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Update on rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) is a malignant childhood tumor of mesenchymal origin that currently has a greater than 70% overall 5-year survival. Multimodality treatment is determined by risk stratification according to pretreatment stage, postoperative group, histology, and site of the primary tumor. Pretreatment staging is dependent on primary tumor site, size, regional lymph node status, and presence of metastases. Unique to RMS is the concept of postoperative clinical grouping that assesses the completeness of disease resection and takes into account lymph node evaluation. At all tumor sites, the clinical grouping, and therefore completeness of resection, is an independent predictor of outcome. Overall, the prognosis for RMS is dependent on primary tumor site, patient age, completeness of resection, extent of disease, including the presence and number of metastatic sites and histology and biology of the tumor cells. Therefore, the surgeon plays a vital role in RMS by contributing to risk stratification for treatment, local control of the primary tumor, and outcome. The current state-of-the-art treatment is determined by treatment protocols developed by the Soft Tissue Sarcoma Committee of the children's Oncology Group.

Rhabdomyosarcoma (RMS) is the most common form of soft-tissue sarcoma, accounting for 4.5% of all cases of childhood cancer.[1,2] It is the third most common extracranial solid tumor of childhood after neuroblastoma and Wilms tumor. RMS is a malignant tumor of mesenchymal origin.[1,2] It is included in the group of small blue round cell tumors of childhood along with neuroblastoma, lymphoma, and primitive neuroectodermal tumors.

Epidemiologically, there is a slight male predisposition, and white patients have a greater incidence than African-American ones (rate ratio 1.2). There is also a bimodal distribution for the age at presentation with a peak between 2 and 6 years and then again between 10 and 18 years of age.[3] This reflects the occurrence of the 2 major histologic subtypes of RMS: embryonal (ERMS) and alveolar (ARMS); the incidence of ERMS is greatest at birth and extends through childhood but decreases in adolescence.[1,4] The incidence of ARMS is much lower in young children and is more prevalent in older children and adolescents. ARMS tumors are also most commonly located on the trunk or extremities.

RMS tumor biology

The pathogenesis of RMS remains unclear; however, many hypotheses exist. It is largely thought that RMS arises because of regulatory disruption of skeletal muscle progenitor cell growth and differentiation.[5] Pathogenic roles have been suggested for the MET proto-oncogene, which is involved in the migration of myogenic precursor cells.[6] The overex-

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pression of macrophage migration inhibitory factor has been implicated in oncogenic transformation and tumor progression of RMS.[7] Zibat et al[8] found that the hedgehog pathway was increased significantly in ERMS and fusion gene-negative ARMS compared with fusion gene-positive ARMS. The expression of tumor suppressor gene protein 53 (p53) in RMS is heterogeneous and either wild-type or mutant genes can be found in tumors.[9,10]

ERMS is characterized by a loss of heterozygosity at the 11p15 locus in up to 80% of ERMS tumors. Within this locus lies the insulin growth factor II (*IGF-II*) gene.[11-13] Loss of heterozygosity at this site leads to loss of imprinting, with secondary induction of *IGF-II*.[14] Increased expression of *IGF-II* has been associated with both ERMS and fusion gene–negative ARMS.[15,16] Insulin-like growth factors (IGFs) and their receptor, IGF-1 receptor (IGF1R), have important roles in growth, development, stress response, and cancer. It has been shown that IGF1R antibody leads to rapid cell death and tumor regression in some RMS cells. The antibody-sensitive cells had greater dependence on AKT signaling because expression of IGF1R enhances AKT and Bcl-x(L)–mediated cell survival.[17] Kurmasheva and colleagues[18] demonstrated synergistic growth inhibition by using a combination of an IGF1R antibody with rapamycin. Fu et al[19] suggest that there may be a pathway independent of IGF that is activated by RMS cells. This pathway is thought to be dependent upon p38, and this is regulated by insulin-like growth factor binding protein-6 (IGFBP-6).

