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# Surgical Resection of Primary Ewing's Sarcoma of Bone Improves Overall Survival in Patients Presenting with Metastasis

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** Metastatic Ewing's sarcoma (ES) of bone has a poor prognosis. Because there have been few previous studies on the prognostic factors and clinical outcome in patients with ES who have metastases at presentation, the aim of this study was to use the Surveillance, Epidemiology, and End Results (SEER) database to compare the clinical outcome following single and combined radiation treatment and surgery.


**Material/Methods:** The SEER database was used to identify patients with ES who presented with bone involvement and metastasis between 1973 to 2015. Prognostic analysis was performed using the Kaplan-Meier method and the Cox proportional hazards regression model.

**Results:** There were 643 patients identified from the SEER database. The 5-year overall survival (OS) and cancer-specific survival (CSS) rates were 33.1% and 34.3%, respectively and the median OS and CSS were 29.0±1.9 and 29.0±2.1 months, respectively. Multivariate analysis identified age <20 years and surgical resection of the primary tumor to be significantly associated with improved OS. Radiation therapy was not an independent predictor of OS or CSS. Radiation therapy alone resulted in a significantly reduced the OS and CSS compared with surgical resection alone. Combined surgery and radiation therapy of the primary tumor did not significantly improve the OS or CSS of patients with ES and metastatic disease when compared with surgery alone.

**Conclusions:** Age <20 years and surgical resection of the primary tumor were significantly associated with improved OS in patients with primary ES of bone who presented with metastasis.

**MeSH Keywords:** **Neoplasm Metastasis • Sarcoma, Ewing • Survival Analysis • Treatment Outcome**

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## Background

Ewing's sarcoma (ES) is the second most common primary malignancy of bone in children and adolescents [1,2]. Approximately one-third of patients with ES present with metastatic disease [3,4]. The demographic, prognostic, and outcome data for ES are well documented. Patient age, primary tumor site, size, grade, and stage, treatment with chemotherapy, surgery, and radiation therapy are all prognostic factors in patients with ES [3,5–10]. It has previously been reported that systemic chemotherapy combined with surgery and/or radiation therapy for local control of ES was associated with a 5-year survival rate of approximately 70% [11]. However, patients with primary ES of bone who presented with metastasis usually have a poor prognosis, with a 5-year event-free survival rate from presentation of between 20–30% [1,11]. A previously reported study that used patient data from the Surveillance, Epidemiology, and End Results (SEER) database showed that the 10-year survival was 28.1% when patients with osseous ES presented with metastasis, tumor size >10 cm, patient age ≥20 years, and axial primary tumor location [3].

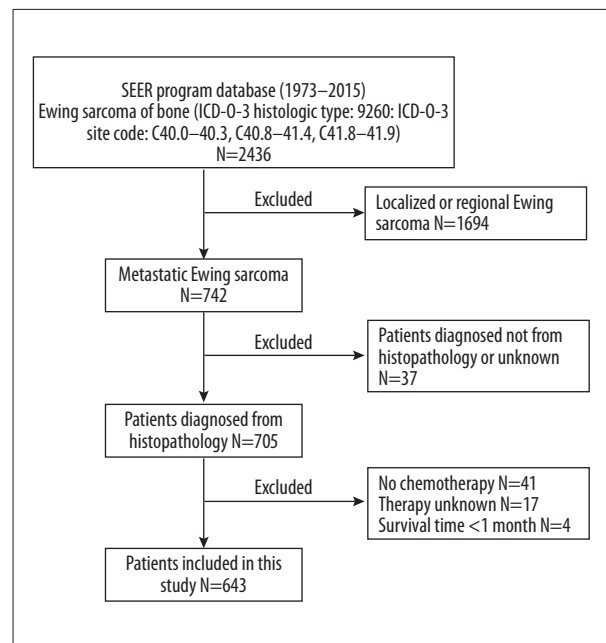
Current standard localized or regional treatment for patients with ES includes systemic chemotherapy and surgery and/or radiation therapy for local control. However, the treatment for metastatic ES remains a challenge and chemotherapy has been the accepted treatment [12]. Whether surgical excision of the primary bone tumor improves the survival of patients who present with metastatic ES is unknown. ES is considered to be a radiosensitive tumor and radiation therapy may provide a survival benefit [6]. However, Arshi et al. [8] reported that radiation therapy did not improve the survival of patients with ES arising in the spine. Therefore, the role of radiation therapy on the prognosis of patients who present with primary osseous ES with metastases requires further study.

Because there have been few previous studies on prognostic factors and clinical outcome in patients with ES who have metastases at presentation, the aim of this large-scale study was to use the Surveillance, Epidemiology, and End Results (SEER) program database of the National Cancer Institute (NCI) to compare the clinical outcome following single and combined radiation treatment and surgery to identify predictors of survival.

