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Pediatric Axial Ewing Sarcoma: A Retrospective Population-Based Survival Analysis

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ABSTRACT

Introduction: Ewing sarcomas of the axial skeleton represent a notable challenge for clinicians because of their aggressive presentation and tendency to obstruct neurovascular structures; however, little data exist regarding axial tumors in children. This study is the first population-based analysis assessing treatment regimens for axial Ewing sarcomas and their effects on cancer-specific survival and overall survival (OS).

Methods: Data from 2004 to 2019 were collected for all patients aged 1 to 24 years from the Surveillance, Epidemiology, and End Results (SEER) database. Primary groups included pelvic tumors, thoracic tumors, and vertebral tumors. Chi-squared and Kaplan-Meier tests were used to assess associations between demographic variables, clinical and treatment characteristics, and patient survival.

Results: Pelvic tumors were most common, and 49.7% received chemotherapy/radiation. Vertebral tumors were least common, and 56.7% received chemotherapy/surgery/radiation. 53.5% of thoracic tumors received chemotherapy/surgery. Surgery was most common for thoracic tumors (80.2%) and rare for pelvic tumors (38.9%). Radiation therapy was most common for vertebral tumors (83.6%) and least common for thoracic tumors (36.0%). Pelvic tumors exhibited the lowest OS (1-year, 5-year, and 10-year OS: 96%, 70%, and 59%), followed by thoracic tumors (1-year, 5-year, and 10-year OS: 97%, 79%, and 66%) and vertebral tumors (1-year, 5-year, and 10-year OS: 92%, 77%, and 68%).

Conclusion: This study underpins the importance of both early detection and chemotherapy-based multimodal therapy in the treatment of axial Ewing sarcoma in a pediatric population. A comparatively large decline in OS was observed between 5 and 10 years for patients with thoracic tumors, and this cohort's 10-year OS has not improved when compared with a similar SEER cohort from 1973 to 2011. Despite a growing body of research supporting definitive radiation therapy, a notable portion of patients with pelvic Ewing sarcoma did not receive radiation, representing an unmet need for this population.

Ewing sarcoma is a malignant musculoskeletal tumor of bone or the soft tissues that most often affects the diaphysis of long bones. The peak incidence of Ewing sarcoma is in the first two decades of life. However, it can also present in later adulthood, where it more commonly presents as a paravertebral mass of the deep soft tissue.[1,2] At presentation, it has been estimated that 20% to 25% of Ewing sarcomas have metastasized and are therefore resistant to even the most aggressive treatment options. When presenting with localized disease, the 5-year survival rate is around 75%. However, metastasis at presentation drops the survival rate to less than 30%.[3] Outcomes can be especially poor for primary tumors of the axial skeleton because of their tendency to be larger, metastasize earlier, and be histologically resistant to chemotherapy. Furthermore, axial tumors are more difficult to treat with radiation and/or surgery because the axial skeleton is essential for structural support of the body, and several vital neurovascular structures traverse the locations at which primary tumors tend to present.[4,5] Literature on Ewing sarcoma of the axial skeleton is sparse, and this is the first study to compare axial tumors across multiple sites in a pediatric and young adult population.

Previous population database research has revealed demographic differences in the incidence and mortality of patients diagnosed with Ewing sarcoma. Specifically, Caucasian patients were markedly more affected, with an incidence almost twice that of the next most affected demographic, Asian/Pacific Islanders (0.155 versus 0.082, respectively from 2004 to 2019). There also appeared to be a survival benefit for women of Caucasian descent; however, this survival benefit has not been identified in women of other racial backgrounds.[6] This study, however, looked broadly at all Ewing sarcoma cases within a specific date range, not those that are specifically axial in terms of anatomic location. Research that has focused on axial presentations of Ewing sarcoma has primarily studied interventions in a specific anatomic region (such as pelvic and lower extremity), with the most common being localized pelvic primary Ewing sarcoma.[7,8]

This study focuses on three primary axial anatomic locations of Ewing sarcoma: vertebral column, rib/sternum/clavicle/associated joints, and pelvis/sacrum/coccyx/associated joints. The aim of this study is twofold: (1) analyze the most common treatment regimens used to treat local and regional Ewing sarcoma by primary location and (2) compare the treatment and survival data of axial Ewing sarcoma and compare them with data reported in the literature.

Methods

Source of Data

The US population-based Survival, Epidemiology, and End Results 18 (SEER-18) database of the National Cancer Institute was used.[9] SEER-18 collects demographic and survival data from 18 population-based regional cancer registries with a catchment of approximately 28% of the US population and has been widely used in sociodemographic and survival analyses.[10,11]

Patient Selection

Patients aged 1 to 24 years who were diagnosed with primary Ewing sarcoma of the axial skeleton between 2004 and 2019 were selected from the SEER-18 database. Twenty-four years was chosen as the upper limit of the cohort because of a lack of consensus on the age interval for the peak incidence of Ewing sarcoma. The International Classification of Disease for Oncology, Third Edition (ICD-O-3) codes were used to identify Ewing bone tumors by histologic subtype (9260, 9364-9365, 9473). Axial skeleton included the vertebral column; rib, sternum, clavicle, and associated joints; and pelvic bones, sacrum, coccyx, and associated joints. Patients with unknown survival time or race were excluded. In addition, patients with more than one primary malignancy, or a first malignancy other than Ewing sarcoma, were excluded.

