Treatment outcome of pediatric rhabdomyosarcoma at national cancer institute, Egypt

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Background
Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in infants and children. It is the third most common solid tumor in children after neuroblastoma and Wilms tumor, making up 10–15% of all solid pediatric tumors. At National Cancer Institute (NCI), Egypt, soft tissue sarcomas represent 3.75% of total malignancies and 27.6% of these occur in the pediatric group. RMS is the most common type.
Aim and objectives
This work aims to study the treatment outcome, overall survival (OS), and event free survival (EFS) of pediatric RMS patients diagnosed and treated at NCI.
Patients and methods
This is a retrospective study that included 54 pediatric patients, newly diagnosed with RMS who were treated at the pediatric oncology department, NCI, Cairo University, Egypt during the period from January 2012 to December 2016.
Results
Totally 54 pediatric patients with RMS with ages ranging from 7 months to 17 years (median age 5 years) were studied. The median follow-up period ranged with a minimum 1 year for the last patient. In this study, we classify our patients into low, intermediate, and high-risk groups according to IRS and we found that 11 (20.4%) patients were eligible for the low-risk group, 27 (50%) patients were eligible for the intermediate risk group and 16 (29.6%) patients were eligible for the high-risk group. The 2-year OS for low-risk group was 90.9%, it was 52.1% for intermediate-risk group, while it was 43.8% for high-risk group (P=0.02). The 2-year EFS for low-risk group was 63.6%, it was 41.2% for intermediate-risk group, while it was 31.3% for high-risk group (P=0.203).
Conclusion
RMS requires combined-modality therapy. Late presentation and advanced local disease compromise treatment options and decrease OS and EFS.

Keywords:
National cancer institute, pediatric, rhabdomyosarcoma

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Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma (STS) in children and adolescents, accounting for ~5% of all pediatric cancers and about one-half of all STSs. It is the third most common extracranial solid tumor in children after neuroblastoma and Wilms tumor [1]. The two most common histologic variants encountered in children and adolescents are the embryonal (ERMS) and alveolar (ARMS) subtypes, while the botryoid and spindle cell variants are also encountered. The ERMS mainly occurs in the head, neck, and genitourinary regions, and ERMS demonstrates a bimodal age of distribution, with a larger peak between 0–5 years and a smaller peak in adolescence. More than one-half of ERMS cases occur before the age of 5 years. Conversely, ARMS is more likely to occur in adolescents [2]. RMS can arise in a variety of anatomic sites throughout the body. The most common primary tumor sites include the head and neck region 35%, followed by the genitourinary and extremity primaries [3]. However, the epidemiology of primary tumor presentation is dependent upon the histologic variant and age. For example, adolescent patients are more likely to have ARMS compared to younger patients. Also, adult RMS patients tend to have an increased likelihood of primary tumors occurring at unfavorable anatomic sites [4]. Risk stratification for RMS is based on a pretreatment Tumor Nodes Metastasis (TNM) staging system and a surgical/pathologic clinical grouping system established by the Intergroup Rhabdomyosarcoma Study Group (IRSG) [5]. The

Table 1 Pretreatment TNM staging system for rhabdomyosarcoma

Stage	Sites	T	Size	N	M
1	Orbit, head and neck excluding parameningeal), Genitourinary (nonbladder/nonprostate), biliary tract	T1 or T2	a or b	N0 or N1 or N_X	M0
2	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, etc.)	T1 or T2	a	N0 or N_X	M0
3	Bladder, prostate, extremity, cranial, para-meningeal, other (includes trunk, retroperitoneum, etc.)	T1 or T2	a	N1	M0
			b	N0 or N1 or N_X	M0
4	Any	T1 or T2	a or b	N0 or N1	M1

RMS, rhabdomyosarcoma. T, tumor. T1= confined to the anatomic site of origin. (1) ≤5 cm in diameter. (2) 5 cm in diameter. T2=extension and or/fixative to surrounding tissue. (1) ≤5 cm in diameter. (2) 5 cm in diameter. N, nodes. N0=regional nodes not clinically involved. N1=regional nodes clinically involved. Nx = regional node status unknown. M, metastasis. M0=no distant metastasis. M1= metastasis present (includes positive cytology in pleural, peritoneal, or cerebrospinal fluid.

Intergroup Rhabdomyosarcoma Study (IRS)-IV or 'D' series conducted by the Children's Oncology group-soft tissue sarcoma (COG-STS) committee included D9602 for 'low-risk' RMS, D9803 for 'intermediate-risk' RMS, and D9802 for 'high-risk' RMS [5]. Currently, multimodality treatment that includes chemotherapy, and surgery with or without RT, has become the standard of care for RMS. For children and adolescents with RMS, the multidisciplinary treatment of the disease according to collaborative group clinical trials has been performed in the United States and Europe [3].

This work aims to study the treatment outcome, overall survival (OS) and event free survival (EFS) of pediatric RMS patients diagnosed and treated at the National Cancer Institute (NCI).

Patients and methods

This is a retrospective study that included 54 pediatric patients, newly diagnosed with RMS who were treated at the Pediatric Oncology Department, National Cancer Institute (NCI), Cairo University, Egypt during the period from January 2012 to December 2016. Patients were included in the study if they fulfilled the following criteria: (a) previously untreated, (b) below 18 years, and (c) patients with pathological proven RMS.

Pretreatment investigations

Complete physical examination including

Weight, height and surface area, site and clinical extent of the tumor, and regional lymph node enlargement were assessed and recorded in all patients.

Laboratory investigations

Complete blood count, liver and renal function tests, bone marrow aspiration and biopsy, CSF cytology (only for parameningeal diseases) and pathological assessment of tissue to confirm the diagnosis (open surgical biopsy or computed tomography (CT) guided biopsy).

Radiological investigations

Contrast CT/or MRI of the primary site, contrast CT chest, contrast CT abdomen and pelvis for testicular disease, and bone scan.

