

# Clinicopathological Features and Treatment Outcomes in Ewing's Sarcoma Patients: A 10-year experience of Alexandria Clinical Oncology Department

## Abstract

**Background:** Ewing's sarcoma (ES) is an aggressive tumor, which is usually associated with micrometastases in the circulation. Thus, systemic chemotherapy in addition to local control modality is essential to improve outcomes. The aim of this study was to evaluate clinicopathological features and treatment outcomes in patients with ES. **Materials and Methods:** Medical files of 74 patients with nonmetastatic ES treated at our centers between 2004 and 2014 were retrospectively evaluated. The clinicopathological parameters were extracted and statistically correlated with event-free survival (EFS) and overall survival (OS). **Results:** The median age of patients was 13 years. The median follow-up duration was 63.8 months. About two-thirds (58.1%) of patients were male. Pain (74.3%) was the most common presenting symptom. Extremities (48.6%) were the frequently affected sites. Thirty-two patients (43.2%) presented by tumors larger than 8 cm. All patients were treated with chemotherapy. Local therapies were surgery and/or radiotherapy. The 5-year EFS and OS were 44% and 57%, respectively. On multivariate analysis, EFS and OS were significantly associated with age, tumor site, and tumor size. **Conclusions:** Despite limited resources in a developing country, the survival rates of ES are comparable to that in developed countries, and prognostic factors are age, tumor site, and tumor size.

**Keywords:** Chemotherapy, Ewing's sarcoma, prognosis, survival

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## Introduction

Ewing's sarcoma (ES) family is a group of malignant small round cell tumors of neuroectodermal origin that vary in their neurogenic differentiation but share the same treatment and prognosis. ES is the second most frequent primary malignant bone tumor that affects mainly children and young adult and constitutes 3% of all pediatric malignancies.<sup>[1]</sup> It rarely occurs in adults over the age of 30.<sup>[1]</sup>

The survival rates in patients with ES have been markedly improved due to the advent of recent chemotherapy protocols, advanced radiotherapeutic techniques with accurate localization and delivery, and improved surgical techniques.<sup>[2-6]</sup> The prognosis of patients with ES depends on the age of the patient, stage of disease, primary tumor site, and tumor size.<sup>[7-10]</sup>

Despite growing literature evaluating the treatment effectiveness in patients with ES from the Western countries, data

assessing outcomes of currently utilized therapy from the Middle East are scarce. Furthermore, conflicting results have been reported.<sup>[2-6,11,12]</sup> Thus, this study was designed to identify the clinicopathological features and treatment results of patients presented to our tertiary centers.

## Materials and Methods

The medical records of patients with histologically confirmed ES presented to Alexandria Main University Hospital and Alexandria Sporting Students' Hospital during the period from January 2004 to December 2014 were reviewed. Patients with metastatic disease at presentation or had incomplete information were excluded from the study. A total of 74 patients were included with a median follow-up duration of 63.8 months. Data regarding age at diagnosis, sex, site and size (based on the greatest reported dimension) of the primary tumor, chemotherapy, surgery, radiotherapy, relapse, and survivals were extracted.

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## Statistical analysis

Data were analyzed using SPSS software version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) (<http://www.ibm.com>). Overall survival (OS) was calculated from the date of diagnosis to the date of death or date of the last follow-up. Event-free survival (EFS) was calculated from the date of diagnosis to the date of occurrence of an adverse event (disease progression, second malignant neoplasm, or death) or date of the last follow-up, whichever came first. Disease progression was further classified as local progression (recurrence at the initial site only), systemic progression (recurrence at a site not initially involved by disease), or local plus systemic progression (at the initial site and another site). Patients without disease recurrence were censored at date of the last follow-up.

Age was considered as a categorical variable (<10 years vs. 10–15 years vs. >15 years) using age group 10–15 years as a reference. Other clinical parameters of sex (male vs. female), primary tumor site (extremities vs. pelvis vs. others), tumor size ( $\leq 8$  cm vs.  $> 8$  cm), and local control modality (radiotherapy vs. surgery vs. surgery + radiotherapy) were considered as categorical variables using the first subset as an indicator. OS and EFS curves were calculated using Kaplan–Meier method and compared using the log-rank test in univariate analysis. The relative influence of different prognostic factors on survival was estimated with the Cox regression model.  $P \leq 0.05$  was considered statistically significant.

