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Incidence, Management, and Outcomes of Adult Spinal Chordoma Patients in the United States

Saavan Patel, BS[1], Ravi S. Nunna, MD[1], James Nie, BS[1], Darius Ansari, BS[1], Nauman S. Chaudhry, MD[1], and Ankit I. Mehta, MD[1]

Abstract

Study Design: Retrospective cohort study.

Objective: Spinal chordomas are rare primary malignant neoplasms of the primitive notochord. They are slow growing but locally aggressive lesions that have high rates of recurrence and metastasis after treatment. Gold standard treatment remains en-bloc surgical resection with questionable efficacy of adjuvant therapies such as radiation and chemotherapy. Here we provide a comprehensive analysis of prognostic factors, treatment modalities, and survival outcomes in patients with spinal chordoma.

Methods: Patients with diagnosis codes specific for chordoma of spine, sacrum, and coccyx were queried from the National Cancer Database (NCDB) during the years 2004-2016. Outcomes were investigated using Cox univariate and multivariate regression analyses, and survival curves were generated for comparative visualization.

Results: 1,548 individuals were identified with a diagnosis of chordoma, 60.9% of which were at the sacrum or coccyx and 39.1% at the spine. The mean overall survival of patients in our cohort was 8.2 years. Increased age, larger tumor size, and presence of metastases were associated with worsened overall survival. 71.2% of patients received surgical intervention and both partial and radical resection were associated with significantly improved overall survival ($P < 0.001$). Neither radiotherapy nor chemotherapy administration improved overall survival; however, amongst patients who received radiation, those who received proton-based radiation had significantly improved overall survival compared to traditional radiation.

Conclusion: Surgical resection significantly improves overall survival in patients with spinal chordoma. In those patients receiving radiation, those who receive proton-based modalities have improved overall survival. Further studies into proton radiotherapy doses are required.

Keywords

spinal chordoma, surgery, resection, radiation, proton therapy

Introduction

Spinal chordomas are malignant neoplasms of the primitive notochord that have an incidence of approximately five out of one million cases per year.[1-5] Chordomas are located on the axial skeleton, specifically in the sacrum (50-60%), skull base (25-35%), cervical region (10%), and thoracolumbar vertebrae (5%).[2-5] Overall 5- and 10-year survival rates have been reported to be as low as 54.6% and 36.5%, respectively.[2] Spinal chordomas are more prevalent in males, with an average age of diagnosis of 60 years old.[1,2,5-7] Symptoms associated with spinal chordoma are generally indolent, as chordomas are slow growing and locally aggressive, and may delay diagnosis.[2,6,8-11] Despite their slow growth, chordomas have high rates of recurrence (up to 67%) and metastasis (30-40%) after treatment.[3,6,7,12]

Currently, en-bloc resection remains the most important factor in tumor recurrence, metastasis, and overall survival.[3,5-7,9,13-15]

[1] Department of Neurosurgery, University of Illinois at Chicago, IL, USA

Corresponding Author:
Ankit I. Mehta, Department of Neurosurgery, University of Illinois at Chicago, 912 South Wood Street, 451-N, Chicago, IL, 60612, USA.
Email: ankitm@uic.edu

However, en-bloc resection can involve significant removal of surrounding nerve and ligamentous structures and may not always be possible or have undesirable morbidity that limits this resection.[2,3,14,16] In addition to the considerable risk associated with en-bloc resection, traditional radiotherapy and chemotherapy are considered largely ineffective.[3,4,6,8,10,14,15,17,18] Traditional radiotherapy is ineffective due to the recurrence of chordomas and subtherapeutic doses used in the brain and spinal cord.[8,17] However, proton-based radiotherapy with and without resection have shown potential promise in regards to survival without the significant effects associated with en-bloc resection.[2,5,10,17,19,20] Because of the slow growth of spinal chordomas, conventional chemotherapy has been shown to have little effect on spinal chordoma.[2-4,6,8]

Due to the rare nature of spinal chordomas, many studies are limited to small case series and fail to comprehensively investigate prognostic factors and survival trends. This study explores the prognostic factors, treatment modalities, and survival outcomes in spinal chordoma using a large, prospectively-collected national database.

Methods

Study Cohort

Data for this investigation was derived from the National Cancer Database (NCDB), a prospectively collected cancer registry maintained jointly by the American College of Surgeons and the American Cancer Society. This database is sourced from over 1,500 cancer centers and represents more than 70% of newly diagnosed cancer cases and more than 34 million historical records. The data used in the study was derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

For the purposes of this study, the database was queried for all adult patients (age >17) diagnosed with spinal chordoma, between the years 2004 and 2016; the query was performed using the International Classification of Disease codes (ICD). All patients with tumors originating from either the vertebral column (primary site code C41.2) and sacrum or coccyx (primary site code C41.4) were first isolated. The histologic subtypes that satisfied chordoma as classified by the ICD for Oncology Third Edition (ICD-O-3) were then further specified. These histologic subtypes included all patients with: chordoma, NOS (9370), chondroid chordoma (9371), and dedifferentiated chordoma (9373). This study included only adult patients for which spinal chordoma was recorded as their first and primary tumor. Subsequent tumors, recurrences, and cases diagnosed at autopsy were excluded. Furthermore, all cases that lacked histopathological confirmation were also excluded.

