Rhabdomyosarcoma: An Overview

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ABSTRACT

Rhabdomyosarcoma (RMS) is a malignant tumor of mesenchymal origin thought to arise from cells committed to a skeletal muscle lineage. With approximately 250 cases diagnosed yearly in the United States, it is the third most common extracranial solid tumor of childhood after Wilms’ tumor and neuroblastoma. Important epidemiologic, biologic, and therapeutic differences have been elucidated within the RMS family. Common sites of primary disease include the head and neck region, genitourinary tract, and extremities. A site-based tumor-nodes-metastasis staging system is being incorporated into use for assessing prognosis and assigning therapy in conjunction with the traditional surgicopathologic clinical grouping system. The development of intensive multimodality treatment protocols tested in large-scale international trials has resulted in significant improvements in outcome, especially for patients with local or locally extensive disease for whom a 60%-70% disease-free survival can be expected. Despite aggressive approaches incorporating surgery, dose-intensive combination chemotherapy, and radiation therapy, the outcome for patients with metastatic disease remains poor. Future challenges include the development of less toxic therapy for patients with localized disease and new approaches for patients with metastatic disease. The Oncologist 1999;4:34-44

Epidemiology

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma of childhood, with an annual incidence of four to seven per million children 15 years of age or younger. Approximately 250 new cases are diagnosed in the U.S. each year [1]. After neuroblastoma and Wilms’ tumor, it is the third most common extracranial childhood solid tumor [2].

Approximately 65% of cases are diagnosed in children less than six years of age with remaining cases noted in the 10- to 18-year-old age group. There is a slight predilection for disease in males, with a male-to-female ratio of 1.3-1.5 [3, 4]. In the U.S., the incidence in African-American females is half that for Caucasian females, while the incidence in males is similar for both groups. The incidence appears to be lower in Asian populations than among mainly white populations of Western countries [3].

Distinctive features appear to cluster around the site of the primary tumor, the age at diagnosis, and the histologic subtype. For example, head and neck RMS are more common in younger children, with orbital tumors being characterized by embryonal histology in most cases. On the other hand, extremity tumors are more commonly found in adolescents and are more likely to have an alveolar histologic subtype. Nearly 80% of genitourinary tract (GU) RMS are embryonal in nature [5]. The botryoid variant of RMS, characterized by a protuberant mass arising from the bladder or vagina, is found almost exclusively in infants.

Genetics and Biology

Most cases of RMS appear to be sporadic in nature, but the disease has been associated with familial syndromes such as neurofibromatosis and the Li-Fraumeni syndrome (LFS). Characterized by the familial clustering of RMS and other soft-tissue sarcomas in childhood as well as adrenocortical carcinoma and early-onset breast carcinoma in adult relatives, the LFS has been associated with germline mutations of the p53 tumor suppressor gene [6]. In a study of 33 cases of RMS, Diller et al. found evidence of germline mutations of p53 in 3 of 13 children less than three years of age compared with none in 20 children older than three years of age [7]. This finding suggests that some young children with seemingly sporadic RMS may have a hereditary predisposition to cancer and raises the question of whether children with p53 mutations should have their therapy altered to

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reduce exposure to ionizing radiation or to chemotherapeutic agents linked to an increased risk of secondary malignancies. It also raises the question of whether children with RMS diagnosed at or below the age of three years should undergo screening for germline p53 mutations. RMS has also been observed in association with Beckwith-Wiedemann syndrome, a fetal overgrowth syndrome associated with abnormalities on chromosome 11p15, where the gene for insulin-like growth factor II (IGF-II) is located [8, 9] (described below).

The two histologic subtypes of RMS, embryonal and alveolar, have been found to have distinct genetic alterations that may 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 as t(2;13)(q35;q14) [10]. This translocation fuses the PAX3 gene (believed to regulate transcription during early neuromuscular development) with the FKHR gene (a member of the forkhead family of transcription factors) [11]. It is hypothesized that this fusion transcription factor inappropriately activates transcription of genes that contribute to a transformed phenotype (Fig. 1). The variant t(1;13)(p36;q14) fuses the PAX7 gene located on chromosome 1 with FKHR. Patients with tumors expressing the PAX7-FKHR fusion tend to be younger and are more likely to present with an extremity lesion, suggesting a distinct clinical phenotype [12]. Polymerase chain reaction (PCR) assays are now available that allow for confirmation of the diagnosis of alveolar RMS based on the presence of these fusion genes.

