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Impact of Treatment Modalities upon Survival Outcomes in Skull Base and Clival Chordoma: An NCDB Analysis

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Abstract

Objectives   Skull base chordomas are locally aggressive malignant tumors derived from the notochord remnant. There are limited large-scale studies examining the role and extent of surgery and radiation therapy.

Design   Analysis of the National Cancer Database (NCDB) was performed to evaluate the survival outcomes of various treatments, and to assess for predictors of overall survival (OS).

Participants   This is a retrospective, population-based cohort study of patients diagnosed with a clival/skull base chordoma between 2004 and 2015 in the NCDB.

Main Outcome Measures   The primary outcome was overall survival (OS).

Results   In all, 468 cases were identified. Forty-nine percent of patients received surgery and 20.7% had positive margins. Mean age at diagnosis was 48.4 years in the surgical cohort, and 55% were males. Of the surgical cohort, 33.8% had negative margins, 20.7% had positive margins, and 45.5% had unknown margin status. Age ≥ 65 (hazard ratio [HR]: 3.07; 95% confidence interval [CI]: 1.63–5.76; $p < 0.001$), diagnosis between 2010 and 2015 (HR: 0.49; 95% CI: 0.26–0.90; $p = 0.022$), tumor size >5 cm (HR: 2.29; 95% CI: 1.26–4.15; $p = 0.007$), and government insurance (HR: 2.28; 95% CI: 1.24–4.2; $p = 0.008$) were independent predictors of OS. When comparing surgery with or without adjuvant radiation, no survival differences were found, regardless of margin status ($p = 0.66$).

Conclusion   Surgery remains the mainstay of therapy. Advanced age (>65 years), large tumor size, and government insurance were predictors of worse OS. Whereas

Keywords
► clival chordoma
► skull base chordoma
► notochord tumors
► radiation
► margins
► skull base surgery
► surgical outcomes
► insurance status
► national cancer database

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negative margins and the use of adjuvant radiation did not appear to impact OS, these may very well reduce local recurrences. A multidisciplinary approach is critical in achieving optimal outcomes in this challenging disease.

Introduction

Chordomas are locally destructive neoplasms that originate from the remnant of the notochord.[1] Although their appearance is benign on histopathology, they exhibit "malignant" behavior and are locally invasive, likely to recur, and are noted to disseminate in advanced stages of disease.[2] Whereas the most frequent location of origin is the sacral spine, 30 to 40% of chordomas arise in the cranial base, most notably the clival and paraclival regions.[1] Chordomas are rare, with an estimated incidence of 0.08 per 100,000 based on prior population-based data.[3] Within the clivus, the lower third is the least likely primary site (upper third 72%, middle third 82%, lower third 42%), but the most frequent site of residual tumor.[4]

Three histologic subtypes of chordomas have been described, which are classical, chondroid, or dedifferentiated chordomas, all of which characteristically stain positive for epithelial markers on immunohistochemistry.[5] Left untreated, patient mortality associated with progressive local disease generally occurs in 12 months.[6] Given the scarcity of this disease, the optimal therapeutic strategy continues to be elucidated, as do the clinical determinants of overall survival (OS). Treatment modalities that have been described for clival chordoma include surgery, radiation, and chemotherapy.

Given its infiltrative nature and predilection to invade critical structures, surgical resection with negative margins remains highly challenging to obtain for chordomas. Additionally, in certain cases, the morbidity of large intradural resection (e.g., brainstem injury, basilar injury, cerebrospinal fluid [CSF] leak) may preclude the ability to achieve negative margin status.[7] Whereas recent database analysis has assessed the roles of radiation, chemotherapy, and surgery, there has not been, to our knowledge, an analysis of the clinical outcomes of positive versus negative margin status in the context of modern adjuvant care.[5] In addition, the role of socioeconomic factors with respect to OS has not been fully interrogated in this patient population. With these outcomes in mind, we undertook an analysis to assess the determinants of survival for clival chordoma in a large-sample, population-based database.