Patient demographic variables including age, race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian or Pacific Islander, non-Hispanic American Indian, and Hispanic), median household income, and geographic density were collected. Biologic race variables in SEER consist of White, Black, Asian, Pacific Islander, and Native American. Race variables were further stratified by cultural ethnicity, which consists of Hispanic or non-Hispanic. The median household income was categorized into $<$ \$35,000, \$35,001 to \$75,000, or $>$ \$75,001. Notably, the median household income refers to the median for that county, not each individual household. Counties designated as 'nonmetropolitan not adjacent to a metropolitan area' with $\leq$ 50,000 population were considered rural, counties in large metropolitan areas with $\geq$ 1 million population were considered urban, and all other counties were considered medium/small metropolitan area per the 2013 census classification. [12] Clinical and pathological variables collected included treatment with surgery,

radiation, and/or chemotherapy; tumor size; and stage at diagnosis. Tumor size was categorized into either ≥ 8 cm or < 8 cm based on previously published analyses.[6]

Statistical Analysis

For each variable, patients with unknown data were excluded from the analysis. Cancer-specific survival and overall survival were compared between groups using Kaplan-Meier survival curves and the log-rank test. CSS refers to deaths in the absence of an underlying cause other than cancer. OS refers to all-cause deaths. Univariate and multivariate Cox proportional hazards models were developed to assess the effect of demographic and clinicopathological variables on CSS and OS. All tests were 2-tailed, and P values ≤ 0.05 were deemed statistically significant. All statistical analyses were conducted using IBM SPSS Statistics 27 (IBM Corp, Armonk) software. Analysis took place in May 2023.

Results

Study Characteristics

A total of 310 patients aged 1 to 24 years who were diagnosed with primary Ewing sarcoma of the axial skeleton between 2004 and 2019 were included. Separating the patients into age groups, it was found that 6.1% were between 1 and 4 years, 16.5% were between 5 and 9 years, 32.3% were between 10 and 14 years, 27.7% were 15 to 19 years, and 17.4% were 20 to 24 years. The sample was 60.3% male (n = 187) and 39.7% female (n = 123; Table 1). When separated by racial/ethnic background, the sample consisted of 59.4% non-Hispanic White, 28.7% Hispanic, 7.7% Asian, 2.6% Black, 1.3% American Indian/Alaska Native, and 0.3% unknown. 57.4% of patients resided in urban areas, 31.0% in suburban areas, 11.0% in rural areas, and 0.6% had residential statuses that were unknown. When stratified by median household income, 36.1% of patients lived in a county with an average annual household income > $75,000, 63.2% between $35,000 and $75,000 annually, and 0.6% lived in a county with a median annual household income below $35,000 (Table 1). No notable associations were observed between tumor location and age, sex, race, geographic density, or median household income.

Disease Presentation

Tumors of the pelvis/sacrum/coccyx/associated joints were the most common site of primary presentation (n = 157), followed by tumors of the rib/sternum/clavicle/associated joints (n = 86) and vertebral column (n = 67). When considering tumor staging at presentation (local versus regional), a chi-squared test found a significant association between the two variables ($P < 0.001$). Specifically, tumors of the vertebral column were more likely to be local at presentation, whereas tumors of the pelvis/sacrum/coccyx/associated joints or rib/sternum/clavicle/associated joints were more likely to be regional (Table 1). A notable relationship between tumor site and size also existed, such that tumors of the pelvis/sacrum/coccyx/associated joints were more likely to be larger than 8 cm at presentation, whereas tumors of the vertebral column and rib/sternum/clavicle/associated joints were more likely to be smaller than 8 cm ($P < 0.001$; Table 1).

Disease Treatment Characteristics

Treatment modality used for each patient consisted of chemotherapy, radiation, surgery, or some combination of the three. Multimodal therapy was nearly ubiquitous, with 91.9% of patients receiving multimodal therapy, and chemotherapy was a staple treatment for all patients, with 96.7% of patients being treated with chemotherapy. Unimodal treatment was uncommon, with only 8.1% (n = 25) of all patients receiving a single treatment modality (Table 1). Of those receiving unimodal treatment, chemotherapy alone for tumors of the pelvis/sacrum/coccyx/associated joints was most common (n = 16) (Table 1). Among multimodal treatment regimens, chemotherapy combined with radiation was the most common (n = 104), followed by triple therapy consisting of chemotherapy, radiation, and surgery (n = 93) and combined surgery and radiation (n = 80; Table 1). When separated by tumor location, triple therapy was most common for vertebral tumors (n = 38, 56.7%), surgery plus chemotherapy was most common for tumors of the rib/sternum/clavicle/associated joints (n = 46, 53.5%), and chemotherapy plus radiation was most common for tumors of the pelvis/sacrum/coccyx/associated joints (n = 78, 49.7%; Table 1). Seven patients received no treatment, with a median survival of 47 months, potentially due to poor prognosis at initial presentation (range: 1 to 128 months).

