Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a fast-growing, malignant tumor of mesenchymal cell origin (A-1), arising from cells capable of some degree of skeletal muscle differentiation. Instead of differentiating into mature striated muscle cells, these malignant cells (called rhabdomyoblasts) continue to divide out of control. Because primitive mesenchymal cells are located throughout the body, RMS can arise in virtually every organ, even those where skeletal muscle is not normally found.

Rhabdomyosarcoma accounts for slightly less than half of the soft tissue sarcomas occurring in children and it is the third most common extracranial solid tumor in children after neuroblastoma and Wilms tumor. Almost two-thirds of cases arise in children less than 6 years of age, though the tumor is also found in older children and adolescents.

The most common sites of origin are the head and neck region (divided into orbital, parameningeal, and non-parameningeal sites), followed by genitourinary tract sites (most commonly bladder, prostate, paratestis, and vagina), and the extremities. Other less common primary sites that occur with some frequency in children include the chest and abdominal wall, paraspinal region, retroperitoneum and pelvis (outside of the genitourinary tract), and the perineal/anal region.

Risk Factors:

In the majority of cases, RMS develops sporadically; however it is also associated with certain genetic disorders, such as neurofibromatosis type 1, Li-Fraumeni syndrome (germline mutation of the p53 tumor suppressor gene), Beckwith-Weideman syndrome (associated with chromosome 11p15 abnormalities), and Costello syndrome. A large autopsy series demonstrated that 32% of patients with RMS were noted to have at least one congenital anomaly, most commonly affecting the central nervous system or genitourinary tract.
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Clinical Signs and Symptoms:

The most common presentation of RMS is a soft tissue mass, with or without accompanying signs and symptoms of organ dysfunction depending on the site of tumor origin. Common clinical findings associated with RMS include:

- **(A – 2) Orbital tumors (9%)**: Eyelid swelling, proptosis; ophthalmoplegia
- Non-orbital parameningeal tumors (20%): nasal, aural, or sinus obstruction; mucopurulent or sanguinous discharge; cranial nerve palsies; signs of increased pressure due to intracranial extension
- Non-parameningeal tumors (10%): buccal or gingival mass, neck mass, scalp mass
- **(A – 3) Genitourinary tract tumors (20%)**: hematuria, urinary obstruction, extrusion of the tumor, vaginal discharge, pelvic or testicular mass, constipation
- **(A – 4) Extremity tumors (20%)**: painless soft tissue mass
- Chest wall: soft tissue mass, respiratory compromise
- Paraspinal: symptoms of spinal cord compression
- Intrathoracic and retroperitoneal/pelvic regions: often large tumors producing few symptoms
- Perineal/perianal region: painful mass often mistaken for perirectal abscess
- Biliary tract tumors: obstructive jaundice, hepatomegaly

Diagnostic Workup:

- Complete history of illness including symptoms referable to the primary tumor, symptoms of metastatic disease (respiratory impairment, regional adenopathy, bone pain), and features of underlying genetic disorder associated with predisposition to RMS
- Careful family history, focusing in particular on neurofibromatosis type 1 and cancers associated with the Li-Fraumeni syndrome
- Physical exam to assess the location and extent of the primary tumor and associated organ impairment, the presence or absence of regional adenopathy, and signs of distant metastatic disease.
- Laboratory studies including CBC with differential, electrolytes, measurements of renal and hepatic function, and urinalysis
- CT or MRI scan of the primary tumor to define the extent of the mass. In general, MRI is preferred for extremity, body wall, and head/neck sites, whereas CT is preferred for intrathoracic/intraabdominal/pelvic/retroperitoneal sites. Imaging should include the regional lymph nodes to identify pathologic adenopathy.
- Ultrasonography (USN) imaging may be helpful for evaluating tumors of the bladder/prostate, paratestis, biliary tree, kidneys, and heart.
- Bone scan to rule out bone metastases
- CT of the chest to rule out lung metastasis
- Tumor biopsy to establish the diagnosis, with molecular testing to identify the characteristic translocations associated with alveolar histology RMS
- Bilateral bone marrow aspirates and biopsies to rule out bone marrow metastasis; and molecular testing
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Classification of Rhabdomyosarcoma

I- (A – 5) Embryonal rhabdomyosarcoma

Most common type (more than 50%), usually found in children under 15 years of age, most commonly in the head and neck region and the genitourinary tract.
   A. Typical: tend to have intermediate outcomes
   B. Spindle cell: tend to have more favorable outcomes
   C. Botryoid: grape-like lesion in mucosal-lined hollow organs such as the vagina and urinary bladder; tend to have more favorable outcomes
   D. Anaplastic: may have slightly less favorable outcomes compared to those with typical embryonal histology

II- (A – 6) Alveolar rhabdomyosarcoma

A more aggressive tumor which often involves the extremities and trunk wall.
   A. Typical
   B. Solid

Alveolar RMS is associated with (A – 7) characteristic translocations t(2;13) and t(1;13) that produce fusion genes where the PAX3 (on chromosome 2) or PAX7 (on chromosome 1) gene is fused to the FKHR gene on chromosome 13.

