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Featured Articles

Update on pediatric rhabdomyosarcoma: A report from the APSA Cancer Committee

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ABSTRACT

Background/Purpose: Rhabdomyosarcoma is the most common soft tissue sarcoma in children and young adults and requires multimodality treatment. The purpose of this review is to present an update on risk stratification as well as surgical and medical management strategies in pediatric rhabdomyosarcoma.
Methods: A comprehensive review of the current literature on pediatric rhabdomyosarcoma, including the most recent Children's Oncology Group studies and several international collaboratives, was performed by the authors and key findings were summarized in the manuscript.
Results: FOXO1 fusion status is a stronger prognostic factor than histology and is now used for risk stratification in treatment protocols. For assessment of regional nodal involvement, FDG-PET-CT shows poor sensitivity and specificity to detect histologically confirmed nodal metastasis. Thus, surgical assessment of regional lymph nodes is required for rhabdomyosarcoma of the extremities or trunk as well as paratesticular rhabdomyosarcoma in patients ≥10 years of age, although adherence to surgical guidelines remains poor. Hemiscrotectomy performed for scrotal violation in paratesticular rhabdomyosarcoma has not shown an improvement in event free survival and is not recommended.
Conclusions: Surgical and medical treatment strategies for rhabdomyosarcoma in children continue to evolve. This review provides current evidence-based treatment standards with an emphasis on surgical care.
Type of Study: Review.
Level of Evidence: Level IV.

Contents

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Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and young adults with approximately 350 cases diagnosed annually in the United States [1]. Long-term survival in children with localized RMS now exceeds 70% with multi-modal treatment. However, little progress has been made in the treatment of children with metastatic and recurrent disease, whose outcomes remain poor despite aggressive multimodal treatment [2–5]. In addition, in the most recently completed Children's Oncology Group (COG) intermediate-risk study, ARST0531, increased rates of local failure were noted, possibly due to multiple factors including reduced cyclophosphamide dosing [6]. Finally, as more patients survive longer, there is a greater understanding for the late effects caused by RMS treatment. In this summary, we review the most recent literature from prospective cooperative group studies with specific focus on the role of surgical care in children with RMS.

1. Rhabdomyosarcoma classification: Histology and fusion status

RMS is classified into embryonal (ERMS) and alveolar (ARMS) histology. ERMS accounts for 60–70% of childhood RMS and is the predominant subtype in younger children and in head, neck, and genitourinary locations [7,8]. ARMS occurs more often in older children and in tumors of the extremities, trunk, and perineum/perianal region. Approximately 70–80% of ARMS are characterized by translocations between the FOXO1 gene on chromosome 13 and either the PAX3 gene on chromosome 2 (t(2;13)(q35;q14)) or the PAX7 gene on chromosome 1 (t(1;13)(q36;q14)) [9,10]. The presence of PAX-FOXO1 fusion drives unfavorable outcomes in children with RMS, and is clinically and biologically different from fusion-negative ARMS and ERMS [11–14]. Fusion-negative ARMS have been shown to have similar gene array analysis and prognosis to ERMS, which are fusion negative [12]. PAX/FOXO1 fusion status is recognized as a more important prognostic factor compared to histologic subtypes, and now will be utilized instead of histology for risk stratification in current and future treatment protocols [15].

2. Risk stratification

Risk stratification in RMS is essential for determining appropriate treatment regimen and involves assignment of a pretreatment clinical stage and postoperative clinical group [5,16]. Pre-treatment staging uses the TNM based system that incorporates the site of the primary tumor, tumor size (widest dimension), tumor invasion of surrounding tissues, regional nodal involvement, and distant metastasis [17,18] (Table 1). Clinical group is determined by the outcome of the initial tumor resection or biopsy, with pathologic assessment of tumor margins, regional lymph node involvement, and presence of distal metastasis [19,20] (Table 2). Tumors that are removed piecemeal are group II even if all gross tumor is resected. The extent of residual disease is one of the most important prognostic factors in RMS, therefore surgical decision making at the initial resection plays an essential role in assigning a clinical group.