NCDB data is publicly available and de-identified, and thus did not require review from our Institutional Review Board or patient consent.

Statistical Analysis

Descriptive analyses were performed to evaluate patient, tumor, and treatment characteristics. Survival status was the variable employed to assess outcomes, and defined as either alive or not alive (i.e. all-cause mortality). This value was determined as the interval in months between the time of diagnosis and death or last follow-up as reported by NCDB. All available demographic and treatment data was analyzed with respect to survival status.

A univariate and all-inclusive multivariate regression analysis was performed based on the Cox proportional hazards model to analyze survival and adjust for confounding variables. Coefficients in the model were converted to hazard ratios (HR) for analysis of survival over the entire study period. A semiparametric Cox approach was used to generate survival curves for comparative visualization of various demographic and treatment variables, with corresponding log-rank testing performed. All p values were reported as 2-sided, with statistical significance defined as $P < 0.05$. Statistical analysis was performed using SPSS Statistics (version 26.0, IBM, Armonk, New York) and R statistical software (version 3.4.0, 2017; R Foundation for Statistical Computing, Vienna, Austria).

Results

Population Baseline Characteristics

The search criteria identified 1548 individuals in the NCDB database who were diagnosed with spinal chordoma between 2004-2016. Most individuals in the population were above 65 years of age (n = 750, 48.5%), while individuals aged 18-35 years constituted the smallest age group (n = 116, 7.5%). The majority of the cohort was classified as white (n = 1375, 88.8%), followed by other (n = 109, 7.0%), and black (n = 64, 4.1%). Males (n = 944, 61.0%) were more common than females (n = 604, 39.0%). Charlson/Deyo Comorbidity Score analysis indicated that most patients (n = 1258, 81.3%) were relatively healthy with a score of 0. Tumors were more common in the sacrum or coccyx (n = 942, 60.9%) than the spine (n = 606, 39.1%). Histologically, tumors were most often classified as chordoma, NOS (n = 1480, 95.6%), with chondroid (n = 45, 2.9%) and dedifferentiated (n = 23, 1.5%) chordomas representing the minority. Most tumors were of unknown size (n = 465, 30.0%), but tumors of known size frequently ranged between 5-10 cm (n = 463, 29.9%). Metastatic disease was absent in most patients at the time of diagnosis (n = 1302, 84.1%). The full baseline characteristics of this study population is presented in Table 1.

Treatment Characteristics

Surgery was performed for 72.2% of patients in the cohort (n = 1117), with radical resection (n = 550, 35.5%) being more common than partial resection (n = 499, 32.2%). Surgical

Table 1. Baseline Characteristics of Spinal Chordoma in Adults.

Characteristics	Total (N = 1,548)
Age	
18-35 years, n (%)	116 (7.5)
36-54 years, n (%)	343 (22.2)
55-64 years, n (%)	339 (21.9)
65+ years, n (%)	750 (48.4)
Sex	
Male, n (%)	944 (61.0)
Female, n (%)	604 (39.0)
Race	
White, n (%)	1375 (88.8)
Black, n (%)	64 (4.1)
Other, n (%)	109 (7.0)
Charlson/Deyo Score	
0, n (%)	1,258 (81.3)
1, n (%)	215 (13.9)
2, n (%)	57 (3.7)
≥3, n (%)	18 (1.2)
Tumor Histology	
Chordoma, NOS, n (%)	1480 (95.6)
Chondroid Chordoma, n (%)	45 (2.9)
Dedifferentiated Chordoma, n (%)	23 (1.5)
Tumor Location	
Spine, n (%)	606 (39.1)
Sacrum or Coccyx, n (%)	942 (60.9)
Tumor Size	
0-5 cm, n (%)	397 (25.6)
5-10 cm, n (%)	463 (29.9)
10+ cm, n (%)	223 (14.4)
Unknown, n (%)	465 (30.0)
Metastases	
None, n (%)	1,302 (84.1)
Present, n (%)	194 (12.5)
Unknown, n (%)	52 (3.4)
Survival	
Overall survival, mean	8.19 years

Table 2. Treatment Characteristics of Spinal Chordoma in Adults.

Characteristics	Total (N = 1,548)
Surgical Treatment	
Extent of resection	
None, n (%)	431 (27.8)
Partial resection, n (%)	499 (32.2)
Radical resection, n (%)	550 (35.5)
Surgery performed, extent unknown, n (%)	54 (3.5)
Surgery performed, days from diagnosis, mean (SD)	47.2 (56.2)
Surgical inpatient stay, days after surgery, mean (SD)	9.6 (12.2)
Systemic Treatment	
Chemotherapy Administration	
None, n (%)	1,412 (91.2)
Administered, n (%)	63 (4.1)
Unknown, n (%)	73 (4.7)
Radiation Treatment	
None, n (%)	855 (55.2)
Traditional, n (%)	522 (33.7)
Proton, n (%)	134 (8.7)
Unknown, n (%)	37 (2.4)
RT started, days from diagnosis, mean (SD)	106.6 (97.9)
Regional dose, cGy, mean (SD)	5,108 (3,576)
Treatment volumes, mean (SD)	26.1 (4.5)
Treatment duration (days), mean (SD)	56.2 (118.4)
Radiation Dose	
None, n (%)	856 (55.3)
0-3,000 cGy, n (%)	112 (7.2)
3,000-6,000 cGy, n (%)	293 (18.9)
6,000+ cGy, n (%)	170 (11.0)
Unknown, n (%)	117 (7.6)

procedures were performed on average 47.2 days (SD, 56.2) following diagnosis resulting in a mean inpatient stay of 9.6 days (SD, 12.2) after surgery (Table 2).

