North American Spine Society Journal (NASSJ) 20 (2024) 100569

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Clinical Studies

Surgical management of skull base and spinal chordomas: A case series with comprehensive review of the literature

Sarah Lee[a], Nahom Teferi[a,*], Juan Vivanco-Suarez[a], Ajmain Chowdhury[b], Stephen Glennon[a], Kyle Kato[b], Tyson Matern[a], Kathryn L. Eschbacher[c], Michael Petronek[d], Patrick Hitchon[a]

[a] Department of Neurosurgery, University of Iowa Carver, College of Medicine, Iowa City, IA, United States
[b] University of Iowa Carver, College of Medicine, Iowa City, IA, United States
[c] Department of Pathology, University of Iowa Carver, College of Medicine, Iowa City, IA, United States
[d] Department of Radiation Oncology, University of Iowa Carver, College of Medicine, Iowa City, IA, United States

ARTICLE INFO

Keywords:
Clival
Spinal
Sacral
Chordoma
Radiotherapy
Proton beam therapy

ABSTRACT

Background: Chordomas are rare, slow growing, locally aggressive malignant bone tumors that arise from remnants of the embryonic notochord with variable presenting symptoms depending on tumor location.
Methods: All patients with craniospinal chordoma managed at our institution between 1982 and 2023 were retrospectively reviewed. Demographics, tumor characteristics, clinical course and treatment, and long-term neurological and survival outcomes were collected. Adjuvant radiotherapy (RT) was stratified into standard dose fractionated radiotherapy (standard XRT) for doses of 50 to 60 Gy at 1.8 Gy fractions or high dose hyperfractionated stereotactic radiotherapy (HD-FSRT) for doses of 60 to 81 Gy at 1.2-1.5 Gy fractions per treatment. Descriptive statistics, univariate analysis, Log-rank test, and Kaplan-Meier survival analysis were performed.
Results: A total of 37 patients were included in our cohort (mean age 46.0 ± 20.8 years; 22 male). Clival chordomas accounted for the majority of patients (56.8%), followed by vertebral (27%) and sacral (10.8%) chordomas. Thirty-five patients (94.6%) underwent gross total resection (GTR) or subtotal resection (STR), and 2 patients underwent excisional biopsy only. Postoperatively, functional status trended towards improvement (KPS: Preop- 80 [range 40–100] vs. Post op- 90 [60–100], p = .0911) and all patients either maintained or improved their neurological function. Median overall survival (OS) after diagnosis was 16.5 years. Age < 65, clival tumor location, post-operative Frankel grade E, and administration of adjuvant RT following initial STR significantly improved OS. OS of GTR patients was not significantly affected by adjuvant RT treatment.
Conclusions: Our results show the best long-term survival outcomes for chordoma patients undergoing GTR of tumor tissue. Higher postoperative neurological function was significantly associated with OS, highlighting the importance of maximal but safe total tumor resection. Moreover, adjuvant RT improved long-term survival for patients that underwent STR but had no effect on survival outcomes for patients that underwent GTR.

Introduction

First described by Virchow in 1857, chordomas are rare, slow growing, locally aggressive malignant bone tumors that arise from remnants of the embryonic notochord [1,2]. These tumors account for 1-4% of all primary bone tumors, with an annual incidence of 0.08 per 100,000 population. Chordomas are more common in men, Caucasians, and patients older than 40 years [3]. Their most common sites of occurrence include the sacrococcygeal region (29%–50%), clivus (32%–40%), and lumbar spine (5%–15%) [1,4]. Depending on tumor location, the presenting symptoms are highly variable and include cranial nerve dysfunction, pain, weakness, sensory abnormalities, and/or bowel/bladder/sexual dysfunction [5].

Chordomas have an aggressive clinical course and poor long-term prognosis, primarily due to their high local recurrence rates rather than metastatic potential [6]. Local recurrence rates ranging from 43%-85% have been reported with an overall survival rate of 61% at 5 years and 41% at 10 years (Fig. 1) [1,3,7–9].

Abbreviations: STR, Subtotal resection; GTR, Gross total resection; OS, Overall survival; PFS, Progression free survival; EOR, Extent of resection.
FDA device/drug status: Not applicable.
Author disclosures: ***SL***: Nothing to disclose. ***NT***: Nothing to disclose. ***JVS***: Nothing to disclose. ***AJC***: Nothing to disclose. ***SG***: Nothing to disclose. ***KK***: Nothing to disclose. ***TM***: Nothing to disclose. ***KLE***: Nothing to disclose. ***MP***: Nothing to disclose. ***PH***: Nothing to disclose.