Embryonal RMS is known to have loss of heterozygosity (LOH) at the 11p15 locus with loss of maternal genetic information and duplication of paternal genetic information [13, 14]. As mentioned above, this is the location of the IGF II gene. This is of interest since it is now known that IGF-II is normally imprinted, with expression occurring exclusively from the paternal allele. Recently, RMS has been shown to have loss of imprinting (LOI), with re-expression of IGF-II from the normally silent maternal allele [15]. Thus, LOH with paternal disomy or LOI with bi-allelic expression could both lead to a 2X-gene dosage effect with overexpression of IGF-II.

Indeed, both alveolar and embryonal RMS appear to overproduce IGF II, a growth factor that has been shown to stimulate RMS tumor cell growth [16]. In addition, monoclonal antibody blockade of the receptor for IGF II has been demonstrated to inhibit growth of RMS [16, 17]. It therefore appears likely that IGF II plays a role in the unregulated growth of these tumors.

Change in DNA content (ploidy) has been described in a variety of tumors and is related to abnormal chromosome number. Embryonal RMS tumors have been found to have DNA contents ranging between diploid and hyperdiploid (1.1 to 1.8 times the normal amount of DNA). It has been reported that diploid embryonal RMS tumors may have a worse prognosis than hyperdiploid tumors [18-20]. However, these findings have yet to be confirmed.

RAS oncogene mutations have been described in RMS cell lines and tumor specimens [21, 22]. It is not known whether these alterations are involved in RMS tumor pathogenesis or reflect secondary abnormalities that occur during tumor progression.

Aberrant expression of the MET oncogene in embryonal and alveolar RMS tumor samples and established cell lines has been described. MET encodes the receptor for HGF/scatter factor, which is known to control cell motility and invasion in epithelial cells. It is hypothesized that the overexpression of MET may provide RMS cells with the same property as embryonal myoblasts to migrate into surrounding connective tissues [23].

**Pathology**

RMS falls into the broader category of small, round, blue-cell tumors of childhood. Light microscopy, immunohistochemistry, electron microscopy, and molecular genetic techniques can be used to identify characteristic features of RMS consistent with a myogenic lineage.

*Figure 1. The characteristic translocation in alveolar RMS: the structure of the PAX3 gene on chromosome 2, the FKHR gene on chromosome 13, and the fusion product of the t(2;13)(q35;q14) translocation. (PB = paired box; HD = homeodomain; FKHR = forkhead).*
By light microscopy, RMS may exhibit cross-striations characteristic of skeletal muscle or rhabdomyoblasts. The two major subtypes of RMS, embryonal and alveolar, each have a characteristic histologic appearance. Alveolar RMS exhibits small, round, densely appearing cells lined up along spaces reminiscent of pulmonary alveoli, giving rise to the term “alveolar RMS.” The embryonal subtype is characterized by spindle-shaped cells with a stroma-rich appearance. Solid alveolar RMS is a variant of the alveolar subtype that is lacking in the typical architecture of septations. Leiomyomatous RMS is an embryonal variant that is predominantly paratesticular in origin (Fig. 2). The botryoid variant of embryonal RMS, seen most commonly in infants, is defined by the presence of subepithelial aggregates of tumor cells known as the cambium layer and is named due to the common “grape-like” appearance of these tumors [24].

There is conflicting evidence concerning the prognostic significance of the histologic subtype. Although histology was found to be an important prognostic variable in the second Intergroup Rhabdomyosarcoma Study (IRS-II), this was not seen in IRS-III. [25, 4]. IRS-IV, which has recently closed to accrual, did not include histology as an independent prognostic factor. There is evidence to suggest that site, which is associated with histologic subtype, is an independent prognostic factor, and that histology is a prognostic factor only because of its association with site and other adverse risk factors [26].