Most patients did not receive radiation treatment (n = 855, 55.2%). Traditional radiation was administered in 522 patients (33.7%), while proton-based therapy was undertaken in fewer patients (n = 134, 8.7%). Radiotherapy was started on average 106.6 days (SD, 97.9) days following diagnosis, was administered for 26.1 volumes (SD, 4.5), at a regional dose of 5,108 cGy (SD, 3576). Of the entire study cohort, 18.9% of patients received a radiation dose between 3000-6000 cGy. Average duration of treatment in days was 56.2 (SD, 118.4).

Chemotherapy administration was uncommon in this cohort (n = 63, 4.1%).

Survival Outcomes

Overall survival (OS) in the study population was 8.19 years on average (Table 1). Increased OS was univariately associated with surgical treatment by partial resection (HR = 0.40; 95% CI, 0.32-0.50; $P < 0.001$) and radical resection (HR = 0.33; 95% CI, 0.27-0.42; $P < 0.001$); decreased OS was univariately associated with age 65+ years (HR = 2.41; 95% CI, 1.58-3.69; $P < 0.001$), tumor size (5-10 cm: HR = 1.46; 95% CI, 1.13-1.89; $P = 0.003$. >10 cm: HR = 1.87; 95% CI, 1.41-2.50; $P < 0.001$), presence of metastasis (HR = 2.91; 95% CI, 1.89-4.47; $P < 0.001$), and chemotherapy administration (HR = 1.83; 95% CI, 1.24-2.71; $P = 0.002$). Analysis with all-inclusive multivariate regression revealed associations between increased OS and surgical treatment by partial resection (HR = 0.43; 95% CI, 0.32-0.58; $P < 0.001$), treatment by radical resection (HR = 0.35; 95% CI, 0.26-0.47; $P < 0.001$), and tumor location within the sacrum or coccyx (HR = 0.73; 95% CI, 0.55-0.97; $P = 0.03$). Conversely, decreased OS was found by multivariate regression to be associated with age 65+ years (HR = 2.88; 95% CI, 1.54-5.40; $P < 0.001$), tumor size (5-10 cm: HR = 1.36; 95% CI, 1.01-1.81; $P = 0.04$. >10 cm: HR = 1.78; 95% CI, 1.26-2.51; $P = 0.001$), and presence of metastasis (HR = 3.37; 95% CI, 1.80-6.30; $P < 0.001$). Notably, while chemotherapy administration was univariately associated with decreased OS, this association was not present upon all-inclusion multivariate analysis. Compared to patients not receiving radiation therapy, treatment with traditional radiotherapy was associated with decreased OS (HR = 1.39; 95% CI, 1.15-1.69; $P < 0.001$), while treatment with proton-based

Table 3. Univariate and Multivariate Cox Regression Analysis of Survival Outcomes of Spinal chordoma in Adults.

	Univariate			Multivariate		
Characteristics	HR	95% CI	*P*	HR	95% CI	*P*
Age						
18-35 years (reference)	-	-	-	-	-	-
36-54 years	0.67	0.41-1.09	0.106	0.92	0.46-1.82	0.80
55-64 years	1.01	0.63-1.62	0.964	1.01	0.51-2.00	0.98
65+ years	2.41	1.58-3.69	<**0.001**	2.88	1.54-5.40	<**0.001**
Sex						
Female (reference)	-	-	-	-	-	-
Male	1.10	0.91-1.33	0.31	1.22	0.96-1.55	0.11
Race						
White (reference)	-	-	-	-	-	-
Black	1.07	0.68-1.67	0.78	1.23	0.70-2.17	0.47
Other	0.89	0.61-1.29	0.53	0.71	0.43-1.18	0.19
Tumor Location						
Spine (reference)	-	-	-	-	-	-
Sacrum or Coccyx	0.91	0.75-1.09	0.30	0.73	0.55-0.97	**0.03**
Tumor Size						
0-5 cm (reference)	-	-	-	-	-	-
5-10 cm	1.46	1.13-1.89	**0.003**	1.36	1.01-1.81	**0.04**
>10 cm	1.87	1.41-2.50	<**0.001**	1.78	1.26-2.51	**0.001**
Metastases						
None (reference)	-	-	-	-	-	-
Present	2.91	1.89-4.47	<**0.001**	3.37	1.80-6.30	<**0.001**
Surgery						
None (reference)	-	-	-	-	-	-
Partial resection	0.40	0.32-0.50	<**0.001**	0.43	0.32-0.58	<**0.001**
Radical resection	0.33	0.27-0.42	<**0.001**	0.35	0.26-0.47	<**0.001**
Chemotherapy						
None (reference)	-	-	-	-	-	-
Administered	1.83	1.24-2.71	**0.002**	0.97	0.58-1.63	0.90
Radiation						
None (reference)	-	-	-	-	-	-
Administered	1.16	0.96-1.40	0.12	0.82	0.64-1.05	0.11
Radiation Modality						
None (reference)	-	-	-	-	-	-
Traditional	1.39	1.15-1.69	<**0.001**	-	-	-
Proton	0.50	0.31-0.80	**0.004**	-	-	-
Radiation Dose						
0-3,000 cGy (reference)	-	-	-	-	-	-
3,000-6,000 cGy	1.15	0.77-1.71	0.49	-	-	-
6,000+ cGy	0.75	0.48-1.17	0.21	-	-	-

HR, hazard ratio; CI, confidence interval.

radiotherapy was associated with increased OS (HR = 0.50, 95% CI, 0.31-0.80; $P = 0.004$) (Table 3).