Increased copy number of FGFR1 has been associated with gains in chromosome 8 in ERMS and fusion gene–negative ARMS.[20,21] The researchers of another study found somatic NRAS mutations in 20% of ERMS tumor samples but did not find any HRAS or KRAS mutations.[22] Genetic amplification of chromosome 2p24 and 12q13-q14 in ARMS leads to increased copies of a variety of genes, including MYCN and CDK4.[23]

The mammalian target of rapamycin (mTOR) pathway has gained recent interest as the result of its involvement with multiple key cellular pathways in RMS tumors, including cell-cycle regulation, angiogenesis, cell survival, and cytoskeletal organization. Increased phosphoinositide 3-kinase/AKT pathway activity leads to up-regulation of mTOR and has been associated with poor outcomes.[24] Houghton et al[25] reported significant growth inhibition in 2 RMS cell lines by using the mTOR inhibitor, rapamycin.

Translocations of the FKHR transcription factor gene from chromosome 13 with either the PAX3 (chromosome 2) or PAX 7 (chromosome 1) transcription factor genes occur frequently in ARMS.[26-28] In these PAX/FKHR fusions, the DNA binding domain of PAX is combined with the regulatory domain of FKHR. This results in increased PAX activity leading to the de-differentiation and proliferation of myogenic cells.[29,30] PAX3-FKHR fusion is more common than the PAX7-FKHR fusion (55% vs 23%) and is associated with worse overall survival. It has been demonstrated that approximately 25% of ARMS tumors are translocation negative. By gene array analysis these fusion negative ARMS tumors more closely resemble ERMS overall and have a similar prognosis to ERMS.[20,31] It has, therefore, been proposed that tumors should be divided into PAX/FKHR fusion-positive and -negative tumors rather than by the more ambiguous alveolar and embryonal histologies. Although PAX/FKHR translocations are present in ARMS tumor cells, simply deregulating PAX-FKHR expression is not sufficient to cause ARMS. Keller and colleagues[32] found that this oncogenic insult must be coupled with either INK4a/ARF or Trp53 pathway disruption to efficiently cause ARMS.

It is also possible that gene array analysis of primary tumors may provide improved prognostic stratification compared to conventional clinical parameters. Davicioni et al[31] identified an expression pattern of 34 genes that was highly predictive of outcome. It was not highly correlated with individual clinical risk factors, such as patient age, stage, tumor size, or histology, but instead was correlated with the risk classification system used by the children's Oncology Group. Other researchers have found that microRNA-206 expression levels correlate with clinical behavior of RMS.[33] Low microRNA-206 expression correlated with poor overall survival and was an independent predictor of shorter survival in metastatic embryonal and alveolar cases without fusion genes.

Although most cases of RMS occur sporadically, the disease is associated with familial syndromes, including Li-Fraumeni syndrome and neurofibromatosis I. Li-Fraumeni syndrome is an autosomal-dominant disorder usually associated with a germ line mutation of p53.[1] Patients with this syndrome present with RMS at an early age and have a family history of other carcinomas, especially premenopausal breast carcinoma.[34-37] The association of RMS with Li Fraumeni and neurofibromatosis appears to involve malignant transformation through the inactivation of the p53 tumor suppressor gene, and hyperactivation of the RAS oncogene.[38,39]

Findings on autopsy suggest that one-third of children with RMS have congenital anomalies, suggesting that prenatal events may also contribute to tumor development.[40] Although no specific carcinogens been identified, benzenediazonium sulfate has been shown to induce RMS in mice.[41] The use of marijuana or cocaine during pregnancy may be an environmental factor that contributes to the development of RMS.[42,43] There are also ongoing trials in which authors are examining the correlation between birth weight and the risk of RMS.[44]

Presentation and evaluation of RMS

Presentation of RMS

RMS typically presents as an asymptomatic mass found by the patient or the parents of younger children.[2] The most

common sites of primary disease are the head and neck region, the genitourinary tract, and the extremities. The 2 histologic subtypes are associated with lesions in different locations.

ERMS is further divided into spindle-cell and botryoid subtypes. Spindle-cell histology is common in paratesticular lesions, whereas botryoid lesions are generally polypoid masses filling the lumen of a hollow viscus, such as the vagina, bladder, and extrahepatic biliary tree. ERMS tumors occur more frequently in the head and neck region as compared with the extremities and in younger children. ARMS tumors occur in older children and tumors are most commonly located on the trunk or extremities.