Materials and Methods

This research was a retrospective, population-based cohort study. Our data were obtained from the National Cancer Database (NCDB), a partnership between the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons, which collects data on a large proportion of newly diagnosed oncologic diseases in the nation every year and is a comprehensive clinical surveillance resource that includes >34 million records from patients diagnosed at over 1,500 CoC-accredited programs.[8] This investigation was given the Institutional Review Board exemption due to the public use and anonymity of patient data within the NCDB. Cases of skull base chordoma were identified by selecting tumors originating in the cranial bones (C41.0) with a histology of unspecified (9370/3), chondroid (9371/3), or dedifferentiated (9372/3) chordoma according to the histologic codes designated by the *International Classification of Diseases for Oncology, Third Revision* (ICD-O-3). Our inclusion criteria consisted of the following: (1) patients aged ≥18 years and (2) those who underwent surgical resection of the primary site with or without adjuvant radiotherapy. Our exclusion criteria consisted of the following: (1) patients receiving other additional treatments, (2) treatment provided at a different facility from the diagnosing facility, (3) patients with additional malignancies, (4) patients receiving palliative care, and (5) patients with follow-up unspecified or less than 30-days from the start of treatment. Of note, within the NCDB additional therapy is used to identify treatment of hematopoietic diseases (such as phlebotomy and transfusions), and as such this modification does not exclude treatment with chemotherapy, radiation therapy, or immunotherapy. There were two patients who received adjuvant chemotherapy, one patient who received adjuvant chemoradiotherapy, and one patient who received adjuvant immunotherapy who were not included in multivariate analysis given the small size of these cohorts.

Cases were classified as either receiving surgery only (SO) or surgery with adjuvant radiotherapy (SXRT) depending on the therapy received and the surgery and radiation sequence as defined by the NCDB variable "RX_SUMM_SURGRAD_-SEQ." SO with negative margins was interpreted as gross total resection (GTR) without adjuvant radiation, SXRT and negative margins as GTR with adjuvant radiation, SXRT and positive margins as STR with adjuvant radiation, and SO with positive margins as STR without adjuvant radiation. Though margin status and macroscopic extent of resection are not interchangeable definitions, negative margin status generally implies that GTR has occurred. The use of negative margin status as a surrogate marker for total resection has previously been utilized in analyses of esthesioneuroblastoma, sinonasal mucosal melanoma, osseous-based skull and mandibular tumors, and skull base chondrosarcoma.[9–12] Clinical covariates included age (<65 or ≥65 years), sex, race (Caucasian, African American, other), presence of comorbidities, year of diagnosis (2004–2009 or 2010–2015), AJCC Analytic Stage (1–2 or 3–4), nodal involvement, metastatic involvement, histology (unspecified, chondroid, or dedifferentiated), and tumor size (<5 or ≥5 cm).

Sociodemographic covariates included facility type (academic or nonacademic) and location (east, central, or west), insurance status (private, government, or uninsured), income quartile (<$48,000 or ≥$48,000), education level of residence (<13% or ≥13% without a high school diploma), population size (<250,000 or ≥250,000 individuals), and distance from provider to patient. Treatment-related covariates included surgical margin status (negative or positive), radiation dose (<60 or ≥60 Gy, and <70 or ≥70 Gy), radiation modality (intensity-modulated radiation therapy [IMRT], stereotactic radiosurgery [SRS], other photon, or proton), and 30-day unplanned hospital readmission.

Statistical analyses were performed using R version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria) via RStudio version 1.1.463 (RStudio, Boston, Massachusetts, United States). The Kaplan–Meier log-rank tests were utilized to compare OS between SO with negative margins, SXRT with negative margins, and SXRT with positive margins. Additionally, the Kaplan–Meier log-rank test was performed to compare OS between patients based on insurance status, radiation dose, and radiation modality. Univariate and multivariate Cox proportional-hazards analyses were performed to further determine clinical and sociodemographic factors predictive of survival. Statistically significant variables on univariate were included in the multivariate analysis. This study utilized a p-value of <0.05 for statistical significance.