When considering cases where surgical intervention was used, significant associations existed between the type of treatment used and the location of the tumor ($P < 0.001$). Tumors of the pelvis/sacrum/coccyx/associated joints were far less likely to be operated on, with 61.1% of these cases receiving no surgery at all, compared with 31.3% of vertebral column tumors and 19.8% of tumors of the rib/sternum/clavicle/associated joints. Surgical intervention of vertebral column tumors was most commonly partial excisions (26.9%) or local tumor destructions (25.4%) while tumors of the rib/sternum/

Table 1. Study Characteristics

	Vertebral Column	%	Rib/Sternum/Clavicle Associated Joints	%	Pelvic Bones/Sacrum/ Coccyx/Associated Joints	%
Overall	67	21.60%	86	27.70%	157	50.60%
Age						
1-4 years	5	7.5%	5	5.8%	9	5.7%
5-9 years	14	20.9%	17	19.8%	20	12.7%
10-14 years	25	37.3%	21	24.4%	54	34.4%
15-19 years	13	19.4%	28	32.6%	45	28.7%
20-24 years	10	14.9%	15	17.4%	29	18.5%
Year						
2004-2011	36	53.7%	42	48.8%	93	59.2%
2012-2019	31	46.3%	44	51.2%	64	40.8%
Sex						
Male	39	58.2%	53	61.6%	95	60.5%
Female	28	41.8%	33	38.4%	62	39.5%
Race						
Hispanic	21	31.3%	24	27.9%	44	28.0%
NH White	41	61.2%	47	54.7%	96	61.1%
NH Black	0	0.0%	3	3.5%	5	3.2%
NH Asian	3	4.5%	9	10.5%	12	7.6%
NH AI/AN	2	3.0%	2	2.3%	0	0.0%
Unknown	0	0.0%	1	1.2%	0	0.0%
Geographic density						
Urban	37	55.2%	50	58.1%	91	58.0%
Suburban	19	28.4%	27	31.4%	50	31.8%
Rural	9	13.4%	9	10.5%	16	10.2%
Unknown	2	3.0%	0	0.0%	0	0.0%
Income		0.0%				
<$35,000	1	1.5%	0	0.0%	1	0.6%
$35,000-$75,000	43	64.2%	60	69.8%	93	59.2%
>$75,000	23	34.3%	26	30.2%	63	40.1%
Stage						
Local	38	56.7%	37	43.0%	42	26.8%
Regional	29	43.3%	49	57.0%	115	73.2%
Tumor size						
<8 cm	36	53.7%	46	53.5%	49	31.2%
>8 cm	6	9.0%	30	34.9%	69	43.9%
Unknown	25	37.3%	10	11.6%	39	24.8%

(*continued*)

Table 1. (*continued*)

	Vertebral Column	%	Rib/Sternum/Clavicle Associated Joints	%	Pelvic Bones/Sacrum/ Coccyx/Associated Joints	%
Treatments						
Surgery in some form	46	68.7%	69	80.2%	61	38.9%
Chemotherapy in some form	64	95.5%	81	94.2%	155	98.7%
Radiation in some form	56	83.6%	31	36.0%	111	70.7%
Treatment regimen						
Surgery	1	1.5%	1	1.2%	0	0.0%
Chemotherapy	3	4.5%	4	4.7%	16	10.2%
Radiation	0	0.0%	0	0.0%	0	0.0%
Surgery + chemotherapy	6	9.0%	46	53.5%	28	17.8%
Surgery + radiation	1	1.5%	0	0.0%	0	0.0%
Chemotherapy + radiation	17	25.4%	9	10.5%	78	49.7%
Chemotherapy + surgery + radiation	38	56.7%	22	25.6%	33	21.0%
No treatment	1	1.5%	4	4.7%	2	1.3%

clavicle/associated joints were most often surgically treated with radical excision or resection of lesion with limb salvage (51.2%; Table 2). Major amputations were almost exclusively used for tumors of the pelvis/sacrum/coccyx/associated joints, which accounted for 16 of the 17 cases treated with this modality. The only other major amputation occurred in a tumor of the rib/sternum/clavicle/associated joints (Table 2).

