# Assessment of the Extent of Surgical Resection as a Predictor of Survival in Patients With Primary Osseous Spinal Neoplasms

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The most common malignant primary bone tumors of the spine include chordomas, osteosarcomas, chondrosarcomas, and Ewing sarcomas.[1] These tumors can cause significant morbidity and mortality secondary to local invasion and destruction of adjacent structures and metastasize to distant organs. Treatment of these tumors usually begins with acquiring tissue for diagnosis.[2] 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 due primarily to the rarity of these malignancies, which account for $< 5\%$ of all osseous neoplasms and $< 0.2\%$ 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.[2]

Studies using the Surveillance, Epidemiology, and End Results (SEER) registry, however, may provide a better source of understanding for rare pathologies. 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 compared with biopsy was associated with improved survival for patients with primary nonmetastatic chordomas, chondrosarcoma, osteosarcomas, and Ewing 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 26% of the US 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 sarcoma, osteosarcoma, chondrosarcoma, and chordoma to assess histology-specific survival during the period from 1973 to 2003.

*International Classification of Disease for Oncology* (ICD-O), third edition, criteria were used to identify cases of histologically confirmed Ewing sarcoma (ICD-O code, 9260), osteosarcoma (ICD-O codes, 9180-9185, 9190), chondrosarcoma (ICD-O code, 9220), and chordoma (ICD-O code, 9370). Histological confirmation was obtained in all patients from either 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) vs sacrum/pelvis (ICD-O code, 414), metastasis status, whether XRT was administered, extent of tumor invasion, and whether surgical resection was performed. Data regarding chemotherapy were not available in the SEER database. Surgical management was defined at the time of care by the treatment team as biopsy for tissue diagnosis or surgical resection. Differentiation between intralesional 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 intraoperative surgeon assessment and classified as confined (tumor confined to cortex of bone or extension beyond cortex but confined within periosteum) or 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.


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For each tumor histology, the association of surgical resection with overall survival was assessed via Cox proportional-hazards regression analysis with adjustment for age, XRT, and extent of local tumor invasion.

## RESULTS

### Patient Population

Eight hundred twenty-seven patients were identified with nonmetastatic primary osseous spinal neoplasms (215 chordoma, 282 chondrosarcoma, 158 osteosarcoma, 172 Ewing sarcoma). Patients presenting with Ewing sarcoma of the spine were on average younger (19 ± 10 years; $P < .01$) and patients presenting with spinal chordoma were on average older (59 ± 16 years; $P < .01$) compared with patients with chondrosarcoma or osteosarcoma (49 ± 20 years). The majority of patients were male for all tumor types, ranging from 55% for osteosarcoma to 70% for Ewing sarcoma. African Americans made up a significantly greater proportion of osteosarcoma than all other tumors (13% vs 4%; $P < .01$). Otherwise, there was not an association between race and histology type.

### Presentation and Treatment

The sacrum vs mobile spine was more frequently the site of tumor location for all tumor types, ranging from 56% for chordoma to 80% for chondrosarcoma. For all histology types, the majority of tumors had invaded through the periosteum (66%) rather than being confined within the periosteum (34%). 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 sarcoma (57%). Radiation therapy was most commonly administered in patients with Ewing sarcoma (67%) and least commonly in patients with chondrosarcoma (19%). Forty-three percent of patients with chordoma and 29% with osteosarcoma received XRT.

### Survival

Among 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. Median survival was 90 months for Ewing sarcoma, 96 months for chordoma, 88 months for chondrosarcoma, and 18 months for osteosarcoma.

After adjustment for age, XRT, and extent of local tumor invasion in patients with isolated (nonmetastatic) spine tumors, surgical resection was associated with significantly improved survival for chordoma (hazard ratio [HR], 0.617; 95% confidence interval [CI], 0.25-0.98), chondrosarcoma (HR, 0.153; 95% CI, 0.07-0.36), osteosarcoma (HR, 0.382; 95% CI, 0.21-0.69), and Ewing sarcoma (HR, 0.494; 95% CI, 0.26-0.96). In patients with chondrosarcoma or Ewing sarcoma, median and 5-year survival was similar for patients undergoing surgery plus XRT and surgery alone. However, in patients with osteosarcoma and chordoma, median and 5-year survival was greater for patients undergoing surgery plus XRT than surgery alone. For osteosarcoma, median survival increased from 37 to 43 months for patients receiving surgery plus XRT compared with surgery alone. For chordoma, median survival increased from 87 to 104 months for patients receiving surgery plus XRT compared with surgery alone. In an analysis of all tumor types, surgery compared with biopsy was associated with improved survival for both tumors confined to and extending beyond the periosteum. Surgical resection compared with biopsy was also associated with improved survival for lesions of both the mobile spine and sacrum/pelvis.