Results

A total of 468 cases (213 SO and 255 SXRT) diagnosed from 2004 to 2015 were identified from the NCDB. Ninety-seven patients had treatment data available for at least 7 years of follow-up. Baseline patient characteristics of clinical and sociodemographic covariates are presented in ►Table 1. The chi-squared analysis between SO and SXRT demonstrated significant differences for year of diagnosis ($p = 0.031$), facility type ($p = 0.014$), facility location ($p = 0.002$), and surgical margin status ($p < 0.001$; ►Table 1).

Univariate Cox proportional hazards analysis demonstrated that age ≥65 years, presence of comorbidities, tumor size ≥5cm, and government insurance were significantly associated with worse OS, while diagnosis during 2010 to 2015 was significantly associated with improved OS (►Supplementary Table S1, available in the online version). On multivariate analysis, age ≥65 years (hazard ratio [HR] = 3.07; 95% confidence interval [CI]: 1.63–5.76; $p < 0.001$), tumor size ≥5 cm (HR = 2.88; 95% CI: 1.26–4.15; $p = 0.007$), and government insurance (HR = 2.28; 95% CI: 1.24–4.22; $p = 0.008$) were significantly associated with increased HR, while diagnosis during 2010 to 2015 was significantly associated with decreased HR (HR = 0.49; 95% CI: 0.26–0.90.25–0.84; $p = 0.022$; ►Table 2).

The Kaplan–Meier log-rank test comparing OS outcomes between patients receiving SO with positive margins, SO with negative margins, SXRT with positive margins, and SXRT with negative margins demonstrated no significant differences in OS ($p = 0.66$; ►Fig. 1). The 1-, 2-, 5-, and 10-year OS for these cohorts are provided in ►Table 3. However,

there was a significant difference in OS comparing patient insurance status ($p < 0.001$), with patients on private insurance demonstrating improved OS compared with those on government insurance (►Fig. 2). Specific radiation modalities of IMRT ($N = 49$), SRS ($N = 54$), other photon ($N = 37$), and proton beam ($N = 92$) radiation were not associated with differences in OS ($p = 0.16$). Similarly, cumulative adjuvant radiation therapy dosages using 60 and 70 Gy as thresholds were not associated with OS benefit ($p = 0.63$ and 0.50, respectively).

Discussion

Surgery is the mainstay of therapy for clival and skull base chordomas, with a recent analysis of the NCDB and Surveillance, Epidemiology, and End Results (SEER) database by Hulou et al demonstrating that 86% of patients received surgery.[5] Numerous surgical approaches have been described for these tumors, including transcranial, transnasal, high anterior cervical retropharyngeal, and transoral techniques.[13–15] Endoscopic endonasal techniques in particular are associated with high rates of GTR for midline disease up to 50 to 90%.[16–18] For disease necessitating resection of dura, reconstruction with vascularized tissue and employing a lumbar drain have been noted to decrease the incidence of CSF leak, though transclival defects generally lead to a high-flow CSF leak and are among the most challenging defects to primarily repair.[18,19] In light of the diversity of strategies and the frequency of operative intervention, developing an evidence-driven approach to surgical resection is paramount. Our findings contribute uniquely to this discussion in that no apparent survival benefit was found when comparing GTR versus subtotal resection (STR), with or without adjuvant radiation, or regardless of margin status. For our analysis, the negative margin status was considered as indicating that GTR had occurred, as a limitation of analysis within the NCDB is that GTR is not a separately coded variable.