* Corresponding author. Department of Neurosurgery, University of Iowa Hospitals and Clinics 200 Hawkins Dr., Iowa City, IA, United States, 52242.
E-mail address: nahom-teferi@uiowa.edu (N. Teferi).

https://doi.org/10.1016/j.xnsj.2024.100569
Received 4 August 2024; Received in revised form 13 October 2024; Accepted 26 October 2024
Available online 4 November 2024

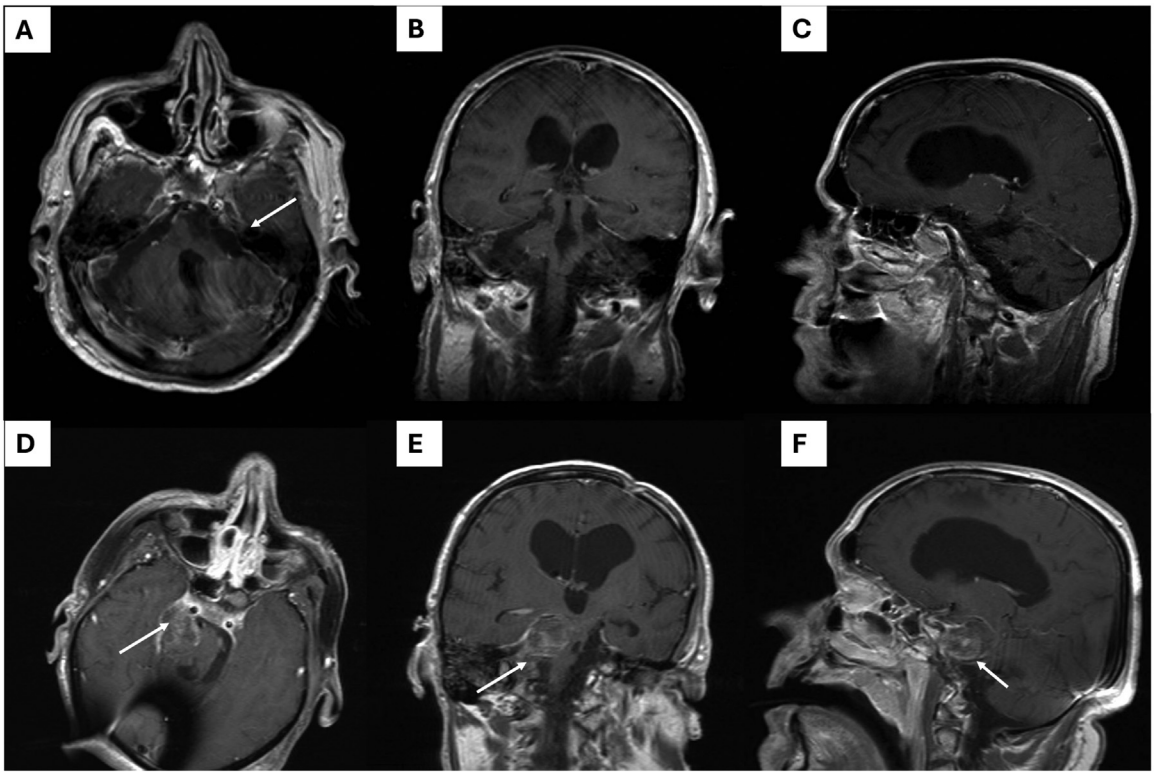

Fig. 1. Recurrent Clival Chordoma in a 64-year-old male patient with prior L sided retro-sigmoid craniotomy and gross total tumor resection, now presenting with new R sided lesion after presenting with an episode of right facial numbness, dysphasia and left sided hemiparesis, 6 years after index surgery. He underwent a repeat craniotomy with a right suboccipital approach for intralesional curettage and gross total excision of underlying recurrent mass. Axial (A), Coronal (B) and Sagittal (C) post-gadolinium T1 MRI brain sequences showing post-surgical changes of L sided retro-sigmoid craniotomy (arrows) with gross total resection of L clival mass. Follow up MRI brain with post-gadolinium T1 Axial (D), Coronal (E) and Sagittal (F) sequences obtained 6 years after initial surgery, showing a new heterogeneously enhancing R petroclival mass (arrows) with mass effect and compression of the R cerebral peduncle. Note the new artifact posteriorly from a shunt that was placed for management of hydrocephalus following his initial tumor resection surgery.

Definitive management typically involves surgical resection, with or without adjuvant radiotherapy (RT), or chemotherapy. Since its introduction in the 1970's by Stener and Gunterberg, en bloc surgical resection with wide margins, followed by (more recently adopted) adjuvant proton beam radiotherapy (PBT) in cases of subtotal resection (STR), is currently considered the standard treatment for chordomas [1,4,7,8,10–12]. However, this treatment paradigm is associated with significant morbidity, and is often difficult to achieve given the tumor's proximity to adjacent critical neural structures like the optic chiasm, brain stem, or cauda equina [13]. Moreover, a recent single-institutional report showed similar local tumor control and overall survival rates with spinal stereotactic body radiotherapy (SBRT) following intralesional curettage and separation surgery for nonresectable chordomas, alleviating the need for aggressive tumor debulking [14]. This approach, however, remains highly controversial. Furthermore, the role of adjuvant RT in the setting of gross total tumor resection (GTR) remains to be clearly elucidated [15–17].

