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Tumour Size, Metastasis and Age as Prognostic Factors in Adult Ewing Sarcoma: A Single-Centre Retrospective Cohort Study

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Abstract

Background

Prognostic data on adults with Ewing sarcoma are limited, and the prognostic value of the AJCC 8-cm size threshold has not been tested in this population. We aimed to determine overall survival (OS) and its prognostic factors in adults with Ewing sarcoma.

Methods

Fifty-five patients aged ≥ 18 years with histologically confirmed Ewing sarcoma treated at a single orthopaedic oncology centre in 2011–2021 were reviewed retrospectively. OS was analysed with the Kaplan–Meier method, the log-rank test and univariable and multivariable Cox regression; tumour size was also assessed with receiver operating characteristic (ROC) analysis.

Results

Median age was 22 years (range 18–65), and 24 patients (43.6%) had metastases at diagnosis. All received neoadjuvant and adjuvant VDC/IE chemotherapy. During a median follow-up of 7 years, 27 patients died; 5-year OS was 54.5% (95% CI 40.6–66.6). Metastasis (5-year OS 29.2% vs 74.2%) and tumour size ≥ 8 cm (16.0% vs 86.7%) were associated with poorer survival (both $p < 0.001$). In multivariable analysis, tumour size ≥ 8 cm was an independent prognostic factor (HR 9.04; 95% CI 3.06–26.72). In an exploratory model, age (HR 2.35 per 10 years; 95% CI 1.41–3.90) and metastasis (HR 2.75; 95% CI 1.02–7.40) were also independent factors. Tumour size predicted 5-year mortality with an area under the curve of 0.92; the optimal cut-off was 8 cm.

Conclusions

In adults with Ewing sarcoma, tumour size ≥ 8 cm, metastasis at diagnosis and older age are associated with poorer OS. The 8-cm threshold is a simple tool for risk stratification; multicentre validation is needed.

Background

Ewing sarcoma is a high-grade small round cell sarcoma of bone or soft tissue defined by fusion of the EWSR1 gene with a member of the ETS family of transcription factors, most commonly FLI1 through the t(11;22)(q24;q12) translocation in approximately 85% of cases [1, 2]. It is the second most common primary malignant bone tumour in children and adolescents after osteosarcoma; most patients are diagnosed in the second decade of life, and the disease is considerably rarer in adults [1, 3].

Current treatment is multimodal and comprises induction chemotherapy, local control with surgery and/or radiotherapy, and consolidation chemotherapy [3]. Adding ifosfamide–etoposide (IE) to vincristine–doxorubicin–cyclophosphamide (VDC) improved survival in localised disease [4], and compressing cycles to every 2 weeks increased this benefit [5]. In the Euro EWING 2012 trial, which also enrolled adults younger than 50 years, interval-compressed VDC/IE was more effective than VIDE induction [6]. Nevertheless, long-term survival remains poor for patients with metastases at diagnosis [7].

Adults have a worse prognosis than children in institutional series and population-based registries [8–10]. Proposed explanations include more frequent extraskeletal, axial and metastatic disease in adults [9, 11], delayed initiation of systemic therapy, less frequent or less intensive chemotherapy [12, 13] and possible biological differences. Metastasis at diagnosis, tumour size or volume, axial or pelvic location and age are the most consistently reported prognostic factors [14, 15]. A recent long-term analysis of 3395 patients younger than 50 years enrolled in Euro-EWING 99 identified age and tumour volume as major prognostic factors for progression-free survival and OS independent of metastatic status, but a separate analysis of adults was not reported [16].

Data on adult Ewing sarcoma come mainly from medical oncology series, and few studies have examined tumour size, surgical margins and treatment sequencing together from an orthopaedic oncology perspective. Moreover, the prognostic value of the 8-cm threshold used for T classification of bone sarcomas [17] has not been adequately tested in adults. The aim of this study was to determine OS and its prognostic factors in adults with Ewing sarcoma treated at a single orthopaedic oncology centre and to evaluate the prognostic value of the 8-cm tumour size threshold.

Methods

Study Design and Patients

This retrospective cohort study was conducted at the Department of Orthopedia and Traumatology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, and is reported according to the STROBE guideline [18]. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (2026-08/189); the requirement for informed consent was waived because of the retrospective design.