Evaluation of the patient with suspected RMS

Patients with suspected RMS require a complete evaluation prior to treatment. Standard laboratory work, including complete blood counts, electrolytes, renal function tests, liver function tests, and urinalysis should be performed. Furthermore, imaging studies of the primary tumor should be performed with computed tomography (CT) or magnetic resonance imaging (MRI). CT is valuable for the evaluation of bone erosion and abdominal adenopathy, whereas MRI frequently provides better definition of the primary tumor and surrounding structures. MRI is preferable for limb, pelvic, and para-spinal lesions. Evaluation for metastatic disease includes a bone marrow aspirate and bone scan, CT of the brain, lungs, and liver, and lumbar puncture for cerebrospinal fluid collection.

Imaging of the primary tumor defines the proximity of the tumor to vital structures and determines size. Proximity to vital structures is important for the determination of whether the tumor can be primarily resected or if neoadjuvant treatment is required to decrease morbidity of resection and increase the chance for complete resection. Tumors that are greater than 5 cm determined by pretreatment imaging have a poor prognosis. Recent evidence would suggest that tumor volume and patient weight may be superior predictors of failure free survival than tumor diameter and patient age in patients with intermediate risk RMS (Rodeberg DAG-H, Norbert, Lyden ER, et al. Prognostic significance and tumor biology of regional lymph node disease in patients with rhabdomyosarcoma: A report from the Children's Oncology Group; unpublished observations, 2010). Evaluation of regional and distant lymph nodes by clinical and radiographic means should be performed. Determination of lymph node involvement is essential as positive regional nodes are irradiated and positive distant nodes are considered metastatic disease. In transit nodes for extremity tumors require evaluation; the incidence of positivity is higher than anticipated and failure to include these nodal basins in the radiation field increases the risk for local/regional tumor failure.[45]

Metabolic imaging using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has become widely used in the adult population with sarcoma to determine the extent of disease.[46,47] There is limited experience in the pediatric population.[48-50] The authors of recent studies have suggested that FDG-PET may be a sensitive and specific tool in the clinical determination of the extent of disease in childhood sarcomas particularly when combined with CT.[49-54] There are several settings in which this imaging modality may improve pretreatment staging and thus alter treatment for patients. FDG-PET may enhance the evaluation of regional adenopathy over traditional cross-sectional imaging modalities. Similarly, FDG-PET may offer improved detection of occult metastases, and persistent viable disease or recurrence in a previously operated field, which is difficult to assess with current imaging methods.

Pretreatment clinical staging

Staging of RMS is determined by the site and size of the primary tumor, degree of tumor invasion, nodal status, and the presence or absence of metastases and is based solely on the preoperative workup of imaging and physical examination. This is expressed in a tumor, nodes, metastases (ie, TNM) classification system, which has been modified for the site of tumor origin (Table 1).

Clinical group

The extent of residual disease after resection is one of the most important prognostic factors in RMS. Patients are assigned to a clinical group based on the completeness of tumor excision and the evidence of tumor metastasis to the lymph nodes or distant organs after pathologic examination of surgical specimens (Table 2). This system differs from TNM staging in that it is a postsurgical staging system. This system provides an important adjunct to the TNM preoperative staging in determining patient risk assessment and prognosis.

Risk stratification

In an effort to tailor the intensity of therapy to patient outcomes, the STS Committee of the Children's Oncology Group has developed a risk-stratification system that incorporates pretreatment staging (based on anatomic site and TNM status) and extent of disease after surgical resection (clinical group). This stratification system is continually changing as new information becomes available but its current format is shown in Table 3.

Patients are divided into low, intermediate, and high risk. This system is a good predictor of patient outcome and allows correlation between intensity of therapy and outcome (Figure 1). For example, overall survival is low and has not improved for patients with high-risk RMS, whereas patients with low-risk RMS have an excellent prognosis. In low-risk patients, investigators are attempting to decrease the intensity of overall therapy by decreasing the duration of therapy and doses of chemotherapeutic agents, without compromis-