In this manuscript, we present a retrospective, single-institution case series of clival, vertebral, and sacral chordomas managed at our institution, analyze our treatment algorithm and patient outcomes, and extensively review the associated literature.

Methods

Institutional setting

The study was approved by the University of Iowa institutional review board (IRB #201902751). A retrospective review of hospital records was performed for patients with a pathological diagnosis of craniospinal chordoma from January 1982 to September 2023. Exclusion criteria included chordomas location outside of the clivus, sacrum, or spine, or chordoma treated at an outside institution. The requirement for informed consent was waived by the IRB for all subjects. Patient information obtained in this study included patients seen in the Department of Neurosurgery, Otolaryngology, and Orthopedics and Rehabilitation at the University of Iowa Hospitals and Clinics, an academic tertiary care facility with a level 1 trauma center and outreach clinics across Iowa. Chart records were obtained from the EPIC (Epic Systems Corporation, Madison, WI) electronic medical record (EMR).

Data collection

The EMRs of 64 patients were initially reviewed. Following initial data collection, 37 patients were identified as having a pathologically confirmed diagnosis of cranial or spinal chordoma managed at our institution and were included in the analysis. The remaining 27 patients had chordomas outside the skull base/spine or underwent their treatment at a different institution.

We collected data on patient demographics, tumor characteristics, clinical presentation and course, treatment modality and characteristics, and long-term neurological and survival outcomes (follow-up history, and vital status as of September 2023). Adjuvant RT was stratified as standard dose fractionated radiotherapy (standard XRT) for doses of 50 to 60 Gy at 1.8 Gy fractions, or high dose hyper-fractionated stereotactic radiotherapy (HD-FSRT) for doses of 60 to 81 Gy at 1.2 to 1.5 fractions per treatment. Radiographic evaluation included computed tomography

(CT) and magnetic resonance imaging (MRI). Imaging was used to evaluate the lesion location, appearance, and presence of tumor recurrence or progression. Gross total resection (GTR) was confirmed through evaluation of postoperative radiological imaging and margins were not examined. En bloc resection was included in the GTR cohort. Neurologic status was documented using pre- and postoperative Frankel grade, and functional status was documented using Karnofsky Performance Scale (KPS) scores.

Statistical methods

Descriptive statistics with mean (± SD) and median (range), as appropriate, were performed for patient demographics, tumor characteristics, clinical course, and treatment factors. Patient demographics obtained included age, sex, and ethnicity. Tumor characteristics included tumor location, appearance, radiological diagnosis, and final pathologic diagnosis. Clinical course included presenting symptoms, pre- and postoperative KPS and Frankel grade, tumor recurrence, follow-up history, and vital status as of September 2023. Treatment factors included extent of resection (EOR), estimated blood loss (EBL), need for reoperation, and the use of adjuvant chemotherapy and/or radiotherapy.

GraphPad Prism9 (Dogmatics LLC, San Diego, CA, USA) was used for quantitative analysis. Categorical variables were compared using Fisher's exact test and Chi-square tests, and numerical variables were analyzed using the Mann-Whitney-Wilcoxon rank-sum test. Survival analysis was performed using Kaplan-Meier estimation and/or Pearson's correlation coefficient. Progression-free survival (PFS) was calculated from the date of the initial surgery to the date of tumor recurrence or progression on radiological evaluation. Overall survival (OS) was calculated from date of initial surgery to the date of death. Patients not documented as deceased or with progressive residual tumor or tumor recurrence were censored from the date of the last follow-up for OS and PFS, respectively. Results were considered significant at $p < .05$.

Results

A total of 37 patients (22 male [59.5%], 15 female [40.5%]) with craniospinal axis chordomas were included in this study. The mean age at diagnosis was 46.0 ± 20.8 years. The most common anatomic locations for tumor presentation were the clivus (n = 21 [56.8%]), lumbar spine (n = 6 [16.2%]), sacrum (n = 4 [10.8%]), cervical (n = 4 [10.8%]) and thoracic spine (n = 2 [5.4%]) (Fig. 2). The baseline demographics and clinical presentation of the patients included in the cohort are shown in Table 1.

