Rhabdomyosarcoma

114

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Rhabdomyosarcoma (RMS) is a malignant tumor of mesenchymal origin. RMS is the most common pediatric soft tissue sarcoma accounting for approximately 5% of childhood cancers. It is the third most common extracranial solid tumor in the pediatric population, with an estimated 350 new cases diagnosed each year in the US. Epidemiologically, RMS shows a male predominance with an increased incidence in Caucasians. There is a bimodal age of distribution with the first between 2 and 6 years and a second between 10 and 18 years of age that correlates with the incidence of the two primary histological disease types. Embryonal rhabdomyosarcoma (ERMS) is more common in birth and early childhood, while alveolar rhabdomyosarcoma (ARMS) typically presents in later childhood and adolescence. RMS can develop throughout the body. The genitourinary tract (30%) and head and neck region (parameningeal 25%) are predominately ERMS histology. Extremities are the next most common site (10–15%) and commonly demonstrate alveolar histology. The majority of ARMS feature FOXO1 translocations, and fusion status has been incorporated into the most recent Children's Oncology Group (COG) risk stratification classification. Large cooperative group trials featuring multimodality therapy have dramatically improved overall RMS 5-year survival to >70%.

The vast majority of RMS are sporadic in nature. RMS is the most common pediatric cancer in Li–Fraumeni syndrome, which has been linked to a germline mutation of *TP53*. Patients with Li–Fraumeni often present with RMS at an early age and are predisposed to other malignancies, including premenopausal breast cancer, acute leukemia, soft tissue and bone sarcoma, and adrenocortical carcinoma. Other syndromes associated with RMS include neurofibromatosis type 1, *DICER1* syndrome, Beckwith–Wiedemann syndrome, Noonan syndrome, and Costello syndrome.

Histology and Tumor Biology

RMS is thought to originate from skeletal muscle or pluripotent mesenchymal stem cells secondary to the disruption of cell growth and differentiation. Immunohistochemistry will demonstrate staining for markers of striated muscle differentiation, including desmin, myoD1, and myogenin. RMS was historically stratified based upon its histologic characteristics with the overwhelming majority demonstrating embryonal or alveolar histology. ERMS is characterized by primitive to small round blue cells with scattered rhabdomyoblasts and a subset demonstrating botryoid patterning characterized by clusters of small, sessile, or pedunculated nodules. ERMS comprise 60–70% of all RMS and commonly arise in the head/neck, genitourinary, and biliary systems. ARMS account for 20–30% of all cases and feature an alveolar pattern of histology with sheets of medium-sized and scattered giant cells. ARMS typically develop in the extremities, trunk, and perineum. Less common histologic variants include spindle cell/sclerosing (~2%) and pleomorphic subtypes. Spindle cell has a predilection for arising at the paratesticular site while pleomorphic RMS most commonly arises in the extremities. ARMS histology is a negative prognostic feature compared to ERMS histology, as reflected by poorer event-free survival (EFS) or implementation of more aggressive treatment regimens to achieve similar outcomes.

Molecular profiling has supplanted histology in risk stratifying RMS in the current COG ARST1431 trial. The majority (80%) of histologic ARMS tumors feature translocations that express oncogenic fusion proteins featuring PAX3 or PAX7 DNA-binding domains fused with the regulatory domain of FOXO1, while ERMS express no fusion protein and commonly feature allelic loss of 11p15.5. Fusion status is determined using RT-PCR or fluorescence in situ hybrid-

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ization (FISH). Twenty percent of RMS with alveolar histology (ARMS) lack PAX3 or PAX7/FOXO1 translocations. Despite their histologic appearance, these fusion-negative RMS (FNRMS) behave more similar to ERMS with frequent loss of heterozygosity at 11p15.5 and comparable OS and EFS. Despite their genetic and prognostic differences, fusion-positive RMS (FPRMS) and FNRMS show similar molecular aberrations with activation of RAS and PI3K signaling pathways and suppression of p53.

Diagnosis

RMS usually presents as an asymptomatic mass. Depending on the location of the primary site, patients may present with signs and symptoms related to mass effect or complications secondary to the tumor. Histological subtype also varies according to primary tumor site. ARMS is more commonly seen in the trunk and extremities, and ERMS is more prevalent in the head/neck and genitourinary system.