## Results

### Patients' characteristics and treatment

Table 1 summarizes the characteristics of patients. The median age of patients was 13 years (range: 4–22 years). About two-thirds (58.1%) of patients were male. Pain was the most common presenting symptom and occurred in 55 patients (74.3%) followed by swelling in 45 patients (60.8%). Extremities were the frequently affected sites (48.6% of patients) followed by pelvis (29.7% of patients). Thirty-two patients (43.2%) presented by tumors larger than 8 cm. All patients received uniform chemotherapy (cycles of vincristine-doxorubicin-cyclophosphamide alternated with cycles of ifosfamide-etoposide and repeated every 3 weeks). Regarding local control modality, 33 patients (44.6%) were treated with radiotherapy alone, 22 patients (29.7%) underwent surgery alone, and 19 patients (25.7%) underwent both surgery and radiotherapy.

The 5-year EFS of patients was 44%. On univariate analysis [Figure 1], EFS was not significantly affected by gender ( $P = 0.625$ ). However, EFS was significantly associated with age ( $P = 0.00$ ), tumor site ( $P = 0.00$ ), tumor size ( $P = 0.005$ ), and local control modality ( $P = 0.007$ ). On multivariate analysis [Table 2], EFS was significantly

**Table 1: Patients and disease characteristics**

Variable	n (%)
Age (years)	
Median (range)	13 (4-22)
<10	19 (25.7)
10-15	32 (43.2)
>15	23 (31.1)
Sex	
Male	43 (58.1)
Female	31 (41.9)
Presentation	
Pain	55 (74.3)
Swelling	45 (60.8)
Others	11 (14.9)
Primary tumor site	
Extremities	36 (48.6)
Pelvis	22 (29.7)
Others	16 (21.6)
Tumor size (cm)	
$\leq 8$	42 (56.8)
$> 8$	32 (43.2)
Local control modality	
Radiotherapy	33 (44.6)
Surgery	22 (29.7)
Surgery + radiotherapy	19 (25.7)

**Table 2: Multivariate analysis for event-free survival of 74 patients with nonmetastatic Ewing's sarcoma**

Variable	SE	P	OR	95% CI
Age (years)		0.001		
<10	0.495	0.005	4.001	1.516-10.555
>15	0.520	0.000	6.885	2.483-19.087
Sex	0.384	0.929	0.966	0.455-2.050
Site		0.009		
Pelvis	0.425	0.027	2.554	1.110-5.874
Others	0.590	0.149	0.427	0.134-1.357
Tumor size	0.385	0.004	2.984	1.404-6.345
Local control modality		0.572		
Surgery	0.521	0.525	0.718	0.258-1.994
Surgery + radiotherapy	0.493	0.320	0.612	0.233-1.610

SE – Standard error; OR – Odds ratio; CI – Confidence interval

associated with age ( $P = 0.001$ ), tumor site ( $P = 0.009$ ), and tumor size ( $P = 0.004$ ).

The 5-year OS of patients was 57%. On univariate analysis [Figure 2], age ( $P = 0.001$ ), tumor site ( $P = 0.00$ ), tumor size ( $P = 0.001$ ), and local control modality ( $P = 0.013$ ) were significantly correlated to OS. However, in multivariate analysis [Table 3], age ( $P = 0.049$ ), tumor site ( $P = 0.043$ ), and tumor size ( $P = 0.012$ ) were significantly associated with OS.

## Discussion

ES is a very aggressive disease, and multimodality treatment approach that involves local control modality