Clival chordomas

There were 21 patients (10 males [47.6%], 11 females [52.4%]) with clival chordomas. The mean age at presentation was 42.8 ± 21.4 years (range, 7-88 years) and the most common presenting symptom was a neurological deficit due to cranial nerve palsy (n=15, 71.4%). The mean duration from symptom onset to clinical presentation was 9.7 ± 14.3 months.

STR was achieved in 15 patients (71.4%), GTR in 5 patients (23.8%), and excisional biopsy without resection was performed in 1 patient (4.8%) (Fig. 2). Among the patients that underwent microsurgical tumor debulking, all underwent intralesional curettage as en bloc resection was not feasible given tumor location. Thirteen patients (65.0%) underwent resection via anterior or anterolateral approach (endoscopic endonasal trans-clival, trans-oral or pterional craniotomy), 3 patients (15.0%) underwent a posterior approach (suboccipital craniotomy), 3 patients (15.0%) underwent a lateral or posterolateral approach (transtemporal or far lateral craniotomy), and 1 patient (5.0%) underwent combined posterior and lateral approach (Table 2). Mean EBL was 182.8 mL (range, 20–400 mL) (Fig. 2). There was a trend towards better improvement in preoperative KPS by surgical approach in favor of posterior approach ($p = .0644$).

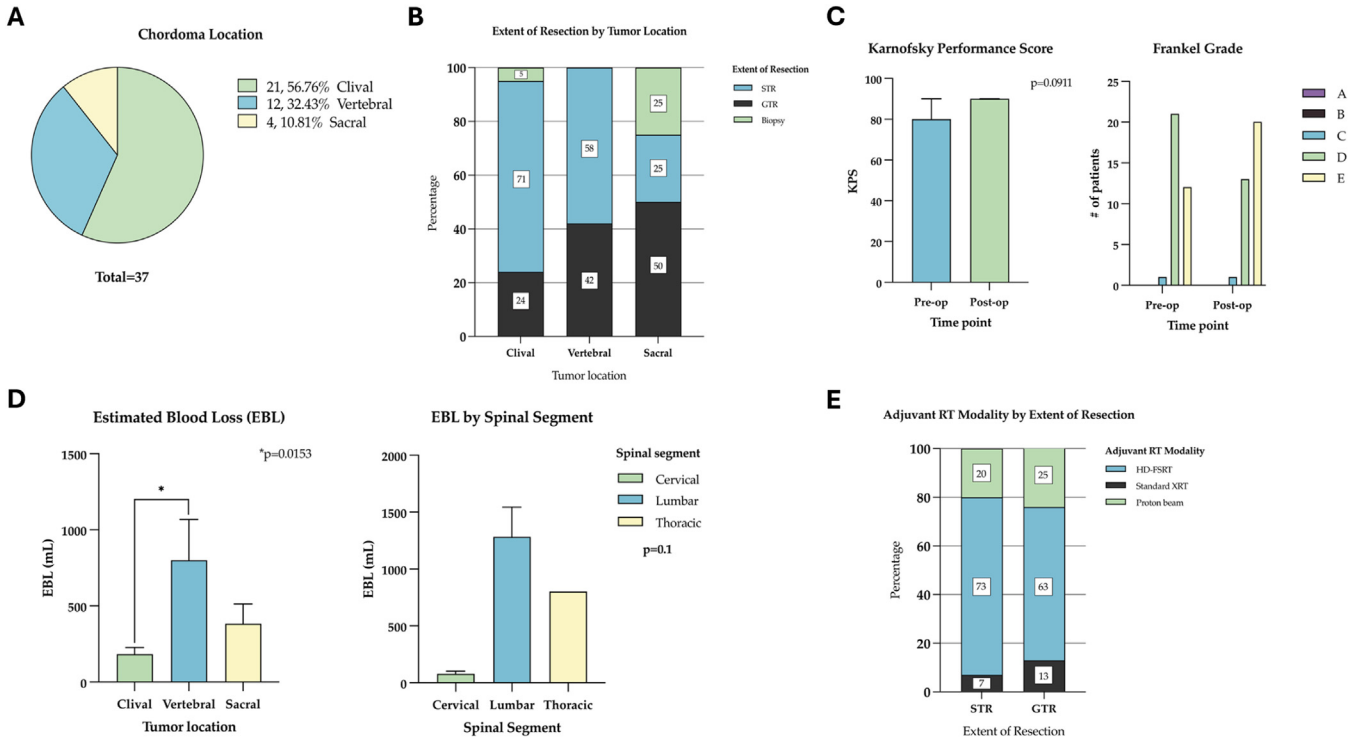

Fig. 2. (A) Pie chart distributions of the cohort by tumor locations. (B) Proportions of EOR during surgical resection by tumor locations (clival, vertebral and sacral). (C) Pre- and postoperative Frankel grade and median KPS. (D) Intraoperative EBL stratified by tumor location (Clival, cervical, thoracic, lumbar, and sacral). (E) Proportions of EOR during surgical resection by tumor locations (clival, vertebral and sacral).

