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Clinical Study

Epidemiologic and survival trends in adult primary bone tumors of the spine

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Abstract

BACKGROUND CONTEXT: Malignant primary spinal tumors are rare making it difficult to perform large studies comparing epidemiologic, survival, and treatment trends. We investigated the largest registry of primary bone tumors, the National Cancer Database (NCDB), to compare epidemiologic and survival trends among these tumors.
PURPOSE: To use the NCDB to describe current epidemiologic trends, treatment modalities, and overall survival rates in patients with chordomas, osteosarcomas, chondrosarcomas, and Ewing sarcomas of the mobile spine. The secondary objective was to determine prognostic factors that impact overall survival rates.
STUDY DESIGN: Retrospective study.
PATIENT SAMPLE: A total of 1,011 patients with primary bone tumors of the spine (377 chordomas, 223 chondrosarcomas, 278 Ewing sarcomas, and 133 osteosarcomas).
OUTCOME MEASURES: Five-year survival.
METHODS: We reviewed the records of 1,011 patients in the NCDB from 2004 through 2015 with histologically confirmed primary osteosarcoma, chondrosarcoma, Ewing sarcoma, or chordoma of the spine. Demographic, clinical, and outcomes data were compiled and compared using chi-squared tests and ANOVA. Long-term survival was compared using the Kaplan-Meier method with statistical comparisons based on the log-rank test. Multivariate analysis was performed to determine survival determinants.
RESULTS: Surgical resection was the primary mode of treatment for chondrosarcoma (90%), chordoma (84%), and osteosarcoma (80%). The treatment for Ewing sarcoma was multimodal involving chemotherapy, radiation therapy, and surgical resection. Five-year survival rates varied significantly with chordomas and chondrosarcomas having the greatest survival (70% and 69%), osteosarcomas having the worse survival (38%), and Ewing having intermediate 5-year survival at 62% (overall log-rank p<.0001). Multivariate analysis demonstrated significantly improved 5-year survival rates with younger age at diagnosis, private insurance status, lower comorbidity score, lower tumor grade, smaller tumor size, surgical resection, and negative surgical margin. Radiation therapy only improved survival for Ewing sarcoma.

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CONCLUSIONS: This study provides the most comprehensive description of the epidemiologic, treatment, and survival trends of primary bone tumors of the mobile spine. Second, patient and tumor characteristics associated with improved 5-year survival were identified using a multivariate model.

Keywords: Chordoma; Chondrosarcoma; Ewing sarcoma; National Cancer Database; Osteosarcoma; Spinal tumors; Survival

Introduction

Primary osseous spinal tumors (POSTs) are rare neoplasms accounting for approximately 5% of all primary bone tumors [1]. The most common malignant POSTs include chordomas, chondrosarcomas, Ewing sarcomas, and osteosarcomas. Historically, the low prevalence of these neoplasms made it difficult to perform high powered studies analyzing epidemiologic, survival, and treatment characteristics for these tumors. The introduction of national tumor registries has improved the ability to collect data on POSTs, and may potentially assist in standardizing treatments for each individual cancer type.

The largest tumor registries in the United States include the Surveillance, Epidemiology, and End Results (SEER) Registry, a federal initiative started by the National Cancer Institute, and the National Cancer Database (NCDB), a database sponsored by the American College of Surgeons and the American Cancer Society. The NCDB has several advantages. The NCDB collects data from over 1,500 accredited hospitals in the United States and captures 70% of all newly diagnosed cancers [2,3]. In comparison, the SEER registry captures 28% of new cancer diagnoses [3]. Additionally, the NCDB includes data on the use of systemic chemotherapy and the patient's surgical margin status, which is not available in the SEER.

An investigation of patients with spinal chordomas, chondrosarcomas, Ewing sarcomas, or osteosarcomas has never been performed using the NCDB. Currently quoted 5-year survival rates and predictors of survival for POSTs were obtained from a review of patients within the SEER from 1973 to 2003 [4]. With the evolution in medical management, surgical techniques, and advanced radiation delivery methods, a current investigation of the survival trends for patients with POSTs is warranted. The primary objective of this study was to use the NCDB to describe current epidemiologic trends, treatment modalities, and overall survival rates in patients with chordomas, osteosarcomas, chondrosarcomas, and Ewing sarcomas of the mobile spine. The secondary objective was to determine prognostic factors that impact overall survival rates for all POSTs.