Cancer-Specific Survival by Primary Tumor Location

Analysis of cancer-specific survival and overall survival yielded multiple results of statistical significance ($P < 0.05$). Geographically, patients living in suburban areas had the best outcomes based on both CSS and OS. No significant differences existed in survival rates among race, age, or sex demographics. However, a greater OS rate approached significance for women than for men (77.2% versus 66.3%, $P = 0.057$; Table 3). Tumors that were local also had better outcomes for both CSS (80.3%) and OS (79.5%) when compared with regional tumors (Table 4). The size of the tumor did not influence either survival statistics. Three of the treatment modalities used demonstrated markedly worse outcomes for their patients. Overall survival for two patients receiving exclusively surgical intervention was 0%, a notable disparity from the 70.4% OS for those receiving no surgery or surgery combined with another treatment modality (Table 4). Another treatment modality that showed a 0% survival, in both CSS and OS, was surgery combined with radiation, which was also notable. It is important to note, however, that only one patient received this treatment combination. Finally, chemotherapy combined with radiation demonstrated worse cancer-specific and overall survival rates, 62.5% for both statistics. This is compared with a CSS of 75.7% and OS of 74.8% for those not receiving combined chemotherapy and radiation (Table 4).

The overall survival rate was greater than 90% for all patients included in the study at the conclusion of the study interval in 2019. The greatest one-year OS rate was among tumors of the rib/sternum/clavicle/associated joints at 97%. Tumors of the vertebral column had the lowest one-year survival at 92%. OS across all tumor locations was 90% at 5 years and 78% at 10 years. Tumors of the pelvis/sacrum/coccyx/associated joints had the worst CSS at 5 and 10 years, 70% and 59%, respectively (Table 5).

Discussion

The poor prognosis of axial Ewing sarcoma necessitates continued research on common treatments and their effect on patient survival. Although it most frequently

Table 2. Surgical Characteristics

	Vertebral Column	%	Rib/Sternum/Clavicle/ Associated Joints	%	Pelvic Bones/Sacrum/ Coccyx/Associated Joints	%
No surgery	21	31.3%	17	19.8%	96	61.1%
Local tumor destruction or excision	17	25.4%	11	12.8%	8	5.1%
Partial excision	18	26.9%	13	15.1%	10	6.4%
Radical excision or resection of lesion with limb salvage	10	14.9%	44	51.2%	26	16.6%
Major amputation	0	0.0%	1	1.2%	16	10.2%
Surgery, unknown procedure	1	1.5%	0	0.0%	1	0.6%

presents in the diaphysis of long bones, 13% of primary Ewing sarcoma tumors originate in the axial skeleton.[13] This analysis has two primary objectives: (1) determine the frequency with which different treatment modalities are used in the treatment of various axial presentations of pediatric Ewing sarcoma and (2) determine which treatment modalities/regimens confer notable advantages in cancer-specific survival and overall survival.

The current standard of care for treating localized Ewing sarcoma involves chemotherapy, ideally

Table 3. Tumor Characteristics and Demographic Survival Outcomes

	CSS	*p*	OS	*p*
Age	—	0.082	—	0.175
1-4 years	94.70%	—	89.50%	—
5-9 years	76.50%	—	74.50%	—
10-14 years	72.00%	—	72.00%	—
15-19 years	67.40%	—	67.40%	—
20-24 years	63.00%	—	63.00%	—
Year	—	0.836	—	0.941
2004-2011	63.20%	—	62.60%	—
2012-2019	81.30%	—	80.60%	—
Sex	—	0.080	—	0.057
Male	67.40%	—	66.30%	—
Female	77.20%	—	77.20%	—
Race	—	0.292	—	0.268
Hispanic	70.80%	—	68.50%	—
NH White	72.30%	—	72.30%	—
NH Black	50.00%	—	50.00%	—
NH Asian	75.00%	—	75.00%	—
NH AI/AN	50.00%	—	50.00%	—
Geographic density	—	0.011	—	0.010
Urban	70.80%	—	69.70%	—
Suburban	75.00%	—	75.00%	—
Rural	67.60%	—	67.60%	—

OS = overall survival

Table 4. Cancer-Specific Survival and Overall Survival by Tumor/Treatment Characteristics

	CSS	*P*	OS	*P*
Primary Site	—	0.351	—	0.507
Vertebral column	73.10%	—	73.10%	—
Rib, sternum, clavicle, and associated joints	77.90%	—	75.60%	—
Pelvic bones, sacrum, coccyx, and associated joints	66.90%	—	66.90%	—
Stage	—	0.005	—	0.006
Local	80.30%	—	79.50%	—
Regional	65.80%	—	65.30%	—
Tumor size	—	0.127	—	0.173
<8 cm	75.60%	—	74.80%	—
>8 cm	63.80%	—	63.80%	—
Unknown	74.30%	—	73.00%	—
Surgery + chemotherapy + radiation	0.34	—	0.274	—
Yes	73.10%	—	73.10%	—
No	70.50%	—	69.60%	—
Surgery only	—	0.403	—	0.022
Yes	50.00%	—	0.00%	—
No	71.40%	—	71.10%	—
Chemotherapy only	—	0.695	—	0.650
Yes	73.90%	—	73.90%	—
No	71.10%	—	70.40%	—
Surgery + chemotherapy	—	0.096	—	0.122
Yes	78.80%	—	77.50%	—
No	68.70%	—	68.30%	—
Surgery + radiation	<0.001	—	<0.001	—
Yes	0.00%	—	0.00%	—
No	71.50%	—	70.90%	—
Chemotherapy + radiation	0.006	—	0.009	—
Yes	62.50%	—	62.50%	—
No	75.70%	—	74.80%	—
No treatment	—	0.259	—	0.254
Yes	100.00%	—	100.00%	—
No	70.60%	—	70.00%	—