Among surgical candidates, several studies have assessed the outcomes of achieving GTR. Whereas this is not a perfect surrogate for the negative margin status, these studies nevertheless provide important context for our findings, and have significantly influenced current surgical practice. The infiltrative, nestlike growth of chordomas presents a challenge in identifying if GTR or negative margins have truly been accomplished, and prior single-series studies have utilized various methods to define the extent of resection including lack of residual disease on postoperative magnetic resonance imaging (MRI), a 90% reduction of tumor on volumetric analysis, removal of all visualized gross disease intraoperatively, and microscopic margin status on gross pathology.[7,20–29] A meta-analysis of 1,050 patients by Labidi et al found that GTR was accomplished 39.9% of the time in chordoma and that achieving this corresponded to decreased recurrence rates.[1] Overall 5-year progression-free survival (PFS) was 49.9%, and 5-year OS was 73.9% in this cohort.[1] These rates were similar to an earlier meta-analysis of observational studies by Di Maio et al who described a 5-year PFS of 50.8% and 5-year OS of 78.4% for their GTR

Table 1 Comparisons of baseline characteristics of skull base chordoma patients treated with surgery only (SO; $N = 213$) versus surgery with adjuvant radiotherapy (SXRT; $N = 255$)

	SO	SXRT	Total cohort	p-value[a]
	$N = 213$	$N = 255$	$N = 468$	
Age, mean (y [SD])	47.31 (16.07)	46.07 (15.78)	48.35 (16.26)	0.126
Age, no. y (%)				
< 65	184 (86.4)	211 (82.7)	395 (84.4)	0.341
≥65	29 (13.6)	44 (17.3)	73 (15.6)	
Sex, no. (%)				
Female	94 (44.1)	117 (45.9)	211 (45.1)	0.775
Male	119 (55.9)	138 (54.1)	257 (54.9)	
Race, no. (%)				
Caucasian	168 (78.9)	204 (80)	372 (79.5)	0.496
African American	23 (10.8)	19 (7.5)	42 (9)	
Other	17 (8)	27 (10.6)	44 (9.4)	
Unknown	5 (2.3)	5 (2)	10 (2.1)	
Comorbidities, no. (%)				
No	171 (80.3)	220 (86.3)	391 (83.5)	0.106
Yes	42 (19.7)	35 (13.7)	77 (16.5)	
Year of diagnosis, no. (%)				
2004–2009	97 (45.5)	90 (35.3)	187 (40)	**0.031**[b]
2010–2015	116 (54.5)	165 (64.7)	281 (60)	
AJCC stage, no. (%)				
0–2	133 (62.4)	177 (69.4)	310 (66.2)	0.195
3–4	2 (0.9)	4 (1.6)	6 (1.3)	
Unknown	78 (36.6)	74 (29)	152 (32.5)	
Nodal involvement, no. (%)				
No	151 (70.9)	202 (79.2)	353 (75.4)	0.074
Yes	1 (0.5)	0 (0)	1 (0.2)	
Unknown	61 (28.6)	53 (20.8)	114 (24.4)	
Metastatic involvement, no. (%)				
No	198 (93)	242 (94.9)	440 (94)	0.673
Yes	1 (0.5)	1 (0.4)	2 (0.4)	
Unknown	14 (6.6)	12 (4.7)	26 (5.6)	
Histology, no. (%)				
Unspecified	186 (87.3)	236 (92.5)	422 (90.2)	0.082
Chondroid	25 (11.7)	19 (7.5)	44 (9.4)	
Dedifferentiated	2 (0.9)	0 (0)	2 (0.4)	
Tumor size, no. (%)				
< 5 cm	136 (63.8)	171 (67.1)	307 (65.6)	0.612
≥5 cm	29 (13.6)	36 (14.1)	65 (13.9)	
Unknown	48 (22.5)	48 (18.8)	96 (20.5)	
Facility type, no. (%)				
Academic	97 (45.5)	150 (58.8)	247 (52.8)	**0.014**[b]
Nonacademic	29 (13.6)	23 (9)	52 (11.1)	
Unknown	87 (40.8)	82 (32.2)	169 (36.1)	