Materials and methods

The NCDB was investigated to identify patients diagnosed with a malignant primary bone tumor of the mobile spine between the years 2004 and 2015. A commitment to data integrity is upheld for the NCDB allowing the database to maintain its status as the largest used tumor registry in the United States. All Commission on Cancer accredited hospitals are required to submit all of their cancer cases to the NCDB. The submitted data are highly standardized, and validated tools are used to submit data to ensure consistency of coding for each submitted case [3].

Patients with a histologic diagnosis of chondrosarcoma, chordoma, Ewing sarcoma, and osteosarcoma were included for review. Exclusion criteria included benign tumors, other histologic tumor types, patients who did not undergo treatment for their tumor, tumors located at the skull base or sacrum, patients with multiple cancer diagnoses, and patients with missing survival data. From the NCDB dataset 1,869 patients were initially identified with a diagnosis of a primary bone tumor of the mobile spine. After selecting patients based on the inclusion and exclusion criteria, a total of 1,011 patients were included for review.

Patient characteristics, tumor characteristics, and treatment variables were obtained for the entire cohort and compared between histologic subtypes. The following data were obtained from the NCDB: (1) patient data included age, sex, race, Charlson comorbidity score (CCS) not including age or the primary spine bone tumor, education level (based on the average education level in the zip code of the patient's home), income (based on the average income level in the zip code of the patient's home), facility type (community cancer program, comprehensive community cancer program, academic/research program), and insurance status (private insurance, Medicare, Medicaid, no insurance); (2) tumor data included Tumor, Node, Metastasis (TNM) stage, tumor size, histologic tumor type, and tumor grade (well-differentiated tumors were considered low grade, moderately differentiated as intermediate grade, and poorly- or undifferentiated tumors as high grade); and (3) treatment data included surgical resection, surgical margin status, use of radiation therapy, and use of chemotherapy. For patients treated with radiation therapy, it was also recorded if "advanced" radiation therapy or conventional external beam radiation therapy was used to treat the patient. Advanced radiation therapy was defined as the use of intensity-modulated radiation therapy, stereotactic radiation therapy, or proton beam radiation therapy. In addition, overall survival data were obtained from the NCDB. The obtained variables were then analyzed using univariate and multivariate statistics to assess their impact on 5-year overall survival.

Statistical analysis

The patient variables, tumor characteristics, and treatment methods for each cancer type were represented using descriptive statistics. Differences between the cancer types were compared using the chi-squared test to compare proportional differences and the ANOVA test to compare mean values. The Kaplan-Meier (KM) method and log-rank test were used to compare 5-year survival between the four tumor types. A Cox proportional hazards regression model was used to perform multivariate analysis. Included variables included age (above or below median age for histologic type), sex, race (Asian, black, other, reference=white), Hispanic ethnicity, income (above or below median), comorbidity score (2+, reference=0−1), insurance (government, none, reference=private), facility type (academic or community), grade (high, intermediate, reference=low grade), size (>5ccm or <5 cm), histology, metastases at diagnosis, and treatment with surgery (no surgery, positive-margin surgery, reference=negative-margin surgery), radiation, or chemotherapy. Patients with missing survival data including endpoint or censorship data were excluded from the analysis, and missing data for the categorical covariates in the model were imputed using the PROC MI/MIANALYZE multiple imputation procedures in SAS. All patient, tumor, and treatment covariates listed above, as well as survival and censorship variables, were included in the imputation process. Fifty imputations were performed using the fully conditional specification method and relative efficiency was >98% for all variables. Interaction terms between tumor type and treatment covariates (surgery, radiation, chemotherapy) were included in the base proportional hazards regression model to assess the survival effects of treatments according to histology. In a second model, the interaction terms for Surgery*Histology and Chemotherapy*Histology were removed to estimate the overall survival effects of negative-margin surgery (vs. no surgery), positive-margin surgery (vs. negative-margin surgery), and chemotherapy (vs. no chemotherapy). The Radiation*Histology interaction was kept in the model as the direction of radiation's effect on survival varied by histology. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for each investigated variable. A p value of <.05 was considered statistically significant. All statistical analyses were performed using SAS/JMP (SAS Institute Inc, Cary, NC, USA).

Results

A total of 1,011 patients in the NCDB were identified with POSTs: chordoma (377 patients), chondrosarcoma (223 patients), Ewing sarcoma (278 patients), and osteosarcoma (133 patients). Five-year survival rates were significantly different between the cancer types: osteosarcoma had the lowest five-year survival of 38%, followed by Ewing sarcoma (62% survival), chondrosarcoma (69% survival), and finally, chordoma (70% survival; p<.001; Fig. 1).