OS = overall survival

neoadjuvant chemotherapy, designed to reduce primary tumor volume as well as treat any subclinical micrometastatic disease.[14,15] While there are multiple chemotherapy regimens that have been shown to treat Ewing sarcoma, the standard in the United States consists of alternating cycles of vincristine/doxorubicin/cyclophosphamide (VDC) and ifosfamide/etoposide (VDC/IE) administered with a hematopoietic growth factor such as filgrastim.[16] The two primary considerations for surgical treatment are involvement of essential local neurovasculature and postoperative biomechanical stability. Tumors of more expendable osseous structures, such as the ribs, are generally more amenable to surgical treatment when compared with a

Table 5. 1-Year, 5-Year, and 10-Year Overall Survival by Tumor Location

Location	1-Year OS	5-Year OS	10-Year OS
Vertebral column	92.0%	77.0%	68.0%
Rib, sternum, clavicle, and associated joints	97.0%	79.0%	66.0%
Pelvic bones, sacrum, coccyx, and associated joints	96.0%	70.0%	59.0%

OS = overall survival

biomechanical keystone such as the pelvis. After tumor resection, patients can be treated with adjuvant chemotherapy and/or radiation therapy when clinically appropriate. Radiation therapy can also be used for local treatment in tumors that are deemed to be inoperable.[17] In some instances, radiation therapy can be used as a neoadjuvant agent.

An uncommon and highly pathological presentation is primary Ewing sarcoma of vertebral origin, which is reported to account for approximately 10% of Ewing tumors.[18] This analysis of SEER data shows it to be the least common variety of Ewing sarcoma of the axial skeleton, accounting for just 21.6% of tumors.[13] It is important to note that for the sake of this study, vertebral tumors were considered tumors of the cervical, thoracic, or lumbar spine. Sacral tumors are grouped with pelvic and coccygeal tumors because of their relatively frequent coexistence and will be discussed accordingly. The first line of treatment for Ewing sarcoma of the spine should begin with multiagent chemotherapy. Our analysis mirrors this sentiment with 95% of all patients in this cohort having received chemotherapy. The primary exception to beginning treatment with multimodal chemotherapy would be when a tumor is causing epidural compression of the spinal cord with neurological symptoms, in which case, radiation or, less likely, surgical decompression may first be performed despite the risk of local contamination with the latter.[19] That being said, a Scandinavian analysis found that emergency epidural decompression was not associated with increased postoperative neurological recovery.[20] This analysis showed that just 46 patients with vertebral tumors (68.7%) were treated surgically, and this was the lowest percentage of any treatment modality. Of these 46 patients, 38 received both chemotherapy and radiation in addition to surgical treatment. When vertebral tumors are amenable to resection after chemotherapy, patients with vertebral tumors tend to undergo either local tumor destruction/excision or partial excision. These two categories accounted for surgical treatment in 76.1% of patients who were treated surgically. Previous analyses of all patients with vertebral Ewing sarcoma report 5-year overall survival estimates of 63% and 64%.[20,21] A single-center study of nonmetastatic patients with spinal or paraspinal Ewing sarcoma found the 5-year OS to be 85%.[22] However, this study included 7 of 32 paraspinal tumors that incorporated extraskeletal Ewing sarcomas and paraspinal rib Ewing sarcomas, both of which are documented to have favorable OS.[23] With this in mind, the 5-year OS of 77% in this study is superior to that of metastatic patients and inferior to that of a cohort of patients with a superior baseline OS. This is the first study to produce survival data for patients with localized skeletal Ewing sarcoma of the spine.

Primary Ewing sarcoma of the rib/sternum/clavicle/associated joints accounts for 27.7% of tumors included in this analysis. Primary tumors are rare in these anatomic locations with literature citing incidence of sternal tumors as 1% of all Ewing diagnoses and the incidence of rib tumors as 10 to 15%.[24,25] The difference in incidence between the literature and this analysis can likely be attributed to a proportionally higher percentage of patients with pelvic primary tumors being excluded because of metastatic presentation. While this cohort was treated with chemotherapy at a similar rate to the other cohorts, there was notable variance in the frequency of both chemotherapy and radiation therapy. Only 36.0% of patients in this cohort were treated with radiation therapy. This is markedly lower than the two other cohorts and is due, in part, to the elevated risk of postradiation complications in other vital structures within the thoracic cavity. That being said, adjuvant radiation is still indicated for patients with positive surgical margins. This cohort also had the greatest percentage of patients who were treated surgically, with the most common operation being 'radical excision or resection of the lesion with limb salvage' in 51.2% of patients. Given these findings, it is not surprising that the most common treatment regimen in this cohort is chemotherapy combined with surgical treatment. If these tumors are more amenable to treatment with