## Material and Methods

### Patient population

Data on patients with primary Ewing's sarcoma (ES) of bone with metastasis at diagnosis were obtained using the case-listing session procedure from the Surveillance, Epidemiology, and End Results (SEER) program. The SEER database is publicly



**Figure 1.** Study flowchart of the selection of the study population. ES – Ewing's sarcoma; SEER – Surveillance, Epidemiology, and End Results; ICD-O-3 – International Classification of Diseases for Oncology, 3<sup>rd</sup> Edition.

available, confidential, and does not contain patient identification data. This study was approved by the Ethics Committee of Yuyao Peoples' Hospital of Zhejiang Province, China.

A total of 2,436 patients were identified who were diagnosed between 1973 and 2015 with primary ES of bone with metastasis at initial presentation. The International Classification of Diseases for Oncology, 3<sup>rd</sup> edition (ICD-O-3) was used to identify patients with ES (ICD-O-3 histologic type: 9260; ICD-O-3 site code: C40.0–40.3, C40.8–41.4, C41.8–41.9), using the case-listing procedure. Only patients with metastatic disease were enrolled, based on tumor stage at diagnosis. Patients with ES arising from the extra-skeletal locations were excluded. The diagnosis in all cases was confirmed histologically, based either on biopsy results or from the surgical resection specimen. Thirty-seven patients were excluded who were diagnosed only by clinical presentation, radiography, or identified as unknown. Forty-one patients who did not receive chemotherapy, 17 patients with unknown therapy, and four patients with a survival time of less than one month were also excluded from the study (Figure 1).

Data extracted from the SEER database included patient age, gender, race, year of diagnosis, tumor location, grade, stage, type, size, surgical treatment, radiation treatment, chemotherapy, the cause of death, and survival time. In this study, surgery or radiation treatment referred to treatment for the local primary bone tumor. Tumor location was identified

**Table 1.** Demographic and clinical characteristics of 643 patients with primary Ewing's sarcoma of bone and metastatic disease at presentation identified in the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2015.

Category	Value
<b>Mean age (years)</b>	20
<b>Median age (years)</b>	17
<b>Age (years)</b>	
<20	411 (63.9%)
≥20	232 (36.1%)
<b>Gender</b>	
Female	236 (36.7%)
Male	407 (63.3%)
<b>Location</b>	
Appendicular	222 (34.5%)
Axial	267 (41.5%)
Rib, sternum and clavicle	91 (14.2%)
Other locations	63 (9.8%)
<b>Tumor size</b>	
Mean (cm)	10
Median (cm)	9
<10 cm	181 (28.1%)
≥10 cm	166 (25.8%)
Unknown	296 (46%)

Category	Value
<b>Surgery</b>	
Yes	243 (37.8%)
No	400 (62.2%)
<b>Radiation treatment</b>	
Yes	395 (61.4%)
No	248 (38.6%)
<b>Local treatment</b>	
Surgery + radiation	147 (22.9%)
Surgery only	96 (14.9%)
Radiation only	248 (38.6%)
No therapy	152 (23.6%)
<b>Alive</b>	
No	412 (64.1%)
Yes	231 (35.9%)
<b>3-year OS rate</b>	43.4%
<b>3-year CSS rate</b>	44.7%
<b>5-year OS rate</b>	33.1%
<b>5-year CSS rate</b>	34.3%

OS – overall survival; CSS – cancer-specific survival; SEER – Surveillance, Epidemiology, and End Results.

by four categories: axial (pelvis and spine; appendicular (long and short bones of the upper and lower extremities); rib, sternum, and clavicle, and; other locations (mandible, skull, and other atypical locations).

**Statistical analysis**

Statistical analysis was performed using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA) and SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). Overall survival (OS) was defined as the time from diagnosis to death from any cause and cancer-specific survival (CSS) was defined as the time from diagnosis to death due specifically to ES. The Kaplan-Meier method was used to draw the OS and CSS curves and calculate the median survival. Observations were statistically censored if the patient was alive at the time of the last follow-up. Univariate analysis was performed using the Kaplan-Meier method with the log-rank test. Variables with a P-value <0.05 from the univariate analysis were included from multivariate analysis. Multivariate analysis was used to determine

the independent predictors of OS and CSS with a Cox proportional hazards regression model. The hazard ratios (HR) and corresponding 95% confidence interval (CI) were used to show the effect of patient factors on OS and CSS. Differences were deemed statistically significant if the P-value was <0.05.