Six COG trials (D9602, D9802, D9803, ARST0331, ARST0431, and ARST0531) with a total of 1727 patients were collectively reviewed to examine risk stratification with FOXO1 status in addition to established clinical outcome predictors. The most significant prognosticator of outcome was metastatic disease at diagnosis. 5-year event free survival (EFS) and overall survival (OS) for patients with localized disease (group I, II, III) were 73% and 84%, compared to 30% and 42% with metastatic disease (group IV). However, FOXO1 fusion status was the next strongest prognostic factor in both localized and metastatic disease. For localized disease, fusion-positive patients had 5-year EFS and OS of 52% and 65% compared to 78% and 88% for fusion-negative.

Table 1
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 >5 cm	N1 N0, N1, NX	No
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.

Table 2
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

For metastatic disease, fusion-positive patients had 5-year EFS and OS of 6% and 19% compared to 46% and 58% for fusion-negative. Based on these data, new risk groups incorporating FOXO1 status were adopted as shown in Table 3 [15].

3. Role of FDG-PET-CT imaging in RMS

Positron emission tomography with ^{18}F-fluorodeoxyglucose scans combined with CT (FDG-PET-CT) uses size and metabolic characteristics of tissue to identify tumor and is an attractive modality to assess regional or metastatic disease not seen by other imaging modalities [21]. FDG-PET-CT is recommended on current COG RMS protocols, however the data on its utility is conflicting [22–26]. A systematic review of 272 patients with RMS in 8 studies found a high sensitivity (80–100%) and specificity (89–100%) with FDG-PET-CT compared to conventional cross-sectional imaging in identifying positive regional nodal disease in RMS [27]. However, studies comparing FDG-PET-CT to sentinel lymph node biopsy (SLNB) with histological confirmation showed only a sensitivity of 57% and specificity of 52%. This prospective study of 28 pediatric and young adult patients compared preoperative FDG-PET-CT imaging with SLNB. This study found that 3 of 7 patients with proven disease on SLNB had normal FDG-PET-CT imaging, and of the 14 FDG-PET-CT positive patients, only 4 of these were proven to have nodal disease, concluding a positive predictive value of 29% and negative predictive value of 79%. [28]. Thus, although recommended, the role of FDG-PET-CT is currently inconclusive regarding how it should be incorporated in treatment and prognostic strategies [29,30].

4. Role of surgery

4.1. Biopsy

Tumors not amenable to a complete primary resection require biopsy for confirmation of histology and for obtaining tissue for molecular genetics. An incisional biopsy is often preferred to ensure adequate tissue for pathology, as well as biology and tissue banking. Careful planning of the biopsy tract is required, as this should be incorporated into subsequent resection. It is essential to maintain meticulous hemostasis and avoid crossing of tissue planes or neurovascular dissections. An incorrect, poorly planned biopsy may unnecessarily contaminate uninvolved compartments and compromise local control, likelihood of limb salvage, or overall outcome [31–33].

Image-guided core needle biopsy may also be considered in the diagnostic workup of both primary and metastatic disease. Given the generally smaller samples of tissue obtained, this technique garners concern for inadequate tissue sampling for molecular biology studies and an increased risk of sampling error. If image-guided percutaneous core needle biopsy is chosen, a generous number of large caliber cores verified by real-time involvement of the pathologist to ensure adequate viable tissue for complete assessment of biologic markers is highly encouraged. Reports on image-guided core needle biopsies have shown excellent diagnostic yields with low complication rates in pediatric solid masses including hepatoblastoma and neuroblastoma [33–35]. However, success in obtaining adequate tissue for ancillary testing is variable, ranging from 64% to 98% [36–39]. Data specific to RMS on number of cores needed for diagnosis and ancillary testing are currently lacking. As with open incisional biopsies, the biopsy tract should still be oriented for planned excision. Tumors of the bladder, prostate and vagina may be amenable to endoscopic biopsy.

Table 3
New rhabdomyosarcoma risk group classification with FOXO1 fusion status.

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

Abbreviations: VAC: vincristine, dactinomycin, cyclophosphamide; VA: vincristine, dactinomycin; VI: vincristine, irinotecan; TEM: temsirolimus.