## DISCUSSION

In our analysis of the 4 most common primary spine tumors recorded in the SEER registry over 3 decades, we evaluated the role of surgical resection compared with biopsy for patients with isolated malignant primary osseous tumors of the spinal column. Overall median survival was histology specific; the median survival was 90 months for Ewing sarcoma, 96 months for chordoma, 88 months for chondrosarcoma, and 18 months for osteosarcoma. Patients who underwent surgical resection had improved survival compared with patients who underwent biopsy, even after adjustment for age at the time of surgery, XRT, and extent of local tumor invasion for all 4 tumor types. Additionally, patients had improved survival with surgical resection regardless of the extent of tumor invasion or spinal location. Interestingly, among patients who underwent surgical resection, adjuvant XRT was associated with prolong survival for patients with osteosarcoma and chordomas.

Approximately 2380 new cases of bone cancer are diagnosed in the United States each year, with approximately 5% involving the spine.[1] Among malignant primary osseous neoplasms, the 4 most common include osteosarcoma (35%), chondrosarcoma (26%), Ewing sarcoma (16%), and chordoma (8%).[3-8] The overall 5-year relative survival rates for spine-limited malignant bone tumors range from 10% to 30% for osteosarcoma,[9-11] 50% to 75% for chondrosarcoma,[12-15] 30% to 65% for Ewing sarcoma,[16-19] and 50% to 85% for chordoma.[20-24] 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,[9-11] 50% to 70% for chondrosarcoma,[12,13,25] 30% to 60% for Ewing sarcoma,[17,18,26,27] and 45% to 65% for chordomas.[28,29] The high recurrence rates, limited survival duration, and functional morbidity associated with these tumors have supported the need for aggressive multimodality strategies for these tumors. Surgical resection decreases tumor burden, may increase chemotherapy and/or XRT efficacy, and may allow neural

decompression and spinal stabilization. Additionally, in some cases, surgery may remove the tumor entirely with negative margins.[2] 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.

Ewing sarcoma is a poorly differentiated, small round cell tumor that typically arises outside the spine.[30] Classic treatment of these malignancies has typically involved chemotherapy and XRT after tissue is obtained for diagnosis.[2] Surgical resection is typically reserved for cases in which the primary tumor can be completely removed, which is often difficult in the spine owing to anatomic limitations.[2] Bacci et al[27] 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[19] evaluated 76 patients with localized Ewing sarcoma (only 11 of which had spine involvement) and found 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 sarcoma, found a survival advantage for patients treated with surgical resection over biopsy of $>$ 2-fold. This was true regardless of the 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 preoperative chemotherapy followed by surgical resection.[31,32] This has resulted in improved survival, but these studies have been limited primarily to patients with limb and not spine involvement. DeLaney et al[33] found a significant 5-year survival advantage between patients who underwent surgical resection (75%) compared with biopsy (25%) for patients with osteosarcoma. Of the 41 patients in this series, patients with metastatic disease were included, and only 8 patients had spine involvement.[33] Ozaki et al[9] 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 and 17 patients (10 biopsy and 7 intralesional) who did not undergo wide excision.[9] Similarly, Sundaresan et al[11] 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 those who underwent biopsy and radiation. The independent effect of surgery, radiation, and/or chemotherapy on survival could not be determined given the low patient numbers.[11] The present study with 158 patients with isolated spinal osteosarcoma without metastasis found a survival advantage for patients treated with surgical resection over biopsy of almost 3-fold. This was true regardless of the 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.[9]

Chondrosarcoma, a cartilage-based bone tumor, is the second most common type of malignant bone tumor.[8] Chordomas are tumors that arise from notochordal elements and typically occur in the clivus and sacrum.[8] Studies evaluating the role of surgery vs medical management alone for these lesions are few and limited. The majority of studies have compared intralesional with wide or en bloc resection and are limited to only resectable lesions.[12,13,20,21,25,28] 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 of $>$ 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 of malignant primary osseous tumors of the spine with sufficient power to evaluate the role of surgical resection on survival. We believe that 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 compared with 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 after surgical resection, as reported in nonspinal osseous malignancies.