Table 1 TNM Pretreatment staging classification

Stage	Sites	T	Size	N
1	Orbit Head and neck (excluding parameningeal) GU nonbladder/nonprostate	T_1 or T_2	a or b	N_0 or N_1 or N_x
2	Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, etc.)	T_1 or T_2	a	N_0 or N_x
3	Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, etc.)	T_1 or T_2	a	N_1
			b	N_0 or N_1 or N_x
4	All	T_1 or T_2	a or b	N_0 or N_1
Definitions	Tumor-			
	$T(site)_1$	Confirmed to anatomic site of origin (a) <5 cm in diameter (b) >5 cm in diameter		
	$T(site)_2$	Extension and/or fixative to surrounding tissue (a) <5 cm in diameter (b) >5 cm in diameter		
	Regional Nodes-			
	N_0	Regional nodes not clinically involved		
	N_1	Regional nodes clinically involved by neoplasm		
	N_x	Clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation)		
	Metastasis-			
	M_0	No distant metastasis		
	M_1	Metastasis present		

GU, genitourinary; TMN, tumor nodes metastases.

ing survival, whereas high-risk patients are receiving more intensive therapy with additional drugs at greater doses.

Treatment of the patient with RMS

Biopsy

Open biopsy of a mass suspected to be malignant should be performed to confirm the diagnosis. Care should be taken to obtain adequate specimens for pathologic, biological, and treatment protocol studies. For small lesions in areas that will be treated with only chemotherapy and radiation or for metastatic disease, open surgical biopsy is the best choice. Core biopsy may not be ideal because of sampling error and insufficient tissue samples. However, image-guided biopsy may increase the accuracy of sampling, particularly if using PET.[55-57] Lymph nodes suspicious for tumor involvement by clinical and radiographic examination should be confirmed pathologically. Sentinel lymph node biopsy is recommended as it may offer a safe and less invasive means of lymph node evaluation for extremity and truncal lesions, although its role in RMS has yet to be assessed, but this will be an upcoming study question.[58-61]

Table 2 Clinical grouping for RMS patients with RMS

Clinical group	Criteria
I	Localized disease, complete resection A. Confined to organ or muscle of origin B. Infiltrating outside organ or muscle of origin; no regional lymph node involvement
II	Compromised or regional resection including:
IIA	A. Gross resection of tumor with microscopic residual tumor
IIB	B. Regional disease, completely resected, with nodal involved and/or tumor extension into an adjacent organ
IIC	C. Regional disease, with involved nodes, gross resection but with evidence of microscopic residual tumor
III	Incomplete resection or biopsy with gross residual disease remaining
IV	Distant metastases present at outset

RMS, rhabdomyosarcoma.

Resection of the mass

The primary goal of surgical intervention for RMS is wide and complete resection of the primary tumor with a surrounding rim of normal tissue. A circumferential margin of 0.5 cm is considered adequate; however, there are minimal data to support this recommendation. Because of these limitations particularly in the head and neck, adequate margins of uninvolved tissue are required unless excision would compromise adjacent organs, result in loss of function, poor cosmesis, or are not technically feasible. All margins should be marked and oriented at the operative field to enable precise evaluation of margins. If a narrow margin occurs, several separate biopsies of "normal" tissue around the resection margin should be obtained to establish clear margins. Communication between the pathologist and surgeon

Table 3 Risk based stratification of patients to guide degree of therapy and prognosis for patients with RMS

Risk group	Pretreatment Stage*	Clinical group	Site†	Histology
Low 1	1 or 2	I or II	Favorable or unfavorable	Embr
	1	III	Orbit	Embr
Low 2	1	III	Favorable	Embr
	3	I or II	Unfavorable	Embr
Intermediate	2 or 3	III	Unfavorable	Embr
	1-3	I–III	Favorable or unfavorable	Alv
High	4	IV	Favorable or unfavorable	Embr
	4	IV	Favorable or unfavorable	Alv

Alv, alveolar rhabdomyosarcoma; Embr, embryonal rhabdomyosarcoma; RMS, rhabdomyosarcoma.
*Pretreatment stage dependent on site of disease.
†Favorable sites: Genitourinary tract, biliary tract, nonparameningeal head and neck, and orbit.

is critical to assure that all margins are accurately oriented and examined. Areas of unresectable residual microscopic or gross tumor should be marked with small titanium clips in the tumor bed to aid radiotherapy simulation and guide subsequent reexcision. Tumors that are removed piecemeal are considered group II even if all gross tumor is thought to be removed by the surgeon.

