ORIGINAL ARTICLE

Rhabdomyosarcoma in adolescents: A CCHE experience

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Abstract

Objective and aim: A lower outcome of rhabdomyosarcoma in elder children and young adolescents is increasingly recognized. Our aim was to focus on the outcome of elder children and adolescents with rhabdomyosarcoma treated at our Center (CCHE).

Patients and methods: Patients between the age 10 and 18 years diagnosed as rhabdomyosarcoma and treated according to IRS –IV, or IRS V protocols determined according to site, stage, and age at diagnosis.

Results: Thirty-two children were recruited at Children's Cancer Hospital-Egypt. They were 12 females (37.5%) and 20 males (62.5%), with a mean age of 12.8y. The mean follow up period was 29.4 months (July 2007 till December 2012). Seventeen patient, were allocated to IRS–IV, and 15 patient to IRS-V. The overall survival and failure free survival were 59.1% and 40.4% respectively. Forty six percent of patients had alveolar pathology, 68.8% presented with tumors at unfavorable sites; 37.5% had metastases at presentation; and 21.9% had intracranial extension at presentation. Risk status, clinical grouping and tumor size affected FFS significantly. Local control was done by radiation therapy in 62.5%, surgery alone in 9.4%, and both radiation and surgery in 25%.

Conclusion: The outcome of adolescent group showed inferior results compared to younger children. More cooperation and knowledge about RMS, in this age category, can help develop more intensive unified management approach for them.

Key words

Rhabdomyosarcoma, Adolescents, Sarcoma, Survival

1 Background

Rhabdomyosarcoma occurs predominantly in children below 7 years, with another peak in adolescence, then the incidence declines in older patients [1, 2].

Survival has improved much in children with rhabdomyosarcoma [3, 4], especially for non-metastatic disease. A lower outcome for older children and young adults with RMS is expected. Age is an important factor to consider as it greatly influences treatment decisions and possibilities. The treatment strategy use multi-agent chemotherapy, with or without local therapy. Although primary or secondary surgical resection, is important for local control, complete resection is not always feasible at certain cases. Radiotherapy (RT) has assumed a major role in the management of many patients [5].

Our aim was to focus on the outcome of our elder children and adolescents with rhabdomyosarcoma treated according to pediatric guidelines.

2 Patients and methods

2.1 Eligibility and consent

Patients aged from 10 to 18 years diagnosed as rhabdomyosarcoma were eligible provided they received no prior treatment, and started chemotherapy within 4 weeks of the date of initial biopsy or surgery. Informed consent was obtained from parent, according to our institutional review board (IRB) guidelines.

2.2 Staging

The disease was evaluated by standard clinical and radiologic techniques. Computed tomography (CT) or MRI were done to assess disease locally and regionally as well as metastatic workup including CT chest, bone scan, bilateral bone marrow aspirate and biopsy and PET assessment for some cases. CSF examination was done for all parameningeal tumors.

Biopsy was done for all presented cases for primary lesion or any suspicious lymph node involvement. Pathological assessment was done using H & E and immunohistochemical studies.

Staging and clinical grouping were done to all cases. Staging was done according to TNM staging and based on IRS-V guidelines (see Table 1).

Table 1. Pretreatment TNM staging system for RMS

M	N	Size	T	Sites	Stage
M_0	N_0 or N_1 or N_x	a or b	T_1 or T_2	Orbit, head and neck (excluding parameningeal), genitourinary (nonbladder/nonprostate), biliary tract	1
M_0	N_0 or N_x	a	T_1 or T_2	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, etc)	2
M_0M_0	N_1N_0 or N_1 or N_x	ab	T_1 or T_2	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, etc)	3
M_1	N_0 or N_1	a or b	T_1 or T_2	Any	4

Notes. Size: a, #5 cm in diameter; b, .5 cm in diameter.
Abbreviations: TNM, TNM Classification of Malignant Tumors; RMS, rhabdomyosarcoma; T, tumor; T_1, confined to anatomic site of origin; T_2, extension and or/fixative to surrounding tissue; N, nodes; N_0, regional nodes not clinically involved; N_1, regional nodes clinically involved; N_x, regional node status unknown; M, metastasis; M_0, no distant metastasis; M_1, metastasis present (includes positive cytology in pleural, peritoneal, or cerebrospinal fluid).