Workup

Evaluation of the patient with suspected RMS should include a comprehensive laboratory workup including CBC, LFTs, renal function tests, electrolytes, and urinalysis. Imaging studies should include CT or MRI of the primary tumor site to assess for size and involvement of surrounding structures or vital organs (Table 114.1). Pretreatment imaging of the primary tumor is essential to determine if resection is possible without significant morbidity or if there is a need for neoadjuvant treatment prior to resection.

Table 114.1 Workup for RMS patients

Patients	Diagnostic study
All patients	CBC with differential Renal and liver function tests Urinalysis Chest X-ray MRI or CT primary site Biopsy
Intermediate risk[a] High risk[a]	Chest CT Bone marrow aspirate Bone scan
Clinically involved lymph nodes	Lymph node sampling
Extremity RMS	Sentinel lymph node biopsy
Parameningeal RMS	CSF cytology MRI brain/skull base

[a]Consider PET CT scan in patients with possible lung, bone or nodal involvement

Clinical and radiographic evaluation of regional lymph nodes should be done in the pretreatment stage, as these results guide staging and therapeutic interventions. Enlarged nodes found on clinical examination or imaging (CT, MRI, and PET) should be biopsied to confirm involvement. However, the absence of these radiographically abnormal findings does not reliably rule out the presence of micrometastatic lymph node involvement. Positive lymph nodes in the regional basin will extend the recommended radiation treatment fields to the affected areas but do not mandate a completion lymphadenectomy. Positive lymph nodes distant to the regional basin are considered a metastatic disease.

Staging of RMS is complex as its behavior is dependent upon its molecular profile, histology, primary site, and age. Intergroup rhabdomyosarcoma study group (IRSG) has historically required staging with CT chest, bone scan, and bilateral bone marrow biopsies for all enrollees. A recent COG trial demonstrated that bone marrow biopsy and bone scan might be safely omitted in patients with low-risk diseases. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is also recommended by current COG RMS protocols. A systematic review of FDG-PET purports 80–100% sensitivity and 89–100% specificity compared with conventional imaging strategies. The utility of FDG-PET for diagnosis of lymphatic disease has been called into question by a prospective trial of SLNB in combination with FDG-PET in the management of pediatric or young adults with soft tissue sarcoma that demonstrated that FDG-PET only had a positive predictive value of 29% and a negative predictive value of 79%. As such, FDG-PET is currently recommended as part of the initial staging of COG protocols, but the utility of these studies in defining locoregional disease burden is unclear. CT abdomen and pelvis is recommended for lower extremity and GU primary tumors. MRI of the skull base and brain and a lumbar puncture with CSF collection is recommended for parameningeal primary tumors.

Staging

Pretreatment staging of RMS is done based only on preoperative physical examination and imaging studies. RMS is somewhat unique in that the anatomic site of the primary tumor is an important but not the only factor in determining the stage of the tumor. Site, size and invasiveness of tumor,

Table 114.2 TNM pretreatment staging system

Stage	Site of primary tumor	T stage[a]	Tumor size	Regional lymph node involvement[b]	Distant metastasis
1	Favorable site-orbit; nonparameningeal head and neck; genitourinary other than bladder, prostate, or kidney; biliary tract	T1 or T2	Any size	N0, N1, NX	No
2	Unfavorable site-bladder/prostate, extremity, parameningeal, trunk, retroperitoneum (any site other than favorable)	T1 or T2	≤5 cm	N0 or NX	No
3	Unfavorable site-bladder/prostate, extremity, parameningeal, trunk, retroperitoneum (any site other than favorable)	T1 or T2	≤5 cm	N1	No
			>5 cm	N0, N1, NX	
4	Any site	T1 or T2	Any size	N0, N1, NX	Yes

[a]T stage: *T1* tumor confined to organ or tissue of origin (noninvasive), *T2* tumor extension beyond organ or tissue of origin (invasive)
[b]Regional lymph node involvement: *N0* no clinical regional lymph node involvement, *N1* positive clinical regional lymph node involvement, *NX* unknown regional lymph node involvement/not examined

clinical nodal status, and the presence or absence of metastatic disease determine tumor stage (Table 114.2). The pretreatment staging is used as part of risk stratification to determine recommended chemotherapy in accordance with COG guidelines.