If only a biopsy of a resectable primary tumor was performed, or a non-oncological operation is performed for tumor removal, or the status of the surgical margins are unclear, pretreatment reexcision (PRE) is advisable. PRE is a wide re-excision of the previous operative site with adequate margins of normal tissue performed prior to the initiation of adjuvant therapy. PRE is most commonly performed on extremity and trunk lesions, but should be considered whenever technically feasible. Outcomes for patients that undergo PRE and are subsequently group I (complete excision) have the same outcome as other patients who are in group I after initial resection.[62]

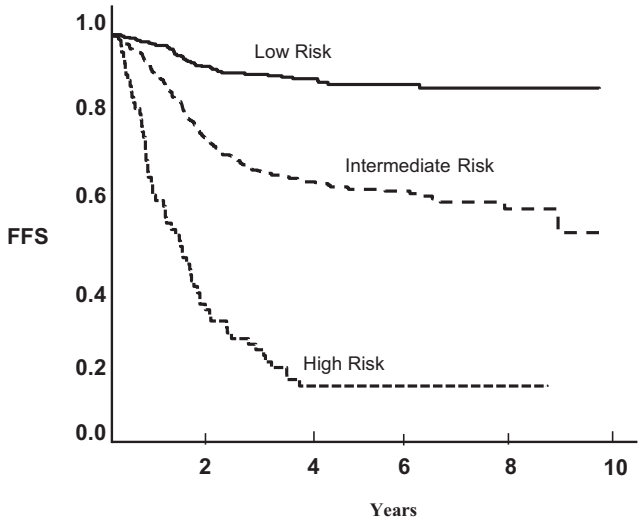

Figure 1 Risk group and survival. Shown is a Kaplan–Meier Survival curve examining survival on the basis of risk stratification. FFS, failure-free survival.

Lymph node sampling/dissection

Lymph node status is an important part of pretreatment staging and directly impacts risk-based treatment strategies in RMS. Regional lymph node disease (N-1) is present in 23% of all RMS patients, predominantly in primary tumor sites, such as the perineum, retroperitoneum, extremity, bladder/prostate, parameningeal, and paratesticular. Positive lymph node status is an independently poor prognostic factor for both failure-free survival and overall survival (Rodeberg DAG-H, Norbert, Lyden ER, et al. Prognostic significance and tumor biology of regional lymph node disease in patients with rhabdomyosarcoma: A report from the Children's Oncology Group; unpublished observations, 2010).[63,64] However, complete lymph node removal has no therapeutic benefit.[65] Clinical and/or radiographic negative nodes do not require pathologic evaluation except in extremity tumors and for children older than 10 years of age with paratesticular tumors.[66,67] In both of these sites the high incidence of nodal disease and false-negative imaging necessitates pathologic evaluation of regional nodal basins. If regional nodes are positive, then distant nodes must be sampled for pathologic evaluation. Tumor identified in these nodes would be considered metastatic disease and would alter therapy.

Second-look operations and resection for recurrence

During, or after completing, adjuvant therapies, patients with RMS are reimaged with CT or MRI. If residual tumor remains, or if the outcome of therapy remains in doubt, a second-look operation (SLO) may be considered. SLO can be performed to confirm and evaluate response, and to remove residual tumor to improve local control.[68] As with the initial operation, the goal of SLO is complete resection of disease without causing loss of function or cosmesis. Data from IRS III suggested that SLO results in the reclassification of 75% of partial responders to complete responders after excision of residual tumors. These operations were most effective in extremity and truncal lesions. Data would

suggest that resection of recurrent RMS confers a 5-year survival of 37% compared to 8% survival in a group of patients without aggressive resection.[69]

Chemotherapy

All patients with RMS receive some form of chemotherapy. Standard therapeutic regimens consist of a combination of vincristine, actinomycin-D, and cyclophosphamide. Although tremendous advances have been made in improving the outcomes of patients with isolated local and regional disease, little progress has been made in improving survival outcomes for children with advanced RMS. The primary limitation has been an inability of new agents and protocols to improve significantly upon standard chemotherapeutic regimens. Dose intensification of vincristine and actinomycin-D is not possible because of their neurotoxic and hepatotoxic adverse effects. Authors who have evaluated dose intensification of cyclophosphamide found that although patients tolerate greater doses, outcomes of intermediate-risk tumors have not shown improvement.[70]