Patient demographics and characteristics between the cancer types were obtained and documented (Table 1). There was an increased prevalence in males for all cancer types ranging from 58% male in chondrosarcoma to 62% male in Ewing sarcoma, with no significant difference in gender bias between cancer types (p=.791). Patients with Ewing sarcoma were diagnosed at an average younger age (22 years), and patients with chordomas were diagnosed at an average older age (57 years; p<.001). Fig. 2 demonstrates the distribution of patient's ages at time of diagnosis. Caucasians were the most common race for all cancer types representing 91% of patients; however, a greater proportion of African Americans were diagnosed with chondrosarcoma (8%) and osteosarcoma (11%) compared with chordoma (3%) and Ewing sarcoma (4%; p=.013). Only 4% of patients

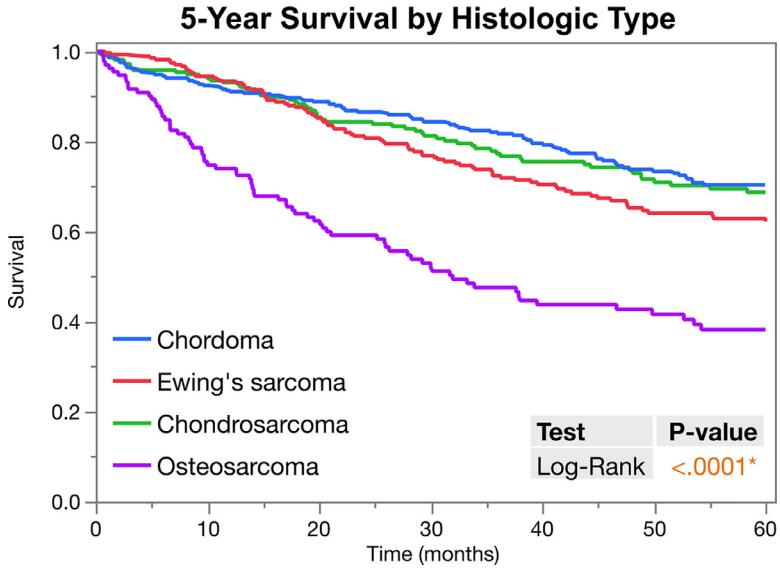


Fig. 1. Kaplan-Meier survival curve based on cancer type.

Table 1
Patient demographics and characteristics

N (%)		Overall (n=1,011)	Chondrosarcoma (n=223)	Chordoma (n=377)	Ewing sarcoma (n=278)	Osteosarcoma (n=133)	p Value
Age, mean (95% CI)		44 (43–45)	50 (48–53)	57 (56–59)	22 (20–24)	43 (40–46)	<.0001***
Female gender		405 (40)	94 (42)	152 (40)	105 (38)	54 (41)	.7914
Race	White	897 (91)	193 (88)	343 (93)	249 (92)	112 (86)	.0130*
	Black	56 (6)	18 (8)	12 (3)	11 (4)	15 (11)	
	Asian	24 (2)	7 (3)	8 (2)	5 (2)	4 (3)	
Hispanic ethnicity		90 (9)	18 (8)	26 (7)	34 (13)	12 (10)	.1364
Comorbidity score ≥2		41 (4)	9 (4)	13 (3)	15 (5)	4 (3)	.5691
Education above median		601 (61)	134 (61)	241 (65)	150 (55)	76 (58)	.0600
Income above median		625 (63)	141 (65)	250 (68)	157 (58)	77 (59)	.0427*
Insurance	Private	569 (58)	135 (63)	189 (51)	173 (64)	72 (56)	<.0001***
	Government	370 (38)	66 (31)	172 (47)	83 (31)	49 (38)	
	None	44 (4)	14 (7)	7 (2)	16 (6)	7 (5)	
Academic facility		340 (59)	88 (55)	185 (61)	22 (58)	45 (63)	.5757

Percentages reflect the relative proportion out of those patients with known values for the variable (unknown values were not included in %).
For numerical variables (age), mean was compared with analysis of variance (ANOVA) test.
For categorical variables, proportions were compared with Pearson chi-square tests for independence.
Statistical significance indicated by * for p<.05, ** for p<.01, *** for p<.001.

had two or more notable medical comorbidities in addition to their POST, and 59% of all patients received treatment at academic facilities. There were no significant differences across the four histologic cancer types in regards to gender, education level, medical comorbidities, or likelihood of treatment at academic or community-based facilities.

