Review Article

Clinical Prognosis of Childhood Rhabdomyosarcoma: Still An Conundrum

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Rhabdomyosarcoma (RMS) is a moderately uncommon soft tissue malignancy that can emerge at any age, with around 600 new cases analyzed every year in the United States, 42% of which happen in adults versus 58% in children. Factually, RMS is infrequent in adults, with soft tissue sarcomas including under 1% of all malignancies, 3% of which are RMS. By differentiation, soft tissue sarcomas represent 10% of all adolescence malignancies, half of which are RMS; accordingly, RMS is an outstanding clinical issue in pediatric oncology. Notwithstanding when rendered disease free, RMS survivors frequently encounter long haul morbidities attributable to escalated multimodal treatment, with pediatric subjects specifically enduring a lifetime hazard for treatment-related malignancies. Medicines for high-risk RMS have not enhanced for three decades, underscoring the need to illustrate the molecular mechanism of the disease. Over the previous year’s delimitations of hereditary and molecular changes, cell mechanism and pathways required in RMS pathogenesis opened opportunities for the modern idea of multimodal treatment of these tumors including surgery, chemo-and radiotherapy. Future objectives of each one of the individuals who treat childhood RMS comprises in nonstop change of current remedial measures for diminishing morbidity and expanding long haul survival together with identification of new powerful methodologies for advanced and metastatic cases.

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INTRODUCTION:
Rhabdomyosarcoma (RMS) is a standout amongst the most well-known extracranial strong tumors in kids. Embryonal and alveolar subtypes of RMS present totally diverse hereditary variations abnormalities. Embryonal RMS (eRMS) is portrayed by loss of heterozygosity on the short arm of chromosome 11 (11p15.5), proposing inactivation of a tumor-suppressor gene. Conversely, the majority (85%) of the alveolar RMS (aRMS) have the reciprocal chromosomal translocations t(2;13)(q35;q14) or t(1;13)(p36;q14). t(2;13) shows up in around 70% of subjects with the alveolar subtype. The molecular partner of this translocation comprises of the generation of a chimeric fusion gene, FOXO1 (also known as FKHR), situated in chromosome 2 and fork-head family, FOXO1. A less frequent translocation t(1;13) includes another PAX family gene, PAX7 situated in chromosome 1 and FOXO1 is available in 15% of instances of the alveolar subtype in RMS. Lately, numerous clinical studies on cancer have exhibited the colossal capability of the genomic slant based on tumor expression profiles. These innovations allow the identification of new regulatory pathways. Molecular identification of insignificant disease by a sensitive method could contribute to better treatment stratification in these subjects. In RMS, the advances in the clinical information of the biological attributes of the tumor are gradually deciphered into the clinical management of youngsters with this tumor.

The cell of origin for RMS stays obscure. It is imagined that ERMS generates from muscle progenitor cells given the comparable expression of skeletal muscle markers in both cell types. The development of ERMS at locales which lack striated muscle, for example, the bladder, prostate and biliary tree, stays unexplained. A few clinical studies have given new bits of knowledge into the genetic origin of RMS. FOXO1 fusion status will substitute histologic grouping for risk stratification in future RMS clinical trials. Thorough genomic examination and mouse models of RMS give novel bits of knowledge into the etiology of RMS and potential helpful targets. Currently randomized chemotherapy trials have failed to enhance result in spite of introduction of more exhaustive treatment. Future clinical trials will refine the utilization of RT, especially in the kids. Newer risk factor, in view of histologic discoveries and molecular portrayals, are facilitating recognize subjects who are at a higher risk of treatment. Embryonal tumors with regions of anaplasia appear to behave more aggressive than other embryonal variations. Alveolar tumors, an aggressive subtype, are known to be linked with two chromosomal translocations (t(2;13) and t(1;13)), which result in the formation of the abnormal transcription factors PAX3-FKHR and PAX7-FKHR (otherwise called PAX3-FOXO1 and PAX7-FOXO1). It is presently clear that these distinctive variations of ARMS have diverse predictions, as well as have diverse metastatic profiles. Deviations in the p53 pathway, brought about by p53 transformations or unusual expression of p53 controllers, for example, MDM2, have been found in rhabdomyosarcomas. MDM2 has been appeared to be over-expressed in an assortment of soft tissue sarcomas, including RMS. Expression of alternative spliced variations of (MDM2-alt) have been connected with advanced disease in RMS too. Comparative discoveries have been accounted with the related protein MDM4. These molecular portrayals may encourage characterize subjects who are at risk for treatment failure, may propose strategies for pathogenesis of these tumors, and ultimately lead to the development of targeted treatments in the treatment of this malady. This is particularly required for youngsters who present with metastatic disease, in whom the anticipation stays poor, in spite of expanding serious chemotherapy regimen.

