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Age-Related Prognostic Factors and Survival Outcomes in Ewing Sarcoma: A Single-Center Experience

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ABSTRACT

Objective: To evaluate age-related prognostic differences in Ewing sarcoma (ES) patients and identify clinical factors influencing outcomes in a tertiary care setting.

Materials and Methods: Seventy-six patients with ES (ages 1–78) treated between 2010 and 2024 were reviewed retrospectively. Clinical features and treatments were compared across four age groups (0–9, 10–17, 18–25, and ≥25 years). Overall survival (OS) and disease-free survival (DFS) were estimated using Kaplan–Meier curves and compared with log-rank tests.

Results: There were no statistically significant differences in 10-year OS or DFS between age groups ($p>0.05$), although patients ≥18 years showed a trend toward worse survival. The presence of metastases at diagnosis was associated with markedly lower survival (5-year OS 20–30% vs. 70% for localized disease). Patients who underwent surgical resection of the primary tumor had significantly better survival than those managed without surgery, while limb-salvage versus amputation showed no difference in outcomes. Relapse was associated with poor prognosis.

Conclusion: Adult ES patients tend to have poorer outcomes than children, though age alone was not a significant predictor in this series. Achieving effective local control with surgery and addressing metastatic disease remain critical to improving survival.

Keywords: Age groups, Ewing sarcoma, Metastasis, Prognostic factors, Surgery, Survival

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INTRODUCTION

Ewing sarcoma (ES) is a rare, aggressive neuroectodermal malignancy that typically affects the bones and soft tissues of children and adolescents.[1,2] Although mainly a pediatric disease, it can also occur in adults, where it often presents with distinct features and worse outcomes.[3,4]

The prognosis of ES depends on age, tumor site, metastatic status, and treatment response.[5,6] In localized disease, modern treatment protocols have improved the 5-year overall survival (OS) rate to 70–80%.[6] However, metastatic disease is associated with a poor 5-year survival rate of approximately 30%.[5] Tumor sites typically include long bones of the extremities or the pelvis, with pelvic localization linked to worse outcomes due to larger tumor volumes and challenges in achieving local control.[6,7]

Age remains a key prognostic factor in ES. Adolescents, young adults, and especially those over 40 have poorer survival than children. They often present with metastatic disease, experience more treatment-related toxicity, and have lower survival, possibly due to biological differences, comorbidities, or difficulty tolerating intensive therapy.[3,4,8] Standard treatment includes neoadjuvant chemotherapy, local control through surgical resection and/or radiotherapy, and adjuvant chemotherapy.[5] However, age-related survival disparities persist, highlighting the need for further research into age-specific factors.

Much of the available literature on ES comes from pediatric populations treated in high-resource settings, while data on adult patients and from tertiary care centers in diverse socioeconomic contexts remain limited.[3,9] This retrospective study evaluates clinical characteristics and age-related prognostic differences in ES patients at a tertiary care center, analyzing tumor location, metastatic status, chemotherapy, radiotherapy, and surgical interventions to identify factors affecting survival and guide individualized treatment strategies.

MATERIALS AND METHODS

This retrospective observational study was conducted on patients diagnosed and treated for ES between 2010 and 2024. The study was reviewed and approved by the Metin Sabanci Baltalimanı Bone Diseases Hospital Institutional Ethics Committee (Meeting no: 28, Decision no: 193, and Date: October 28, 2024) and carried out in accordance with the principles of the Declaration of Helsinki. All data were obtained from existing medical records, with patient confidentiality preserved.

All patients who had been treated at our center and had a histopathologically confirmed diagnosis of ES were included. This definition encompassed both bone-origin tumors and extraskeletal ESs arising from soft tissue. Patients of all age groups and both sexes were included, regardless of metastatic status at presentation (localized or metastatic at diagnosis). After excluding patients with incomplete clinical data or unconfirmed diagnoses, a total of 76 patients were included in the study.