Clinical Group

Grouping of patients with RMS is done following surgical resection and after pathologic analysis has taken place. Residual disease after surgical resection is one of the most important prognostic factors in RMS. Patients are grouped based on pathologic evaluation of specimens evaluating margin of resection, nodal involvement, and evidence of tumor metastasis. The clinical group is used to determine the need for radiation therapy and is a part of overall risk stratification to determine recommended chemotherapy protocols. Group 1 means no regional nodes and complete tumor excision with a negative margin. Group 2 means microscopic residual after excision or positive regional nodes. Group 3 have gross residual after resection or biopsy-only. Group 4 have metastatic disease (Table 114.3).

Table 114.3 Children's Oncology Group clinical group classification

Group	Definition
I	Localized tumor, completely resected with microscopically clear margins and no regional lymph node involvement
II	Localized tumor resected with microscopic residual disease; regional disease with involved regional lymph nodes, completely resected with or without microscopic residual disease
III	Localized tumor with gross residual disease after biopsy or subtotal resection
IV	Distant metastasis present at diagnosis

Risk Stratification

The Soft Tissue Sarcoma Committee of the Children's Oncology Group (STS-COG) developed a risk stratification system for RMS. The risk stratification system uses the pretreatment TNM staging, clinical group classification, fusion status, and age to distribute patients into low-, intermediate-, and high-risk tiers (Table 114.4). This risk stratification is used to determine the recommended chemotherapeutic regimen.

Table 114.4 New rhabdomyosarcoma risk stratification classification with fusion status

Risk group	Stage	Group	Age	Fusion	Therapy
Low	1	I–II			VACx4, VAx4 24 weeks
	1	III (orbit)	Any	FOXO1−	
	2	I–II			
Intermediate	1	III (non-orbit)	Any	FOXO1−	VAC/VI +/− TEM 42 weeks
	3	I–II		FOXO1−	
	2–3	III		FOXO1−	
	1–3	I–III		FOXO1+	
	4	IV	<10 year	FOXO1−	
High	4	IV	>10 year	FOXO1−	VAC/VI+?
			Any	FOXO1+	

Treatment

The standard of care in the treatment of patients with RMS is a multimodal approach that includes surgical resection, systemic chemotherapy, and radiotherapy (XRT). Cure rates for RMS have improved drastically from 25% in the 1970s to more than 70% in the 1990s. Current studies aim to improve or maintain the high EFS of low-risk patients while reducing the intensity and duration of therapy.

Biopsy

Masses that are thought to be malignant but unresectable without considerable morbidity at presentation should undergo a biopsy to confirm the diagnosis, taking care to obtain adequate tissue samples for diagnosis, biological, cytogenetic, and treatment protocol studies. The biopsy tract (open or core) should be planned such that it may be easily excised at a future resection. Trials validating core needle biopsy in RMS specifically are currently lacking. Bladder, prostate, and vagina primary sites may be amenable to endoscopic biopsy techniques.

Surgical Resection

Once the diagnosis of RMS is confirmed pathologically, the mainstay of surgical treatment is complete and wide resection of the mass with a circumferential margin of at least 0.5 cm. Morbid or disfiguring procedures should not be performed. Complete marginal resection is particularly difficult in the head and neck region and retroperitoneum. Primary resection of large pelvic rhabdomyosarcomas that present with partial bowel and bladder obstruction is usually delayed due to the anticipated morbidity of undertaking a complete resection of this particular pelvic tumor