**Molecular findings in RMS**
Chromosomal aberrations are the commonly known molecular abnormalities in RMS. Specifically, alveolar RMS is unequivocally linked with two chromosomal rearrangements. The t(2;13)(q35;q14) and t(1;13)(p36;q14) represent roughly 66% of alveolar RMS tumors (around 33% have no translocation). The t(2;13) translocation results in the fusion of the gene encoding the DNA binding domain of PAX3 with the gene encoding the transcriptional activation domain of FKHR (FOXO1) on chromosome 13. PAX3 is helps in the movement of myogenic cells to the limb buds amid early embryonic development. The resultant abnormal transcription factor PAX3-FOXO1 is a more powerful transcriptional activator than wild-type PAX3, in spite of the fact that the fusion gene is infrequently amplified. A few transcriptional targets of the PAX3-
FOXO1 translation factor have been considered. The anti-apoptotic protein BCL-XL was seemed to be up-regulated in the presence of PAX3-FOXO1. PAX3-FOXO1 restrain myogenic separation and block normal PAX3 function\textsuperscript{17}. Various gene involved in myogenesis, for example, transcription factor (MYOD, MYOG, SIX1) and insulin-like growth factor II (IGF-II), are additionally up-regulated by PAX3-FOXO1. These discoveries may clarify why alveolar tumors are more aggressive and oftentimes metastasize\textsuperscript{18-20}. The t(1;13) translocation similarly brings about an abnormal transcription factor, for this situation PAX7-FOXO1. Whereas PAX7 is involved in myogenic separation. Albeit less common than t(2;13) in alveolar RMS, a few studies have recommended that subjects with the t(1;13) translocation have a tendency to have a superior anticipation (however still poor) than those with t(2;13)\textsuperscript{21-23}. This clinical information must be translated with vigilant, however, as the number of subjects with the t(1;13) translocation is diminutive.

### Table: Rhabdomyosarcoma subtypes with histological morphology

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Histology</th>
<th>Location</th>
<th>Age (years)</th>
<th>% of all RMS cases</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonal</td>
<td>Small, round-to-elongated cells with interspersed loose myxoid stroma</td>
<td>Genitourinary tract, head and neck,</td>
<td>&lt;10 years</td>
<td>60-65%</td>
<td>Favourable</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>Large anaplastic cells with enlarged, hyperchromatic nuclei, multipolar mitotic figures</td>
<td>Extremities, chest and abdomen</td>
<td>55-80 years</td>
<td>10-15%</td>
<td>Unfavourable</td>
</tr>
<tr>
<td>Spindle cell</td>
<td>Relatively differentiated spindle cells with features reminiscent of smooth muscle neoplasms</td>
<td>Paratesticular, head and neck in children and in adults</td>
<td>&lt;10 and &gt;45 years</td>
<td>10-15%</td>
<td>Favourable(Children) Unfavourable (Adult)</td>
</tr>
<tr>
<td>Alveolar</td>
<td>Discohesive primitive round cells within interwoven fibrous septa</td>
<td>Extremities, head and neck, chest, genital organs, abdomen</td>
<td>15-30 years</td>
<td>15-20%</td>
<td>Unfavourable</td>
</tr>
</tbody>
</table>