Records of patients treated and followed for Ewing sarcoma between January 2011 and December 2021 were reviewed. Inclusion criteria were age ≥ 18 years at diagnosis, histopathologically confirmed Ewing sarcoma and surgical treatment at our centre. Patients without histopathological confirmation, those whose primary surgery was performed elsewhere, those with incomplete clinical data and surviving patients with less than 5 years of follow-up were excluded. Fifty-five patients met these criteria.

Variables and Definitions

Age, sex, tumour site, tumour size, soft-tissue extension, pathological fracture, metastasis at diagnosis, type of surgery, surgical margin, chemotherapy, radiotherapy and survival status were retrieved from the hospital information system and archived files. Age was analysed as a continuous variable (per 10-year increase) and in two groups (18–25 and > 25 years), in line with the adolescent and young adult literature [8]. Site was grouped as lower limb, upper limb, shoulder girdle (scapula and clavicle) and pelvis; pelvic and non-pelvic sites were also compared.

Tumour size was defined as the greatest tumour diameter (cm) on magnetic resonance imaging (MRI) at diagnosis. The 8-cm threshold separating T1 from T2 in the AJCC 8th edition staging of bone tumours was used as a prespecified cut-off [17]. Metastasis at diagnosis was defined as distant metastasis on staging imaging. Surgical margins were classified from pathology reports as negative (R0) or positive/close (R1/R2 or < 1 cm from the tumour). Procedures were grouped as wide resection with or without reconstruction (limb salvage) and amputation.

Systemic Therapy and Radiotherapy

Chemotherapy and radiotherapy were delivered by the medical and radiation oncology departments according to standard protocols after multidisciplinary tumour board review. All patients received neoadjuvant (induction) and adjuvant (consolidation) chemotherapy. The regimen consisted of 14 cycles of alternating VDC (vincristine 1.5 mg/m², maximum 2 mg; doxorubicin 75 mg/m²; cyclophosphamide 1200 mg/m²) and IE (ifosfamide 1800 mg/m²/day and etoposide 100 mg/m²/day for 5 days) given every 2 weeks with G-CSF support; dactinomycin replaced doxorubicin once a cumulative doxorubicin dose of 375 mg/m² was reached [4–6]. Surgery was performed 2–4 weeks after the last induction cycle, and consolidation cycles were completed postoperatively. Preoperative radiotherapy was indicated for tumours that were unresectable or whose resection would cause major functional loss, and postoperative radiotherapy for positive or close margins. Radiotherapy timing was recorded as neoadjuvant, adjuvant or both.

Outcome

The primary outcome was OS, defined as the time from diagnosis to death from any cause. Patients alive at last follow-up were censored at that date. Because survival time was recorded in years, analyses were performed on a yearly time scale.

Statistical Analysis

IBM SPSS v.26.0 was used for statistical analyses. Continuous variables are presented as mean ± standard deviation (SD) and median (interquartile range, IQR), and categorical variables as number (%). Categorical variables were compared with Fisher's exact test and continuous variables with the Mann–Whitney U test. Median follow-up was calculated with the reverse Kaplan–Meier method. OS was

estimated with the Kaplan–Meier method; 1-, 3- and 5-year rates are given with log–log transformed 95% confidence intervals (CI), and groups were compared with the log-rank test.

Univariable HRs were estimated with Cox proportional hazards regression. To avoid overfitting, the rule of approximately 10 events per variable was considered [19]; with 27 events, each multivariable model included at most three variables. Model 1 included metastasis at diagnosis, tumour size (≥ 8 vs < 8 cm) and surgical margin, prespecified for their clinical relevance. In the exploratory Model 2, surgical margin was replaced by age (per 10 years) on the basis of published evidence on the prognostic role of age [8, 11, 16]. The proportional hazards assumption was tested with Schoenfeld residuals, and discrimination was measured with Harrell's C-index. As a measure independent of proportional hazards, the 5-year restricted mean survival time (RMST) and between-group differences (95% CI) were calculated.

The ability of continuous tumour size to discriminate metastasis at diagnosis and 5-year mortality was assessed with receiver operating characteristic (ROC) analysis. The 95% CI of the area under the curve (AUC) was obtained by bootstrapping with 2000 replicates; the optimal cut-off was determined with the Youden index, and the sensitivity and specificity of the 8-cm threshold were reported. A two-sided $p < 0.05$ was considered statistically significant.

