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Original Article

Ewing sarcoma outcomes in a country with limited resources: Egypt as an example

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Abstract: As the scarcity of published research that comprehensively and meticulously analyzed the patient, disease, and treatment factors of prognostic significance in Ewing sarcoma (EWS) in Egypt; This study aimed at assessing survival outcomes of EWS in Upper Egypt, delineating factors of prognostic significance in comparison to other leading oncology centers in Egypt and internationally. By retrospectively reviewing medical records of 85 patients with a verified diagnosis of EWS in the period from 2001 to 2015 at Pediatric and Medical Oncology Departments at South Egypt Cancer Institute; We gathered data relevant to the patient, disease, and treatment variables of the study. Survival was estimated using the Kaplan Meier method and differences between various groups were determined by log rank test. Univariable and multivariable analyses were performed using Cox regression. With a median follow-up period of 62.7 months (95% CI 52.2-73.2, SE=5.4) for the study patients, the estimates of event-free survival (EFS) and overall survival (OS) at 3 and 5 years were 42.1% and 50.6%, and 40.8% and 48.5%, respectively. Metastatic disease at initial presentation (HR=8.91, 95% CI, 4.00-19.9; P<0.0001) stood as the most powerful predictor of OS in the multivariable analysis, followed by surgery used as a local modality (HR=0.16, 95% CI, 0.06-0.44; P=0.0004). Response to neoadjuvant chemotherapy (HR=2.61, 95% CI, 1.11-6.13; P=0.028), primary tumor size (HR=2.49, 95% CI, 1.03-6.03; P=0.044) were also shown to be significantly associated with OS. Radiotherapy as a local modality, whose effect, apparently shown to increase the hazard of events occurrence in the univariable analysis, an effect that was reversed to reveal EFS advantage (HR=0.41, 95% CI, 0.18-0.95; P=0.036) after control of other variables. With 5-year OS of 48.5%, our survival results were comparable to those previously published from Egypt; however, differences still exist between centers due to varied representative study samples. However, outcomes in Egypt in general are still inferior to internationally published studies.

Keywords: Ewing sarcoma, primitive neuroectodermal tumor, Ewing sarcoma family of tumors, bone neoplasms, soft tissue neoplasms, WHO classification of tumors

Introduction

Ewing sarcoma family of tumors (ESFT) is an obsolete term [1] that has been used to refer to a group of rare and aggressive malignant small round cell tumors [2] that shares the same spectrum of a proposed neuroectodermal origin [3, 4] with varying degrees of histopatho-

logic differentiation and various clinical presentations, affecting mainly the bones (osseous) and soft tissues (extraosseous) to a lesser extent [5-9]. Historically, these tumors arose as two distinct entities; Namely, primitive neuroectodermal tumors (PNET) first described by Stout in 1918 for a tumor originating from the ulnar nerve, and the second was diffuse endothelioma involving the diaphysis of a long bone described by James Ewing in 1921 and named after his name later on as Ewing sarcoma (EWS) [10-12].

Despite still distinct morphologically [7, 13], both entities now represent the same biological continuum with identical treatment approaches [14, 15]. With the term "primitive neuroectodermal tumor" abolished, the World Health Organization (WHO) classification of tumors of soft tissue and bone in 4th Edition, approved simultaneously the term of "Ewing sarcoma" for general use [1]; however, we will keep the initial nomenclature of these clinicopathologic entities for the purpose of the present study [16, 17].

Treatment of EWS has evolved significantly after introducing multiagent chemotherapy regimens in the context of multimodality therapy using surgery, radiation therapy, or both for local control [18, 19]. Whereas, EWS patients' survival in the prechemotherapy era using local measures only either by surgery or radiotherapy was poor reaching less than 10% regardless the tumor stage [20-22]. However, the 5-year survival (OS) after using multiagent chemotherapy in combination with surgery ± radiotherapy was improved to reach 65-75% in localized stage, while rates barely exceeded 30% in metastatic stage [23, 24].

As the prognosis of patients with EWS has been shown to depend on several factors like the patient age, stage of disease, primary site, size of tumor, and the received treatment [25, 26]. Hereby, we will report for the first time our experience from Upper Egypt; Assessing survival outcomes, delineating factors of prognostic significance, comparing our results with reference to those reported from other leading large oncology centers in Egypt, and providing a preliminary overview on the current state of EWS in Egypt at the national level.

Materials and methods

Study patients

A retrospective study was conducted at the Pediatric Oncology Department and Medical Oncology Department. Our institutional database was screened for all patients who were diagnosed and received treatment for EWS, in either of its initial nomenclature EWS or PNET in the period from 2001 to 2015, where the histopathologic diagnosis had been verified by two experienced pathologists by a combination of characteristic morphology and a panel of immunohistochemistry markers (Figure S1), and hence the medical records of 85 patients were eligible to be retrospectively reviewed to extract the study relevant data. An agreement was made between two experienced radiologists to categorize the primary tumor size according to the largest diameter into 3 subgroups ≤5 cm; >5-≤8 cm; >8 cm. Surgical reports were revised by orthopedic and oncologic surgeons for surgical resection margins for adequacy and were categorized as wide, close, or intralesional [27-29].

Collected data for the study included the following: patients' age and gender; the treatment period; the treatment department; tumor stage; primary tumor site that further categorized according to anatomic location whether appendicular or axial; tumor size; tumor origin whether osseous or extraosseous; tumor histopathologic subtype whether EWS or PNET; sites of metastatic disease at diagnosis and at relapse; treatment adequacy as per standard protocols, as shown in **Table 1**; chemotherapy protocol used; radiologically assessed response to neoadjuvant chemotherapy (RECIST) [30]; local control modality; adequacy of surgical resection margin; systemic and local recurrences.

