Advances in Radiation Oncology (2024) 9, 101561

advances in radiation oncology

www.advancesradonc.org

Scientific Article

The Prognostic Significance of Early Tumor Volume Change in Rhabdomyosarcoma

Patrick Debs, MD,[a,1] Rohini Bhatia, MD,[b,1] Jacqueline Kruglyakova, MD,[c] Suqi Ke, MS,[d] Chen Hu, PhD,[d] Matthew Ladra, MD,[b] Christine A. Pratilas, PhD, MD,[c] Shivani Ahlawat, MD,[a] Laura M. Fayad, MD,[a,c,e] and Sahaja Acharya, MD[b,*]

[a]The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland; [b]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; [c]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland; [d]Bloomberg School of Public Health, Division of Biostatistics, Johns Hopkins University School of Medicine, Baltimore, Maryland; and [e]Department of Orthopedic Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland

Received 8 April 2024; accepted 8 June 2024

Purpose: To describe early tumor volume change in patients with rhabdomyosarcoma (RMS) and investigate its association with overall survival (OS) and local failure.

Methods and Materials: This retrospective study included patients who received diagnoses of group III/IV RMS with available computed tomography and/or magnetic resonance imaging scans at 2 time points: (1) pretherapy and (2) early therapy (acquired during weeks 8-12 of chemotherapy). Relative volumetric change (RVC) was calculated as the percentage of (early therapy − pretherapy volume) / (pretherapy volume). Cox regression was used to identify variables associated with OS. The Fine-Gray model was used to estimate local failure.

Results: Eligible patients (n = 55) had the following characteristics: median age at diagnosis, 9.6 years and median follow-up, 30.4 months. Most tumors were alveolar (61.8%), followed by embryonal (34.6%) and spindle cell/sclerosing (4%). The median RVC was −86.4% with larger decreases observed in alveolar versus nonalveolar RMS (−89.4% vs −69.8%, $P = .043$). For embryonal and spindle cell/sclerosing RMS, all of which were FOXO1 fusion negative, RVC was independently associated with OS (hazard ratio for every 50% reduction in RVC [HR_{RVC}], 0.5; 95% CI, 0.26-0.96; $P = .037$) and local failure (HR_{RVC}, 0.57; 95% CI, 0.33-0.99; $P = .049$). The predominant pattern of failure in embryonal and spindle cell/sclerosing RMS was local, and most were group III.

Conclusions: There was a greater reduction in tumor volume in alveolar versus nonalveolar RMS. Early tumor volume reduction was associated with OS and local failure in embryonal or spindle cell/sclerosing RMS, all of which were confirmed FOXO1 fusion negative and had higher incidence of local compared with distant failures.

Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and adolescents, with approximately 350 cases diagnosed every year in the United States.[1] In North America, patients with group III or IV

Sources of support: This work had no specific funding.

Data are available on request to the corresponding author and approval by the institution's review board.

[1]Co-first authors.

*Corresponding author: Sahaja Acharya, MD; Email: sachary7@jhmi.edu

https://doi.org/10.1016/j.adro.2024.101561

disease have a long treatment course, typically starting with induction chemotherapy followed by radiation therapy (RT) and/or surgery for local control and continuing with adjuvant chemotherapy.[2] The prognostic value of change in primary tumor volume during induction chemotherapy is controversial. Three large cooperative group studies, the Malignant Mesenchymal Tumor 95 study, the Intergroup Rhabdomyosarcoma Study IV, and the Children's Oncology Group (COG) D9803 study, did not show an association between response to induction chemotherapy and survival in children with RMS.[3-5] However, all 3 studies used 2-dimensional (2D) measurements and stratified responses into 4 categories: (1) complete response; (2) partial response; (3) no response; and (4) progressive disease. In contrast, a study pooling data from Cooperative Weichteilsarkom trials demonstrated an association between stable/progressive disease and worse overall survival (OS), but only in patients with localized embryonal RMS.[6] This study used 2D measurements as well but had a different categorization for tumor response. Two more recent studies using 3-dimensional (3D) tumor volume measurements have demonstrated an association between the change in volume and OS[7] as well as local failure.[8]

Given the mixed results published thus far, the primary objective of this study is to describe the early relative volumetric change (RVC) of the primary tumor and investigate the association of RVC with OS and local failure. If an early change in tumor volume is prognostic, it could potentially be used to selectively identify patients who may benefit from RT dose escalation. This study is not designed to answer the question of whether change in tumor volume is predictive of response to a particular chemotherapy regimen because eligible patients have been treated with different chemotherapy regimens.

