What is Rhabdomyosarcoma?

There are two kinds of muscle cells in the body: smooth muscle cells and skeletal muscle cells. Smooth muscles control involuntary activities; skeletal muscles control voluntary activities. Rhabdomyosarcoma (RMS) is a malignant tumor ("cancer") that arises from a normal skeletal muscle cell. Not very much is known about why normal skeletal muscle cells become cancerous. Because skeletal muscle cells are found in virtually every site of the body, RMS can develop in almost any part of the body.

The first description of RMS was by Weber in 1854. However, the "definitive" publication is usually considered to be by Stout in 1946, 92 years later.


RMS is a very rare cancer. There are only about 350 cases of RMS diagnosed each year in the United States in children under the age of 21 years. About four children per million healthy kids under the age of 15 will develop RMS each year. It is slightly more common in boys than in girls and it is most common in young children under the age of five.

Rhabdomyosarcoma is very uncommon in adults. There have been five "large" published series, totaling just over 400 cases of "adult" RMS (including some "children") seen at major cancer centers in the United States and Europe over the past 20-30 years (Ref. 1-5). Although
"pleomorphic" histology is more common in the adult population (and rarely seen in children), treatment principles for managing adults with RMS are similar to those for children, and outcome is not intrinsically worse for adults treated with "modern", multi-modality therapy.

**Adult Cases:** Treatment principles for managing adults with RMS are similar to those for children. The five series mentioned above are from:

1. Instituto Nazionale Tumori, Milan, Italy, 190 patients 18 years of age or older over a 25 year period, (Ref. 1)
2. Memorial Sloan-Kettering Cancer Center, New York City, NY, 84 patients 16 years of age or older over a 17 year period, (Ref. 2)
3. M.D. Anderson Cancer Center, Houston, TX, 82 patients 17 years of age or older over a 28 year period, (Ref. 3)
4. Dana-Farber Cancer Institute, Boston, MA, 39 patients 16 years of age or older over a 23 year period, (Ref. 4)
5. Armed Forces Institute of Pathology (Washington, D.C., 38 patients 21 years of age or older over a 30 year period, all with pleiomorphic RMS, (Ref. 5)

They highlight several key points about "adult" RMS: (1) they are as intrinsically responsive to chemotherapy as "pediatric" RMS with response rates to chemotherapy as high as 85%; (2) "unfavorable" histologies, including alveolar and pleiomorphic, are more common than embryonal histology; (3) the proportion of patients with Group I, II, III, and IV tumors are comparable to that seen in "pediatric" seri; and, (4) with appropriate treatment, even accounting for differences in the proportion of patients with "unfavorable" histologies, survival rates comparable to that seen in "pediatric" series can be achieved.

Although these tumors can arise almost anywhere, the most common locations for these tumors to develop are in the structures of the head and neck (nearly 40% of all cases), the male or female genitourinary tract (about 25% of all cases), and the extremities (about 20% of all cases).

**Table 1: Incidence of RMS by site of primary tumor**

<table>
<thead>
<tr>
<th>Location</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameningeal</td>
<td>16</td>
</tr>
<tr>
<td>Orbit</td>
<td>10</td>
</tr>
<tr>
<td>Head / Neck</td>
<td>10</td>
</tr>
<tr>
<td>GU (all)</td>
<td>23</td>
</tr>
<tr>
<td>Extremity</td>
<td>19</td>
</tr>
<tr>
<td>Other</td>
<td>22</td>
</tr>
</tbody>
</table>

Approximately 40% of newly diagnosed RMS arise in head and neck structures including parameningeal sites (16% of all cases, and almost half of all head and neck cases), the orbit or eyelid (10% of all cases), and other non-orbit, non-parameningeal sites (10% of all cases). Approximately 25% of cases arise in one of the structures of the genitourinary system including the paratesticular region, the female genitourinary tract (vulva, vagina, cervix, uterus), the urinary bladder, and the prostate. Approximately 20% of cases arise in an extremity. The remainder of cases (*"other") arise in diverse sites including the chest wall and retroperitoneum.

Tumors that arise in the orbit, non-parameningeal head and neck sites (for example, the cheek or the ear lobe), and the male (paratesticular) or female (vagina, vulva, cervix, or uterus) genital tracts are considered "favorable." All other sites are considered "unfavorable." Most children who develop RMS don’t have any clear risk factor for getting cancer. After taking a careful family history and doing a thorough physical examination, approximately one child in five to one child in ten will have an identifiable "genetic risk factor": the most common of these
genetic "syndromes" include the Li-Fraumeni syndrome (Ref. 6), neurofibromatosis (Ref. 7), Beckwith-Wiedemann syndrome (Ref. 8), and Costello syndrome (Ref. 9).

**Genetic Risk Factors:** Although the overwhelming majority of cases of RMS occur sporadically, between 10-33% of children who develop RMS are thought to have an underlying genetic risk factor (Ref. 10). The development of RMS has been associated with a number of rare familial "cancer syndromes" such as the Li-Fraumeni syndrome (LFS), which includes familial clustering of RMS and other soft tissue tumors in children, with adrenocortical carcinoma and early-onset breast carcinoma in adult relatives. The LFS has been associated with germline mutations of the p53 tumor suppressor gene (Ref. 11). One study of 33 cases of sporadic RMS, found that three of 13 children younger than three years of age at diagnosis (compared with none of the 20 children older than three years of age) had germline mutations in their p53 gene (Ref. 12). RMS has also been seen in association with Beckwith-Wiedemann syndrome, a fetal overgrowth syndrome associated with abnormalities on 11p15, where the insulin-like growth factor II (IGFII) gene is located. Studies of children with Costello’s syndrome, likely an autosomal dominant disorder characterized by postnatal growth retardation, typical coarse facies, loose skin and developmental delay, have noted an increased risk for development of solid tumors, most commonly rhabdomyosarcoma. There have been ten cases of RMS reported in approximately 100 known children with Costello syndrome.

**Rhabdomyosarcoma Symptoms**
The symptoms that are associated with RMS can vary widely depending on where the tumor develops. Children with orbital RMS (about 10% of all cases of RMS), may present with a bulging or swollen eye (proptosis). Although this can sometimes be mistaken for a sinus infection, children with tumors in this location usually do not have the other symptoms that children with sinus infections experience (pain, fever, purplish discoloration of the eye).
Case 1
A 7-year old boy presented with one week of swelling and pain of the left eye, without fever or purulent rhinorrhea. Intravenous antibiotics were administered for treatment of presumptive periorbital cellulitis. A MRI (shown below) was obtained and demonstrated an approximately four cm soft-tissue mass arising in the supero-medial aspect of the left orbit displacing the globe anteriorly and laterally. Biopsy of the mass was accomplished by a small, medially placed incision.

The diagnosis of embryonal RMS was confirmed. No distant metastases were found on CT chest, bone scan, or bone marrow biopsy. The patient was Stage 1, Group III and was treated successfully with VA chemotherapy plus 45 Gy local XRT).

Figure 2: Case 1: A 7-year old boy with orbital RMS. MRI of the orbit shows a soft tissue mass arising in the supero-medial aspect of the left orbit displacing the globe outward and laterally.

Children with tumors arising in the one of the parameningeal sites (basically the sinuses, the middle ear, and the back of the throat) may complain for weeks or months of a stuffy nose, sometimes with nasal discharge; occasionally, a mass may be visible in the nostril or the back of the throat. Unlike sinus and throat infections, these tumors usually don’t spread to the lymph nodes in the neck. If they do, they usually are non-tender. If erosion of the skull base occurs, they may complain of headache or develop cranial neuropathies from infiltration or compression of affected cranial nerves.
Case 2
A 14-year old girl presented with a two week history of rapidly worsening right-sided proptosis and "swollen glands" on the right side of her neck. MRI demonstrated a multi-compartmental nearly seven cm soft tissue mass (shown below) centered in the sinonasal cavity and extending through the cribriform plate into the anterior cranial fossa. No edema was seen within the frontal lobes to suggest direct parenchymal extension of the tumor. Multiple enlarged lymph nodes were also seen in the right lateral retropharyngeal region and in the right anterior cervical chain. Physical examination was notable for marked right-sided proptosis and ophthalmoplegia with preserved vision. A mass was visible in the right nares. Rock-hard cervical lymphadenopathy was present. A fine needle aspiration (FNA) of the cervical nodes revealed a small, round blue cell tumor suspicious for RMS. A biopsy of the mass in the nasal cavity demonstrated the characteristic "alveolar" appearance of alveolar RMS. Immunostains were strongly positive for desmin, vimentin, and myogenin. RT-PCR confirmed the presence of a t(2;13) PAX3-FKHR translocation. CSF cytology was negative for malignant cells. No evidence of distant metastases was found on CT chest, bone scan, PET scan, or bone marrow biopsy.