Diagnosis and staging

Initial diagnosis was typically performed by obtaining tissue specimens either by a Tru-Cut needle biopsy or occasionally form tumors resected by upfront surgery and sent for histopathologic examination. All patients were subjected to initial diagnostic workup included magnetic resonance imaging (MRI) or computed tomography (CT) for the assessment of primary tumor; and chest CT, bone scan, and bone

Table 1. Patient, disease, and treatment characteristics (n=85)

Variables	Categories		Freq.	(%)
Gender	Male		47	55.3%
	Female		38	44.7%
Age by gender within histopathologic subtype Mean (SD)	Ewing Sarcoma (N=59)	Male (N=36, 61%)	16.6±6.0	
		Female (N=23, 39%)	12.7±6.3	
	PNET (N=26)	Male (N=11, 42.3%)	11.3±5.4	
		Female (N=15, 57.7%)	12.9±10.2	
Treatment Period	(2001-2009)		31	36.5%
	(2010-2015)		54	63.5%
Treatment Department	Pediatric Oncology		59	69.4%
	Medical Oncology		26	30.6%
Gender	Male		47	55.3%
	Female		38	44.7%
Age Categories (years)	Age 0-4		8	9.4%
	Age 5-9		14	16.5%
	Age 10-14		23	27.1%
	Age 15-18		21	24.7%
	Age >18		19	22.4%
Primary Tumor Site	Distal Extremities		17	20.0%
	Proximal Extremities		22	25.9%
	Pelvic		17	20.0%
	Intra-thoracic (Deeply-seated)		9	10.6%
	Chest Wall (Externally exposed)		8	9.4%
	Intra-abdominal		8	9.4%
	Paraspinal		3	3.5%
	Head & Neck		1	1.2%
Anatomic Location	Appendicular (Extremities)		39	45.9%
	Axial (Central)		46	54.1%
Histopathologic Type	Ewing Sarcoma		59	69.4%
	PNET		26	30.6%
Tumor Origin	Extraskeletal “Non-osseous”		31	36.5%
	Skeletal “Osseous”		54	63.5%
Size of Primary Tumor (the Largest Diameter)	≤5 cm		7	8.2%
	>5 or ≤8 cm		31	36.5%
	>8 cm		47	55.3%
Stage of Disease at Diagnosis	Localized		59	69.4%
	Metastatic		26	30.6%
Sites of Metastases at Diagnosis (N=26)	Lung only		15	57.7%
	Bone ± others (excluding B.M.)		6	23.1%
	Bone Marrow ± others		5	19.2%
Sites of Metastases at Relapse (N=40)	Lung only		20	50.0%
	Extrapulmonary		20	50.0%
Treatment Adequacy According to Standard Protocols	As per protocol		64	75.3%
	Upfront Surgery		4	4.7%
	No local Intervention		4	4.7%
	Delayed Local >6 wks.		13	15.3%
Chemotherapy Protocol	VACD/IE		41	48.2%
	VACD (or VACA)		18	21.2%
	VAID (or VAIA)		26	30.6%
Response to Neoadjuvant CTH (N=81)	Good (CR/PR)		70	86.4%
	Poor (SD/PD)		11	13.6%
Local Treatment following Neoadjuvant CTH (N=77)	Surgery		28	36.4%
	Surgery & RTH		28	36.4%
	Definitive RTH		21	27.3%
Surgery Used as Local Modality	No		25	29.4%
	Yes		60	70.6%

Surgical Resection Margin (N=60)	Wide excision	29	48.3%
	Marginal (Close margin)	28	46.7%
	Intralesional	3	5.0%
Radiotherapy Used as Local Modality	No	36	42.4%
	Yes	49	57.6%
Systemic Progression/Recurrence	No	37	43.5%
	Yes	48	56.5%
Local Progression/Recurrence	No	70	82.4%
	Yes	15	17.6%

marrow biopsy for evaluation of metastatic disease.

Clinical management, treatment strategies, and follow-ups

A multimodality approach was instituted, including multidrug chemotherapy, besides surgery and or radiotherapy for local control. Induction (neoadjuvant) chemotherapy was planned for 3 to 4 cycles, to be followed by local control at week 9-12, then by maintenance chemotherapy to the end of the protocol.

All patients received chemotherapy by either of the following regimens; (1) VACD/IE protocol [31] adopted by American cooperative groups (INT-0091, CCG-7881/POG-8850) in which (vincristine, doxorubicin replaced with actinomycin D after reaching the cumulative dose at week 36, and cyclophosphamide), alternating with (ifosfamide and etoposide) every 3 weeks for 54 weeks, and was adopted in the Pediatric Oncology Department by the year 2008, Or (2) VACA [25, 32, 33] (vincristine- doxorubicin-cyclophosphamide- actinomycin), a chemotherapy protocol adopted by the European Intergroup Cooperative Ewing Sarcoma Studies (CESS and UKCCSG), and used in the Pediatric Oncology Department before the year 2008, or (3) VAIA [25, 33-35] which evolved from VACA by (substituting ifosfamide for cyclophosphamide), and was used in the Medical Oncology Department in the entire treatment period.

Local control as per protocol, which included surgery and/or radiotherapy planned to be performed at week 9-12, was individualized according to many factors, including tumor site, size, response to chemotherapy, amenability to surgery, surgical resectability, the adequacy of surgical resection margin. After finishing treatment, patients were subjected to serial follow-ups by clinical examination, MRI/CT on local tumor, chest CT, and evaluation of metastatic site if needed. The patients were followed every 3 months for 2 years and then every 6 months.

Statistical analysis

Data were analyzed using SPSS software version 20. OS was measured from the date of diagnosis to the date of death or last follow-up. Event free survival (EFS) was measured from the date of diagnosis to the date of any adverse event (disease progression, recurrence or death), whichever came first; or date of the last follow-up. OS and EFS curves were calculated using Kaplan-Meier method and compared using the log-rank test. The effect of different prognostic factors on survival in both the univariable and multivariable analysis was calculated using the Cox regression model. Two-sided P value ≤ 0.05 was considered statistically significant.