(Continued)

Table 1 (Continued)

Facility location, no. (%)				
East	65 (30.5)	77 (30.2)	142 (30.3)	**0.002**[b]
Central	41 (19.2)	40 (15.7)	81 (17.3)	
West	20 (9.4)	56 (22)	76 (16.2)	
Unknown	87 (40.8)	82 (32.2)	169 (36.1)	
Insurance status, no. (%)				
Private	135 (63.4)	152 (59.6)	287 (61.3)	0.695
Government	62 (29.1)	87 (34.1)	149 (31.8)	
Uninsured	10 (4.7)	10 (3.9)	20 (4.3)	
Unknown	6 (2.8)	6 (2.4)	12 (2.6)	
Income quartile, no. (%)				
$< \$48,000$	78 (36.6)	97 (38)	175 (37.4)	0.734
$\geq\$48,000$	133 (62.4)	157 (61.6)	290 (62)	
Unknown	2 (0.9)	1 (0.4)	3 (0.6)	
Education level, no. (%)				
% no HSD $<13\%$	116 (54.5)	148 (58)	264 (56.4)	0.591
% no HSD $\geq13\%$	95 (44.6)	106 (41.6)	201 (42.9)	
Unknown	2 (0.9)	1 (0.4)	3 (0.6)	
Population size, no. (%)				
$< 250,000$	45 (21.1)	51 (20)	96 (20.5)	0.903
$\geq250,000$	161 (75.6)	194 (76.1)	355 (75.9)	
Unknown	7 (3.3)	10 (3.9)	17 (3.6)	
Distance from provider to patient, mi (mean [SD])	165.25 (353.18)	151.15 (312.24)	177.02 (384.24)	0.423
Margin status, no. (%)				
Negative	72 (33.8)	49 (19.2)	121 (25.9)	**<0.001**[b]
Positive	44 (20.7)	105 (41.2)	149 (31.8)	
Unknown	97 (45.5)	101 (39.6)	198 (42.3)	
30-d unplanned hospital readmission, no. (%)				
No	200 (93.9)	238 (93.3)	438 (93.6)	0.9
Yes	10 (4.7)	12 (4.7)	22 (4.7)	
Unknown	3 (1.4)	5 (2)	8 (1.7)	

Abbreviations: AJCC, American Joint Committee on Cancer; HSD, high school diploma; SD, standard deviation.
[a]p-value calculated by comparing primary surgery and salvage surgery cohorts using Pearson's chi-squared test or unpaired two-sample t-test.
[b]p-value below threshold for statistical significance ($p < 0.05$).

cohort.[19] As in the study by Labidi et al, complete resection conferred a 20.5% higher 5-year PFS than incomplete resection, along with 5.85-fold decrease in mortality. Previous studies evaluating surgical management of chordomas of the axial skeleton have found that en bloc resection of sacral and mobile spine contributes to decreased local recurrence rates, leading to recommendations to pursue en bloc resection, or at least GTR, within the clivus and skull base wherever feasible.[13,30] In our analysis, 33.8% of patients attained negative margin status, but this was not associated with a benefit in OS. Moreover, negative margin resection alone did not confer a survival benefit relative to patients with positive

margins who also received radiation therapy, and no additional survival benefit was demonstrated in patients who received negative margin resection alone versus positive margin resection with adjuvant radiation therapy. This finding was robust on matched cohort analysis of treatment positive variables on univariate analysis (age, comorbidities, year of diagnosis, tumor size, insurance status; ►**Supplementary Figure S1**, available in the online version). As GTR is not expressly coded for within the NCDB, and many prior studies have used differing definitions of GTR, caution must be taken in applying our findings too broadly given the robust body of research demonstrating improved survival

Table 2 Multivariate Cox proportional hazards for skull base chordoma patients ($N = 468$)