4.2. Primary resection

Primary upfront resection should be performed if the location and size of the tumor allow a complete resection without compromising function or form. Resection should only be attempted if it is anticipated that all gross tumor can be resected, as leaving gross residual disease has no better outcome than biopsy alone. If intraoperatively it is determined that unresectable gross or suspected microscopic disease remains, titanium clips should be placed strategically to guide radiotherapy or a subsequent repeat resection. Complete resection is achieved when the specimen includes an uninvolved rim of tissue surrounding the tumor [40,41]. A margin of 0.5 cm is considered adequate although there is minimal objective data to support this recommendation [42]. All margins should be marked and oriented at the operative field with direct communication with the pathologist to ensure precise margin assessment.

4.3. Pretreatment re-excision

Pretreatment re-excision (PRE) is a complete wide local resection of a biopsied or incompletely excised tumor or tumor bed prior to the initiation of chemotherapy. This should be considered in cases where only a biopsy was performed, residual gross or microscopic disease is present, a non-oncologic operation was initially performed, or the status of margins are unclear [43]. PRE should be offered only if resection of the entire tumor or bed with a margin can be performed without loss of form or function. This is most commonly possible on extremity or trunk lesions. Clinical group is assigned based on resection status after PRE and patients undergoing PRE with negative margins achieve favorable outcomes similar to other group I patients who underwent initial complete primary excision [43].

4.4. Delayed primary excision

Delayed primary excision (DPE) is resection of residual tumor after induction chemotherapy. For patients with initially unresectable tumors, DPE can be considered if a grossly complete resection is anticipated without unacceptable loss of function or form. A complete (R0) or microscopic residual (R1) resection can allow for reduction in RT dosing. This is more feasible in extremity and truncal tumors, and less useful for head and neck tumors, but should be used for any site when possible [44]. Debulking surgery leaving gross disease behind has not been shown to improve outcomes over biopsy alone at any time point and therefore is not recommended for any site [45].

The COG Soft Tissue Sarcoma Committee tested the local control strategy of DPE and RT dose reduction in select low-risk (D9602) and

intermediate-risk (D9803) RMS patients with tumors amenable to complete resection. In the intermediate-risk RMS study, eligibility criteria included Group III patients with ERMS or ARMS at bladder dome, extremity or trunk primary tumor sites. After 12 weeks of chemotherapy, patients amenable to DPE underwent resection and RT dose was adjusted by completeness of resection: 36 Gy for complete resection, 41.4 Gy for microscopic residual, and 50.4 Gy for gross residual disease. Of the 161 patients evaluated, 73 (45%) underwent DPE and of these, 61 (84%) were eligible for reduced RT dose. There was no compromise in local failure rates at these sites compared to similar historical controls in IRS-IV, which did not have DPE and RT dose reduction [44]. This study concluded that a significant portion of patients amenable to DPE can have RT dose reduction without compromising local control.

4.5. Evaluation of regional lymph nodes

Regional nodal involvement is an important unfavorable prognostic factor. Lymph node involvement is more common in older patients, alveolar (fusion-positive) RMS, extremity and trunk locations, paratesticular RMS in children >10 years of age, and larger tumors [46]. Enlarged nodes found on clinical examination or on imaging (CT, MRI, PET) should be biopsied to confirm involvement. Typically, lymph nodes that are FDG-PET avid or greater than 1 cm on cross sectional imaging are considered suspicious and require pathologic evaluation. However, absence of these radiographically abnormal findings does not reliably rule out the presence of micrometastatic lymph node involvement. For this reason, regional nodes should undergo surgical evaluation in all patients with extremity and trunk tumors, and paratesticular RMS patients older than age 10 years. In addition, surgical lymph node evaluation is strongly recommended to evaluate lymph nodes in all PAX/FOXO fusion positive tumors. FDG-PET-CT has shown a poor positive and negative predictive value compared to sentinel lymph node biopsy (SLNB) (29% and 79% respectively) and surgical assessment of regional lymph nodes remains necessary [28]. There is no therapeutic benefit to completion nodal dissection since positive nodal basins should receive radiotherapy.

Studies from the surveillance, epidemiology, and end results (SEER) database found poor adherence to surgical guidelines with only 25.7% of patients with extremity RMS and 47.7% - 61% with paratesticular RMS in children ≥10 years undergoing indicated nodal sampling. Furthermore, a survival benefit was seen with nodal sampling in both extremity and paratesticular RMS [47,48]. These findings highlight the need for improved education to adhere to surgical guidelines and optimize surgical quality in cancer care.