**Results**

**Clinical characteristics of 643 patients with metastatic Ewing's sarcoma (ES)**

In total, 643 patients with metastatic Ewing's sarcoma (ES) identified from the Surveillance, Epidemiology, and End Results (SEER) database were eligible for the study. In terms of primary tumor location, 34.5% of primary tumors were located in the extremities, 41.5% in the axial skeleton, and 14.2% in the rib, sternum, or clavicle. Information on the tumor size was available in 54% of the cases and was categorized based on the mean tumor size (10 cm). All patients underwent chemotherapy.

**Table 2.** Median survival data (in months) of patients with Ewing's sarcoma of bone and metastatic disease at presentation.

Category	Overall survival	95% CI	Cancer-specific survival	95% CI
<b>Overall</b>	29.0±1.9	25.2–32.8	29.0±2.1	24.9–33.1
<b>Age (years)</b>				
<20	33.0±2.7	27.7–38.3	34.0±2.7	28.6–39.4
≥20	21.0±1.9	17.2–24.8	22.0±3.2	15.7–28.3
<b>Gender</b>				
Female	34.0±4.6	25.0–43.0	36.0±5.4	25.5–46.5
Male	28.0±1.9	24.2–31.8	28.0±2.2	23.6–32.4
<b>Location</b>				
Appendicular	32.0±3.1	26.0–38.0	32.0±3.2	25.8–38.2
Axial	25.0±2.0	21.0–29.0	26.0±2.1	21.9–30.1
Rib, sternum and clavicle	57.0±10.9	35.7–78.3	57.0±11.7	34.2–79.8
Other locations	21.0±4.9	11.4–30.6	26.0±6.1	14.1–37.9
<b>Tumor size</b>				
<10 cm	43.0±8.1	27.2–58.8	47.0±14.3	18.9–75.1
≥10 cm	32.0±3.4	25.4–38.6	33.0±3.9	25.4–40.6
<b>Surgery</b>				
Yes	40.0±6.7	27.0–53.0	43.0±7.6	28.1–57.9
No	22.0±1.7	18.6–25.4	22.0±1.9	18.4–25.6
<b>Radiation treatment</b>				
Yes	32.0±2.3	27.6–36.4	34.0±2.4	29.3–38.7
No	23.0±2.4	18.3–27.7	26.0±2.3	21.4–30.6
<b>Local treatment</b>				
Surgery + radiation	41.0±8.1	25.1–56.9	41.0±8.0	25.4–56.6
Surgery only	39.0±14.7	10.2–67.8	50.0±16.3	18.0–82.0
Radiation only	28.0±3.0	22.1–33.9	28.0±3.3	21.5–34.5
No therapy	18.0±1.9	14.3–21.7	18.0±1.9	14.2–21.8

CI – confidence interval.

About one-third of the patients (37.8%) received local surgery and more than half (61.4%) received radiation treatment. There were 412 (64.1%) patients who died, and 387 patients died from metastatic ES. The 3-year and 5-year OS rates for the entire cohort were 43.4% and 33.1%, respectively. The 3-year and 5-year CSS rates were 44.7% and 34.3%, respectively (Table 1). The median OS and CSS were 29.0±1.9 and 29.0±2.1 months, respectively, indicating a poor prognosis for this cohort (Table 2).

#### Univariate analysis of variables associated with OS and CSS for patients with metastatic ES

Table 2 summarizes the median survival data, in months, for patients with ES of bone and metastatic disease at presentation.

Table 3 shows the results of Kaplan-Meier univariate survival analysis. Univariate analysis showed that gender and tumor size were not associated with OS or CSS. Younger patients had a significantly better outcome, with a longer median survival time, compared with older patients (Figures 2A, 3A). Patients with axial tumors had poorer outcomes than those with appendicular, rib, sternum, or clavicle tumors.

In terms of treatment, patients who underwent surgical treatment had a better OS and CSS than those who did not (Figures 2B, 3B). Radiation treatment significantly prolonged the OS of patients with ES who presented with metastasis. However, radiation treatment had no significant effect on CSS and the addition of radiation treatment did not significantly improve the OS and CSS of patients who underwent

**Table 3.** Univariate analysis of variables in patients with Ewing's sarcoma of bone and metastatic disease at presentation using the Kaplan-Meier method.