Pretreatment staging

Patients were assigned according to the clinical TNM pretreatment staging system based on site, size, clinical regional nodal status, and distant spread, using preoperative imaging and physical findings (Table 1):

Postoperative clinical grouping

IRS clinical grouping is a surgical-pathologic grouping based on intraoperative findings and postoperative pathologic status including comment on margins, residual, node involvement and cytological examination of pleural, peritoneal fluid and CSF (Table 2).

Risk stratification

Patients were classified according to stage, clinical group, and histopathological subtype into low-risk, intermediate-risk and high-risk (Tables 3 and 4).

Table 2 Current Children's Oncology group postoperative clinical grouping for rhabdomyosarcoma

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

Table 3 Current Children's Oncology group risk stratification for rhabdomyosarcoma

Risk group	Histology	Stage	Clinical group
Low	ERMS	1, 2	I, II
		1	III (Orbit/(Nonorbit))
		3	I, II
Intermediate	ERMS	2, 3	III
	ARMS	1, 2, 3	I, II, III
High	ERMS, ARMS	4	IV

Chemotherapy doses (Table 5).

Guidelines to start chemotherapy

Chemotherapy cycles begin when the absolute neutrophilic count (ANC) greater than 750/ml and platelets greater than 100 000/ml after nadir, hepatic functions are as follows: total bilirubin less than 1.5×upper limit of normal for age and serum glutamate pyruvate transaminase (SGPT) less than 2.5×upper limit of normal for age, adequate cardiac function ejection fraction greater than 47% by echocardiogram with no history of prior cardiac disease and adequate renal functions.

Local control management with surgery and/or radiation therapy (RT) by primary sites of disease

Surgery

Only in patients who were initially clinical group III with a large field for radiation therapy and will not be able to tolerate radiation therapy dose.

Radiation therapy

Radiation therapy was scheduled to begin at week 13 for patients with low-risk group, at week 4 for patients with intermediate-risk group, and at week 10 for patients with high-risk group.

Table 4 Treatment plan according IRS IV study

(1) Low-risk group																	
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13			
	Surgery	VAC	V	V	VAC	V	V	VAC	V	V	AC	–	***	VA LC			
Week	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	
	V	V	VA*	V	V	VA**	V	V	A	–	***	VA	V	V	VA	V	
Week	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
	V	VA	V	V	A	–	***	VA	V	V	VA	V	V	VA	V	V	A
(2) Intermediate-risk group																	
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13			
	Surgery	VAC	V	V	VAC	V	V	VC	V	V	VC	V	V	VAC			
		PET scan			PET scan		Radiation therapy										
Week	15	16	17	18	19	20	21	22	23	24	25	26	27	28			
	***	VAC			VAC	V	V	VAC	V	V	VAC			VAC			
	PET scan																
Week	30	31	32	33	34	35	36	37	38	39	40	41	42	43			
	***	VAC	V	V	VAC	V	V	VAC			VAC			***			
(3) High-risk group (para-meningeal)																	
Week	0	1	2	3	4	5	6	6	7	8	9	10	11	12	13		
	VAC	V	V	VAC	V	V	***	VAC	V	V	VAC	V	V	VAC	V		
			Radiation therapy										Radiation therapy				
Week	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	
	***	V	VC	V	V	VC	–	–	–	VAC	V	V***	VAC	V	–	VAC	
		Radiation therapy															
Week	30	31	32	33	34	35	36	37	38	39	40	41	44				
	–	–	VAC	V	V	VAC	–	–	VAC	–	–	VAC	***				
(4) High-risk group (nonparameningeal)																	
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13			
	Surgery	VAC	V	V	VAC	V	V	VAC	V	***	V	VC	V	V			
											Radiation therapy						
Week	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	
	VC	–	–	–	VAC	V	V***	VAC	V	–	VAC	–	–	VAC	V	V	
		Radiation therapy															
Week	30	31	32	33	34	35	36	37	38	39							
	VAC	–	–	VAC	–	–	VAC	–	–	–							

A, Actinomycin; C, Cyclophosphamide; LC, Local control; V, Vincristine. *Give (A) before radiation therapy. **Omit (A) during radiation therapy. ***Evaluation.

Table 5 Chemotherapy doses of rhabdomyosarcoma

	Drug	Age	Dose
V	Vincristine (VCR)	Infants <1 year	0.025 mg/kg/dose (maximum dose 2 mg) IV push
		≥1 year and <3year	0.05 mg/kg/dose (maximum dose 2 mg) IV push
		≥3 year	1.5 mg/m^2/dose (maximum dose 2 mg) IV push
A	Dactinomycin (DACT)	<1 year	0.025 mg/kg (maximum dose 2.5 mg) IV
		≥1 year	0.045 mg/kg IV
C	Cyclophosphamide (CTX)	<3 year	40 mg/kg/dose
		≥3 year	1200 mg/m^2/dose

MESNA and fluids will be used with cyclophosphamide. MESNA: The recommended total daily dose is equal to 100% of the daily cyclophosphamide dose given at 0, 3, 6, and 9 h after the start of cyclophosphamide.

Table 6 Radiation therapy dose according to rhabdomyosarcoma group, histology, and site of disease according to Children's Oncology group

Group	Treatment
Group I	
Embryonal	No RT.
Alveolar	36 Gy to involved (prechemotherapy) site. The use of RT is under investigation.
Group II	
N0 (microscopic residual disease after surgery)	36 Gy to involved (prechemotherapy) site.
N1 (resected regional lymph node involvement)	41.4 Gy to involved (prechemotherapy) site and nodes.
Group III	
Orbital and nonorbital tumors	50.4 Gy with volume reduction after 36 Gy if excellent response to chemotherapy and noninvasive pushing tumors; no volume reduction for invasive tumors
Group IV	
	As for other groups and including all metastatic sites, if safe and possible. Exception: lung (pulmonary metastases) treated with 15 Gy if aged 6 years or older, 12 Gy if younger than 6 years.