SLNB is more accurate than random lymph node sampling and is commonly used in extremity and trunk sarcomas but also may be applicable in paratesticular and head and neck tumors. SLNB can be performed through intradermal or mucosal injection of technetium 99 m and/or blue dye such as isosulfan blue (lymphazurin) or methylene blue. Both agents are often used in combination as studies suggest it improves the success rate of the SLNB by providing the surgeon with both auditory and visual clues to the lymph node [49]. SLNB in non-orbital head and neck RMS has been shown to be safe and feasible in pediatric patients, and shows promise to improve locoregional control without excess morbidity [50]. Indocyanine green (ICG) and fluorescent imaging has shown promise as an alternative to blue dye for SLN identification. Use of ICG for SLNB in melanoma has shown superior rates of SLN detection compared to blue dye (88.5% vs 59.6%) and similar rates to technetium-99 m (96.2%). Furthermore, combining the use of ^{99m}Tc lymphoscintigraphy with ICG has been shown to improve SLN-positive rates in melanoma, and this combination shows promise for SLNB use in RMS [51–54].

4.6. Radiation therapy

Radiation therapy (RT) is indicated to improve local control for patients with microscopic (Group II) or gross (Group III) residual tumor in fusion negative disease and in all patients with fusion positive tumors. RT can be omitted for children with localized and completely excised fusion negative RMS. However, omission of RT in younger children in order to avoid treatment related morbidity has been found to increase the risk of local recurrence and is discouraged [55]. Review of children ≤24 months of age enrolled in ARST0331 (low risk) and ARST0531 (intermediate risk) found that 43% of these patients had individualized local control therapy outside of protocol guidelines, most often a delay or omission of radiation therapy. Local failure was significantly higher in this individualized group compared to those following protocol guidelines (35% vs 16%) [56].

As previously discussed, patients amenable to DPE may benefit from dose modification of RT without compromising local failure rates. DPE with R0 or R1 resections receive decreased RT doses (36 Gy for no evidence of disease, 41.4 Gy for microscopic residual) compared to 50.4 Gy for gross residual disease or definitive RT only for local control [44]. Tumors ≥5 cm in size are associated with an increased rate of local failure [57]. Accordingly, the current study for intermediate-risk RMS ARST1431 mandates dose escalation of RT to 59.4 Gy for these tumors at study entry.

5. Summary of recent Children's Oncology Group (COG) studies

The three most recently completed phase III clinical trials from COG include ARST0331 [58,59], ARST0531 [60,61], and ARST0431 [62] for low-, intermediate-, and high-risk RMS, respectively. ARST1431 is currently open and recruiting patients with intermediate risk RMS. Table 4 summarizes the findings from active and recently closed COG studies. Here, we discuss the recently completed and active intermediate-risk trials and their impact on local failure. Oberlin risk factors pertaining to high-risk RMS (ARST0431) are shown in Table 5.

ARST0531, the intermediate risk trial, found that compared to standard chemotherapy using vincristine, dactinomycin, and cyclophosphamide (VAC), alternating VAC with vincristine and irinotecan (VAC/VI) decreased hematologic toxicity and lowered cumulative cyclophosphamide dose while providing similar outcomes [60]. However, both arms in this study had higher rates of local failure compared to historical controls (D9803). This increased local failure was most pronounced in group III ERMS where 5-year local failure cumulative incidence increased to 27.9% from 19.4% on D9803 ($p = 0.03$) [6]. One possible explanation for this finding is the significantly lower cumulative cyclophosphamide dose in ARST0531 (8.4–16.8 g/m^2) compared to D9803 (25.1–30.8 g/m^2). Ironically, secondary investigational goals of ARST0531 were to improve local control through early introduction of RT at week 4, and concurrent delivery of RT with irinotecan, a potential radiosensitizer. In addition, in order to avoid clouding the RT question, delayed primary excision (DPE) was discouraged but permitted in ARST0531. Therefore, the timing of RT and decreased utilization of DPE may also be possible contributors for the observed increased local failure.

In response to the increased local failure seen on the previous ARST0531, the current open intermediate-risk trial, ARST1431, encourages utilization of DPE when feasible, an increased boost of radiotherapy (RT) to 59.4 Gy for all tumors >5 cm, and 24 weeks of maintenance therapy with cyclophosphamide and vinorelbine after completion of all planned chemotherapy. The benefit of maintenance therapy was demonstrated in the European pediatric Soft tissue sarcoma Study Group (EpSSG), where patients in remission after standard treatment who received maintenance therapy had improved disease-free and overall survival [61].