Category	Overall survival (log-rank p-value)	Cancer-specific survival (log-rank p-value)
<b>Age at diagnosis</b>	0.000	0.000
<b>Gender</b>	0.080	0.065
<b>Location</b>	0.003	0.008
Axial vs. appendicular	0.019	0.030
Axial vs. rib, sternum, and clavicle	0.001	0.003
Axial vs. other locations	0.639	0.792
Appendicular vs. rib, sternum and clavicle	0.222	0.186
Appendicular vs. other locations	0.055	0.113
Rib, sternum and clavicle vs. other locations	0.008	0.018
<b>Tumor size (&lt;10 cm vs. ≥10 cm)</b>	0.095	0.124
<b>Surgery</b>	0.000	0.000
<b>Radiation treatment</b>	0.048	0.067
<b>Local treatment</b>	0.000	0.000
Surgery + radiation vs. surgery only	0.706	0.966
Surgery + radiation vs. radiation only	0.004	0.008
Surgery + radiation vs. no therapy	0.000	0.000
Surgery only vs. radiation only	0.044	0.024
Surgery only vs. no therapy	0.000	0.000
Radiation only vs. no therapy	0.013	0.010

surgery (Figures 2C, 3C). The group treated with surgery or radiation therapy alone had considerably better outcomes when compared with the non-treated group (Figures 2C, 3C).

### Multivariate analysis of independent predictors of OS and CSS for patients with metastatic ES

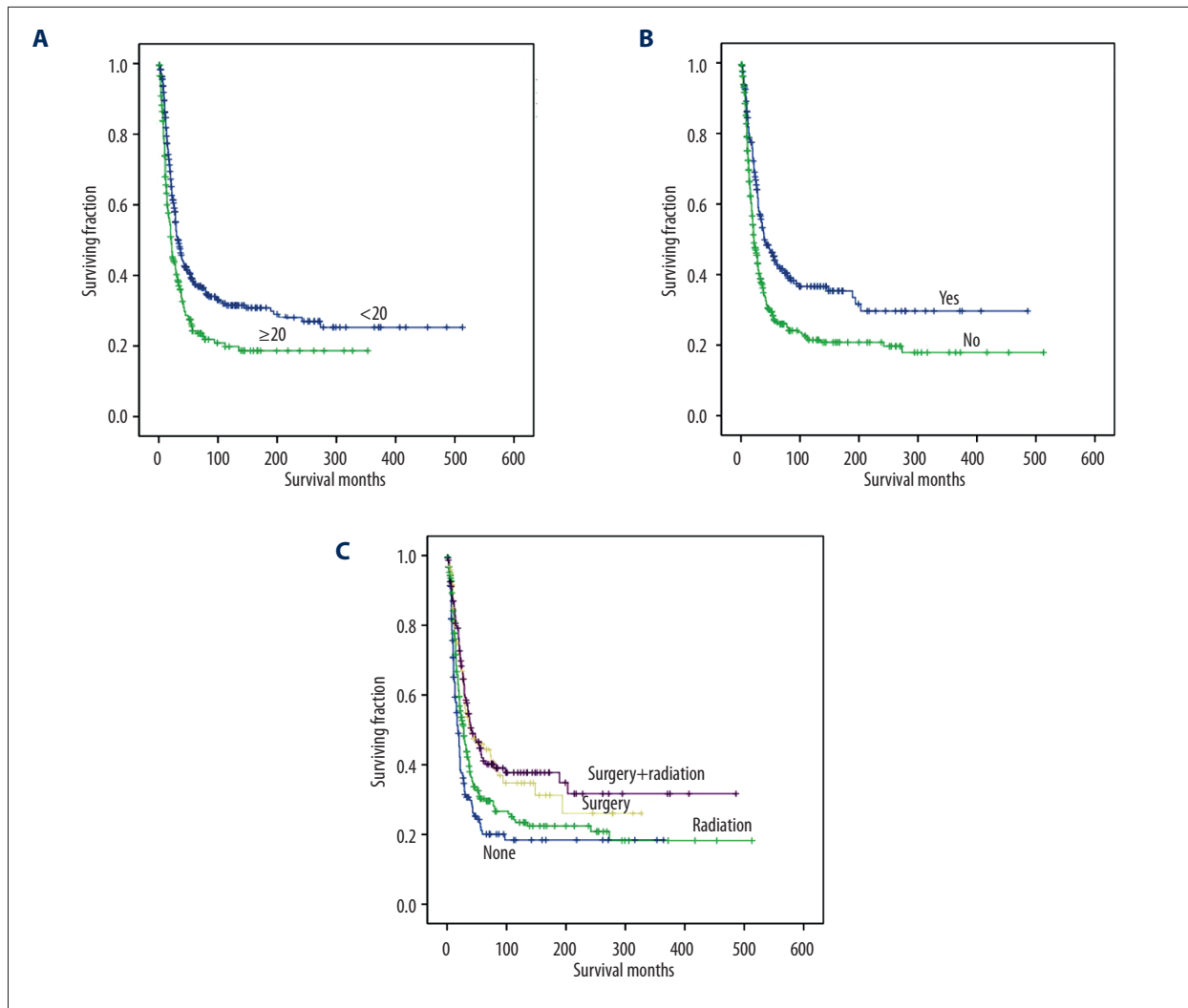
Multivariate analysis of all patients identified age at diagnosis and surgery for primary tumors to be independent predictors of OS and CSS. Multivariate analysis identified no significant difference in either OS or CSS based on tumor location and showed that radiation treatment was not an independent prognostic factor for OS (Table 4).