The combination of ifosfamide and etoposide was tested in a phase 2 therapy window in IRS IV. Other chemotherapeutic regimens being developed to treat advanced-stage RMS have incorporated doxorubicin and the topoisomerase inhibitor, irinotecan. Preliminary data from the Children's Oncology Group suggests some benefit from the use of irinotecan and vincristine in patients with progressive disease and/or relapses.[71] Intensified chemotherapeutic regimens with even 5 drug combinations did not improve outcomes in this subgroup of patients.[72]

Radiation therapy

Radiotherapy (RT) is an important treatment option for many children diagnosed with RMS, with both improved local control and outcome. Candidates for RT primarily include those with group II (microscopic residual) or group III (gross residual) disease. The impact of therapy is influenced by the location of the primary tumor and the amount of local disease at the time radiotherapy is initiated.[73,74] Among patients with group II disease, low-dose radiation (40 Gy at 1.5-1.8 Gy/fraction) is associated with local tumor control rates of at least 90%.[75] For patients with group III disease, radiation doses are more commonly 50 Gy.[76] Ongoing studies continue to evaluate the dose of radiation necessary for local control of the tumor. A recent study looking at conservative surgery plus brachytherapy (internal radiotherapy) suggests promising results in conserving structure and function while still providing appropriate oncological treatment.[77]

RT in very young children with RMS poses a unique therapeutic challenge. Concerns with the technical difficulties associated with delivering external-beam radiation in young children and the significant late effects of therapy has led to the development of strategies which reduce the total burden of therapy without sacrificing local control, these include intensity-modulated RT and proton.[78,79]

Specific anatomic sites

RMS is unique among most solid tumors in that it may occur in many different areas of the body. Tumors in different sites may often behave differently and offer unique obstacles to surgical resection.

Head and Neck

Approximately 35% of all RMS arises in the head and neck region. Of these tumors, 75% occur in the orbit. Other sites include the buccal, oropharyngeal, laryngeal, or parotid areas.[80] ERMS more commonly arises in the superior nasal quadrants, whereas ARMS generally originates within the inferior orbit.[81] For all head and neck RMS, biopsy is required for diagnostic confirmation. Resection may be limited by the inability to obtain an adequate margin, therefore, the success of resection is heavily dependent on location with superficial parotid being most amenable to complete resection.[82-84] Lymph nodes that are clinically or radiographically involved must be biopsied to guide the field of radiotherapy for local control. Most tumors in this region are primarily treated with RT and chemotherapy. Outcome correlates strongly with tumor location.

Superficial nonparameningeal

Orbital RMS carries the best prognosis and is least likely to extend to the meninges. Tumors arising in nonorbital parameningeal locations have an increased likelihood of meningeal extension with very poor outcomes.

Parameningeal

Parameningeal RMS includes tumors that arise in the middle ear/mastoid, nasal cavity, parapharyngeal space, paranasal sinuses, or the pterygopalatine/infratemporal fossa region. These tumors are high-risk because of their propensity to cause cranial nerve palsy, bony erosion of the cranial base, and intracranial extension.[85] Wide local excision is recommended but often is not feasible because of the location. For patients with unresected tumors and/or lymph node-positive disease, the use of 3 drug chemotherapy regimens plus radiation may be beneficial. The recognition of poor outcomes associated with meningeal extension led to recommendations for early radiation therapy of primary tumors and adjuvant chemotherapy.[86] Significant concern about the late effects of RT in young children led some clinicians to omit or decrease the dose of radiotherapy, regrettably this practice reduces the prospects for cure.[87]

Trunk, abdominal wall, and chest wall

Trunk

RMS of the trunk comprises 6%-7% of tumors and is associated with a poor prognosis. Complete surgical resection is difficult, particularly when the pleura and peritoneum are involved. Resection may require major chest wall or abdominal wall reconstruction with prosthetic materials or with flaps.[88,89] Poor prognostic features include advanced stage at presentation, alveolar histology, tumor size greater than 5 cm, lymph node involvement, and the inability to undergo a gross total resection.[90,91]