The diagnosis of ES was established through histopathological examination of tumor specimens. All tumors were confirmed as part of the ES family by characteristic light microscopic findings of small round cell malignancy and positive immunohistochemical staining (e.g., diffuse membranous CD99 positivity), supported by appropriate histological features. In selected cases, the diagnosis was further corroborated by molecular testing (e.g., *EWSR1* gene rearrangement analysis) when available. In this study, extraskeletal ES was defined as a tumor arising in soft tissues without bone involvement detected by imaging or surgery, whereas bone ES referred to cases involving a primary bone lesion. Only patients with a confirmed diagnosis of ES were included; other small round cell tumors were excluded or reclassified based on pathology results.

Detailed demographic and clinical data were collected from each patient's file. Recorded variables included age and sex at diagnosis, anatomical location of the tumor (bone or soft tissue), and the exact site of the primary tumor. The presence and location of distant metastases at diagnosis (lung, bone, or both) were documented. Disease extent at presentation was categorized as localized or metastatic. All patients were noted to have received multi-agent systemic chemotherapy according to standard ES protocols. Radiotherapy use was recorded as neoadjuvant or adjuvant. In addition, the type of surgical management for the primary tumor was documented for each patient.

Age at diagnosis was categorized into four groups (0–9, 10–17, 18–25, and ≥25 years) to align with pediatric, adolescent, young-adult, and adult clinical categories and to capture known age-related differences in the distribution of primary and metastatic sites in ES.[10] These age categories were chosen to reflect pediatric, adolescent, young adult, and older adult subgroups, enabling comparisons of outcomes between different age groups. Our hospital is a specialized orthopedic center that has been providing services in the field of bone and soft tissue tumor surgery for many years. Over the years, patients have been operated on by different experienced orthopedic oncology surgeons, all of whom have applied similar surgical approaches. Surgical treatment types were categorized as follows: (1) No surgical resection (systemic therapy ± radiotherapy only), (2) limb-sparing surgery with

adjunctive cryotherapy using liquid nitrogen, (3) limb-sparing resection with endoprosthetic reconstruction, (4) limb-sparing resection with biological or allograft reconstruction, (5) simple resection/curettage without major reconstruction, and (6) amputation. These groups were used to compare outcomes, such as survival or recurrence rates, by surgical modality. For outcome analyses, patients were also grouped according to survival status (alive vs. deceased) and event occurrence (recurrence or metastasis present vs. absent). Surgical margin status was not consistently documented across the entire cohort and was therefore not included as a predictor in the primary analyses. In our institutional practice, positive margins are generally managed with re-excision when feasible or with adjuvant radiotherapy.

All patients underwent comprehensive staging at diagnosis according to standard orthopedic oncology protocols. Baseline imaging included local radiological assessment of the primary tumor and distant metastasis screening. The local extent of the primary tumor (intraosseous spread and soft tissue extension) and its relationship to adjacent structures were evaluated using plain radiography and magnetic resonance imaging (MRI). Thoracic computed tomography (CT) was used to detect distant metastases, and positron emission tomography–CT (PET-CT) was used to survey for metastatic disease in bone or other sites. Staging results were used to classify patients as localized or metastatic. During treatment, imaging was also used to assess response (e.g., tumor shrinkage after neoadjuvant chemotherapy) and to guide surgical planning.