All diagnoses by our pathologists were classified according to the international classification [6].

2.3 Treatment schedule

Patients were treated with combined modality treatment including surgery, multi-agent chemotherapy and/or radio-therapy, adapted according to Risk stratification.

Therapy was assigned based on the IRSG rhabdomyosarcoma risk group classification (see Table 2). All our Patients were categorized according to the stage, clinical group and histological subtype into:

1) **Low risk group**: Included patients with embryonal RMS or botryoid who had:

   - Non-metastatic tumors arising in favorable sites (stage 1), clinical group I, II, or III
   - Non-metastatic tumors in unfavorable sites (stage 2 or 3) that are grossly resected with or without microscopic residual (clinical group I or II)

2) **Intermediate risk group**: Included patients with:

   - Embryonal RMS or botryoid who had stage 2 or 3 and clinical group III
   - Alveolar RMS who had stage 1, 2, or 3 and clinical group I, II, or III
   - Non metastatic Parameningeal primary site regardless the histology who had clinical group I, II, or III

3) **High risk group**: Included all metastatic patients with stage 4

Table 2. COG clinical group classification of RMS

Definition	Group
Localized disease, completely resected	Group I
Total gross resection, with evidence of regional spread	Group II
Grossly resected tumor with microscopic residual disease	A
Involved regional nodes completely resected with no microscopic residual disease	B
Involved regional nodes grossly resected with evidence of microscopic residual disease	C
Biopsy only or incomplete resection with gross residual disease	Group III
Distant metastatic disease (excludes regional nodes and adjacent organ infiltration)	Group IV

Note. COG, Children's Oncology Group; RMS, rhabdomyosarcoma

2.4 Chemotherapy

Figure 1 shows Summary of treatment protocol (Low Risk):

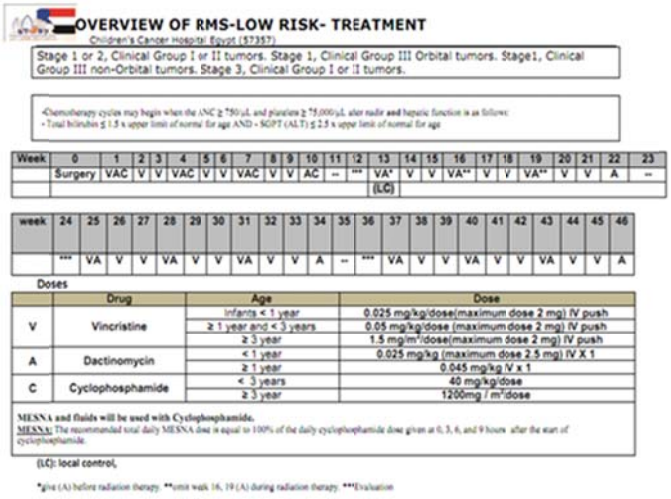

Figure 1. Treatment protocol (low risk)

Figure 2 shows treatment protocol (Intermediate Risk):

OVERVIEW OF RMS-INTERMEDIATE RISK- TREATMENT

Children's Cancer Hospital Egypt (57357)

Patient must have Intermediate-risk RMS defined as: a) Embryonal, botryoid, or spindle cell RMS, or ectomesenchymma: Stage 2 or 3 and Group III OR b) Alveolar RMS: Stage 1-3 and Group I-III.

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	15
	For Surgery	VAC	V	V	VAC	V	V	VC	V	V	VC	V	V	VAC	***
					Radiation Therapy										
		PET Scan			PET Scan										PET Scan

week	16	17	18	19	20	21	22	23	24	25	26	27	28	30
	VAC			VAC	V	V	VAC	V	V	VAC			VAC	***

week	31	32	33	34	35	36	37	38	39	40	41	42	43
	VAC	V	V	VAC	V	V	VAC			VAC			***

Doses

	Drug	Age	Dose
V	Vincristine	≥ 3 years	1.5 mg/m² x 1 (maximum dose 2 mg) IV push
		≥ 1 year and < 3 years	0.05 mg/kg x 1 (maximum dose 2 mg) IV push
		< 1 year	0.025 mg/kg x 1 (maximum dose 2 mg) IV push
A	Dactinomycin	≥ 1 year	0.045 mg/kg (maximum dose 2.5 mg) IV X 1
		< 1 year	0.025 mg/kg IV x 1
C	Cyclophosphamide	≥ 3 years	1200 mg/m² IV X 1
		< 3 years	40 mg/kg IV X 1