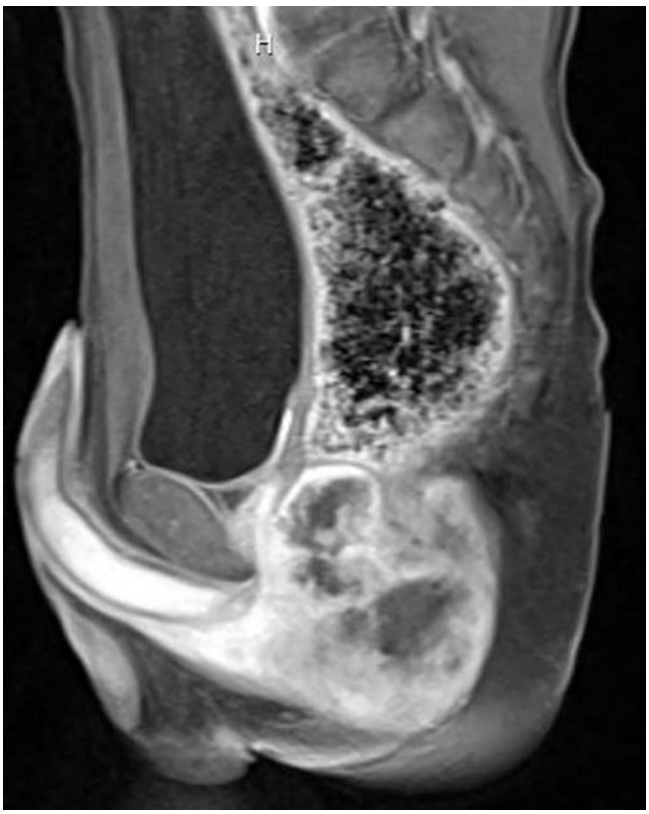

Fig. 114.1 Pelvic rhabdomyosarcoma resulting in partial bowel and bladder obstruction

(Fig. 114.1). All margins of the specimen should be marked to allow for precise evaluation of margins. If microscopic or gross residual disease occurs, the surgical bed should be marked with clips to guide future XRT. Piecemeal removal of the tumor is considered clinical group II even if all gross disease is removed.

Nodal Sampling

Lymph node involvement in patients with RMS is an independent poor prognostic factor. Regional lymph nodes should be pursued when tumors have risk factors for lymph node metastasis, or suspicion is raised by imaging or physical examination findings. RMS-specific high-risk features for nodal spread include extremity and trunk sites, paratesticular RMS in children >10 years of age, and larger tumors (≥5 cm or invasive into surrounding tissues). Regional lymph node disease is present in ~25% of patients with extremity RMS. Sentinel lymph node biopsy (SLNB) is recommended for extremity and trunk RMS. We inject both radioisotope and blue dye to facilitate sentinel node localization. The initial subcutaneous injection is performed 2–4 h prior to the planned biopsy in four quadrants around

the tumor with ^{99m}Tc in the nuclear medicine suite. We have found CT lymphoscintigraphy to be helpful for anatomic localization of the draining nodal basin (Fig. 114.2a, b). Isosulfan blue and a hand-held gamma probe are used in the operating room to guide dissection. Maximal field counts are obtained, and the hand-held probe is used to guide the resection of lymph nodes until gamma counts are <10% of the maximum. Nodes are sent fresh to pathology, where a specific protocol with 100 μm sectioning is performed. Indocyanine green (ICG) has an evolving role in SLNB demonstrating superior sentinel lymph node detection to blue dye (Fig. 114.3a, b). Select studies in melanoma have demonstrated increased sentinel node positivity by using the combination of ICG and ^{99m}Tc.

Patients with paratesticular tumors >10 years of age have a 40% incidence of nodal disease and COG protocols require unilateral retroperitoneal lymph node sampling (RPLNS). Open or laparoscopic approaches are both acceptable with greater than six to seven nodes to be harvested. A recent query of the SEER data (Walterhouse et al. 2018) demonstrated low rates of lymph node sampling (45–50%) in patients with paratesticular RMS >10 years of age. Failure to perform a lymph node excision in this population is associated with significantly worse 5 year overall survival (>90% vs. 60–65%, Lobeck et al. 2017).