Table 1
Baseline demographics and clinical characteristics.

Characteristic	Clivus n = 21	Vertebral n = 12	Sacral n = 4	p-value
Age in years, mean ± standard deviation (range)	42.8 ± 21.4 (7–88)	46.3 ± 21 (14–75)	61.8 ± 10.3 (52–73)	0.2521
Male sex, n (%)	10 (47.6)	9 (75.0)	3 (75.0)	0.3089
Symptoms on presentation, n (%)				
Cranial nerve palsy	15 (71.4)	-	-	
Headache	2 (9.5)	-	-	
Back/neck pain	-	7 (58.3)	2 (50.0)	
Paresthesia	-	3 (25.0)	-	
Bowel/bladder incontinence	-	-	1 (25.0)	
Saddle anesthesia	-	-	1 (25.0)	
Other*	4 (19.0)	2 (16.7)	-	
Preoperative radiological diagnosis, n (%)				
Chordoma	9 (47.4)	6 (50.0)	3 (75.0)	
Meningioma	2 (10.5)	-	-	
Primary bone tumor	-	2 (16.7)	-	
Neoplasm	-	-	1 (25.0)	
Other†	8 (42.1)	4 (33.3)	-	
Preoperative Frankel grade, n (%)				0.999
C	1	-	-	
D	12	7	3	
E	8	4	1	
Unknown	-	1	-	
Preoperative KPS, median (range)	80 (40–90)	80 (40–100)	80 (60–90)	0.3846

* Sinus pressure, tinnitus, facial numbness, dysphagia, asymptomatic and not available, each in one patient apiece.
† Skull base mass, clival lesion, cystic lesion, pseudotumor, paraganglioma, pituitary adenoma, metastatic process, sacral mass, epidural mass, lytic lesion, and mass lesion.

Table 2
Treatment characteristics.

Characteristic	Clival n = 21	Vertebral n = 12	Sacral n = 4	p-value
Initial surgical approach, n (%)				
Intralesional curettage - Clival		-	-	
Anterior	13 (65.0)			
Posterior	3 (15.0)	-	-	
Lateral	3 (15.0)	-	-	
Anterior + Posterior	1 (5.0)	-	-	
En bloc resection	-	5 (41.7)	2 (50.0)	
(Spondylectomy/Sacrectomy)				
Intralesional curettage	-	3 (25.0)	1 (25.0)	
Intralesional curettage + fusion	-	4 (33.3)	-	
Nonsurgical/biopsy	1 (5.0)	-	1 (25.0)	
Extent of initial resection, n (%)				
GTR	5 (23.8)	5 (41.7)	2 (50.0)	
STR	15 (71.4)	7 (58.3)	1 (25.0)	
Biopsy	1 (4.8)	-	1 (25.0)	
Estimated blood loss in mL, mean (range)	182.8 (20–400)	800.8 (55–1750)	383.3 (150–600)	.033
Adjuvant radiation, n (%)	15 (71.4)	6 (50.0)	2 (66.7)	

Fifteen patients (71.4%) received adjuvant RT after initial resection. Two patients (13.3%) received standard XRT, 9 (60.0%) received HD-FSRT and 4 patients (26.7%) received PBT (Fig. 2). The overall median OS was 13.3 years (range, 0.07–34.6 years). The median OS for patients who underwent STR and adjuvant RT (23.8 years, range, 0.2–25.6 years) was significantly higher than the patients who didn't receive adjuvant RT (4.1 years, range, 0.07–6.8 years) (p = .0005). However, the median OS of patients that underwent GTR only (34.6 years, range, 25.3–34.6 years) was not significantly different to the median OS of patients that underwent GTR and adjuvant RT (17.3 years, range, 13.0–18.6 years) (p = .3173).

Tumor recurrence and survival outcomes

Following initial tumor resection, preoperative neurologic status improved postoperatively in 5 patients (25%), 15 patients (75%) maintained their neurologic status, and no patients experienced worsening neurological function. There was a trend towards improvement in median KPS score postoperatively (90, range, 60–100) from a preoperative median KPS score of 80 (range, 40–90) (p = .1).

Two GTR patients (40%) and 8 STR patients (53.3%) experienced local recurrence or progression, with a median PFS of 13.3 years (range, 6.3–20.3 years) and 6.7 years (range, 0.5–23.5 years), respectively. All patients had received adjuvant RT following initial resection. Of these, 7 patients (70%; 1 GTR, 6 STR) underwent re-resection, 1 patient (10%) underwent stereotactic radiosurgery, 1 patient (10%) succumbed shortly after recurrence, and 1 patient (10%) had a recurrence on initial follow up imaging that has since remained stable on subsequent follow-ups. There was a trend towards an increased risk of tumor progression/recurrence in STR patients compared to GTR patients (p = .0886).