This study, however, has limitations. One limitation is that the variations in specific treatment strategies, including chemotherapy and spine stabilization techniques, cannot be accounted for. Even though most of these osseous tumors are chemoresistant, the SEER registry does not contain chemotherapy-specific regimens. Additionally, the SEER registry lacks information on en bloc vs intralesional resection. Previous studies have shown that surgical technique may have an impact on survival, as may chemotherapy regimens.[24,34-38] Moreover, the functional outcome for patients who underwent surgical resection vs biopsy was not available. Although not the focus of this study, neural decompression and stabilization may improve pain and disability in many

 

patients.[2] Despite these inherent limitations, our study focuses on a uniform patient population by using 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 perioperative confounding variables (age, metastatic disease, extent of invasion, radiation). Hence, the decreased survival obtained with nonsurgical 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 compared with biopsy for patients with isolated primary malignant osseous tumors of the spine. Patients with osteosarcomas, chondrosarcomas, Ewing sarcoma, and chordomas who underwent surgery experienced prolonged survival compared with patients who underwent medical management alone. This was statistically significant even after controlling for age, XRT, degree of local invasion, and tumor location. Radiation therapy was associated with prolonged survival for patients with osteosarcoma and chordomas but not Ewing 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 survival.

## Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

## REFERENCES


1. Facts and figures. 2008. http://www.americancancersociety.org. Accessed November 19, 2008.
2. Sciubba DM, Okuno SH, Dekutoski MB, Gokaslan ZL. Ewing and osteogenic sarcoma: evidence for multidisciplinary management. *Spine (Phila Pa 1976)*. 2009;34(22)(suppl):S58-S68.
3. Dorfman HD, Czerniak B. Bone cancers. *Cancer*. 1995;75(1)(suppl): 203-210.
4. Bovill EG Jr, Kung'u A, Bencivenga A, Jeshrani MK, Mbindyo BS, Heda PM. An epidemiological study of osteogenic sarcoma in Kenya: the variations in incidence between ethnic groups and geographic regions, 1968-1978. *Int Orthop*. 1985;9(1):59-63.
5. Larsson SE, Lorentzon R. The incidence of malignant primary bone tumours in relation to age, sex and site: a study of osteogenic sarcoma, chondrosarcoma and Ewing's sarcoma diagnosed in Sweden from 1958 to 1968. *J Bone Joint Surg Br*. 1974;56B(3):534-540.
6. Oyemade GA, Abioye AA. Primary malignant tumors of bone: incidence in Ibadan, Nigeria. *J Natl Med Assoc*. 1982;74(1):65-68.
7. Price CH, Jeffree GM. Incidence of bone sarcoma in SW England, 1946-74, in relation to age, sex, tumour site and histology. *Br J Cancer*. 1977; 36(4):511-522.
8. Sundaresan N, Rosen G, Boriani S. Primary malignant tumors of the spine. *Orthop Clin North Am*. 2009;40(1):21-36, v.
9. Ozaki T, Flege S, Liljenqvist U, et al. Osteosarcoma of the spine: experience of the Cooperative Osteosarcoma Study Group. *Cancer*. 2002; 94(4):1069-1077.
10. Shives TC, Dahlin DC, Sim FH, Pritchard DJ, Earle JD. Osteosarcoma of the spine. *J Bone Joint Surg Am*. 1986;68(5):660-668.
11. Sundaresan N, Rosen G, Huvos AG, Krol G. Combined treatment of osteosarcoma of the spine. *Neurosurgery*. 1988;23(6):714-719.
12. Bergh P, Gunterberg B, Meis-Kindblom JM, Kindblom LG. Prognostic factors and outcome of pelvic, sacral, and spinal chondrosarcomas: a center-based study of 69 cases. *Cancer*. 2001;91(7):1201-1212.
13. Boriani S, De Iure F, Bandiera S, et al. Chondrosarcoma of the mobile spine: report on 22 cases. *Spine (Phila Pa 1976)*. 2000;25(7):804-812.
14. Shives TC, McLeod RA, Unni KK, Schray MF. Chondrosarcoma of the spine. *J Bone Joint Surg Am*. 1989;71(8):1158-1165.
15. York JE, Berk RH, Fuller GN, et al. Chondrosarcoma of the spine: 1954 to 1997. *J Neurosurg*. 1999;90(1)(suppl):73-78.
16. Evans RG, Nesbit ME, Gehan EA, et al. Multimodal therapy for the management of localized Ewing's sarcoma of pelvic and sacral bones: a report from the second intergroup study. *J Clin Oncol*. 1991;9(7):1173-1180.
17. Grubb MR, Currier BL, Pritchard DJ, Ebersold MJ. Primary Ewing's sarcoma of the spine. *Spine (Phila Pa 1976)*. 1994;19(3):309-313.
18. Marco RA, Gentry JB, Rhines LD, et al. Ewing's sarcoma of the mobile spine. *Spine (Phila Pa 1976)*. 2005;30(7):769-773.
19. Paulino AC, Nguyen TX, Mai WY. An analysis of primary site control and late effects according to local control modality in non-metastatic Ewing sarcoma. *Pediatr Blood Cancer*. 2007;48(4):423-429.
20. Bergh P, Kindblom LG, Gunterberg B, Remotti F, Ryd W, Meis-Kindblom JM. Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. *Cancer*. 2000;88(9):2122-2134.
21. Boriani S, Bandiera S, Biagini R, et al. Chordoma of the mobile spine: fifty years of experience. *Spine (Phila Pa 1976)*. 2006;31(4):493-503.
22. Cheng EY, Ozerdemoglu RA, Transfeldt EE, Thompson RC Jr. Lumbosacral chordoma: prognostic factors and treatment. *Spine (Phila Pa 1976)*. 1999;24(16):1639-1645.
23. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973-1995. *Cancer Causes Control*. 2001;12(1):1-11.
24. York JE, Kaczaraj A, Abi-Said D, et al. Sacral chordoma: 40-year experience at a major cancer center. *Neurosurgery*. 1999;44(1):74-79.
25. Hsieh PC, Xu R, Sciubba DM, et al. Long-term clinical outcomes following en bloc resections for sacral chordomas and chondrosarcomas: a series of twenty consecutive patients. *Spine (Phila Pa 1976)*. 2009; 34(20):2233-2239.
26. Arai Y, Kun LE, Brooks MT, et al. Ewing's sarcoma: local tumor control and patterns of failure following limited-volume radiation therapy. *Int J Radiat Oncol Biol Phys*. 1991;21(6):1501-1508.
27. Bacci G, Boriani S, Balladelli A, et al. Treatment of nonmetastatic Ewing's sarcoma family tumors of the spine and sacrum: the experience from a single institution. *Eur Spine J*. 2009;18(8):1091-1095.
28. Fourney DR, Rhines LD, Hentschel SJ, et al. En bloc resection of primary sacral tumors: classification of surgical approaches and outcome. *J Neurosurg Spine*. 2005;3(2):111-122.