### Clinical Trials

The standard chemotherapy regimens for RMS is Vincristine and dactinomycin (VA) with cyclophosphamide (VAC) for the subjects who are at higher risk. The low risk RMS class incorporates all non-metastatic ERMS at primary sites and completely resected ERMS at unfavorable sites. The low risk RMS can be further divided into two subsets\textsuperscript{24}. The latest COG trial for low risk RMS (ARST0331) demonstrated that Subset 1 subjects have a superb result (two-year EFS, 88%; general survival (OS), 98%) with short treatment span (22 weeks) and a modest cumulative dosage (4.8 g/m\textsuperscript{2}) of cyclophosphamide. Conversely, Subset 2 had a lower than foreseen 3-year EFS, (66%) with a lower dose of cyclophosphamide, when contrasted with the past COG low risk RMS trial, D9602 (cyclophosphamide dosage, 28.6 g/m\textsuperscript{2}, 3-year EFS, 83%, p=0.06). The moderate risk RMS classification incorporates non-metastatic ARMS and unresected ERMS at unfavorable primary sites.

The latest COG intermediate risk RMS trial, D9803, demonstrated no dissimilarity in 4 year EFS amongst VAC and VAC plus topotecan (73% and 68%, separately)\textsuperscript{25}. These outcomes were like the earlier IRS-IV trial, which found no advantage to including ifosfamide +/- - etoposide. The latest MMT clinical study for localized RMS randomly compared the European standard RMS treatment ifosfamide, vincristine, and dactinomycin (IVA) to the more intricate IVA in addition to carboplatin, epirubicin, and etoposide with a comparable (yet not indistinguishable) risk stratification for intermediate risk RMS; no distinction in result was seen. As opposed to the COG, local treatment in MMT studies were custom fitted to radiographic reaction and the ability to perform a deferred resection, with the objective of minimizing the utilization of radiotherapy and conceivably decrease the total burden of local therapy. Juxtaposed with comparable subjects treated with the COG local control methodology (which
underlines the normal utilization of radiotherapy), EFS and OS were lower, especially for ARMS\textsuperscript{26}.

Subjects with pelvic as a primary sites are specific contender for omission of RT because of the significant effect on growth. In any case, exclusion of RT results in a higher recurrence rate, requiring more forceful second-line treatment and possibly trading off general survival. Investigation have shown that bladder/prostate ERMS brought about a marginally higher relapse risk however comparative general survival juxtaposed with the COG methodology\textsuperscript{27}.

**CLOSING REMARKS**

We have seen striking advances in the battery of model frameworks that are presently accessible to dissect RMS pathobiology, and new provocative models keep on being developed. These models likewise demonstrate viable methodologies for the genetic and molecular dissection of other clinically awkward non-RMS sarcomas. As further bits of knowledge are collected, the field doubtlessly will concentrate progressively on the molecular signature of one's individual tumor through the force of subject-determined tumor xenografts — a methodology that is coming to fruition. An ongoing challenge confronting the RMS community and pediatric cancer community, is the relative lack of subjects, which muddles the design and statistical power of new clinical studies. Along these lines, new clinical trials regularly require the endeavors of cooperative consortiums. Increased dose intensity of known compelling agents with hematopoietic growth factor support, new agents, and hyperfractionated illumination are being assessed with expectations of further refining treatment. Latest discovery of novel genetic features in this tumor ought to prompt better strategies for diagnosis and risk evaluation, and eventually to the identification of molecular targets for particular treatment. New initiatives keep on being produced, which will expand our general comprehension of RMS genomics. These endeavors will take into consideration of refined risk stratification, which will inspire tailored therapy towards every subject's specific tumor, also known as 'precision therapy'. Accomplishing this will require multidisciplinary translational investigation to further interrogate preclinical models and advance new treatment regimens.

**REFERENCES:**