Tumor and treatment-related characteristics varied between the cancer types (Table 2). Of those patients with a documented tumor grade, high-grade tumors were more common in Ewing sarcoma (97%) and osteosarcoma (79%) compared with chordoma (26%) and chondrosarcoma (12%; p<.001). The presence of metastatic disease at the time of diagnosis varied between cancer types, with the lowest rate of metastatic disease being chordoma at 3%, followed by chondrosarcoma (4%), osteosarcoma (15%), and Ewing sarcoma (18%; p<.001). Chondrosarcoma and osteosarcoma were more likely to present as large (>5 cm) tumors (p<.001). Surgical resection was the most common treatment modality for chondrosarcoma (90%), chordoma (84%), and osteosarcoma (80%). Ewing sarcoma patients were most commonly treated with chemotherapy and radiation therapy; however, surgical resection was still performed in 68% of patients. Following surgical resection, 37% of patients had a positive surgical margin with no significant difference in achieving a negative margin between histologic types (p=.314). The use of radiation therapy varied between cancer types, and was used the least in osteosarcoma (30%) and chondrosarcoma (34%); radiation therapy was used more frequently in chordoma (56%) and Ewing sarcoma (72%). Advanced radiation techniques were used most commonly for the management of chordomas. Chemotherapy as a treatment modality varied between cancer types; it was

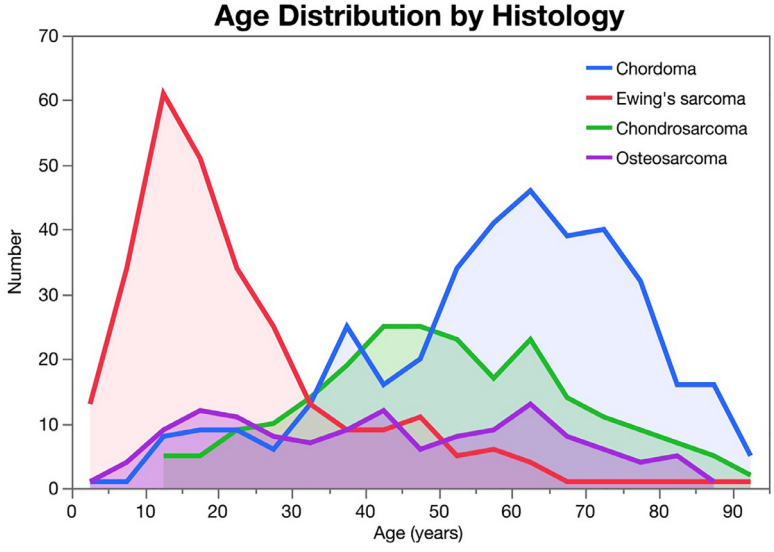


Fig. 2. Distribution of patients ages for primary bone tumors of the spine.

Table 2
Tumor and treatment characteristics

N (%)		Overall (n=1,011)	Chondrosarcoma (n=223)	Chordoma (n=377)	Ewing sarcoma (n=278)	Osteosarcoma (n=133)	p Value
Tumor size ≥5 cm		277 (48)	97 (64)	86 (38)	66 (45)	28 (49)	<.0001***
Tumor grade	High	167 (46)	20 (12)	10 (26)	70 (97)	67 (79)	<.0001***
	Intermed.	102 (28)	77 (45)	12 (31)	2 (3)	11 (13)	
	Low	98 (27)	74 (43)	17 (44)	0 (0)	7 (8)	
Metastases		83 (9)	8 (4)	10 (3)	46 (18)	19 (15)	<.0001***
Surgery		810 (80)	201 (90)	315 (84)	187 (68)	107 (80)	<.0001***
Margins positive		170 (37)	42 (37)	61 (35)	44 (45)	23 (33)	.3139
Radiation	Any	518 (52)	75 (34)	206 (56)	198 (72)	39 (30)	<.0001***
Type	Advanced	245 (48)	35 (48)	125 (62)	74 (38)	11 (31)	<.0001***
Chemo		361 (37)	15 (7)	13 (4)	254 (94)	79 (61)	<.0001***

Percentages reflect the relative proportion out of those patients with known values for the variable (unknown values were not included in %).
For categorical variables, proportions were compared with Pearson chi-square tests for independence.
Statistical significance indicated by * for p<.05, ** for p<.01, *** for p<.001.

infrequently used in chordomas (4%) and chondrosarcomas (7%). However, it had a higher use in osteosarcoma (61%) and Ewing sarcoma (94%; p<.001).

