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Treatment Approach and Outcomes in Infants with Localized Rhabdomyosarcoma: A Report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group

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Abstract

Purpose: For infants with localized rhabdomyosarcoma enrolled on Children's Oncology Group (COG) ARST0331 and ARST0531, local therapy guidelines were provided but adherence was not mandated given toxicity concerns. We examined adherence to protocol local therapy guidelines, treatment variations, and outcomes for these infants.

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Methods: Children 24 months enrolled on ARST0331 and ARST0531 were evaluated. Data were verified through radiologic, surgical, pathologic, and clinical records. Local therapy was assessed for adherence to protocol guidelines, with variations termed individualized local therapy. Subdistribution hazards model assessed local failure (LF); Kaplan-Meier product limit method assessed event-free survival (EFS), and overall survival (OS); log-rank test was used to evaluate prognostic impact.

Results: 124 patients were eligible. Median age was 14 months. Common primary sites were genitourinary (40%), parameningeal (14%), and extremity (11%). Most patients had unresected disease (group III, 64%) and embryonal histology (73%).

58% of patients received radiation therapy (RT) at a median of week 12 (week 1–45). Median radiation dose was 48.6Gy (30.6–54Gy). 43% received individualized local therapy (outside protocol guidelines), typically omission or delay of RT. Delayed primary excision (DPE) was performed in 28% at a median of week 14 (week 7–34). With a median follow-up of 5.6 years, the 5-year LF, EFS, and OS rates were 24%, 68%, and 82%. Local failure was significantly higher in patients receiving individualized local therapy (35%) than in patients who received protocol-specified local therapy (16%; $p=0.02$). Site of failure was local in 64%, local and distant in 5%, and distant only in 23%. EFS was significantly higher among patients aged 12–24 months, tumors <5cm, group I/II disease, and use of protocol-specified therapy.

Conclusions: Local recurrence was the predominant pattern of failure and more common in those receiving individualized local therapy. De-escalation of effective therapies due to concerns about treatment toxicity should be considered cautiously.

Summary

Infants (<24 months old) enrolled on Children's Oncology Group ARST0331 and ARST0531 protocols were permitted to undergo individualized local therapy. This retrospective review assesses the treatment approach and outcomes for these infants. While local control, event-free survival, and overall survival did not differ from older children on these protocols, individualized therapy was associated with a lower 5-year event-free survival and double the rate of local failure compared to protocol-specified therapy.

Introduction

Rhabdomyosarcoma (RMS) is the most common childhood sarcoma, and curative therapy includes systemic chemotherapy and local therapy consisting of surgery, radiation therapy (RT), or both (1). Patient age has prognostic importance, with inferior outcomes in adolescents >10 years and infants <1 year (2, 3). Although failure-free survival (FFS) for children with localized RMS has increased over the past 50 years, the youngest children have not experienced the same improvement in outcome. FFS has been significantly worse for infants <1 year of age compared to those aged 1 to 9 years on both North American (4) and European (5) treatment protocols. When controlled for stage and group, age <1 year remains an independent prognostic factor for inferior outcome (2, 6). These differences in outcome have been attributed to a decrease in therapy for infants due to concerns about treatment toxicity (6, 7).

In recent Children's Oncology Group (COG) low- and intermediate-risk protocols (ARST0331 and ARST0531, respectively), treating physicians were encouraged to adhere to local therapy protocol guidelines; however, given toxicity concerns, adherence to local therapy guidelines was not mandated for patients ≥ 24 months of age (8–10). For these young children, individualized local therapy that varied from the protocol guidelines was not considered a protocol deviation. Allowance of local therapy variance could improve the ability to recruit and retain infants on the protocol. We report the outcomes and treatment strategies employed for children aged ≥ 24 months enrolled on the COG ARST0331 and 0531 protocols.

Materials and Methods

Study Population

Children ≥ 24 months of age (infants) at the date of enrollment on COG protocols ARST0331 (low-risk) and ARST0531 (intermediate-risk) were eligible for retrospective analysis. These protocols were approved by institutional review boards and informed consent was obtained prior to enrollment. All 126 eligible patients had localized disease. Primary site, disease stage, and group were defined according to COG standard definitions (4). Stage and group were verified by reviewing radiographic, surgical, pathologic, and clinical records, resulting in ineligibility for 2 patients with higher-risk disease.