6. Site-specific considerations

6.1. Extremity

For extremity RMS, complete resection at initial surgical intervention is the most important predictor of FFS and primary resection or PRE should be encouraged when possible without loss of function or form [63]. Regional lymph node involvement occurs in >20% of

Table 4
Summary of studies from the Children's Oncology Group for rhabdomyosarcoma.

Study	Primary specific aims	Key study conclusions	Status
ARST1431 A Randomized Phase III Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) vs VAC/VI Plus Temsirolimus (TORI, Torisel, NSC#683864) in Patients with **Intermediate Risk** Rhabdomyosarcoma	To compare the EFS of patients with intermediate risk RMS treated with surgery, radiotherapy, and either VAC/VI with maintenance vs. VAC/VI with maintenance + temsirolimus	**Study ongoing**	Active
ARST0331 Vincristine, Dactinomycin, and Lower Doses of Cyclophosphamide With or Without Radiation Therapy for Patients with Newly Diagnosed **Low-Risk** Embryonal/Botryoid/Spindle Cell Rhabdomyosarcoma	1) To estimate the FFS for low risk RMS in subset I (Stage 1, clinical group I/II or orbital clinical group III, or stage 2, clinical group I/II) when treated with 4 cycles of VAC with reduced dose cyclophosphamide (cumulative cyclophosphamide dosing from 26.4 g/m^2 to 4.8 g/m^2) followed by 4 cycles of VA plus radiation therapy (reduction in length of therapy from 45 to 22 weeks) 2) To estimate FFS for patients with stage I, clinical group IIB or C or stage 2, clinical group II low risk RMS when treated as subset I patients using 4 cycles of VAC with reduced dose cyclophosphamide followed by four cycles of VA plus radiation therapy 3) To estimate FFS for patients with low risk RMS in subset 2 (stage I, non-orbital clinical group III or stage 3, clinical group I/II) when treated with four cycles of VAC with reduced dose cyclophosphamide followed by 12 cycles of VA plus radiation therapy	Shorter duration of therapy that included lower dose cyclophosphamide and RT did not compromise FFS for patients with subset I low risk EMS. The 3-year FFS and OS were 89% and 98%, respectively, similar to historical controls. The estimated FFS was lower than expected compared to historical controls in subset 2 low-risk RMS. 3-year FFS was 70% compared to 83% for historical controls. Conclusions cannot be made regarding the efficacy of RT in the setting of decreased cyclophosphamide dosing	Completed
ARST0531 Randomized Study of Vincristine, Dactinomycin and Cyclophosphamide (VAC) versus VAC Alternating with Vincristine and Irinotecan (VI) for Patients with **Intermediate-Risk** Rhabdomyosarcoma (RMS).	To compare the early response rates, FFS, and survival of patients with intermediate risk RMS treated with surgery, radiotherapy, and vincristine, dactinomycin and cyclophosphamide (VAC) or VAC alternating with vincristine, irinotecan (VI) which lowers cumulative cyclophosphamide dosing from 16.8 g/m^2 to 8.4 g/m^2.	Patients receiving VAC/VI demonstrated no improvement in EFS compared to those receiving VAC. 4-year EFS 63% with VAC and 59% with VAC/VI ($p = 0.51$) and 4-year OS 73% for VAC and 72% for VAC/VI ($p = 0.80$). However, VAC/VI resulted in fewer hospitalizations, reduced need for growth factors, and similar adverse events. VAC/VI had lower hematologic toxicity and lower cumulative cyclophosphamide dose (from 16.8 g/m^2 to 8.4 g/m^2) Higher rates of local failure were found in both arms compared to historical controls	Completed
ARST0431 Intensive Multi-Agent Therapy, Including Dose-Compressed Cycles of Ifosfamide/Etoposide (IE) and Vincristine/Doxorubicin/Cyclophosphamide (VDC) for Patients with **High-Risk** Rhabdomyosarcoma	1) To improve early disease control interval for patients with high-risk RMS using an intensive, interval compression therapy that permits maximal early exposure to known effective agents 2) To determine the feasibility and assess immediate and short term side effects of delivery of concurrent irinotecan with irradiation	Overall 3-year EFS was 38%. Improvement in EFS was seen in patients with 0–1 Oberlin risk factors (3 year EFS 69%), but no improvement was found in patients with 2 or more Oberlin risk factors (3 year EFS 20%).	Completed
ARST0921 A Randomized Phase II Trial of Bevacizumab (IND# 7921, Avastin) and Temsirolimus (IND# 61010, Torisel) in Combination with Intravenous Vinorelbine and Cyclophosphamide in Patients with **Recurrent/Refractory** Rhabdomyosarcoma	1) To determine the feasibility of administering bevacizumab in combination with intravenous vinorelbine and cyclophosphamide in patients with recurrent rhabdomyosarcoma 2) To determine the feasibility of administering temsirolimus in combination with VC in patients with recurrent RMS 3) To estimate the EFS of patients with recurrent/refractory RMS treated with bevacizumab and VC and compare with the EFS of those treated with temsirolimus and VC	Temsirolimus arm had superior results compared to bevacizumab and the trial was stopped early based on interim analysis. The 6 month EFS for the bevacizumab arm was 50% (95% CI 32%, 66%) and for temsirolimus arm 65% (95% CI 44%, 79%). The rate of progressive disease was 26% with bevacizumab compared to 9% with temsirolimus	Completed
ARST08P1 A Pilot Study to Evaluate Novel Agents (Temozolomide and Cixutumumab [IMC-A12, Anti-IGF-IR Monoclonal Antibody, IND #100947, NSC #742460]) in Combination with Intensive Multi-Agent Interval Compressed Therapy for Patients with **High-Risk** Rhabdomyosarcoma	1) To determine the feasibility of administering IMC-A12 in combination with a multi-agent intensive chemotherapy regimen for the treatment of high risk RMS 2) To determine the feasibility of adding Temozolomide to vincristine/irinotecan cycles and to access immediate and short term side effects of delivery of concurrent vincristine-irinotecan-temozolomide with irradiation in patients with high-risk RMS	Cixutumumab and/or temozolomide does not improve survival for high-risk disease. The estimated 2-year FFS is 26% (95% CI 17%, 34%), with those treated with IMC-A12 37% (95% CI 25%, 50%) and Temozolomide 9% (95%CI 3%, 20%). The estimated 2-year OS was 60% (95%CI 50%, 69%) with those treated with IMC-A12 71% (95%CI 59%, 80%) and Temozolomide 43% (95%CI 28%, 57%) Outcomes for patients treated with IMC-A12 regimen are superior to those with Temozolomide suggesting IMC-A12 arms have outcomes similar to historical experience with ARST0431 backbone. Recommendations cannot be made at this time.	Completed