A multivariate proportional hazards analysis demonstrated older patient age (HR 1.93, 95% CI 1.47−2.53), government insurance (HR 1.61, 95% CI 1.23−2.10), lack of insurance (HR 1.99, 95% CI 1.14−3.47), CCS >1 (HR 1.73, 95% CI 1.02−2.94), tumor size >5 cm (HR 1.52, 95% CI 1.08−2.14), intermediate tumor grade (HR 1.91, 95% CI 1.07−3.40), high tumor grade (HR 4.62, 95% CI 2.35 −9.05), and metastatic disease (HR 2.69, 95% CI 1.89 −3.83) to be associated with worse overall survival (Table 3). Surgical resection was associated with improved survival, both overall (HR 0.58, 95% CI 0.40−0.84) and individually for Ewing sarcoma (HR 0.51, 95% CI 0.28 −0.92) and osteosarcoma (HR 0.41, 95% CI 0.22−0.80). Surgical resection trended toward improved survival for chordoma and chondrosarcoma; however, these were not statistically significant. Positive-margin status was associated with worse survival (HR 1.43, 95% CI 1.01−2.02) when tumor types were combined, but only trended toward worse survival for individual tumor types. Radiation therapy significantly improved survival for Ewing sarcoma patients (HR 0.60, 95% CI 0.38−0.97), but only trended toward improved survival for chordoma (HR 0.83, 95% CI 0.63−1.08) and chondrosarcoma (HR 0.74, 95% CI 0.48 −1.14). Osteosarcoma trended toward decreased survival with radiation therapy (HR 1.35, 95% CI 0.94−1.94). Chemotherapy was associated with improved survival for all tumors types (overall HR 0.64, 95% CI 0.42−0.98), but was only individually significant for Ewing sarcoma (HR 0.28, 95% CI 0.12−0.62) and osteosarcoma (HR 0.79, 95% CI 0.62−1.00).

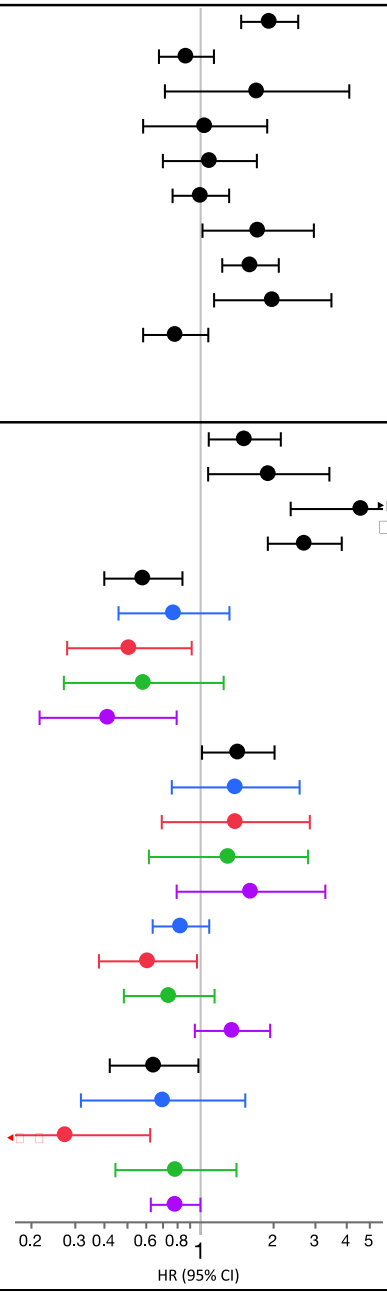
Discussion

This is the first investigation of POSTs within the NCDB. The NCDB is the most complete tumor registry for musculoskeletal neoplasms, and our data represent the largest collection of mobile spine chordoma, chondrosarcoma, Ewing sarcoma, and osteosarcoma patients managed with current practices. Overall 5-year survival rates improved in a stepwise fashion between osteosarcoma, Ewing sarcoma, chondrosarcoma, and chordoma with survival rates of 38%, 62%, 69%, and 70%, respectively. The results of this investigation associated the following prognostic factors with improved 5-year survival across all tumor types: younger age, CCS <2, private medical insurance, low tumor grade, non-metastatic disease, and negative surgical margins. Surgical resection was associated with improved survival for all tumor types; however, this only achieved statistical significance individually for Ewing sarcoma and osteosarcoma. Radiation therapy was associated with improved survival in Ewing sarcoma, and associated with decreased 5-year survival for osteosarcoma. In general, socioeconomic factors did not greatly influence survival with both yearly income and race not impacting survival in multivariate analysis. The patient's insurance status did influence survival with private health insurance having improved survival rates compared with government insurance and no insurance. It has been previously reported that uninsured and underinsured tumor patients have poorer outcomes due to limited access to cancer screening, increased surgical complications, and decreased ability to enroll in clinical trials [5,6].

