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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

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Abstract

Background—The prognostic significance of response to induction therapy for rhabdomyosarcoma (RMS) by anatomic imaging [computerized tomographic (CT) or magnetic resonance imaging (MRI) scan] is controversial. We previously reported no relationship between early response and failure-free survival (FFS) on Intergroup Rhabdomyosarcoma Study IRS-IV. We repeated the same analysis using a more recent clinical trial as an independent cohort of patients with non-metastatic, initially unresected RMS.

Methods—A total of 338 patients enrolled in Children's Oncology Group (COG) study D9803 met the inclusion criteria for this analysis: (1) non-metastatic, initially unresected (Group III); (2) embryonal (ERMS) or alveolar (ARMS) histology; (3) documented protocol week 12 response to induction chemotherapy (excluding progressive disease) based on anatomic imaging (CT/MRI); and (4) documented protocol therapy beyond week 12. Response at week 12 was determined by the treating institution as complete response (CR), partial response (PR), or no response (NR). FFS

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was estimated using the Kaplan-Meier method and comparisons between patient subsets were made using the log-rank test.

Results—Overall objective response rate (CR+PR) at week 12 of therapy was 85% and was similar between ERMS and ARMS. FFS was similar among all patients with CR, PR, or NR ($p=0.49$). Restricting the analysis to either ERMS or ARMS, there was no difference in FFS by response within either histology subset ($p=0.89$ and $p=0.08$, respectively).

Conclusions—These findings provide additional evidence that anatomic imaging to assess early response to therapy among patients with RMS does not predict outcome and has questionable use in tailoring subsequent therapy.

Keywords

Rhabdomyosarcoma; Pediatric Cancer; Survival Outcomes; Sarcoma

INTRODUCTION

Collaborative research has enabled dramatic improvements in outcomes for patients with rhabdomyosarcoma (RMS), and current, risk-based treatment strategies aim to optimize survival while minimizing acute and long-term toxicities.(1) Pre-treatment risk stratification for RMS is based on stage (including tumor size, site, invasiveness, and regional nodal status)(2) and clinical grouping (the extent of surgical resection prior to systemic chemotherapy).(3) Other known prognostic factors include age and tumor histology, with embryonal RMS (ERMS) associated with superior outcomes compared to alveolar RMS (ARMS).(4) Combining stage, Group, and histology, an intermediate risk category includes all non-metastatic ARMS patients and incompletely resected (Group III) ERMS patients with an unfavorable primary site.(1) Overall, intermediate-risk RMS is associated with failure-free survival (FFS) rates of 65% to 73%.(5–7)

Response to initial chemotherapy is related to outcome in several pediatric cancers and provides potential for further risk-stratification and/or early treatment modification. For example, microscopic measurement of residual disease is related to outcome among patients with acute lymphoblastic leukemia,(8) Ewing sarcoma,(9) and osteosarcoma.(10, 11) Functional imaging modalities such as fluorodeoxyglucose positron emission tomography (FDG PET) and metaiodobenzylguanidine (MIBG) predict outcome among patients with Hodgkin Lymphoma(12–14) and neuroblastoma,(15, 16) respectively. Among patients with RMS, response assessments have historically been determined by anatomic imaging assessments such as computed tomography (CT) or magnetic resonance imaging (MRI), despite evidence that the predictive power of these assessments may be limited in patients with soft tissue sarcomas,(17) and other cancer-types.(12, 18) The relationship between early anatomic imaging response and outcome among patients with RMS is unclear. On Intergroup Rhabdomyosarcoma Study (IRS)-IV, anatomic imaging response at week 8 of therapy was unrelated to FFS,(19) leading to the conclusion that anatomic assessment could not reliably distinguish viable from necrotic tumor or scar tissue. However, other RMS clinical trials, including the Cooperative Soft Tissue Sarcoma (CWS) (20–22) and the Société Internationale d' Oncologie Pédiatrique (SIOP) Malignant Mesenchymal Tumor (MMT) (23, 24) studies, have used early anatomic response to tailor subsequent therapy, based upon observations in CWS trials that change in tumor volume is associated with outcome.(20, 21)