Results

Patient, Tumour and Treatment Characteristics

Fifty-five patients were included. Mean age was 25.1 ± 8.5 years (median 22; IQR 20–27; range 18–65), and 43 patients (78.2%) were male. The lower limb was the most common site (n = 34, 61.8%), and the femur (n = 15) and tibia (n = 12) were the most frequently involved bones. Median tumour size was 7 cm (IQR 5–9), and 25 tumours (45.5%) measured ≥ 8 cm. Twenty-four patients (43.6%) had metastases at diagnosis, 35 (63.6%) had soft-tissue extension and 11 (20.0%) had a pathological fracture (Table 1).

Fifty-one patients (92.7%) underwent wide resection with or without reconstruction and 4 (7.3%) underwent amputation. Margins were negative in 40 patients (72.7%) and positive/close in 15 (27.3%). All patients received neoadjuvant and adjuvant chemotherapy. Radiotherapy was given to 32 patients (58.2%): neoadjuvant only in 5, adjuvant only in 16 and both in 11. Of the 15 patients with positive/close margins, 14 received adjuvant radiotherapy; in the remaining patient, the segment resected after neoadjuvant radiotherapy was irradiated extracorporeally and used for reconstruction (Table 1).

Table 1
Patient, tumour and treatment characteristics (n = 55)

Characteristic	Value
Age, years	
Mean ± SD	25.1 ± 8.5
Median (IQR); range	22 (20–27); 18–65
18–25 years	36 (65.5)
> 25 years	19 (34.5)
Sex	
Male	43 (78.2)
Female	12 (21.8)
Site	
Lower limb	34 (61.8)
Upper limb	9 (16.4)
Shoulder girdle (scapula/clavicle)	7 (12.7)
Pelvis	5 (9.1)
Tumour size	
Median (IQR), cm	7 (5–9)
< 8 cm	30 (54.5)
≥ 8 cm	25 (45.5)
Metastasis at diagnosis	
No (M0)	31 (56.4)
Yes (M1)	24 (43.6)
Soft-tissue extension	
Yes	35 (63.6)
No	20 (36.4)
Pathological fracture	
Yes	11 (20.0)
No	44 (80.0)
Surgery	

Characteristic	Value
Age, years	
Wide resection ± reconstruction	51 (92.7)
Amputation	4 (7.3)
Surgical margin	
Negative (R0)	40 (72.7)
Positive/close	15 (27.3)
Chemotherapy (VDC/IE)	
Neoadjuvant + adjuvant	55 (100)
Radiotherapy	
None	23 (41.8)
Neoadjuvant only	5 (9.1)
Adjuvant only	16 (29.1)
Neoadjuvant + adjuvant	11 (20.0)
Follow-up and outcome	
Median follow-up, years (reverse Kaplan–Meier)	7
Death	27 (49.1)

Values are n (%) unless otherwise indicated. SD: standard deviation; IQR: interquartile range; VDC/IE: vincristine–doxorubicin–cyclophosphamide alternating with ifosfamide–etoposide.

Overall Survival

Median follow-up was 7 years (range among survivors 5–9 years). Twenty-seven patients (49.1%) died, 22 (81.5%) of them within the first 3 years. In the whole cohort, 1-, 3- and 5-year OS was 87.3% (95% CI 75.1–93.7), 60.0% (45.9–71.5) and 54.5% (40.6–66.6), respectively; median OS was 6 years (Fig. 1A).

Univariable Analysis

Univariable results are summarised in Table 2. Five-year OS was 29.2% with metastases at diagnosis and 74.2% with localised disease (HR 4.14; 95% CI 1.84–9.29; log-rank $p < 0.001$), and 16.0% for tumours ≥ 8 cm versus 86.7% for tumours < 8 cm (HR 11.47; 95% CI 4.24–31.00; $p < 0.001$) (Fig. 1B and 1C). Each 1-cm increase in tumour size was associated with a 40% higher risk of death (HR 1.40; 95% CI 1.23–1.59; $p < 0.001$).

Five-year OS was numerically lower with positive/close margins (40.0% vs 60.0%), but the difference was not significant (p = 0.385). Age group (18–25 vs > 25 years; p = 0.580), continuous age (HR 1.37 per 10 years; p = 0.167), sex, site (four groups, p = 0.950; pelvic vs other, p = 0.756), soft-tissue extension, pathological fracture and type of surgery were not associated with OS. Receipt of radiotherapy was not associated with OS (p = 0.697). Five-year OS tended to be higher with neoadjuvant radiotherapy (75.0% vs 46.2%; p = 0.055) and lower with adjuvant radiotherapy (40.7% vs 67.9%; p = 0.105), but neither difference was significant. Most patients given neoadjuvant radiotherapy had localised disease (12/16) and tumours < 8 cm (11/16), whereas 14 of the 27 patients given adjuvant radiotherapy had positive/close margins.