Chordomas are neoplasms that present along the axial skeleton and arise from notochordal remnants [1]. Chordomas were the most common POST in the NCDB representing 37% of the cohort. Chordomas were most commonly low-grade neoplasms, with metastatic disease only reported in 3% of patients, although only a minority (10%) of chordomas were reported with a known tumor grade in our cohort. The 5-year survival rate was 70%, which is comparable to previous reports in the literature, which range from 61% to 68% [4,7−9]. Chordomas were more common in males, which is consistent with previous epidemiologic reports [7,9,10]. African Americans represented only 3% of chordoma patients within the NCDB. A low prevalence of chordomas in the African American population has been

Table 3
Independent predictors of mortality in multivariate proportional hazards analysis

Patient Variables		HR (95% CI)	P-Value
Age above median		1.93 (1.47-2.53)	<0.0001 ***
Female sex		0.87 (0.67-1.13)	0.3132
Race (vs. White)	Asian	1.71 (0.71-4.11)	0.2329
	Black	1.04 (0.58-1.88)	0.8976
Hispanic ethnicity		1.09 (0.70-1.71)	0.7164
Income above median ($48,000)		1.00 (0.76-1.31)	0.9972
Comorbidity Score >1		1.73 (1.02-2.94)	0.0429 *
Insurance (vs. Private)	Government	1.61 (1.23-2.10)	0.0006 ***
	None	1.99 (1.14-3.47)	0.0160 *
Academic facility type		0.79 (0.58-1.07)	0.1307
Tumor and Treatment Variables			
Tumor size >5 cm		1.52 (1.08-2.14)	0.0166 *
Grade (vs. Low)	Intermediate	1.91 (1.07-3.40)	0.0277 *
	High	4.62 (2.35-9.05)	<0.0001 ***
Metastases at diagnosis		2.69 (1.89-3.83)	<0.0001 ***
Surgery	**Combined†**	0.58 (0.40-0.84)	0.0040 **
	Chordoma	0.77 (0.46-1.31)	0.3491
	Ewing	0.51 (0.28-0.92)	0.0244 *
	Chondrosarcoma	0.58 (0.27-1.24)	0.1623
	Osteosarcoma	0.41 (0.22-0.80)	0.0081 **
Positive Margins	**Combined†**	1.43 (1.01-2.02)	0.0424 *
	Chordoma	1.39 (0.76-2.56)	0.2878
	Ewing	1.40 (0.69-2.83)	0.3591
	Chondrosarcoma	1.30 (0.61-2.78)	0.5038
	Osteosarcoma	1.61 (0.79-3.28)	0.1866
Radiation	Chordoma	0.83 (0.63-1.08)	0.1701
	Ewing	0.60 (0.38-0.97)	0.0347 *
	Chondrosarcoma	0.74 (0.48-1.14)	0.1725
	Osteosarcoma	1.35 (0.94-1.94)	0.0986
Chemotherapy	**Combined†**	0.64 (0.42-0.98)	0.0387 *
	Chordoma	0.70 (0.32-1.53)	0.3753
	Ewing	0.28 (0.12-0.62)	0.0018 **
	Chondrosarcoma	0.79 (0.44-1.40)	0.4285
	Osteosarcoma	0.79 (0.62-1.00)	0.0464 *



†Model repeated without Histology interaction terms for surgery/margins and chemotherapy, as all hazard ratios trended together toward improved survival for surgery and chemotherapy, and toward worse survival for positive margin status. In contrast, there was more variation by tumor type seen in the effect of Radiation, trending toward worse survival for osteosarcoma and improved survival for other tumor types. Statistical significance indicated by * for p<.05, ** for p<.01, *** for p<.001.

