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Outcome of Ewing sarcoma in children: Twenty years experience from a single center

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ABSTRACT

Objective: Ewing sarcoma (ES) is a significant malignancy in pediatric patients, with a notable impact on bone health. Despite advances in treatment, ES still poses challenges, particularly in cases of metastasis or relapse. This study aims to evaluate the outcomes of ES in children treated at our center over a twenty-year period.

Patients and Methods: We retrospectively reviewed pediatric patients diagnosed with ES at our center between January 2004 and February 2024. Data including demographic information, tumor characteristics, treatment modalities, and survival outcomes were analyzed.

Results: Among 986 pediatric solid tumor cases, 137 (13.8%) were diagnosed with ES. After excluding ineligible cases, 115 ES cases were included in the study. The most common sites of involvement were the lower extremities. Metastatic disease was observed in 35.8% of cases, with the lungs being the most common site. Advanced age, and pelvic involvement were associated with poor prognosis. Histopathological response to neoadjuvant chemotherapy, represented by tumor necrosis rate, metastatic and relapse disease significantly influenced survival outcomes.

Conclusion: Despite multimodal therapies, ES in children, especially with metastatic disease or relapse, presents a challenging prognosis. Early diagnosis and the development of novel treatment strategies are imperative to improve outcomes for these patients.

Keywords: Ewing sarcoma, Children, Survival, Prognosis

1. INTRODUCTION

Ewing sarcoma (ES) is the second most common primary bone malignancy in pediatric patients, comprising less than 5% of all childhood cancers, with the most commonly affected bones being the femur and pelvic bones [1-4]. While, it is most commonly seen in the adolescent and pre-adolescent periods, the peak age is fifteen [5,6]. Typically, these tumors occur in bone, but sometimes they can originate in soft tissue. Soft tissue tumors constitute approximately 20% of all cases and are less frequently observed [7]. These tumors are aggressive, and treatment involves multidrug chemotherapy, radiotherapy, and surgery. With this multidisciplinary therapy, overall survival has significantly increased. The 5-year survival rate for localized ES is about 70-75% [1-3].

At the time of diagnosis, distant metastases can be detected in 25% of cases, which is a poor prognostic factor. The lungs are the most common site of metastasis. Event-free survival (EFS) rates in isolated lung metastases are around 40%, while in combined metastases, this rate drops to the 15% range [8]. Other factors affecting prognosis include histopathological response to induction therapy, primary tumor localization, the age of the patient, and the volume of the primary tumor [9].

The recurrence rate is approximately 30-40% in patients with ES [10]. The recurrence rate is higher for patients who have metastases at presentation [10]. The 5-year survival rate is less than 15% in patients with relapse [11-13]. The aim of this study was to determine the outcomes of ES in pediatric patients who were treated at our center.

2. PATIENTS and METHODS

Patients diagnosed with ES and treated at our center between January 2004 and February 2024, were retrospectively evaluated.

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Apart from demographic data, factors such as tumor localization, origin, presence of metastasis at diagnosis, surgical treatment, necrosis rate in the excised tumor, radiotherapy, presence of relapse disease, current status, and last follow-up dates were assessed to analyze patient survival and factors influencing survival. The time interval from diagnosis to death or last follow-up for surviving patients were used for overall survival (OS) analysis, while the time from diagnosis to relapse of disease in patients who achieved complete remission, progression, or death was used for event-free survival (EFS) analysis. Diagnosis of ES at our center is based on clinical, radiological, and histopathological findings. All patients underwent metastasis assessment including local magnetic resonance imaging (MRI), thoracic computed tomography (CT), bone scintigraphy, and in some cases, positron emission tomography (PET)-CT, bone marrow aspiration, and biopsy. Based on evaluation results, patients with only local disease are categorized as having localized disease (LD), while those with distant metastases are classified as having metastatic disease (MD). All patients received the same chemotherapy protocol. According to the protocol of American Intergroup POG-CCG Ewing's trial (POG-9354/CCG-7942), the patients received alternating IE (ifosfamide 1800mg/m^2/d and etoposide 100 mg/m^2/d for 5 days), and VDC/VAC (vincristine 2 mg/m^2/d, day 1, doxorubicin 75 mg/m^2/d, day 1, cyclophosphamide 1200 mg/m^2/d, day 1) therapies for 48 weeks [14]. Following three cycles of neoadjuvant chemotherapy, surgery was performed for the patients. Radiotherapy was administered to patients with more than 10% viable cells or positive surgical margins detected during pathological examinations

