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ORIGINAL ARTICLE

Association of surgical resection and survival in patients with malignant primary osseous spinal neoplasms from the Surveillance, Epidemiology, and End Results (SEER) database

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Abstract
Objective Malignant osseous spinal neoplasms are aggressive tumors associated with poor outcomes despite aggressive multidisciplinary measures. While surgical resection has been shown to improve short-term local disease control, it remains debated whether surgical resection is associated with improved overall survival in patients with malignant primary osseous spinal neoplasms. The aim of this manuscript is to review survival data from a US cancer registry spanning 30 years to determine if surgical resection was independently associated with overall survival.
Methods The SEER registry (1973–2003) was queried to identify cases of histologically confirmed primary spinal chordoma, chondrosarcoma, osteosarcoma, or Ewing's sarcoma of the mobile spine and pelvis. Patients with systemic metastasis were excluded. Age, gender, race, tumor location, and primary treatments were identified. Extent of local tumor invasion was classified as confined within periosteum versus extension beyond periosteum to surrounding tissues. The association of surgical resection with overall survival was assessed via Cox analysis adjusting for age, radiotherapy, and tumor invasiveness.
Results 827 patients were identified with non-metastatic primary osseous spinal neoplasms (215 chordoma, 282 chondrosarcoma, 158 osteosarcoma, 172 Ewing's sarcoma). Overall, median survival was histology specific (chordoma, 96 months; Ewing's sarcoma, 90 months; chondrosarcoma, 88 months; osteosarcoma, 18 months). Adjusting for age, radiation therapy, and extent of local tumor invasion in patients with isolated (non-metastatic) spine tumors, surgical resection was independently associated with significantly improved survival for chordoma [hazard ratio (95 % confidence interval; 0.617 (0.25–0.98)], chondrosarcoma [HR (95 %CI); 0.153 (0.07–0.36)], osteosarcoma [HR (95 %CI); 0.382 (0.21–0.69)], and Ewing's sarcoma [HR (95 %CI); 0.494 (0.26–0.96)].
Conclusion In our analysis of a 30-year US population-based cancer registry (SEER), patients undergoing surgical resection of primary spinal chordoma, chondrosarcoma, Ewing's sarcoma, or osteosarcoma demonstrated prolonged overall survival independent of patient age, extent of local invasion, or location. Surgical resection may play a role in prolonging survival in the multi-modality treatment of patients with these malignant primary osseous spinal neoplasms.

Keywords Biopsy · Chondrosarcoma · Chordomas · Ewing's sarcoma · Osteosarcoma · Survival · Surgery

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Introduction

The most common malignant primary bone tumors of the spine include chordomas, osteosarcomas, chondrosarcomas, and Ewing's sarcomas [1]. These tumors can cause significant morbidity and mortality secondary to local invasion and destruction of adjacent structures as well as

metastasize to distant organs. Treatment of these tumors usually begins with acquiring tissue for diagnosis [29]. This tissue can be obtained by needle biopsy or surgical resection. The efficacy of surgical resection in prolonging survival, however, is poorly understood. This lack of understanding is primarily due to the rarity of these malignancies, which account for less than 5 % of all osseous neoplasms and less than 0.2 % of all cancers [1]. As a result, previous studies on the efficacy of surgical resection have been limited to small institutional series and controlled trials [29].

Studies, however, using the Surveillance, Epidemiology, and End Results (SEER) registry may provide a better source of understanding for pathologies that are rare. This registry is the most comprehensive source of cancer information because it collects incidence and survival data for patients with cancer from 26 % of the population in the United States. The goal of the present study was to conduct a large population-based study using the SEER registry to understand whether surgical resection as compared to biopsy was associated with improved survival for patients with primary non-metastatic chordomas, chondrosarcoma, osteosarcomas, and Ewing's sarcoma. This understanding may help clarify the role of surgery in maximizing survival for patients with malignant primary bone tumors.