Table 2
Univariable analysis of overall survival

Variable	n	Deaths	1-year OS (%)	3-year OS (%)	5-year OS, % (95% CI)	Log-rank p	HR (95% CI)
Whole cohort	55	27	87.3	60.0	54.5 (40.6–66.6)	–	–
Sex							
Female	12	4	91.7	66.7	66.7 (33.7–86.0)	0.215	Reference
Male	43	23	86.0	58.1	51.2 (35.5–64.8)		1.90 (0.66–5.50)
Age							
18–25 years	36	17	91.7	63.9	58.3 (40.7–72.4)	0.580	Reference
> 25 years	19	10	78.9	52.6	47.4 (24.4–67.3)		1.24 (0.57–2.71)
Continuous, per 10 years	55	27				0.167[a]	1.37 (0.88–2.16)
Site							
Lower limb	34	15	82.4	61.8	58.8 (40.6–73.2)	0.950	
Upper limb	9	5	88.9	55.6	55.6 (20.4–80.5)		
Shoulder girdle	7	4	100	71.4	42.9 (9.8–73.4)		
Pelvis	5	3	100	40.0	40.0 (5.2–75.3)		1.25 (0.38–4.15)[b]
Metastasis at diagnosis							
No (M0)	31	9	93.5	80.6	74.2 (55.0–86.2)	< 0.001	Reference
Yes (M1)	24	18	79.2	33.3	29.2 (13.0–47.6)		4.14 (1.84–9.29)
Tumour size							
< 8 cm	30	5	96.7	93.3	86.7 (68.3–94.8)	< 0.001	Reference
≥ 8 cm	25	22	76.0	20.0	16.0 (5.0–32.5)		11.47 (4.24–31.00)

Variable	n	Deaths	1-year OS (%)	3-year OS (%)	5-year OS, % (95% CI)	Log-rank p	HR (95% CI)
Continuous, per cm	55	27				< 0.001[a]	1.40 (1.23–1.59)
Soft-tissue extension							
No	20	10	80.0	55.0	50.0 (27.1–69.2)	0.471	Reference
Yes	35	17	91.4	62.9	57.1 (39.3–71.5)		0.76 (0.34–1.66)
Pathological fracture							
No	44	21	84.1	56.8	52.3 (36.7–65.7)	0.912	Reference
Yes	11	6	100	72.7	63.6 (29.7–84.5)		1.04 (0.42–2.58)
Surgical margin							
Negative (R0)	40	18	87.5	65.0	60.0 (43.2–73.3)	0.385	Reference
Positive/close	15	9	86.7	46.7	40.0 (16.5–62.8)		1.45 (0.65–3.22)
Surgery							
Limb salvage	51	25	90.2	60.8	54.9 (40.3–67.3)	0.643	Reference
Amputation	4	2	50.0	50.0	50.0 (5.8–84.5)		1.36 (0.32–5.74)
Radiotherapy (any)							
No	23	11	95.7	60.9	60.9 (38.3–77.4)	0.697	Reference
Yes	32	16	81.2	59.4	50.0 (31.9–65.7)		1.14 (0.53–2.46)
Neoadjuvant radiotherapy							
No	39	23	89.7	51.3	46.2 (30.2–60.7)	0.055	Reference
Yes	16	4	81.2	81.2	75.0 (46.3–89.8)		0.36 (0.13–1.05)
Adjuvant radiotherapy							

Variable	n	Deaths	1-year OS (%)	3-year OS (%)	5-year OS, % (95% CI)	Log-rank p	HR (95% CI)
No	28	11	96.4	67.9	67.9 (47.3–81.8)	0.105	Reference
Yes	27	16	77.8	51.9	40.7 (22.5–58.2)		1.84 (0.85–3.96)

OS: overall survival; CI: confidence interval; HR: hazard ratio (univariable Cox regression). Survival rates were estimated with the Kaplan–Meier method. Chemotherapy was not analysed because all patients received neoadjuvant and adjuvant chemotherapy. [a]Wald test from Cox regression. [b]Pelvic vs non-pelvic site (log-rank p = 0.756).