After completion of initial treatment, patients were followed clinically at regular intervals in accordance with our institutional follow-up protocols for ES. Follow-up evaluations typically included physical examination and appropriate imaging (e.g., thoracic CT, MRI of the primary site, PET-CT) to detect recurrence or metastasis. During follow-up, the occurrence and timing of distant metastases and local recurrences were recorded. Specifically, the time to metastasis for patients who developed metastatic disease during follow-up and the time to local recurrence were determined. For survival analysis, patient vital status at the last contact was recorded (alive or deceased) and, if applicable, the date of death was noted. OS was defined as the time from diagnosis to death from any cause or to the last known follow-up for living patients. Disease-free survival (DFS) was defined as the time from completion of primary treatment (definitive surgery or completion of initial therapy) to the first occurrence of either tumor recurrence (local relapse) or a new distant metastasis, or to the last follow-up for those without an event. Patients without an event were censored at their last disease-free follow-up visit. OS and DFS were calculated in months.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 29. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used to evaluate the study data. The normality of distribution for continuous variables was assessed using the Shapiro–Wilk test and graphical methods. The Mann–Whitney U test was used to compare two independent groups of continuous variables that were not normally distributed. The Pearson Chi-square test, Fisher's exact test, and Fisher–Freeman–Halton test were used to compare categorical variables. Survival outcomes were evaluated using the Kaplan–Meier survival analysis method, and comparisons between groups were performed using the log-rank test. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 76 patients were included, with a mean age of 17.7±12.1 years (range 1–78). Most patients (60.5%) were younger than 18 years. The median follow-up was 43.6 months. Mortality occurred in 40.8% (*n*=31), and extraskeletal involvement was present in 13.2% (*n*=10). At diagnosis, 10.5% (*n*=8) had distant metastases, most commonly in the lung. During follow-up, 11.8% developed metastasis and 9.2% experienced local recurrence.

All patients received neoadjuvant chemotherapy; 35.5% also received neoadjuvant radiotherapy, 36.8% adjuvant chemotherapy, and 3.9% adjuvant radiotherapy. Primary orthopedic treatments included systemic therapy only (26.3%), resection (25.0%), liquid nitrogen–treated autograft (19.7%), tumor prosthesis reconstruction (15.8%), other reconstructions (10.5%), and amputation (2.6%). Baseline patient and treatment characteristics are summarized in Table 1.

There was no statistically significant difference in mortality by age, tumor site, extraskeletal disease, radiotherapy, chemotherapy, or local recurrence ($p>0.05$). However, metastasis—either at presentation (77.8% vs. 29.3%, $p=0.001$) or during follow-up (87.5% vs. 35.8%, $p=0.02$)—was strongly associated with higher mortality. Patients experiencing any event (metastasis/recurrence) had significantly worse outcomes (73.9% vs. 26.4%, $p=0.001$). Importantly, survival differed by primary surgical approach ($p=0.001$): Patients treated with liquid nitrogen–treated autografts demonstrated markedly improved survival compared to those undergoing systemic therapy only, resection, or tumor prosthesis reconstruction (Table 2).

Survival Analysis

Of the 76 patients, 45 (59.2%) were alive, and 31 (40.8%) had died at last follow-up. The mean OS was 78.3 ± 5.6 months, with a 10-year OS rate of 49.7% (SE 7.1%) (Fig. 1).

Table 1. Distribution of descriptive characteristics

Age	
Mean±SD	17.7±12.1
Median (Min–Max)	15 (1–78)
0–9 years	12 (15.8)
10–17 years	34 (44.7)
18–25 years	20 (26.3)
≥25 years	10 (13.2)
Follow-up time (months)	
Mean±SD	54.62±37.42
Median (Min–Max)	43.6 (7–120)
Mortality	31 (40.8)
Extraskeletal involvement	10 (13.2)
Neoadjuvant chemotherapy	100 (100)
Neoadjuvant radiotherapy	27 (35.5)
Adjuvant chemotherapy	28 (36.8)
Adjuvant radiotherapy	3 (3.9)
Total metastasis	16 (21)
Lung	9
Bone	3
Lung + Bone	4
Initial disease stage	
Local disease	68 (89.5)
Metastatic disease	8 (10.5)
Metastasis during follow-up	8 (11.8)
Time to metastasis (months) (*n*=8)	
Mean±SD	17.8±11.7
Median (Min–Max)	16.5 (4–36)
Local recurrence	7 (9.2)
Time to recurrence (months) (*n*=7)	
Mean±SD	28.29±14.91
Median (Min–Max)	24 (14–52)
Type of primary orthopedic treatment	
Systemic therapy only (no surgery	20 (26.3)
Liquid nitrogen–treated autograft	15 (19.7)
Tumor prosthesis reconstruction	12 (15.8)
Resection (limb-sparing surgery)	19 (25.0)
Other reconstruction (bone graft/implant)	8 (10.5)
Amputation	2 (2.6)

SD: Standard deviation.