Methods

The SEER registry, a database maintained by the National Cancer Institute, collects incidence and survival data from 17 population-based cancer registries covering approximately 25 % of the United States population. The database contains information on primary tumor site, histology, stage at diagnosis, treatment regimens including surgery and radiation therapy (XRT), and year of death. We searched the SEER database to identify all registered cases of Ewing's sarcoma, osteosarcoma, chondrosarcoma, and chordoma in order to assess histology-specific survival during the period from 1973 to 2003.

International classification of disease for oncology, third edition criteria were used to identify cases of histologically confirmed Ewing's sarcoma (ICD-O code: 9260), osteosarcoma (ICD-O code: 9180–9185, 9190), chondrosarcoma (ICD-O: 9220), and chordoma (ICD-O: 9370). Histological confirmation was obtained in all patients, either from biopsy or surgical pathology. The study population included patients within the SEER database diagnosed between 1973 and 2003. Covariates identified were patient age at diagnosis, year of diagnosis, and site of primary tumor, including vertebral column (ICD-O code: 412) versus (ICD-O code: sacrum/pelvis), metastasis status, whether XRT was administered, extent of tumor invasion, and whether surgical resection was performed. Data regarding chemotherapy was not available in the SEER database. Surgical management was defined at the time of care by the treatment team as: (1) biopsy for tissue diagnosis or (2) surgical resection. Differentiation between intra-lesional and en bloc resection was not made in the SEER registry. Extent of local tumor invasion was defined at the time of care by histological specimen, radiographic analysis, or intra-operative surgeon assessment and classified as: (1) confined (tumor confined to cortex of bone or extension beyond cortex but confined within periosteum) or (2) local invasion (extension beyond periosteum to surrounding tissues, including adjacent skeletal muscle, adjacent bone/cartilage, or skin).

For the purposes of this study, patients presenting with distal site metastasis were excluded. Only patients with isolated primary osseous spine tumors were included. The primary outcome of interest was overall survival. Estimated Kaplan–Meier survival was calculated as the time from diagnosis to death or last follow-up. Observations were censored when a patient was alive at the time of last follow-up. For each tumor histology, the association of surgical resection with overall survival was assessed via Cox proportional-hazards regression analysis adjusting for age, XRT, and extent of local tumor invasion.

Results

Patient population

A total of 827 patients were identified with non-metastatic primary osseous spinal neoplasms (215 chordoma, 282 chondrosarcoma, 158 osteosarcoma, 172 Ewing's sarcoma). Patients presenting with Ewing's sarcoma of the spine were on average younger (19 ± 10 years, $p < 0.01$) and patients presenting with spinal chordoma were on average older (59 ± 16 years, $p < 0.01$) compared to patients with chondrosarcoma or osteosarcoma (49 ± 20 years) (Table 1). The majority of patients were male for all tumor types, ranging from 55 % for osteosarcoma to 70 % for Ewing's sarcoma (Table 1). African-Americans comprised a significantly greater proportion of osteosarcoma than all other tumors (13 vs. 4 %, $p < 0.01$). Otherwise, there was no association between race and histology type.

Presentation and treatment

The sacrum versus mobile spine was more frequently the site of tumor location for all tumor types (Table 1). For all histology types, the majority of tumors had invaded through the periosteum (66 %) rather than being confined

Table 1 Characteristics of 827 patients with malignant primary osseous spinal neoplasms without metastasis from the surveillance, epidemiology, and end results (SEER) registry 1973–2003