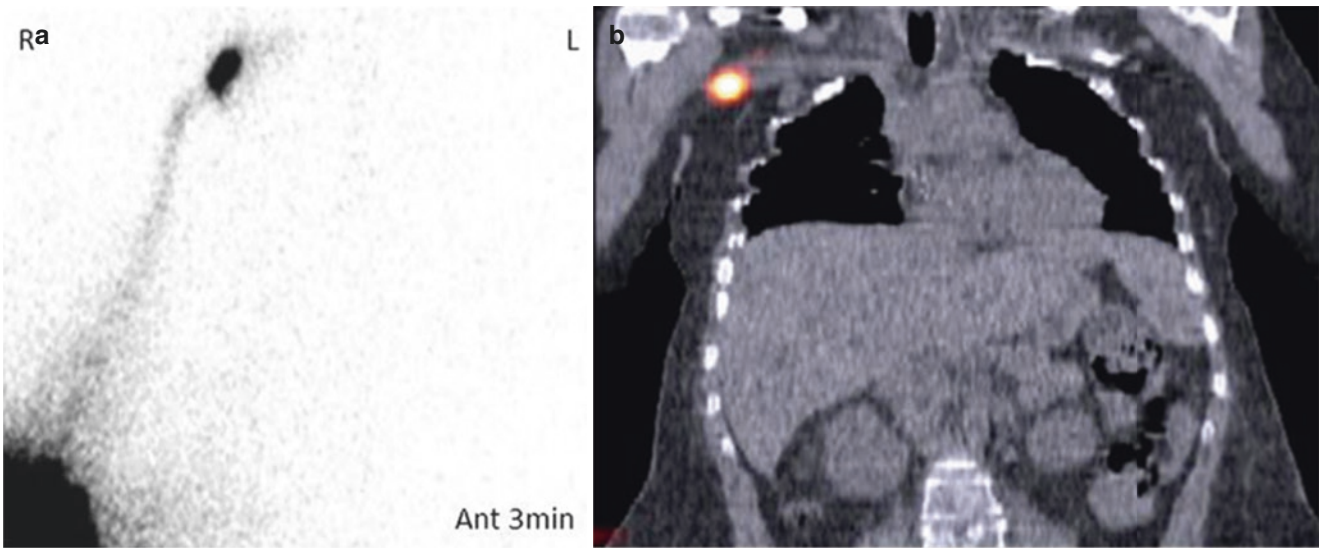

Fig. 114.2 Comparison of (**a**) lymphoscintigraphy and (**b**) CT lymphoscintigraphy

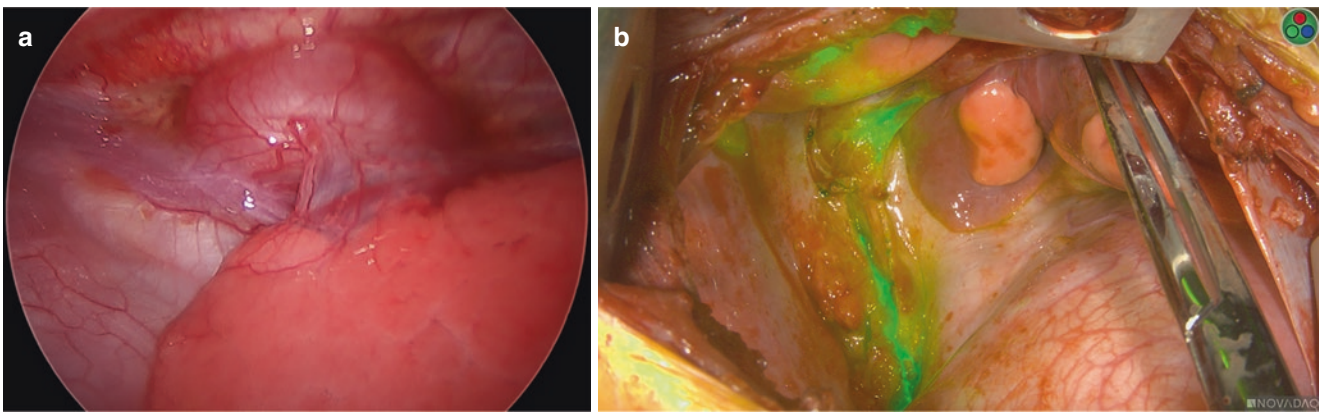

Fig. 114.3 (**a**) Thoracoscopic resection of mediastinal lymph node in a patient with thoracic rhabdomyosarcoma. (**b**) Utilization of ICG for intraoperative lymph node detection

Pretreatment Re-excision

Pretreatment re-excision (PRE) should be considered in instances where surgical margins were not clear, a nononcologic procedure was performed, or only a biopsy was performed. PRE consists of wide local re-excision with the goal of achieving negative margins prior to the beginning of adjuvant therapy. PRE is most commonly performed in extremity and trunk RMS but should be done whenever technically possible. Patients with RMS undergoing PRE and achieving group I status have the same outcome as patients with negative margins on initial presentation. In general, there is no role for tumor debulking in RMS.

Delayed Primary Excision

Delayed primary excision (DPE) for patients with RMS should be considered during or after induction of chemotherapy. The goal of DPE, as with primary resection, is to achieve complete (R0) or microscopic residual (R1) resection of disease without compromising form or function. Better results are seen in the extremity and trunk than in head/neck primaries. A recent STS-COG trial (Rodeberg et al. 2015) demonstrated that implementation of DPE following 12 weeks of induction chemotherapy permitted dose reduction of radiation therapy (R0–36 Gy; R1–41.4 Gy) with comparable local control outcomes to historical results with radiation therapy alone (50.4 Gy). DPE also plays a role in recurrent RMS, with re-excision conferring a 5-year survival benefit over patients who did not undergo an operation (37% vs. 8).