III- Pleomorphic rhabdomyosarcoma

Typically seen in adults, most often arising in the muscles of the extremities

RMS Staging Systems:

Accurate staging at the time of diagnosis is necessary because staging not only guides the selection of treatment but also correlates with overall prognosis. Two systems are routinely used in combination for staging childhood rhabdomyosarcoma: stage and clinical group. Stage is based on the site of origin and size of the primary tumor and the presence or absence of regional nodal metastases and distant metastases:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Site of Origin</th>
<th>Tumor Size</th>
<th>Lymph Nodes</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Favorable</td>
<td>Any</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Unfavorable</td>
<td>≤ 5 cm</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Unfavorable</td>
<td>≤ 5 cm</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Favorable sites include the orbit, non-parameningeal head and neck, genitourinary (not bladder or prostate), and biliary tree. Unfavorable sites include parameningeal head and neck, bladder and prostate, extremity, and other sites.
The surgicopathologic clinical grouping system defines the extent of disease following surgical resection:

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Primary tumor completely resected with no microscopic residual; no involved lymph nodes or distant metastases</td>
</tr>
<tr>
<td>IIA</td>
<td>Primary tumor grossly resected but with microscopic residual disease; no involved lymph nodes or distant metastases</td>
</tr>
<tr>
<td>IIB</td>
<td>Primary tumor completely resected with no microscopic residual, regional lymph nodes involved but completely resected; no distant metastases</td>
</tr>
<tr>
<td>IIC</td>
<td>Primary tumor grossly resected but with microscopic residual disease, regional lymph nodes involved but completely resected, no distant metastases</td>
</tr>
<tr>
<td>III</td>
<td>Primary tumor incompletely resected with gross residual disease, regional lymph nodes may or may not be involved; no distant metastases</td>
</tr>
<tr>
<td>IV</td>
<td>Primary tumor, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor</td>
</tr>
</tbody>
</table>

Prognosis;

Outcome in childhood rhabdomyosarcoma depends on several variables, including distant metastases (present vs. absent), nodal metastases (present vs. absent), primary tumor site (favorable vs. unfavorable), primary tumor size (< 5 cm vs. ≥ 5 cm), extent of disease after surgical resection (clinical group I/II vs. III vs. IV), histologic subtype (embryonal and its variants vs. alveolar), and age (<10 years vs. ≥ 10 years). These variables have been utilized in recent studies of the Intergroup Rhabdomyosarcoma Study Group (now the Soft Tissue Sarcoma Committee of the Children’s Oncology Group) to stratify patients into risk groups:

| Very Low Risk                  | Embryonal, stage 1, clinical group I or II, N0 |
|                               | Embryonal, stage 1, clinical group III, orbit only |
|                               | Embryonal, stage 2, clinical group I |
| Low Risk                      | Embryonal, stage 1, clinical group II, N1 |
|                               | Embryonal, stage 1, clinical group III |
|                               | Embryonal, stage 2, clinical group II |
|                               | Embryonal, stage 3, clinical group I or II |
| Intermediate Risk              | Embryonal, stage 2 or 3, clinical group III |
|                               | Embryonal, stage 4, clinical group IV, < 10 years of age |
|                               | Alveolar, stage 2 or 3 |
| High Risk                     | Embryonal, stage 4, clinical group IV, ≥ 10 years of age |
|                               | Alveolar, stage 4, clinical group IV |

Current event-free survival rates according to risk group are: very low risk (>85%), low risk (70-85%), intermediate risk (50-70%), high risk (<30%).
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**Treatment:**

The treatment of rhabdomyosarcoma includes multi-agent chemotherapy in combination with local treatment (surgery and/or radiotherapy) for sites of gross disease. The Children’s Oncology Group (COG) assigns patients to treatment protocols based on risk group, as outlined above. For protocol purposes, patients are categorized as low risk (including the “very low” and “low” risk categories above), intermediate risk, or high risk.