Protocol Specified Treatment

Radiation was not recommended for embryonal RMS group I disease. However, RT was administered at 36 Gy for alveolar RMS group I disease except in situations where the tumor bed no longer exists following surgery. Clinical group II patients received either 36 Gy for node-negative or 41.4 Gy for node-positive disease. Clinical group III patients received 50.4 Gy. In both studies, gross tumor volume (GTV) was determined by imaging at diagnosis (GTV1) and after induction chemotherapy (GTV2). An additional 1-cm margin, edited for normal anatomic barriers, comprised the clinical target volume (CTV) 1 and CTV2, respectively. An additional 0.5 cm margin yielded the planning target volumes (PTV) 1 and PTV2, respectively. A reduction of the RT field to GTV2/CTV2/PTV2 was only permitted in treatment responsive tumors if the total prescribed dose was 50.4 Gy. Major deviations were defined as a $>10\%$ deviation between delivered and protocol-specified RT dose, $<90\%$ CTV coverage by 95% of the prescribed dose, and exclusion of GTV or CTV from the treatment field. Minor deviations were defined as a 6–10% variance between delivered and protocol-prescribed doses, $<100\%$ of the CTV coverage by 95% of the prescribed dose, and CTV/PTV margin less than or significantly greater than protocol specifications.

RT dosing was adjusted, but not omitted, based upon the completeness of delayed primary excision (DPE): 36 Gy for complete R0 resection, 36–41.4 Gy for microscopic residual disease (R1 resection), and 50.4 Gy for gross residual disease (R2 resection). Biopsy only was noted, but not categorized as DPE. DPE was permitted but neither encouraged nor prohibited on ARST0331 and ARST0531. The completeness of both initial resection (group) and DPE (R status) was assessed based on operative, pathologic, and imaging records. From these records it was determined whether resection resulted in the permanent loss of organ

function (loss of function) or loss of a structure that was associated with decreased cosmesis or morbidity (resection of vital structures).

All patients received chemotherapy that included vincristine, dactinomycin, and cyclophosphamide with age-specific dosing guidelines (8–10). The timing of local therapy differed between the 2 protocols: week 13 on ARST0331 and week 4 on ARST0531.

Analysis

Infants were assessed for variations to the protocol local therapy guidelines that were required for older children. Treatment of infants with variation that met the protocols' criteria for major deviation was termed "individualized local therapy," while those without major variation was termed "protocol-specified." The original ARST0331 protocol did not recommend adjuvant radiation for patients with group II or III vaginal primaries that had a biopsy proven complete response to chemotherapy or underwent R0 resection through DPE. However, due to a high local recurrence rate with this approach, the protocol was amended in 2009 to require RT in this situation (11). For our analysis, omission of radiation in group II or III patients with vaginal primaries was considered individualized local therapy. Variations that met the protocols' definitions of minor deviation were not considered individualized local therapy. Chemotherapy modifications were not assessed. The RT treatment records were reviewed at the Imaging and Radiation Oncology Core (IROC) Rhode Island (formerly Quality Assurance Review Center [QARC]) including contours, dose, fields, isodose lines, and dose-volume histograms. DPE within the first 15 weeks from initiation of chemotherapy was considered protocol-specified, but beyond week 15 was considered individualized local therapy. RT initiated more than 3 weeks before or after the protocol-specified timing was considered individualized local therapy, as was RT delivered more than 8 weeks after DPE. These are categorized as delayed radiation in this analysis.

The Chi-square test was used to compare demographic and clinical features between infants and older children. The subdistribution hazards model {Fine, 1999 #32} was used to assess the cumulative incidence of local failure; The Kaplan-Meier product limit method was used to compute the event-free survival (EFS) and overall survival (OS) rates. Local failure was defined as recurrence at the primary site with or without failure elsewhere. The method proposed by Peto-Peto was used to construct the 95% confidence interval (CI). The log-rank test was used for evaluating the prognostic impact of patient characteristics and the impact of protocol deviations.