To assess the relationship between anatomic imaging response and FFS among patients with Group III RMS, we used the same methodology we applied to IRS-IV in an independent

data-set from the more recent Children's Oncology Group (COG) clinical trial for intermediate risk RMS, D9803.(6)

PATIENTS AND METHODS

The methods of COG D9803 have been described previously.(6) Briefly, patients with newly diagnosed, intermediate risk RMS were enrolled between 1999 and 2005. All patients were randomly assigned to treatment with either vincristine, dactinomycin, and cyclophosphamide (VAC) or VAC alternating with vincristine, topotecan, and cyclophosphamide (VAC/VTC, Table 1). Response assessments were conducted at weeks 12, 24, and at the end of therapy. No changes in chemotherapy were made based upon radiographic response. Patients with primary parameningeal tumors with intracranial extension (ICE) were non-randomly assigned to treatment with VAC and up-front radiation therapy (RT). For all other patients, RT was delayed until after the week 12 assessment. Delayed primary excision was encouraged when feasible after the week 12 assessment for selected primary sites, including the extremity, dome of the bladder, and trunk. Patients whose tumor was completely resected with negative margins at week 12 received 36 Gy of RT; those with microscopic residual tumor following resection or those with clinical complete remission by imaging and biopsy confirmation received 41.4 Gy. All other Group III patients received 50.4 Gy. Depending on whether delayed primary excision was or was not performed, RT respectively began either within 3 weeks after surgery or within 3 days of completion of induction chemotherapy (week 12).

The goal of this analysis was to evaluate the relationship between anatomic image-defined response to induction chemotherapy and FFS. Since there were no differences in FFS by chemotherapy regimen used on COG D9803,(6) both chemotherapy arms and the non-randomized VAC arm were combined for analysis. Included patients had central pathology review and confirmation of their diagnoses, Group III, ERMS or ARMS histology, documentation of response to induction therapy (excluding patients with progressive disease prior to or at week 12), and documented therapy beyond week 12. Response at week 12 was determined by the treating institution based on standard anatomic imaging (CT/MRI) and defined by the World Health Organization criteria:

- Complete Response (CR): complete resolution of disease;
- Partial Response (PR): decrease of 50% or more in the sum of products of the maximum perpendicular diameters of all measureable lesions, no evidence of progression in any lesion, no new lesions;
- No Response (NR): less than 50% decrease and less than 25% increase in the sum of products of the maximum perpendicular diameters of measurable lesions at any involved site;
- Progressive Disease (PD): 25% or greater increase in the sum of products of the maximum perpendicular diameters of all measurable lesions at any involved site, or the appearance of new lesions.

Histologic classification as ERMS or ARMS reflected the final central pathologic review using the most recently defined criteria.(25) FFS was defined as the time interval from study enrollment to disease progression, relapse, or death. FFS was estimated using the Kaplan-Meier method(26) and comparisons between patient subsets were made using the log-rank test.(27) We compared FFS by response at week 12, by histologic subgroup among patients who received standard RT after week 12, and by delivery and timing of RT.

RESULTS

The clinical characteristics and treatment-related outcomes of patients enrolled in COG D9803 have been described elsewhere.⁽⁶⁾ Of the 616 eligible patients enrolled, 338 met the criteria for inclusion in the current analysis. Reasons for exclusion included histology other than ERMS or ARMS (n=90), non-Group III (n=139), response not documented at week 12 (n=20), PD by week 12 (n=6), and no documented therapy beyond week 12 (n=23).

Most of the included patients were between 1 and 9 years-old and 62% were male (Table 2). Most tumors (65%) were stage 3, ERMS (61%) and greater than 5 cm (59%). Parameningeal was the most common primary site.

Overall objective response rate (ORR) at week 12 of therapy was 85% (CR 28%, PR 57%; Table 3). FFS was similar among all patients with CR, PR, or NR (Figure 1, p=0.49). Restricting the analyses to patients who received standard week 12 RT, those with ERMS and CR (n=43), PR (n=98), and NR (n=44) after 12 weeks of therapy had 5-year FFS of 86%, 80%, and 78%, respectively (p=0.89). Among ARMS patients, those with CR (n=33), PR (n=34) and NR (n=5) after 12 weeks of therapy had 5-year FFS was 59%, 63%, and 20%, respectively (p=0.08).