Multivariable Analysis

In Model 1, tumour size ≥ 8 cm remained an independent prognostic factor (HR 9.04; 95% CI 3.06–26.72; p < 0.001), whereas metastasis (HR 1.66; p = 0.256) and surgical margin (HR 1.05; p = 0.907) were not significant (C-index 0.80) (Table 3). This attenuation of the effect of metastasis was consistent with the strong association between the two variables: 72.0% (18/25) of tumours ≥ 8 cm and 20.0% (6/30) of tumours < 8 cm were metastatic at diagnosis (p < 0.001). In the exploratory Model 2, tumour size ≥ 8 cm (HR 10.87; 95% CI 3.61–32.73; p < 0.001), metastasis at diagnosis (HR 2.75; 95% CI 1.02–7.40; p = 0.046) and each 10-year increase in age (HR 2.35; 95% CI 1.41–3.90; p = 0.001) were independently associated with poorer OS (C-index 0.84).

Schoenfeld residuals indicated a departure from proportional hazards for tumour size (p = 0.019); 20 of the 22 deaths (90.9%) in the ≥ 8 cm group occurred within the first 3 years. The 5-year RMST was 4.73 years for tumours < 8 cm and 2.56 years for tumours ≥ 8 cm (difference 2.17 years; 95% CI 1.53–2.77). The RMST difference was 1.51 years (95% CI 0.73–2.24) for metastasis and 0.38 years (95% CI − 0.53 to 1.32) for surgical margin.

The effect of tumour size persisted after stratification by metastatic status. In localised disease, 5-year OS was 87.5% for tumours < 8 cm (n = 24) and 28.6% for tumours ≥ 8 cm (n = 7) (p < 0.001); in metastatic disease, the corresponding rates were 83.3% (n = 6) and 11.1% (n = 18) (p = 0.017).

Table 3
Multivariable Cox regression models for overall survival

Variable	HR (95% CI)	p	C-index
Model 1 (n = 55; 27 events)			
Metastasis at diagnosis (M1 vs M0)	1.66 (0.69–4.01)	0.256	0.80
Tumour size (≥ 8 vs < 8 cm)	9.04 (3.06–26.72)	< 0.001	
Surgical margin (positive/close vs negative)	1.05 (0.47–2.36)	0.907	
Model 2, exploratory (n = 55; 27 events)			
Metastasis at diagnosis (M1 vs M0)	2.75 (1.02–7.40)	0.046	0.84
Tumour size (≥ 8 vs < 8 cm)	10.87 (3.61–32.73)	< 0.001	
Age (per 10 years)	2.35 (1.41–3.90)	0.001	

HR: hazard ratio; CI: confidence interval. Schoenfeld residuals indicated a departure from the proportional hazards assumption for tumour size (p = 0.019); the HR should therefore be interpreted as an average effect over follow-up. Difference in 5-year restricted mean survival time (< 8 cm minus ≥ 8 cm): 2.17 years (95% CI 1.53–2.77).

ROC Analysis

Continuous tumour size discriminated metastasis at diagnosis (AUC 0.80; 95% CI 0.68–0.91; p < 0.001) and 5-year mortality (AUC 0.92; 95% CI 0.84–0.98; p < 0.001). The optimal cut-off according to the Youden index was 8 cm for both outcomes. At this threshold, sensitivity and specificity were 75.0% and 77.4% for metastasis and 84.0% and 86.7% for 5-year mortality (Fig. 2).

Sensitivity Analyses

With tumour size as a continuous variable, each 1-cm increase remained independently associated with poorer OS in Model 1 (HR 1.35; 95% CI 1.17–1.57) and Model 2 (HR 1.32; 95% CI 1.16–1.50), without departure from proportional hazards. In Model 1 with continuous size, metastasis (HR 2.01; 95% CI 0.85–4.79) and margin (HR 1.00; 95% CI 0.43–2.33) were not significant, whereas in Model 2 metastasis (HR 3.59; 95% CI 1.35–9.54) and age (HR 2.19 per 10 years; 95% CI 1.23–3.88) remained significant. After exclusion of the two patients older than 45 years (53 patients, 26 events), tumour size ≥ 8 cm (HR 8.69; 95% CI 2.96–25.49), metastasis (HR 2.97; 95% CI 1.10–8.04) and age (HR 2.70 per 10 years; 95% CI 1.25–5.81) remained significant in Model 2.