## Discussion

In childhood and adolescence, Ewing's sarcoma (ES) is the second most common primary sarcoma of bone and this tumor metastasizes to the lungs, bones, and other organs at an early stage [1,2]. Despite intensive treatment, patients with ES of bone and metastasis usually have a poor prognosis, with

a 5-year OS rate <30% [13–15]. The findings of the present study showed that the 5-year OS and CSS rates for the entire cohort were 30.9% and 37.6%, respectively. Therefore, there is a significant need to improve these clinical outcomes. Few studies have documented the prognosis of patients with metastatic primary ES of bone. To our knowledge, this study is the first to assess the demographic information with surgical and radiation treatment information of patients with metastatic primary ES of bone and to explore possible predictors of survival using the Surveillance, Epidemiology, and End Results (SEER) database.

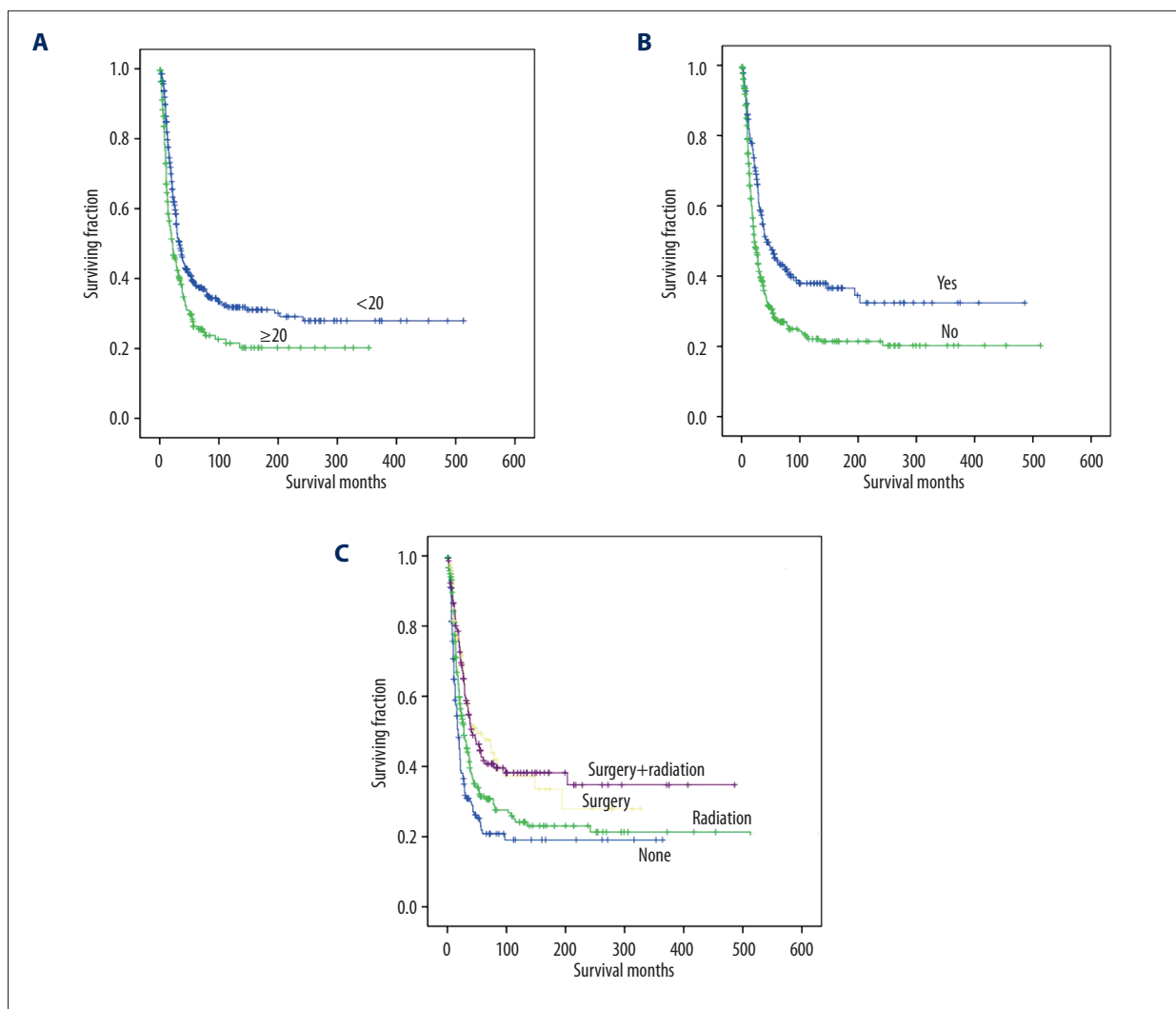
The mean and median age at diagnosis of this cohort was 20 and 17 years, respectively, with a male predominance (1.7: 1.0), which was similar to previously reported findings [3]. Univariate analysis of the cohort of patients studied showed that gender was not associated with significant differences in either OS or CSS, which was also supported by the findings of previous studies [3,8,16–18]. However, Bacci et al. [19] reported that female gender was an independent favorable prognostic factor for patients with non-metastatic ES. Several previously published studies have shown that young age at diagnosis