COG, Children's Oncology Group; RMS, rhabdomyosarcoma; RT, Radiation therapy.

Radiation therapy was given on week 0 for patients with parameningeal tumors with evidence of intracranial extension.

Standard RT of children with RMS includes the following (Table 6).

Evaluation criteria

Complete response (CR): disappearance of all lesions, with no evidence of disease for a minimum of 4 weeks. Partial response (PR): at least 30% decrease in the disease measurements for a minimum 4 weeks. Progressive disease (PD): at least 20% increase in the disease measurements for a minimum 4 weeks. Relapse/recurrence (R): appearance of new lesions or reappearance of old lesions for patients in CR.

Statistical methods

Statistical analysis was done using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Pearson's χ^2 test or Fisher's exact test was used to examine the relation between qualitative variables. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. All tests were two-tailed. A *P*-value less than 0.05 was considered significant.

Results

Table 7

Treatment

The 54 patients were stratified to receive treatment according to their risk groups into 11 (20.4%) patients were low-risk, 27 (50%) patients were intermediate-risk and 16 (29.6%) patients were high-risk group.

Low-risk group patients

Of the 11 patients, initial surgical excision was performed in eight patients (five patients had genitourinary tumors, one patient had a head and neck tumor, one patient had an orbital tumor and one patient had a chest wall tumor), while the biopsy was the only surgical procedure in three

Table 7 Clinical and epidemiologic characteristics of the studied patients

Characteristics	Total number of patients (*n*=54) (Percentage %)
Age	
<1 year	4 (7.4)
=1 : 10 years	38 (70.4)
>10 years	12 (22.2)
Sex	
Males	34 (63)
Females	20 (37)
Primary site	
Head and neck	22 (40.7)
Orbital	3 (5.6)
Parameningeal	11 (20.4)
Other head and neck	8 (14.8)
Genitourinary	9 (16.7)
Extremities	9 (16.7)
Retroperitoneal and pelvis	5 (9.3)
Bladder and prostate	2 (3.7)
Others	7 (13)
Tumor size	
>5 cm	36 (66.7)
≤5 cm	18 (33.3)
Histopathological subtypes	
Embryonal	42 (77.8)
Alveolar	10 (18.5)
Pleomorphic	2 (3.7)
IRS stage	
Stage 1	12 (22.2)
Stage 2	3 (5.6)
Stage 3	23 (42.6)
Stage 4	16 (29.6)
IRS clinical group	
Clinical group I	8 (14.8)
Clinical group II	1 (1.9)
Clinical group III	29 (53.7)
Clinical group IV	16 (29.6)
Risk group	
Low-risk	11 (20.4)
Intermediate-risk	27 (50)
High-risk	16 (29.6)
Clinical response	
CR	30 (55.5)
PR	10 (18.5)
PD	14 (25.9)

patients (one patient had orbital tumor, one patient had head and neck tumor and one patient had genitourinary tumor).

At time of local control

Surgery

None of the 11 patients underwent surgical excision at time of local control (eight patients underwent initial total surgical excision; one patient was in CR at time of local control had orbital tumor and two patients had disease progression at time of local control and started second line chemotherapy (one patient had head and neck tumor and one patient had genitourinary tumor).

Radiation therapy

Of the 11 patients, nine patients did not receive radiation therapy (seven patients were clinical group I with embryonal histopathologic subtype and two patients showed disease progression at time of evaluation and started second-line chemotherapy), only two patients received radiation therapy as the only type of local control and both of them had orbital site of tumor.

Intermediate-risk group patients

Of the 27 patients initial surgical excision was performed in one patient (had extremity tumor), initial debulking was performed in two patients (one patient had extremity tumor and one patient had a urinary bladder tumor), while biopsy was the only surgical procedure in 24 patients (seven patients had parameningeal tumors, one patient had orbital tumor, three patients had other head and neck tumors, four patients had retroperitoneal tumors, one patient had genitourinary tumor, two patients had urinary bladder tumors, two patients had extremity tumors, two patients had perineal tumors, one patient had gluteal tumor and one patient had paraspinal tumor).

At time of local control

Surgery

Of the 27 patients, three patients underwent total surgical excision at time of local control, they were initial clinical group III (two patients had retroperitoneal tumors and one patient had extremity tumor).

Radiation therapy

Of the 27 patients, 24 patients received radiation therapy (three patients received radiation therapy postoperative and 21 patients received radiation therapy as the only type of local control) and the remaining three patients who did not receive radiation therapy showed disease progression at the time of evaluation before local control and shifted to second-line chemotherapy.

As for intermediate-risk group patients with enlarged regional lymph nodes who received radiation therapy, these nodal sites were involved in the field of radiation.

High-risk group patients

Of the 16 patients, initial surgical excision was performed in three patients (two patients had genitourinary tumor and one patient had extremity

tumor), initial debulking was performed in two patients (one patient had extremity tumor and one patient had perianal tumor), while biopsy was the only surgical procedure in 11 patients (four patients had parameningeal tumors, three patients had other head and neck tumor, two patients had extremity tumors, one patient had retroperitoneal tumor and one patient had chest mass tumor).

At the time of local control

Surgery

Of the 16 patients, two patients underwent complete surgical excision at time of local control; they were initially clinical group III (one patient had head and neck tumor and one patient had extremity tumor, but he had disease progression postoperative and started second line chemotherapy).

Radiation therapy

Of the 16 patients 13, patients received radiation therapy (one patient received radiation therapy postoperative for head and neck tumor and 12 patients received radiation therapy as the only type of local control, 2 of them received upfront radiation therapy as they had parameningeal tumors with intracranial extension).