Table 2. Comparison of patient characteristics by survival status

	Mortality		
	Survivors (*n*=45)	**Non-survivors (*n*=31)**	***p***
Age at diagnosis			
Mean±SD	15.20±8.70	21.35±15.27	
Median (Min–Max)	14 (1-50)	18 (5-78)	
0–9 years	10 (83.3)	2 (16.7)	[a]0.157
10–17 years	21 (61.8)	18 (38.2)	
18–25 years	10 (50.0)	10 (50.0)	
≥25 years	4 (40.0)	6 (60.0)	
Tumor location			
Axilla (soft tissue)	1 (100.0)	0 (0.0)	[a]0.464
Foot (soft tissue)	0 (0.0)	1 (100.0)	
Femur	6 (46.2)	7 (53.8)	
Fibula	3 (42.9)	4 (57.1)	
Gluteal region (soft tissue)	0 (0.0)	2 (100.0)	
Humerus	3 (60.0)	2 (40.0)	
Calcaneus	2 (100.0)	0 (0.0)	
Clavicle	1 (100.0)	0 (0.0)	
Metatarsal	2 (66.7)	1 (33.3)	
Shoulder (soft tissue)	2 (100.0)	0 (0.0)	
Pelvis	5 (50.0)	5 (50.0)	
Radius	1 (100.0)	0 (0.0)	
Sacrum	3 (75.0)	1 (25.0)	
Scapula	3 (100.0)	0 (0.0)	
Tibia	10 (71.4)	4 (28.6)	
Ulna	1 (100.0)	0 (0.0)	
Thigh (soft tissue)	2 (50.0)	2 (50.0)	
Vertebra	0 (0.0)	2 (100.0)	
Follow-up duration (months)			
Mean±SD	70.71±37.52	31.27±22.01	[d]0.001**
Median (Min–Max)	70.2 (10–120)	24.5 (7-99)	
Ekstraskeletal involvement			
Absent	40 (60.6)	26 (39.4)	[b]0.732
Present	5 (50.0)	5 (50.0)	
Neoadjuvant radiotherapy			
Absent	31 (63.3)	18 (36.7)	[c]0.333
Present	14 (51.9)	13 (48.1)	

Table 2. Continue

	Mortality		
	Survivors (*n*=45)	Non-survivors (*n*=31)	*p*
Adjuvant chemotherapy			
Absent	26 (54.2)	22 (45.8)	[c]0.241
Present	19 (67.9)	9 (32.1)	
Adjuvant radiotherapy			
Absent	44 (60.3)	29 (39.7)	[b]0.563
Present	1 (33.3)	2 (66.7)	
Metastasis			
Absent	41 (70.7)	17 (29.3)	[c]0.001**
Present	4 (22.2)	14 (77.8)	
Initial stage			
Localized disease	43 (63.2)	25 (36.8)	[b]0.057
Metastatic disease	2 (25.0)	6 (75.0)	
Metastasis during follow-up			
Absent	43 (64.2)	24 (35.8)	[b]0.02*
Present	1 (12.5)	7 (87.5)	
Time to metastasis (months)			
Mean±SD	68.30±40.40	22.58±22.26	[d]0.001**
Median (Min–Max)	70.2 (0-120)	18 (0-99)	
Local recurrence			
Absent	43 (62.3)	26 (37.7)	[b]0.114
Present	2 (28.6)	5 (71.4)	
Time to recurrence (months)			
Mean±SD	69.50±37.97	29.71±21.26	[d]0.001**
Median (Min–Max)	70 (10–120)	23.2 (7-99)	
Any event (Metastasis or recurrence)			
Absent	39 (73.6)	14 (26.4)	[c]0.001**
Present	6 (26.1)	17 (73.9)	
Time to any event (months)			
Mean±SD	67.09±40.74	21.44±20.62	[d]0.001**
Median (Min–Max)	70 (0–120)	18 (0-99)	
Primary surgical treatment			
Systemic therapy only	6 (30.0)	14 (70.0)	[a]0.001**
Liquid nitrogen	15 (100.0)	0 (0.0)	
Tumor prosthesis	7 (58.3)	5 (41.7)	
Resection	11 (57.9)	8 (42.1)	
Reconstruction (other)	5 (62.5)	3 (37.5)	
Amputation	1 (50.0)	1 (50.0)	