Ethical considerations

The study is registered with ID NCT04300179 on clinical trial.gov under the title “Ewing Sarcoma Family of Tumors (ESFT): a 15-year Experience from a Tertiary Care Cancer Center in Upper Egypt”, where the study was initially confined to the Pediatric Oncology Department and was extended later on to include adult patients by collaboration and participation of the Medical Oncology Department. Ethical approval was obtained from our institutional ethical committee SECI-IRB by number IORG0006563-503.

Results

Patient characteristics

Of 85 patients of the study cohort, 69.4% (59/85) were treated in the Pediatric Oncology Department, while 30.6% (26/85) were treated in the Medical Oncology Department. Males constituted 55.3% (47/85) of the study popula-

tion. The male to female ratio was 1.2:1. The median age (range) for the entire cohort was 14 y (1-35 y), while it was 11 y (1-18 y), and 22 y (16-35 y) for those treated in the Pediatric and Medical Oncology Departments, respectively. Patient, disease, and treatment characteristics were shown in **Table 1**. Comparison between our study findings, and those obtained from other local papers [36-39] published in Egypt were shown in **Table 2**.

Survival outcomes

With a median follow-up period of 62.7mo (95% CI 52.2-73.2, SE=5.4) for the study patients, the estimates of EFS and OS at 3 and 5 years were 42.1% and 50.6%, and 40.8% and 48.5%, respectively. Of the 85 patients, disease progressed in all 26 patients who presented with metastatic disease at initial diagnosis except 1 patient lost follow up during treatment; while out of 59 patients with localized disease at presentation, 34 patients remained continuously disease free at the time of last follow-up. Overall, for the entire cohort, a distant recurrence/progression occurred in 35 patients, a combined local & distant recurrence occurred in 13 patients, whereas 2 patients experienced isolated local relapse. The median time to recurrence/progression was 16.3 mo (range: 1.9-39.1 mo), and median post-recurrence survival time was 4.2 mo (range: 0.1-16 mo). Fifty patients died; all of them succumbed to their uncontrolled, progressive disease by the time of analysis. Metastatic sites at diagnosis & at relapse; and rate of either systemic or local recurrence/progression were shown in **Table 1**.

Survival curves for OS at 5 years, according to: (A) Stage of disease, (B) Tumor size, (C) Metastatic sites at diagnosis, (D) Metastatic sites at relapse/progression, were shown in **Figure 1**; and as regard to (A) Age categories, (B) Primary tumor site, (C) Surgery as local modality, and (D) Radiotherapy as local modality, were shown in **Figure 2**.

Analyses of prognostic factors

EFS: Both stage of disease at diagnosis (HR=16.0, 95% CI, 6.51-39.5; P<0.0001), and surgery used as a local modality (HR=0.089, 95% CI, 0.04-0.25; P<0.0001) stood as the most powerful predictors of the EFS in the multivariable analysis, followed in significance by histopathologic subtype (HR=4.00, 95% CI, 1.89-8.35; P=0.0003), and primary tumor size (HR=3.38, 95% CI, 1.54-7.38; P=0.002); while both anatomic location and treatment adequacy lost their statistical significance as predictors of EFS in multivariable analysis. On the other hand, radiotherapy used as a local modality, whose effect, apparently shown to increase the hazard of events occurrence in the univariable analysis, an effect that was reversed to reveal EFS advantage (HR=0.41, 95% CI, 0.18-0.95; P=0.036) after control of other variables. Predictors of EFS in the univariable and multivariable analysis were shown in **Table 3**.

OS: Stage of disease at diagnosis (HR=8.91, 95% CI, 4.00-19.9; P<0.0001) stood as the most powerful predictor of OS in the multivariable analysis, followed by surgery used as a local modality (HR=0.16, 95% CI, 0.06-0.44; P=0.0004). Response to neoadjuvant chemotherapy (HR=2.61, 95% CI, 1.11-6.13; P= 0.028), primary tumor size (HR=2.49, 95% CI, 1.03-6.03; P=0.044) were also shown to be significantly associated with OS. Radiotherapy used as a local modality came next in significance with only marginally better OS (HR=0.48, 95% CI, 0.21-1.11; P=0.086) in the multivariable analysis. Predictors of OS in the univariable and multivariable analysis were shown in **Table 4**.

Discussion

With a median follow up duration of 62.7 months, retrospectively reviewing EWS over 15 years, we presented the largest cohort in Egypt next to that published by the Clinical Oncology Department affiliated to Alexandria University located on the Mediterranean coast in northern Egypt [39]. Our institutional study performed at the South Egypt Cancer Institute involved both pediatric and adult groups treated in two distinct departments that serve patients with cancer in Upper Egypt. Our cohort comprising as well a heterogeneous set of anatomic locations of diverse primary tumor sites and age groups, including those with metastatic disease at initial presentation, seemingly, was the most representative study sample over Egypt so far.