Of the 16 patients, four patients showed disease progression; three patients showed disease progression at time of evaluation before local control (one patient had genitourinary tumor, one patient had a retroperitoneal tumor and one patient had parameningeal tumor with intracranial extension), one patient showed disease progression before end of treatment.

As for high-risk group of patients with enlarged regional lymph nodes who received radiation therapy, these nodal sites were involved in the field of radiation, and at the end of treatment patients received radiation therapy on metastatic sites.

Initial total surgical excision was performed in (20%), while debulking was performed in (10%) and biopsy was the only surgical procedure in (70%) of patients.

Table 8 Prognostic factors and survival

	2 y Overall survival	*P*-value	2Y event free survival	*P*-value
Rhabdomyosarcoma	57.90%		43.40%	
Patients				
Age (y)				
<1 year and >10 years	37.50%	**0.004***	12.50%	**0.002***
1 : 10 years	67.00%		56.70%	
Sex				
Male	52.30%	**0.187**	38.20%	**0.271**
Female	67.80%		51.60%	
Size				
≤5 cm	77.80%	**0.053**	55.60%	**0.238**
>5 cm	47.20%		36.80%	
Pathology				
Embryonal	58.30%	**0.804**	46.80%	**0.814**
Alveolar and pleomorphic	58.30%		33.30%	
IRS staging				
Stage 1, 2	80.80%	**0.054**	60.00%	**0.126**
Stage 3, 4	48.90%		36.40%	
IRS clinical grouping				
Clinical group I, II	100%	**0.042**	66.70%	**0.164**
Clinical group III	51.40%		42.00%	
Clinical group IV	43.80%		31.30%	
IRS Risk stratification				
LR	90.90%	**0.022**	63.60%	**0.203**
IR	52.10%		41.20%	
HR	43.80%		31.30%	
Radiation use				
Alone	56.20%	**0.710**	44.30%	**0.252**
Postoperative	80.00%		62.50%	
Non	53.30%		33.30%	

*Significant as *P* less than 0.05. EFS, event-free survival; OS, overall survival.

All patients with testicular tumor underwent high inguinal orchiectomy initially except 1 patient had trans-scrotal biopsy.

All patients with suspicious lymph nodes underwent lymph node assessment initially.

Response to chemotherapy

Of the 54 patients 14 (25.9%) patients showed disease progression and started second-line chemotherapy.

At the end of treatment, 30 (55.5%) patients were in complete remission while 10 (18.5%) patients still had residual disease proved by CT or MRI (those patients did not undergo definitive surgery and considered in complete remission with fibrotic residual as there is no available PET CT) (Table 8).

Discussion

RMS is the most common STS in children and adolescents. It is the third most common extracranial solid tumor in children after neuroblastoma and Wilms tumor [1].

The aim of our work is to study the epidemiologic data, treatment outcome, OS, and EFS of newly diagnosed, pediatric RMS patients treated at NCI during a 4 year period.

Patient's characteristics

The median age of our patients was 5 years at diagnosis and 77.7% of patients aged below 10 years with male to female ratio; 1.7 : 1, this is similar to that reported by two previous Egyptian NCI studies where the median age of their patients was 5 years where 74% of patients were below 10 years with male to female ratio 2.57 : 1 (Mohamed *et al.*, 2009) [6], 5 years where two third of the patients aged below 10 years with male to female ratio 1.66 : 1 (El-Badawy, 2005) [7] and The IRS study IV also reported a median age of 5 years and 72% of their patients aged below 10 years with male to female ratio 1.6 : 1 (Crist *et al.*, 2001) [8], but it differs from that reported by another previous NCI study where it was 3.5 years with male to female ratio was 2.3 : 1 (Mahmoud *et al.*, 2013) [9] and that reported by reported by a single institution study in Taiwan where the mean age of their patients at diagnosis was 8 years old with 62.2% patients less than or equal to 10 years (Chou *et al.*, 2019) [10].

The most common primary sites in our study were the head and neck 40.7% [orbital sites 5.6%, Parameningeal 20.4% and other head and neck 14.8%], followed by nonbladder/nonprostate genitourinary sites and extremities each 16.7%, then retroperitoneal and pelvis sites 9.3%, prostate and urinary bladder 3.7% and other sites 13%. This is almost the same as that reported by three previous Egyptian NCI studies where the most common primary sites were head and neck 42.5%, followed by retroperitoneal-trunk region 27.5%, then extremities, and genitourinary sites 15% each (Mahmoud *et al.*, 2013) [9], head and neck were 36%, extremities 22%, and genitourinary sites 20% (Mohamed *et al.*, 2009) [6] and head and neck 40%, extremities 24% and genitourinary 20% (El-Badawy, 2005) [7], also it was similar to that reported by the MMT 89 study as the head and neck sites 41%, genitourinary 30% and extremities 10% (Stevens *et al.*, 2005) [11] and to that reported by the IRS IV study where head and neck sites 41% while genitourinary sites 31% and extremities 13% (Crist *et al.*, 2001) [8], but it differs from that reported by a single institution study in Taiwan where the most common primary site was trunk 24.3%, followed by nonbladder/nonprostate genitourinary sites and extremities each 21.6%, then the head and neck 16%, prostate and urinary bladder 5.4% and other sites 5.4% (Chou *et al.*, 2019) [10].

The most common pathological subtypes in the current study were embryonal and its variants 77.8% of the patients, followed by alveolar subtype 18.5% and pleomorphic subtype 3.7%. This is nearly similar to that reported by two previous Egyptian NCI studies as the most common pathological subtype was embryonal 77.5% and 74% while the alveolar subtype represented 22.5% and 22%, respectively, (Mahmoud *et al.*, 2013) [9] and (Mohamed *et al.*, 2009) [6], also similar to that reported by the IRS IV study as embryonal histology was found in 70% and alveolar in 20% of their patients (Crist *et al.*, 2001) [8], but it differs from what reported by a single institution study in Taiwan that 53.7% of patients had Favorable histology while 41.5% had unfavorable histology (Chou *et al.*, 2019) [10].