	Multivariate analysis	
	HR (95% CI)	*p*-value
Age, y		
< 65	1 [Reference]	
≥65	3.069 (1.634–5.762)	<0.001[a]
Comorbidities		
No	1 [Reference]	0.072
Yes	1.844 (0.946–3.593)	
Year of diagnosis		
2004–2009	1 [Reference]	
2010–2015	0.486 (0.261–0.902)	0.022[a]
Tumor size		
< 5 cm (Reference)	1 [Reference]	0.007[a]
≥5 cm	2.288 (1.261–4.154)	
Insurance status		
Private	1 [Reference]	
Government	2.284 (1.237–4.218)	0.008[a]
Uninsured	2.665 (0.78–9.109)	0.118

Abbreviations: CI, confidence interval; HR, hazard ratio.
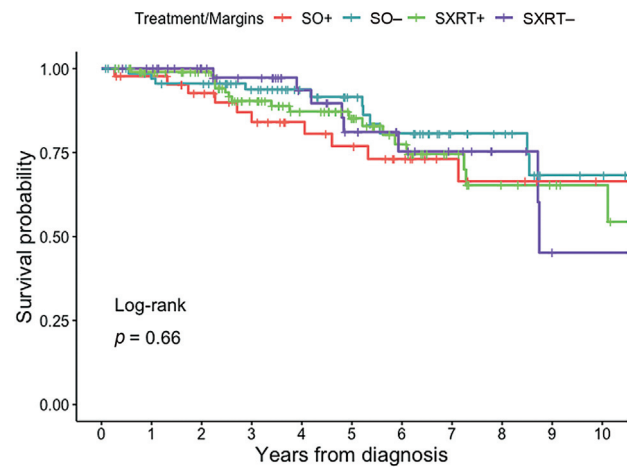[a]*p*-value below threshold for statistical significance ($p < 0.05$).

Fig. 1 Kaplan–Meier curves of overall survival (OS) for skull base chordoma patients receiving surgery only with positive margins (SO +; $N = 44$), surgery only with negative margins (SO−; $N = 72$), surgery with adjuvant radiotherapy with positive margins (SXRT +; $N = 105$), or surgery with adjuvant radiotherapy with negative margins (SXRT−; $N = 49$).

and decreased recurrence in association with GTR. One possible explanation of our data is that the increased efficacy of adjuvant therapy has provided a similar survival benefit to that previously accomplished by GTR. In light of these data, STR may be considered in the cases where GTR entails significant morbidity, as long as adjuvant radiation therapy is provided. One example is in patients with limited intradural disease, where extradural resection may be considered followed by adjuvant radiation therapy, thereby avoiding the possible risks and morbidity associated with a transclival skull base defect.

With respect to radiation therapy, there is emerging literature that postoperative chordoma patients treated with adjuvant radiation therapy have improved OS with proton therapy at 5 years relative to conventional radiation

therapy and that improved outcomes are associated with high-dose treatment, if tolerated by the patient.[31] Chordomas are known to be relatively radioresistant, often requiring treatment with at least 70 Gy.[32] Modern radiation treatment strategies include IMRT, SRS, and particle therapies including proton and carbon ions.[33] There is emerging evidence that particle radiation therapy (either proton or carbon ion therapy) offers high local control while minimizing damage to organs at risk, though their effectiveness is decreased by higher gross tumor volume.[34] Current best practices from the Chordoma Global Consensus Group advise that in selecting between radiation therapy and surgical resection for locoregional recurrence, there are insufficient data to support generalized recommendations and treatment must by tailored to the individual.[32] In our analysis, no survival benefit was associated with higher doses of radiation therapy (►**Supplementary Figure S2**, available in the online version) or specific radiation modality (►**Fig. 3**).