neoadjuvant chemotherapy, resection with negative margins, and no need for adjuvant radiation, why is the 10-year OS so low? Previous analyses have found 5-year OS in patients with thoracic Ewing sarcoma to be as low as 58.7% and as high as 75%.[15,26-30] An analysis of a cohort of nonmetastatic patients at the University of Florida produced a 5-year OS of 78.9%.[31] The 5-year OS in this analysis is consistent with this previously mentioned single-study analysis with a 5-year OS of 79% over a similar period. From 5 years to 10 years, however, OS decreases to 66%. This 13% decrease is the largest in this study. An analysis of SEER data on nonmetastatic chest wall tumors reported 65% 10-year OS between 1973 and 2011. Comparing the 10-year OS between these two cohorts shows no evidence of improved patient survival over time. This could be attributed to stagnation in therapy or a lack of increasingly early diagnoses; however, additional investigation will be necessary to identify a specific etiology. Although this same study did not report 5-year OS for a nonmetastatic cohort, it did report 60% 5-year OS and 55% 10-year OS for all patients with thoracic Ewing sarcoma (including metastatic). While these cohorts are not identical, this finding warrants additional investigation because a 5% decrease in survival is markedly lower than the 13% present in this analysis.

Primary Ewing sarcoma of the pelvis accounts for approximately 25% of Ewing diagnoses and is notorious for being associated with poor outcomes. [32] For the sake of this study, pelvic tumors were grouped with tumors of the coccyx, sacrum, and associated joints such as the sacroiliac joint. The reason for such poor outcomes in this cohort has been attributed to the frequency with which it presents at later stages. [32] This analysis confirms this attribution because this cohort showed statistical significance ($P < 0.001$) in the stage at presentation with the highest percentage of patients with regional disease (73.2%) and the lowest percentage with localized disease (26.8%). This cohort also presented with the greatest percentage of tumors with a diameter > 8 cm (43.9%). This finding was both statistically significant ($P < 0.001$) and consistent with the current literature.[33] Chemotherapy was received by virtually every patient in this cohort, with the only two instances of patients not being treated with chemotherapy being in cases in which no treatment was received. The treatment of Ewing sarcoma of the pelvis/sacrum/coccyx/associated joints is complicated by tumors that are frequently inoperable. Even when these tumors are deemed amenable to surgical treatment, patients can often expect notable postoperative functional deficits because of either impaired hip mobility or major amputation.[33] For the 38.9% of patients in this cohort who were treated surgically, 42.6% received complete resection with limb salvage and 26.2% were treated with major amputations. While it is ideal to treat pelvic tumors with neoadjuvant chemotherapy/surgery, there is a growing body of research supporting the use of definitive radiation therapy in treating inoperable tumors or in lieu of surgical treatment for tumors in locations, such as the sacrum, which are associated with high morbidity.[34-36] Given the notable amount of literature that endorses the efficacy of radiation therapy in this cohort as well as continued improvements in radiation delivery mechanisms, it is peculiar that only 70.7% of patients received radiation therapy.[8,34,37] In the last decade, focus has shifted away from the surgical treatment of axial/pelvic tumors and toward radiation with most of the supporting data having been published since 2017.[34-36] Given that a SEER study from 2004 to 2015 reported 67.6% of all pelvic tumors (including metastatic) received radiation, it is likely that this statistic will continue to trend upward.[32] Regardless, future analyses will be necessary to follow the large-scale trend in the use of radiation in this cohort, specifically the efficacy of modern techniques like stereotactic radiation. For nonmetastatic pelvic Ewing sarcoma, the current literature cites a 5-year OS of 40.7% from 1977 to 2009 and an analysis of SEER data between 2004 and 2015 reported 65.3%.[32,38] This analysis further builds upon this trend, reporting a 5-year OS of 70%. Figures for 10-year OS follow a similar trend with 36.2% from 1977 to 2009, 55.7% from 2004 to 2015, and now 59% from 2004 to 2019.[32,38] These numbers suggest continuous improvement in the prognosis of the most lethal subtype of Ewing sarcoma.

There are multiple prognostic factors for Ewing sarcoma that have been identified in the current literature. These include age, sex, localization, primary tumor size/volume, metastasis, baseline hemoglobin, baseline lactate dehydrogenase, and treatment regimen.[39,40] In terms of demographic prognostic factors, this analysis found cancer-specific survival benefits to be associated with geographic density ($P = 0.011$) and tumor stage ($P = 0.005$). Patients inhabiting suburban regions experienced the highest CSS and patients from rural regions experienced the lowest CSS. Patients with regional disease showed decreased CSS relative to patients with local disease. One notable divergence from the prognostic factors identified in the literature is the lack of significance associated with tumor size at presentation ($P = 0.127$), age ($P = 0.082$), and sex ($P =$

0.080). A total of three treatment modalities were found to have a notable relationship with CSS/OS. Two of these three (surgery only and surgery/radiation) are statistical artifacts because of the very small number of patients who received them. Patients who were treated with chemotherapy and radiation experienced markedly worse CSS and OS than patients who did not. This, however, reflects less on the efficacy of the treatment modality itself and more on the disease presentations for which it is typically used. This is evidenced by the fact that 78 of the 104 patients treated with this regimen were in the pelvic cohort.