As regards the size of primary tumor it was greater than 5 cm in 66.7% of patients while it was less than or equal to 5 cm in 33.3%. This is similar to that reported by two previous Egyptian NCI studies where 68% and 67% of tumors were greater than 5 cm and 32% and 33% of tumors were less than or equal to 5 cm, respectively (Mohamed *et al.*, 2009) [6] and (El-Badawy, 2005) [7]. It was also reported by a single institution study in Taiwan that 27% of patients had tumor size less than or equal to 5 cm while 73% had tumor size greater than 5 cm (Chou *et al.*, 2019) [10]. In contrast, in the IRS IV study and the MMT.89 study the size of primary

tumor was greater than 5 cm in 51% and 49%, respectively (Crist *et al.*, 2001) [8] and (Stevens *et al.*, 2005) [11]. This may reflect late diagnosis in Egyptian patients.

As regards clinical grouping in our study, 14.8% of patients were clinical group I, 1.9% were clinical group II, 53.7% were clinical group III and 29.6% were clinical group IV, as compared to that reported by two previous Egyptian NCI studies where clinical group I patients 10% and 8% and clinical group III patients 65% and 72%, respectively (Mahmoud *et al.*, 2013) [9] and (Mohamed *et al.*, 2009) [6], also it was reported by a single institution study in Taiwan that 8% of patients were clinical group I, 16.2% were clinical group II, 43.2% were clinical group III and 32.4% were clinical group IV (Chou *et al.*, 2019) [10]. In the IRS IV study clinical group I patients were 23% and clinical group III patients were 62% (Crist *et al.*, 2001) [8].

During assessment of response to induction chemotherapy considering the large proportion of our patients were clinical group III, 55.5% of patients achieved CR and 18.5% showed PR versus 25.9% showed disease progression. Compared with that reported by two previous Egyptian NCI studies where (20%) and 37% of patients achieved CR and 60% and 63% showed PR versus (12.5%) had disease progression, respectively (Mahmoud *et al.*, 2013) [9] and (Mohamed *et al.*, 2009) [6]. It was also reported by STS committee of the COG that 22% of group III patients in IRS IV achieved CR and 59% showed PR (Burke *et al.*, 2007) [12].

In our study, disease progression in response to induction chemotherapy was higher than that reported by previous two Egyptian studies. However, there was a higher incidence of CR after induction chemotherapy which could be due to the higher proportion of clinical group I in our patients and the proportion of clinical group III patients despite it is high in our study, but it is lower than that reported by the compared studies.

In this study, 37% of patients underwent wide surgical excision either initially 30% or after induction chemotherapy 7%, while 70% of patients had done biopsy only without definitive surgery at the start of treatment. This is similar to that reported by the previous Egyptian NCI study where the percentage of patients who had undergone wide surgical excision either initially or after induction chemotherapy was 39% (El-Badawy, 2005) [7], it is lower than that reported by other two previous Egyptian NCI studies 55% and 70% respectively (Mohamed *et al.*, 2009) [6] and (Mahmoud *et al.*, 2013) [9], and all are much lower than that reported by SEER according to local regional experience as initial surgical excision was performed in 81% of patients (Perez *et al.*, 2011) [13]. It was also reported by a single institution study in Taiwan that 62% of patients underwent GTR/STR (Chou *et al.*, 2019) [10].

In this study, 72% of patients received radiation therapy either postoperative or as the only type of local control. This is similar to that reported in two previous Egyptian NCI studies as 72% and 71% of patients received radiation therapy, respectively (Mahmoud *et al.*, 2013) [9] and (El-Badawy, 2005) [7].

Survival

In our study the 2-years EFS for whole group was 43.4%, compared with two previous Egyptian NCI studies it was reported that it was 45% and 61%, respectively (Mahmoud *et al.*, 2013) [9] and (Mohamed *et al.*, 2009) [6], also it was reported by a single institution study in Taiwan that the 5-years event-free survival was 48.5% (Chou *et al.*, 2019) [10].

The 2-years OS in our patients was 57.9%, which was lower than that reported by three previous Egyptian NCI studies where it was 87.8% (Mohamed *et al.*, 2009) [6], 77.5% (Mahmoud *et al.*, 2013) [9] and 78% (El-Badawy, 2005) [7], also it differs from that was reported by The IRS IV study where the 3-years OS was 84% (Crist *et al.*, 2001) [8] and from that was reported by a single institution study in Taiwan where the 5-years OS was 54.7% (Chou *et al.*, 2019) [10].

This could be explained by large proportion of our patients with high risk criteria and late stages at presentation; also, we had a higher incidence of disease progression in response to induction chemotherapy.

As regards to risk groups in our study, the 2-years OS and EFS rates of patients with LR had better outcomes than those with IR and HR disease.

The 2-years OS for low, intermediate and high-risk patients was 90.9%, 52.1%, and 43.8%, respectively (*P.* value=0.022), While EFS was 63.6%, 41.2%, and 31.3% (*P.* value=0.203). Compared with that reported in the previous Egyptian NCI studies the 2-years OS for the LR, IR, and HR patients was 100%, 90.9%, and 66.7%, respectively (*P*=0.07), while EFS was 66.7%, 40.9%, and 33.3% (*P.* value=0.45) (Mohamed *et al.*, 2009) [6] and OS was

84.6% for LR and 78.6% for HR patients (Mahmoud *et al.*, 2013) [9].

Data reported by IRS IV showed a 2-years FFS for low-risk patients was 90% and 77% for high-risk patients (Meza *et al.*, 2006) [14].