Methods and Materials

Study population

This retrospective study was approved by our institutional review board at Johns Hopkins. Patients were identified using a retrospective institutional sarcoma database. Inclusion criteria consisted of patients aged ≤39 years who received diagnoses of group III or group IV RMS between 2007 and 2022 and treated with RT at either Johns Hopkins Hospital or Sibley Memorial Hospital. In addition, patients must have undergone either a magnetic resonance imaging or computed tomography at diagnosis before any therapy and between weeks 8 and 12 of chemotherapy. Chemotherapy was administered at Johns Hopkins Hospital or a referring pediatric hospital. Patients with scans that showed substantial artifacts resulting in nondiagnostic images were excluded. The following data were extracted from medical records: race, biologic sex, age at diagnosis, tumor histology, primary tumor site, group, location of primary, FOXO1 fusion status, date of diagnosis, dates of treatment and treatment regimen, tumor recurrence, and location of recurrence.

Chemotherapy

Most chemotherapy regimens followed North American protocols from the COG. Most patients were treated according to D9803 Regimen A (n = 18, 32.7%), which consisted of vincristine, actinomycin D, and cyclophosphamide. The next most common regimen was ARST1431 Regimen A (n = 12, 21.8%), which consisted of vincristine, actinomycin D, and cyclophosphamide alternating with vincristine and irinotecan. Fewer patients were treated according to ARST0431 (n = 10, 18.2%), ARST0531 Regimen A (n = 5, 9.1%), ARST0531 Regimen B (n = 4, 7.2%), ARST0331 (n = 2, 3.6%), ARST2031 (n = 2, 3.6%), ARST1431 Regimen B (n = 1, 1.8%), and SIOP MMT98 (n = 1, 1.8%). The 2 patients treated on the low-risk ARST0331 protocol had FOXO1 fusion-negative group III embryonal tumors of the orbit. The median time between scans was 10.1 weeks (IQR, 8.5-11.1 weeks). One patient had clinical signs concerning disease progression early in the induction chemotherapy course, which prompted early restaging imaging at 6.1 weeks.

Radiation therapy

All patients underwent RT at the primary site. The median time to RT from the start of induction chemotherapy was 13.7 weeks (IQR, 12.2-16.1 weeks). The median RT dose to the primary site was 50.4 Gy with an IQR limited to 50.4 Gy. One patient with an orbital primary was treated to 45 Gy after a complete response to induction chemotherapy. Five patients were treated with delayed primary excision before RT and received reduced RT dose in the range of 26 to 40 Gy.

Measurements

All measurements were performed by 1 musculoskeletal radiologist with 12 years of clinical experience. The reader knew the primary tumor site only and was blinded to all other clinical data and outcomes. For volumetric measurements, either coronal T2-weighted MR images or coronal computed tomography images were transferred to Velocity AI (v.3.0.1; Varian Medical Systems) in a Digital Imaging and Communications in Medicine format. Manual segmentation of the region of interest was performed using the Velocity AI smart brush tool for all slices showing the tumor in question, and average tumor volumes were automatically computed. The volume change for every tumor was calculated by subtracting the

early (weeks 8-12) tumor volume from the pretherapy tumor volume. The RVC was computed by calculating the absolute volume change as a percent of pretherapy tumor volume.

$$RVC = \frac{early\ therapy\ volume - pretherapy\ volume}{pretherapy\ volume}$$

Definitions of outcome variables

OS was defined as the time from diagnosis to death from any cause, and progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death. Local failure was defined as the first failure at the primary site with or without distant failure. Distant failure was defined as the first failure outside of the primary site without local failure.

Statistical analysis

All statistical analyses were conducted using Stata version 18.0. The Fischer's exact test and Wilcoxon rank sum tests were used to compare the frequency of continuous and categorical variables, respectively. OS and PFS were estimated using the Kaplan-Meier method. The univariable Cox proportional hazard regression models were used to evaluate the association of RVC with OS and PFS. Cumulative incidence of local failure was calculated using the Fine and Gray method using death and distant failures as competing risks. Cumulative incidence of distant failure was also calculated using the Fine and Gray method using death and local failures as competing risks. Competing-risk regression was used to determine the effect of RVC on local failure across different patient subgroups.