A diagnosis of Stage 3, Group III alveolar RMS with a parameningeal primary (likely the ethmoid sinus) with intracranial extension was made. All sites of initially visible tumor disappeared completely on follow-up MRI and PET scan following just two cycles of chemotherapy. Despite the administration of additional chemotherapy and full-dose (50.4 Gy) XRT to the primary site and all involved lymph nodes, rapidly progressive and ultimately fatal leptomeningeal recurrence was documented within the radiation field six months from the start of therapy.

Figure 3: Case 2 A 14-year old girl with parameningeal RMS. MRI of the sinuses shows a large, invasive soft tissue mass centered in the sinonasal region invading into both the right and left orbits and extending intra-cranially through the base of the skull.

Children with tumors arising in the genitourinary tract may present with a painless scrotal mass (paratesticular tumors), a protruding grape-like mass in the vagina ("botryoidal" rhabdomyosarcoma), blood in the urine (bladder tumors), or frequent urination, sometimes with burning or hesitancy. Occasionally, tumors that arise in the prostate gland (not the same as the more common type of prostate cancer that adult men get) can grow very large before they are diagnosed; these tumors may present as a visible mass in the pelvis or abdomen, sometimes with urinary frequency and urgency, sometimes with constipation, nausea and vomiting from compression of the bowels.
**Case 3**

An 18-year old college student developed erectile dysfunction, acute abdominal pain, right-sided flank pain, urinary frequency, hesitation, and decreased stream. Oral antibiotics were administered without improvement. A CT scan demonstrated a 10 x 6.5 x 7.3 cm pelvic mass arising in the vicinity of the prostate, inseparable from the posterior wall of the bladder and anterior wall of the rectum, obstructing the right ureter and causing right hydronephrosis, with associated bilateral external and left internal iliac adenopathy. Similar findings were seen on MRI (shown below). A transrectal needle biopsy yielded material that was comprised of a densely cellular small round blue cell tumor, strongly positive for desmin, vimentin, actin, and myogenin on immunostaining, and containing a t(2;13) PAX3-FKHR translocation on RT-PCR. A temporary percutaneous nephrostomy tube was placed to relieve the right-sided hydronephrosis. No distant metastases were seen on CT chest, bone scan, or bone marrow biopsy.

A diagnosis of Stage 3, Group III alveolar RMS of the prostate was made and aggressive, multi-agent chemotherapy was commenced to which the patient achieved a complete response. Erectile function returned to normal. Additional chemotherapy and full-dose (50.4 Gy) pelvic XRT was administered; treatment was complicated by the development of hemorrhagic cystitis and radiation enteritis. The patient returned to college less than three months after the completion of eight months of treatment and remains in continuous complete remission 18 months from diagnosis.

![Figure 4: Case 3: An 18-year old man with prostate RMS. MRI of the prostate showing a large soft tissue mass on the right side of the pelvis compressing the posterior wall of the urinary bladder and the anterior wall of the rectum.](image)

Tumors that arise in the legs or arms are usually amongst the most aggressive types of RMS. These tumors may grow from the size of a mosquito bite or a small marble to the size of a baseball or grapefruit in the course of only a few weeks. The tumors are usually hard, but only rarely are they painful unless they start pressing on nearby nerves. These tumors are the most likely to spread to nearby lymph nodes; it is not uncommon for a child with a RMS in the hand or arm to also have "swollen glands" in the armpit, or for a child with a RMS in the foot or calf to also have "swollen glands" in the groin.
**Case 4**

A 7-year old boy was found to have a firm, painless "lump" in his left calf while being bathed. Physical examination confirmed a rock-hard mass in the calf with obviously enlarged lymph nodes in the popliteal and inguinal regions. MRI demonstrated a large soft-tissue mass in the calf with evidence of hemorrhage (shown), extending cephalad through the popliteal fossa. CT scan of the chest abdomen and pelvis demonstrated the presence of inguinal and pelvic lymphadenopathy, and "suspicous" para-aortic lymphadenopathy; PET scan confirmed that these nodes were hypermetabolic, consistent with metastases. An incisional biopsy of the calf mass and inguinal node demonstrated a "classic" alveolar RMS; RT-PCR confirmed the presence of a "consensus" PAX-FKHR translocation. Except for the nodal metastases, no other distant metastases were found in the lung, bones, or bone marrow.

A diagnosis of Stage 4, Group IV alveolar RMS of the extremity with regional (popliteal and inguinal) and distant (pelvic and para-aortic) nodal metastases was made. Within one week of starting chemotherapy, the calf tumor had shrunk by more than 50% and the hypermetabolic nodal disease had resolved. Treatment is ongoing on a MSKCC single-institutional pilot protocol for "high-risk" patients.

![Figure 5](image)

Occasionally, children with RMS will also have unexplained fevers as one of the symptoms that are noticed at the time of diagnosis. Appetite may or may not be depressed. Fatigue and easy bruising are relatively uncommon symptoms unless the tumor has spread to the bone marrow.
**PROGNOSTIC FACTORS**

Although RMS is considered one disease, there are important differences in how these tumors behave depending on where they arise in the body, how they look under the microscope, how big the tumor is and whether it has spread anywhere, how much of the tumor remains after the initial operation, and the patient’s age at the time of diagnosis. These are called "prognostic factors." They describe "statistical probabilities" for cure but are never able to determine whether an individual child, regardless of how “favorable” or "unfavorable" her prognostic factors, will be cured.

About Table 2: The following table summarizes how the combination of site, tumor size, regional nodal status, distant metastases, age at diagnosis, and histology is used to generate risk-stratified therapy for patients with RMS. The Column entitled "Risk" stratifies patients into one of four risk group (Low-A, Low-B, Intermediate, and High) that is used to assign the appropriate treatment on the Fifth Intergroup Rhabdomyosarcoma Study (IRS-V). The specific protocol number is indicated in the parentheses as the letter "D" followed by a four-digit figure.

**D9602** is the "low-risk" study consisting of approximately eleven months of chemotherapy treatment on either Arm A (2-drug chemotherapy with vincristine plus dactinomycin [VA], with or without radiation therapy) or Arm B (3-drug chemotherapy with vincristine plus dactinomycin plus cyclophosphamide [VAC], with radiation for almost all patients); **D9803** is the "intermediate-risk" study consisting of a randomization between chemotherapy according to Arm A (14 cycles of VAC) or Arm B (eight cycles of VAC alternating with six cycles of vincristine plus topotecan plus cyclophosphamide), plus radiation therapy; **D9802** is the "high-risk" study consisting of a "phase II window" with irinotecan administered on the "daily x 5 x 2 schedule" developed in the Houghton lab at St. Jude Children’s Research Center (Ref. 13) either as a single-agent or in combination with vincristine, followed by either eight cycles of VAC plus four cycles of vincristine plus irinotecan for patients responding to irinotecan, or 12 cycles of VAC chemotherapy for patients not responding to irinotecan, plus radiation therapy. The various IRS-V studies are expected to complete accrual by the end of 2004. Successor studies are planned to open in 2005-2006.