In line with the widely recognized effect of the initial metastatic disease upon prognosis in previous literature [26, 40-43], the distant metastasis was the most significant prognostic factor for survival outcomes. Patients with dis-

Table 2. Comparison between our study findings, and those published from other leading large local oncology centers in Egypt

	National Cancer Institute (NCI-Cairo)	Ain Shams University	Children's Cancer Hospital (CCHE 57357) Unpublished[a]	Alexandria Clinical Oncology Department	South Egypt Cancer Institute (SECI)
	N=20	N=22	N=155	N=74	N=85
Treatment Period	1997 to 2008	January 2003 to July 2016	January 2008 to December 2014	2004 to 2014	2001 to 2015
No. of Patients	20 out of total 280 patients (7%) with EWS of Head & Neck were analyzed for purpose of the study.	22	155	74	Total 85 patients: Ped Oncol Depart.: 59 Med Oncol Depart.: 26
Study Population	Localized: 14 (70%) Metastatic: 6 (30%)	Localized: 21 (95.5%) Metastatic: 1 (4.5%)	Localized Ewing sarcoma family	Localized Ewing sarcoma	Localized: 59 (69.4%) Metastatic: 26 (30.6%)
Gender	Male: 10 (50%) Female: 10 (50%) M/F ratio =1:1	Male: 7 (31.8%) Female: 15 (68.2%) M/F ratio =0.5:1	N/A	Male: 43 (58.1%) Female: 31 (41.9%) M/F ratio =1.4:1	Male: 47 (55.3%) Female: 38 (44.7%) M/F ratio =1.2:1
Age Range of Participants (Median)	(5 mo-22 y) Median: 11.5 y	(2-15 y) Median: 5 y	Median: 11 y	(4-22 y) Median: 13 y	Overall range & median: (1-35 y); 14 y For Ped Oncol Depart.: (1-18 y); Median: 11 y For Med Oncol Depart.: (16-35 y); Median: 22 y
Age Categories	NA	NA		<10 y: 19 (25.7%) 10-15 y: 32 (43.2%) >15 y: 23 (31.1%)	<10 y: 22 (25.9%) 10-14 y: 23 (27.1%) 15-18 y: 21 (24.7%) >18 y: 19 (22.4%)
Tumor Size	≤ 8 cm: 17 (85%)	NA		≤ 8 cm: 42 (56.8%)	≤ 5 cm: 7 (8.2%) 5-8 cm: 31 (36.5%)
	>8 cm: 3 (15%)			>8 cm: 32 (43.2%)	>8 cm: 47 (55.3%)
Surgical Resection Margin	Negative: 4 (57%) Positive: 3 (43%)	NA			Wide margin: 29 (48.3%) Close margin: 28 (46.7%) Intralesional: 3 (5.0%)
Type of Surgical Plan	7/20 (35%) of the patients: Attempt for radical surgery	8/8 (100%) of extremity tumors: Limb salvage surgery			
Anatomic Location (Primary tumor site)	Head & Neck	Extremity: 8 (40%)	Appendicular skeleton: 84 (54.2%)	Extremities: 36 (48.6%)	Appendicular: 39 (45.9%)
		Non-Extremity: 12 (60%)	Trunk: 71 (45.8)		
				Pelvis: 22 (29.7%)	Axial: 46 (54.1%)
	Mandibular ramus: 9 (45%) Neck: 4 (20%) Clavicle: 3 (15%) Parapharyngeal: 2 (10%)	Femur: 7 (35%) Humerus: 1 (5%) Chest wall: 4 (20%) Other axial: 8 (40%)		Others: 16 (21.6%)	
Study Follow-up Period	NA	NA	Median FU: 34 mo (4 mo-8 y)	Median FU: 63.8 mo	Median FU: 62.7 mo (2 mo-10.4 y)
Treatment Protocol	VAC/IE (95% received chemotherapy)	VAC/IE	VAC/IE	VAC/IE	VACD/IE: 41 (48.2%) VACA: 18 (21.2%) VAID (VAIA): 26 (30.6%)

Outcome Measure	3 y OS: 50% 3 y PFS: 67% 3y OS (metastatic): 14% 3y OS (localized): 69%	3 y OS: 18.2% 3 y EFS: 18.2%	5 y OS: 74% 5 y RFS: 73.6%	5 y OS: 57% 5 y EFS: 44%	For the entire cohort: 5 y OS: 48.5% 5 y EFS: 40.8% For the localized group: 5 y OS: 68.7% 5 y EFS: 57.1%
Local control modality					
Surgery	2 (10%)		80 (51.6%)	22 (29.7)	28 (32.9%)
RTH	8 (40%)	NA	50 (32.2%)	33 (44.6)	21 (24.7%)
Surgery + RTH	5 (25%)		25 (16.1%)	19 (25.7)	28 (32.9%)
NO local TTT	3 (15%), lost FU				4 (4.7%)
Upfront Surg.					4 (4.7%)
Reference	Ahmed, et al., 2017 [36]	Mokhtar et al., 2019 [37]	Maarouf, et al., 2016[a] [38]	Nazeer, et al., 2017 [39]	The present study

[a]Abstract was published as conference proceedings in the 48th Congress of the International Society of Paediatric Oncology (SIOP), 2016.