Results

Baseline characteristics

Clinical characteristics are summarized in Table 1. In total, 55 patients met the eligibility criteria, of whom 23 (41.8%) were female and 32 (58.2%) were male. The median age at diagnosis was 9.6 years (IQR, 4.3-16.6), and median primary tumor size at diagnosis was 5.7 cm (IQR, 3.7-8.2 cm). Slightly over half of the patients had group III disease (n = 31, 56.4%), and most primary sites were unfavorable (n = 49, 89.1%). Parameningeal head and neck represented the most common primary site (n = 16, 29.1%), followed by extremity (n = 11, 20%) and bladder/prostate (n = 9, 16.4%).

Most tumors were alveolar (n = 34, 61.8%), followed by embryonal (n = 19, 34.5%) and spindle cell/sclerosing (n = 2, 3.6%). As expected, alveolar tumors were more likely to be in patients who were older (P = .018), with group IV disease (P = .027), and with confirmed FOXO1 fusion within the tumor (P < .001). Certain primary tumor sites such as parameningeal head and neck and extremity were more common in alveolar versus embryonal or sclerosing/spindle cell RMS. All embryonal and spindle cell/sclerosing tumors were confirmed FOXO1 fusion negative. Both spindle cell/sclerosing tumors had MYOD1 L122R mutations. The 3-year OS rates for group III and group IV RMS were 83.2% and 35.8%, respectively.

Relative volume change

The median RVC of the total population was −86.4% (IQR, −98.8 to −58.5). Figure 1 shows pretherapy and early therapy (acquired during weeks 8-12 of chemotherapy) images of 3 tumors with different patterns of volumetric changes: 1 orbital tumor with near complete resolution (Fig. 1A, B), 1 prostatic tumor with significant but incomplete reduction in volume (Fig. 1C, D), and 1 mandibular tumor with interval increase in volume (Fig. 1E, F). RVC was lower (ie, higher primary tumor volume reduction) in alveolar compared with nonalveolar tumors (P = .043) and group IV compared with group III (P = .04) (Table 2). Most group IV tumors were of alveolar histology (n = 19/24, 79%). There were 13 complete responses whereby no measurable tumor was detected on computed tomography/magnetic resonance imaging, and 11 (84.6%) of these were in alveolar tumors. A waterfall plot demonstrating each patient's RVC by histology is shown in Fig. 2.

Association of RVC with OS and PFS

Greater tumor volume reduction, as measured by RVC, was not associated with OS (P = .311) or PFS (P = .474) for the entire cohort (Table 3).

However, for patients with embryonal or spindle cell/sclerosing tumors, all of which were confirmed FOXO1 fusion negative, greater tumor volume reduction was associated with OS. For every 50% reduction in primary tumor volume (RVC of −50%), there was 50% reduction in overall mortality (hazard ratio [HR] for every 50% reduction in RVC [HR_{RVC}], 0.5; 95% CI, 0.26-0.96; P = .037) (Table 3). RVC was the only variable associated with OS in this subgroup. There was no association between RVC and PFS (P = .218).

Although group could be a confounding variable, there were only 5 patients with embryonal or spindle cell/sclerosing tumors who had group IV disease. Given that most

Table 1 Patient and tumor characteristics

Characteristic	All patients (%) (N = 55)	Embryonal or sclerosing/spindle cell (%) (N = 21)	Alveolar (%) (N = 34)	*P* value*
Follow-up (mo), median (IQR)	30.4 (15.4-44.4)	23.5 (10.8-49.5)	31.6 (21.4-42.3)	.346
Sex				.049
Female	23 (41.8)	5 (23.8)	18 (52.9)	
Male	32 (58.2)	16 (76.2)	16 (47)	
Age (y), median (IQR)	9.6 (4.3-16.6)	7.2 (3.1-9.9)	12.7 (6.4-17.2)	.018
Group				.027
III	31 (56.4)	16 (76.2)	15 (44.1)	
IV	24 (43.4)	5 (23.8)	19 (55.9)	
Tumor location				.002
PM HN	16 (29.1)	4 (19.1)	12 (35.3)	
BP	9 (16.4)	8 (38.1)	1 (2.9)	
Extremity	11 (20)	1 (4.8)	10 (29.4)	
Abdomen/pelvis	9 (16.4)	4 (19.1)	5 (14.7)	
Non-PM HN	4 (7.3)	1 (4.8)	3 (8.8)	
Orbit	2 (3.6)	2 (9.5)	0 (0)	
Perianal/gluteal	4 (7.3)	2 (4.8)	3 (8.8)	
Histology				<.001
Alveolar	34 (61.8)	0 (0)	34 (100)	
Embryonal	19 (34.5)	19 (90.5)	0 (0)	
Sclerosing/spindle cell	2 (3.6)	2 (9.5)	0 (0)	
FOXO1 fusion				
Present	25 (45.5)	0 (0)	25 (73.5)	
Absent	25 (45.5)	21 (100)	4 (11.6)	
Not tested	5 (9.1)	0 (0)	5 (14.7)	
Primary site				.416
Favorable	6 (10.9)	3 (14.3)	3 (8.8)	
Unfavorable	49 (89.1)	18 (85.7)	31 (91.2)	
Tumor size (cm), median (IQR)	5.7 (3.7-8.2)	7.5 (5.1-8.9)	5.2 (3.7-7.6)	.664
Time to scan from start of chemotherapy (wk), median (IQR)	10 (8.5-11.1)	9.4 (8.6-11.4)	10.1 (8.6-11)	.881
Complete response at early imaging				.100
No	42 (76.4)	19 (90.5)	23 (67.7)	
Yes	13 (23.6)	2 (9.5)	11 (32.4)	