The differential diagnosis for malignant chest wall masses includes Ewing's sarcoma, primitive neuroectodermal tumors, and RMS. Wide local excision of chest wall lesions should have at least a 0.5 cm margin, including the previous biopsy site, involved chest wall muscles and involved ribs. Involved or adherent underlying lung should be resected with a wedge excision. Thoracoscopy may be helpful in determining the extent of pleural involvement and tumor extension to the underlying lung. Reconstruction of the chest wall can be performed using several techniques, including prosthetic mesh, myocutaneous flaps, and titanium ribs. Chest wall lesions have a significantly worse prognosis than other lesions of the trunk with a 1.8-year survival rate of 42%.[88] Although radiotherapy may be beneficial for local control of tumor, this option is associated with significant morbidity, including pulmonary fibrosis, decreased lung capacity, restrictive defects from altered development of the thoracic cavity, and scoliosis without any proven survival benefit.[92]

Biliary Tract

Classically, patients with biliary RMS present at a young age with jaundice and abdominal pain. Gross total resection of biliary tract RMS is rarely possible and is often unnecessary because of favorable outcomes with treatment with chemotherapy and radiation alone[93,94] Biopsy is the only current role of surgery in the treatment of biliary RMS.

Retroperitoneum/pelvis

Retroperitoneal and pelvic lesions are often discovered at an advanced stage and carry a poor prognosis. RMS at this site can envelop vital structures, making complete surgical resection challenging. Neoadjuvant chemotherapy may play a role in tumors that cannot be safely resected at the time of diagnosis. With the exception of group IV metastatic disease, aggressive resection is recommended and has been shown to enhance survival.[95] Patients who have metastatic embryonal RMS and are younger than 10 years of age may also undergo surgical debulking, which has been shown to improve survival only in this subgroup of patients.[96,97]

Perineum/perianal

Perineal tumors are rare and usually present at an advanced stage. Characteristics associated with improved survival include a primary tumor size less than 5 cm, less advanced clinical group and stage, negative lymph node status, and age less than 10 years. Interestingly, histology does not affect overall outcome at this site. Resection can be challenging because of the proximity to the urethra and anorectum. At resection, particular care should be taken to preserve continence. If anorectal obstruction exists, a temporary colostomy may be necessary. Patients presenting in Clinical Group I had 100% overall survival at 5 years compared to 25% for Group IV patients.[98]

Extremity

RMS of the extremity accounts for 20% of all new diagnoses. The majority have alveolar histology and thus a poor prognosis. As with many sites of RMS, complete gross resection at initial surgical intervention is the most important predictor of failure-free survival. The primary goal of local tumor control in extremity tumors is limb-sparing complete resection. Amputation is rarely necessary for tumor excision.[99] Positive regional lymph nodes are found in 20%-40% of patients and are associated with decreased overall survival (46% survival rate for node-positive patients compared to 80% survival for node-negative patients).

Genitourinary: bladder/prostate

RMS of the bladder or prostate typically presents with urinary obstructive symptoms. These lesions are typically of embryonal histology (73%). The major goal of surgery is complete tumor resection with bladder salvage. This can be achieved in 50%-60% of patients.[100,101] Tumors in the dome of the bladder frequently can be completely resected, whereas more distal bladder lesions frequently require ureteral reimplantation or bladder augmentation. Prostatic tumors require prostatectomy, often combined with an attempt at bladder salvage with or without ureteral reconstruction.[102] Continent urinary diversion may be necessary if tumors are unresectable or have a poor response to medical therapy. Lymph nodes are involved in up to 20% of cases. Therefore, during biopsy or resection, iliac and para-aortic nodes should be sampled, as well as any other clinically involved nodes. Further studies are required to find the optimal therapies for bladder/prostate RMS to improve overall survival because these patients may appear to have a distinctive disposition to develop epithelial neoplasms later in life.[103]

Genitourinary: vulva/vagina/uterus

These tumors respond well to chemotherapy with impressive tumor regression that often precludes the need for radical operations like pelvic exenteration. Vaginectomy and hysterectomy are performed only for persistent or recurrent disease. Primary uterine tumors require resection with preservation of the distal vagina and ovaries if they do not respond to chemotherapy. Oophorectomy is indicated only in the setting of direct tumor extension. Prognosis for

this site with only loco-regional disease is excellent with an estimated 5-year survival of 87%.[104]