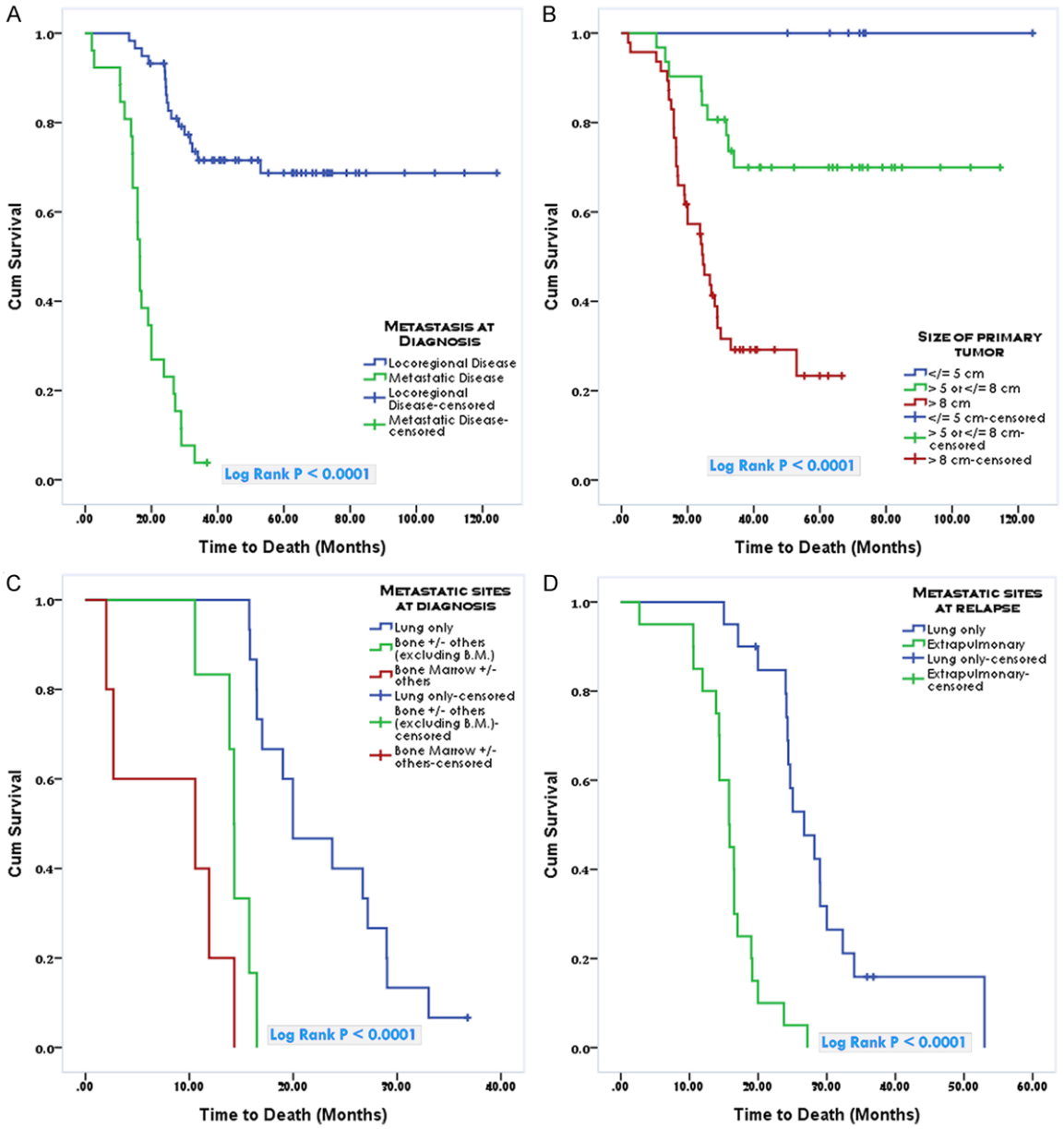

Figure 1. Overall survival differences for each of (A) Stage of disease; locoregional vs. metastatic (B) Tumor size; ≤5, >5-≤8, or >8 cm (C) Metastatic sites at diagnosis; Lung only, Bone ± others excluding B.M, or Bone Marrow ± others (D) Metastatic sites at relapse/progression; lung only vs. extrapulmonary.

tant metastases in the present study had an estimated 5-year OS of 3.9% compared with 68.7% in those with nonmetastatic disease. Not only was the mere presence of distant metastasis, but also the site of these metastases, where those disseminated to bone marrow and/or bone in our study, were significantly worse than those confined only to lung [44]. Also, consistent with previous studies, our results showed besides the disease stage that both, surgery as a local modality [26, 45, 46], and primary tumor size [26, 47], were consistently associated with either of EFS or OS after controlling for other confounding variables.

Using a radiologically assessed overall response rate in our study; patients whose disease response to neoadjuvant chemotherapy were shown to be progressive or stationary after chemotherapy (PD/SD) had a significantly worse OS at both univariable and multivariable analyses than those who had complete or par-