**Figure 2.** Kaplan-Meier plots of the overall survival (OS) in patients with primary Ewing's sarcoma of the bone and metastatic disease at presentation stratified by age, surgery, and radiation therapy. **(A)** OS in patients with primary Ewing's sarcoma of the bone and metastatic disease at presentation stratified by age (years) at diagnosis. **(B)** OS in patients with primary Ewing's sarcoma of the bone and metastatic disease at presentation stratified by treatment with surgery alone. **(C)** OS in patients with primary Ewing's sarcoma of the bone and metastatic disease at presentation stratified by treatment with surgery and radiation therapy.

was associated with improved patient prognosis [3,16–19]. Bacci et al. [19] reported that an age  $\leq 14$  years was an independent predictor of positive outcomes for patients with non-metastatic ES. The findings of the present study also showed that patient age  $\geq 20$  years was independently associated with decreased OS and CSS in patients with primary ES of bone with metastasis. Although age is an important prognostic factor for patients with ES, with or without metastasis at presentation, some recent studies have found age not to be a predictor of outcome for patients with ES, which has been attributed to the similar treatment of adults and children [20–22].

ES frequently presents as an axial mass, which was also the case for the cohort of patients in the present study [13,14]. An appendicular location of ES has previously been shown to be associated with a better outcome compared with an axial location [3]. In the present study, tumor location was significantly associated with both OS and CSS but was not an independent prognostic factor. Tumor size has been shown to be an important predictor of outcome in patients with ES [3,9,18,23]. Although the findings of the present study showed that tumor size was not associated with either OS or CSS, trends toward increased OS and CSS were observed for patients with tumor size  $< 10$  cm compared with patients with a tumor size  $\geq 10$  cm.



**Figure 3.** Kaplan-Meier plots of the cancer-specific survival (CSS) in patients with primary Ewing's sarcoma of the bone and metastatic disease at presentation stratified by age, surgery, and radiation therapy. **(A)** CSS in patients with primary Ewing's sarcoma of the bone and metastatic disease at presentation stratified by age (years) at diagnosis. **(B)** CSS in patients with primary Ewing's sarcoma of the bone and metastatic disease at presentation stratified by treatment with surgery alone. **(C)** CSS in patients with primary Ewing's sarcoma of the bone and metastatic disease at presentation stratified by treatment with surgery and radiation therapy.

Current treatment for ES arising in bone consists of systemic chemotherapy in addition to local control with surgical excision and/or radiation therapy. However, little is known about the optimal standard treatment for patients with ES of bone who have metastasis at presentation. Surgical resection is the main local treatment for patients with ES and can prolong survival [24]. In the cohort in the present study, surgical resection of the primary tumors also prolonged the survival of patients with ES who presented with metastasis. Also, in patients with metastasis, removing the primary tumor can reduce pain, improve quality of life, and prolong survival. Therefore, local surgery is an appropriate treatment for patients with metastatic ES. Raciborska et al. [25] reported that treatment of isolated lung

metastases may have a role in improving prognosis in patients with ES. Letourneau et al. [26] reported that resection of pulmonary metastases in pediatric patients with ES improved survival. Liu et al. [27] reported that radiation therapy for local control of metastatic sites was effective and tolerable in children with metastatic ES. Therefore, for these patients, both primary and metastatic lesions should be actively treated in order to maximize survival time.

Although ES is considered to be a radiosensitive tumor, radiation therapy is favored for central or unresectable tumors [28]. The effect of radiation therapy on the prognosis for metastatic ES is unclear. Previous studies have shown that patients with

**Table 4.** Multivariate analysis of overall survival (OS) and cancer-specific survival (CSS) for patients with primary Ewing's sarcoma of bone and metastatic disease at presentation.