The median follow-up period was 2158 days (range, 23–9319 days). As of November 2023, 9 patients (40.9%) in this cohort had succumbed due to progression of their disease. Four patients (20.0%) experienced postoperative complications. The most common complications were CSF leak (n = 3, 75%) and wound dehiscence (n = 1, 25%) (Table 3).

Vertebral chordomas

There were 12 patients (9 males [75%], 3 females [25%]) with vertebral chordomas; 4 patients (33.3%) had cervical chordomas, 2 patients

Table 3
Outcomes.

Characteristic	Clival n = 21	Vertebral n = 12	Sacral n = 4	p-value
Neurological function (Frankel grade)				
Improved neurological function, n (%)	5 (23.8)	2 (18.2)	1 (25.0)	
Maintained preoperative neurological function, n (%)	15 (71.4)	9 (81.8)	2 (50.0)	
Nonsurgical, n (%)	1 (4.8)	-	1 (25.0)	
Postoperative KPS, median (range)	90 (60–100)	90 (60–100)	90 (80–90)	
Postoperative complications, n (%)				
CSF leak	3 (75.0)	-	-	
Wound dehiscence	1 (25.0)	-	-	
Wound infection	-	-	1 (100.0)	
Recurrence outcomes				
Repeat resection performed, n (%)	7 (35.0)	5 (41.7)	1 (33.3)	
Overall survival in years, median (range)				.2205
No repeat resection	16.5 (1.4–16.5)	4.0 (0.3–25.1)	-	
Repeat resection	23.8 (6.8–25.6)	8.0 (3.4–12.8)	5.7 (5.7–5.7)	
Follow-up time in days, median (range)	2158 (23–9319)	1731 (114–4653)	208.5 (13–2031)	
5-year survival rate (%)	88.9	77.8	100.0	
10-year survival rate (%)	81.3	44.4	0.0	
Overall survival in years, median (range)	23.8 (0.07–34.6)	9.3 (0.3–25.1)	6.5 (0.3–7.4)	.0424
Progression-free survival in years, median (range)	21.8 (0.5–23.5)	3.3 (0.2–9.0)	1.1 (1.1–1.1)	.0438

(16.7%) had thoracic chordomas, and 6 patients (50.0%) had lumbar chordomas. The mean age at presentation was 46.3 ± 21 years (range, 14–75 years). Back/neck pain was the most common symptom upon initial presentation (n = 7, 58.3%), followed by radiculopathy/paresthesia (n = 3, 25.0%). One patient (8.3%) was asymptomatic on presentation (Table 1). The mean duration between symptom onset and clinical presentation was 9.9 ± 11.6 months.

STR was achieved in 7 patients (n = 7, 58.3%). Five patients (41.7%) received en bloc resection via spondylectomy, and 7 patients (58.3%) received intralesional curettage with or without fusion (Table 2). Improvement from pre- to postoperative KPS was not significantly different between surgical approaches (p = .2212).

After initial tumor resection, 6 patients (50.0%) received adjuvant therapy; 5 patients (83.3%) received HD-FSRT, and 1 patient (16.7%) received PBT (Fig. 2). Surprisingly, the median OS of patients that underwent STR only (10.3 years, range, 3.4–14.4 years) was not significantly different to the median OS of patients that underwent STR with adjuvant RT (9.3 years, range, 4.0-12.8 years) (p = .4456), likely due to an underpowered cohort. Similarly, the median OS of patients that underwent GTR only was not significantly different to the median OS of patients that underwent GTR with adjuvant RT (p = .3173). The median OS of patients that underwent GTR only was undefined, with both patients alive at 2.8 years and 25.1 years post-surgery.

Tumor recurrence and outcomes

Neurological status improved in 2 patients (16.7%), 9 patients (75%) maintained preoperative neurological status and no patients experienced worsening of neurological status following initial resection. Preoperative neurological status was not available for 1 patient (8.3%). The median pre- and postoperative KPS were 80 (range, 40–100) and 90 (range, 60–100), respectively (p = .6761). There was no significant difference in change in KPS between patients that underwent STR compared to GTR (p = .5455).

Two GTR patients (40%) and 4 STR patients (57.1%) experienced local recurrence or progression, with a median PFS of 2.9 years (range, 0.99–4.8 years) and 4.8 years (range, 0.22–9.0 years), respectively. All patients with recurrent disease underwent re-resection which yielded STR given extensive local invasion of tumor. There was a significant risk of tumor progression in patients that underwent STR compared to patients that underwent GTR (p < .0001) and no significant difference in PFS (p = .4643). There was a trend towards significance in improvement of the median OS of patients with recurrent disease that underwent a repeat resection (8.0 years, range, 3.4-12.8 years) compared to patients that did not (4.0 years, range, 0.3–25.1 years) (p = .062).