All cases under 18 years of age who received treatment at our center and continued regular follow-ups were included in the study. Cases who did not continue regular follow-up, received treatment at a different center, or did not consent to participate were excluded from the study. Ethical approval was obtained from the Marmara University School of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 09.2024.377). Consent for study participation was obtained from all patients or their guardians.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 29 (IBM Corp., Armonk, New York, USA) statistical package program. Socio-demographic characteristics were compared for progression-free and overall survivals using the Log-rank test. Factors influencing progression-free and overall survivals were evaluated with univariate Cox regression analysis and Kaplan Meier analysis. The backward Wald elimination method was used in multivariate Cox regression analysis to reach the result model. A p-value <0.05 was considered statistically.

3. RESULTS

During a twenty-year period, among 986 pediatric patients diagnosed and treated for solid tumors in our pediatric oncology clinic, 137 (13.8%) were diagnosed with Ewing sarcoma (ES). Three of these cases declined to participate in the study, seven received treatment at different centers, and twelve did not attend regular follow-ups, thus they were excluded from the study. The remaining 115 pediatric cases diagnosed with ES were evaluated retrospectively. The demographic data of the cases are summarized in Table I.

Table I. *Characteristics of the patients (n=115)*

Gender	n (%)
Female/ Male	52 (45%) / 63 (55%)
Median age (years)	10.6 (range 1-17)
Primary tumor location	
Lower extremity	32 (27.8%)
Femur	21(18.2%)
Tibia	7 (6%)
Fibula	4 (3.4%)
Soft tissue	20 (17.4%)
Extremity	7 (6.0%)
Trunk	6 (5.2%)
Head and neck	5 (4.3%)
Finger	1 (0.8%)
Intraabdominal	1 (0.8%)
Upper extremity	15 (13%)
Humerıs	11(9.5%)
Scapula	4 (3.4%)
Pelvis	14 (12.1%)
Costa	19 (16.5%)
Other	15 (13%)
Metastatic at Initial Diagnosis	42 (36.5%)
Isolated Lung	18 (15.6%)
Isolated Bone	10 (8.7%)
Others	14 (12.1%)
Necrosis Rate	
More than %90	27 (23.4%)
Less than %90	38 (33%)
Undetermined	50 (43.4%)
Local treatment	112 (97.3%)
Surgery	46 (40%)
Surgery followed by radiotherapy	3 (2.6%)
Just radiotherapy	
Relapse	
Patients with relapse	30 (26%)
Patients without relapse	85 (74%)
Median Relapse Time (months)	20
Relapse Location	
Isolated Lung	13 (11.3%)
Isolated Local	6 (5.2%)
Distant Bone Relapse	11 (9.5%)
Outcome	
Complete Remission	58 (50.4%)
Exitus	50 (43.4%)
Living with Disease	7 (6%)

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The median age at the diagnosis was 10.6 years (range 1-17) and 68% of patients diagnosed at age 10 or older. Among our patients, 20 (17.3%) had extraosseous Ewing sarcoma (EES), while 95 (82.6%) had primary bone tumors. Among primary bone tumors, 32 (27.8%) were located in the lower extremities, 15 (13%) in the upper extremities, 14 (12.1%) in the pelvis, 19 (16.5%) in the ribs, and 15 (13%) in other bones. At the time of diagnosis, metastases were detected in 42 (36.5%) cases, with 18 (15.6%) having isolated lung metastases and 10 (8.7%) having isolated bone metastases. Upon examination of necrosis rates in materials obtained post-surgery, more than 90% necrosis was observed in 27 (23.4%) patients, while less than 90% necrosis was observed in 38 (33%) patients. Necrosis rates could not be determined in 14 (12.1%) patients due to irradiation, and data on necrosis rates were unavailable for 36 (31%) patients. When evaluated in terms of local treatments, total resection with mass excision was performed on all cases except for the three cases that were lost due to progressive disease. Local radiotherapy was applied to a total of 49 (42.6%) cases, including the three cases for which surgical treatment could not be performed. Among these cases, 38 (33%) had a low necrosis rate, 3 (2.6%) were not suitable for surgical treatment, and the remaining 8 (6.9%) cases received radiotherapy based on various reasons determined by the council.

Relapse was observed in 30 (26%) patients, with a median relapse time of 20 months (range 1-60 months). Isolated lung relapse was observed in 13 (11.3%) patients, while isolated local relapse was observed in 6 (5.2%) patients.