MESNA and fluids will be used with Cyclophosphamide.
MESNA: The recommended total daily MESNA dose is equal to 100% of the daily cyclophosphamide dose and is administered at 0, 3, 6, and 9 hours after cyclophosphamide start. Fluids: Suggested hydration prior to cyclophosphamide dose is 200 mL/m² hour. Urine specific gravity should be ≤ 1.010 before cyclophosphamide is begun. Suggested hydration after cyclophosphamide dose is 3L/ m² over 24 hours.

If there is an age change during treatment, use the new appropriate age dosing in the next cycle.

***Evaluation

Figure 2. Treatment protocol (Intermediate risk)

Figure 3 shows treatment protocol (High Risk):

OVERVIEW OF RMS-HIGH RISK- TREATMENT (Non-Parameningeal)

Children's Cancer Hospital Egypt (57357)

Treatment for patients with non-parameningeal tumors and those with parameningeal primaries, stage 4 alveolar or embryonal without evidence of intracranial extension.

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	For surgery	VAC	V	V	VAC	V	V	VAC	V	***	V	VC	V	V	VC	-	-	-	VAC	V	V ***
											Radiaton Therapy (weeks 10-17)										

week	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
	VAC	V	--	VAC	-	-	VAC	V	V	VAC	---	--	VAC	--	--	VAC	V	V	VAC	***

For V, A, C, patients will be dosed according to their age at the time of scheduled treatment (For instance, if a patien enters the study at age 50 weeks, they will be dosed according to age < year, but at subsequent treatment weeks they will be dosed according to losing for current age. Similarly, if a child turns 3 years while still receving therapy, use dosing guidelines for children ≥ 3 years).

Age	(V) Vincristine dose	(A) Actinomycin dose	(C) Cyclophosphamide dose
≥ 3 years	1.5 mg/m² IV Push (max dose 2.0 mg)	0.045 mg/kg one dose (max dose 2.5mg)	1200 mg / m² IV as 30-60 minute infusion with IV fluids and MESNA
≥ 1 year < 3 years	0.05 mg/kg IV Push (max dose 2.0 mg).	0.045 mg/kg one dose (max dose 2.5mg)	40 mg/kg/dose IV as 30-60 minute infusion with IV fluids and MESNA
< 1 year	0.025 mg/kg IV Push	0.025 mg/kg one dose.	40 mg/kg IV as 30-60 minute infusion with IV fluids and MESNA

N.B: Omit Actinomycin during radiotherapy.
MESNA with cyclophosphamide is required. MESNA will not to be held during radiation therapy. The total daily MESNA dose is equal to at least 100% of the daily cyclophosphamide dose given at 0, 3, 6, 9 hours after cyclophosphamide. The oral dose of MESNA is 2; the IV dose.
Fluids: Suggested hydration prior to Cyclophosphamide dose is 200 mL/m² hour Urine specific gravity should be ≤ 1.010 before cyclophosphamide is begun. Suggested hydration after Cyclophosphamide dose is 3L/ m² over 24 hours.
***Evaluation

Figure 3. Treatment protocol (High Risk)

2.5 Local therapy

A delayed surgery if possible was performed for patients with clinical group III disease on week 12. No radiotherapy was given in non-metastatic embryonal tumors with clinical group I. All other patients received radiotherapy following week 12 except in cases of parameningeal sites with criteria of meningeal extension, where radiotherapy was given on day 0.

The gross tumor volume (GTV) was defined as the pre-treatment visible and for palpable disease detected by physical examination, operative findings, CT or MRI including any involved lymph nodes. For all clinical groups, the clinical target volume (CTV) was defined by adding one cm safety margin to GTV. Those who have clinical group III disease who do not undergo a second look operation may have a second CTV defined for a core down boost. The planning tumor volume (PTV) is created by adding safety margins that deals with the setup position uncertainties. Clinical group II (stage I and II) without nodal involvement received 36 Gy, while those with nodal involvement (N_1) received 41.4 Gy. Clinical group III received 45 Gy if in the orbit and 50.4 Gy in non-orbit sites. Patients received radiotherapy to metastatic sites which can be localized and imaged (i.e. excluding the bone marrow).