Results

Patient and disease characteristics

The median age of the 124 eligible patients was 14.0 months (range, 0.07 to 23.4 months). The median follow-up for living patients was 5.6 years (range, 1.2 to 10.9 years). The majority of patients were male (54%), had group III disease (64%), and had embryonal histology (73%). The most common primary sites were genitourinary (GU; 40%), parameningeal (14%), and extremity (11%). Compared to older children, the infants more commonly had an unfavorable primary site (64.5% vs. 54.9%; $p=0.048$) (Table 1).

Enrollment of infants was similar between the ARST0331 and ARST0531 protocols (16%; 124/787) and the earlier D9602 (low-risk) and D9803 (intermediate-risk) protocols (15%; 149/1019) in which individualized local therapy was not permitted (12, 13).

Local therapy

Radiation was delivered using intensity-modulated photon RT in 46% of cases (33/72), 3Dconformal photons in 24% (17/72), and proton therapy in 19% (14/72). Brachytherapy (n=3), electrons alone (n=3), and intraoperative RT (n=1) were used infrequently. For one patient, radiation modality was unknown. RT was given at a median of week 12 (range, 1 to 45) for all patients. For those enrolled on ARST0331, RT was given at a median of week 16 (range, 12 to 45), and for ARST0531 patients, the median week of RT was 4 (range, 1 to 43). The median radiation dose was 48.6 Gy (range, 30.6–54 Gy). 19% (24/124) of the infants enrolled on ARST0331 and ARST0531 had omission of indicated RT, including one group I patient and 23 group II or III patients. Local therapy for group II and III infants is described in Figure 1. Of the 17 group I patients on ARST0331, none received radiation, in keeping with the protocol guidelines. On ARST0531, 1 of 3 group I patients with alveolar RMS received radiation. Per protocol guidelines, 2 patients should have received adjuvant radiation, while the third had a testicular primary tumor treated with orchiectomy and chemotherapy and thus no radiation per protocol guidelines.

DPE was utilized as a component of local therapy in 28% (29/104) of infants with group II (n=3) and III (n=26) disease at a median of week 14 (range, week 7–34). Most patients had R0 (28%) or R1 (41%) resections, while 14% had R2 resection and 17% had an unknown extent of resection. DPE altered the RT dose in 38% of patients and radiation was omitted after DPE in 41% of patients. In addition, 2 patients did not receive RT following exam-under-anesthesia (n=1) and biopsy-only (n=1) at the time local therapy was due. Table 2 identifies both initial surgeries and DPE that resulted in loss of function or resection of vital structures.

Local therapy was individualized in 43% of infants (53/124), most commonly due to delay or omission of RT (Figure 2). Group III patients (51%) were more likely to receive individualized local therapy compared to group I/II patients (30%; $p=0.019$). While no major variations were found in target coverage or CTV/PTV expansions, minor variations occurred in 25% of the infants receiving radiation.

Outcomes

Infant 5-year EFS was 68.3% (95% CI: 57.2% to 79.4%) and OS was 81.9% (95% CI: 72.9% to 91.0%). By univariate analysis, age <1 year, primary tumor size >5 cm, and group III disease were associated with inferior EFS (Table 3). Local therapy performed later than protocol specifications did not affect EFS. However, 5-year EFS after individualized local therapy (55.6%) was lower than protocol-specified therapy (77.5%) ($p=0.04$). Overall survival did not differ between infants treated with individualized local therapy compared to protocol-specified therapy (78.5% vs. 84.3%, $p=0.42$).

EFS and OS were not significantly different between infants and older children (>24 months) on ARST0331 and ARST0531 or from infants <24 months enrolled on the

preceding COG RMS trials, D9602 and D9803 (Figure 3) (12, 14). No differences in EFS or OS were identified based on subgroup analysis including risk group and histology.