Patient characteristic (n, %)	Ewing's sarcoma ($n = 172$)	Osteosarcoma ($n = 158$)	Chondrosarcoma ($n = 282$)	Chordoma ($n = 215$)
Age				
Mean ± SD (years)	19 ± 10	46 ± 23	49 ± 18	59 ± 16
Female sex	51 (30)	72 (45)	93 (33)	82 (38)
Race				
Caucasian	158 (90)	125 (79)	253 (90)	192 (89)
African-American	5 (3)	20 (13)	15 (5)	7 (3)
Native American	2 (1)	1 (1)	1 (0.4)	2 (1)
Asian	7 (4)	12 (7)	13 (4.6)	14 (7)
Primary site				
Vertebral column	58 (33)	50 (32)	58 (20)	95 (44)
Sacrum/pelvis	114 (67)	108 (68)	224 (80)	120 (56)
Extent invasion				
Confined	53 (31)	37 (23)	114 (40)	80 (37)
Local invasion	119 (69)	121 (77)	168 (60)	135 (63)
Radiation therapy	116 (67)	45 (29)	54 (19)	94 (43)
Surgical treatment data available	80	80	134	95
Diagnostic biopsy	34 (43)	26 (32)	12 (9)	10 (11)
Surgical resection	46 (57)	54 (68)	122 (91)	85 (89)
Median survival				
All patients	90 months	18 months	88 months	96 months
No surgery	43 months	11 months	16 months	53 months
Surgery	Undetermined[a]	37 months	192 months	87 months
Surgery + XRT	72 months	43 months	Undetermined[a]	104 months
5-year survival				
No surgery	37	0	33	50
Surgery	74	27	71	71
Surgery + XRT	60	43	65	80

Values in parentheses are expressed in percentage

Confined tumor confined within periosteum; *local invasion* extension beyond periosteum to adjacent skeletal muscle, bone/cartilage, or skin

[a] Undetermined: median survival not reached during follow-up period

within the periosteum (34 %) (Table 1). Surgical resection was performed in the vast majority of patients presenting with chordoma (89 %) and chondrosarcoma (91 %), and in the slight majority for osteosarcoma (68 %) and Ewing's sarcoma (57 %). XRT was most commonly administered in patients with Ewing's sarcoma (67 %) and least commonly in patients with chondrosarcoma (19 %) (Table 1).

Survival

For all patients, 401 (48 %) died during their SEER follow-up period. Mean follow-up for surviving patients was 85 ± 50 months. Overall median survival was histology specific (Table 1). Median survival was 90 months for Ewing's sarcoma, 96 months for chordoma, 88 months for chondrosarcoma, and 18 months for osteosarcoma.

Adjusting for age, XRT, and extent of local tumor invasion in patients with isolated (non-metastatic) spine tumors, surgical resection was associated with significantly improved survival for chordoma [hazard ratio (95 % confidence interval (CI); 0.617 (0.25–0.98)], chondrosarcoma [HR (95 %CI); 0.153 (0.07–0.36)], osteosarcoma [HR (95 %CI); 0.382 (0.21–0.69)], and Ewing's sarcoma [HR (95 %CI); 0.494 (0.26–0.96)] (Fig. 1). In patients with chondrosarcoma or Ewing's sarcoma, median and 5-year survival was similar for patients undergoing surgery + XRT versus surgery alone. However, in patients with osteosarcoma and chordoma, median and 5-year survival was greater for patients undergoing surgery + XRT versus surgery alone (Table 1). In analysis of all tumor types, patients undergoing surgery had better survival for both tumors confined to and extending beyond the periosteum relative to patients in the biopsy cohort (Fig. 2). Patients undergoing surgical resection also had better survival for both lesions of the mobile spine and sacrum/pelvis relative to patients in the biopsy cohort (Fig. 3).

Discussion

In our analysis of the four most common primary spine tumors recorded in the SEER registry over three decades,

we evaluated the role of surgical resection and biopsy for patients with isolated malignant primary osseous tumors of the spinal column. Overall median survival was histology specific, where the median survival was 90 months for Ewing's sarcoma, 96 months for chordoma, 88 months for chondrosarcoma, and 18 months for osteosarcoma. Patients who underwent surgical resection had improved survival as compared to patients who underwent biopsy, even after adjusting for age at the time of surgery, XRT, and extent of local tumor invasion for all four tumor types. Additionally, patients had improved survival with surgical resection regardless of extent of tumor invasion or spinal location. Interestingly, among patients who underwent surgical resection, adjuvant XRT was associated with prolonged survival for patients with osteosarcoma and chordomas.