This study is limited by the typical constraints associated with retrospective studies conducted with data from national data registries. There is no standardization of procedures for data collection/reporting, treatment, and follow-up between treatment facilities. In addition, it is not possible to address treatment questions related to specific chemotherapy agents, surgical margins, and goal of radiation therapy (palliative or curative). Another piece of data that is absent from SEER is information pertaining to tumor differentiation as well as cytologic and genetic characteristics of tumors. The overall broad scope of SEER treatment data prohibits precise conclusions or recommendations regarding specific regimens. This is a retrospective analysis that must be corroborated and expanded upon by future prospective studies to further shape clinical practice. Despite these limitations, the population-based data found in SEER incorporate national data, which makes the results of this study broadly applicable to the US population.

Conclusion

This review reinforces the importance of early detection and treatment while providing surgeons with a detailed account of how axial Ewing sarcoma has been surgically treated since 2004. The data show that chemotherapy-based multimodal therapy produces optimal outcomes for young patients with Ewing sarcoma of the axial skeleton. Survival data for thoracic tumors were consistent with the current literature but showed a concerning decrease between 5-year and 10-year OS and failed to show improved 10-year OS compared with the same SEER cohort from 1973 to 2011. Pelvic tumors experienced the lowest survival and had a notable percentage of patients who were not treated with radiation therapy despite the notoriously poor prognosis and the growing body of literature in support of definitive radiation in this cohort. Future analyses of national population-based data will be important to continue monitoring treatment trends and outcomes for this cohort and all patients diagnosed with Ewing sarcoma.

References

1. Zöllner SK, Amatruda JF, Bauer S, et al.: Ewing sarcoma-diagnosis, treatment, clinical challenges and future perspectives. *J Clin Med* 2021;10:1685.

2. Sbaraglia M, Righi A, Gambarotti M, Dei Tos AP: Ewing sarcoma and Ewing-like tumors. *Virchows Archiv: Int J Pathol* 2020;476:109-119.

3. Esiashvili N, Goodman M, Marcus RB Jr: Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End Results data. *J Pediatr Hematol Oncol* 2008;30:425-430.

4. Meazza C, Luksch R, Luzzati A: Managing axial bone sarcomas in childhood. *Expert Rev Anticancer Ther* 2021;21:747-764.

5. Hesla AC, Papakonstantinou A, Tsagkozis P: Current status of management and outcome for patients with ewing sarcoma. *Cancers (Basel)* 2021;13:1202.

6. Jawad MU, Cheung MC, Min ES, Schneiderbauer MM, Koniaris LG, Scully SP: Ewing sarcoma demonstrates racial disparities in incidence-related and sex-related differences in outcome: An analysis of 1631 cases from the SEER database, 1973-2005. *Cancer* 2009;115:3526-3536.

7. Muratori F, Totti F, Cuomo P, et al.: Multimodal treatment in pelvic ewing sarcoma: A prognostic factor analysis. *Surg Technol Int* 2019;34:489-496.

8. Guder WK, Hardes J, Nottrott M, Steffen AJ, Dirksen U, Streitbürger A: Pelvic ewing sarcoma: A retrospective outcome analysis of 104 patients who underwent pelvic tumor resection at a single supra-regional center. *J Orthop Surg Res* 2020;15:534.

9. About the SEER program. Available at: https://seer.cancer.gov/about/. Accessed December 01, 2022.

10. Hu S, Zhang W, Guo Q, et al.: Prognosis and survival analysis of 922,317 lung cancer patients from the US based on the most recent data from the SEER database (april 15, 2021). *Int J Gen Med* 2021;14:9567-9588.

11. Cole S, Gianferante DM, Zhu B, Mirabello L: Osteosarcoma: A surveillance, epidemiology, and end results program-based analysis from 1975 to 2017. *Cancer* 2022;128:2107-2118.

12. Ingram DD, Franco SJ: 2013 NCHS urban-rural classification scheme for counties. *Vital Health Statistics Ser 2, Data Eval Methods Res* 2 2014:1-73.

13. Burchill SA: Ewing's sarcoma: Diagnostic, prognostic, and therapeutic implications of molecular abnormalities. *J Clin Pathol* 2003;56:96-102.

14. Gaspar N, Hawkins DS, Dirksen U, et al.: Ewing sarcoma: Current management and future approaches through collaboration. *J Clin Oncol* 2015;33:3036-3046.

15. Denbo JW, Shannon Orr W, Wu Y, et al.: Timing of surgery and the role of adjuvant radiotherapy in ewing sarcoma of the chest wall: A single-institution experience. *Ann Surg Oncol* 2012;19:3809-3815.

16. Brennan B, Kirton L, Marec-Bérard P, et al.: Comparison of two chemotherapy regimens in patients with newly diagnosed ewing sarcoma (EE2012): An open-label, randomised, phase 3 trial. *Lancet* 2022;400:1513-1521.