2.6 Statistical analysis

Patients' data were tabulated and processed using (SPSS) statistical package [7] for Windows [8]. Qualitative data were expressed as frequency and percentage, while quantitative data were expressed as mean SD and median. The chi-square test and Fisher Exact test were used for comparative analysis. Statistically significant level was considered at $p \leq .05$.

Survival was calculated using the Kaplan-Meier method. Patients without adverse events were censored on the date of the last reported contact. The differences between curves were tested for statistical significance using the log rank test [9].

Failure-free survival (FFS) was defined as the time from the start of treatment to disease progression, recurrence, or death as a first event.

Overall survival (OS) was defined as the time from start of treatment to death whatever the cause is.

3 Results

At a follow up period ranging from 6.7 m to 61.3 m with a mean of 29.4 months from July 2007 till end of December 2012, 32 children and adolescents between 10 and 18 years were newly diagnosed with rhabdomyosarcoma at "The Children's Cancer Hospital-Egypt". They were 12 females (37.5%) and 20 males (62.5%), with a mean age of 12.8 year (range 10 -17.7 year) (see Table 3).

Table 3. Showing patients' characteristics, and survival

	OS	*p*-value	FFS	*p*-value
Sex				
Male (n=20)	75%		36.6%	
Female (n=12)	50.3%	.255	47.6%	.6
Risk-Status				
High (n=12)	19.4 %		12.5%	
Intermediate (n=17)	69.1%		56.6%	
Low (n=3)	100 %	.07	66.7%	.03
Tumor size				
<5cm (n=10)	100 %		77.1%	
>5cm (n=18)	35.6 %		18.7%	
Unknown (n=4)	50 %	.005	37.5%	.008
Clinical Group				
I (n=2)	100 %		50 %	
III (n=18)	71 %		59.2%	
IV (n=12)	19.4 %	.08	12.5%	.035
L.Node involvement				
Yes (n=12)	46.5%		38.9%	
No (n=20)	90%	.05	39%	.6
Pathology				
Embryonal (n=17)	60.4%		33.3%	
Alveolar (n=15)	60%	.6	46.6%	.13
Local control				
Radiotherapy only (n=20)	61.9 %		45.3%	
Surgery only (n=3)	66.7%		33.3%	
Both (n=8)	46.9%	.9	37.5%	.9

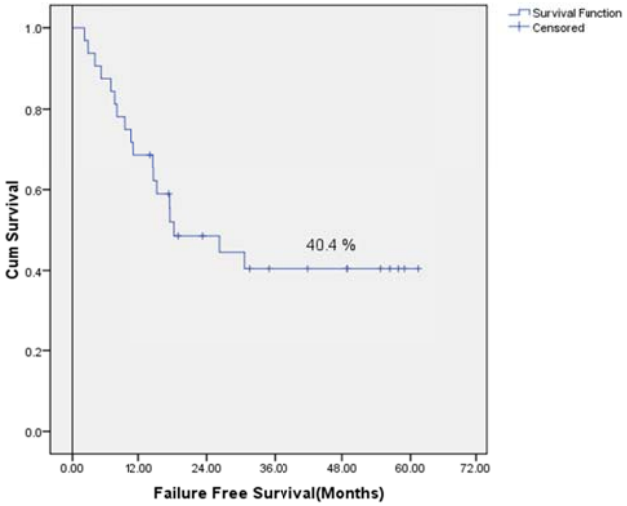

Figure 4. Failure free survival (40.4%)