**Rhabdomyosarcoma risk groups definition:**

**Favorable** = Orbit/eye lid, head and neck (excluding parameningeal), genito-urinary (not bladder or prostate)

**Unfavorable** = Bladder, prostate, extremity, parameningeal, other (trunk, retroperitoneal, etc)

a = Tumor size <= Five cm in diameter

b = Tumor size > Five cm in diameter

EMB = Embryonal, botryoid or spindle variants or ectomesenchymomas with embryonal features

ALV = Alveolar or undifferentiated sarcomas, or ectomesenchymomas with alveolar features

N0 = Regional nodes not clinically involved

N1 = Regional nodes clinically involved

NX = Node status unknown
Table 2: Risk-stratification for patients with newly diagnosed RMS

<table>
<thead>
<tr>
<th>Risk</th>
<th>Stage</th>
<th>Group</th>
<th>Site</th>
<th>Size</th>
<th>Age</th>
<th>Histology</th>
<th>Metastasis</th>
<th>Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low A</td>
<td>1</td>
<td>I</td>
<td>favorable</td>
<td>a or b</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N0 or N1 or NX</td>
</tr>
<tr>
<td>(D9602)</td>
<td>1</td>
<td>II</td>
<td>favorable</td>
<td>a or b</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N0 or NX</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>III</td>
<td>orbit only</td>
<td>a or b</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N0 or N1 or NX</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I</td>
<td>unfavorable</td>
<td>a</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N0 or NX</td>
</tr>
<tr>
<td>Low B</td>
<td>1</td>
<td>II</td>
<td>favorable</td>
<td>a or b</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N1</td>
</tr>
<tr>
<td>(D9602)</td>
<td>1</td>
<td>III</td>
<td>orbit only</td>
<td>a or b</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>III</td>
<td>favorable</td>
<td>a or b</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N0 or N1 or NX</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>II</td>
<td>unfavorable</td>
<td>a</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N0 or NX</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I or II</td>
<td>unfavorable</td>
<td>a</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>III</td>
<td>unfavorable</td>
<td>a</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N0 or N1 or NX</td>
</tr>
<tr>
<td>(D9803)</td>
<td>3</td>
<td>III</td>
<td>unfavorable</td>
<td>a</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>III</td>
<td>unfavorable</td>
<td>b</td>
<td>&lt;21</td>
<td>EMB</td>
<td>M0</td>
<td>N0 or N1 or NX</td>
</tr>
<tr>
<td></td>
<td>1 or 2</td>
<td>I or II</td>
<td>favorable or unfavorable</td>
<td>a or b</td>
<td>&lt;21</td>
<td>ALV</td>
<td>M0</td>
<td>N0 or N1 or NX</td>
</tr>
<tr>
<td>or III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>IV</td>
<td>favorable or unfavorable</td>
<td>a or b</td>
<td>&lt;10</td>
<td>EMB</td>
<td>M1</td>
<td>N0 or N1 or NX</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
<td>IV</td>
<td>favorable or unfavorable</td>
<td>a or b</td>
<td>&gt;=10</td>
<td>EMB</td>
<td>M1</td>
<td>N0 or N1 or NX</td>
</tr>
<tr>
<td>(D9802)</td>
<td>4</td>
<td>IV</td>
<td>favorable or unfavorable</td>
<td>a or b</td>
<td>&lt;21</td>
<td>ALV</td>
<td>M1</td>
<td>N0 or N1 or NX</td>
</tr>
</tbody>
</table>

The combination of Stage, Group, Site, Size, Age, Histologic Subtype, and the presence or absence of regional nodes or distant metastases is used to stratify patient into one of four “risk-groups.”

Oncologists use a special set of short-hand terms to describe pronostic factors. For children with RMS, there are two sets of terminology that are used to describe these factors. One is called Stage and the other is called Clinical Group (or "Group" for short). The Stage of RMS is dependent upon three factors:

1. What part of the body the tumor arose in
2. How big the tumor is
3. Whether or not the tumor has spread (see below) regionally or distantly
The **Group** of RMS is dependent upon how much tumor is still present after the initial surgery. There are four Stages (Stage 1, 2, 3, and 4) and four Groups (Groups I, II, III, and IV). Each patient with RMS is assigned a Stage and a Group based upon the combination of these factors.

**About Tables 3 and 4:** The following tables contain the detailed site-modified TNM staging system and surgico-pathologic Clinical Group system used to categorize patients with RMS. These "short-hand" systems are one of the more confusing aspects of caring for children with RMS. Any tumor that arises in one of the favorable locations is Stage 1 as long as it has not visibly spread to another "distant" part of the body (see below). Any tumor that has visibly spread to another "distant" part of the body is always Stage 4. Tumors that arise in any of the unfavorable locations will either be Stage 2 (if they are "small" and have not spread to the lymph nodes) or Stage 3 (if they are "big" or have spread to the lymph nodes). Most children with RMS have Stage 2 or Stage 3 tumors. Since the TNM "staging" system does not require pathologic confirmation of imaging abnormalities, problems with accurately classifying patients can arise when, for example, a patient would be Stage 4 based on the presence of a pulmonary nodule on CT scan that is believed to represent a metastasis but is then found to not contain tumor when surgery is done to remove it.

### Table 3: Site-modified Tumor, Nodes, Metastasis (TNM) Staging System for patients with newly diagnosed RMS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Site</th>
<th>T Status</th>
<th>Size</th>
<th>Node Status</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Favorable</td>
<td>T1 or T2</td>
<td>a or b</td>
<td>N0, N1, or NX</td>
<td>M0</td>
</tr>
<tr>
<td>2</td>
<td>Unfavorable</td>
<td>T1 or T2</td>
<td>a</td>
<td>N0 or NX</td>
<td>M0</td>
</tr>
<tr>
<td>3</td>
<td>Unfavorable</td>
<td>T1 or T2</td>
<td>a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>4</td>
<td>Favorable or Unfavorable</td>
<td>T1 or T2</td>
<td>a or b</td>
<td>N0 or N1</td>
<td>M1</td>
</tr>
</tbody>
</table>

Any tumor that is completely removed at the time of the initial operation is Group I. A tumor that has visibly spread to another "distant" part of the body is always Group IV. A tumor that is still visible (on scans or on physical examination) after the initial operation is Group III. Group II is when all of the visible tumor is removed but there is still "microscopic" amounts of tumor cells left behind - with or without spread to the regional nodes (as long as they are also removed). Half of all children with RMS have Group III tumors.

### Table 4: Intergroup Rhabdomyosarcoma Group (IRSG) Clinical Group staging system for patients with newly diagnosed RMS

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Complete resection, (-) margins</td>
</tr>
<tr>
<td>IIa</td>
<td>Complete resection, (+) margins</td>
</tr>
<tr>
<td>IIb</td>
<td>Complete resection, (-) margins resected nodes positive</td>
</tr>
<tr>
<td>IIc</td>
<td>Complete resection, (+) margins resected nodes positive</td>
</tr>
<tr>
<td>III</td>
<td>Gross residual disease (includes unresected regional nodes)</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>
**PATTERNS OF SPREAD**

RMS can spread locally, regionally, or distantly.

1. Local spread means that the tumor infiltrates or invades the tissues in the immediate vicinity of where it started.
2. Regional spread means that the tumor has traveled to the lymph nodes that drain the area where it arose. The highest chance that RMS will spread to the lymph nodes is for children with tumors that arise in the extremities and in older boys (ten years of age or older) with paratesticular tumors.
3. Distant spread means that the tumor has traveled through the bloodstream to another part of the body. The most common places that RMS travels to are the lungs, bones, and bone marrow.

It is very uncommon for RMS to spread to the brain or other organs such as the liver or spleen. When tumors have spread visibly to a "distant" location they are called "metastases." Only about one child in five with RMS will have distant metastases.

A variety of different tests are needed to evaluate the primary tumor and to look for signs that it may have spread to other parts of the body. The first test is always a thorough history and physical examination. Generally, the best imaging test to evaluate the primary tumor is a MRI. This provides 3-dimensional imaging and is frequently helpful for the purposes of planning radiation or surgery. CT scans of the chest are routinely done to look for the possibility of tumor having "metastasized" to the lungs. Depending on the location of the primary tumor, CT scans of the abdomen and pelvis are sometimes also done to look for spread of the tumor to lymph nodes. A bone scan is a nuclear medicine test that looks at the entire skeleton to determine if the tumor might have spread to the bones. Another nuclear medicine test that is being utilized increasingly is called a PET scan (Positron Emission Tomography). This test is relatively unique in that it images the entire body, both bones and soft tissues, can often be used to clarify an ambiguous finding on CT or MRI and can also be used to assess response to treatment. Because RMS can spread to the bone marrow, patients with RMS also undergo bone marrow aspirates and biopsies; a needle is placed into the hip bones and a specimen of the bone marrow is removed for testing; these tests are almost always done at the same time that anesthesia is being given for the biopsy of the tumor or insertion of the central venous catheter (CVC). Patients with tumors arising in one of the parameningeal locations must always have a lumbar puncture ("spinal tap") performed to obtain a sample of their cerebrospinal fluid (CSF) for testing to make sure that the lining of the brain has not become infiltrated by RMS.