There are approximately 2,380 new cases of bone cancer diagnosed in the United States each year, with approximately 5 % involving the spine [1]. Among malignant primary osseous neoplasms, the four most common include osteosarcoma (35 %), chondrosarcoma (26 %), Ewing's sarcoma (16 %), and chordoma (8 %) [8, 11, 18, 24, 27, 33]. The overall 5-year relative survival rates for spine-limited malignant bone tumors range from 10 to 30 % for osteosarcoma [25, 30, 34], 50–75 % for chondrosarcoma [4, 7, 31, 37], 30–65 % for Ewing's sarcoma [12, 15, 20, 26], and 50–85 % for chordoma [5, 6, 9, 22, 38]. These tumors also are known for having high recurrence rates. The repeated 5-year progression-free survival has ranged from 0 to 25 % for osteosarcoma [25, 30, 34], 50–70 % for chondrosarcoma [4, 7, 16], 30–60 % for Ewing's sarcoma [2, 3, 15, 20], and 45–65 % for chordomas [13, 17]. The high recurrence rates, limited survival duration, and functional morbidity associated with these tumors have supported the need for aggressive multi-modality strategies for these tumors. Surgical resection decreases tumor burden, may increase chemotherapy and/or XRT efficacy, and allow for neural decompression and spinal stabilization. Additionally, in some cases, surgery may entirely remove the tumor with negative margins [29]. Despite these reported advantages, the overall benefit of surgical resection of various types of primary malignant bone tumors has yet to be demonstrated in a population-based study.