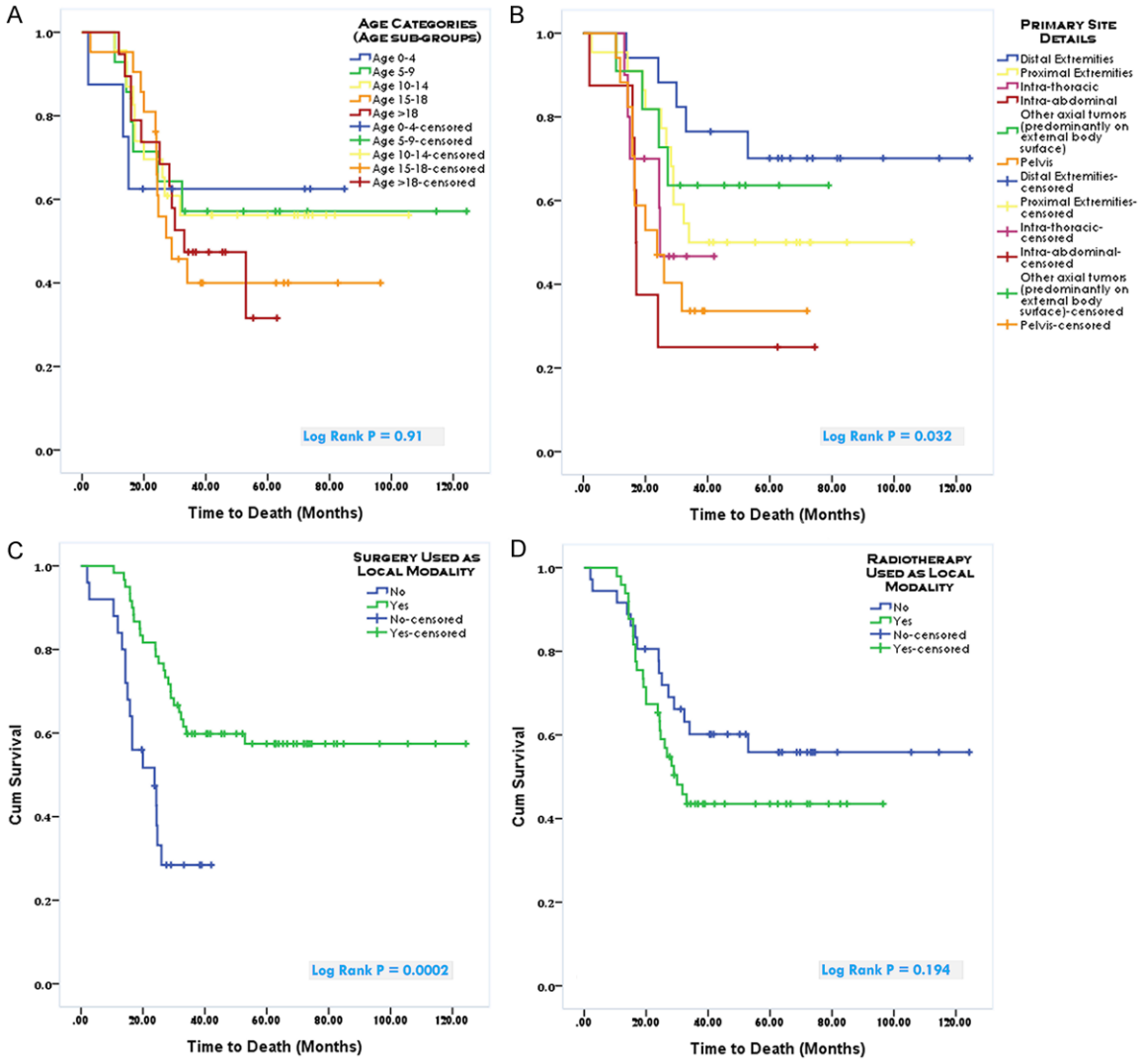

Figure 2. Overall survival differences for each of (A) Age categories; 0-4, 5-9, 10-14, 15-18, or >18 y (B) Primary tumor site; Distal extremities, Proximal extremities, Intrathoracic, Intra-abdominal, Other axial tumors predominantly on external body surfaces, or Pelvis (C) Surgery as local modality; No or Yes (D) Radiotherapy as local modality; No or Yes.

tial response (CR/PR), consistent with a previous report from Saudi Arabia [48]. On the other hand, histopathologic subtype whose prognostic impact was shown to be controversial in previous studies [6, 16, 43, 49], our study revealed that the more differentiated "PNET" compared to "EWS" histopathologic subtype was prominently worse only on EFS; An effect on the OS that probably was mitigated by the eventual response of tumors to neoadjuvant chemotherapy.

As regards to other controversial factors in the literature, whilst the anatomic location was found to significantly effect both EFS and OS only in the univariable analysis [25, 26]; on the other side, we didn't find any significant impact of the age of patients on survival either in the univariable or multivariable analyses [50]. Relatively a small sample size may play a role.

Consistent with findings of Rodríguez-Galindo, et al., neither treatment period, nor chemotherapy protocol used [26], nor treatment department had a significant effect on survival; likewise, the hazardous effect of treatment inadequacy on the survival disappeared in the multivariable analysis. Interestingly, a trend towards an increase in the incidence of EWS in the second treatment period (2010-2015) in comparison to the period (2001-2009) consistent with another study performed at the same institute

Table 3. Predictors of event-free survival (EFS) in patients with Ewing sarcoma by univariate & multivariable analyses using cox regression

Variables	Category	n	Univariable				Multivariable		
			HR	95% CI	5-year estimate (%)	*P*	HR	95% CI	*P*
Treatment period	(2001-2009)	31	Ref		38.7		Not included in the model[a]		
	(2010-2015)	54	0.91	0.52-1.62	42.1	0.75			
Treatment Department	Pediatric Oncology	59	Ref		47.1		Not included in the model[a]		
	Medical Oncology	26	1.54	0.87-2.73	26.4	0.14			
Gender	Male	47	Ref		39.8		Not included in the model[a]		
	Female	38	0.91	0.52-1.60	42.1	0.75			
Age at diagnosis (years)	Continuous (per year)	85	Ref		N/A		Not included in the model[a]		
			1.01	0.97-1.05	N/A	0.74			
Age Categories	Age <10	22	Ref		45.5		Not included in the model[a]		
	Age 10-18	44	1.01	0.51-2.01	42.6	0.83			
	Age >18	19	1.23	0.56-2.69	30.7				
Anatomic Location	Appendicular	39	Ref		59.0		Ref		
	Axial	46	2.75	1.51-5.00	25.1	0.001	0.60	0.25-1.42	0.24
Histopathologic Type	Ewing Sarcoma	59	Ref		45.1		Ref		
	PNET	26	1.64	0.92-2.92	30.8	0.092	4.00	1.89-8.35	0.0003
Tumor Origin	Extraskeletal	31	Ref		32.3		Not included in the model[a]		
	Skeletal	54	0.64	0.36-1.12	45.7	0.12			
Stage of disease at diagnosis	Localized	59	Ref		57.1		Ref		
	Metastatic	26	9.32	5.00-17.5	3.85	<.001	16.03[a]	6.51-39.5	<.0001
Size of primary tumor (cm)	≤8 cm	38	Ref		65.8		Ref		
	>8 cm	47	4.14	2.18-7.90	20.3	<.001	3.38	1.54-7.38	0.002
Treatment Adequacy	As per protocol	64	Ref		48.0		Ref		
	Others	21	2.29	1.27-4.12	19.0	0.005	1.24	0.62-2.46	0.54
Chemotherapy Protocol	VACD/IE	41	Ref		45.8		Not included in the model[a]		
	Others	44	1.21	0.69-2.11	36.2	0.50			
Response to Neoadjuvant CTH (N=81)	Good (CR/PR)	70	Ref		42.3		Not included in the model[a]		
	Poor (SD/PD)	11	1.82	0.85-3.89	27.3	0.12			
Surgery Used as Local Modality	No	25	Ref		4.80		Ref		
	Yes	60	0.24	0.14-0.43	54.9	<.001	0.089	0.04-0.25	<.0001
RTH Used as Local Modality	No	36	Ref		55.4		Ref		
	Yes	49	1.87	1.03-3.40	29.9	0.038	0.41	0.18-0.95	.036
Surgical Resection Margin (N=60)	Wide excision	29	Ref		68.8		Not included in the model[b]		
	Others	31	2.43	1.09-5.44	41.9	0.025			