Local failure was the predominant pattern of failure (Table 4). The 5-year cumulative incidence of local failure was not significantly different between infants and older children on ARST0331 and ARST0531 (23.6% vs. 17.7%, respectively; $p=0.09$) (Figure 4). Most failures were local alone (64%) or had a local component (74%). Individualized local therapy was associated with inferior 5-year cumulative incidence of local failure (34.8%; 95% CI: 21.6% to 48.0%) compared to protocol-specified therapy (15.5%; 95% CI: 7.0% to 24.0%; $p=0.02$). Delayed local therapy did not significantly impact cumulative incidence of local failure (26.3% vs. non-delayed 16.2%; $p=0.29$). Of the 24 patients who received individualized local therapy due to omission of RT (with or without DPE), 11 failed locally. Infants recurred within a range of 0.1 to 3.3 years and older children between 0.03 and 5.8 years. The median time to failure cannot be determined as the survival curve did not cross the 0.5 reference line. Distant metastases ($n=12$) most commonly developed in the brain ($n=4$), lung ($n=3$), and bone ($n=3$; range, 0.3 to 1.6 years). Distant metastases alone comprised the first site of failure in 23% of patients with disease progression.

Progression during therapy occurred more frequently in infants compared to older children (15.3% vs. 5.1%; $p<0.0001$). Progression on protocol therapy was not associated with protocol-specified vs. individualized local therapy ($p=0.57$) or delayed vs. on-time local therapy ($p=0.80$).

Discussion

The guiding principles of local therapy for RMS include disease control while maintaining form, function, and quality of life. These goals may conflict, especially in infants who are in the earliest stages of development. Because of this, varying treatment philosophies have emerged to balance these management principles. Through COG, RT has been employed in initial management to maximize local control, with a primary endpoint of EFS (15). However, the International Society of Paediatric Oncology (SIOP) withholds RT unless there is a lack of response to chemotherapy or recurrent disease, with a primary endpoint of OS (15). One goal of permitting enrollment of infants despite individualized local therapy was to increase infant accrual compared to prior COG RMS studies, like D9602 and D9803, which did not permit individualized local therapy for infants. Interestingly, the percentage of infant accrual was similar on ARST0331 and ARST0531 compared to D9602 and D9803.

For the infants 24 months old enrolled on ARST0331 and ARST0531, the 5-year EFS was 68.3% and OS was 81.9%. These outcomes are comparable to published outcomes of infants from previous COG studies. Although most other series define infant as 12 months, this report includes children 24 months. We selected 24 months to correspond to the age cut-off used by ARST0331 and ARST0531 to allow individualized local therapy without classification as a protocol deviation. European series frequently report lower EFS with an approach that minimizes initial RT. Orbach et al (16) reported the outcomes of 102 infants aged 12 months. Most survivors (78%) were treated with minimal initial RT. After a complete response to therapy, 34% of patients relapsed, 23% developed metastatic disease,

and 69% developed a local recurrence. RT was not recommended for patients of any age in these protocols. Notably, 5 infants were treated with RT and all maintained local control, although definitive conclusions cannot be drawn given the small number. The EFS was 57% and OS was 72% for infants at 5 years. Unlike other COG trials, in this analysis of ARST0331 and ARST0531, no significant difference in local relapse, EFS, or OS occurred for infants compared to older children for the entire cohorts. Ferrari et al (17) described 50 patients aged 12 months enrolled on Italian Cooperative Group protocols. Local failure was 54% when RT was omitted due to young age, compared to 28% in those who had RT omitted per protocol. In this study, RT was used only in cases of gross, unresectable disease after induction chemotherapy. At 5 years, the infant EFS was 42.3% and OS was 61.7%, which were lower than older children (OS 67.2%). Historically, 5-year FFS of 57% and OS of 76% were achieved in the infants 12 months of age treated on IRS-IV, D9602, and D9803 (7). Infants 24 months on ARST0331 and ARST0531 experienced similar EFS and OS as infants 24 months enrolled on D9602 and D9803.

