk children have improved outcome, while high risk fare worse. Response is measure with follow up imaging: MRI or CT after three courses of chemotherapy as complete (no tumor), good (reduced 2/3), poor (>1/3 and < 2/3), and progressive (> 1/3). Radiotherapy is used in almost all RMS children to improve local control and outcome. Radiation therapy is often utilized to improve local control in patients with Group II (microscopic residual), or Group III (gross residual) disease and in all patients with FOXO1 fusion positive tumors. Surgery is essential local treatment. The quality of resection is defined by the worst pathological margin essential for risk stratification. Surgical removal of the entire tumor should be considered initially if possible, and only if major functional or cosmetic impairment is not expected to result. The goal of surgery is complete tumor removal with normal surrounding margins (0.5 cm) and without loss of function to the child. No role for debulking tumor in RMS. If a complete resection is not possible, an open biopsy should be done. Core biopsy is not ideal due to insufficient tissue. Tumors in cavities such as bladder, prostate or vagina undergo endoscopic biopsy. Lymph node disease is present in 23% of all RMS children, predominantly in primary tumors sites such as perineum, retroperitoneum, extremity, bladder/prostate, parameningeal and paratesticular. Positive lymph node status is an independent poor prognostic factor Children requiring nodal evaluation include those with positive clinical nodes, extremity/trunk primary tumors, paratesticular patients > 10 years of age, and in patient with fusion positive alveolar RMS. If positive upon sentinel or regional node sampling (sentinel is preferred; more accurate), the lymph node bed should undergo radiation therapy. Indocyanine green has been reported to stage lymph nodes in paratesticular and extremity RMS. Complete nodal dissection does not improve outcome. Delayed primary excision can be evaluated between 9 and 12 weeks of induction chemotherapy with imaging. In a few instances mutilating surgery should be considered with insufficient response to chemotherapy. RMS is curable in most children

with localized disease who receive combined modality therapy with a survival rate > 70% at 5 years of diagnosis. Approximately 15% of children with RMS present with metastatic disease and have a poor prognosis with 25% survival.

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***Edited by: Humberto Lugo-Vicente, MD, FACS, FAAP**
Professor of Pediatric Surgery, UPR - School of Medicine, UCC School of Medicine & Ponce School of Medicine.
Director - Pediatric Surgery, San Jorge Children's & Woman Hospital.
Postal Address: P.O. Box 10426, San Juan, Puerto Rico USA 00922-0426.
Tel (787) 340-1868 E-mail: *pediatricsurgerypr@gmail.net*
Internet: pedsurgeryupdate.com

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