5-year survival outcomes were found to be increased in patients receiving radical resection (74.1%) compared to those receiving partial resection (63.7%) or no surgical treatment (50.3%) (Table 4). Patients administered chemotherapy had lower 5-year survival (51.1%) compared to those untreated with chemotherapy (63.7%). Although 5-year survival in patients receiving radiation and not receiving radiation were approximately the same (62.8% and 62.9%, respectively), stratification by modality revealed a 5-year survival of 58.5% in those receiving traditional radiation therapy compared to 84.0% in those receiving proton-based therapy. Additionally, patients receiving a radiation dose of 6000+ cGy were found to have 70.7% 5-year survival, while survival was lower in patients receiving 3000-6000 cGy (59.0%) or 0-3000 cGy (58.2%). 5-year survival was decreased in individuals with tumor size $\geq$ 10 cm (54.8%) compared to smaller tumors (0-5 cm, 72.2%; 5-10 cm, 65.8%). Patients with tumors in the spine had decreased 5-year survival (58.1%) compared to patients with tumors in the sacrum or coccyx (65.3%). Individuals with metastases had lower 5-year survival (43.2%) than those who did not (64%).

Table 4. 5-Year Survival Outcomes in Adults With Spinal Chordoma Stratified by Treatment and Demographic Factors.

Characteristics	5-year Survival
Surgery	
None	50.3%
Partial resection	63.7%
Radical resection	74.1%
Chemotherapy	
None	63.7%
Administered	51.1%
Radiation	
None	62.8%
Performed	62.9%
Radiation Modality	
Traditional	58.5%
Proton	84.0%
Radiation Dose	
0-3,000 cGy	58.2%
3,000-6,000 cGy	59.0%
6,000+ cGy	70.7%
Tumor Size	
0-5 cm	72.2%
5-10 cm	65.8%
10 cm and greater	54.8%
Tumor Location	
Spine	58.1%
Sacrum or Coccyx	65.3%
Metastases	
None	64%
Present	43.2%

Cox survival analyses revealed that advanced age ($P < 0.0001$, Figure 1A), increased tumor size ($P < 0.0001$, Figure 2B), presence of metastasis ($P < 0.0001$, Figure 2C), and treatment by chemotherapy ($P = 0.002$, Figure 3B) were associated with decreased OS. On the other hand, both partial and radical surgical resection were associated with improved OS ($P < 0.0001$, Figure 3A). Radiotherapy overall did not significantly affect overall survival; however, further analysis shows that amongst patients who received radiation, proton-based radiotherapy was associated with improved OS ($P < 0.0001$, Figure 4A). An association between radiation dose and OS neared but did not reach statistical significance ($P = 0.057$, Figure 4B).

Discussion

Chordomas are exceedingly rare, malignant bone sarcomas that can occur anywhere along the skull base, spine, and sacrum