It was also reported by a single institution study in Taiwan that the 5-year OS rate of patients in LR group, IR group, and HR group were 100%, 62.5%, and 0%, respectively and the 5-year EFS rates of patients in LR group, IR group, and HR group were 66.7%, 62.5%, and 0%, respectively (Chou *et al.*, 2019) [10].

Other data also showed that risk stratification had statistical significance in OS, as 4-years OS for low, intermediate and high-risk patients were 88%, 79%, and 17%, respectively (Al-Jumaily *et al.*, 2013) [15]. The relatively higher OS among our patients might be due to a shorter period of follow up.

The outcome in this study was strongly affected by the type of surgery and clinical grouping of the patients, where the patients who underwent upfront surgical resection (CG I, II) showed better 2-years OS than the patients who experienced biopsy only (CG III and CG IV) 100%, 51.4%, and 43.8%, respectively (P=0.042), Compared to that reported by previous Egyptian NCI study OS was 78.6% for (CG I, II) patients and 59.1% for (CG III) patients (P=0.321) (Mohamed *et al.*, 2009) [6].

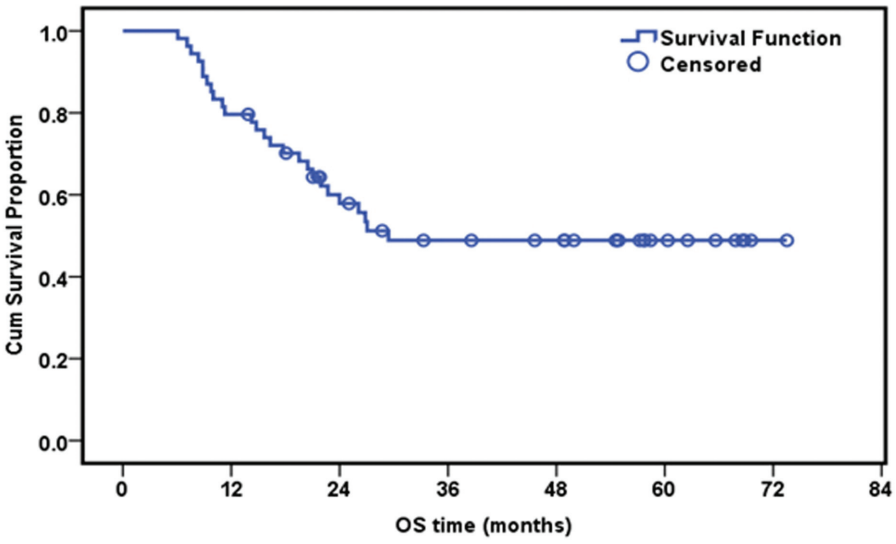
SEER population-based study supported our results as surgical resection was associated with improved survival (5 year survival; 69% vs. 47%for no surgery) (P=0.0001) (Perez *et al.*, 2011) [13].

As regards the use of radiation therapy in this study, the 2-years EFS for patients who received radiation therapy alone, post-operative and those who didn't receive radiation therapy was 44.3%, 62.5%, and 33.3%, respectively (P-value=0.252).

In contrast, outcome was strongly affected by the use of radiation therapy in two previous Egyptian NCI studies where the 2-years EFS for patients who received radiation therapy was 75% while it was 0.00% for those who did not receive radiotherapy (P<0.001) (Mohamed *et al.*, 2009) [6].

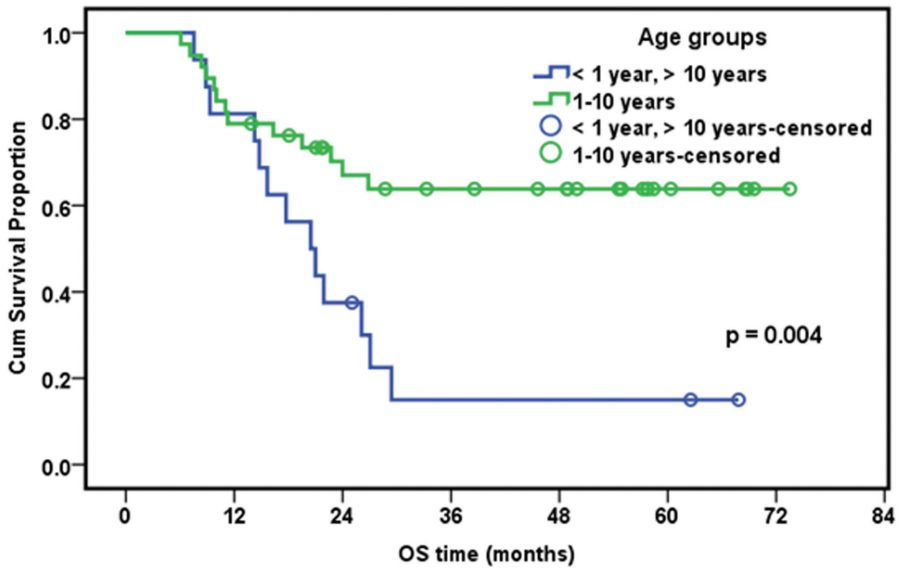
This difference could be explained by large proportion of our patients who did not receive radiation therapy were not eligible for according to the IRS study recommendations (embryonal histology, clinical group I), also higher number of high risk group patients who received radiation therapy and higher incidence of disease progression at time of evaluation before local control than that reported by previous Egyptian NCI studies. However, more reports concluded that local relapses are more frequent for patients who did not receive radiotherapy especially pelvic sites and they suggested that radiotherapy might have positive influence on local control of completely resected non-alveolar RMS.

Figure 1



Overall survival of Rhabdomyosarcoma patient.

Figure 2



Age and overall survival of Rhabdomyosarcoma patients.