[a]Not included in the multivariable analysis due to statistically non-significant results in the univariable analysis, as *p*-value arbitrarily set to (P=0.1). [b]Not included in the model despite *P* value was <0.1 due to singularity & multicollinearity based on the collinearity diagnostic test.

Table 4. Predictors of overall survival (OS) in patients with Ewing sarcoma by univariate & multivariable analyses using cox regression

Variables	Category	n	Univariate				Multivariable		
			HR	95% CI	5-year estimate (%)	*P*	HR	95% CI	*P*
Treatment period	(2001-2009)	31	Ref		42.8		Not included in the model[a]		
	(2010-2015)	54	0.82	0.44-1.52	52.4	0.53			
Treatment Department	Pediatric Oncology	59	Ref		54.5		Not included in the model[a]		
	Medical Oncology	26	1.43	0.77-2.66	31.7	0.26			
Gender	Male	47	Ref		44.2		Not included in the model[a]		
	Female	38	0.77	0.42-1.43	53.4	0.41			
Age at diagnosis (years)	Continuous (per year)	85	Ref		N/A		Not included in the model[a]		
			1.01	0.97-1.05	N/A	0.69			
Age Categories	Age <10	22	Ref		58.0		Not included in the model[a]		
	Age 10-18	44	1.15	0.53-2.50	48.7	0.84			
	Age >18	19	1.30	0.54-3.15	31.6				
Anatomic Location	Appendicular	39	Ref		58.5		Ref		
	Axial	46	2.04	1.09-3.83	41.7	0.023	0.86	0.36-2.10	0.73
Histopathologic Type	Ewing Sarcoma	59	Ref		50.2		Not included in the model[a]		
	PNET	26	1.39	0.73-2.64	45.0	0.32			
Tumor Origin	Extraskeletal	31	Ref		50.9		Not included in the model[a]		
	Skeletal	54	0.86	0.46-1.62	48.3	0.64			
Stage of disease at diagnosis	Localized	59	Ref		68.7		Ref		
	Metastatic	26	9.88	5.10-19.2	3.85	<.001	8.91[a]	4.00-19.9	<.0001
Size of primary tumor (cm)	≤8 cm	38	Ref		73.0		Ref		
	>8 cm	47	4.29	2.09-8.79	26.4	<.001	2.49	1.03-6.03	0.044
Treatment Adequacy	As per protocol	64	Ref		55.7		Ref		
	Others	21	2.33	1.23-4.40	25.8	0.007	1.51	0.73-3.13	0.27
Chemotherapy Protocol	VACD/IE	41	Ref		53.8		Not included in the model[a]		
	Others	44	1.21	0.66-2.23	43.8	0.54			
Response to Neoadjuvant CTH (N=81)	Good (CR/PR)	70	Ref		51.6		Ref		
	Poor (SD/PD)	11	2.28	1.05-4.96	27.3	0.032	2.61	1.11-6.13	0.028
Surgery Used as Local Modality	No	25	Ref		28.4		Ref		
	Yes	60	0.32	0.17-0.60	57.4	<.001	0.16	0.06-0.44	0.0004
RTH Used as Local Modality	No	36	Ref		55.9		Ref		
	Yes	49	1.52	0.81-2.85	43.5	0.19[b]	0.48	0.21-1.11	0.086
Surgical Resection Margin (N=60)	Wide excision	29	Ref		67.0		Not included in the model[c]		
	Others	31	2.66	1.26-5.62	48.4	0.082			

[a]Not included in the multivariable analysis due to statistically non-significant results in the univariable analysis, as *p*-value arbitrarily set to (P=0.1). [b]Included in the multivariable analysis, albeit *P* value >0.1, due to increased model fitness based on Likelihood Ratio in addition to the demonstrated significance on EFS. [c]Not included in the model despite *P* value was <0.1, due to singularity & multicollinearity based on the collinearity diagnostic test.

[51], where incidence in the former period was about 3.4 patients/year vs. 9 patients/year in the latter period (i.e., there was about 3-fold increase in the incidence rate). It is unknown whether these findings are real increase or just a referral bias.

Whilst, the survival outcomes reported by the Pediatric Hematology/Oncology department of Ain Shams University, third-oldest public Egyptian university located in Cairo the capital of Egypt, were 18.2% at 3 years for either EFS or OS [37]. Their results were seemingly the worst published in Egypt, despite the disease being localized in almost all 21/22 (95.5%) patients. Their poor outcomes could be attributed to that the majority of their study population (60%) had a tumor in an axial location, and the remainder of patients who had extremity tumors in their study (40%), their tumors were proximally located at the limb (7 in femur and one in humerus). It is known that a proximal location in the extremity is usually associated with a larger tumor size and a greater propensity to distant metastatic spread [52, 53] and less frequent resectability [48]. Moreover, there were no adequate details about surgical resection margins or adequacy of radiotherapy for those with inadequate or close margins.