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**Distant Metastases**: Approximately 20% of newly diagnosed patients will present with one or more sites of "distant" metastases. A disproportionate number of these patients will have alveolar histology tumors. Of 127 patients with metastatic RMS treated on IRS-IV, 46% of patients had alveolar tumors compared to 22% of the nearly 900 patients with non-metastatic tumors treated on IRS-IV (Ref. 14). Nearly 60% of patients had metastases confined to one location; the commonest site of metastatic spread was the lungs (39%), followed by the bone marrow (32%), lymph nodes (30%), and bones (27%). Although bone marrow aspirations and biopsies are routinely recommended as part of the staging evaluation of patients with known or suspected newly diagnosed RMS, isolated bone marrow involvement was found in only 12 of 900 patients without other sites of known metastases; thus, the "yield" of bone marrow aspiration and biopsy in patients with otherwise localized RMS is less than 2%.

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**GENERAL PRINCIPLES OF RHABDOMYOSARCOMA TREATMENT**

All children with RMS are treated with chemotherapy. Depending upon the size and location of the primary tumor, and how much of it can be surgically removed, most children will also receive some combination of radiation therapy and surgery.
BIOPSY, DIAGNOSIS AND SURGERY

The diagnosis of RMS can never be made without obtaining a specimen of the tumor for testing in the laboratory. The initial process for obtaining this specimen is called a biopsy. A biopsy is usually considered a "small" operation; most of the time it does not require an overnight stay in the hospital. There are different ways that a specimen of the tumor can be obtained:

1. A percutaneous needle biopsy: in this procedure, a needle is placed through the skin into the tumor and a small piece of the tumor is removed inside the needle. Sometimes this procedure is done using an ultrasound or CT scan to guide the person doing the biopsy. This procedure is usually not done with anesthesia, although intravenous sedation may be required depending on the site of the tumor and age of the child. Depending on the location of the tumor, this procedure may or may not be safer than one of the procedures discussed below. A needle biopsy is able to provide an adequate specimen to make a correct diagnosis about 90% of the time.

2. An open incisional biopsy: in this procedure, which is almost always done under anesthesia, a small cut is made in the skin through which a small piece of the tumor is removed. This procedure provides an adequate specimen to make a correct diagnosis about 100% of the time.

3. An open excisional biopsy: in this procedure, which is almost always done under anesthesia, a cut is made in the skin and an attempt is made to remove the entire tumor. This is a bigger operation than either of the two other procedures. This operation is appropriate for children whose tumors have been fully imaged if the surgeon believes that the entire tumor can be removed and doing so will not result in either a functional deficit (that is, if a calf tumor could be taken out without doing an amputation or otherwise compromising the ability to ambulate) OR a cosmetic defect (that is, if a tumor of the sinuses could be taken out without producing a big facial scar or facial deformity).

Because imaging studies can fail to detect many instances of tumor spread to regional lymph nodes, surgical evaluation of regional nodes is mandatory in two specific cases, children with extremity RMS and boys ten years of age or older with paratesticular tumors. In the former instance, surgical sampling of lymph nodes behind the knee or in the groin should be performed for lower extremity tumors, and sampling of lymph nodes behind the elbow or in the armpit should be performed for upper extremity tumors (Ref. 15). The role of lymphoscintigraphy for identifying a sentinel node is under investigation. PET scanning may be helpful at identifying worrisome nodes not otherwise clearly seen on conventional imaging such as CT or MRI.

In the case of boys with paratesticular tumors, and ideally at the same time that the primary tumor is removed (an inguinal incision should be performed, as would be done for a hernia operation, and the tumor and testicle should both be extracted in contiguity from the scrotal sac and resected), surgical evaluation of ipsilateral (same side as the tumor) retroperitoneal regional lymph nodes should be performed; this latter procedure is increasingly being done laparoscopically, minimizing post-operative recovery and potentially shortening the time until chemotherapy is able to be initiated (Ref. 16).

It is important to remember that surgery by itself is never curative for children with RMS. It is also important to remember that the role of surgery is very dependent on the site of the tumor. While initial complete surgical removal of tumors arising in an extremity or in the pelvis may help improve the chance of cure, complete removal of a tumor arising in the orbit or vagina is almost never necessary to achieve a very high rate of cure (and is almost never appropriate). Although most families whose child is suspected of having RMS want the whole tumor taken out as quickly as possible, this initial surgical procedure is almost never an emergency and it is imperative that proper imaging of the tumor be obtained before a biopsy is performed if RMS is being considered. Failure to image the primary tumor before a biopsy can result in an irreversible loss of opportunity to properly plan critically needed radiation therapy. Similarly, it is important to ensure that the biopsy is obtained at a facility with experienced pathologists who will process the
specimen in the appropriate fashion to ensure that all necessary testing is performed in a timely and thorough manner (Ref. 17).

**PATHOLOGY**

Once biopsied, the tumor is studied under the microscope in the laboratory. The defining characteristic of RMS is the demonstration of evidence of skeletal muscle lineage—either by its appearance under the microscope or by the pattern of chemical staining ("immunostaining"). There are two basic kinds of RMS – embryonal and alveolar. Approximately two-thirds of children with RMS have the more common embryonal type (or the spindle-cell or botryoid variants). These tumors are more common in younger children, particularly those with tumors arising in the head and neck sites (including parameningeal sites) and the genitourinary system (including the bladder and prostate). The tumor cells tend to be more elongated and less densely cellular.

Figure 7: Microscopic appearance of Alveolar RMS. Alveolar RMS cells are typically smaller and rounder and more densely cellular. Architecturally, they may have the appearance of "lining-up" along pseudo-spaces that are reminiscent of the small air sacs in the lung (alveoli).

About 5-10% of children will have tumors that cannot be more definitively categorized and are considered either "undifferentiated" sarcomas or "rhabdomyosarcoma, not otherwise specified."

When a tumor has been biopsied and the pathologist (the doctor who studies the tumor in the laboratory) suspects that it is RMS, she will usually order confirmatory tests called "immunostains." These are chemical reactions that stain different structures in the tumor cell. RMS tumors will usually stain "positively" for a number of different stains including desmin and myogenin. The demonstration of myogenin positivity is virtually diagnostic of RMS.

A final level of testing is sometimes done on RMS tumor cells. This is called "molecular diagnostic testing." Although not much is known about why a normal skeletal muscle cell becomes cancerous, there is quite a lot known about the genetic changes that occur in the cell once it does become a cancer cell. In virtually all cases of embryonal RMS, an abnormality can be found in the cancer cells (and only in the cancer cells – so this is not an inherited abnormality!) that causes an "over-dosage" of a gene that is important in the growth of normal muscle cells.
Figure 8: Over-expression of Insulin-Like Growth Factor Type II (IGF-II) through Loss-of-Heterozygosity at 11p15.

Cases of embryonal RMS typically demonstrate evidence of over-expression of the IGF-II gene located on the short arm of chromosome 11. This is believed to result from loss of the maternal allele and duplication of the paternal allele. It is thought that the expression of two copies of this gene leads to an "overdose" effect whereby too much IGF-II produces a constant proliferative signal that allows the pre-cancerous (or already transformed) muscle cell to grow in an unrestrained fashion and prevents it from dying in response to what would otherwise be lethal environmental stresses. This process is known as "loss of heterozygosity."

This process results in an "overdosage" of a "growth promoting gene", insulin-like growth factor Type II (IGF-II), that is located on chromosome 11. Normally, only one copy (usually the gene that is inherited from the father) of this gene is "active" and the other is "silent" (it's believed that a chemical modification of the DNA structure near the gene, known as "methylation" is responsible for one gene being "on" and another nearby growth suppressing gene [H19] being "off"). In most cases of embryonal RMS, either both genes are activated or the copy of the mother’s gene is lost and the father’s gene is duplicated and both copies are "active." This is thought to lead to the production of a constant "proliferative" signal that tells the cell to continue to grow and prevents it from dying in response to the normal environmental stresses that cells face.

Figure 9: Reciprocal translocation between PAX and FKHR creates a hybrid "oncogene."

Many cases of childhood cancer are associated with specific translocations whereby a piece of one normal gene and a piece of another normal gene break apart and switch places. In approximately 90% of cases of alveolar RMS, a portion of one of the PAX genes (most commonly the PAX 3 gene located on chromosome 2, less commonly the PAX 7 gene located on
chromosome 1) fuses with a portion of the FKHR gene (located on chromosome 13) to create a new "hybrid" gene (PAX-FKHR) that turns on growth-stimulatory genes that would otherwise be "inactive" and turns off growth-inhibitory genes that are normally active. Since this abnormal "hybrid" gene is found only in cases of alveolar RMS, it can be used for diagnostic purposes and, potentially in the future, as a target for immune-mediated cancer therapies.