Exploratory analyses comparing outcomes based on delivery of RT demonstrated similar results. Patients receiving standard RT at week 12 or beyond had an overall response rate (ORR) of 88% (CR 32%, PR 56%), those with parameningeal primary site and ICE receiving upfront RT had an ORR of 73% (7% CR, 66% PR), and those who did not receive RT at all had an ORR of 89% (39% CR, 50% PR; Table 3). Among patients receiving RT at week 12 or beyond, upfront RT, or no RT, there was no difference in 5 year FFS by anatomic response category, although some of the comparisons were limited by small sample sizes.

DISCUSSION

Patients with Group III, intermediate risk RMS enrolled on COG D9803 demonstrated excellent response to induction, with ORR of 85% based on week 12 anatomic imaging assessments. However, this radiographic response did not predict FFS. Although patients with ERMS had superior FFS than those with ARMS, there were no statistical differences in FFS within either histologic subgroup based on 12-week response to therapy using type I error rates of <5%.

These findings are strikingly similar to prior analyses from IRS-IV, where anatomic response assessments at week 8⁽¹⁹⁾ and the end of therapy⁽²⁸⁾ were unrelated to FFS in Group III patients. Indeed, isolated anatomic imaging may not accurately estimate active residual disease in patients with soft-tissue sarcomas.⁽¹⁷⁾ In IRS-IV, for example, only 50% of pathologic specimens from patients whose best response was a PR or NR, and who also had surgical sampling of their end-of-treatment residual mass, demonstrated viable tumor.⁽²⁸⁾ Recognizing that a residual radiographic abnormality at the end therapy may be non-malignant, both CWS⁽²²⁾ and MMT⁽²⁴⁾ classify patients as CR if they have a stable residual mass for more than 6 months. Still, there are conflicting data on the prognostic significance of early radiographic response. In CWS-81, CWS-86, and CWS-91, patients with poor response to induction chemotherapy had inferior FFS than those who achieved a good response.^(20–22)

Ferrari, et. al. have suggested that modeling response as a continuous, rather than categorical, variable is more predictive of survival outcomes among patients with RMS.⁽²⁹⁾ These authors also described a high correlation between one- and three-dimensional

measurements, suggesting that volumetric assessment is not a superior technique for response assessment.(29) Rather, wide inter-observer variability among radiologists reporting linear tumor measurements(30) may account for some of the discrepancies in the literature.(29)

Several factors confound direct comparisons between the European and North American cooperative group studies. First, the CWS, MMT, and Milan institutional studies included relatively few Group III patients with response assessments (76, 134, 150 in CWS-81, -86, and -91, respectively, 62 in MMT-89, and 77 in the Milan series). Most of these studies also included sarcoma patients with histologies other than ERMS and ARMS. Second, poorly responding patients in CWS and MMT studies received alternative therapies, making it difficult to determine the true relationship between initial response and outcome. Third, our analysis used three response categories (CR, PR, NR) measuring tumor size in two dimensions, in contrast to two response categories ($\geq 66\%$, $<66\%$ reduction) measuring tumor size in three dimensions as used in CWS and MMT, which might result in different response classification. Fourth, our analysis focused on FFS, excluding patients with early tumor progression. Early tumor progression on-therapy is rare (occurring in less than 3% of Group III RMS patients) and associated with inferior overall survival.(31) It is possible that combining this particularly poor prognosis group with other patients with $<66\%$ tumor response may explain the inferior outcomes seen in CWS trials.

The purpose of the present study was to validate prior findings that anatomic imaging does not predict FFS among patients with Group III RMS. Our results corroborate IRS-IV analyses(19) and complement the primary findings of D9803(6). We utilized the same methodology as in IRS-IV, but with an independent data-set of patients from D9803 who received contemporary treatment regimens and potentially more modern imaging techniques. Because the imaging modality used to measure tumor size was not recorded on either study, we cannot determine whether MRI was used more frequently on D9803, although that is likely. The combined results from IRS-IV and D9803 imply that institutional anatomic imaging assessments of response by change in tumor size are unable to predict outcome in RMS and should not be used to tailor patient therapy.