Chemotherapy is not commonly utilized for clival and skull base chordoma, though targeted therapies are under investigation based on whole-transcriptome analysis, with
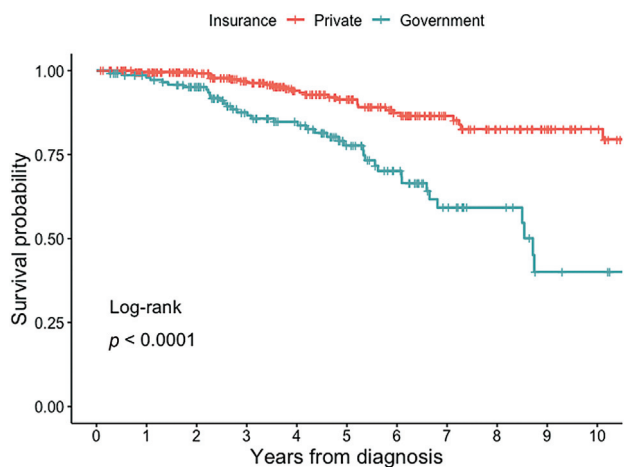
Table 3 One-, 2-, 5-, and 10-year OS for skull base chordoma patients receiving surgery only with positive margins (SO +; $N = 44$), surgery only with negative margins (SO−; $N = 72$), surgery with adjuvant radiotherapy with positive margins (SXRT +; $N = 105$), or surgery with adjuvant radiotherapy with negative margins (SXRT−; $N = 49$)

	% OS (95% CI)			
	1 y	2 y	5 y	10 y
SO+	98 (93–100)	93 (85–100)	77 (64–93)	66 (50–88)
SO−	97 (93–100)	96 (91–100)	92 (85–99)	68 (52–90)
SXRT+	99 (97–100)	99 (97–100)	85 (77–94)	65 (51–84)
SXRT−	100 (100–100)	100 (100–100)	81 (67–98)	45 (21–96)

Abbreviations: CI, confidence interval; OS, overall survival.

Fig. 2 Kaplan–Meier curves of overall survival (OS) for skull base chordoma patients with private ($N = 287$) and government ($N = 149$) insurance.

Fig. 3 Kaplan–Meier curves of overall survival (OS) for skull base chordoma patients receiving intensity-modulated radiotherapy (IMRT; $N = 49$), stereotactic radiosurgery (SRS; $N = 54$), other photon ($N = 37$), and proton ($N = 92$) radiation.

potential targets including the epidermal growth factor receptor, c-Met, and HER2/neu pathways.[35]

As in prior studies, patients with larger tumors (size ≥ 5 cm) and older age (age ≥ 65 years) had worse OS. Larger volume disease represents a greater challenge to both surgical resection and radiation therapy given proximity to critical structures.[7] Proximity to the optic apparatus and brainstem is particularly associated with high local recurrence rates.[36,37] Prior NCDB analysis has shown that age greater than 60 years is an independent risk factor for decreased survival in cranial chordoma, which is concordant with our analysis.[5]