Site-Specific Considerations

Extremity

Complete resection is the most important predictor of failure-free survival (FFS), and primary resection or PRE should be pursued without compromising form or function. Regional lymph node involvement occurs in >20% of extremity RMS and is associated with worse outcomes. The regional, and when applicable, in-transit nodes must be evaluated to ensure appropriate risk stratification. All extremity RMS should include surgical evaluation of regional lymph node basins (inguinal or axillary). Distal extremity lesions require a staging of in-transit nodes (popliteal, epitrochlear, brachial, etc.).

Bladder/Prostate

Few bladder/prostate RMS are amenable to upfront resection. Recent pooled analysis demonstrated that upfront resection was only attempted in 12% of patients, and gross resection was only achieved in 5% of those cases. As such, the majority of bladder/prostate RMS are treated with upfront chemotherapy. DPE may be feasible to permit XRT dose reduction. Overall, bladder preservation is achieved in approximately 80% of patients, but only 40% maintain normal bladder function. For unresected lesions, a residual mass at the end of all planned therapy may be present. Lautz et al. (2021) demonstrated that this mass is usually composed of well-differentiated rhabdomyoblasts, and surgical resection is not indicated.

Female Genital Tract

RMS arising from the vulva, vagina, or uterus is typically managed with a biopsy. Upfront radical surgery is not indicated. Neoadjuvant chemotherapy and adjunctive radiation (or brachytherapy) for residual disease (Group II or III) result in excellent 5-year survival rates. Omission of radiation therapy in ARST0331 for group III vaginal RMS, in conjunction with reduced cyclophosphamide dosing, resulted in increased local recurrence (3-year FFS of 57% vs. 77%).

Paratesticular

Paratesticular RMS should be removed by radical orchiectomy through an inguinal approach with proximal vascular ligation and resection of the spermatic cord. Trans-scrotal biopsy is contraindicated due to concern for increased local recurrence and tumor dissemination to both the inguinal and iliac lymph nodes. Trans-scrotal biopsy still occurs in up to 25% of cases. Hemiscrotectomy has historically been pursued when trans-scrotal biopsy or resection occurred, but a recent trial from the Cooperative Soft Tissue Sarcoma Group demonstrated no difference in 5-year EFS when hemiscrotectomy was completed in the setting of a trans-scrotal resection. The most recent COG guidelines do not recommend hemiscrotectomy for scrotal violation at biopsy or resection, and hemiscrotectomy is only recommended for gross tumor invasion at the time of initial tumor resection. Paratesticular RMS in males >10 years of age has a 40% incidence of nodal disease and COG protocols require unilateral RPLND.

Radiotherapy

Radiotherapy is essential to the multimodal treatment of RMS. XRT is indicated to improve local control for patients with microscopic (Group II) or gross (Group III) residual tumor in FNRMS and in all patients with FPRMS. XRT can be omitted for children with localized and completely excised FNRMS.

Dosage and timing of RT are based on anatomic site, the extent of residual disease, and lymph node involvement. Initiation of RT ranges from 6 to 12 weeks after the beginning of chemotherapy, except in patients with parameningeal RMS with intracranial extension in which earlier XRT confers better local control. XRT dosing ranges from 41.4 Gy for microscopic residual disease (Group II) to 50.4 Gy for patients with gross residual disease (Group III).

Systemic Therapy

The mainstay of chemotherapy in patients with RMS is a combination of vincristine, actinomycin-D, and cyclophosphamide (VAC) regardless of risk stratification. A recently completed trial found that a decrease in the overall length of therapy and cumulative cyclophosphamide dosing could be accomplished in a subset of low-risk RMS without compromising FFS. A VAC backbone is also used in intermediate-risk patients. ARST0531 compared standard VAC chemotherapy to a regimen alternating VAC with vincristine and irinotecan (VAC/VI). The VAC/VI regimen decreased hematologic toxicity and lowered cumulative cyclophosphamide dose while providing similar outcomes (Casey et al. 2019). Current intermediate-risk trials are evaluating the efficacy of adding temsirolimus to a VAC/VI regimens. High-risk RMS continues to be challenging to treat. VAC chemotherapy remains the standard of care in this subgroup. ARST0431 combined dose intensification by interval reduction to allow maximal early exposure to known effective agents and use irinotecan as a radiation sensitizer. Improved EFS was reported in a subset of patients with high-risk RMS and 0–1 Oberlin risk factors (age <1 or ≥10 years, bone or bone marrow disease, unfavorable primary site, ≥3 metastatic sites).