It is disappointing that response to initial chemotherapy is not a predictive marker for outcome. The early identification of higher-risk patients may be critical to improving outcomes; radiographic determination of risk is easy and relatively inexpensive. Such predictors are of particular interest in intermediate risk RMS, where recent studies of chemotherapeutic regimens have failed to demonstrate improvements in survival.(5, 6)

Initial response to therapy has been linked to outcome in several other childhood malignancies, including by pathologic evaluation in acute lymphoblastic leukemia,(8) osteosarcoma,(11) and Ewing sarcoma.(9) Limitations of anatomic imaging methods have been described for patients with Ewing sarcoma,(18) Hodgkin lymphoma,(12, 32) and soft tissue sarcomas.(17) Functional imaging modalities, either alone or in combination with anatomic assessments, may be more accurate. For example, FDG PET shows promise in RMS,(33) other soft tissue sarcomas,(34, 35) Ewing sarcoma,(36) and osteosarcoma,(37) and may ultimately prove to be a superior assessment of response in patients with RMS. The predictive value of FDG PET is being evaluated prospectively on the recent completed COG intermediate-risk RMS study, ARST0531.

Our results suggest a trend towards inferior FFS among ARMS patients who had no response based on week 12 anatomic imaging. In comparison, on IRS-IV, the 16 ARMS patients with NR at week 8 had a FFS similar to those with CR, while those with PR did worse.(19) In each study, the number of patients in the ARMS/NR sub-group was small, and

differences between the two studies (e.g., timing of radiographic assessments and lack of histologic re-review in IRS-IV) preclude pooled analyses. These limitations, in combination with the inconsistent findings, prevent strong conclusions. Similarly, it is possible that we have not identified the optimal timing for response assessment. The observed similarities in response based on imaging performed after 8 weeks(19) and the end of therapy on IRS-IV, (28) and after 12 weeks on D9803, suggest that no time of response assessment is more predictive of outcome.

One potential confounder in our analysis is the variable use of local control, including delayed primary excision and RT.(1) Since RT was used in almost all patients with Group III RMS on IRS-IV and D9803, it is unlikely that post-response assessment RT confounds the analysis. Indeed, induction response was not related to FFS among patients who received up-front RT on IRS-IV,(19) and our analyses showed similar overall response rates between patients who received standard RT at or after week 12 and patients with parameningeal primary site and ICE who received RT earlier than week 12. D9803 encouraged surgical excision of the primary tumor after week 12 if it was feasible and the tumor was in a select site (extremity, dome of the bladder, trunk). In these patients, radiation doses were adjusted according to the amount of residual tumor.(6) It is possible that patient-specific surgical plans may have affected outcomes; our analysis could not adjust for individual provider practice. Only 20% of all Group III patients in D9803 underwent delayed primary excision, the response rate at week 12 was similar between patients who did and did not have a delayed primary excision, and the local failure rate with this strategy was similar to that of IRS-IV.(38) Therefore, it is unlikely that variable use of delayed primary excision confounded our observations.

Rather than using central imaging review of response, investigators at local institutions determined response based on locally preferred modalities (CT/MRI). Centralized review of radiographic response may have provided more uniform assessments, with the potential to demonstrate the predictive value of early response assessment. Likewise, while measuring response as a continuous variable may be more predictive of outcome,(29) it is neither as feasible nor as consistently defined as categorical response assessments. To address these limitations, central imaging review of FDG PET is part of the recent COG intermediate risk RMS study, ARST0531, to determine if functional imaging is useful in assessing early response to therapy.

The results from IRS-IV and those reported here from D9803 provide additional evidence that anatomic imaging alone to assess early response to therapy among patients with Group III RMS does not consistently predict FFS and should not be used to tailor subsequent therapy. Alternative imaging modalities, including FDG PET, should be explored.