While EFS and local control did not vary between infants and older children when the entire cohorts were compared, individualized local therapy within the infant cohort was associated with inferior local control and EFS compared to protocol-specified therapy. EFS, local control, and OS may have been maintained because over 50% of infants were treated with protocol-specified therapy. Similarly, for infants 12 months of age treated on IRS-IV, D9602 and D9803, adherence to protocol guidelines was associated with higher FFS and OS (70% and 85%) compared to individualized therapy (FFS 46% and OS 64%, $p=0.07$ and $p=0.03$, respectively) (7). Our current study also shows improved EFS and local control with protocol-specified therapy, supporting the use of protocol directed local therapy in infants.

The most common RT variations in this study were delayed delivery of RT and omission of indicated RT. CTV and PTV margins were commonly below those specified by protocol, but only to the extent of yielding minor variations according to the protocol guidelines. Results from other series support the importance of RT use and quality. In an analysis of group II RMS patients, 12% recurred locally, and 55% of recurrences had a deviation in RT (41% omission, 37% dose, 20% volume) (18). In group III embryonal RMS patients who achieved gross total resection with DPE, local FFS was 91% with RT compared to 69% without ($p=0.14$) (19).

There are several limitations of this retrospective review. Given that local failure is the dominant first failure, this report focused solely on the individualization of local therapies. Other studies have found that chemotherapy is also individualized in these young patients (7). Indeed, ARST0331 and ARST0531 included age-specific chemotherapy dosing guidelines given toxicity concerns (20). Another limitation of this study is the lack of detailed toxicity data, affecting a balanced evaluation of the therapeutic ratio. While a primary goal is to preserve form and function, toxicity attributable to local therapy has not been collected for these patients. The surgical toxicity was estimated by assessing the organs resected and categorizing these into *loss of function* and *resection of vital structures*. The late RT toxicity for this cohort is not known. Late effects of RT in children from other series are well-documented, but few specifically report on infants, who are at the highest risk of radiation toxicity. One example is Ferrari et al (17) who reported bone and soft tissue

hypoplasia in all 6 infant long-term survivors after RT. In addition, we acknowledge that while much of the published data use age < 12 months as a division for age and outcome, this report assesses those aged 24 months and less, in keeping with the protocol stipulation regarding the permissibility of individualized local therapy.

Conclusions

Infants with low- and intermediate-risk RMS treated on the ARST0331 and ARST0531 protocols experienced similar EFS and OS compared to their older counterparts. Local failure predominated as the primary pattern of failure. Individualized local therapy was common in infants and those treated with individualized local therapy had inferior EFS and local control. The use of high-quality local therapy is critical to disease control in this young patient population and adherence to protocol-specified therapy is recommended.

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Figure 1.

Local therapy for group II and III infants on ARST0331 and ARST0531 protocols consisted of radiation alone, surgery alone, surgery and radiation, and omission of local therapy

Figure 2.
t Types of individualized local therapy for infants treated on ARST0331 and ARST0531.
Some patients had multiple factors contributing to individualized local therapy.

Figure 3.

(A) Event-free survival and (B) overall survival for infants on ARST0331 and ARST0531, older children on ARST0331 and ARST0531, and infants on D9602 and D9803

Figure 4.
Cumulative incidence of local failure for infants compared to older children treated on ARST0331 and ARST0531

Table 1.

Patient characteristics on ARST0331 and ARST0531.

		Age ≤24 months (N=124)	Age >24 months (N=663)	
Characteristic		No. of patients (%)	No. of patients (%)	P (chi-square)
Sex				
	Male	67 (54.0)	398 (60.0)	0.21
	Female	57 (46.0)	265 (40.0)	
Histology *				
	Alveolar	33 (26.6)	169 (25.5)	0.79
	Embryonal	91 (73.4)	494 (74.5)	
Primary tumor site				
	Favorable	44 (35.5)	299 (45.1)	0.05
	Unfavorable	80 (64.5)	364 (54.9)	
Specific site				
	GU ^o , non-bladder/prostate	25 (20.2)	142 (21.4)	Not applicable
	Bladder/prostate	25 (20.2)	44 (6.6)	
	Extremity	13 (10.5)	51 (7.7)	
	Head and neck	10 (8.0)	66 (10.0)	
	Intrathoracic	1 (0.8)	3 (0.5)	
	Orbit	7 (5.6)	82 (12.4)	
	Other	4 (3.2)	20 (3.0)	
	Parameningeal	17 (13.7)	191 (28.8)	
	Perineum/anus	2 (1.6)	9 (1.4)	
	Retroperitoneum	9 (7.3)	37 (5.5)	
	Trunk	11 (8.9)	18 (2.7)	
Stage				
	1	44 (35.5)	292 (44.0)	0.08
	2	33 (26.6)	125 (18.9)	
	3	47 (37.9)	246 (37.1)	
Group				
	I	20 (16.1)	115 (17.4)	0.94
	II	25 (20.2)	128 (19.3)	
	III	79 (63.7)	420 (63.4)	
Tumor size (cm)				
	≤5	77 (62.1)	372 (56.1)	0.24 [†]
	>5	45 (36.3)	276 (41.6)	
	Unknown	2 (1.6)	15 (2.3)	