On the other hand, a report was published for a subset of patients 20/220 (7%) with head and neck EWS analyzed at the National Cancer Institute (NCI-Cairo) affiliated to Cairo University which is Egypt's premier public university [36]. Overall survival outcomes in their results at 3 years were 50%, and 69%, for the entire subset and localized disease sub-group, respectively, which were superior, but comparable to results of axial tumors in our study that were 41.7%, and 65.2%, respectively. EWS in a head and neck location was reported in one report as a favorable axial site [48]. Also, a minority of their sample subset 3/20 (15%), had a primary tumor size >8 cm.

Our experience was more or less similar to those of Alexandria group as regard to their study population characteristics of gender, age, treatment period, duration of follow up with the exception of that metastatic disease wasn't included in their cohort; but by comparing the corresponding groups of localized EWS in both, we had more frequent extremity location 31/59 (52.5%) and less pelvic sites 8/59 (13.6%) vs. 36/74 (48.6%), and 22/74 (29.7%) in their cohort, respectively. The pelvic location has been known to be more frequently associated with metastatic disease [26, 43], as well it accounted for a greater proportion 9/26 (34.6%) in those with metastatic disease in our study, P=0.025. Our better survival outcomes may be also attributed to less frequent tumor size >8 cm in 40.7% vs. 43.2%, while more frequent use of surgery only in 40.7% in our study population versus 29.7% of theirs, respectively.

A preliminary report of Children's Cancer Hospital (CCHE) study that encompassed 144 patients of localized EWS over the period from 2008 to December 2014 showed a 5 y OS of 74% (Unpublished) [38]; Our study revealed a comparable 5 y OS of 68.7% in localized EWS. Seemingly, the relatively higher survival rates in our cohort and those of CCHE compared to other centers in Egypt could be due higher proportion of patients in whom surgery was used alone as a local control modality that were 40.7% and 51.6% in ours and theirs, respectively. It is possible that it may be an inherent advantage for surgery over radiotherapy as a local control measure or may be a result of selection bias of patients in whom tumor resectability is better to undergo surgery with eventual better outcomes. However, use of radiotherapy as a local modality in our study was demonstrated to have a beneficial independent effect on survival; despite being less important than that shown while using surgery as a local modality.

Considering the outcome of those patients with nonmetastatic disease, we have a 5-year OS of 68.7% that is consistent with internationally published studies whose outcomes averaged between 65-75%. On the other hand, the 5-year OS for those patients with metastatic disease was 3.9% indicating a dismal outcome for this group of patients, a finding that was far inferior to the internationally reported results that could be as high as 30%. Unavailability of centers specialized in performing highly sophisticated surgical techniques, necessary for example for a removal of metastatic disease "metastatectomy" in selected cases, in addition to unavailability of bone marrow transplant services for those with recurrent disease; One or more of these factors may eventually impact the final outcomes.

Having a national policy to raise public awareness, as well as providing continuous financial and logistical support along with sustainability, are of paramount importance and imperative to improve outcomes in our institute and in low-resource countries in general. In line with that policy adopted to improve some of these issues, a bone marrow transplant unit was recently established in our institute as the first and the only unit in Upper Egypt; however, it started its services later to treatment periods included in the present study; Therefore, it is still too early to assess its success rate.

Being an institutional study, so the sample size was relatively small; Nevertheless, our analysis was rather comprehensive regarding the inclusion of the most potential variables implicated in the prognosis of EWS with meticulously performed multivariable analysis that enabled us to elucidate the important beneficial and hazardous risk factors affecting the survival after control of other confounding factors, then comparing our results with local centers and internationally.

Conclusion

With a 5-year OS of 48.5%, survival outcome in our study was within the reported range of 18.2-64.4% of the survival results of EWS published in Egypt. A future collaboration between large leading cancer centers in Egypt towards building a national cancer registry could provide a more informative and consistent view of the state of EWS in Egypt.

Disclosure of conflict of interest

None.

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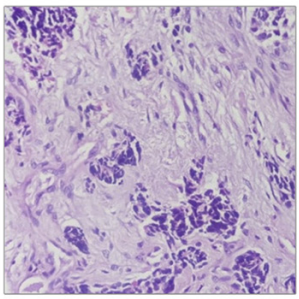

Fig. S1 a): (x400), PNET case; Tumor cells are uniform, ovoid and show areas of Homer Wright rosettes.

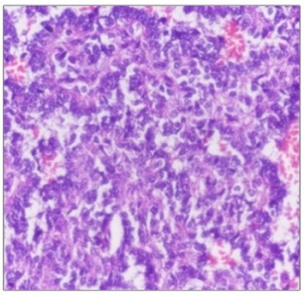

Fig. S1 b): (x400), EWS case; Tumor cells are arranged in lobulated and trabecular pattern.

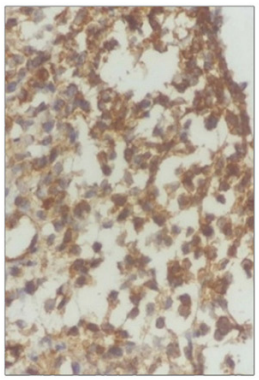

Fig. S1 c): (X 400) PNET case; Tumor cells show positive immunoreactivity for synaptophysin.

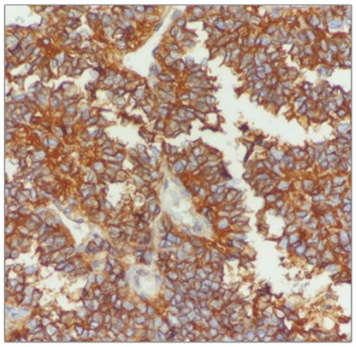

Fig. S1 d): (x400), EWS case; Tumor cells show strong diffuse positive immunoreactivity for CD99.

Figure S1. A: (×400), PNET case; Histopathology (Eosin & Hematoxylin). B: (×400), EWS case; Histopathology (Eosin & Hematoxylin). C: (×400), PNET case; Immunohistochemistry (Synaptophysin). D: (×400), EWS case; Immunohistochemistry (CD 99).