Abbreviations: BP = bladder/prostate; PM HN = parameningeal head and neck.
**P* value is comparing embryonal or sclerosing/spindle cell versus alveolar histology.

embryonal or sclerosing/spindle cell tumors were group III ($P = .027$), it is not surprising that for group III RMS, greater tumor volume reduction was associated with OS (HR_{RVC}, 0.49; 95% CI, 0.26-0.91; $P = .025$). RVC and age at diagnosis (HR, 1.1; 95% CI, 1.01-1.26; $P = .045$) were the only variables associated with OS in this subgroup. There was no association between RVC and PFS ($P = .148$).

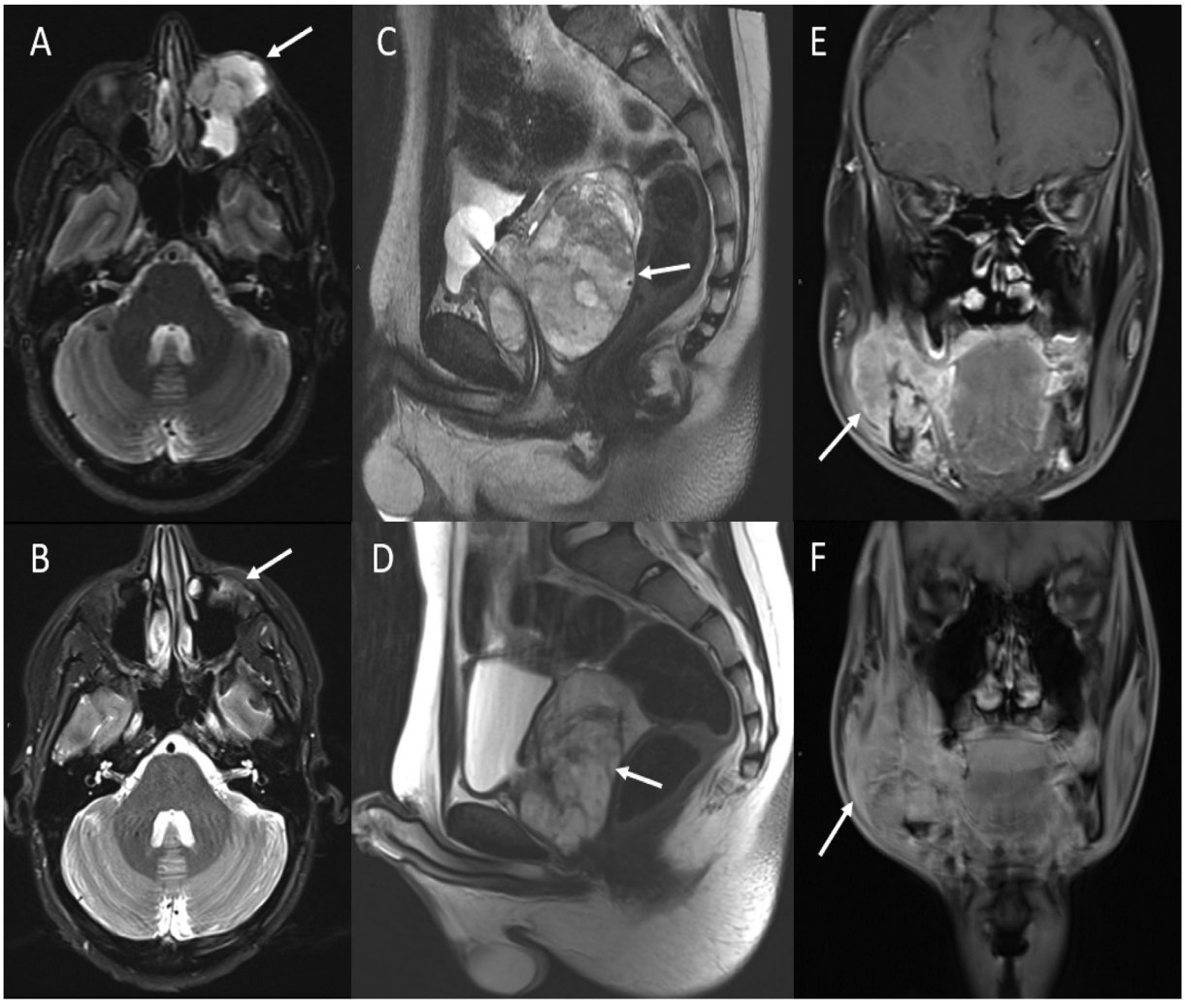

Figure 1 Pre- and posttreatment magnetic resonance imaging images of 3 tumors with different patterns of volumetric changes. (A) Pretreatment axial STIR image shows a hyperintense and diffusely enhancing periorbital alveolar RMS (arrow), and (B) posttreatment axial T2-Dixon shows near complete resolution of the lesion with thin peripheral enhancement (arrow) of the cavity (RVC = −100%). (C) Pretreatment sagittal T2 STIR image shows a heterogeneous prostatic embryonal RMS (arrow), and (D) posttreatment sagittal T2 STIR image shows a smaller lesion (arrow) in comparison (RVC = −60.9%). (E) Pretreatment coronal T1 fat-suppressed postcontrast image shows a heterogeneously hyperintense diffusely enhancing embryonal RMS in the right mandible (arrow), and (F) posttreatment coronal T1 fat-suppressed postcontrast image shows interval increase in size and heterogeneity of the mandibular lesion (arrow) with continued diffuse enhancement (RVC = 197%). *Abbreviations:* RMS = rhabdomyosarcoma; RVC = relative volume change; STIR = short tau inversion recovery.

Association between RVC and local failure

There were 14 local and 13 distant failures (Table 4). The predominant pattern of failure was local for patients with the following disease characteristics: FOXO1 fusion-negative RMS, embryonal and spindle cell/sclerosing histology, and group III disease. The predominant pattern of failure was distant for patients with the following disease characteristics: FOXO1 fusion-positive RMS, alveolar histology, and group IV disease.