* Histology from the institution was used for 16 patients (1 ≤24 months; 15 >24 months)

^o GU = Genitourinary

[†]Unknown excluded

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Table 2.

Surgical resections affecting function of vital structures.

A. LOSS OF FUNCTION		
<i>Site</i>	<i>At diagnosis</i>	<i>At time of local therapy</i>
Genitourinary and/or gynecologic	Orchiectomy (n=10)	Hysterectomy, bilateral salpingectomy (n=1) Hysterectomy, cystectomy, vaginectomy (n=1) Cystourethrectomy (n=1) Urethrectomy (n=1)
Extremity	Amputation of foot (n=1)	Amputation of leg, below-knee (n=1)
B. RESECTION OF VITAL STRUCTURES		
<i>Site</i>	<i>At diagnosis</i>	<i>At time of local therapy</i>
Genitourinary and/or gynecologic	Partial cystectomy with or without resection of bladder neck (n=2) Partial vaginectomy (n=1)	Partial cystectomy (n=1) Partial vaginectomy (n=2) *
Extremity		Radial nerve resection (n=1)
Head and Neck	Partial rhinectomy and partial maxillectomy (n=1) Medial maxillectomy (n=1) Infraorbital nerve resection (n=1)	Parotidectomy, resection of zygomatic arch and mandibular coronoid (n=1) Superficial parotidectomy, resection of mandibular ramus and angle, resection of mandibular branch of trigeminal nerve (n=1)
Trunk	Resection of costal cartilage and portion of diaphragm (n=1) Hepatic lobectomy, resection of bile duct, cholecystectomy (n=1)	

* Presumed (operative data incomplete)

Table 3.

Univariate analysis of event free survival for infants enrolled on ARST0331 and ARST0531.

Characteristic		No. of patients (%)	5-year Event Free Survival	P (log-rank)
Age (months)				
	<12	52 (42)	0.58	0.04
	12	72 (58)	0.76	
Site				
	Favorable	44 (36)	0.73	0.58
	Unfavorable	80 (65)	0.66	
Histology				
	Alveolar	33 (27)	0.63	0.56
	Embryonal	91 (73)	0.70	
Tumor size (cm)				
	5	77 (62)	0.75	0.05 [*]
	>5	45 (36)	0.55	
	Unknown	2 (2)		
Stage				
	1	44 (35)	0.73	0.16
	2	33 (27)	0.79	
	3	47 (38)	0.57	
Group				
	I	20 (16)	0.90	0.04
	II	25 (20)	0.71	
	III	79 (64)	0.62	
Individualized therapy				
	Yes	53 (43)	0.56	0.04
	No	71 (57)	0.77	
Local therapy				
	None	21 (17)	0.46	
	Not delayed	68 (55)	0.78	0.17 [†]
	Delayed	35 (28)	0.62	

^{*} Unknown excluded[†] No local therapy excluded

Table 4.

Patterns of failure for infants on ARST0331 and ARST0531.

Location of failure	No. of patients (%)
Primary site only	25 (64)
Primary site + regional	1 (3)
Primary site + distant	2 (5)
Primary site + regional + distant	1 (3)
Regional only	1 (3)
Distant only	9 (23)