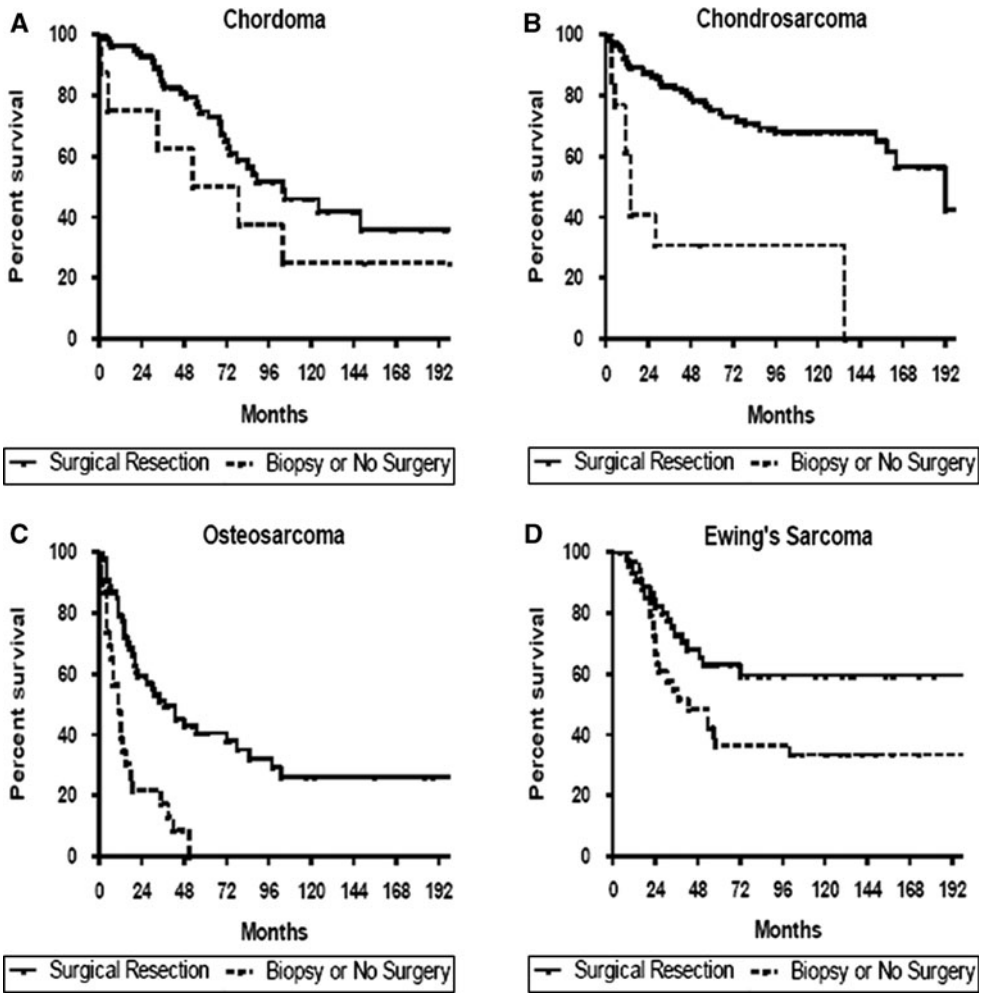

Fig. 1 Kaplan–Meier estimated survival in patients with primary osseous spinal tumors **a** chordoma, **b** chondrosarcoma, **c** osteosarcoma, or **d** Ewing's sarcoma stratified by surgical resection versus no surgery. Adjusting for age, radiation therapy, and extent of local tumor invasion in patients with isolated (non-metastatic) spine tumors, surgical resection was associated with significantly improved survival for chordoma [Hazard Ratio (95 % confidence interval; 0.617 (0.25–0.98)], chondrosarcoma [HR (95 %CI); 0.153 (0.07–0.36)], osteosarcoma [HR (95 %CI); 0.382 (0.21–0.69)], and Ewing's sarcoma [HR (95 %CI); 0.494 (0.26–0.96)]

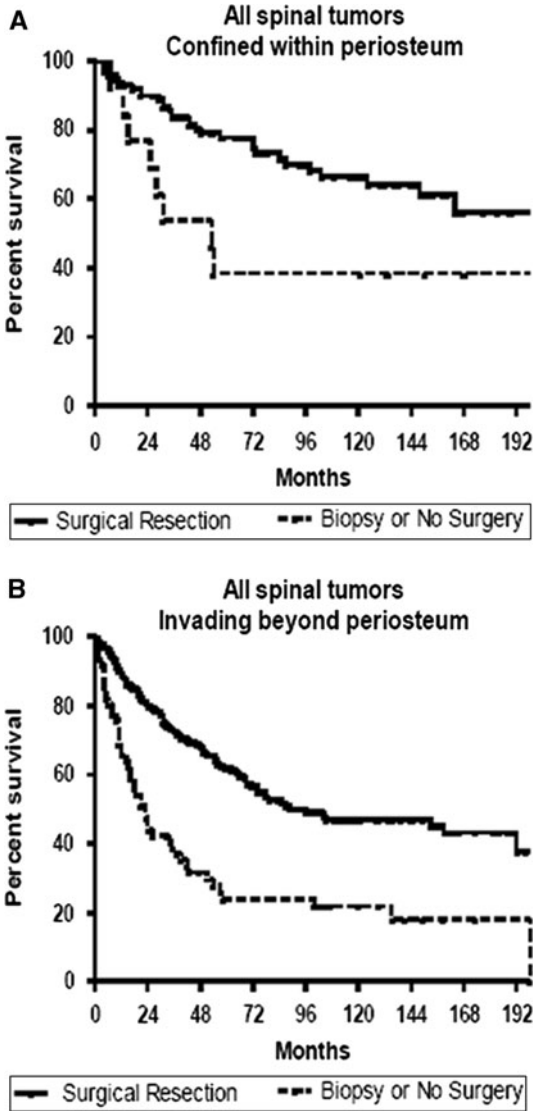

Fig. 2 Kaplan–Meier estimated survival in patients with primary osseous spinal tumors that were: **a** confined (tumor confined to cortex of bone or extension beyond cortex but confined within periosteum) or **b** locally invasive (extension beyond periosteum to surrounding tissues, including adjacent skeletal muscle, adjacent bone/cartilage, or skin). Surgery was associated with increased survival for both primary spinal tumors that were confined ($p < 0.01$) or locally invasive ($p < 0.001$)