The 2-year cumulative incidence of local and distant failures in the entire cohort was 25.4% (95% CI, 14.4%-37.9%) and 22.1% (95% CI, 11.7%-34.3%), respectively. The 2-year cumulative incidence of local and distant failures in patients with embryonal or spindle cell/sclerosing RMS was 25% (95% CI, 9%-44.9%) and 6.9% (95% CI, 0.4%-26.7%), respectively. The 2-year cumulative incidence of local and distant failures in patients with group III disease was 14.4% (95% CI, 4.5%-29.8%) and 7.7% (95% CI, 13.3%-21.8%), respectively. Given the higher

Table 2 Variables associated with RVC

Characteristic	Median RVC (%) (IQR)	*P* value
Sex		1.0
Female	−84.7 (−100 to −40.8)	
Male	−88.8 (−98 to −60.7)	
Age group		.211
Age ≤18 y	−88.6 (−98.7 to −68.4)	
Age >18 y	−59.5 (−100 to −17.6)	
Histology		.043
Nonalveolar	−69.8 (−93.3 to −4.3)	
Alveolar	−89.4 (−100 to −68.5)	
Group		.04
III	−83.5 (−97.1 to −40.8)	
IV	−92.5 (−100 to −61.3)	
Primary site		.849
Favorable	−88.4 (−97.3 to −52.6)	
Unfavorable	−86.4 (−98.8 to −60.4)	
Fusion		.599
Negative	−88.3 (−97.3 to −32.3)	
Positive	−84.7 (−98.7 to −60.4)	
Tumor size (cm), median (IQR)		.428
Size <5 cm	−88.3 (−100 to −60.5)	
Size ≥5 cm	−85.4 (−98.4 to −58.5)	

Abbreviation: RVC = relative volume change.

incidence of local failure compared with distant failure rates in these subgroups, we tested whether RVC was associated with a higher risk of local failure (Table 3). For every 50% decrease in RVC, there was a reduction in local failure risk of both embryonal or spindle cell/sclerosing tumors (HR_{RVC}, 0.57; 95% CI, 0.33-0.99; P = .049) and for group III disease (HR_{RVC}, 0.52; 95% CI, 0.33-0.82; P = .005). There was no significant association between RVC and local failure in fusion-positive RMS, alveolar histology tumors, or group IV disease. There was a higher incidence of distant failures in alveolar compared with other histology (HR, 7.67; 95% CI, 1.03-56.7; P = .046) and group IV compared with group III (HR, 8.55; 95% CI, 1.9-38.4; P = .005).