previously reported with African Americans representing only 2.2% to 3.3% of reported cases [7,8,11]. Despite this recurrent observation, the reason for the racial discrepancy in the epidemiology of this cancer remains unclear. The currently recommended treatment protocol for chordoma patients in the United States is en bloc resection with or without adjunct radiation therapy [12]. Previous studies have demonstrated en bloc resection with a negative surgical margin to have lower recurrence rates compared with intralesional resection [10]. Chordomas have historically been considered radioresistant; however, advanced radiation techniques have allowed higher radiation doses to be used without injury to surrounding structures [12]. Specifically, proton beam radiation therapy is being utilized

for chordoma patients with initial studies demonstrating improved survival compared with conventional radiation modalities [13]. In the NCDB cohort, 84% of chordoma patients underwent surgical excision, and a negative surgical margin was achieved in 65% of reported cases. Radiation therapy was used in 56% of patients, and an advanced radiation delivery method was used in 62% of those cases receiving radiation therapy. Surgical resection and radiation therapy both trended toward improving survival in the multivariate model, but these did not achieve statistical significance. Although outside of the scope of this epidemiologic review, future NCDB studies focused on chordoma patients will hopefully reveal which patients benefit most from adjunct radiotherapy and what dose and modality of radiation delivery is most effective at improving overall survival.

Chondrosarcomas are neoplasms composed of a cartilaginous matrix without osteoid. Chondrosarcomas accounted for 22% of the POSTs within the NCDB. The majority of chondrosarcomas were reported as low and intermediate grade, and only 4% of patients were reported to have metastatic disease. The 5-year survival in the cohort was 69%. Previously, the largest review of spinal chondrosarcomas was performed from the SEER database consisting of 973 cases between the years 1973 and 2012, and in this study the 5-year survival was 53% [14]. Chondrosarcomas were more common in males compared with females, which is consistent with previous reports [14,15]. Caucasian was the most common race representing 88% of cases. The average age at diagnosis was 50 years old, and most patients were diagnosed either in their fifth or sixth decades of life. The ideal treatment of spinal chondrosarcomas is en bloc surgical resection with negative surgical margins [1]. Intralesional resections have been associated with nearly 100% recurrence rates [16]. Chondrosarcomas are radioresistant tumors. However, in the setting of positive surgical margins, some authors support the use of adjunct radiotherapy [17]. In the NCDB cohort, 90% of patients underwent surgical resection, and a negative surgical margin was obtained in 63% of reported patients. Radiation therapy was used in 34% of patients. Five-year KM survival for chondrosarcoma was significantly improved by surgical resection (71% vs. 43%, log-rank p=.0004), though surgical resection only trended toward improved survival in the multivariate analysis (HR 0.58, 95% CI 0.27−1.24) and did not obtain statistical significance. Surgical resection has been well documented to improve survival in extremity chondrosarcoma, and the failure of surgical resection to achieve statistical significance may indicate that the multivariate analysis remains underpowered despite the relatively large sample size, and with additional patients a survival benefit would be observed. Radiation therapy or chemotherapy was not associated with improved survival in the multivariate analysis.

Ewing sarcomas are small, round cell neoplasms that commonly present during childhood and adolescence [18]. The median age of diagnosis in the NCDB cohort was 22 years old, and Figure 2 clearly demonstrates the peak of diagnoses in the first and second decades of life. Ewing sarcomas accounted for 27% of the POSTs in the NCDB. Of the Ewing sarcomas, 97% were reported as high grade, and the rate of metastatic disease was 18%. The 5-year survival was 62%, which is comparable to previous reports in the literature [4,19]. Ewing sarcomas were more common in males with females only representing 38% of cases. Caucasians represented 92% of the patients diagnosed with Ewing sarcoma, and African Americans accounted for 4% of patients. The current recommendation for the treatment of Ewing sarcoma consists of neoadjuvant chemotherapy followed by surgical resection and/or radiation therapy [1]. In parallel with the current treatment recommendations, 94% of the Ewing sarcoma patients in the NCDB were treated with chemotherapy. A previous study demonstrated decreased 5-year survival rates for patients with Ewing sarcoma of the spine compared with the extremities (61.2% vs. 70.6%), and found improved 5-year survival with surgical resection and radiation therapy compared with radiation therapy alone [20]. In our cohort, surgical resection was performed in 68% of patients, and radiation therapy was used in 72% of the patients, with 132 patients receiving both radiation and surgery (48% of all patients with known surgery and radiation status). In the multivariate analysis, surgical resection, radiation therapy, and chemotherapy all conferred significantly improved survival (HR [95% CI] 0.51 [0.28−0.92], 0.60 [0.38−0.97], 0.28 [0.12−0.62], respectively). The results of this study support the previous reports in the literature that for Ewing sarcoma of the mobile spine, a multimodal approach involving chemotherapy, surgical resection, and/or radiation therapy should be considered for the greatest chance for improved survival.