Treatment of clival and skull base chordomas appears to be becoming more effective with time, as OS was improved in patients diagnosed with the disease after 2009 as compared with prior to this date. This finding likely reflects treatment trends toward improved surgical techniques and knowledge of surgical access and anatomy, multimodal treatment, and the advent of techniques to deliver high-dose radiation.[5] Anatomic limitations of external surgical approaches have been significantly expanded by advent and widespread adoption of endoscopic approaches.[38] Of particular note are the transcavernous corridor approach to the superior clivus, the supravidian transpterygoid approach to the middle clivus, and the transpterygoid infravidian approach to the inferior clivus.[38] Although an endoscopic approach is often sufficient for GTR of midline lesions, a combination of endoscopic and external approaches may be appropriate in tumors with significant lateral or inferior extension.[38] With an experienced skull base team, GTR can be achieved in up to 88.9% of primary cases.[39] Though not yet universally available, treatment modalities such as proton therapy are increasing in availability throughout the United States, which is promising in light of studies demonstrating excellent outcomes.[40] Whereas proton therapy was first described for chordomas over 20 years ago, availability of this technique and subsequent utilization have increased to the point that it is now more commonly employed than photon
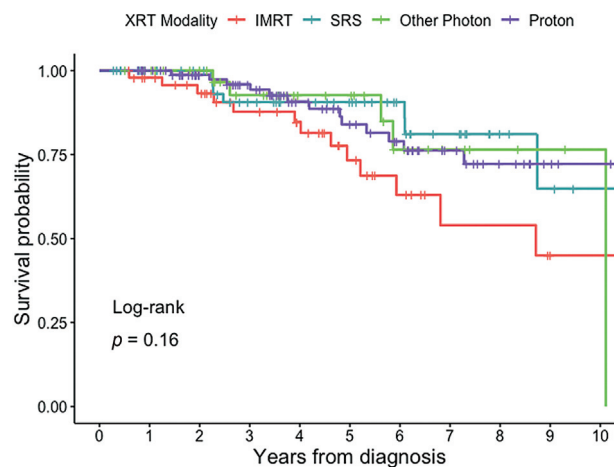
radiation within NCDB studies, including our current study.[5,36] Carbon ion therapy is much less accessible, with the first U.S. site to be created at the Mayo Clinic in Minnesota.[41] Two benefits of particle therapy over photon therapy are secondary to the sharp penumbra, allowing (1) better tumor coverage and (2) dose escalation despite tumors that are close to dose-limiting structures such as the optic apparatus, brainstem, and spinal cord. Whereas the radiation doses are not universally agreed upon, recommendations have been made for at least 74 Gy to gross disease.[42] Improved image-guidance and IMRT techniques often make such high doses possible using conventional photon therapy.[43] Alternatively, there have been very good results with the use of SRS, with excellent local control rates in one small series from Memorial Sloan Kettering Cancer Center (MSKCC).[44] Chordomas are radioresistant and less vulnerable to sublethal DNA damage, which means there is a theoretical advantage to higher doses per fraction that can deliver more irreparable DNA damage.[45]

Another notable finding in our analysis was decreased OS in patients with government insurance relative to private insurance. This is consistent with a recent NCDB study by Carey et al, who demonstrated decreased OS for patients with no insurance or government insurance who were diagnosed with head and neck malignancy.[46] Part of this effect has been attributed to advanced stage at presentation, as highlighted in one study, where patients with Medicaid were both more likely to present with metastatic head and neck cancer and more likely to not receive definitive treatment relative to patients with private insurance.[47]

Limitations of this study include the retrospective nature of our data. Although our overall study size was comparable to prior observational studies, our work was nevertheless underpowered to evaluate the role of adjuvant chemotherapy, chemoradiotherapy, or immunotherapy in the treatment

of this disease, which represents an opportunity for future research. The NCDB does not offer data on disease-specific survival, nor does it provide detailed descriptions of the surgical approaches utilized during treatment. Given the deidentified nature of the NCDB, review of individual patient data to identify the specific means of determining margin status was not possible. In addition, postoperative complications are not readily available for analysis, which may represent a potential confounding variable with respect to mortality outcomes. Prospective data are needed to further elucidate the optimal treatment of skull base and clival chordoma.

Conclusion

Surgery remains the mainstay of therapy for skull base and clival chordoma. Advanced age, large tumor size, and government insurance were all predictors of worse OS. General consensus for skull base chordomas is to pursue maximal safe resection, and the decision for adjuvant radiation is generally based on margin status. In this study, neither negative margins nor adjuvant radiation were associated with improved survival, although progression and recurrence data were unknown. A multidisciplinary approach to these challenging tumors is critical to optimize treatment outcomes.

Presentations
Portions of this work were presented as a poster at the Triological Society Combined Sections Meeting, Coronado, CA, January 23–25, 2020.

Conflict of Interest
None declared.

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