Abbreviations: EFS, event free survival; FFS, failure free survival; OS, overall survival; VAC, vincristine, dactinomycin, cyclophosphamide; VI, vincristine, irinotecan; VDC, vincristine, doxorubicin, cyclophosphamide.

Table 5
Oberlin risk factors for metastatic rhabdomyosarcoma.

Age < = 1 or > = 10 years
Unfavorable site: limbs, other[a]
Bone or bone marrow involvement
≥3 metastatic sites

Oberlin O. et al. J Clin Oncol. 2008.
[a] Other described as those not in a favorable sites. Favorable sites include orbit, parameningeal, non-parameningeal, bladder/prostate, paratesticular, and vagina.

extremity alveolar RMS and is associated with poorer outcomes [46]. This necessitates accurate staging of regional and in-transit nodes to ensure proper treatment [64]. All patients with extremity RMS should undergo surgical lymph node evaluation of axillary or inguinal nodes as indicated. In transit nodes include brachial or epitrochlear for upper extremity and popliteal for lower extremity tumors; failure to evaluate these in-transit locations is associated with worse outcomes [64].

A pooled analysis from four international cooperative groups including the COG, the Cooperative Weichteilsarkom Studiengruppe (CWS), Italian Cooperative Group for Pediatric Soft Tissue Sarcomas (ICG), and the International Society of Pediatric Oncology Malignant Mesenchymal Tumor Committee (SIOP) analyzed 643 patients treated over 14 studies to identify factors predictive of outcomes in extremity RMS. Relapse occurred in 40% of these patients with locoregional failure seen in 63% of these relapses. Patients who did not receive initial radiation therapy had higher rates of local failure (31% vs 22%; $p = 0.02$). After relapse, 5-year OS was 32% after isolated local relapse and 12% after metastatic relapse. Age ≥3 years, T2 status, lymph node involvement, and incomplete initial surgery were strongly correlated with lower survival. Tumors of the hand and foot were also found to have worse outcomes than other sites [57].