Chemotherapy is given to all children with rhabdomyosarcoma, regardless of whether or not there is evidence of metastatic disease at the time of diagnosis. The standard regimen includes vincristine (Oncovin) and actinomycin-D (Dactinomycin), with or without cyclophosphamide (Cytoxan) depending on risk category. Typical length of therapy is approximately 48 weeks, though upcoming COG studies will be evaluating a 24-week regimen for lower risk patients.

Other agents that are active in rhabdomyosarcoma include doxorubicin (Adriamycin), ifosfamide (Ifex), etoposide (VP-16), cisplatin, topotecan (Hycamtin), and irinotecan (CPT-11). However, none of these drugs used in combination have been proven to be superior to standard vincristine/actinomycin D/cyclophosphamide chemotherapy. Thus, they are reserved for use in clinical trials and for patients with recurrent or refractory disease.

The goal of surgical management of rhabdomyosarcoma is wide resection of the primary tumor with an adequate margin of normal tissue, if this can be accomplished without significant compromise of form or function. Wide resection is not feasible in many anatomic locations and it might produce substantial morbidity. In these settings, adjuvant radiotherapy may be used to achieve local tumor control. Adjuvant radiotherapy at a slightly lower dose may also be used to achieve adequate local control following marginal resection. Optimally, decisions regarding the choice of local therapy (surgery alone vs. radiotherapy alone vs. surgery + radiotherapy) should be made by an experienced multidisciplinary team that includes surgeons, radiation oncologists, and pediatric oncologists.

Radiotherapy for the primary tumor is generally given about 3 months after starting chemotherapy, to allow time for tumor shrinkage and treatment planning. The exception to this rule is parameningeal rhabdomyosarcoma associated with intracranial extension or cranial nerve palsies; in this setting, radiotherapy is given at the time of initial diagnosis. Studies have demonstrated that early radiotherapy improves the outcome for patients with invasive parameningeal tumors.

Metastatic sites (other than bone marrow) also require local treatment. Involved regional lymph nodes may be excised and/or irradiated, depending on the extent, location, and resectability of the disease. Pulmonary metastases are typically treated with focal radiotherapy if feasible. The use of whole lung radiotherapy for patients with pulmonary metastases is controversial. Bone metastases are treated with radiotherapy. The timing of metastatic site irradiation is individualized, and may be deferred to the end of chemotherapy, particularly if substantial fractions of the bone marrow-producing bones will be treated.
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Multimodal therapy for RMS has an overall likelihood of 5-year survival of approximately 70%. However, treatment is also associated with both acute and long-term toxicities. Late effects can produce long-term functional impairment and decreased quality of life. Therefore, the goal is to minimize therapeutic exposures while still achieving a cure.

**Disease Recurrence:**

Approximately 30% of children with rhabdomyosarcoma will experience tumor recurrence, and most of these patients will eventually die of progressive disease. Most tumor recurrences occur within 3 years of diagnosis, though late recurrence (after 5 years) does occur. The estimated 5-year survival rate from first recurrence is about 20%. Patients who have botryoid tumors, stage I/clinical group I embryonal tumors, and group I alveolar tumors at initial presentation have an anticipated survival after relapse of about 50%. The survival for the remaining 80% of patients who experience tumor recurrence is only 10%.

Tumor recurrence is generally treated with combinations of agents known to be active in RMS, such as doxorubicin/cyclophosphamide, ifosfamide/etoposide, topotecan/cyclophosphamide, and vincristine/irinotecan. Dose intensification via hematopoietic stem cell transplant has not been shown to improve outcome. If the tumor is chemoresponsive, then local control may be achieved either with surgery or radiotherapy (or a combination of both). For patients previously treated with radiotherapy, ablative surgery (including amputation or an exenterative procedure) may be the only option. However, a small proportion of patients achieve durable tumor control after less aggressive surgery and additional radiotherapy.

**Future Directions:**

There are many challenges facing those who seek to advance the care of patients with RMS. Approximately 30% of patients die of the disease, so novel therapeutic approaches are needed. For those who can be cured, the acute and long-term toxicities of the disease and its treatment are not negligible. Further studies are needed to identify treatment approaches that ameliorate toxicity. Interventions to identify and remediate long-term complications are also needed.
Rhabdomyosarcoma

Helpful Related weblinks:

Pediatric Oncology Resource Center
http://www.acor.org/ped-onc/diseases/rhabdo.html

American Cancer Society
http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_is_rhabdomyosarcoma_53.asp?sitearea=

The National Cancer Institute – MedNews
http://www.meb.uni-bonn.de/cancer.gov/CDR0000062792.html