Other lines of evidence suggest that histology is an independent prognostic factor. An evaluation of 159 patients with RMS treated at the National Cancer Institute and St. Jude Children’s Research Hospital over a 15-year period revealed a better outcome for embryonal tumors than identically treated alveolar or solid tumor variants [27]. Although histology was not found to be an independent prognostic factor in IRS-III, patients with alveolar tumors were treated more intensely than their counterparts with embryonal histology. Finally, preliminary results of IRS-IV suggest improved outcome for intermediate-risk embryonal histology tumors but not for alveolar histology tumors treated in an equivalent fashion [28].

Immunohistochemistry is useful in identifying skeletal muscle proteins or genes. Muscle-specific proteins include alpha-actin, myosin, desmin, myoglobin, Z-band protein, and Myo-D [29, 30]. Expression of members of the Myo-D family of transcription factors (MYF3, MYF4, MYF5, and MYF6) in these tumors is indicative of commitment to the myogenic cell lineage: MYF3 transcripts have been identified in all cases of RMS examined [31, 32].

Electron microscopy can provide additional information. The finding of actin-myosin bundles or Z-band material on electron microscopic analysis provides strong support for a diagnosis of RMS.

The application of molecular diagnostic approaches is becoming more widely available in the evaluation of these tumors and should be included in the initial diagnostic evaluation whenever possible. The characteristic t(2;13)(q35;q14) abnormality or variant t(1:13)(p36;q14) can be determined by reverse transcriptase polymerase chain reaction (RT-PCR) and provides definitive evidence of an alveolar RMS. LOH of 11p15 in embryonal RMS can also be identified using PCR technology [33].

**Clinical Presentation**

The presenting signs and symptoms of RMS are variable and are influenced by the site of origin of the primary tumor, the age of the patient, and the presence or absence of metastatic disease. Common sites of primary disease include the head
and neck region, the GU tract, and extremities. Figure 3 provides salient features of RMS clinical presentation.

Head and neck RMS (Fig. 4) arises in the orbit, parameningeal sites (middle ear, nasal cavity, paranasal sinuses, nasopharynx, and infratemporal fossa), and other sites (scalp, parotid gland, oral cavity, pharynx, thyroid and parathyroid glands, and neck). These tumors are most commonly of the embryonal subtype and rarely spread to regional lymph nodes [34, 35]. Orbital tumors produce proptosis, and, occasionally, ophthalmoplegia. Those arising from parameningeal sites often produce nasal, aural, or sinus obstruction with or without a mucopurulent or sanguinous discharge. Head and neck RMS arising from sites other than the orbit or parameningeal sites often presents as a painless, enlarging mass which tends to remain localized [36, 37].

GU tract RMS often arises from the bladder or prostate. Bladder tumors produce hematuria and urinary obstruction. Prostate tumors can produce large pelvic masses resulting in urinary frequency or constipation if significant compression of the bladder or intestinal tract occurs. RMS can also arise from the male or female genital tracts. Vaginal tumors tend to occur in very young children accompanied by a mucosanguineous discharge, whereas cervical and uterine tumors are more common in older girls [38, 39]. Paratesticular tumors produce scrotal or inguinal enlargement in pre- or post-pubertal males. The overwhelming majority of GU tract RMS are of the embryonal subtype.

The extremities represent the third most common site of origin of RMS. These tumors typically arise in adolescents who present with a painful mass or swelling with or without erythema of the overlying skin (Fig. 5). Nearly 50% of extremity RMS are of the alveolar subtype and are more likely than head and neck RMS to spread to regional lymph nodes and along fascial planes [40, 41].

Less common sites of primary disease include the trunk, intrathoracic region, perineal-perianal region, and biliary tract [42-44]. Primary RMS of the liver, brain, trachea, heart, breast, and ovary has been reported [45-50].

Fewer than 25% of patients have metastatic disease at diagnosis. The lung is the most frequent site of metastasis followed by bone, bone marrow, and lymph nodes. Visceral organ metastases are rare in newly diagnosed patients. Distant failure at these same sites can occur in patients who relapse after receiving systemic therapy [51-52].