Discussion

These hypothesis-generating data highlight several clinically relevant findings. First, early volumetric change of the primary tumor was not prognostic for all patients. However, for patients with fusion-negative embryonal or spindle cell/sclerosing RMS, most of which were group III, early changes in primary tumor volume might be prognostic in terms of OS and associated with local failure. This could be explained by the higher cumulative incidence of local compared with distant failures in this subgroup. In contrast, in patients with fusion-positive RMS, alveolar histology, and group IV disease, distant failures predominate, and therefore, early volumetric change of the primary tumor may not be as relevant. Additionally, there was a greater reduction in primary tumor volume when comparing alveolar with embryonal or spindle cell/sclerosing RMS.

Differing conclusions regarding the prognostic value of early tumor volume change might be explained by the differing proportions of embryonal versus alveolar tumors in the study cohort and the inclusion of patients with progressive disease. Those studies that excluded patients with progressive disease during induction chemotherapy did not demonstrate an association between tumor response and OS.[3-5] Furthermore, although 1 study in embryonal parameningeal head and neck RMS demonstrated an association between tumor volume change and OS as well as local failure, other studies have not reproduced this result even when investigating the same primary site, but

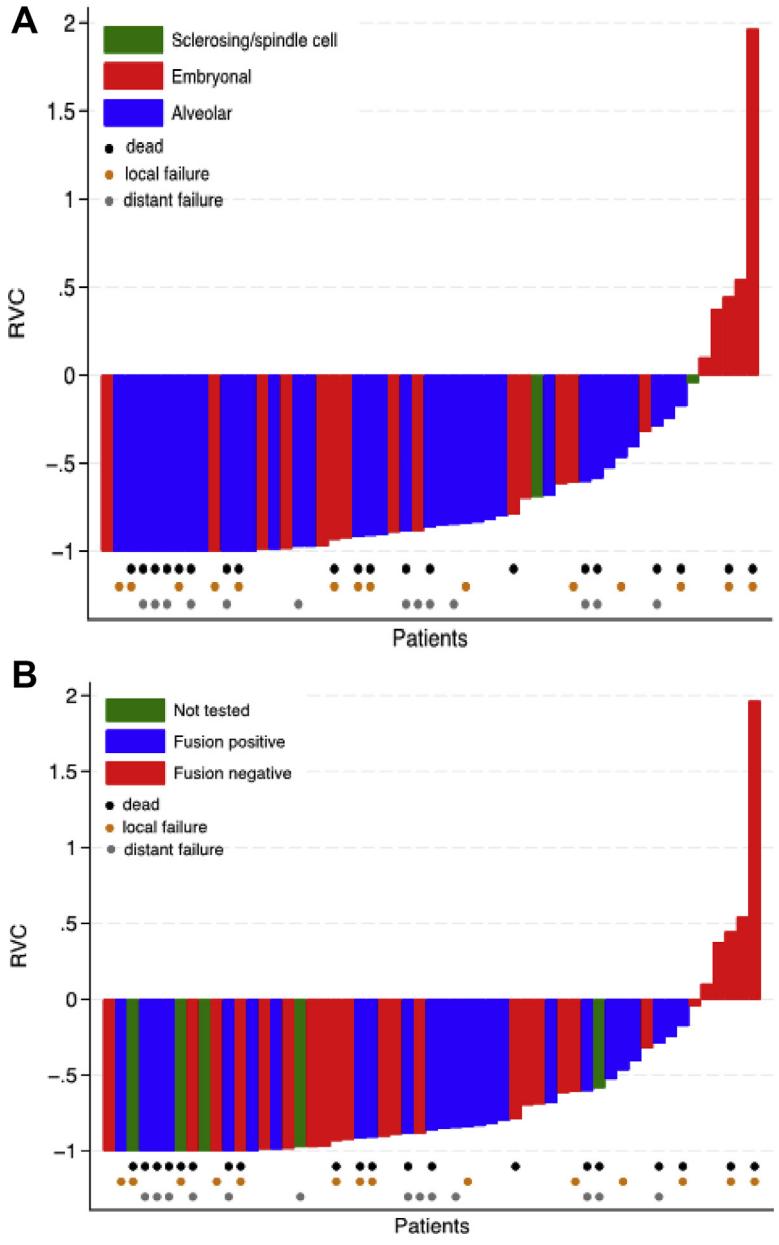

Figure 2 Waterfall plot showing relative volume change values by (A) rhabdomyosarcoma histology and (B) fusion status.