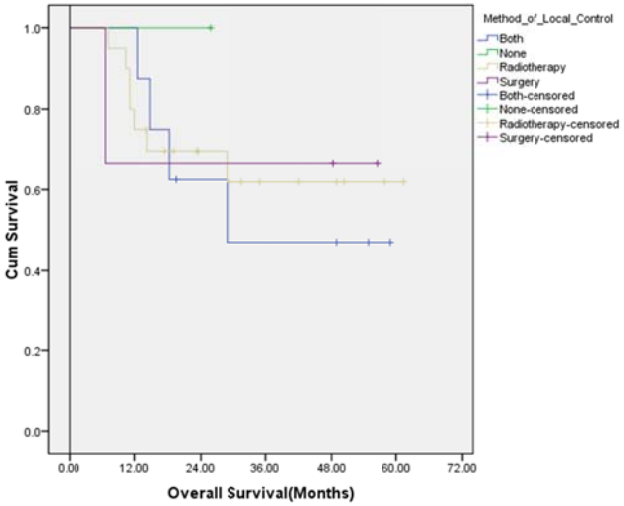

Figure 5. Overall survival for patients categorized by type of local control

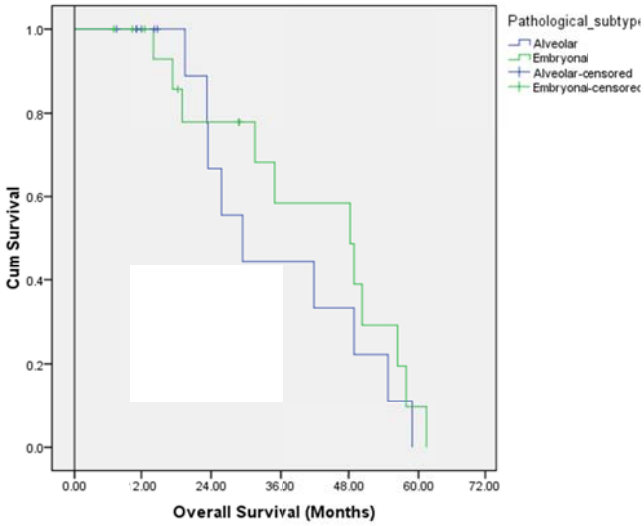

Figure 6. Overall survival for different pathological subtypes

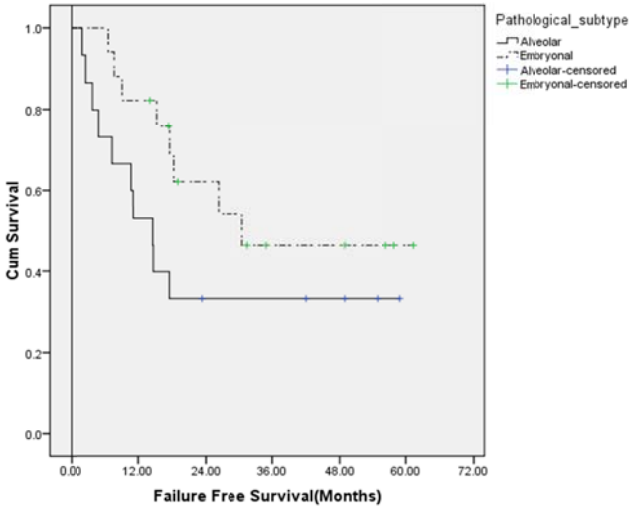

Figure 7. Failure free survival of pathological subtypes

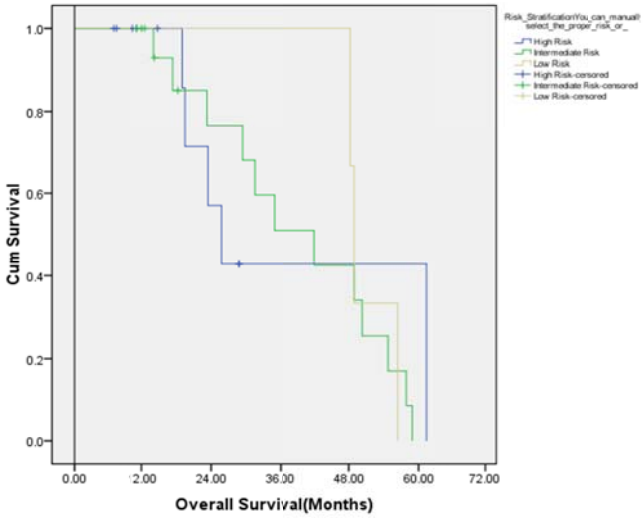

Figure 8. Overall survival of different Risk groups

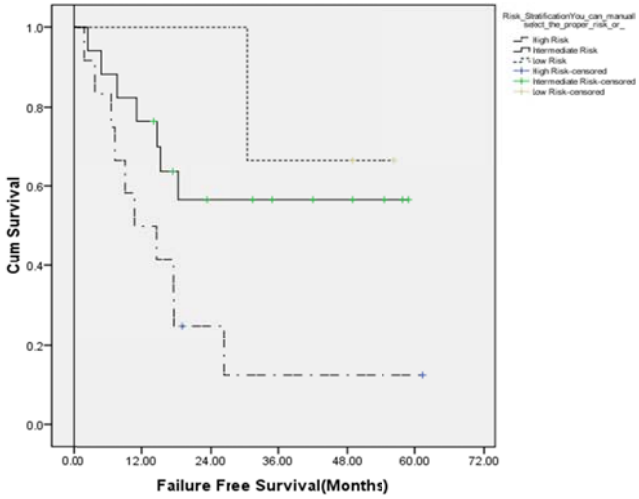

Figure 9. Failure free survival of different Risk groups

Seventeen patient, were allocated to IRS –IV, and the rest (15 patients) to IRS V treatment schedules by site and stage. We distributed our patients according to tumor site, clinical group, stage, size, median age, and treatment group according to IRS-V guidelines into low, intermediate and high risk groups. Of the 32 children recruited, 15 (46.8%) patients had alveolar, and 17 patients had embryonal pathology. Seven patients (21.9%) had intracranial extension at presentation, while 22 patients (68.8%) presented with tumors at unfavorable sites, and 12 patients (37.5%) had metastases at presentation. By risk stratification 12 patients (37.5%) were high risk, 17 (53.1%) were intermediate risk and only 3 patients (9.4%) had low risk disease. Local control was done by radiation therapy in 20 patients (62.5%), surgery alone was performed for 3 patients (9.4%), and both radiation and surgery in 8 patients (25%). One patient received no local control due to early disease progression.

Our patients overall Survival was 59.1% while failure free survival was 40.4%. Presence of metastases at presentation, showed inferior results significantly (p=.01). Risk stratification, was correlated significantly with failure free survival (p=.03), while tumor size and clinical grouping were statistically significant in overall and failure free survival outcome.

In response to first line chemotherapy, twelve patients (37.5%) attained C.R, 7 patients (21.9%) showed P.R, while disease progression was seen in 13 patients (40.6%). At a mean follow up period of 29.4 months (range = 6.7- 61.3 months) 17 patients (53.1%) showed relapse or disease progression post first line chemotherapy, while 15 patients (46.9%) continued in complete remission (see Figures 4-9).