**Diagnostic Evaluation**

Key components of the evaluation of a suspected RMS include the determination of the extent of primary disease...
and the presence or absence of metastatic spread. A complete physical examination should be performed, with special attention to regional lymphatic structures. Laboratory studies should include a complete blood count with differential, serum electrolytes, blood urea nitrogen, and liver function tests, as well as serum creatinine, phosphorus, magnesium, uric acid, and calcium. Although uncommon, hypercalcemia related to bone absorption can occur in patients with bone metastases [53, 54]. Bilateral bone marrow aspiration and biopsy of the iliac crests should be obtained even in the absence of abnormal peripheral blood counts or obvious bone metastases. Baseline coagulation studies should be performed, although disseminated intravascular coagulation is uncommon [54].

Radiologic evaluation should include plain radiographs of the primary site as well as a computed tomography (CT) scan of the primary and surrounding structures. In some cases, the ascertainment of the extent of disease can be aided by the use of magnetic resonance imaging (MRI) (such as in tumors of the extremity or head and neck region), or ultrasonography (in pelvic RMS) [55, 56]. Patients with paramegival disease should be evaluated with a gadolinium-enhanced MRI.

Radiologic evaluation for possible metastatic disease should include a chest CT and a technetium-99m diphosphonate bone scan. Sites that appear abnormal on bone scan should be investigated further as warranted.

Certain tumor sites have a propensity for specific patterns of spread, and this should be considered in the evaluation process. For example, patients with paramegival primaries should undergo lumbar puncture, as disease spread to the meninges can occur. Patients with a primary paratesticular tumor should be evaluated with an abdominal CT to look for retroperitoneal nodal involvement.

Adequate tissue for routine pathology as well as cytogenetic and molecular genetic studies should be obtained at the time of biopsy or initial resection.

**STAGING**

Assessment of disease extent is critical, because therapy and prognosis depend on the degree to which the mass has spread beyond the primary site. The most widely used surgicopathologic staging system has been the clinical grouping (CG) system developed by the IRS in 1972 (Table 1). This system recognizes four categories of disease based on the amount of tumor remaining after initial surgery and the degree of tumor spread at the time of diagnosis.

Although the CG system has been useful in assigning treatment groups, it is not without shortcomings. Surgical options/techniques vary among institutions, making comparisons among groups of patients from different institutions problematic. Another criticism is that the CG system excludes other important prognostic factors, such as tumor size and site [57].

A pretreatment tumor-nodes-metastasis (TNM) staging system modified for site of origin was incorporated into IRS-IV, which opened in 1992 and completed accrual in 1997 (Table 2). The CG system was retained for planning radiation therapy. This modified TNM system includes the evaluation of site of disease, local extension, size, regional nodal involvement, and the presence or absence of metastatic disease. It has been shown to be highly predictive of outcome when evaluated by several investigators [58, 59].

**THERAPY**

Treatment approaches to RMS incorporate surgery, radiation therapy, and chemotherapy. Radiation therapy is used to
control local microscopic or gross residual disease, whereas systemic chemotherapy plays a role in primary cytoreduction as well as eradication of gross and micrometastatic disease. Combined modality therapy using these approaches has been developed through large collaborative trials such as those of the Intergroup Rhabdomyosarcoma Study Group (IRSG).

**Surgery**

Complete surgical resection is currently recommended if it will not be mutilating or cosmetically damaging. In cases where complete resection is not feasible, initial biopsy followed by neoadjuvant chemotherapy and definitive local control measures are appropriate.

Second-look surgery has been evaluated in two different clinical circumstances. In cases of an apparently complete (radiographic) remission, second-look surgery has been contemplated as a method of documenting pathologic response in the hope of eliminating further local control measures such as radiotherapy. The International Society of Pediatric Oncology (SIOP) has addressed this issue in their 1984 Malignant Mesenchymal Tumors Study [60]. Patients received three to six cycles of chemotherapy following biopsy or limited surgery. Additional local therapy was not given to patients having no evidence of residual tumor after induction therapy. Fifty percent of these patients ultimately had a local recurrence with no difference in the recurrence rate between patients undergoing biopsy confirmation and those followed clinically. Therefore, pursuing this strategy for the purpose of withholding definitive local therapy after achieving a complete clinical response is considered inappropriate.