Paratesticular

Paratesticular RMS generally presents as a painless scrotal mass. Radical orchiectomy via an inguinal approach with resection of the spermatic cord to the level of the internal ring is the standard of care. Open biopsy should be avoided because the flow of lymphatics in this region facilitates spread of the disease. If a trans-scrotal biopsy/resection has been performed, subsequent resection of the hemiscrotum is required. If unprotected spillage of tumor cells occurs during tumor resection, patients are considered Clinical Group IIa regardless of the extent of resection.[105] The incidence of nodal metastatic disease for paratesticular RMS is 26%-43%.[106,107] Patients older than 10 years of age or those with enlarged nodes have a much higher incidence of node involvement.[68] Those patients should, therefore, undergo an ipsilateral retroperitoneal lymph node resection. Suprarenal nodes should be evaluated because positive nodes in this area place a patient in group IV with disseminated metastatic disease. Survival rates are >90% for patients presenting with group I or II disease.[108,109]

Metastatic disease

RMS metastasizes through both hematogenous and lymphatic routes. Children with metastatic RMS have very poor rates of survival. The authors of a recent study evaluated the combination of ifosfamide and doxorubicin for the treatment of children with metastatic disease who are younger than 10 years of age, have embryonal histology, and lack nodal, bone, or bone marrow involvement. This treatment strategy increased 5-year failure-free survival to 28% and 5-year overall survival to 34%.[110] Studies for other subsets of patients have not shown any improvement in survival and more intensive research into chemotherapeutic regimens for group IV disease is required.[111]

Prognosis

The prognosis of patients with RMS depends on many factors. Favorable prognostic factors include embryonal/botryoid histology, primary tumor sites in the orbit and nonparameningeal head/neck region and genitourinary excluding the bladder/prostate regions, a lack of distant metastases at diagnosis, complete gross removal of tumor at the time of diagnosis, tumor size less than or equal to 5 cm, age less than 10 years at the time of diagnosis, and time to relapse.[76,112]

Tumor size is an integral prognostic variable for RMS and plays a major role in clinical grouping.[113] Clinical grouping has also been identified as one of the most important predictors of failed treatment and tumor relapse.[63,76] These factors become important in the designation of treatment groups for risk-based therapy. Group 1 patients generally have overall good prognosis, and studies are underway looking at reduction of therapy.

For patients in group II, studies have shown that alveolar/undifferentiated histology, unfavorable primary sites, regional disease with residual tumor after resection and node involvement had the worst outcomes.[114] Overall prognosis for patients with group II tumors results in 85% survival long-term, indicating that risk-based therapeutic strategies have assisted with achieving failure-free survival.[114]

Patients with group III disease have incomplete resection or biopsy only prior to treatment with chemotherapy and irradiation. Predictors of failure-free survival in group III include tumor size <5 cm, primary sites of orbit and bladder/prostate, and TNM staging equivalent to T1/N0Nx tumors in stage I or stage II. Because radiotherapy is important for local control of group III disease, the incidence of local failure was stratified by radiotherapy dosing (<42.5 vs 42.5-47.5 vs >47.5 Gy) and was not significantly different among these dose ranges.[115]

Approximately 15% of patients with RMS present with metastases (group IV) at the time of diagnosis.[116] Patients in this group have poor outcomes despite aggressive multimodality treatments with only 25% expected to be free of disease three years after diagnosis.[116,117] A review of prognostic factors and outcomes for children and adolescents with metastatic RMS in IRS-IV found that three-year overall survival and failure-free survival was improved if there were 2 or fewer metastatic sites and the histology of the tumor was embryonal.

Studies have shown that time to relapse had significant influence on prognosis in relapsed RMS. It influences survival independent of other features, such as type of relapse, histology, tumor site, primary treatment time or irradiation in primary treatment.[112]

Multimodal therapy has improved outcomes of the vast majority of children diagnosed with RMS. However, little if any progress has been made in the treatment of high-risk RMS tumors and future clinical trials will focus on the molecular biology driving RMS tumor behavior, which may assist with developing customized clinical therapies that will improve outcome and failure-free survival in these patients.

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