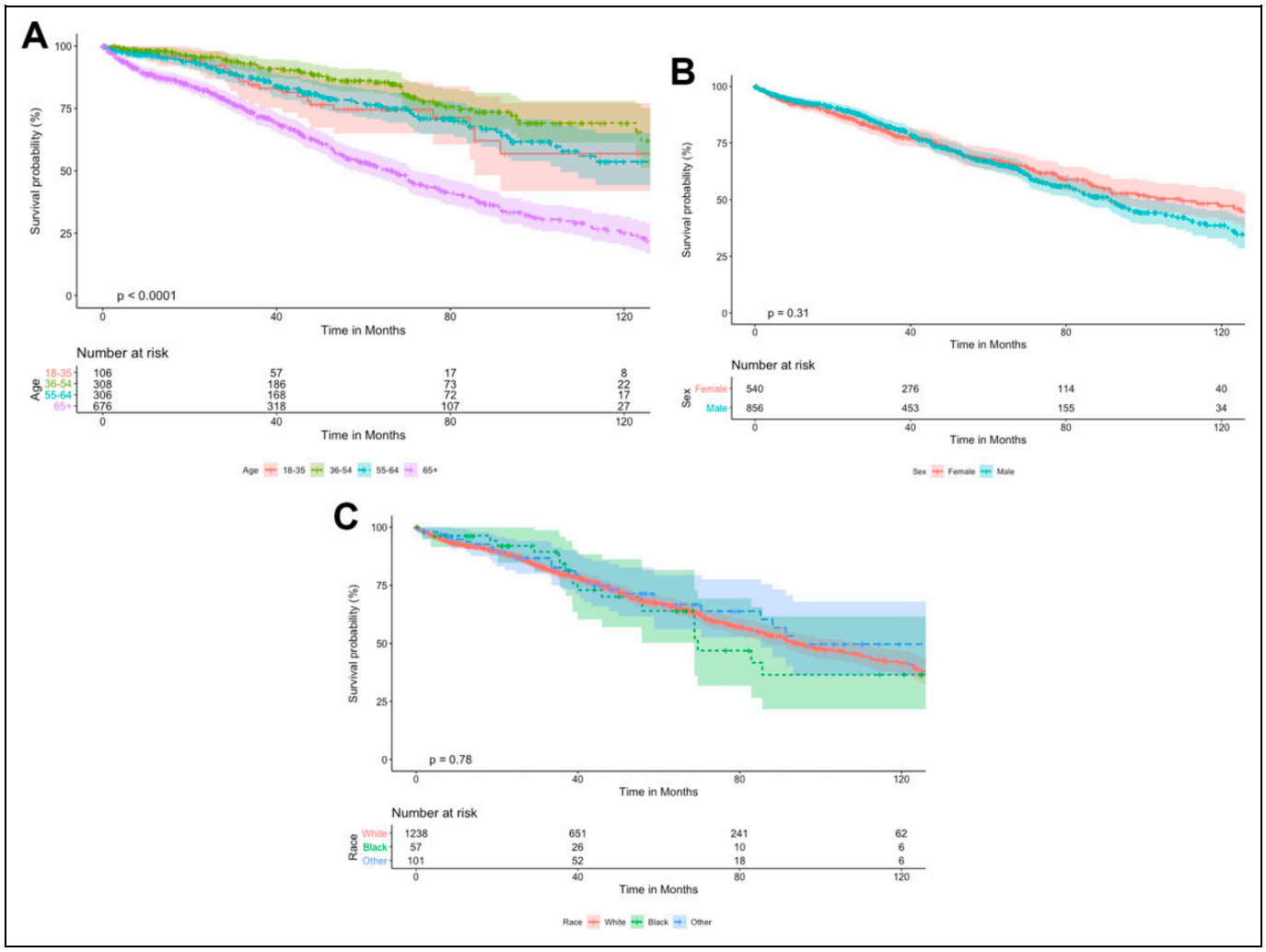

Figure 1. Cox survival analysis of adult spinal chordoma patients by demographic factors. A, Survival by age group. B, Survival by sex. C, Survival by race.

along the distribution of the primitive notochord. The rarity of the tumor, considered alongside its slow-growing nature, renders identification of reliable endpoints difficult and accounts for the paucity of large clinical studies regarding treatment efficacy.[21] A few prior database studies have examined incidence, prognostic factors, and treatment, but data directly comparing survival outcomes of radiotherapy, chemotherapy, and extent of surgical management is scarce.[1,2,22,23]

Previous studies have identified several prognostic factors and in patients with spinal chordomas based on sociodemographic and treatment characteristics. These include factors such as age, type of treatment center, tumor size, metastasis, and treatment modalities. Demographically, our patient cohort largely appears to be in concordance with existing literature, with the highest rates of spinal chordoma found in whites, males, and the elderly population. Previous literature has reported overall survival as 94 months, but as little as 69 months in the elderly.[1] Our cohort was found to have a mean overall survival of 8.2 years, with patients above the age of 65 having nearly a three-fold increase in the odds of death. Large tumor size (>8 cm) has been shown to be an indicator for an increased incidence of recurrence, metastasis, and reduced survival.[3,4] Similarly, our multivariate analysis identified an association between increased tumor size and decreased survival. The presence of metastasis was also found to have the greatest negative impact on survival, with a greater than three-fold increase in odds of death.

En-bloc surgical resection remains the gold standard for treatment of spinal chordoma.[2,4,6,13,24] Pan et al. conducted a retrospective study of 808 patients using the SEER Registry database. While this study noted the benefits of surgical therapy, it did not examine the extent of resection as a prognostic variable.[1] Zhou et al. performed a retrospective analysis of 682 patients from 110 studies. This study similarly shows the benefit of surgical resection but separates the overall survival into positive surgical margin (HR 1.05, 95% CI 0.50-2.22, $P = 0.888$), negative surgical margin (HR 0.75, 95% CI 0.34-1.66, $P = 0.475$), and no surgery.[2] Our study shows that