Second-look surgery has also been undertaken to resect viable tumor after the administration of definitive local therapy. In IRS-III, patients with CG-III disease underwent induction chemotherapy and completed radiotherapy prior to second-look surgery, which was delayed until 20 weeks after initiation of therapy when possible [4]. Sixty-four percent of CG-III patients who underwent secondary operations (with partial remission radiographically) were found to be in complete remission. Fifty-two percent of those undergoing secondary operations after achieving only a minor response were converted to a complete remission.

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**Table 1. Clinical group stage system for rhabdomyosarcoma**

<table>
<thead>
<tr>
<th>Clinical group</th>
<th>Extent of disease/surgical result</th>
</tr>
</thead>
</table>
| I             | A. Localized tumor, confined to site of origin, completely resected.  
                 B. Localized tumor, infiltrating beyond site of origin, completely resected. |
| II            | A. Localized tumor, gross total resection, but with microscopic residual disease.  
                 B. Locally extensive tumor (spread to regional lymph nodes), completely resected.  
                 C. Locally extensive tumor (spread to regional lymph nodes), gross total resection, but microscopic residual disease. |
| III           | A. Localized or locally extensive tumor, gross residual disease after biopsy only.  
                 B. Localized or locally extensive tumor, gross residual disease after major resection (≥50% debulking). |
| IV            | A. Any size primary tumor, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor. |

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**Table 2. TNM staging of rhabdomyosarcoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites</th>
<th>T-invasiveness</th>
<th>T-size</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Orbit</td>
<td>$T_1$ or $T_2$</td>
<td>a or b</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td></td>
<td>Head and neck</td>
<td>$T_1$ or $T_2$</td>
<td>a or b</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td></td>
<td>Genitourinary</td>
<td>$T_1$ or $T_2$</td>
<td>a or b</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td>II</td>
<td>Bladder/prostate</td>
<td>$T_1$ or $T_2$</td>
<td>a</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td></td>
<td>Extremity</td>
<td>$T_1$ or $T_2$</td>
<td>a</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td></td>
<td>Cranial parameningeal</td>
<td>$T_1$ or $T_2$</td>
<td>a</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td></td>
<td>Other*</td>
<td>$T_1$ or $T_2$</td>
<td>a</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td>III</td>
<td>Bladder/prostate</td>
<td>$T_1$ or $T_2$</td>
<td>a</td>
<td>$N_0$</td>
<td>$M_0$</td>
</tr>
<tr>
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<td>Extremity</td>
<td>$T_1$ or $T_2$</td>
<td>b</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td></td>
<td>Cranial parameningeal</td>
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<td>b</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td></td>
<td>Other*</td>
<td>$T_1$ or $T_2$</td>
<td>b</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
<tr>
<td>IV</td>
<td>All</td>
<td>$T_1$ or $T_2$</td>
<td>a or b</td>
<td>$N_0$, $N_1$, or $N_x$</td>
<td>$M_0$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T = Tumor</th>
<th>N = Regional nodes</th>
<th>M = Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1$</td>
<td>Confined to anatomic site of origin</td>
<td>$N_0$, Not clinically involved</td>
</tr>
<tr>
<td>$T_2$</td>
<td>Extension</td>
<td>$N_1$, Clinically involved</td>
</tr>
<tr>
<td>a ≤5 cm in diameter</td>
<td>$N_1$, Clinical status unknown</td>
<td></td>
</tr>
<tr>
<td>b ≥5 cm in diameter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Excluding parameningeal.

*Nonbladder/nonprostate.

*Includes trunk, retroperitoneum, etc.

*TNM pretreatment staging classification for the Intergroup Rhabdomyosarcoma Study-IV.

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status by the procedure. However, it is not known whether this leads to increased survival in such patients.