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Figure 1.
Failure free survival based upon week 12 anatomic imaging assessment of response

Table 1Treatment Schema for Children's Oncology Group Study D9803.⁶

<u>Induction (week)</u>													<u>Local Control (week)</u>												E V A L U A T I O N	
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		E V A L U A T I O N
VAC	V A C ¹	V	V	V	V	V	V	V	V	V	V	V	V		V			V	V	V	V	V	V			
				A C ¹					A C ¹			A C ¹			C ¹			C ¹			A C ¹					
VAC/VTC	V A C ¹	V	V	V	V	V	V	V	V	V	V	V	V		V			V			V	T C ²				
				T C ²					A C ¹			T C ²			C ¹			C ¹								
													RADIATION THERAPY													
<u>Continuation (week)</u>																									E V A L U A T I O N	
24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42								
VAC	V A C ¹			V			V			V	V	V	V			V										
				A C ¹			A C ¹			A C ¹			A C ¹			A C ¹										
VAC/VTC	V A C ¹			V			V			V	V	V	V			V										
				T C ²			A C ¹			T C ²			A C ¹			T C ²										
Treatment schema: randomized schedule of either vincristine (V), dactinomycin (A), and cyclophosphamide (C) (VAC) or VAC alternating with V, topotecan (T), and CVAC/VTC) at weeks 3, 9, 21, 27, 33, and 39. Doses of drugs for children age 3 years and older were V 1.5 mg/m ² (maximum dose, 2 mg) × 1 day; A 0.045 mg/kg × 1 day (maximum dose, 2.5 mg); T 0.75 mg/m ² × 5 days; C ¹ 2.2 g/m ² × 1 dose (with mesna uroprotection);C ² 250 mg/m ² /dose for 5 days.																										

Table 2

Patient Characteristics

Characteristic (N=338)	n	(%)
Age, years¹		
<1	5	1
1 to 9	244	72
10+	89	26
Sex		
Male	211	62
Female	127	38
Stage		
1	21	6
2	96	28
3	221	65
Node Status		
N-0	274	81
N-1	64	19
T stage²		
T-1	152	45
T-2	185	55
Size, cm		
≤ 5 cm	139	41
> 5 cm	199	59
Histology		
Alveolar	132	39
Embryonal	206	61
Primary site¹		
Extremity	49	15
Genito-urinary	43	13
Head and neck	7	2
Intrathoracic	3	1
Orbit	12	4
Other	24	7
Parameningeal	155	46
Perineum	6	2
Retroperitoneum	34	10
Trunk	5	1

¹ Sum of percents not 100% due to rounding² One patient missing T-stage information

Table 3

Estimates of FFS among all patients and by histologic subtype and delivery of RT

Week 12 Response	n (%)	5 year FFS (95% CI)	p-value ^I
All Patients	(N=338)		
CR	95 (28)	74% (64%, 82%)	0.49
PR	193 (57)	75% (63%, 83%)	
NR	50 (15)	64% (47%, 82%)	
Week 12 or later RT	(N=237)		
CR	76 (32)	75% (63%, 83%)	0.66
PR	132 (56)	76% (68%, 83%)	
NR	29 (12)	68% (47%, 82%)	
Embryonal histology	(N=165)		
CR	43 (26)	86% (72%, 93%)	0.89
PR	98 (59)	80% (71%, 87%)	
NR	24 (15)	78% (55%, 90%)	
Alveolar histology	(N=72)		
CR	33 (46)	59% (40%, 74%)	0.08
PR	34 (47)	63% (44%, 77%)	
NR	5 (7)	20% (0.8%, 58%) ^I	
Parameningeal primary with ICE, early RT	(N=65)		
CR	5 (7)	100% (--)	0.44
PR	43 (66)	74% (58%, 85%)	
NR	17 (26)	68% (38%, 86%)	
No RT	(N=36)		
CR	14 (39)	63% (33%, 83%)	0.39
PR	18 (50)	67% (40%, 83%)	
NR	4 (11)	25% (0.9%, 67%) ²	

^I Based on log-rank test**Abbreviations:** failure-free survival, FFS; complete response, CR; partial response, PR; no response, NR; radiation therapy, RT; intracranial extension, ICE