Discussion

In this cohort of adults with Ewing sarcoma, 5-year OS was 54.5%. Metastasis at diagnosis and tumour size ≥ 8 cm were strongly associated with poorer survival; tumour size was the most consistent

independent prognostic factor and remained so in all sensitivity analyses. In exploratory analysis, older age was independently associated with poorer survival even in this adult-only cohort. The data-driven optimal ROC cut-off for both metastasis and mortality coincided with the AJCC 8-cm threshold.

Tumour size or volume is a long-established prognostic factor in Ewing sarcoma. In the EICESS series of 975 patients, metastasis, axial location and older age were associated with poorer survival [14], and a systematic review of 21 studies identified a tumour volume ≥ 200 mL or a greatest diameter ≥ 8 cm as adverse factors together with metastasis and axial/pelvic location [15]. Tumour volume is not always calculated in routine orthopaedic oncology practice, whereas the greatest diameter is readily available and integrated into staging [17]. Gupta et al. likewise reported that tumour size > 8 cm, metastasis and fewer than 15 chemotherapy cycles were independently associated with poorer survival in 81 patients [20]. In our series, 5-year OS fell to 16.0% for tumours ≥ 8 cm, and 8 cm was also the data-driven optimal cut-off, suggesting that this simple measure can be used for risk stratification in adults. The persistence of the size effect within both localised and metastatic subgroups indicates that it is not merely a reflection of metastatic disease. Most deaths among patients with large tumours occurred within 3 years, which explains the departure from proportional hazards and points to early treatment failure, underlining the need for close surveillance in this group.

Metastasis at diagnosis is regarded as the strongest prognostic factor in Ewing sarcoma [7, 14]. The 5-year OS of 29.2% in our metastatic patients is consistent with large series of primary disseminated disease [7, 21] and with the 27.5% reported for metastatic disease in adults older than 40 years [22]. The 5-year OS of 54.5% in the whole cohort is similar to the 54.3% reported in SEER for patients younger than 40 years [11], and the 74.2% in localised disease is comparable to the 68% reported in a referral-centre series of 105 adults [23]. The loss of significance of metastasis in Model 1 can be explained by its strong association with tumour size; with only 27 events, the power to separate two correlated variables is limited. Indeed, metastasis was independently significant in Model 2 and in its sensitivity analysis with continuous size. This finding therefore reflects an overlap between tumour burden and metastatic potential rather than a lack of prognostic importance of metastasis. The higher proportion of metastatic disease in our series (43.6%) than in population-based data (30–36%) [11] may reflect referral bias at a tertiary centre. A Turkish referral-centre series of 222 patients also reported a 3-year OS of only 54% [24], indicating that real-world outcomes lag behind those of clinical trials.

Valentin et al. identified age as a major prognostic factor for progression-free survival and OS independent of metastatic status in 3395 patients from Euro-EWING 99 [16]. Because adults were not analysed separately, whether the effect of age persists beyond 18 years remains unclear, which increases the value of adult-only series. In our cohort, the 25-year cut-off did not separate outcomes, but when age was analysed continuously and adjusted for tumour size and metastasis, each 10-year increase was associated with an approximately 2.3-fold higher risk of death. This agrees with the decline in survival with age in the Polish Sarcoma Group series of 569 patients [8] and with the approximately twofold risk of death in patients older than 40 years in SEER and National Cancer Database analyses (HR 2.04 and 1.96, respectively) [11, 12]. Together with the findings of Valentin et al., our data suggest that

the adverse effect of age continues into adulthood and that age should be regarded as a graded risk factor in adults. However, Model 2 was exploratory, age was not significant in univariable analysis and confidence intervals were wide, so this finding should be interpreted with caution.

All patients received neoadjuvant and adjuvant interval-compressed VDC/IE, the standard regimen also for adults, and underwent surgery 2–4 weeks after the last induction cycle [5, 6]. This homogeneity allowed the effects of size, metastasis and age to be assessed largely free of confounding by different chemotherapy approaches; for the same reason, the effect of chemotherapy timing could not be examined. Survival tended to be better with neoadjuvant and worse with adjuvant radiotherapy, but the differences were not significant and most likely reflect selection by indication: most patients given neoadjuvant radiotherapy had localised small tumours, whereas adjuvant radiotherapy was given largely for positive/close margins. These trends should not be interpreted causally.