6.2. Bladder/prostate

Local control for bladder and prostate RMS has moved toward less aggressive operative management to improve bladder conservation and function, with bladder preservation rates now exceeding 80% [65–67]. Although bladder preservation rates have improved, normal bladder function is maintained in only 40% [65]. A similar pooled analysis of 379 patients from the COG, CWS, ICG, and SIOP with bladder/prostate RMS found that primary resection was attempted in only 12% of patients, and gross total resection achieved in 5% overall, emphasizing that very few are amenable to upfront primary resection [66]. These patients may be more amenable to DPE after induction chemotherapy, allowing dose reduction of RT as described previously. For unresected lesions, a residual mass at the end of all planned therapy may be present. This is usually composed of well-differentiated rhabdomyoblasts and surgical resection is not indicated [68,69].

6.3. Female genital tract

Omission of RT in ARST0331 for group III vaginal RMS, in conjunction with reduced cyclophosphamide dosing, led to a higher rate of local recurrence with a 3 year FFS of 57% compared to 77% for those who received radiation therapy. For that reason, RT was reinstituted and the patients are currently being enrolled on the intermediate-risk trial [59]. A pooled analysis of 237 patients from COG, SIOP, ICG, and the European pediatric soft tissue sarcoma study group (EpSSG) of localized female genital RMS found a 10-year EFS of 74% and OS 92%. Eighty-four percent of recurrences occurred in patients who did not receive radiation initially, although this did not affect OS [70,71].

6.4. Paratesticular

Paratesticular RMS requires radical orchiectomy through an inguinal approach with proximal clamping as well as resection of the spermatic cord to the level of the internal ring. Trans-scrotal biopsies or resections are contraindicated, as scrotal contamination theoretically increases the risk of local recurrence and drainage into the inguinal and iliac lymph nodes [72]. Unfortunately, these protocol violations are reported in up to 25% of cases [73]. Hemiscrotectomy has traditionally been recommended, however, the benefit of hemiscrotectomy in these cases on outcome and local relapse is unclear. Results from the Cooperative Soft Tissue Sarcoma Group studies found that in patients who underwent trans-scrotal approach for paratesticular ERMS, there was no difference in EFS for the 12 patients who underwent hemiscrotectomy, compared to the 16 who did not (5-year EFS 91.7% vs 93.8%) [74–76]. Given the available evidence at this time, the COG is not recommending hemiscrotectomy for scrotal violation but only for direct tumor invasion at the time of initial tumor resection.

In a pooled analysis of 842 patients from COG, CWS, EpSSG, and ICG, age ≥10 years, tumors >5 cm, and retroperitoneal lymph node involvement were poor prognostic factors and surgical assessment of regional nodes was associated with improved EFS in patients ≥10 years, further highlighting the importance of adhering to surgical guidelines for lymph node evaluation in this population [77]. Retroperitoneal lymph node sampling of 7–12 nodes is recommended for children >10 years of age or those with enlarged lymph nodes on imaging. (reference manuscript in review).

7. Special populations

7.1. Infants

Infants continue to have worse outcomes compared to older children with 5-year FFS of 57% for children <1 year of age, 81% for 1–9 years, and 68% for older than 10 years. 5-year OS for age <1 year, 1–9 years, and ≥10 years are 76%, 87%, and 75%, respectively [78]. This finding may be secondary to poor adherence to protocols due to concerns of treatment toxicity, resulting in inadequate or diminished treatment intensity [56,78–80]. As previously discussed, 43% of children ≤24 months of age enrolled on COG ARST0331 (low risk) and ARST0531 (intermediate risk) received individualized local therapy, most commonly a delay or omission of radiation therapy. These patients experienced a decreased 5-year EFS compared to those receiving protocol specified therapy (55.6% vs 77.5%; $p = 0.04$) and an inferior 5-year cumulative incidence of local failure, although no differences in OS was seen [56].