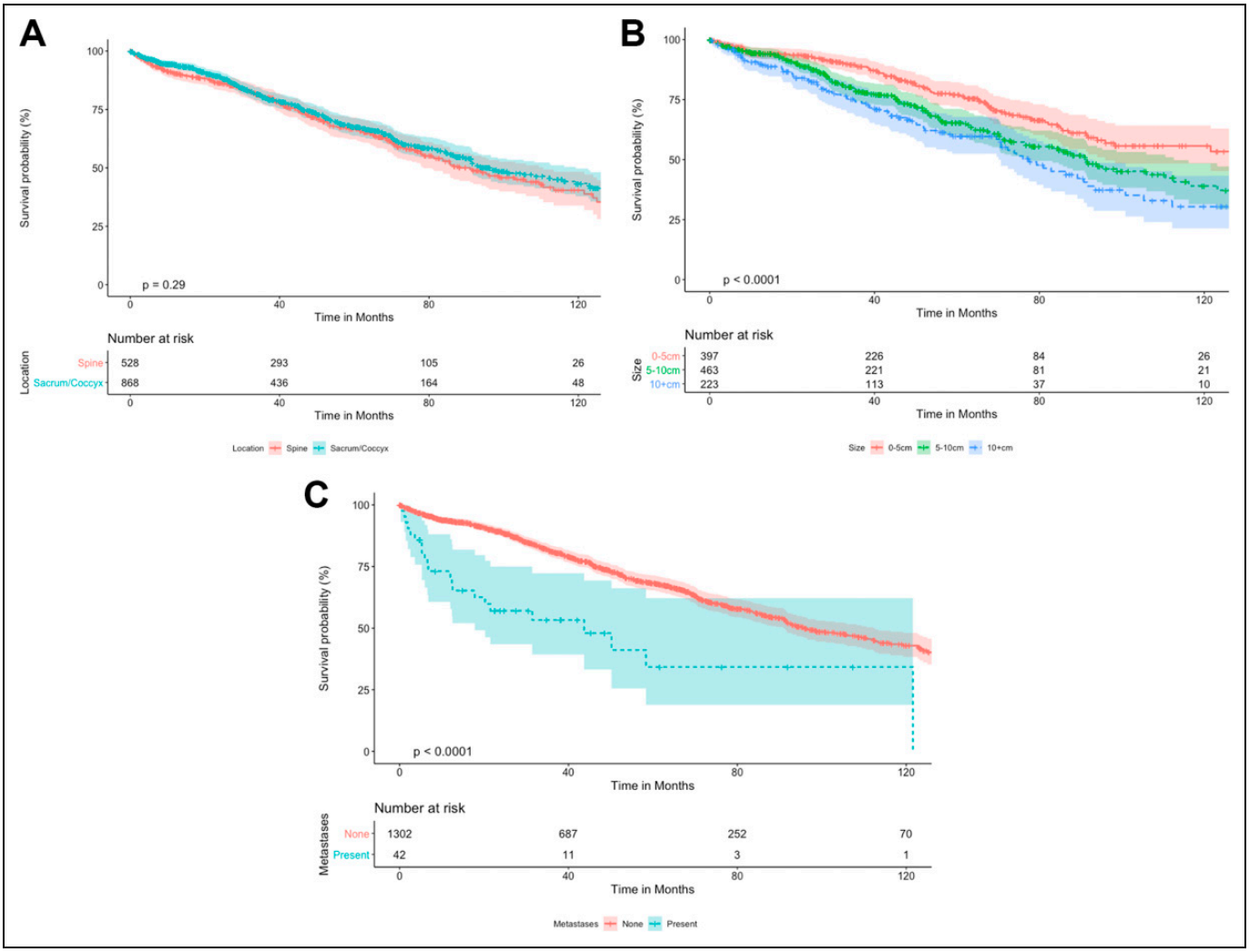

Figure 2. Cox survival analysis of adult spinal chordoma patients. A, Survival by tumor location. B, Survival by tumor size. C, Survival by presence of metastases.

surgical resection, both partial and radical resection, provide significant benefit in overall survival in both univariate and multivariate analysis relative to no surgery. Though the advantages of surgical intervention over non-surgical intervention are well known, the benefits of partial resection contrasts with most existing studies.[1,4,20] However, Eid et al found that subtotal resection with adjunctive radiotherapy showed comparable rates of local control and survival compared to wide resection, which may potentially account for the similar outcomes of both partial and radical resection in our study.[25]

Although chordomas are more resistant to radiotherapy, radiotherapy may provide benefit in patients with spinal chordoma, especially in patients with a positive surgical margin.[2,3,19] Yang et al. conducted an integrated analysis of 523 patients to determine the efficacy of radiotherapy, reported as 5-year overall survival. For patients with a positive surgical margin, overall survival was higher (69.1%) for patients who received radiotherapy compared to no radiotherapy (39.4%, $P = 0.021$).[19] Though our results do not specify whether radiotherapy was used in conjunction with positive surgical margins, our results show significant positive outcomes using proton-based radiotherapy and unclear survival benefit using traditional radiotherapy. Though the efficacy of proton-based and traditional radiotherapy is well documented, the therapeutic dosage is uncertain.[3,20] Chen et al found high-dose proton-based radiation to be beneficial in patients with unresected or inoperable spinal chordomas, and Holliday et al found that early primary adjuvant proton radiotherapy was associated with higher rates of local disease control.[26,27] Additionally, it is important to recognize that the relatively limited availability of proton-based radiotherapy nationwide may necessitate many patients to travel in order to receive this treatment modality; thus, the patients receiving proton therapy may be in inherently better clinical condition permitting them to travel. Nonetheless, there may exist a role for adjuvant high-dose proton radiotherapy, especially for those patients undergoing partial surgical resection. However, further investigation is warranted into the