[a]Fisher Freeman Halton test, [b]Fisher's Exact test, [c]Pearson Chi-square test, [d]Mann–Whitney U test, *p<0.05, **p<0.01. SD: Standard deviation.

Survival by Age Group

Kaplan–Meier survival analysis stratified by age group is summarized in Table 3.

When stratified by age, 10-year OS rates were 75.0% for patients aged 0–9 years, 49.9% for 10–17 years, 42.1% for 18–25 years, and 40.0% for ≥25 years, without a statistically significant difference between groups (Log-rank p=0.155) (Fig. 2).

DFS (Metastasis-and Recurrence-Free Survival)

Table 4 presents the DFS analysis by age group, considering any disease-related event (defined as the occurrence of metastasis or local recurrence) as the endpoint.

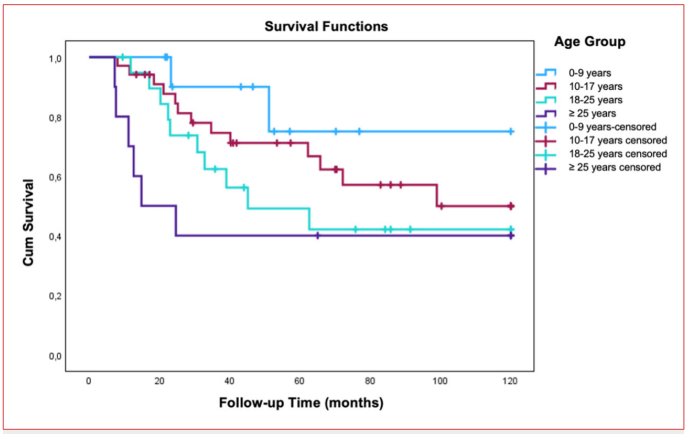

Figure 1. Overall survival curve. (X-axis: Follow-up time in months; Y-axis: Cumulative survival. The curve represents the Kaplan–Meier overall survival for all patients, with tick marks indicating censored observations).

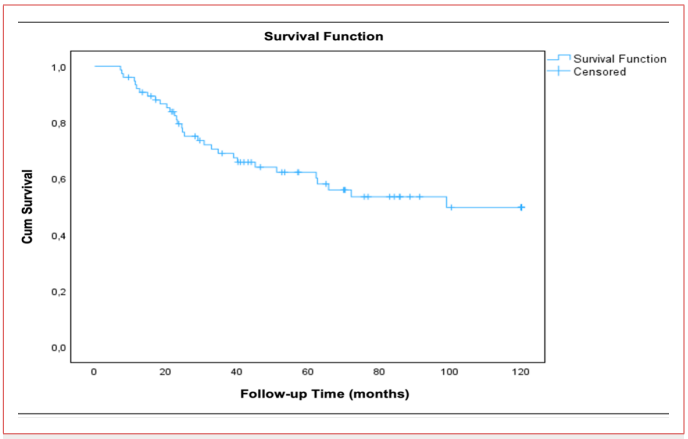

Figure 2. Kaplan–Meier overall survival curves by age group. (Survival curves are shown for each age category: 0–9 years, 10–17 years, 18–25 years, and ≥25 years. X-axis: Follow-up time in months; Y-axis: Cumulative survival probability. Tick marks on each curve indicate censored observations for that group).