such studies included both embryonal and alveolar histology.[8,9]

Volume reduction has been used to de-escalate the RT dose in specific circumstances. For example, in the COG minimal risk study ARST0331, patients with group III orbital RMS were treated to 45 Gy instead of 50.4 Gy, irrespective of tumor volume reduction.[10,11] None of the patients with a complete response experienced local failures; however, 6 out of 38 patients (15.8%) without a complete response did experience local failures. As a result of these findings, the current low-risk COG study ARST2032 (Clinicaltrials.gov: NCT05304585) is only reducing the dose to 45 Gy for tumors that have a complete response at week 12. In another example, ARST1431 investigated RT dose de-escalation to 36 Gy for group III tumors that have achieved a complete response at week 9, irrespective of histology or fusion status (Clinicaltrials.gov: NCT02567435). This study is now closed, and results are pending. Tumor volume change has not been used to identify cases for which RT dose escalation might be beneficial. Both ARST1431 and ARST2031 recommend dose escalation to 59.4 Gy for tumors larger than 5 cm (about 1.97 in) at diagnosis based on data suggesting that larger tumors are associated with worse outcomes, but do not modify RT dose based on early tumor response.[12]

This is a retrospective study and has limitations inherent to its study design. We assess 3D tumor volumes at any point between weeks 8 and 12 of chemotherapy. We

Table 3 Univariate association between a reduction in RVC by 50% and OS, PFS and local failure

Patient subgroup	OS		PFS		Local failure	
	HR_{RVC}† (95% CI)	*P* value	HR_{RVC}† (95% CI)	*P* value	HR_{RVC}† (95% CI)	*P* value
All patients	0.79 (0.5-1.25)	.311	0.98 (0.63-1.55)	.947	0.66 (0.35-1.23)	.19
Fusion positive	0.75 (0.20-2.7)	.67	1.33 (0.41-4.32)	.631	0.52 (0.9-3.09)	.476
Fusion negative	0.62 (0.36-1.07)	.088	0.78 (0.46-1.31)	.346	0.61 (0.35-1.06)	.077
Alveolar‡	0.92 (0.29-2.86)	.882	1.26 (0.44-3.56)	.666	1.15 (0.04-36.7)	.934
Embryonal or spindle cell/sclerosing§	0.5 (0.26-0.96)	.037*	0.71 (0.41-1.22)	.218	0.57 (0.33-0.99)	.049*
Group III	0.49 (0.26-0.91)	.025*	0.67 (0.39-1.15)	.148	0.52 (0.33-0.82)	.005*
Group IV	0.54 (0.22-1.32)	.181	1.03 (0.44-2.42)	.937	0.82 (0.26-2.58)	.731

Abbreviations: HR = hazard ratio; OS = overall survival; PFS = progression-free survival; RVC = relative volume change.
*indicates p-value <0.05.
†This represents HR for every 50% reduction in RVC.
‡Most alveolar tumors are fusion positive (n = 25/34, 73.5%) and 5 are unknown fusion status (14%).
§All embryonal or spindle cell/sclerosing tumors are confirmed fusion negative.

Table 4 Cumulative incidence of local versus distant failure

	Local failure		Distant failure	
Patient subgroup	No. of failures	2-y cumulative incidence (95% CI)	No. of failures	2-y cumulative incidence (95% CI)
All patients	14	25.4% (14.4%-37.9%)	13	22.1% (11.7%-34.3%)
Fusion positive	6	21.4% (7.6%-39.4%)	9	33.4% (15.8%-52.1%)
Fusion negative	6	26.2 (10.5%-45.2%)	2	9.4% (1.6%-26.1%)
Alveolar*	9	24.5% (11.6%-41.4%)	12	30.3% (15.8%-46.2%)
Embryonal or spindle cell/sclerosing†	5	25% (9%-44.9%)	1	6.9% (0.4%-26.7%)
Group III	5	14.4% (4.5%-29.8%)	2	7.7% (13.3%-21.8%)
Group IV	9	38.4% (19.4%-57.2%)	11	39.1% (19.8%-57.9%)

*Most alveolar tumors are fusion positive (n = 25/34, 73.5%) and 5 are unknown fusion status (14%).
†All embryonal or spindle cell/sclerosing tumors are confirmed fusion negative.

chose this period because it represented the first restaging imaging time point before local control. Unlike prior studies, our study included group IV patients in addition to group III patients because most group IV patients are treated with RT to the primary site. We also did not exclude patients who had progressive disease on chemotherapy because we were interested in understanding how changes in tumor volume (either increase or decrease) influenced survival and local failure outcomes. Finally, there were only 2 patients with spindle cell/sclerosing RMS, both of whom were FOXO1 fusion negative and had MYOD1 L122R mutations, so it is unclear whether our results are generalizable to all patients with this histology.