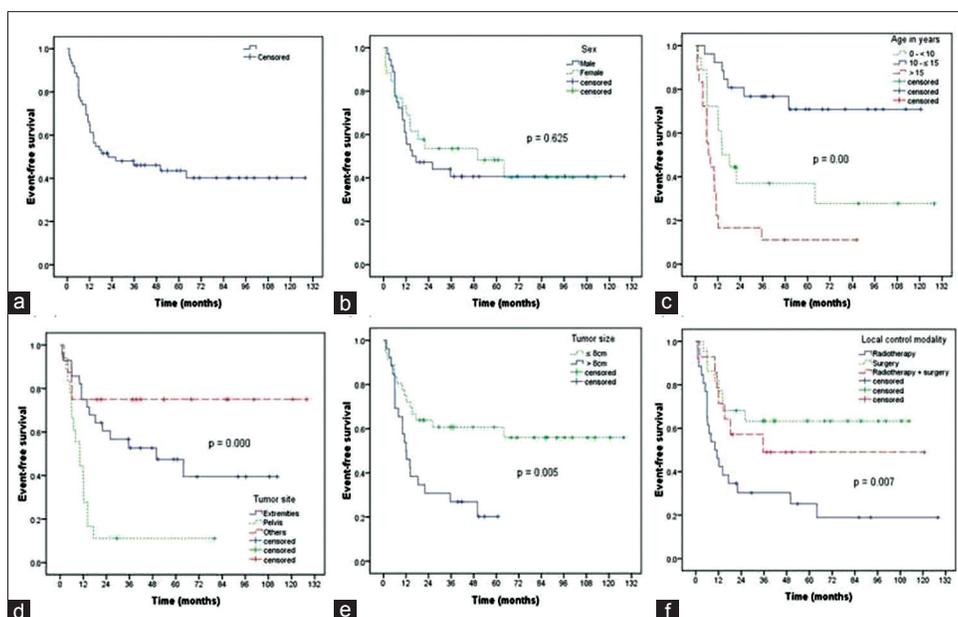


Figure 1: Kaplan–Meier estimate of event-free survival for 74 patients with nonmetastatic Ewing's sarcoma (a) and shown according to sex (b), age (c), tumor site (d), tumor size (e), and local control modality (f)

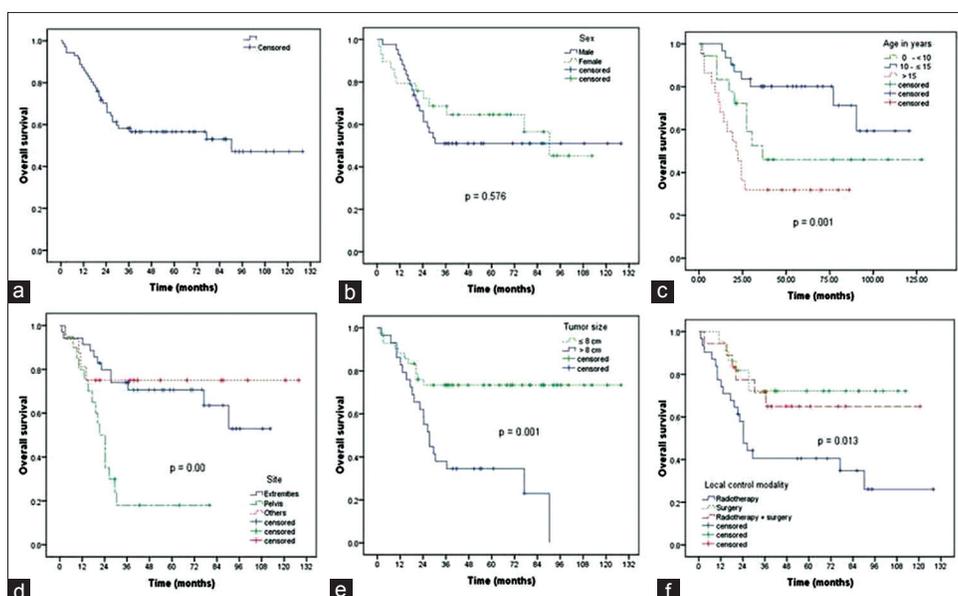


Figure 2: Kaplan–Meier estimate of overall survival for 74 patients with nonmetastatic Ewing's sarcoma (a) and shown according to sex (b), age (c), tumor site (d), tumor size (e), and local control modality (f)

with attempts to preserve the function, and eradication of micrometastases using chemotherapy is the current standard treatment of ES.<sup>[2-7]</sup> We tried in this work to determine the clinicopathological features and treatment outcomes of patients with nonmetastatic ES in an Egyptian population.

The median age of our patients was 13 years. Consistently, the median age was 13.7 years in the review of St. Jude Children's Research Hospital studies carried out by Rodríguez-Galindo *et al.*<sup>[7]</sup> Other studies by Biswas *et al.* and Paulussen *et al.* reported that the median age was 15 years which is not significantly different from ours.<sup>[8,13]</sup>

In this study, 58% of patients were male. Male predominance was also seen in other studies. Rodríguez-Galindo *et al.* reported that 60.9% of ES were male.<sup>[7]</sup> Paulussen *et al.* analyzed 301 patients and found that 60% of patients were male.<sup>[13]</sup> Akhavan *et al.* evaluated 32 patients with ES and reported 65.2% were male.<sup>[12]</sup> Jurgens *et al.*, Obata *et al.*, and Haeusler *et al.* found the same results.<sup>[2,4,14]</sup>

Pain was the most common presenting symptom in our patients (74.3%). This is similar to Akhavan *et al.*, who reported that pain was the first symptom in 83.8% of patients with ES.<sup>[12]</sup> In another study, the authors evaluated