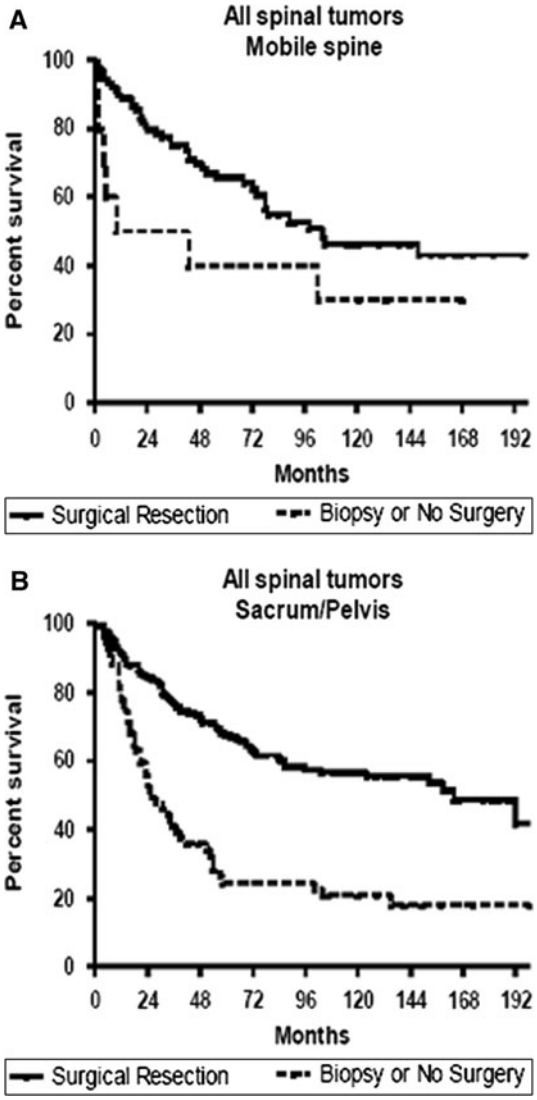

Fig. 3 Kaplan–Meier estimated survival in patients with primary osseous spinal tumors that were located **a** in the mobile spine or **b** the sacrum/pelvis. Surgery was associated with increased survival for both primary tumors located in the mobile spine ($p < 0.05$) as well as those located in the sacrum/pelvis ($p < 0.001$)

Ewing's sarcoma is a poorly differentiated, small round cell tumor that typically arises outside of the spine [36]. Classic treatment of these malignancies has typically involved chemotherapy and XRT after obtaining tissue for diagnosis [29]. Surgical resection is typically reserved for cases in which the primary tumor can be completely removed, which is often difficult in the spine due to anatomical limitations [29]. Bacci et al. [3] evaluated 43 patients with spine tumors over an approximate 20-year time span at a single institution and found no difference in survival between patients who were treated locally with radiation and those treated by radiation and surgery. Likewise, Paulino and colleagues [26] evaluated 76 patients with localized Ewing's sarcoma (only 11 of which had spine involvement) and found there was no difference in survival for patients with radiation, surgery, and radiation with surgery. However, these limited studies were far too underpowered to assess the role of surgery or survival. The present study, however, with 182 patients with isolated spinal Ewing's sarcoma found a survival advantage for patients treated with surgical resection over biopsy by more than twofold. This was true regardless of extent of local tumor invasion, spine location (mobile vs. sacrum/pelvis), or age.

Osteosarcoma is the most common type of malignant bone cancer. Classic treatment involves a multidisciplinary

approach including pre-operative chemotherapy followed by surgical resection [14, 19]. This has resulted in improved survival, but these studies have been primarily limited to patients with limb and not spine involvement. Delaney et al. [10] found a significant 5-year survival advantage between patients who underwent surgical resection (75 %) relative to those who underwent biopsy (25 %) for patients with osteosarcoma. Of the 41 patients in this series, patients with metastatic disease were included and only eight patients had spine involvement [10]. Ozaki et al. [25] evaluated 22 patients with spinal osteosarcoma, with 6 patients having metastatic disease. They found a significant survival difference between 5 patients who underwent wide excision relative to 17 patients (10 biopsy and 7 intra-lesional) who did not undergo wide excision [25]. Similarly, Sundaresan et al. [34] evaluated 24 patients with spinal osteosarcoma treated between 1949 and 1984, and found that patients who underwent more aggressive treatment (surgery, radiation, chemotherapy) had improved survival over biopsy and radiation. The independent effect of surgery, radiation, and/or chemotherapy on survival could not be determined given the low patient numbers [34]. The present study with 158 patients with isolated spinal osteosarcoma without metastasis found a survival advantage for patients treated with surgical resection over biopsy by almost threefold. This was true regardless of extent of local tumor invasion spine location (mobile vs. sacrum/pelvis), or age. Radiation was associated with enhanced survival for those patients who underwent surgery, which has been seen in prior studies [25].