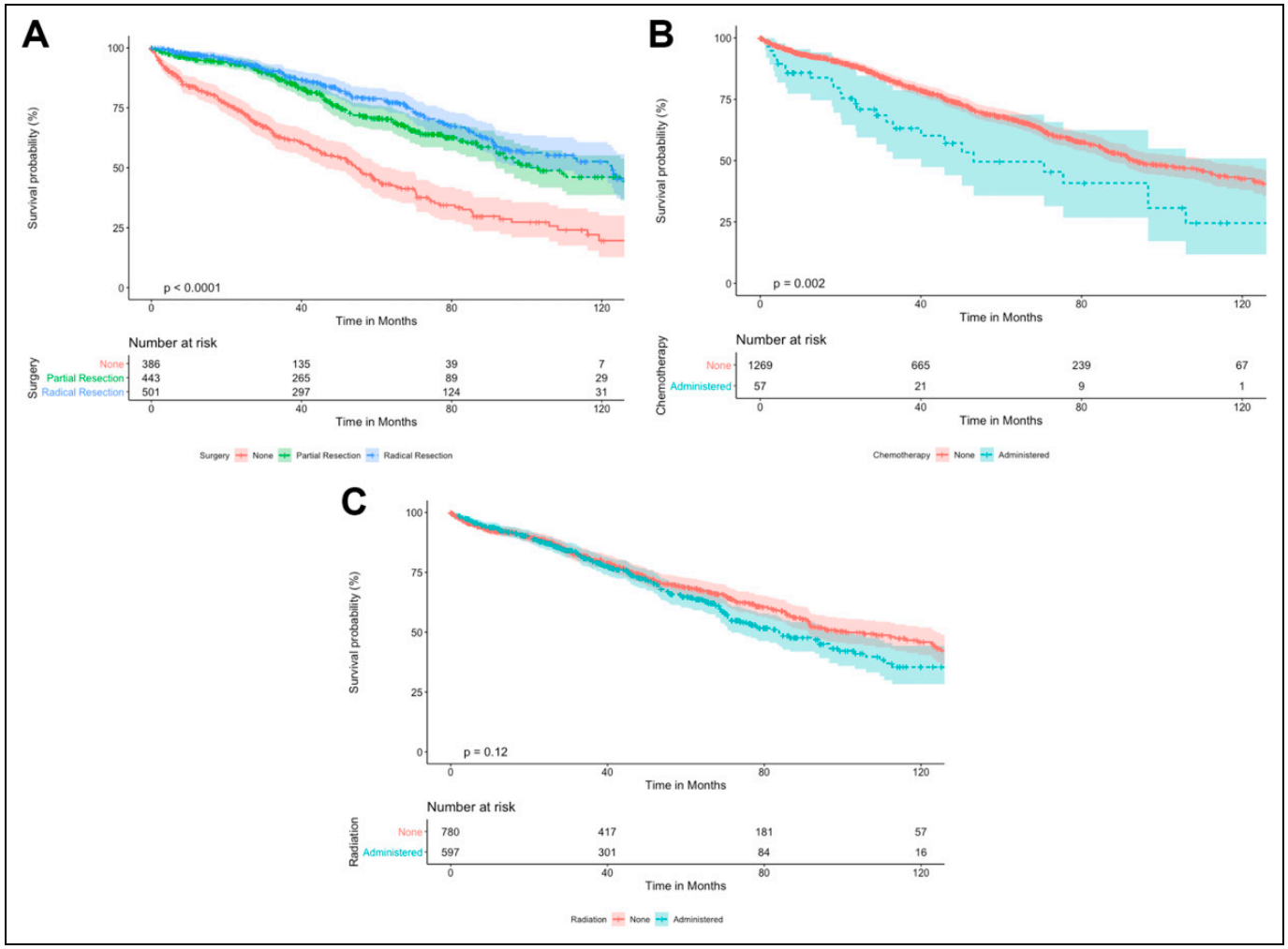

Figure 3. Cox survival analysis of adult spinal chordoma patients. A, Survival by extent of surgical resection. B, Survival by chemotherapy administration. C, Survival by radiation.

dosage of proton-based radiotherapy for spinal chordoma patients before definitive recommendations can be made.

Conventional usage of chemotherapy is largely ineffective against spinal chordoma.[2,3,6,13] Zhou et al. specified that the progression free survival for patients that received chemotherapy is detrimental (HR 2.07, 95% CI 1.11-3.85, $P = 0.022$).[2] Our results illustrate similar results for univariate analysis. This association, however, was not observed on multivariate analysis, possibly suggesting that chemotherapy may have been more commonly administered as salvage therapy in patients with poorer prognosis due to other factors such as presence of recurrence and/or metastasis. However, given the limitations of the NCDB and lack of neurologic presentation, we are unable to know for certain whether this is the case. Additionally, the lack of granularity regarding specific chemotherapeutic agents compared to others must also be considered when making broad conclusions regarding the utility of chemotherapy. New targeted therapies have shown promise, and further investigation is necessary to validate these therapies.[6,10]

Limitations

Limitations of our study include several that are inherent to the retrospective nature of data collection and the use of a large, generalized database. All-cause mortality, as reported in the NCDB, does not allow for quantification of deaths directly related to the effects of spinal chordomas themselves. Although the NCDB contains over a decade of data, tumors that are the result of recurrence cannot be reliably differentiated from primary tumors, thereby preventing survival analysis of this patient subgroup. Moreover, the NCDB does not provide detailed information regarding clinical decision-making or symptomatic presentation. For example, we are unable to assess neurologic status at presentation and why certain patients were deemed surgical candidates. Additionally, there is a lack of granularity in treatment data such as chemotherapeutic regimen which precludes broad conclusions from being drawn regarding the utility and potential impact on outcomes.