**Radiation**

Radiation therapy plays an important role in the treatment of RMS. In sites such as the head and neck or pelvis, tumors often cannot be completely removed with surgery. Radiation therapy can eradicate residual tumor cells in such instances. Early guidelines recommended doses as high as 5,500 to 6,000 cGy for control of the primary tumor site. General radiation therapy guidelines have evolved with sequential intergroup studies. For residual microscopic disease, 4,000-4,500 cGy appears sufficient to achieve local control. Doses of 4,500-5,000 cGy appear to be necessary in cases of gross residual disease and for tumors >5 cm. In patients with parameningeal tumors, improvements in the ability to define the radiation field and the use of 4,500-5,500 cGy have led to dramatic increases in survival.

In IRS-IV, radiation therapy was defined by clinical group. Patients with completely resected CG I TNM stages 1 and 2 tumors received no radiotherapy. Patients with completely resected CG I TNM stage 3 and patients with CG-II tumors received conventional external-beam radiation to a total dose of 4,140 cGy. CG-III patients were randomized to receive 5,040 cGy external-beam radiation or hyperfractionated radiotherapy to a dose of 5,940 cGy. It is hoped that hyperfractionation will result in a lower local relapse rate with the potential added benefit of fewer late adverse effects.

In children with small, critically located tumors (such as head and neck, bladder, prostate, vagina), implants may be considered in an attempt to deliver radiation to a restricted volume of tissue with less scatter to adjacent structures [61, 62].

**Chemotherapy**

As in other childhood sarcomas, localized RMS is associated with micrometastatic disease. Prior to combination therapy, surgery alone resulted in survival rates <20%. The development of adjuvant and neoadjuvant therapy has increased survival in patients with localized disease to approximately 60%. Agents with known activity in the treatment of RMS include vincristine (V), actinomycin D (A), doxorubicin (Dox), cyclophosphamide (C), ifosfamide (I), and etoposide (E). Melphalan and cisplatin were evaluated for their potential role in combination chemotherapy for patients with locally extensive or metastatic disease and did not improve outcome compared with other options in the randomized trials involving patients with clinical group III or IV disease [4, 63].

VAC has been the gold standard for combination chemotherapy in the treatment of most cases of RMS. Consecutive large randomized trials have allowed for modifications of this combination tailored to specific subgroups according to clinical group and site of disease. For patients with CG I embryonal histology tumors, results of IRS-III showed equivalent survival for patients treated with VA only versus VAC [4]. In IRS-IV, patients with CG I paratesticular or orbital disease were treated with VA alone for two years. In an IRS-V pilot study, VA chemotherapy is reserved for patients with "low-risk" disease, including: A) Stage 1 CG I/II (N0) orbital, head and neck (non-parameningeal), GU tract (non-bladder/prostate); B) Stage 2 CG I, and C) Stage 1 CG-III (orbit only N0) [64].

As evidence has emerged for the efficacy of etoposide and ifosfamide in RMS therapy [65], there has been an attempt to incorporate these two agents into treatment protocols. IRS-IV included a randomization of VAC versus VAI versus VIE in patients with nonmetastatic RMS. This randomization should permit a direct comparison of the efficacy of equitoxic doses of cyclophosphamide and ifosfamide as well as a comparison of the efficacy of the ifosfamide-etoposide versus the ifosfamide-dactinomycin regimen.

Improving therapy for patients with intermediate-risk disease may be accomplished by the introduction of new agents. Dose intensification using known active chemotherapeutic agents should also be considered. Preliminary IRS-IV results have shown an improvement in failure-free survival for intermediate-risk embryonal RMS, likely related to an increased cyclophosphamide dose [28]. Based on the known sensitivity of RMS to alkylating agents and the premise that the dose-limiting toxicity of vincristine and actinomycin D has already been approached, an IRS-V pilot of vincristine, actinomycin D, and escalating-dose cyclophosphamide for patients with intermediate-risk RMS is being conducted [66].

Dox/cisplatin may have a role in the treatment of some RMS patients when added to the VAC backbone. In IRS-III, addition of Dox/cisplatin to VAC resulted in improved survival for CG-I and CG-II alveolar histology tumors (80% five-year survival estimate) [4]. Patients with CG-III bladder tumors received VAC, dox, and cisplatin with second-look surgery at 20 weeks in IRS-III; coupled with continuation therapy, this strategy resulted in improved survival with a doubling of the bladder salvage rate [4].