Chondrosarcoma is a cartilage-based bone tumor and is the second most common type of malignant bone tumor [33]. Chordomas are tumors that arise from notochordal elements, and typically occur in the clivus and sacrum [33]. Studies evaluating the role of surgery versus medical management alone for these lesions are few and limited. The majority of studies for have compared intra-lesional versus wide or en bloc resection, and are limited to only resectable lesions [4–7, 13, 16]. The majority of these studies suggest that surgery improved local disease control and prolongs survival when en bloc resection is achieved. The present study with 282 and 215 patients with isolated spinal chondrosarcoma and chordomas found a survival advantage for patients treated with surgical resection over biopsy by more than 6- and 2-fold, respectively. This was true regardless of extent of local tumor invasion, spine location (mobile vs. sacrum/pelvis), or age. Radiation was associated with prolonged survival for patients with chordomas, but not chondrosarcomas.

The present study is the first population-based study on malignant primary osseous tumors of the spine with sufficient power to evaluate the role of surgical resection on survival. We believe this study provides several useful insights. Importantly, this study supports the notion that patients may experience a survival benefit from surgical resection of their lesion. Previous studies on the efficacy of surgical resection as compared to biopsy for patients with primary malignant bone tumors of the spine have been limited to small institutional studies and clinical trials. Additionally, this survival advantage for patients undergoing surgical resection was independent of variables that may affect survival including metastasis status, age, XRT, and degree of invasion which minimizes the bias associated with retrospective analysis. Furthermore, radiation may play a role in enhancing survival following surgical resection, as reported in non-spinal osseous malignancies.

This study, however, has limitations. One limitation is that the variations in specific treatment strategies cannot be accounted for including chemotherapy and spine stabilization techniques. Even though most of these osseous tumors are chemo-resistant, the SEER registry does not contain chemotherapy-specific regimens. Additionally, the SEER registry lacks information on en bloc versus intralesional resection. Previous studies have shown that surgical technique may have an impact on survival as may chemotherapy regimens [21, 23, 28, 32, 35, 38]. Moreover, the functional outcome for patients who underwent either surgical resection or biopsy was not available. Although not the focus of this study, neural decompression and stabilization may improve pain and disability in many patients [29]. Despite these inherent limitations, our study focuses on a uniform patient population by utilizing a strict inclusion and exclusion criteria, thus providing more relevant information for patients with primary malignant osseous neoplasms. We included only patients with primary malignant osseous neoplasms and excluded patients with any distant metastatic disease. Furthermore, we performed multivariate analyses and controlled for potential peri-operative confounding variables (age, metastatic disease, extent of invasion, radiation). Hence, the decreased survival obtained with non-surgical patients was not due to increased local invasion and decreased respectability, increased age, or greater distant tumor burden, which decreases but does not eliminate treatment bias. Given these statistical controls and a relatively precise outcome measure, we believe our findings offer useful insights into the management of patients with malignant osseous neoplasms of the spine. Prospective controlled studies are needed to clarify the observations made here.

Conclusion

In our analysis, using the SEER registry over a 30-year period, this study is the largest to evaluate the efficacy of surgery or biopsy for patients with isolated primary

malignant osseous tumors of the spine. Patients with osteosarcomas, chondrosarcomas, Ewing's sarcoma, and chordomas who underwent surgery experienced prolonged survival as compared to patients who underwent medical management alone. This was statistically significant even after controlling for age, XRT, degree of local invasion, and tumor location. XRT was associated with prolonged survival for patients with osteosarcoma and chordomas, but not Ewing's sarcoma and chondrosarcoma. The findings of this study may help guide treatment strategies aimed at prolonging survival for patients with malignant primary osseous neoplasms of the spine and support the need for a trial to definitively assess the efficacy of surgery at prolonging.

Conflict of interest None.

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