Osteosarcomas are neoplasms composed of malignant cells, which produce osteoid. Osteosarcomas of the spine were the least common POST representing 13% of the patients in this NCDB study. Osteosarcomas of the extremity occur in a bimodal fashion with the majority presenting during the adolescent growth spurt. An interesting finding from this review demonstrated the average age at diagnosis for mobile spine osteosarcomas to be 43 years old, and the tumors presented at a fairly consistent rate between ages 10 and 60 (interquartile range of 23−61 years). This distribution of ages at diagnosis is different than the distribution for extremity osteosarcomas in the NCDB, which have a mean of 27 years old (interquartile range of 14−37 years). The majority of osteosarcomas in the mobile spine were high grade at diagnosis (79%), and metastatic disease was reported in 15% of patients. The 5-year survival rate for spinal osteosarcomas was 38%. In a review of the SEER database between the years 1973 and 2012, the 5-year survival rate for spinal osteosarcomas was reported to be 18% [19]. The most likely reason for improved survival in the current study was the increased use of chemotherapy. The advent of chemotherapy in the 1970s has had the greatest impact

on survival in osteosarcoma in the last 50 years [21]. Spinal osteosarcomas, like all the other POSTs, were more common in males. Caucasians represented 86% of patients, and African Americans represented 11% of patients. The current recommendation for the treatment of spinal osteosarcoma is neoadjuvant chemotherapy followed by en bloc resection with a negative surgical margin [22]. The role of radiation therapy remains controversial; however, current published studies fail to demonstrate a survival benefit from radiation therapy [19]. In the NCDB, 61% of patients received chemotherapy. Surgical excision was performed in 80% of patients, and a negative surgical margin was achieved in 67% of reported cases. Radiation therapy was utilized in 30% of cases. Surgical resection was associated with improved survival for spinal osteosarcoma patients, with a 5-year KM survival rate of 43% compared with only 22% without surgery (log-rank $p<.0001$). This survival benefit was observed in the multivariate analysis as well (HR 0.41, 95% CI 0.22−0.80). Radiation therapy was associated with decreased survival in the multivariate model. One potential for this finding would be selection bias, and only patients who were deemed to be unfit surgical candidates were treated with radiation therapy. Chemotherapy has greatly improved survival for extremity osteosarcoma patients, and in multivariate analysis it was associated with improved survival for osteosarcomas of the spine as well (HR 0.79, 95% CI 0.62−1.00).

Although the NCDB has several advantages, including a greater representation of new cancer diagnoses, more details about treatment data, and better quality control than other population databases, it is not without limitations [3]. One limitation of this study was that the database does not differentiate between en bloc and piecemeal surgical resections. We used positive and negative surgical margins as a surrogate for the surgical approach, but with the understanding that outcomes following an en bloc resection are generally improved compared with piecemeal resections. The NCDB does document on surgical approach, but the definitions are for extremity and visceral tumors and could not be reliably applied to spinal tumor resections. An additional limitation of this study, inherent to retrospective database reviews, was incomplete patient data reporting for individual variables assessed. Missing data limit both descriptions of the patient cohort and introduce the possibility for bias in both univariate and multivariate survival analyses. Tables 1 and 2 report the numbers of patients with data represented for each investigated variable. The percentages in these tables only include patients with documented data, all other patients were recorded as having unknown data and were not included in the percentages or descriptive statistical comparisons. Another limitation is the lack of reporting on recurrence-free survival within the NCDB. This is an important acknowledgment as positive margin status and piecemeal resections have been previously associated with increased rates of local recurrence, which leads to poorer overall survival in bone tumors [23]. In addition, the NCDB does not differentiate if these are primary or recurrent primary bone tumors. By including recurrent tumors in the cohort, the actual overall survival may be underestimated.

This study represents the first investigation of patients with malignant spinal neoplasms in the NCDB. The study provides descriptive statistics for the demographics, socioeconomic status, treatment methods, tumor details, and survival trends for patients with these neoplasms. Additionally, factors prognostic for 5-year survival were identified. The information from this study can be used to better predict overall prognosis for patients and to better inform patients of current survival trends with individual malignant neoplasms of the mobile spine. Hopefully with the use of big data series from tumor registries, treatment regimens can become further standardized to eliminate unnecessary or harmful treatment modalities, and future studies of these databases will help answer remaining controversies in regards to the treatment of POSTs.

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