4 Discussion

Adolescent RMS is rare, and it has an inferior outcome if compared to younger patient population.

Improved survival rates occurred over the past years, resulting in a 5-year survival rate of approximately 70%-80% for children with RMS [10-13], while survival rates in adults are not exceeding 56% (range 21%-56%) [14-17].

Our study survival data resulted in a few observations; First, a high percent of patients presented with unfavorable features, as (37.5%) of the study population presented with metastatic RMS, 46.8% of patients, had alveolar pathology, 68.8%, had tumors arising in unfavorable sites, and 21.9% had intracranial extension at presentation which is unexpectedly high. In spite the small number of our studied population which doesn't permit a reliable statistical conclusions, yet this might give an explanation of the inferior outcome for this group of patients.

Second, adolescent patients with RMS showed a lower overall Survival of 59.1% while failure free survival was 40.4%. This outcome was comparable to results from adult population with RMS, the 5-year rate of OS was 45% for patients with non-metastatic disease [7]. Failure rates for patients with non-metastatic disease at 5 years were 34% for local failure and 42% for distant failure [7]. Our results also coincide with another study reporting that infants and adolescents were more prone to have unfavorable features, including alveolar pathology, undifferentiated tumors and advanced group or Stage. They also showed a significantly poor FFS than did children aged 1-9 years (51% vs. 72%, P<.001) [18]. At a median follow-up of 4.3 years, in a COG study D9803 , the 4-year FFS was 73% with VAC and 68% with VAC/VTC (P =.3) [19].

Another study, showed a 4-year EFS being 83% for alveolar/undifferentiated sarcoma (UDS) stage 1 group I; 74% for embryonal stage 2/3 group III; 68% for parameningeal disease with intracranial extension; 60% for alveolar/UDS stage 2/3 and group II/III patients and 59% for patients with embryonal group IV disease [8].