Table 3. Survival analysis by age group

Age	*n*	Non-survivors	Survivors	Survival rate (%)	Mean survival time	95% Confidence interval
						Lower-upper
0–9 years	12	2	10	83.3	100.00±12.42	75.65–124.35
10–17 years	34	13	21	61.8	83.33±7.88	67.88–98.78
18–25 years	20	10	10	50.0	69.08±10.87	47.76–90.39
≥25 years	10	6	4	40.0	55.82±16.63	23.21–88.42

Kaplan–Meier analysis.

Table 4. Disease-free survival (recurrence+metastasis free) by age group

Age	*n*	Event (+)	Event (-)	10-year event-free survival rate (%)	Mean event-free survival (months±SE)	95% Confidence interval	
						Lower	Upper
0–9 years	12	4	8	66.7	79.75±16.36	47.69	111.82
10–17 years	34	9	25	73.5	89.54±8.70	72.49	106.59
18–25 years	20	7	13	65.0	76.70±12.61	51.98	101.41
≥25 years	10	3	7	70.0	84.76±16.72	52.00	117.53
Overall	76	23	53	69.7	84.38±6.14	72.36	96.41

Kaplan–Meier analysis. SE: Standard error

For DFS, 69.7% of patients remained free of recurrence or metastasis at 10 years. Mean DFS was 84.4±6.1 months, with no significant differences observed across age groups (Log-rank p=0.915) (Fig. 3).

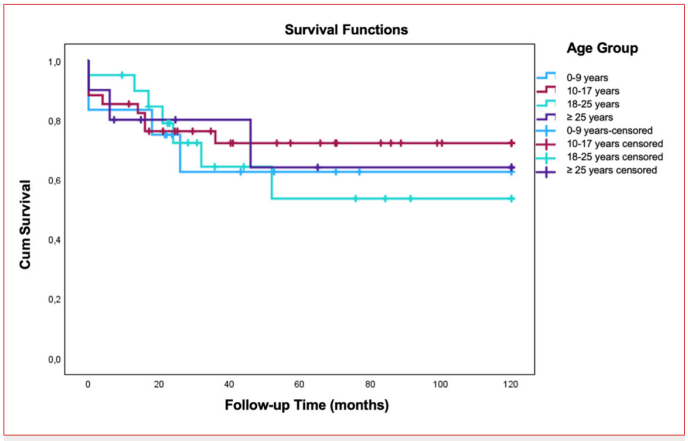

Figure 3. Kaplan–Meier disease-free survival curves by age group. (Curves represent metastasis- and recurrence-free survival for age groups 0–9, 10–17, 18–25, and ≥25 years. X-axis: Follow-up time in months; Y-axis: Cumulative proportion of patients without metastasis or recurrence. Tick marks indicate censored observations).

DISCUSSION

This study observed a trend toward worse survival outcomes in adult ES patients compared to pediatric patients, although age was not an independent predictor of survival in this cohort. The lack of a statistically significant correlation between age and oncological outcomes suggests that other factors, such as metastatic status or treatment modalities, may have a stronger influence on prognosis in our series. These findings align with larger population studies reporting poorer survival in adults, with 5-year survival rates of approximately 40–50% in adults versus 65–70% in children.[11,12] The inferior survival in older patients has been attributed to multiple factors, including more advanced disease at presentation and potential biological differences. Indeed, adults are more often diagnosed with metastases, axial or extraosseous primary tumors.[11,12] Some evidence suggests that when adults can be treated with the same intensive protocols as children, outcomes may improve, supporting aggressive therapy for fit adult patients.[13] Nonetheless, our findings reinforce the consistently poorer prognosis of adult ES and underscore the need for age-tailored strategies to close this survival gap.[11,12]

The presence of metastases at diagnosis was strongly associated with inferior outcomes in our study, in line with the well-established prognostic impact of metastatic disease.