Patients with metastatic disease have a poor prognosis despite aggressive therapy. Intensive, multiagent combinations have been utilized in an attempt to improve survival. Upfront therapy with VM, IE, or I-dox followed by VAC has been utilized in IRS-IV for patients with metastatic disease; results have yet to be released [63]. The SIOP has reported a 53% response rate to carboplatin/epirubicin/vincristine in previously untreated patients with metastatic RMS [67].
The use of methotrexate in front-line treatment regimens offers the potential advantages of relative lack of additive myelosuppression and a different mechanism of action. In a phase II trial, Pappo et al. have reported a 33% response rate to high-dose methotrexate in patients with previously untreated, advanced-stage RMS [68].

Topotecan, a camptothecin analog which acts as an inhibitor of topoisomerase I, is being examined for its potential role in RMS. The IRSG has recently reported a 45% response rate to topotecan used in a window setting in newly diagnosed patients with nonparameningeal metastatic RMS [69]. An IRS-V pilot for metastatic RMS is currently evaluating topotecan in combination with cyclophosphamide in an upfront window prior to VAC/radiation therapy [70].

Autologous bone marrow transplantation (ABMT) has been utilized in a variety of childhood solid tumors. To date, the use of ABMT has failed to improve outcome in patients with metastatic RMS [71, 72].

**Outcome**

Figure 6 summarizes treatment outcome (by stage) for IRS-III. Sixty percent to 70% of newly diagnosed patients with nonmetastatic disease can be cured with combined modality therapy. Despite aggressive multimodality treatment, less than 20% of patients with metastatic RMS are currently cured of their disease.

**Late Effects**

As more patients survive for increasingly longer periods of time, potentially serious complications of therapy are becoming more apparent. Patients with bladder or prostate primaries are at risk for bowel complications from surgery or radiation therapy. Poor bladder function, hemorrhagic cystitis, and sex hormone deficiency are also potential concerns [73]. The introduction of ifosfamide into treatment regimens may result in a higher incidence of renal damage, especially in young children [74]. Adriamycin can put patients at risk for the development of a characteristically “late” cardiomyopathy [75]. The use of higher doses of cyclophosphamide may increase the risk for hepatic dysfunction [76].

The development of a second malignant neoplasm is a potentially devastating late complication of therapy. Secondary leukemias linked to etoposide use and bone sarcomas in sites of previous radiation treatment have been reported [77].

**Future Challenges**

For patients with localized disease who have an excellent chance of cure, the development of less toxic therapy has the potential for decreasing long-term morbidity and reducing the risk for secondary neoplasms.

Patients with metastatic disease continue to do poorly despite dose intensification, the use of multiagent chemotherapy, aggressive local control, as well as other strategies, such as ABMT. Although investigational agents continue to be evaluated in a window setting prior to standard therapy in newly diagnosed patients with metastatic disease, it is doubtful whether the addition of supplemental agents with similar mechanisms of action will significantly improve outcome.

*Figure 6. Progression-free survival on IRS-III by clinical group. Patients with completely (CG-I) and grossly totally (CG-II) resected tumors did significantly better than did those with more advanced disease (CG-III). Patients with metastatic disease (CG-IV) had the poorest outcome. Reprinted with permission from [4].*
It is likely that biologic studies exploring the basic molecular mechanisms of tumorigenesis and metastases will lead to novel strategies which we can add to the current armamentarium. Anti-angiogenic agents or agents aimed at specific targets involved in metastatic behavior are potential modalities that are being explored. In animal models, the antiangiogenic agent TNP-470 and an antibody to vascular endothelial growth factor have been shown to inhibit RMS tumor growth [78, 79]. Peptides derived from the PAX3/FKHR fusion protein have been shown to function as tumor antigens for cytolytic T cells in animal studies, raising the possibility of using tumor-specific peptide vaccination as part of an immunotherapy strategy [80]. All of these and newer approaches will require ongoing clinical evaluation to allow continued progress in the treatment of RMS.

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