Third, most of our patients had either Intermediate (53.1%) or high (37.5%) risk categories while only (9.4%) had low risk disease. Currently, low-risk patients are defined as patients with an excellent outcome of 85% to 95%. These are patients with nonmetastatic disease of embryonal histology at favorable sites and at unfavorable sites if totally resected. They have an excellent outcome (2-year event-free survival [EFS] 88%, OS 98%) with short duration therapy with low cumulative

alkylator dose [20]. Further classification is done by COG to stratify those patients, of which a patient subset might be futurely transferred to intermediate risk group [21, 22].

High-risk patients include all patients with metastatic disease; however, this is also a diverse group with various subsets which differ in prognosis which ranges from 5% to 50% 3-year EFS [23].

Fourth, almost half of adolescent age group (46.9%) had pathological subtype "Alveolar", while ERMS is found in approximately 70% of all childhood RMS. Although the embryonal and alveolar histologic variants are more commonly seen in pediatric patients, the pleomorphic variant is seen more often in adults [24]. Few studies focused on the age-related biological and molecular differences of RMS [25]. RMS is possibly a different biological and clinical entity in patients aged 10 years or greater. As the subtype and translocation status have prognostic significance, the different pattern of histology across age, for instance the pleomorphic subtype higher presentation, may explain the difference in outcome.

In our study, metastatic tumor in adolescent age group (>10 years), had less 5-year overall survival or failure free survival than their non metastatic counterparts, and this difference was highly significant (For OS P=.034; for FFS P=.01). This raises the question that patients over 10 years of age with localized disease may be treated less effectively than their counterparts who have metastatic disease at diagnosis.

In one study after adjusting other prognostic factors, age at diagnosis has been shown to be an independent prognostic factor with infants under 1 and children 10 and older having a worse outcome [25].

Several studies mentioned age as a prognostic factor with some emphasizing a strong interrelationship between age, site, and histology [8]. In other studies, age and sex had no impact on OS, despite a trend for an increased relative risk in children aged >10 years [9], but in this study, a relative under-representation of older patients (81% aged < 10 years), reduced the power of the analysis [9].

RMS is a malignant tumor, arising from skeletal muscle. Since gross total excision is not always possible, and various studies have advocated aggressive surgical intervention in a belief that reduction of tumor bulk affects the outcome, there are reports indicating very good response either to chemo and radiotherapy, or delayed surgery after chemotherapy [26].

In our study only 9.4% of adolescent age group did gross total excision while 25% did partial excision followed by radiation therapy. This, relatively lower portion of patients suffering RMS undergoing surgery, might share in the lower survival as adequate local control is better with proper surgical excision.

None of our patients underwent a second look surgery. Induction chemotherapy, followed by concurrent chemoradiation, is the current standard of care for patients with unresected disease, those with residual disease after surgery for patients with lymph node involvement, and for patients with alveolar histology [27, 28].

The major cause of treatment-failure in rhabdomyosarcoma remains inadequate local control. Assessment for initial surgical resection followed by chemotherapy and local RT, with or without further surgery, achieves local control in more than 80% of patients. Such good results are not achieved at all sites (e.g., trunk and limbs) or all patients (e.g., those with large [>10 cm] primary tumors), and failure rates of 11% to 18% are still reported even at favorable sites [29]. Our data showed 56.3% to have large tumors (>5 cm) and that tumor size had a significant impact on OS (p=.005) and FFS (p=.008).

In one study, although outcomes were inferior in adolescents, it was unclear whether the differences in toxicity observed in this study had an impact on outcome. The authors concluded that future studies examining the age-related and sex-related differences in pharmacokinetics of chemotherapy are necessary [30].

The higher prevalence of unfavorable tumor characteristics noted among adolescents as well as the lack of unified protocols for this category of patients seem to explain their worse outcome compared to children. However, the limited number of our study, enrolling adolescent patients is calling for more cooperation between various oncological centers for conducting more reliable statistically randomized studies addressing this category of patients.

In our conclusion, the outcome of adolescent rhabdomyosarcoma showed inferior results to children when using childhood protocols. An increase in knowledge about RMS, especially biological characteristics in older children and adolescence can help to develop worldwide standardized treatment for this group of patients. Increased use of multidisciplinary therapy may improve older patient clinical outcome.

Despite its limitations, this study highlights the need to improve the management of patients with RMS over 10 years of age. We should ensure that these patients benefit as much from clinical management and research progress as younger patients with RMS.

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