[12] Patients who presented with metastases had markedly lower survival rates, roughly on the order of 20–30% 5-year OS, compared to about 70% in those with localized disease. [14] Notably, the site and extent of metastasis influence prognosis: Isolated pulmonary metastases carry a somewhat better outlook than extrapulmonary or combined metastases. [14] Prior cooperative group trials have reported around 30% long-term survival for patients with isolated lung metastases, whereas those with bone or bone marrow involvement fare significantly worse (often <20% survival).[14] Our findings are consonant with these patterns, as metastatic patients in our cohort had outcomes that reflect the lower end of survival expectations. This underscores that initial metastatic spread remains the strongest adverse predictor in ES, and despite modern multimodal therapy, improvements for this high-risk group have been minimal.[12] Aggressive systemic therapy (e.g., interval-compressed chemotherapy and consolidative whole-lung irradiation for lung metastases) is standard, yet clearly new approaches are needed to substantially improve survival in the metastatic setting.[14]

Our analysis of recurrence patterns highlights the dire prognosis associated with ES relapse. Among patients who experienced recurrence, the majority had distant metastatic relapse rather than isolated local failure, reflecting the tumor's aggressive biology. The post-relapse survival in our series was poor, which aligns with published data showing that fewer than 15% of patients survive 5 years after a recurrence.[14] In fact, large retrospective studies have reported 5-year post-relapse survival on the order of only ~10%.[14] Prognostic factors in the relapsed setting include the timing and location of recurrence. Patients who relapse more than 2 years after initial therapy, or with localized (or lung-only) recurrences, have a better chance of prolonged survival than those with early or multifocal relapse. [15] For example, one study noted 2-year post-relapse survival of ~40% for patients with late or lung-confined recurrence, versus under 10% in those with early or disseminated relapse. [15] These observations suggest that a subset of relapsed patients can achieve long-term remission with aggressive salvage treatments (such as surgery for solitary lesions, high-dose chemotherapy with stem cell rescue, or novel agents), but overall, refractory ES remains overwhelmingly lethal. Our findings reinforce the urgent need for effective salvage therapies and early identification of relapse. Currently, relapsed ES is typically managed with various second-line chemotherapy regimens or clinical trials, but responses are often transient, and cure is rare.[15] This reality should temper clinical expectations and motivates exploration of innovative approaches to improve outcomes after recurrence.

Surgical management emerged as a pivotal factor in our cohort, affecting both local disease control and survival. Notably, we observed no significant difference in OS between patients who underwent limb-salvage surgery and those who required amputation, provided that complete tumor resection was achieved. This finding is consistent with the broader orthopedic oncology experience that limb-sparing surgery, when combined with chemotherapy and (if indicated) radiotherapy, can attain equivalent oncologic outcomes to amputation while preserving function.[16] Prior studies in extremity sarcomas have shown that although limb-salvage may carry a slightly higher risk of local recurrence than amputation in some cases, it does not compromise OS as long as clear margins are obtained and effective adjuvant therapy is given.[16] In our series, the use of amputation was reserved for cases where limb-salvage was not feasible (due to neurovascular involvement or extensive disease), or for certain locally recurrent tumors. The fact that survival did not differ by surgical modality underscores that local control – rather than the specific surgical technique – is the key determinant for outcome, allowing most patients to avoid amputation without increasing mortality risk.