Five-year OS was numerically lower with positive/close margins, but the difference was not significant. Positive margins were similarly frequent in localised and metastatic disease (9/31 vs 6/24), so confounding by metastasis does not explain this result. Radiotherapy in all patients with positive/close margins, the small subgroup (n = 15) and the primary relationship of margins with local recurrence may explain the absence of an OS difference; local recurrence data were not available.

This study has limitations. The retrospective single-centre design and the limited number of events restricted the multivariable models to few variables and produced wide confidence intervals. Survival times were recorded in years, so estimates rely on a coarse time scale. Local recurrence, event-free survival and functional outcomes were beyond the scope of the study. Because all patients received the same chemotherapy protocol, chemotherapy timing could not be assessed, and comparisons of radiotherapy timing are subject to selection by indication. Model 2 was exploratory, and because the optimal ROC cut-off was derived from the same sample, discrimination may be overestimated; external validation is required. Nevertheless, this adult-only cohort treated at one multidisciplinary centre, with a minimum follow-up of 5 years (median 7 years) in survivors, adds to the limited evidence on this rare patient group.

Conclusions

In adults with Ewing sarcoma, tumour size ≥ 8 cm, metastasis at diagnosis and older age are associated with poorer OS. Tumour size was the most consistent prognostic factor in all analyses, and the AJCC 8-cm threshold is a prognostically meaningful cut-off in adults. Adults with large tumours should be regarded as high risk and followed closely. These findings should be confirmed in prospective multicentre studies that include event-free survival and local control data.

Abbreviations

AJCC
American Joint Committee on Cancer

AUC
Area under the curve
CI
Confidence interval
EICESS
European Intergroup Cooperative Ewing’s Sarcoma Study
G-CSF
Granulocyte colony-stimulating factor
HR
Hazard ratio
IE
Ifosfamide–etoposide
IQR
Interquartile range
MRI
Magnetic resonance imaging
OS
Overall survival
RMST
Restricted mean survival time
ROC
Receiver operating characteristic
SD
Standard deviation
SEER
Surveillance, Epidemiology, and End Results
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
VDC
Vincristine–doxorubicin–cyclophosphamide
VIDE
Vincristine–ifosfamide–doxorubicin–etoposide

Declarations

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (2026-08/189).

Consent to participate

Owing to the retrospective design and the use of anonymised data, the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital waived the requirement for every individual informed consent to participate.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

TCG conceived and designed the study, collected the data, performed the statistical analysis and wrote the first draft of the manuscript. AP contributed to data collection and to the literature review. MG contributed to data collection, interpretation of the data and preparation of the tables and figures. MT contributed to patient management, data acquisition and critical revision of the manuscript. HHT contributed to data analysis, interpretation of the results and critical revision of the manuscript. CU supervised the study, contributed to its design and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