The mean follow-up duration for all cases was 44±38.3 months. Median duration was 34 months. Upon assessing their current status, complete remission was achieved in 58 (50.4%) patients, while 50 (43.4%) patients died during follow-up. Among those who died, 9 (7.8%) died due to sepsis and 32 (27.8%) due to progressive disease. For all cases, the 5-year OS and EFS rates were determined as 51% and 45%, respectively (Figure 1). Five year OS and EFS rates for the cases with LD were 66%, 56% while the cases with MD were 28%, 27% (p<0.001).

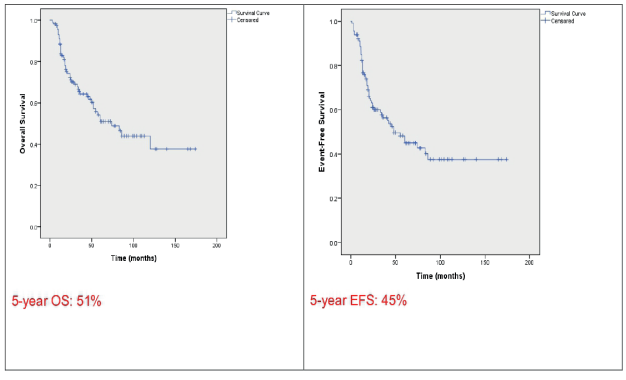

Figure 1. *Five year overall and event free survival rates of the patients with Ewing Sarcoma*

Table II. *Comparison of Overall and Event-Free Survival by Sociodemographic Characteristics (n=115)*

	Overall Survival			Event-free survival		
	Survival time (months)	P	Cumulative proportion surviving at the 5-years	Survival time (months)	P	Cumulative proportion surviving at the 5-years
Gender						
Male (n: 63)	101.8±10.3	0.241	55.3%	91.4±10.5	0.353	51%
Female (n: 52)	79.2±11.6		45.2%	71.8±11.7		37%
Age						
<10 years (n: 36)	106.7±12.3	0.090	59.7%	95.0±12.4	0.179	47.7%
≥10 years (n: 79)	82.2±10.2		46.2%	75.3±10.2		45%
Primary Tumor Site						
Bone (n: 95)	86.1±8.9	0.683	48.5%	77.0±8.5	0.349	41.1%
Lower ext. (n: 32)	78.5±9.4	0.821	53.4%	65.1±8.2	0.759	46.4%
Upper ext. (n: 15)	108.3±20.0		61.1%	82.5±21.2		43.1%
Pelvis (n: 14)	60.1±7.1		36.5%	49.7±9.3		26.7%
Costa (n: 19)	78.4±18.5		38.6%	70.5±18.2		35.4%
Other (n: 15)	72.0±14.8		44.8%	66.1±14.4		40.7%
Soft tissue (n: 20)	101.7±17.6		50.1%	101.2±17.7		58.7%
Metastasis						
None (n: 73)	116,5±10.7	**<0.001**	66.1%	108.2±9.9	**<0.001**	56%
Present (n: 42)	51.9±7.5		28.7%	45.2±7.6		27.4%
Metastasis Site						
Isolated Lung (n: 18)	46.1±9.7	0.354	21.7%	41.5±9.6	0.630	20.8%
Isolated Bone (n: 19)	37.8±11.0		30%	33.8±11.9		30%
Others (n: 15)	69.9±14.3		40%	55.7±15.1		34.9%
Necrosis Rate						
More than 90% (n: 27)	118.2±14.4	0.219	0.649±0.104	118.6±14.4	**0.026**	0.667±0.098
Less than 90% (n: 38)	74.0±9.0		0.469±0.097	57.1±8.7		0.316±0.089
Relapse						
None (n: 85)	113.7±9.4	**0.002**	65.1%	112.4±9.4	**<0.001**	64.4%
Present (n: 30)	51.2±7.3		22.7%	43.1±5.0		3.4%
Relapse Location						
Isolated Lung (n: 13)	35.6±5.5	0.159	7.7%	35.6±5.5	**0.049**	7.7%
Distant Bone Relapse (n: 11)	70.3±13.7		45.5%	53.8±9.6		9.1%
Local (n: 6)	44.3±13.9		25%	39.6±12.8		16.7%