Outcomes

Multiple factors dictate the prognosis and outcomes of patients with RMS. Favorable prognostic factors include age less than 10, tumor size less than 5 cm, embryonal histology, fusion-negative status, favorable primary tumor site (orbit, non-parameningeal head/neck, bladder/prostate), and non-metastatic disease. Complete gross surgical removal at the time of diagnosis has been shown to be a positive prognostic factor. Patients with completely resected disease (group I) have an overall good prognosis (90% survival). In patients with the regional disease (group II), the overall long-term survival is 85%; however, the presence of alveolar histology, fusion positivity, residual tumor, or nodal involvement is associated with a worse prognosis. Metastatic disease (group IV) is seen in approximately 15% of RMS patients at initial diagnosis with an estimated 3-year EFS of 25% despite multimodal therapy (Table 114.5).

Table 114.5 RMS overall survival

Risk stratification	Overall survival (%)
Low risk	90
Intermediate	60–80
High	20–40

Editor's Comments

Rhabdomyosarcoma arises from a mesodermal pluripotent cell but does not necessarily develop within skeletal muscle. Unlike most other tumors, the prognosis and approach to treatment of rhabdomyosarcomas vary greatly depending specifically on the site of origin, with certain sites being considered favorable and others unfavorable. This characterization mostly correlates with the histologic subtype—tumors that arise in favorable sites are usually embryonal, while those from unfavorable sites are typically alveolar. Rhabdomyosarcomas that arise within hollow organs (bladder, vagina, nasal cavity, biliary tree) are often described as botryoid (*cluster of grapes*), which is a subtype of embryonal rhabdomyosarcoma and associated with the best prognosis. Age is also an important prognostic factor, mostly because it correlates with histology and site of origin—in general, children <1 or ≥10 years old have a worse prognosis.

Like other small round blue cell tumors (lymphoma, Ewing/PNET, neuroblastoma), rhabdomyosarcomas tend to metastasize to the bone marrow, which is why bone marrow biopsy is usually performed as part of the initial workup for intermediate- and high-risk tumors. Tumors in favorable sites that are not amenable to complete surgical resection are treated with biopsy. Complete resection with margin is important, as long as it is not mutilating, since it allows lower doses (and fewer late effects) of radiation. Tumors arising in unfavorable sites, on the other hand, require sometimes elaborate attempts at local control with either aggressive surgery or, if surgical resection is not feasible or safe, external beam radiation. Multiple operative attempts to render the patient free of tumor might be reasonable in certain situations.

For certain sites, such as an extremity or the trunk, sentinel lymph node biopsy might be requested. The technique is straightforward and starts with lymphoscintigraphy. Some still use injection of a vital dye as well. Often two lymph nodes are identified, sometimes in different nodal regions (popliteal and inguinal), both of which need to be excised. At delayed primary excision (DPE), the scar and all tissue planes violated at the previous operation must be excised with a margin, which can result in a significant soft tissue defect. Entering the previous site increases the risk of recurrence but can be difficult to avoid even with preoperative high-resolution three-dimensional imaging. An ideal margin is at least 1 cm, but if the tumor is adjacent to vital structures or bone, any negative tissue fascia plane is acceptable. As a general rule, debulking of an unresectable tumor is neither beneficial nor recommended. (Resection to achieve microscopic margins (R1) is different and can help reduce the radiation dose.)

Botryoid tumors arising from the vagina should be biopsied and treated with chemotherapy. Mutilating surgery is almost never indicated in this site and the prognosis is usually excellent. Biliary rhabdomyosarcoma also carries a relatively good prognosis. Biopsy can be performed by common duct exploration or through the cystic duct after cholecystectomy. At planned reoperation, we have used choledochoscopy to confirm the absence of residual tumor after chemotherapy. Depending on the stage and extent of disease, some of these patients will also require liver resection or the addition of radiation therapy. Extremity tumors often occur in adolescents, are usually alveolar, and carry a guarded prognosis. Although therapy to control the primary tumor must be aggressive, limb salvage should be considered whenever possible.

Further Reading

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