Equally important is the comparison of surgical versus non-surgical local therapy. Our results echo the evidence that definitive surgery for the primary tumor is associated with significantly better outcomes in ES. Patients who underwent surgical resection had markedly higher survival than those managed without surgery, reflecting the critical contribution of surgery to durable local control.[11] A surveillance, epidemiology, and end results analysis by Verma et al.[11] similarly demonstrated that resection of the primary tumor conferred a major survival advantage in both pediatric and adult ES patients (5-year OS ~70% with surgery vs ~25% without in that series). The rationale is clear: Uncontrolled primary tumors can be a source of pain, disability, and further metastasis, whereas achieving local tumor clearance improves both quality of life and survival likelihood. In instances where surgery is not possible (e.g., unresectable axial tumors), radiation therapy serves as an alternative for local control, but it is generally less effective than surgery. For example, an analysis of pelvic ES s found that the 5-year local recurrence rate was 22–40% with radiotherapy alone, compared to only ~4–13% with surgical resection (with or without radiation).[16] Our institution's practice of combining surgery with adjuvant radiotherapy for selected cases (such as large pelvic tumors or those with marginal resection margins) is supported by reports that multimodal local therapy can further reduce recurrence risk in challenging anatomic sites.[16] Taken together, our findings reinforce the paradigm that aggressive local control – preferably through surgical resection – is a cornerstone of ES treatment. The type of surgery (limb-salvage vs amputation) can be individualized based on tumor extent and functional

considerations, without adversely impacting survival, as long as complete resection and appropriate adjuvant therapies are achieved. Meanwhile, patients who do not undergo surgery must be monitored closely, as they face higher odds of local failure, which can translate into worse overall outcomes.

Several limitations of this study should be acknowledged when interpreting the results. Most importantly, our analysis is retrospective and from a single institution, which introduces inherent biases in patient selection, treatment approaches, and data completeness. The cohort spanned a wide range of ages (1–78 years) and a long treatment period, during which therapy protocols evolved; thus, heterogeneity in management (pediatric vs adult regimens, older vs newer chemotherapy protocols) could confound the outcomes attributed to age or other factors. Tumor size at diagnosis and surgical margin status were not consistently available across the entire cohort and could not be analyzed, which limits granularity regarding established prognostic factors. Tumor localization was heterogeneous in our cohort, and because the primary site is prognostic and age-dependent in ES, this variability may have confounded age-based comparisons. Being a single-center study, the sample size of certain subgroups (e.g., patients over 40, or those treated with amputation) was relatively small, limiting the statistical power to detect nuanced differences. In addition, unmeasured variables, such as socioeconomic factors, referral patterns, and individual comorbidities in older patients, were not accounted for, yet they may have influenced survival (for instance, some older patients may have received less aggressive therapy due to comorbid conditions). We also lacked granular details on chemotherapy dose intensity and histologic response in all cases, which are known prognostic indicators. Finally, outcomes, such as quality of life and functional status following different surgical treatments, were beyond the scope of this study, but are relevant to patient-centered decision making.

Despite these limitations, our study provides valuable insight into the comparative outcomes across age groups and treatment modalities in ES, a relatively rare cancer. It adds to the growing evidence base that can inform clinical practice. Going forward, multi-center collaborations or prospective registries are warranted to validate our findings in larger, more diverse patient populations. Such studies would help to confirm, for example, whether the survival disparity between adult and pediatric patients persists when care is optimized, and how novel therapies might be altering outcomes over time. Another important future direction is research into the biology of ES across the age spectrum – understanding if there are genomic or tumor microenvironment differences in adult-onset cases could elucidate why older patients fare worse and suggest targeted interventions.

CONCLUSION

In summary, our findings support the continued emphasis on a multidisciplinary, aggressive treatment approach for all ES patients, while also highlighting specific gaps – such as the management of adults and the treatment of metastatic/recurrent disease – where further research and innovative therapies are urgently needed. By addressing these gaps, future studies can build upon the progress to date and hopefully move the needle on survival for those patients who still face a poor prognosis.

DECLARATIONS

Ethics Committee Approval: This study was approved by the Metin Sabanci Baltalimanı Bone Diseases Hospital (Date: 28.10.2024, Decision no: 193).

Informed Consent: All data were obtained from existing medical records, with patient confidentiality preserved.

Conflict of Interest: None declared.

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