Variable	Overall survival		Cancer-specific survival	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
<b>Age (years)</b>		0.001		0.001
<20	1		1	
≥20	1.396 (1.138–1.712)	0.001	1.416 (1.149–1.744)	0.001
<b>Location</b>		0.117		0.197
Appendicular	1		1	
Axial	1.214 (0.967–1.524)	0.095	1.180 (0.936–1.488)	0.162
Rib, sternum and clavicle	0.890 (0.642–1.233)	0.482	0.871 (0.618–1.227)	0.428
Other locations	1.284 (0.904–1.822)	0.162	1.240 (0.861–1.785)	0.248
<b>Surgery</b>		0.000		0.000
Yes	1		1	
No	1.477 (1.192–1.829)	0.000	1.501 (1.203–1.873)	0.000
<b>Radiation treatment</b>		0.095		–
Yes	1		–	
No	1.187 (0.970–1.453)	0.095	–	–

ES who received only radiation therapy as the local treatment, had significantly reduced OS and CSS compared with patients who underwent surgery alone [24,29,30], which is consistent with the findings of the present study. However, some studies have reported that radiation therapy alone improved local control and survival that was comparable to surgery [31–33]. In the present study, radiation therapy was not an independent predictor of OS and was not associated with CSS and patients who received local radiation therapy alone or no local treatment had the worst outcomes (Table 2) (Figures 2C, 3C). Also, the combination of surgery and radiation therapy appeared to be unnecessary as the addition of radiation treatment did not significantly improve the OS and CSS of patients with metastatic ES who underwent surgery (Table 3).

This study had several limitations. Data on other known prognostic factors for cancer survival, including the surgical method used and the use of neoadjuvant chemotherapy were not available in the database. Also, data indicating whether surgery was performed before or after chemotherapy was not available, and tumor size was only available for 54% of the patients. Despite these limitations, the SEER database provides important insights into rare cancers, including ES, and was an important resource for data on patients with primary ES of bone who presented with late-stage disease and tumor metastasis.

## Conclusions

To our knowledge, this was the largest population-based study that included patient demographics, clinical presentation, treatment, and clinical outcome to analyze the prognostic factors in patients with primary Ewing's sarcoma (ES) of bone and metastatic disease at diagnosis. The study included for 643 patients, and the 5-year overall survival (OS) and cancer-specific survival (CSS) rates were 33.1% and 34.3%, respectively. The median OS and CSS were 29.0±1.9 and 29.0±2.1 months, respectively. The independent predictors of both OS and CSS were age at diagnosis and surgical excision of the primary tumors. It is hoped that the findings for this study on the OS, CSS, and risk factors for patients with primary ES of bone who present with metastasis, will provide the basis for future research on ES and for the development of standardized treatment.

## Conflict of interest

None.