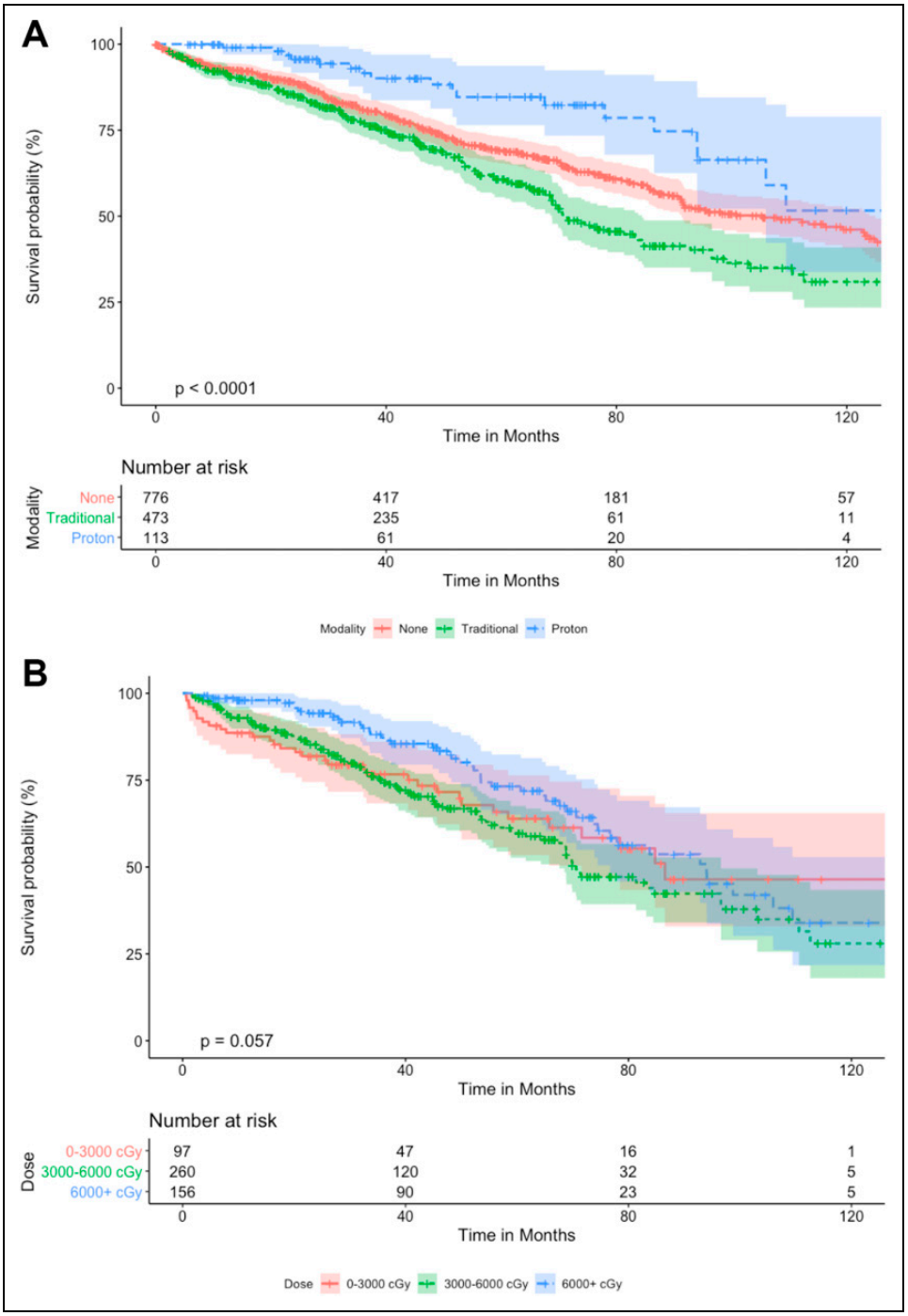

Figure 4. Cox survival analysis of adult spinal chordoma patients. A, Survival by radiation modality. B, Survival by radiation dose.

Conclusion

Spinal chordoma is a rare primary malignant bone tumor that is locally aggressive with high rates of recurrence and metastasis after treatment. The anatomical location of these lesions does not always permit complete radical resection without neurological consequences. Surgical resection is considered the gold standard of treatment with a goal of wide, en-bloc resection; however, the balance for surgical cure with significant lifestyle modification requires extensive discussion when counseling the patient for their best treatment strategy. The current study found that both partial and radical resection significantly improve overall survival. Adjunctive therapies such as chemotherapy and radiotherapy do not significantly improve overall survival. However, in patients undergoing radiation, those who received proton-based radiotherapy had significantly improved overall survival compared to traditional radiation. Further studies are required in order to elucidate the optimal

dosage of proton-based radiotherapy as well as optimal combinations and time-courses of available treatment modalities to maximize outcomes.

Declaration of Conflicting Interests

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ORCID iDs

Saavan Patel, BS https://orcid.org/0000-0003-1553-1229
Ravi S. Nunna, MD https://orcid.org/0000-0003-2516-5445
James Nie, BS https://orcid.org/0000-0002-6680-009X
Ankit I. Mehta, MD https://orcid.org/0000-0001-6931-6095

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