This abnormality can often be detected using one of several specialized techniques for looking at the chromosomal content of the tumor cells.

Nearly 90% of cases of alveolar RMS will have a characteristic "translocation" involving one of the "PAX" genes (most commonly the PAX 3 gene, located on chromosome 2, less commonly the PAX 7 gene, located on chromosome 1) and the "forkhead" (FKHR) gene (located on chromosome 13).

A translocation is a fairly common "event" in childhood cancers in which a piece of a normal gene breaks away from its usual location and joins a piece of another normal gene. Specifically, by fusing the "paired box" (PB) and "homeodomain" (HD) DNA binding regions of the PAX 3 gene with the "transcriptional activation domain" (TAD) of the FKHR gene, a new "hybrid" gene is created that appears to play a critical role in the process by which the RMS cell becomes cancerous in two ways. First, it turns "off" other genes that are normally "active" and serve as "brakes" on cell growth; and, second, it turns "on" other genes that are normally "inactive" and serve as stimulators of cell growth, survival, and spread. This abnormality is never seen in embryonal RMS so if there is a question about which type of RMS a patient has based on how it looks under the microscope, the demonstration of a PAX-FKHR translocation proves conclusively that it is alveolar RMS. This abnormality is usually tested for using a technique known as RT-PCR (reverse transcriptase polymerase chain reaction), however, this test may only be available in specialized reference laboratories at large Cancer Centers or Children's Hospitals.
Pathology of Rhabdomyosarcoma Subtypes: The two major histologic subtypes of RMS, namely embryonal and alveolar, have been found to have characteristic but distinct genetic alterations that are presumed to play a role in the pathogenesis of these tumors. Alveolar RMS has been demonstrated to have a characteristic translocation between the long arm of chromosome 2 and the long arm of chromosome 13, referred to in shorthand notation as t(2;13)(q35;q14), Refs. 18-19. This translocation has been molecularly cloned and has been shown to involve the juxtaposition of the PAX3 gene (or, rarely, the PAX7 gene located at chromosome 1p36), believed to regulate transcription during early neuromuscular development, and the FKHR gene, also known as FOXO1a, a member of the forkhead family of transcription factors (Refs. 20-21). It is presumed that the consequence of this fusion transcription factor is the abnormal activation of transcription from a gene or genes that contribute to the transformed phenotype. Although the precise consequence of this tumor-specific translocation remains to be elucidated, it has been shown using cDNA microarray analysis that the PAX-FKHR fusion expressed in fibroblasts specifically turns on an array of myogenic factors (Ref. 22). Furthermore, PAX-3-FKHR has been found to upregulate c-MET expression, a receptor tyrosine kinase that has been implicated in transformation (Ref. 23).

The use of polymerase chain reaction (PCR) for precise confirmation of the diagnosis of alveolar RMS based on genetics is likely to become more widely used in the near future. Recently, a novel amplicon has been identified at 13q31 in approximately 20% of cases of ARMS suggesting that one or more genes at this locus contribute to the pathogenesis of these tumors (Ref. 24).

The other major histologic subtype, embryonal RMS, is known to have loss of heterozygosity (LOH) at the 11p15 locus (Refs. 25-26). Furthermore, it has been shown that this LOH involves loss of maternal genetic information with duplication of paternal genetic material at this locus (Ref. 27). This region is of particular interest because it is the location of the IGFII gene, which codes for a growth factor believed to play a role in the pathogenesis of RMS (see later discussion). IGFII has been demonstrated to be imprinted with only the paternal allele being transcriptionally active (Refs. 28-29). It is therefore conceivable that in this tumor, LOH with paternal disomy may lead to overexpression of IGFII. However, it is also possible that LOH at 11p15 may reflect the loss of a tumor suppressor activity that has not been identified, or that both activation of IGFII and loss of tumor suppressor activity result from LOH at 11p15 in embryonal RMS (Ref. 30).

Several investigators have recently reported findings using comparative genomic hybridization (CGH) analysis of RMS tumors and cell lines. Three features stand out. Firstly, regions of genomic amplifications are seen in ARMS and anaplastic ERMS, suggesting that these subtypes share similar genetic events (Ref. 31). Secondly, several studies have noted significant amplification of 15q25-26, the locus for the IGF1 receptor (Refs. 24, 31) and specific IGF1R amplification was confirmed by PCR and FISH (Ref. 31). This is of particular note since IGF signaling is implicated in RMS. Finally, two studies have demonstrated loss at 9q22 in approximately 33% of tumors. This region corresponds to the PTH locus, a tumor suppressor gene implicated in RMS development in a mouse model of Gorlin syndrome (Refs. 31-32).

Once all of the imaging studies have been completed, and the biopsy has been performed, and the diagnosis of RMS has been confirmed, it is possible to classify patients with RMS into one of four "risk groups" based on the combination of their Stage (site, size, nodal involvement), their Group (extent of residual tumor post-operatively), their age at diagnosis, their histologic sub-type (embryonal versus alveolar), and the presence or absence of distant metastases. These risk groups provide important information about the potential curability of the tumor with treatments of lesser or greater intensity:

1. **Standard-risk, subgroup A**: These patients, relatively few in number, have a survival of better than 85% using relatively non-intensive, 2-drug chemotherapy, with or without radiation therapy. This group is essentially comprised of patients with orbital tumors (as long as they have not metastasized), patients with "favorable" site tumors (Stage 1) that have been either completely removed surgically (Group I) or gross totally removed with...
only microscopic residual disease (Group II), and patients with small unfavorable site
tumors (Stage 2) that have been completely resected (Group I).

2. **Standard-risk, subgroup B**: These patients, slightly more numerous, have a survival of
better than 80% but need relatively more intensive, 3-drug chemotherapy, usually with
radiation therapy (with one important exception, see below). This group is comprised of
all patients with non-metastatic, non-orbital favorable site tumors (Stage 1) that are still
visible (Group III) after initial surgery, patients with non-metastatic, small unfavorable site
tumors without regional nodal spread (Stage 2) that have been gross totally resected
(Group II), and patients with unfavorable site tumors that are large or have spread to
regional nodes (Stage 3) but have been completely or gross totally resected (Groups I
and II). Approximately 15-20% of all newly diagnosed RMS patients will be considered
"standard-risk." Patients with alveolar RMS are never considered standard-risk.

3. **Intermediate-risk**: These patients comprise the majority of patients with newly
diagnosed RMS and include those with unfavorable site tumors (Stages 2 and 3) that
have not been completely resected (Group III), patients under the age of ten with
embryonal RMS that has spread to other parts of the body (Stage 4, Group IV), and all
patients with non-metastatic alveolar RMS. Although this is a diverse group of patients,
the prognosis for cure with 3 (or more) drug chemotherapy and radiation therapy is
usually better than 50%, and perhaps as high as 70% for certain sub-groups.

4. **High-risk**: These patients comprise approximately 10-15% of patients with newly
diagnosed RMS. The prognosis for cure for these children is usually quite poor, generally
between 20% and 35%, even with very aggressive chemotherapy, radiation, and surgery.
This group includes all patients with metastatic alveolar RMS, patients ten years of age or
older with metastatic embryonal RMS, and probably two other groups currently
considered intermediate-risk: infants under one year of age with metastatic embryonal
RMS, for whom the 5-year survival is less than 20% (Ref. 33), and children with extremity
tumors with regional nodal spread, almost all of whom have alveolar RMS, for whom the
5-year survival is approximately 30% (Ref. 15).

**RHABDOMYOSARCOMA TREATMENT**

The treatment of patients with RMS is multi-disciplinary and begins even before the start of
treatment with the availability of skilled radiologists who can accurately interpret the results of
imaging studies, skilled pathologists who are familiar with the evaluation and testing of pediatric
"small round blue cell tumors", and skilled surgeons who understand the role of initial surgery in
the overall management of patients with RMS. It includes radiation oncologists and pediatric
oncologists who are familiar with national (or institutional) treatment guidelines (also known as
protocols) for treating this rare form of cancer. Ideally, treatment will be given at a facility where
regular meetings of all of these disciplines (known as Tumor Boards) are held so that all of the
health care providers involved in the child’s care can see the important imaging tests, biopsy
results, and on-treatment evaluations that are necessary to give optimal care.