17. Dunst J, Schuck A: Role of radiotherapy in Ewing tumors. *Pediatr Blood Cancer* 2004;42:465-470.

18. Ilaslan H, Sundaram M, Unni KK, Dekutoski MB: Primary Ewing's sarcoma of the vertebral column. *Skeletal Radiol* 2004;33:506-513.

19. Sharafuddin MJ, Haddad FS, Hitchon PW, Haddad SF, el-Khoury GY: Treatment options in primary ewing's sarcoma of the spine: Report of seven cases and review of the literature. *Neurosurgery* 1992;30:610-619.

20. Hesla AC, Bruland ØS, Jebsen N, Styring E, Eriksson S, Tsagozis P: Ewing sarcoma of the mobile spine; predictive factors for survival, neurological function and local control. A Scandinavian sarcoma group study with a mean follow-up of 12 years. *J Bone Oncol* 2019;14:100216.

21. Charest-Morin R, Dirks MS, Patel S, et al.: Ewing sarcoma of the spine: Prognostic variables for survival and local control in surgically treated patients. *Spine* 2018;43:622-629.

22. Indelicato DJ, Vega RBM, Viviers E, et al.: Modern therapy for chest wall ewing sarcoma: An update of the university of Florida experience. *Int J Radiat Oncol Biol Phys* 2022;113:345-354.

23. Applebaum MA, Worch J, Matthay KK, et al.: Clinical features and outcomes in patients with extraskeletal Ewing sarcoma. *Cancer* 2011;117: 3027-3032.

24. Paulussen M, Fröhlich B, Jürgens H: Ewing tumour: Incidence, prognosis and treatment options. *Paediatr Drugs* 2001;3:899-913.

25. Gladish GW, Sabloff BM, Munden RF, Truong MT, Erasmus JJ, Chasen MH: Primary thoracic sarcomas. *Radiographics* 2002;22:621-637.

26. Seitz G, Urla C, Sparber-Sauer M, et al.: Treatment and outcome of patients with thoracic tumors of the ewing sarcoma family: A report from the cooperative weichteilsarkom studiengruppe CWS-81, -86, -91, -96, and -2002P trials. *Pediatr Blood Cancer* 2019;66:e27537.

27. Provost B, Missenard G, Pricopi C, et al.: Ewing sarcoma of the chest wall: Prognostic factors of multimodal therapy including en bloc resection. *Ann Thorac Surg* 2018;106:207-213.

28. Bedetti B, Wiebe K, Ranft A, et al.: Local control in ewing sarcoma of the chest wall: Results of the EURO-EWING 99 trial. *Ann Surg Oncol* 2015; 22:2853-2859.

29. Harris CJ, Helenowski I, Murphy AJ, et al.: Implications of tumor characteristics and treatment modality on local recurrence and functional outcomes in children with chest wall sarcoma: A pediatric surgical Oncology research collaborative study. *Ann Surg* 2022;276:e969-e975.

30. Jacobs AJ, Fishbein J, Levy CF, Glick RD: Chest wall ewing sarcoma: A population-based analysis. *J Surg Res* 2016;204:475-480.

31. Indelicato DJ, Vega RBM, Viviers E, et al.: Modern therapy for spinal and paraspinal ewing sarcoma: An update of the university of Florida experience. *Int J Radiat Oncol Biol Phys* 2022;113:161-165.

32. Brown JM, Rakoczy K, Tokson JH, Jones KB, Groundland JS: Ewing sarcoma of the pelvis: Clinical features and overall survival<sup/>. *Cancer Treat Res Commun* 2022;33:100634.

33. Rödl RW, Hoffmann C, Gosheger G, Leidinger B, Jürgens H, Winkelmann W: Ewing's sarcoma of the pelvis: Combined surgery and radiotherapy treatment. *J Surg Oncol* 2003;83:154-160.

34. Ahmed SK, Robinson SI, Arndt CAS, et al.: Pelvis Ewing sarcoma: Local control and survival in the modern era. *Pediatr Blood Cancer* 2017; 64.

35. Akagunduz OO, Kamer SA, Kececi B, et al.: The role of radiotherapy in local control of nonextremity Ewing sarcomas. *Tumori* 2016;102: 162-167.

36. Ng VY, Jones R, Bompadre V, Louie P, Punt S, Conrad EU: 3rd: The effect of surgery with radiation on pelvic Ewing sarcoma survival. *J Surg Oncol* 2015;112:861-865.

37. Lex JR, Kurisunkal V, Kaneuchi Y, et al.: Pelvic Ewing sarcoma: Should all patients receive pre-operative radiotherapy, or should it be delivered selectively?. *Eur J Surg Oncol* 2021;47:2618-2626.

38. Dramis A, Grimer RJ, Malizos K, Tillman RM, Jeys L, Carter LR: Non-metastatic pelvic ewing's sarcoma: Oncologic outcomes and evaluation of prognostic factors. *Acta Orthop Belg* 2016;82:216-221.

39. 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; 18:3108-3114.

40. 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: 189-195.