## References:

- Grier HE, Krailo MD, Tarbell NJ et al: Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med*, 2003; 348(8): 694-701
- Ginsberg JP, Goodman P, Leisenring W et al: Long-term survivors of childhood Ewing sarcoma: Report from the childhood cancer survivor study. *J Natl Cancer Inst*, 2010; 102(16): 1272-83
- Duchman KR, Gao Y, Miller BJ: Prognostic factors for survival in patients with Ewing's sarcoma using the surveillance, epidemiology, and end results (SEER) program database. *Cancer Epidemiol*, 2015; 39(2): 189-95
- Fizazi K, Dohollou N, Blay JY et al: Ewing's family of tumors in adults: Multivariate analysis of survival and long-term results of multimodality therapy in 182 patients. *J Clin Oncol*, 1998; 16(12): 3736-43
- Nesbit ME Jr., Gehan EA, Burgert EO Jr. et al: Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: A long-term follow-up of the First Intergroup Study. *J Clin Oncol*, 1990; 8(10): 1664-74
- Lee CY, Yen CC, Yen HJ et al: Outcomes of 50 patients with Ewing sarcoma family of tumors treated at a single institution in Taiwan. *Medicine*, 2016; 95(22): e3830
- Werier J, Yao X, Caudrelier JM et al: A systematic review of optimal treatment strategies for localized Ewing's sarcoma of bone after neo-adjuvant chemotherapy. *Surg Oncol*, 2016; 25(1): 16-23
- Arshi A, Sharim J, Park DY et al: Prognostic determinants and treatment outcomes analysis of osteosarcoma and Ewing sarcoma of the spine. *Spine J*, 2017; 17(5): 645-55
- Wan ZH, Huang ZH, Chen LB: Survival outcome among patients with Ewing's sarcoma of bones and joints: A population-based cohort study. *Sao Paulo Med J*, 2018; 136(2): 116-22
- Shoubash L, Nowak S, Vogelgesang S et al: Surgical management of an adult manifestation of Ewing sarcoma of the spine – a case report. *AME Case Rep*, 2018; 2: 34
- Womer RB, West DC, Krailo MD et al: Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: A report from the Children's Oncology Group. *J Clin Oncol*, 2012; 30(33): 4148-54
- Marco RA, Gentry JB, Rhines LD et al: Ewing's sarcoma of the mobile spine. *Spine*, 2005; 30(7): 769-73
- Balamuth NJ, Womer RB: Ewing's sarcoma. *Lancet Oncol*, 2010; 11(2): 184-92
- Krakovova DA, Kubackova K, Dusek L et al: Advantages in prognosis of adult patients with Ewing sarcoma: 11-years experiences and current treatment management. *Pathol Oncol Res*, 2018; 24(3): 623-30
- Gaspar N, Hawkins DS, Dirksen U et al: Ewing sarcoma: Current management and future approaches through collaboration. *J Clin Oncol*, 2015; 33(27): 3036-46
- Cotterill SJ, Ahrens S, Paulussen M et al: Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. *J Clin Oncol*, 2000; 18(17): 3108-14
- Serlo JA, Helenius IJ, Sampo M et al: Ewing's sarcoma family of tumors in Finland during 1990-2009: A population-based study. *Acta Oncol*, 2013; 52(4): 767-75
- Lee J, Hoang BH, Ziogas A, Zell JA: Analysis of prognostic factors in Ewing sarcoma using a population-based cancer registry. *Cancer*, 2010; 116(8): 1964-73
- Bacci G, Forni C, Longhi A et al: Long-term outcome for patients with non-metastatic Ewing's sarcoma treated with adjuvant and neoadjuvant chemotherapies. 402 patients treated at Rizzoli between 1972 and 1992. *Eur J Cancer*, 2004; 40(1): 73-83
- Martin RC 2<sup>nd</sup>, Brennan MF: Adult soft tissue Ewing sarcoma or primitive neuroectodermal tumors: Predictors of survival? *Arch Surg*, 2003; 138(3): 281-85
- Yamada K, Sugiura H, Takahashi M: Single center experience of treatment of Ewing's family of tumors in Japan. *J Orthop Sci*, 2006; 11(1): 34-41
- Verrill MW, Judson IR, Harmer CL et al: Ewing's sarcoma and primitive neuroectodermal tumor in adults: Are they different from Ewing's sarcoma and primitive neuroectodermal tumor in children? *J Clin Oncol*, 1997; 15(7): 2611-21
- Miller BJ, Gao Y, Duchman KR: Does surgery or radiation provide the best overall survival in Ewing's sarcoma? A review of the National Cancer Data Base. *J Surg Oncol*, 2017; 116(3): 384-90
- Biswas B, Rastogi S, Khan SA et al: Outcomes and prognostic factors for Ewing-family tumors of the extremities. *J Bone Joint Surg Am*, 2014; 96(10): 841-49
- Raciborska A, Bilka K, Rychlowska-Pruszyńska M et al: Management and follow-up of Ewing sarcoma patients with isolated lung metastases. *J Pediatr Surg*, 2016; 51(7): 1067-71
- Letourneau PA, Shackett B, Xiao L et al: Resection of pulmonary metastases in pediatric patients with Ewing sarcoma improves survival. *J Pediatr Surg*, 2011; 46(2): 332-35
- Liu AK, Stinauer M, Albano E et al: Local control of metastatic sites with radiation therapy in metastatic Ewing sarcoma and rhabdomyosarcoma. *Pediatr Blood Cancer*, 2011; 57(1): 169-71
- Ning MS, Perkins SM, Borinstein SC et al: Role of radiation in the treatment of non-metastatic osseous Ewing sarcoma. *J Med Imaging Radiat Oncol*, 2016; 60(1): 119-28
- Bacci G, Longhi A, Briccoli A et al: The role of surgical margins in treatment of Ewing's sarcoma family tumors: Experience of a single institution with 512 patients treated with adjuvant and neoadjuvant chemotherapy. *Int J Radiat Oncol Biol Phys*, 2006; 65(3): 766-72
- Becker RG, Gregianin LJ, Galia CR et al: What is the impact of local control in Ewing sarcoma: Analysis of the first Brazilian collaborative study group – EWING1. *BMC Cancer*, 2017; 17(1): 420
- Yock TI, Krailo M, Fryer CJ et al: Local control in pelvic Ewing sarcoma: Analysis from INT-0091 – a report from the Children's Oncology Group. *J Clin Oncol*, 2006; 24(24): 3838-43
- Dunst J, Jurgens H, Sauer R et al: Radiation therapy in Ewing's sarcoma: An update of the CESS 86 trial. *Int J Radiat Oncol Biol Phys*, 1995; 32(4): 919-30
- Scully SP, Temple HT, O'Keefe RJ et al: Role of surgical resection in pelvic Ewing's sarcoma. *J Clin Oncol*, 1995; 13(9): 2336-41