Given the young age of these patients, the treatment team should also include anesthesiologists
to sedate patients for scans and procedures (including sometimes for the entire 5-6 week course
of radiation treatment), and nursing staff familiar with the unique medical needs and
complications of children with cancer. Finally, it includes Social Work, Chaplaincy, and Child Life
staff to help a family (and child) whose world has been shattered by the words "your child has
cancer."

Treatment for children with RMS focuses on achieving "local control" and "systemic control."
Local control refers to the permanent eradication of the "primary tumor." This is usually
accomplished by surgical removal or irradiation of the tumor (or both) and any involved nearby
areas, in addition to chemotherapy treatment. Systemic control refers to the permanent control of
invisible "micrometastases" or visible "metastases", generally by chemotherapy (sometimes with
additional surgery or radiation therapy). The risk that treatment will fail to be curative varies by
"risk group." For most children with non-metastatic tumors (that is, Standard and Intermediate Risk), the greatest risk is that the primary tumor will not be permanently controlled. More than half of all treatment failures in these groups are "locoregional" (that is, at or near the primary site). Failure to control the primary tumor is associated with a markedly increased risk of relapse at other parts of the body; this is probably a reflection of intrinsic or early-acquisition of resistance to chemotherapy and radiation therapy. For most children with metastatic tumors (that is, High Risk), the overwhelmingly greater risk of treatment failures is that the metastases will not be controlled even if the primary tumor is controlled. Although there are exceptions, because post-relapse survival is poor for the vast majority of children with recurrent RMS (less than 20% of patients who relapse will be cured), it is critical that optimal therapy be given at the time of diagnosis.

Clinical Trial Results: Treatment of most children with RMS is administered either on a cooperative group or single-institution or limited-institution clinical trial, or following the guidelines of the appropriate trial. Since 1972, the Intergroup Rhabdomyosarcoma Study Group (IRSG) has completed four large, sequential, prospective clinical trials treating over 4000 patients with RMS. For patients with non-metastatic tumors, the most recently completed study, IRS-IV, asked two major "research" (randomized) questions:

1. Would replacement of cyclophosphamide by ifosfamide (VAI), or dactinomycin by etoposide (VIE) improve outcome for children with Group III tumors compared to standard VAC chemotherapy?
2. Would hyperfractionated radiation (5940 cGy in twice daily fractions of 110 cGy) improve local control compared to conventional radiation (5040 cGy in daily fractions of 180 cGy)?

For patients with metastatic tumors, the most recently completed trial attempted to evaluate the anti-tumor activity and ultimate treatment efficacy of one of three two-drug pairs (ifosfamide plus doxorubicin, vincristine plus melphalan, and ifosfamide plus etoposide) added to "conventional" VAC chemotherapy.

The results of these studies have been published over the past several years (Ref. 14 and Refs. 34-38). For children with non-metastatic tumors, no difference in outcome was seen between any of the three arms: VIE, VAI, VAC (Ref. 35). On this basis, VAC chemotherapy continued to be recommended by the IRSG as the "gold standard" for children with RMS. Compared to the prior study, IRS-III, outcome was improved for only a small number of children with embryonal tumors, those with unresected (Group III) tumors arising in "favorable" locations, and those with completely or gross totally resected (Groups I and II) tumors arising in "unfavorable sites" (Stages 2 and 3) (Ref. 34). Overall 3-year failure-free survival [FFS] for the entire group of patients was 77%; patients with alveolar histology fared significantly worse (66% 3-year FFS versus 83% for patients with embryonal tumors). Hyperfractionated radiation therapy did not produce superior rates of local control (or have any impact on overall survival) compared to conventionally fractionated therapy (Ref. 36). The overall rate of local control was 87%. The greatest risk of local treatment failure (local recurrence) was seen in patients with bladder/prostate (19%) and parameningeal (16%) tumors.

For patients with metastases, while all 3 drug pairs were highly active with response rates of between 60-80% (Refs. 37-38), outcome remained poor. Overall survival for the entire group was less than 30%; there was a suggestion of better outcome in patients receiving IE in addition to VAC (Ref. 38). The use of melphalan was found to be associated with impaired tolerability of subsequent chemotherapy. Although the outcome for patients with metastatic RMS remains poor, no benefit has been found to consolidation with high-dose chemotherapy and autologous bone marrow rescue (Ref. 39).

Chemotherapy
All patients with RMS require chemotherapy to maximize the chance for cure. Most children in the United States are treated on (or following) an International Clinical Trial formerly known as the "Intergroup Rhabdomyosarcoma Study" (now known as the Soft Tissue Sarcoma Committee of
the Children’s Oncology Group). Over the past 30 years, four Intergroup Rhabdomyosarcoma Studies have been completed with over 4000 patients with RMS treated. The 5th generation of these studies will complete accrual this year. For select patients, usually those with Intermediate or High-Risk RMS, treatment on a "pilot" single- or limited-institution clinical trial may be available.

Chemotherapy treatments for RMS are always given through an intravenous line; generally, a special type of "permanent" intravenous line is placed prior to the start of treatment. Most patients with RMS receive chemotherapy treatments lasting 6-12 months (rarely longer, although depending on the severity of side effects, treatment that is scheduled to last ten months can sometimes last 15 months). Chemotherapy is generally given in two to five (or sometimes ten) day "pulses" or "cycles" every 3-4 weeks. Some chemotherapy drugs can be given on a weekly basis.

Chemotherapy side effects can be "drug-specific" (that is, only seen with one or two drugs) or "general" (that is, seen with many drugs). The following is a list of the most common drugs that are used to treat RMS in the United States and in Europe:

- Vincristine
- Dactinomycin
- Cyclophosphamide
- Topotecan
- Irinotecan
- Etoposide
- Ifosfamide
- Doxorubicin
- Carboplatin

Common side effects that may be seen (to lesser or greater degrees) with virtually all of the chemotherapy drugs that are used to treat RMS include hair loss, nausea and vomiting, loss of appetite, fatigue, mouth sores, and the development of low-blood cell counts. These side effects typically develop because of the effects of chemotherapy on rapidly dividing cells. While tumor cells are usually the most rapidly dividing cells in the body, other normal cells, such as hair cells, "mucosal cells" (the cells that line the mouth and intestines), and blood cells, are also rapidly dividing. Fortunately, there is usually a greater supply of these normal cells than of tumor cells so these side effects are usually temporary.

The development of low blood cell counts is the side effect that most limits the ability to give chemotherapy all the time (the way an infection would be treated) and is one of the most dangerous side effects. There are three major kinds of blood cells: red blood cells, white blood cells, and platelets. Typically, about seven or eight days from the start of a "cycle" of chemotherapy, the blood cells drop to very low levels and may remain low for 5-10 days. Red blood cells carry oxygen from the lungs throughout the body; when the red blood cell count is low this is called anemia and may produce fatigue. White blood cells are the body’s infection fighting cells; when the white blood cell count is low this is called leukopenia and may increase greatly the risk of developing a serious infection from the "germs" that are already in/on one’s own body. When the most important infection-fighting white blood cell count is low, this condition is called neutropenia. Platelets are the cells that help the blood to clot; when the platelet count is low, this increases the risk of bleeding, either spontaneously or from a cut. When the red blood cell count is low, a transfusion can be given to help improve fatigue; when the platelets are low, a transfusion can be given to reduce the risk of bleeding. Most children with RMS, even those with Standard-Risk, Subgroup A tumors who receive relatively less-intensive 2-drug chemotherapy with vincristine and dactinomycin, will require transfusion support with red blood cells and/or platelets at some point during their treatment. The one type of blood cell that can’t be transfused is the infection-fighting white blood cell; however, a medicine (G-CSF, filgrastim, Neupogen®) is available that can help the white blood cells return to a safe level more quickly.

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A Resource from The Liddy Shriver Sarcoma Initiative
Inflammation of the liver, though an uncommon side effect, can occur and can be life-threatening, particularly in very young children, and requires a heightened level of awareness to monitor and evaluate promptly laboratory tests of "liver function."

**Chemotherapy-induced hepatopathy** can be a life-threatening complication. This condition is characterized by hyperbilirubinemia, ascites, coagulopathy, and reversal of flow in the portal vein on Doppler ultrasound. Age less than three years increases the risk. Age-based chemotherapy dose modifications may reduce the risk of hepatopathy, particularly in young children (Ref. 40).