7.2. Refractory or recurrent disease

Long-term prognosis for recurrent or progressive RMS remains poor and relapse may occur locally or distally in the lung, bone, or bone marrow [81]. Prognosis for unfavorable risk (initial diagnosis of stage 2–4, clinical group II to IV ERMS, ARMS, or stage I, group I ERMS previously treated with VAC) is especially dismal with 3-year FFS 14–21% and OS 22–39%. Favorable risk patients (botryoid histology or stage I, group I ERMS not treated with cyclophosphamide) had a much higher chance of cure with second line therapy with 3-year FFS 79% and OS 84% [82].

Aggressive surgical resection and/or RT may be indicated for local or regional recurrence, with complete resection improving overall survival from 8% to 37% [83]. Relapse is associated with unfavorable sites, group III or IV patients, regional lymph node involvement, alveolar histology, tumors ≥5 cm, and children older than 10 years of age [84]. Early time to relapse is a poor prognostic factor [41]. A retrospective review of the German CWS found worse 4-year OS for children with first relapse at <6 months (12%) and 6 to 12 months (21%), compared to relapse after 12 months (41%) [85,86].

The significance of a radiographic mass at the end of therapy was evaluated by the COG. Patients with initially unresected RMS were

assessed for image-defined completeness of response, with a complete response seen in 65.4%. Improved FFS was seen with complete response compared to partial or no response in primary parameningeal sites, but no difference was found for non-parameningeal primary sites. Radiographic response was also not associated with OS. Furthermore, there was no benefit in FFS or OS found for patients who underwent resection of end of therapy mass, thus resection of this mass is not indicated [69].

7.3. Late effects

Children with RMS receive multimodal therapy including alkylator- and anthracycline-based chemotherapy, RT, and surgery, and long-term effects can be devastating. In a German CWS study, secondary malignancies were found in 6% and long-term toxicity in 21%, including cardiac and renal toxicities, growth deficiency, and neuropathy. Resection related impairment was seen in 33% [79]. Reduced fertility or ovarian insufficiency can also result from high-intensity alkylating chemotherapy (cyclophosphamide) or RT (pelvic, whole abdomen, cranial, or total body) [87].

Long-term effects in RMS are also site-specific. Treatment of head and neck RMS may lead to pituitary dysfunction, thyroid complications, hearing loss, and dental and craniofacial alterations [88]. Patients with extremity RMS may develop soft tissue or bone defects or impaired growth due to resection or radiation. Patients receiving RT for bladder/prostate RMS suffer increased rates of bladder dysfunction, with higher rates in patients receiving >40 Gy (61%) compared to <40 Gy (17%). Urinary incontinence is seen in 27–31% [89]. Long-term consequences also include urgency, frequency, hematuria, dysfunctional sphincter, and decreased compliance as well as sexual dysfunction [90–92].

Late effects in females treated for pelvic RMS are significant, and are increased in those who received pelvic RT versus not (median 9.5 effects versus 1 effect per patient, respectively). Endocrine dysfunction, including ovarian hormonal production failure, short stature, or central growth hormone deficiency are seen in more than 75% of females treated for pelvic RMS. Psychological effects such as depression, anxiety, and insomnia are seen in 38% and secondary malignancies in 12%. Gastrointestinal, renal, neurologic, and cardiovascular late effects also occur [93]. Finally, all-cause mortality was found to be higher in children and young adults in the SEER database who underwent treatment for soft-tissue sarcomas compared to the general population, largely attributable to secondary malignancies and non-cancer causes including cardiovascular diseases and infections [94]. These data highlight that continuing efforts to limit treatment toxicity while maintaining oncologic outcomes are essential for the quality of life of survivors of RMS.

8. Conclusion

This review discusses current updates on the risk stratification and treatment considerations in RMS, including the findings from the most recent COG studies as well as the pooled analysis from cooperative study groups from Europe and North America. Although advances in multimodal therapy have improved outcomes in most children diagnosed with RMS, many challenges remain ahead. With little progress made for children with high-risk RMS, identification of effective treatments for this cohort remains a priority. In addition, improving measures of local control while preserving function and limiting treatment toxicity and late effects continue to evolve. Collaborative efforts through the pooled analysis of multiple international cooperative groups for RMS has provided utmost value in understanding our management of RMS and will play a large role in identifying areas where further efforts require focus.

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