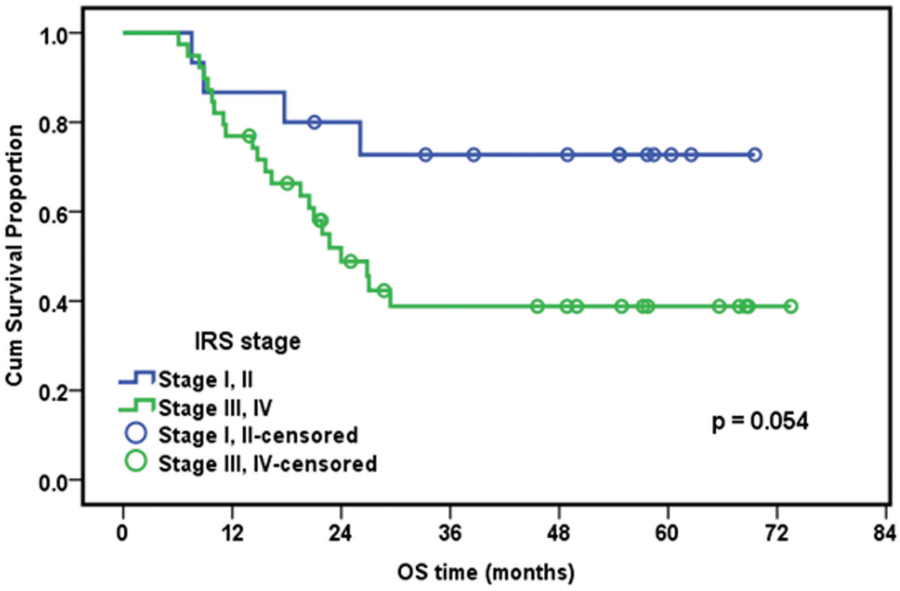
As regards the 2-years OS for age in this study, it was 37.5% for patients aged less than 1year and greater than 10 years, while it was 67% for patients aged 1 : 10 years (*P*=0.004), also it was reported by a previous Egyptian NCI study that the 2-years OS for patients above 10 years was 43% while it was 89% for those between 2 and 10 years (*P*=0.028) (Mohamed *et al.*, 2009) [6].

SEER population-based study documented better 5-years OS for age between 1 and 4 years 74% and worst for ages greater than 10 years 51% (Perez *et al.*, 2011) [13].

In this study there was no impact of gender on OS and EFS, this is similar to what reported by two previous Egyptian NCI studies (Mahmoud *et al.*, 2013) [9] and (Mohamed *et al.*, 2009) [6].

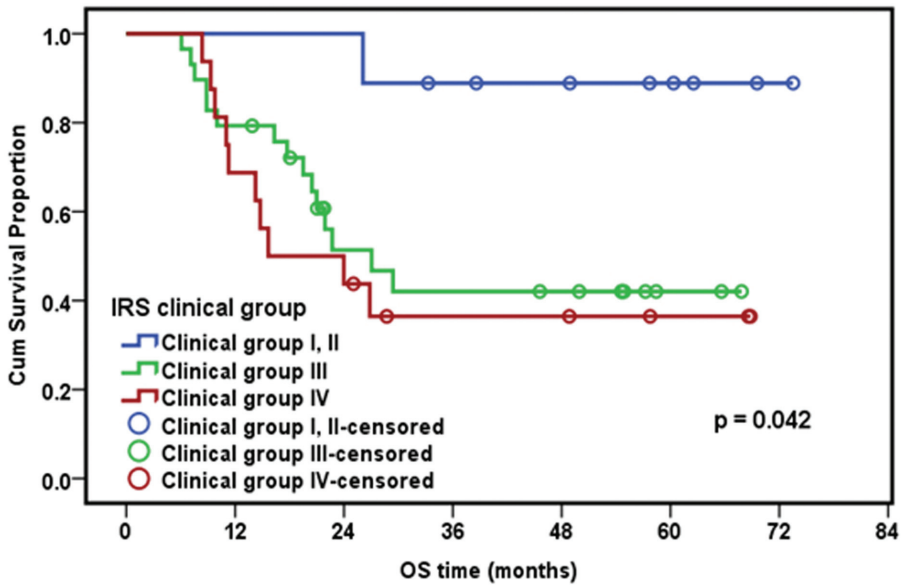
Both OS and EFS were not significantly correlated to histological types in our patients. However embryonal

Figure 3



IRS stage and overall survival of Rhabdomyosarcoma patients.

Figure 4



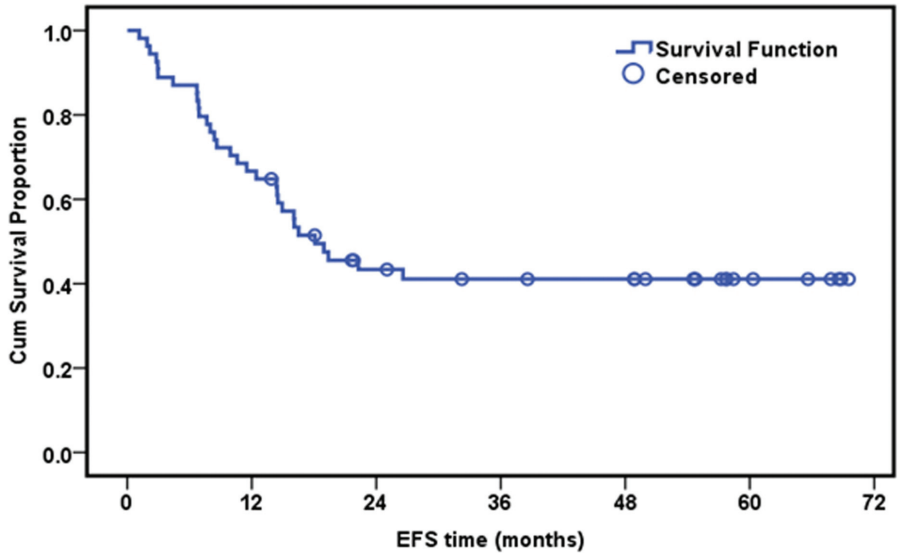
IRS clinical group and overall survival of Rhabdomyosarcoma patients.

subtypes showed lower OS and EFS (58.3% and46.8%) compared with alveolar histology (58.3% and 33.3%). This may be explained by small percentage of alveolar subtypes.