There was a significant difference in median OS between cervical (13.6 years, range, 9.3-14.4 years), thoracic (3.4 years, 2.8-3.4 years), and lumbar (7.1 years, range, 0.3–25.1 years) chordoma (p = .0096). The median follow-up period was 1731 days (range, 114-4653 days). As of November 2023, 6 patients (50.0%) had succumbed in this cohort; 2 patients died due to complications of their cancer and the remaining 4 patients died due to unknown causes. No patients experienced surgical complications postoperatively.

Sacral chordomas

There were 4 patients (3 male [75%], 1 female [25%]) with sacral chordomas (Fig. 3). The mean age at presentation was 61.8 ± 10.3 years (range, 52-73 years). Two patients (50%) presented with sacral pain, 1 patient (25%) presented with bowel and bladder incontinence, and 1 patient (25%) presented with both saddle anesthesia and bowel and bladder incontinence. The mean duration between symptom onset and clinical presentation was 11.3 ± 16.8 months.

GTR was achieved in 2 patients (50.0%), STR was achieved in 1 patient (25.0%), and 1 patient (25.0%) elected to undergo HD-FSRT radiotherapy as primary treatment following excisional biopsy (Fig. 2). In the surgical group, 2 patients (66.7%) underwent en bloc resection and sacrectomy and 1 patient (33.3%) underwent resection via intralesional curettage.

Two patients (66.7%) received adjuvant HD-FSRT following initial GTR. These patients experienced no recurrent disease, while the patient who underwent STR and no adjuvant RT experienced progression with a PFS of 1.1 years and OS of 5.7 years. Survival analyses comparing treatment groups were limited due to a small sample size.

Tumor recurrence and outcomes

Neurological status improved postoperatively in 1 patient (33.3%), 2 patients (66.7%) maintained preoperative neurological status, and no patients experienced worsening of neurological status after resection. The median preoperative KPS and postoperative KPS were 80 (range, 60–90) and 90 (range, 80–90), respectively. 2 patients had an improvement in overall functional status. One patient, who elected radiotherapy as primary treatment, was censored from this analysis.

One patient (33%) had tumor progression following initial STR and no adjuvant RT. Sacrectomy was performed for repeat resection followed by adjuvant RT. The OS for this patient was 5.7 years compared to both GTR patients that are still alive at 1 year of follow up following surgery. Survival analysis and comparative analyses according to treatment modality were limited in this cohort due to a small sample size.