When factors influencing survival were evaluated, gender, primary tumor site, and metastasis site did not have a statistically significant effect on survival (Table II). Children younger than 10 years of age had a higher survival rate than children older than 10 years but this difference was not statistically significant for OS and EFS (p=0.09). At the time of diagnosis, cases with MD had statistically significantly lower survival times (p<0.001,

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p<0.001) (Figure 2). When comparing patients with necrosis rates above 90% to those with rates below 90%, it was observed that patients with higher necrosis rates had longer survival times, although, this difference was not statistically significant for OS but significant for EFS (p=0.219, p=0.026). Since, the rate of bone necrosis could not be determined in cases with irradiated prostheses, the survival outcomes were compared with the survival outcomes of cases with reported necrosis rate. Cases with necrosis rate below 90% and irradiated cases were analyzed in pairs and it was found that cases with irradiated had longer survival time. This difference was not statistically significant (p>0.05). The cases with necrosis rate above 90% had longer survival time than irradiated cases, but this difference was not statistically significant (p>0.05).

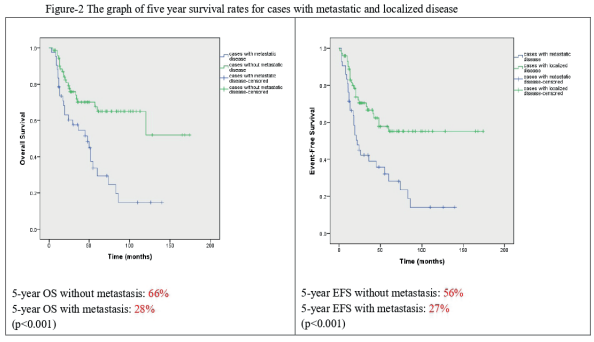

Figure 2. *The graph of five year survival rates for cases with metastatic and localized disease*

In the presence of relapse, 5-year OS and EFS rates were statistically significant lower in patients with relapse disease (p=0.002, p<0.001) (Figure 3). When comparing relapse locations (isolated lung, isolated bone, and local relapses) in patients, the difference was not statistically significant for OS, but the cases with isolated bone relapse had longer survival times than the others and this difference was statistically significant for EFS (p=0.049). Relapse disease was observed in 15% of the cases with EES, and the mortality rate was 45% in all cases. However, 40% of cases started treatment with metastatic disease at diagnosis.

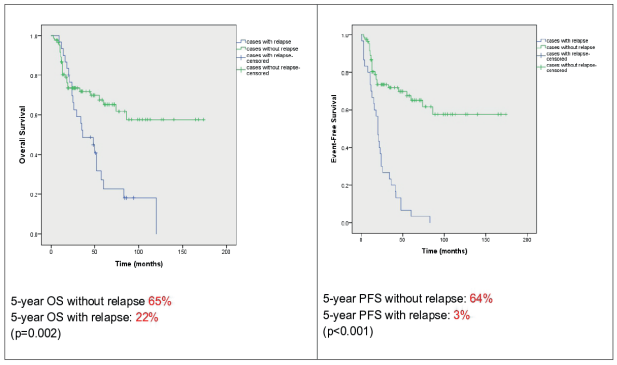

Figure 3. *The Graph depicts the 5-year survival rates of the cases according to the relapse disease.*

4. DISCUSSION

In our study, cases diagnosed with ES accounted for 13.8% of all cases diagnosed with malignancy. In the literature, the incidence rate during childhood is reported to be around 2-5%, and the higher prevalence in our hospital is attributed to our multidisciplinary approach involving the orthopedic and radiation oncology departments, which has established our hospital as a referral center for bone sarcomas. The peak age for childhood ES is reported as 15 years old, and it is usually seen in children over 10 years old [1,2]. In our study, the median age at diagnosis was 10.6 years, with 68% of cases diagnosed at age 10 or older, which is consistent with the literature. Upon evaluation, based on age groups, although, not statistically significant, survival times were found to be longer in cases diagnosed under the age of 10 compared to older children. Advanced age (age 14 years or 18 years) is also noted as a poor prognostic factor in previous studies [15-17].

In terms of gender, the incidence rate in male cases is approximately 1.5 times higher than in female cases [4]. Consistent with the literature, male cases were more frequently observed in our study as well. However, similar to the findings in the literature, gender did not have a statistically significant impact on survival [6].