This is consistent with others who had also no significant difference between embryonal and alveolar histological types (Al-Jumaily *et al.*, 2013) [15]. In contrast, MMT-89 study reported that patients with embryonal tumors had 2-years EFS of 67% versus 37% for those with alveolar tumors (Stevens *et al.*, 2005) [11]. In addition, analysis of IRS III and IRS IV data showed better FFS for patients with embryonal tumors 83% as compared with those with alveolar tumors 66% (Meza *et al.*, 2006) [14].

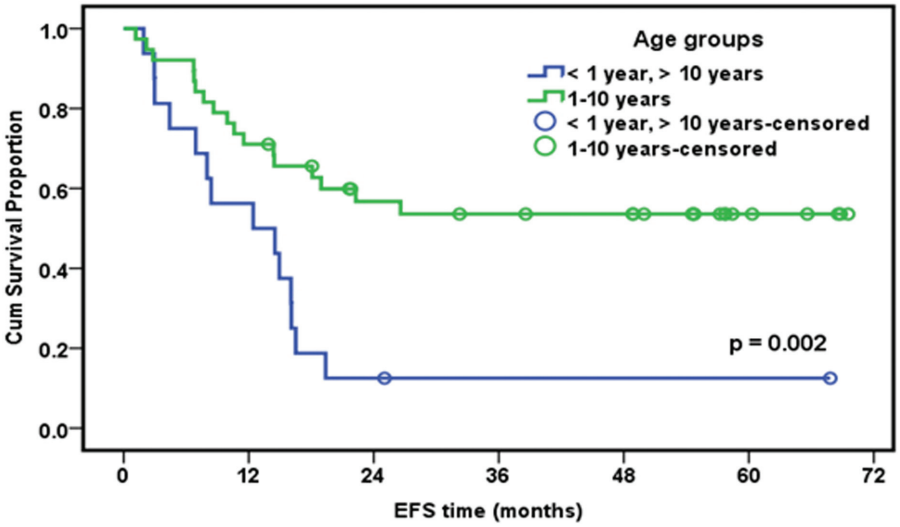
In this study the 2-years OS for stage I, II were 80.8% versus stage III, IV 48.9%, also it was reported by two previous Egyptian NCI studies that OS was 100% for stage I, 91.6% for stage III and 66.6% for stage IV

Figure 5



Event-free survival of Rhabdomyosarcoma patients.

Figure 6



Age and Event-free survival of Rhabdomyosarcoma patients.

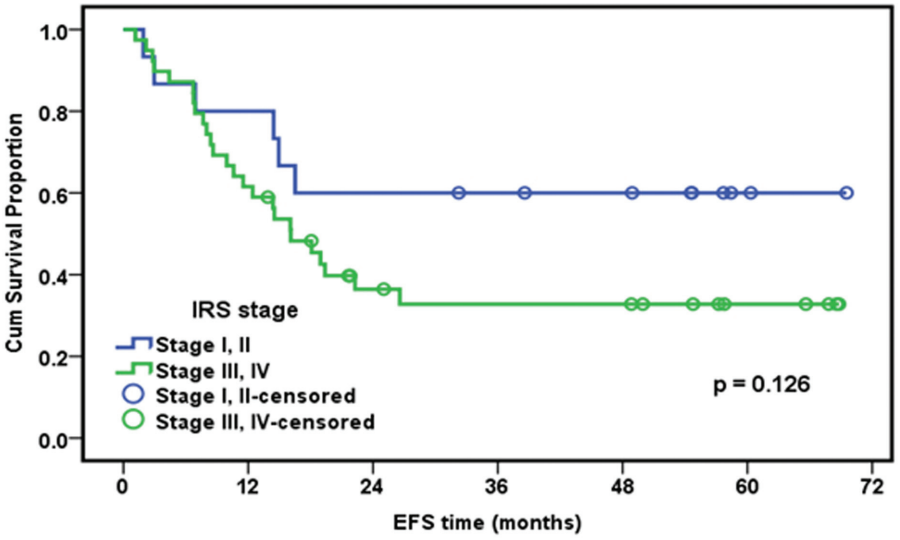
(Mohamed *et al.*, 2009) [6] and it was 83% for stage I patients and 55.6% for stages II and III (Mahmoud *et al.*, 2013) [9].

Recommendations

Further molecular studies to detect specific chromosomal translocations of RMS are recommended. Translocations t(2; 13)(q35; q14) and t(1; 13)(p36; q14) result in the expression of chimeric transcription factors PAX3-FKHR (PAX3-FOXO1) or PAX7-FKHR (PAX7-FOXO1), respectively. The clinical behavior and molecular characteristics of ARMS without a fusion gene are indistinguishable from ERMS cases and significantly different from fusion-positive ARMS cases as reported by other studies. Thus, fusion gene status may play a role as a factor in risk stratification in RMS, irrespective of histology. Encourage upfront total surgical excision. PET CT evaluated in staging pediatric RMS for better identifying nodal, bone, and bone marrow involvement.

All patients with clinical group III tumors especially with retroperitoneal-pelvic primaries should undergo complete surgical excision to be followed by local irradiation for better local control. For metastatic

Figure 7



IRS clinical group and Event-free survival of Rhabdomyosarcoma patients.

patients, further effort and newer therapeutic approaches required to improve the survival in these patients.

Finally, further efforts for screening and early detection of the disease should be done for better outcome.

Conclusion

RMS requires combined-modality therapy. Late presentation and advanced local disease compromise treatment options and decrease OS and EFS (Figs 1–7).

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Conflicts of interest

There are no conflicts of interest.

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