**Vincristine** is a drug that is given to virtually all children with RMS. Uniquely, it can cause pain in the hands and feet or in the jaw or abdomen. It can also produce weakness in the hands and feet due to (usually reversible) nerve damage (peripheral neuropathy). Presently, there are no proven "protective" medications to prevent this nerve damage, but there is some evidence that nerve damage that is caused by other chemotherapy drugs (not typically used to treat RMS), specifically cisplatin and paclitaxel, may be ameliorated by the use of Vitamin E and glutamine, respectively.

Management of vincristine-associated peripheral neuropathy remains problematic. Although there have been no formal prospective studies, clinical experience indicates that patients over eight years of age tolerate the intensive use of vincristine less well than do younger patients. Two other commonly used chemotherapy drugs, cisplatin and paclitaxel, also cause peripheral neuropathy. Two studies have indicated that the concurrent use of glutamine with cisplatin (Ref. 41), and Vitamin E with paclitaxel (Ref. 42), can reduce the incidence and severity of peripheral neuropathy. Although neither agent has been formally evaluated in children with vincristine-associated peripheral neuropathy, anecdotal clinical experience suggests that they are both safe and well-tolerated and may be helpful in some instances.

**Irinotecan** is a newer drug that was found to be very effective at treating RMS in newly diagnosed patients with metastatic tumors and in patients with recurrent RMS (that is, RMS that relapsed after treatment finished or that never disappeared completely with initial treatment). Uniquely, it is given for ten days every three weeks and although it only infrequently causes severe nausea or vomiting, low blood cell counts, or hair loss, it can produce very severe diarrhea.

**Cyclophosphamide** (usually given in combination with vincristine and dactinomycin, or vincristine and doxorubicin) and ifosfamide (usually given in combination with etoposide) can cause damage to the urinary bladder resulting in blood in the urine. Both drugs are given with a "protective" medication, called "mesna" that is effective at reducing the risk of this specific side effect.
Doxorubicin can cause damage to the heart, particularly at higher total (cumulative) doses. Increasingly, in RMS and other types of cancer, it is given with a "protective" medication, called "dexrazoxane", that is effective at reducing the risk of this potentially quite serious complication. Despite its marked anti-tumor activity, the development of potentially life-threatening cardiac damage, even years after its administration, was one factor leading to the elimination of doxorubicin from recent cooperative group clinical trials for patients with RMS. The use of dexrazoxane has been shown to reduce significantly the risk of cardiac damage associated with doxorubicin therapy (Ref. 45) with no reduction in the anti-tumor effectiveness of the doxorubicin (Ref. 46).

Radiation Therapy
All patients with alveolar RMS – even those whose tumors have been completely removed prior to the start of chemotherapy – and almost all patients with Group II (microscopic residual disease) and Group III (gross residual disease) embryonal RMS – require radiation to maximize their chance for cure. Girls with embryonal RMS of the genital tract (vagina, vulva, cervix, and uterus), for whom initial conservative surgical management is the rule of thumb, can often be managed with serial biopsies, beginning after approximately 12 weeks of chemotherapy treatment, without radiation. Radiation treatments are generally given after 4-5 cycles of chemotherapy have been given (that is, after about 12 weeks), although in selected cases (generally limited to children with parameningeal RMS that has eroded through the base of the skull to extend intracranially) radiation may begin at the same time (or as shortly thereafter as possible) as chemotherapy.

Depending on the site and size and Group of the tumor, between 20 and 28 radiation treatments are given. Ideally, treatment should be planned based on 3-dimensional imaging of the pre-biopsy, pre-chemotherapy tumor. The skill of the Radiation Oncologist in the successful treatment of RMS cannot be overemphasized. Because these are rare tumors, and because most children with RMS are treated on protocols that specify the details of their therapy, the Radiation Oncologist must not only be able to accurately interpret relevant imaging studies to design an appropriate "treatment field" that encompasses all of the original tumor, plus a "margin" of normal surrounding tissue, but to do so at the time specified in the protocol and with an awareness of the "normal tissue tolerance" of surrounding normal structures and the risks of long-term complications of irradiating growing tissue in a young child.

Some of the European cooperative groups that treat children with RMS have tried to reduce or eliminate the use of radiation in very young children or in children whose tumors have disappeared completely after a period of chemotherapy or that were gross totally resected prior to the start of chemotherapy. Unfortunately, although some children can be cured in this fashion, the risk of relapse is significantly greater and it is unclear whether the chance for subsequent cure is as good. Consequently, with the exception of girls with genital tract embryonal RMS, radiation is recommended for all patients with Group III RMS, for all patients with Group II RMS, and for all patients with Group I alveolar RMS. The role of radiation to sites of metastatic disease in children with Stage 4 (or Group IV) RMS is less clear, although children with lung metastases that have disappeared after chemotherapy may have an improved prognosis following low-dose (usually eight treatments) whole-lung irradiation (WLI).
**Study Results Involving Radiation Therapy:** No difference was seen in the IRS-IV study with the use of hyperfractionated versus conventionally fractionated radiation therapy (XRT) (Ref. 36). While most patients with Group III tumors will achieve local control with full-dose XRT, lymph node involvement at diagnosis is correlated with a two-fold increased risk of local treatment failure (Ref. 47). The same observation has been made for patients with Group II tumors, where the highest risk of local recurrence was seen in patients with microscopic residual disease and regional nodal involvement (Group IIC) (Ref. 48). All patients with alveolar RMS, even those with completely resected tumors, should receive local irradiation (Ref. 49). European investigators have tried to avoid or limit the use of local irradiation in patients with Groups II (Ref. 50) and Group III (Ref. 51) tumors. Significantly greater local recurrence rates were seen with this approach. The familiarity of the radiation oncologist with treatment guidelines for children with RMS cannot be overstated (Ref. 52). Use of 3-dimensional imaging and conformal or intensity-modulated radiation therapy (promising new techniques for delivering highly targeted XRT) have produced superior rates of local control particularly for patients with "high-risk" localized tumors such as those with large parameningeal tumors with intracranial extension (Refs. 53-54). Uniquely among patients with Group II and Group III tumors, girls with unresected genital tract embryonal tumors may not require XRT for local control; optimal management of these patients consists generally of limited initial surgery followed by serial biopsies beginning after a period of approximately twelve weeks of chemotherapy, with definitive surgery or radiation after 24-30 weeks if there is persistent tumor (differentiated rhabdomyoblasts are generally not considered evidence of active tumor in this location), Ref. 55.

**Delayed (Second-Look) Surgery**

Some children with RMS undergo "delayed" or second-look surgery after their tumor has shrunk following chemotherapy. The reasons for doing this type of operation include trying to eliminate the need for radiation therapy (infrequent) or to allow a "clinically significant" lower dose of radiation to be given post-operatively (common), or to maximize the chance that post-operative radiation will work effectively (particularly for tumors that were very large at the time of diagnosis). Occasionally, a child whose tumor has been treated with radiation will have imaging results that are worrisome and suggest that the tumor has not been killed by the radiation. In these instances, if feasible, surgery may be necessary to remove the residual cancer that has survived the radiation to try to prevent a recurrence at the primary site.

**The role of surgery in the management of patients with RMS** is clearly site-specific. Superior outcome has been suggested when initial complete, gross total, or even debulking surgery is performed for patients with unfavorable site tumors (Refs 56-58). Since a randomized trial of surgical resection is unlikely to ever be accomplished, it will likely never be possible to say whether this improved outcome is a function of surgical resection per se, or whether surgical resectability is merely associated with other factors known to be associated with better outcome such as the presence of gross residual tumor at the time of pre-treatment re-exploration in patients thought to have undergone a "complete" initial resection, smaller tumor size, non-invasive tumors, no nodal involvement, and better response to neoadjuvant chemotherapy. As a general rule, particularly for patients with unfavorable site tumors, maximal function- and cosmetic-sparing surgery is appropriate at the time of diagnosis. For tumors that cannot be resected at the time of diagnosis, second-look surgery should be considered particularly if a complete or gross-total resection is felt to be likely and doing so will permit a significant reduction in the dose of post-operative radiation therapy, or if there is concern about the presence of residual viable tumor after radiation therapy (Ref. 59). Although "non-mutilating" surgery has been a guiding principle over the past two decades, particularly for patients with bladder/prostate tumors, a recent report has highlighted the important cautionary note that organ retention is not necessarily equated with normal organ function (Ref. 60).
Newer Treatments
Post-relapse survival for the majority of patients with recurrent RMS remains dismal. 95% of recurrences occur within three years of diagnosis. With the exception of a small "favorable risk" group (approximately 20% of relapsing patients) whose 5-year survival approaches 50%, half of patients with recurrent RMS will die of their disease within one year of relapse and 90% of patients will die within five years of relapse (Ref. 61).