Conclusions

In conclusion, early volumetric tumor change was associated with OS and local failure in certain subgroups of patients, including those with embryonal or spindle cell/sclerosing RMS, all of which were confirmed fusion negative, and those with group III RMS. Patients with alveolar RMS and those with group IV RMS did not demonstrate an association between RVC and OS, PFS, or local failure. This could be explained by the predominant pattern of failure being local in embryonal or spindle cell/sclerosing RMS and group III RMS. Patients with these subgroup characteristics who do not demonstrate a large early reduction in tumor volume may benefit from RT dose escalation because they are most likely to experience local failures. These findings should be validated in a larger cohort of patients.

Disclosures

None.

Acknowledgments

We would like to thank Dhara Vyas, BS, for her administrative assistance. Suqi Ke, Chen Hu, and Sahaja Acharya were responsible for statistical analysis.

References

1. *Childhood Rhabdomyosarcoma Treatment (PDQ®). 2023. Accessed.* National Institutes of Health (NIH; July 12, 2023. https://www.cancer.gov/types/soft-tissue-sarcoma/hp/rhabdomyosarcoma-treatment-pdq.
2. Haduong JH, Heske CM, Allen-Rhoades W, et al. An update on rhabdomyosarcoma risk stratification and the rationale for current and future Children's Oncology Group clinical trials. *Pediatr Blood Cancer*. 2022;69:e29511. https://doi.org/10.1002/pbc.29511.
3. Vaarwerk B, van der Lee JH, Breunis WB, et al. Prognostic relevance of early radiologic response to induction chemotherapy in pediatric rhabdomyosarcoma: A report from the International Society of Pediatric Oncology Malignant Mesenchymal Tumor 95 study. *Cancer*. 2018;124:1016-1024.
4. Burke M, Anderson JR, Kao SC, et al. Assessment of response to induction therapy and its influence on 5-year failure-free survival in group III rhabdomyosarcoma: The Intergroup Rhabdomyosarcoma Study-IV experience—a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol*. 2007;25:4909-4913.
5. Rosenberg AR, Anderson JR, Lyden E, et al. Early response as assessed by anatomic imaging does not predict failure-free survival among patients with Group III rhabdomyosarcoma: A report from the Children's Oncology Group. *Eur J Cancer*. 2014;50:816-823.
6. Dantonello TM, Stark M, Timmermann B, et al. Tumour volume reduction after neoadjuvant chemotherapy impacts outcome in localised embryonal rhabdomyosarcoma. *Pediatr Blood Cancer*. 2015;62:16-23.
7. Orsatti G, Morosi C, Giraudo C, et al. Pediatric rhabdomyosarcomas: Three-dimensional radiological assessments after induction chemotherapy predict survival better than one-dimensional and two-dimensional measurements. *Cancers (Basel)*. 2020;12:3808.
8. Ladra MM, Mandeville HC, Niemierko A, et al. Local failure in parameningeal rhabdomyosarcoma correlates with poor response to induction chemotherapy. *Int J Radiat Oncol Biol Phys*. 2015;92:358-367.
9. Bradley JA, Indelicato DJ, Uezono H, et al. Patterns of failure in parameningeal alveolar rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys*. 2020;107:325-333.
10. Ermoian RP, Breneman J, Walterhouse DO, et al. 45 Gy is not sufficient radiotherapy dose for Group III orbital embryonal rhabdomyosarcoma after less than complete response to 12 weeks of ARST0331 chemotherapy: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Pediatr Blood Cancer*. 2017;64.
11. Breneman J, Meza J, Donaldson SS, et al. Local control with reduced-dose radiotherapy for low-risk rhabdomyosarcoma: A report from the Children's Oncology Group D9602 study. *Int J Radiat Oncol Biol Phys*. 2012;83:720-726.
12. Casey DL, Chi YY, Donaldson SS, et al. Increased local failure for patients with intermediate-risk rhabdomyosarcoma on ARST0531: A report from the Children's Oncology Group. *Cancer*. 2019;125:3242-3248.