Extraosseous ES cases constitute approximately 15-20% of all cases [7], and in our study, this rate was 16.3%. Generally, the prognosis is better for EES compared to ES originating from bone [8,18]. In a meta-analysis examining twenty-nine studies, the 5-year OS in pediatric EES cases was reported as 69%, with mortality and recurrence rates of 29% and 35%, respectively [19]. In our study, recurrent disease was observed in 15% of the 20 cases diagnosed with EES, and the mortality rate was higher (45%) in all cases. It is thought that the fact that 40% of cases started treatment with metastatic disease at diagnosis may have contributed to this rate. When considering its impact on survival, the survival times of EES cases were longer compared to cases originating from bone, although, this difference was not statistically significant. This may be attributed to the high incidence of metastatic disease at the time of diagnosis in our EES cases.

The most common sites of involvement are the lower extremities, pelvis, and ribs [20]. Our study showed that lower extremities are the most common site of involvement, followed by rib and pelvic involvements. In a study evaluating thirty-one cases, the frequencies of primary tumor sites were reported as extremities (51.6%), the thoracic cage (19.4%), and the pelvis (16.1%), which is similar to our study [21]. Axial tumor localization and pelvic involvement have been associated with poor prognosis [15,16], Our study showed that the shortest survival time was in cases with pelvic origin, although this difference was not statistically significant.

In our study, 35.8% of cases had MD, with the lungs being the most common metastatic site (72.7%), followed by bone metastases (47.7%). In a study evaluating twenty-four cases, the MD rate was 25%, with the lungs being the most common metastatic site [22]. The presence of MD at diagnosis is the most

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important poor prognostic factor [1], with OS rates reported as 20-30% [15,16]. In our study, the 5-year OS rates in MD and LD cases were 28% and 66%, respectively. This difference was statistically significant and was consistent with the literature.

Another important prognostic factor is the histopathological response to neoadjuvant chemotherapy, represented by the tumor necrosis rate [6]. In our study, the survival time of cases with a necrosis rate above 90% were found to be longer compared to those with a necrosis rate below 90%. In a study evaluating complete remission (100% necrosis) in 427 cases, patients with 100% necrosis had significantly higher survival rates compared to other cases [23]. In another study, the 5-year disease-free survival was significantly better in patients with <5% viable tumors than in patients with >30% viable tumors (75% vs. 20%, p<0.001) [24]. Consistent with this study, the necrosis rate exceeded 90% in approximately one-third of the cases, and these cases exhibited significantly longer event-free survival times in our research. In 14 cases (12.1%), the necrosis rate could not be determined due to the placement of irradiated endoprostheses. The cases with irradiated endoprotheses exhibited a longer survival time than the cases with necrosis rate below 90%, and a shorter survival time than the cases with necrosis rate above 90%. Despite this, the diffrences were not statistically significant. However, this is the first research that compares the outcomes of irradiated protheses with those of other prostheses.

In patients with relapse, the prognosis is very poor, and the survival rate is around 10-30%. Response to salvage therapy is also a prognostic indicator in this patient group [2]. In our study, relapsed disease developed in 26% of cases, with the lungs being the most common site of relapse (43.7%). Our local relapse rate was 18.75%. In cases with relapse, the 5-year EFS and OS rates were 16% and 22%, respectively. In our study, the survival rates in cases with relapse were significantly lower, which were consistent with the literature. In contrast to expectations, patients with isolated bone relapse exhibited longer survival times and rates compared to those with isolated lung relapse. It has been postulated that the increased mortality rate due to sepsis and respiratory distress contributed to the shorter survival times observed in our patients with isolated lung relapse. Limitations of our study include: its retrospective nature and the inability to measure tumor volume for all patients due to the unavailability of diagnostic imaging at the time of diagnosis.

Conclusion

Despite the implementation of multimodal therapies, the prognosis for childhood ES remains poor, particularly in cases where the disease has metastasised or relapsed. Consequently, the significance of prompt diagnosis to ascertain that these cases are diagnosed as non-metastatic remains paramount. Furthermore, there is a pressing need for the development of new treatment options for metastatic and relapsed cases. The potential for early detection and intervention to significantly impact the outcome of ES is clear, emphasising the importance of ongoing research and development of innovative therapies for better management of this disease.

Compliance with Ethical Standards

Ethics committee approval: Ethical approval was obtained from the Marmara University School of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 09.2024.377). Consent for study participation was obtained from all patients or their guardians.

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Authors contribution: NE and AGT: Concept and design, AGT and KT: Data Collection or processing, GT: Analysis or interpretation, NE and OS: Literature search, NE and ZO: Writing the manuscript. All authors approved the final version of the manuscript.

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