St. Jude Children’s Research Hospital, Memphis, TN
http://www.stjude.org/disease-summaries/0,2557,449_2167_3001,00.html

Related www.Cure4kids.org Seminars

Seminar #382 M & M: Respiratory Failure of Unclear Etiology
Presenter: Christine Hartford, MD, Fredric Hoffer, MD and Christine Fuller, MD
http://www.cure4kids.org/seminar/382

Seminar #310 Paratesticular Rhabdomyosarcoma
Presenter: William Spurbeck, MD, Stephen Shochat, MD, Christine Fuller, MD and Fred Laningham, MD
http://www.cure4kids.org/seminar/310

Seminar #282 Alveolar Rhabdomyosarcoma: the Role of Camptothecins in Therapy
Presenter: Victor M. Santana, MD, Mary-Ann Bjornsti, PhD, Peter Houghton, PhD and Clinton Stewart, PharmD
http://www.cure4kids.org/seminar/282

Seminar #325 Non-Complete Response in Rhabdomyosarcoma
Presenter: Christine Hartford, MD, Stephen Skapek, MD, Beth McCarville, MD, Jesse J. Jenkins, III, MD and Andrew Davidoff, MD
http://www.cure4kids.org/seminar/325

Seminar #314 Orbital Rhabdomyosarcoma: Treatment and Its Late Effects
Presenter: Sheri Spunt, MD, Christine Fuller, MD, Beth McCarville, MD, Barrett Haik, MD, Robert Danish, MD and Matthew J. Krasin, MD
http://www.cure4kids.org/seminar/314

Seminar #211 Recurrent Alveolar Rhabdomyosarcoma with Brain Metastasis
Presenter: Sheri Spunt, MD, Jesse J. Jenkins, III, MD and Beth McCarville, MD
http://www.cure4kids.org/seminar/210

Seminar #471 Where to Next in Rhabdomyosarcoma
Presenter: Michael Stevens, MD
http://www.cure4kids.org/seminar/471
Appendix:

A – 1 RMS - Small round cells

A malignant tumor of mesenchymal origin: the pattern of growth suggests RMS
A – 2 Orbital Tumors – proptosis and ophthalmoplegia

Left orbital swelling (proved rhabdomyosarcoma by histopathology) and macroglossia.

Fig. 2. Rhabdomyosarcoma regressed completely with chemotherapy and in remission

Indian Pediatrics, Department of Pediatrics, New Delhi, India
A – 3  Botryoid RMS of the bladder

Bostwick Laboratories, Glen Allen, VA

A – 4
A 7-year-old with painless swelling of the leg, diagnosed with alveolar RMS by biopsy

Sheri L. Spunt, MD (St. Jude Children's Research Hospital)
An 8-year-old with asymmetry of the hands: lower hand appears larger due to RMS

A – 5  Embryonal RMS

low power field high power field

J. Jenkins, MD (St. Jude Children's Research Hospital)
Rhabdomyosarcoma

A – 6  Alveolar RMS – left calf

J. Jenkins, MD (St. Jude Children’s Research Hospital)

A – 7  Characteristic Translocations

t(2;13)(q35;q14)  G-banding

[Diagram of translocations]

Courtesy G. Reza Hafez, Eric B. Johnson, and Sara Morrison-Delap, UW Cytogenetic Services; R-banding (below) - Courtesy Jean-Luc Lai

http://atlasgeneticsoncology.org//Tumors/rhab5004.html

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### A - 8 Treatment Late Effects:

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Late Effects</th>
</tr>
</thead>
</table>
| Surgery            | Loss of function – bladder, bowel  
|                    | Change of function – retrograde ejaculation  
|                    | Lymphedema  
|                    | Palsies, weakness  |
| Radiotherapy       | Cataracts  
|                    | Visual loss  
|                    | Hormonal imbalance; endocrinopathies  
|                    | Hearing loss  
|                    | Pulmonary fibrosis  
|                    | Growth retardation  
|                    | Cognitive impairment (for head and neck irradiation)  
|                    | Bladder fibrosis  
|                    | Intestinal strictures and fistulas  
|                    | Vaginal stenosis/sexual dysfunction  
|                    | Hematuria  
|                    | Radiation pneumonitis  
|                    | Scoliosis  
|                    | Leg length discrepancy  
|                    | Muscle and skin fibrosis  
|                    | Secondary malignant tumors  |
| Chemotherapy       | Reproductive effects – infertility  
|                    | Hemorrhagic cystitis and bladder fibrosis  
|                    | Second malignancies |
Acknowledgments:

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