29. Ito E, Saito K, Okada T, Nagatani T, Nagasaka T. Long-term control of clival chordoma with initial aggressive surgical resection and gamma knife radiosurgery for recurrence. *Acta Neurochir (Wien)*. 2010;152(1): 57-67.
30. Weber KL. Current concepts in the treatment of Ewing's sarcoma. *Expert Rev Anticancer Ther*. 2002;2(6):687-694.
31. Gherlinzoni F, Picci P, Bacci G, Campanacci D. Limb sparing versus amputation in osteosarcoma: correlation between local control, surgical margins and tumor necrosis: Istituto Rizzoli experience. *Ann Oncol*. 1992; 3(suppl 2):S23-S27.
32. Link MP, Goorin AM, Horowitz M, et al. Adjuvant chemotherapy of high-grade osteosarcoma of the extremity: updated results of the Multi-Institutional Osteosarcoma Study. *Clin Orthop Relat Res*. 1991(270): 8-14.
33. DeLaney TF, Park L, Goldberg SI, et al. Radiotherapy for local control of osteosarcoma. *Int J Radiat Oncol Biol Phys*. 2005;61(2):492-498.
34. Marmor E, Rhines LD, Weinberg JS, Gokaslan ZL. Total en bloc lumbar spondylectomy: case report. *J Neurosurg*. 2001;95(2)(suppl):264-269.
35. Rao G, Suki D, Chakrabarti I, et al. Surgical management of primary and metastatic sarcoma of the mobile spine. *J Neurosurg Spine*. 2008;9(2):120-128.
36. Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. *Cancer*. 2008;113(2):419-425.
37. Stacchiotti S, Marrari A, Tamborini E, et al. Response to imatinib plus sirolimus in advanced chordoma. *Ann Oncol*. 2009;20(11):1886-1894.
38. Wagner LM, McAllister N, Goldsby RE, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. *Pediatr Blood Cancer*. 2007;48(2):132-139.

 