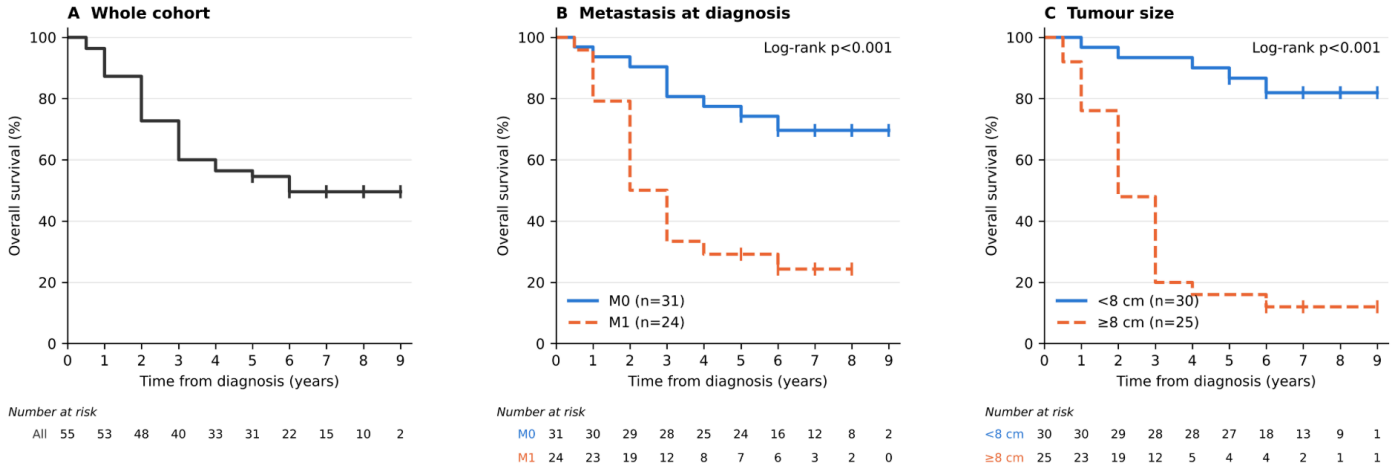


Figure 1

Kaplan–Meier curves for overall survival. (A) Whole cohort (n=55); (B) by metastatic status at diagnosis; (C) by tumour size (<8 cm vs ≥8 cm). Tick marks indicate censored observations; numbers at risk are shown below the curves.

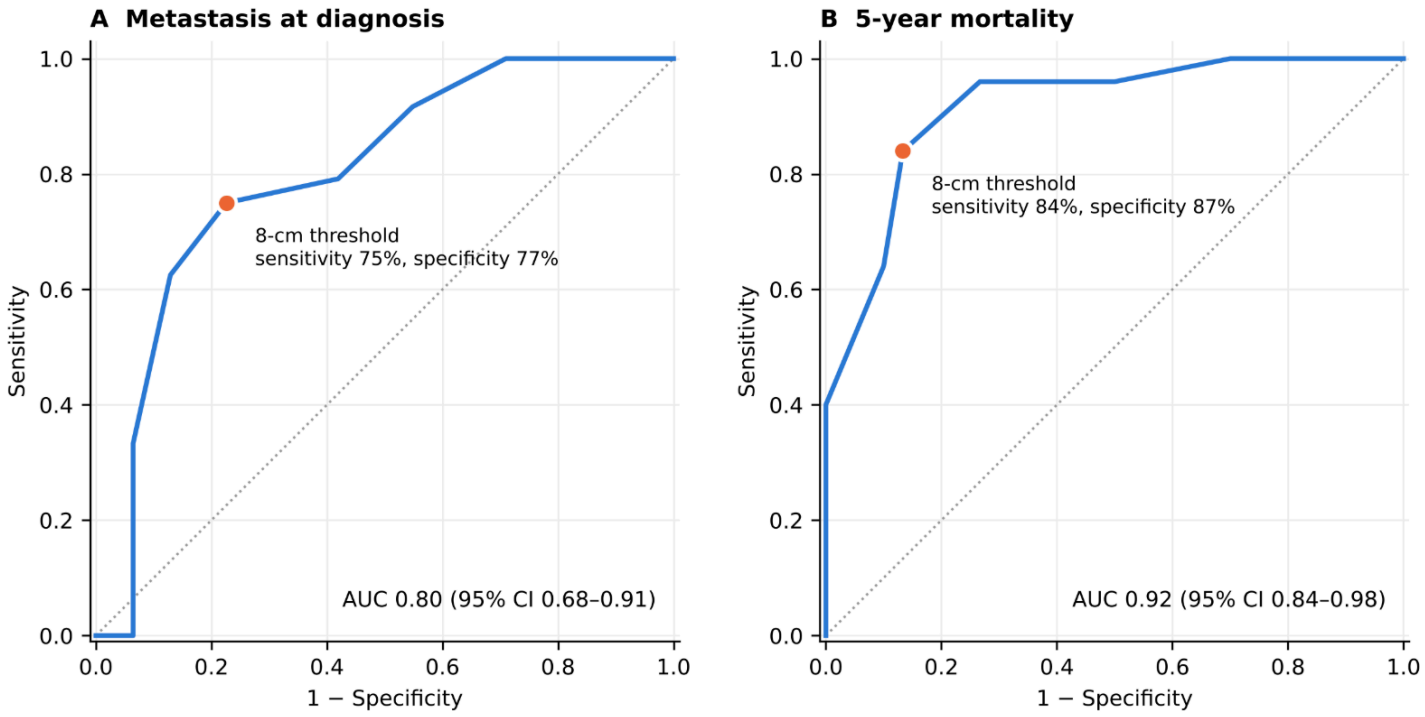


Figure 2

Receiver operating characteristic curves of continuous tumour size for (A) metastasis at diagnosis and (B) 5-year mortality. The orange dot marks the 8-cm threshold, which was the optimal cut-off according to the Youden index for both outcomes. AUC: area under the curve; CI: confidence interval.