Novel therapies are desperately needed for this group of patients.

More about New Treatments: As better insights are gained into the critical processes of "rhabdomyosarcomagenesis" (Refs. 62-64), new avenues into biologically-based treatments are being gained. Treatments targeted at interrupting critical growth-factor receptor-ligand interactions, or their downstream targets, appear particularly promising. An autocrine IGF-II pathway plays a role in the growth of RMS (Ref. 65); disrupting this pathway is one potential biologically "smart" therapy. Growth of RMS xenografts in nude mice can be inhibited using monoclonal antibodies directed against the IGF-I receptor, the receptor that binds IGF-II and mediates its mitogenic signal (Ref. 66). A newer monoclonal antibody recognizing the human IGF-I receptor was shown to inhibit IGF-I stimulated proliferation in a RMS cell line (Ref. 67). Highly specific small molecule tyrosine kinase inhibitors targeted against the IGF-I receptor tyrosine kinase have been synthesized and shown to inhibit tumor xenograft growth, both alone and in combination with cytotoxic chemotherapy (Ref. 68).

The recognition that intracellular proteins can be processed and presented as peptides on the cell surface by major histocompatibility complex (MHC) class I molecules has suggested the possibility that tumor-specific mutant gene products may be targets for cytotoxic T cells (Refs. 69-70). For example, investigators have shown that a peptide derived from a mutant p53 protein is specifically recognized by cytotoxic T cells (Refs. 71-72). In a similar way, translocation-specific fusion proteins could also potentially be targeted by cytotoxic T cells (CTL). Specifically, the PAX-FKHR fusion protein generated by the t(2;13)(q35;q14) translocation in alveolar RMS is a potential target for CTL therapeutic approaches. Based on pre-clinical murine studies demonstrating that bone-marrow derived Dendritic Cells (DCs) pulsed with Tumor-Associated Antigens (TAA) can generate both Natural Killer (NK) and CD8+ Cytotoxic T-Lymphocytes (CTLs) against RMS (Ref. 73), pilot clinical studies using PAX-FKHR specific peptide pulsed dendritic cell vaccinations are ongoing. The success of this approach will depend on the ability of tumor cells to present a processed fusion peptide bound to MHC on the cell surface. If this can occur, multiple approaches could then be taken to overcome potential deficits that allowed the tumor to initially escape cellular immunity (Refs. 74-75).

As greater insights are gained into the basic biology of RMS, novel treatment approaches are being developed to try to exploit these "Achilles' heels" of the tumor cells. Because of the dependency of RMS on IGF-II, promising new drugs have been developed that either block the interaction of the type I IGF receptor with IGF-II, or that block the downstream biological effects that occur after IGF-II binds to its receptor. These agents, though not yet clinically available, offer great promise as both "stand-alone" treatments, or in combination with chemotherapy.

Finally, because of the presence of the unique, tumor-cell specific "translocation" gene in cases of alveolar RMS, the potential exists to utilize immune-based therapies to recognize and kill cells that contain this abnormal gene. Pilot clinical trials are ongoing to evaluate the ability to "vaccinate" patients with alveolar RMS to develop immunity against their own tumors; simultaneously, pilot clinical trials are also ongoing to evaluate the ability of a "genetically matched" sibling's immune system to control a patient's alveolar RMS tumor following a "mini"-allogeneic stem cell transplant.
LATE EFFECTS OF RHABDOMYOSARCOMA TREATMENT
The adoption of risk-based therapy for children with RMS is intended to maximize the chance for cure while minimizing the development of short-, intermediate-, and long-term complications. Treatment related late-effects may develop anywhere from months to years after the completion of therapy. Individual chemotherapy agents may have unique toxicities that may not become manifest until many years after the end of therapy, or that may steadily worsen with increased length of follow-up. Damage from radiation therapy, and late complications from surgery, may not become apparent for many years, particularly in growing children. Select well-described complications of treatment include:

1. **Infertility** (associated especially with the use of alkylating agents such as cyclophosphamide and ifosfamide): The risk of chemotherapy-induced infertility is much greater for boys than for girls (Ref. 76). Whenever feasible, even for boys on the cusp of pubertal development, an evaluation should be made of the possibility of sperm cryopreservation (Ref. 77). Although the subject of intensive laboratory investigation, neither cryopreservation of ovarian tissue nor of ova is currently available as a routinely effective means of fertility preservation for girls (Ref. 78); fortunately, the risk of infertility appears to be much lower in girls. For girls undergoing pelvic irradiation, or for boys undergoing scrotal irradiation, surgical transposition of the gonad(s) out of the radiation field may be helpful at preserving hormonal function and/or fertility.

2. **Bladder dysfunction**: Although "non-mutilating" conservative surgery and full-dose irradiation has become the treatment of choice for bladder preservation in children with bladder/prostate RMS, approximately half of children with "intact" bladders will have one or more symptoms of bladder dysfunction including dribbling, incontinence, and enuresis (Ref. 60).

3. **Radiation damage of head and neck structures**: The use of radiation to treat tumors arising in head and neck structures is frequently unavoidable due to the lack of "non-essential" surrounding structures that could be "sacrificed" if complete surgical resection were attempted. Well described complications of radiation include cataract formation after doses to the globe as low as 1000 cGy (Ref. 79); asymmetric facial growth as a result of permanently arrested bone development and fibrosis ("scarring") of surrounding tissues; chronic sinus infections; growth failure due to pituitary damage (Ref. 80); and complex and multiple dental abnormalities (Ref. 81). It is unknown whether more precisely targeted, newer radiation techniques such as Intensity Modulated Radiation Therapy (IMRT), will reduce the risk of late complications from irradiation of head and neck structures (Ref. 53).

4. **Secondary cancer**: Perhaps the most devastating late complication of treatment for any type of cancer, not just RMS, is the development of a second form of cancer. The use of chemotherapy and radiation can cause second cancers to develop. Chemotherapy-associated secondary cancers are most commonly leukemias (typically Acute Myeloid Leukemia [AML]), and may be associated with the use of alkylating agents (cyclophosphamide and ifosfamide), and topoisomerase II inhibitors (etoposide and doxorubicin). The risk of secondary leukemia is, fortunately, quite low (generally between 1 and 2%). Radiation is also associated with the development of second cancers, most commonly other sarcomas (either in bone or soft tissue). At the doses of radiation that are currently used to treat children with RMS, the risk of secondary sarcomas is approximately 5% at 20 years (Ref. 82). Unlike the situation with secondary leukemias, which typically develop within four years of treatment, most cases of secondary sarcomas do not develop until 5+ years after the end of treatment (Ref. 82). The contribution of underlying "genetic risk factors" to the development of treatment-induced cancers is being actively investigated.
Secondary Cancers: Twenty-two second malignant neoplasms developed among 1770 patients entered onto IRS-I and IRS-II, including 11 radiation-related bone sarcomas and five cases of acute nonlymphoblastic leukemia, at a median of seven years after therapy (Ref. 83). Three of the affected patients had neurofibromatosis, and the families of seven other of the affected patients had histories compatible with LFS; this suggests that genetic susceptibility plays a significant role in the development of a second malignant neoplasm after treatment for RMS. Early results from IRS-III described the early occurrence of five cases of acute myeloid leukemia in children, as well as one case of osteosarcoma and one case of myelodysplastic syndrome (Ref. 84). A preliminary reports of SMN in IRS-IV found 14 cases in 13 patients at a median of 3.2 years from diagnosis (Ref. 85). A more recent update of the IRS experience noted 67 SMN and 2 third malignancies in 4367 patients enrolled on IRS studies from 1972-1997 (Ref. 86). Only seven had a recognized genetic predisposition syndrome. The estimated cumulative incidence for SMN at 20 years was 3.5%. Early concerns about an increased risk of AML/MDS in patients receiving etoposide do not appear to have been substantiated, however, prospective monitoring of the contribution of a strong family history of cancer to the risk of developing a treatment-related SMN is prudent (Ref. 87).

REFERENCES