**Table 3: Multivariate analysis for overall survival of 74 patients with nonmetastatic Ewing's sarcoma**

Variable	SE	P	OR	95% CI
Age (years)		0.049		
<10	0.496	0.153	2.032	0.768-5.377
>15	0.495	0.018	3.220	1.219-8.504
Sex	0.395	0.702	0.860	0.396-1.865
Site		0.043		
Pelvis	0.414	0.016	2.704	1.201-6.088
Others	0.587	0.977	1.017	0.322-3.213
Tumor size	0.420	0.012	2.855	1.254-6.504
Local control modality		0.669		
Surgery	0.573	0.738	0.825	0.268-2.537
Surgery + radiotherapy	0.532	0.370	0.621	0.219-1.759

SE – Standard error; OR – Odds ratio; CI – Confidence interval

47 patients with ES and concluded that the initial symptom was pain.<sup>[15]</sup>

In our study, extremities were the frequently affected sites (48.6% of patients). This agrees with literature. Extremities were the primary site of disease in 47%, 46%, and 31.6% of patient in studies performed by Obata *et al.*, Oksüz *et al.*, and Haeusler *et al.*, respectively.<sup>[2,14,16]</sup>

In the current study, the 5-year EFS for patients with nonmetastatic ES was 44%. Our results are consistent with the results of the Japanese study carried out by Obata *et al.*, who reported that the 5-year disease-free survival rates in nonmetastatic patients with ES were 46.6%.<sup>[14]</sup> Oksüz *et al.* retrospectively evaluated 65 patients with nonmetastatic ES of the bone and reported that the 5-year EFS was 44%.<sup>[16]</sup>

In this study, the 5-year OS for patients with nonmetastatic ES was 57%. This is similar to the results obtained in other studies. Biswas *et al.* reviewed 158 patients and reported that the 5-year OS was 57.6% for nonmetastatic ES patients.<sup>[8]</sup> Obata *et al.* in the Japanese study found that the 5-year OS in nonmetastatic ES patients was 54.9%.<sup>[14]</sup> Lee *et al.* demonstrated that the 5-year OS for nonmetastatic ES patients was 61.6%.<sup>[17]</sup>

In the present study, the most important prognostic factors for both EFS and OS for nonmetastatic ES were age at diagnosis, tumor site, and tumor size. Older patients with age >15 years, patients with tumor size  $\geq 8$  cm, or patients with pelvic primary tumor had significantly poor EFS and OS in our study. Consistent with our results, Oksüz *et al.* found in a multivariate analysis that age, tumor site, and tumor size were the prognostic factors for ES patients.<sup>[16]</sup> The authors reported that both EFS and OS were worse for patients >17 years of age, tumor size >8 cm in diameter, or an axial location.<sup>[16]</sup> In the Japanese study, Obata *et al.* demonstrated that patients who had primary site in the trunk and age  $\geq 16$  years had a significantly worse prognosis.<sup>[14]</sup>

Consistent with our results, studies have showed that tumor size has an important effect on the outcome.<sup>[7,9,10]</sup>

Paulussen *et al.* analyzed 301 patients with ES and found in multivariate analysis that sizable tumor volume had negative impacts on EFS.<sup>[13]</sup> Both Tural *et al.* and Arpaci *et al.* reported that patients with tumor size  $\geq 8$  cm had significantly worse EFS and OS.<sup>[9,10]</sup> Large tumors are associated with worse outcomes, as large tumors are usually irresectable and associated with micrometastases. Large tumors are more radioresistant due to increased hypoxia and necrosis. Moreover, the number of cancer stem cells requiring sterilization increases in direct proportion with tumor size.<sup>[18]</sup>

Our results are supported by literature where several reports have suggested that patients with pelvic ES had an unfavorable prognosis.<sup>[19-21]</sup> This might be due to difficulties in the surgical approach of the tumor, sizable tumor at presentation, or the intrinsic behavior of the pelvic tumor. In a Finnish nationwide study on bone and soft tissue ES, Serlo *et al.* found that young age at diagnosis and a peripheral primary tumor site were associated with a better prognosis.<sup>[21]</sup> Donaldson *et al.* found that site of primary tumor correlated with 5-year EFS.<sup>[19]</sup> Cotterill *et al.* demonstrated in multivariate analysis that tumor site and age group (<15 vs.  $\geq 15$  years) had a significant impact on EFS.<sup>[20]</sup>

To our knowledge, this is the first study on ES treated with uniform chemotherapy and either surgical resection and/or radiation therapy with the longest follow-up period from Egypt.

## Conclusions

Despite genetic differences and limited resources, it seems that the clinical features, prognostic factors, and treatment outcome of ES patients in our centers are comparable to the outcomes observed in other parts of the world. This is because of the use of multidisciplinary approach and following international protocols.

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## Conflicts of interest

There are no conflicts of interest.

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