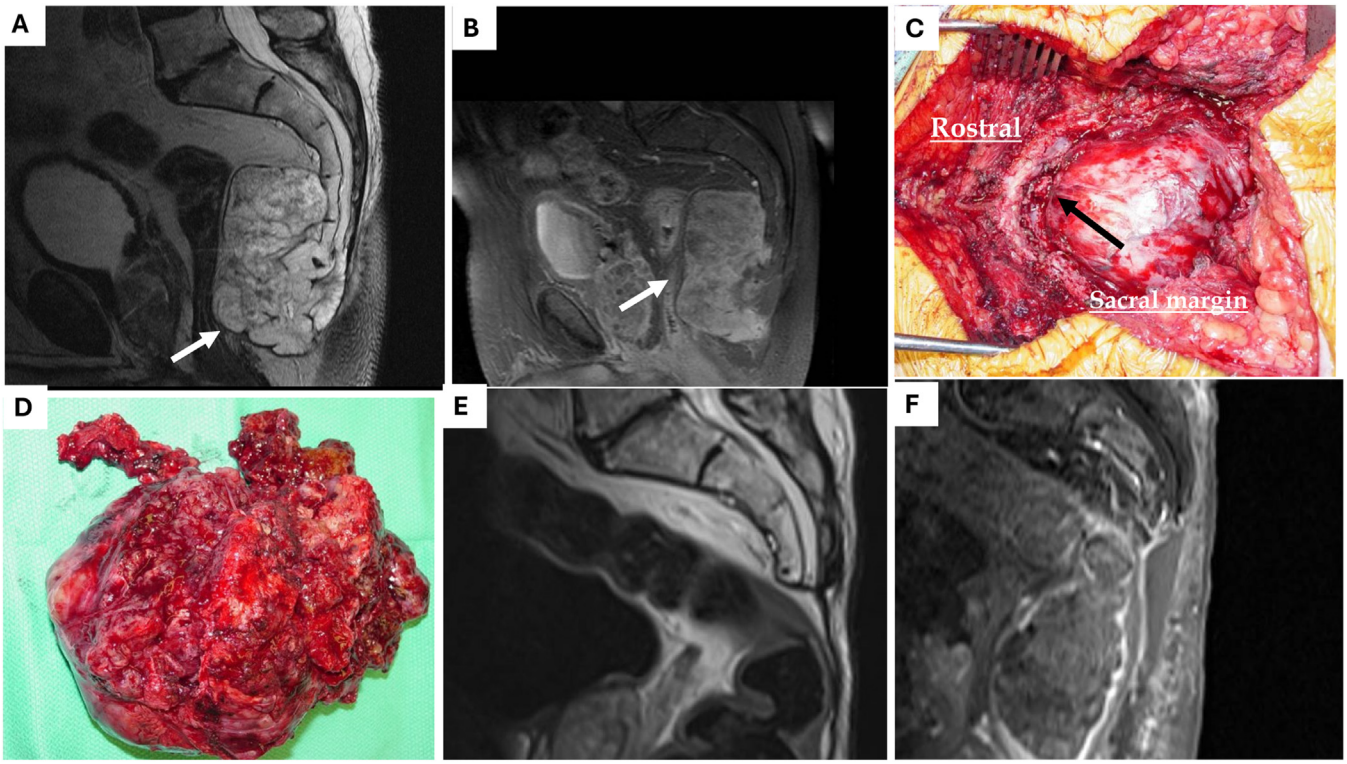

Fig. 3. Large sacral chordoma in a 78 y.o. male patient that presented with a 3-year history of intermittent sacral pain, worse with prolonged sitting. MRI Pelvis was obtained with sagittal T2 (A) and T1 post-gadolinium (B) sequences showing a 9.8 cm X 5.8 cm lobulated, T2 hyperintense lesion with heterogeneous enhancement arising from the ventral coccygeal region. Patient underwent CT-guided excisional biopsy which confirmed a diagnosis of chondroid chordoma. He later underwent an en bloc resection of the mass with sacrectectomy (C) with the tumor appearing as a gelatinous, lobulated mass with regions of necrosis and hemorrhage along with nodes of calcifications (D). Follow up post op MRI pelvis with sagittal T2 (E) and post-T1 gadolinium sequences showing GTR of the mass with post-operative changes and no evidence of residual disease or CSF leak.

The median follow-up period was 208.5 days (range, 13–2031 days). As of November 2023, 2 patients (50.0%) in this cohort had succumbed due to disease progression. One patient (25.0%) experienced postoperative wound infection.

Comparative outcomes

Estimated blood loss

When comparing mean EBL by tumor location, the mean EBL for vertebral tumors was significantly higher (800.8 mL ± 656.1 mL), compared to clival (182.8 mL ± 133.6 mL) and sacral (383.3 mL ± 225.5 mL) tumors (p = .033) (Fig. 2).

Functional and neurological outcomes

The median preoperative KPS of all patients in this cohort was 80 (range, 40–100) and the median postoperative KPS was 90 (range, 60–100), with a trend towards improvement from pre- to postoperative KPS (p = .0911). Stratification by favorable postoperative outcomes (KPS > 70 and KPS ≤ 70) showed no significant difference in favorable outcome rates between clival, vertebral, and sacral subgroups following initial resection (p = .6376) (Fig. 2).

Adjuvant radiotherapy outcomes

Twenty-three patients (65.7%) received adjuvant RT following initial resection. Standard XRT was used in 2 patients with clival chordoma, HD-FSRT was used in 16 patients (clival [n = 9], vertebral [n = 5], and sacral [n = 2]) and PBT was used in 5 patients (clival [n = 4] and vertebral [n = 1]) (Fig. 2). There was a trend toward improved median OS in patients that underwent STR and received adjuvant PBRT (25.6 years, range, 0.6–25.6 years) as compared to adjuvant standard XRT (23.8 years, range, 23.8–23.8 years) and HD-FSRT (16.5 years, range, 0.2-20.3 years) (p = .0901). However, the median OS was not significantly different between RT modalities in GTR patients (p = .179). Similarly, there was an improvement in median PFS in patients that underwent STR and adjuvant PBRT (23.5 years, range, 23.5–23.5 years) as compared to adjuvant standard XRT (21.8 years, range, 21.8–21.8 years) and HD-FSRT (5.0 years, range, 1.0–9.0 years) (p = .0175).

Survival outcomes

The median OS was 16.5 years (range, 0.07–34.6 years) with a 5-year survival rate of 86.20% and a 10-year survival rate of 62.96% (Fig. 5). Patients who were 65 years of age or older on presentation had a significantly lower median OS (5.7 years, range, 0.07–16.5 years) than patients who were under 65 (23.8 years, range, 0.2–34.6 years) (p = .001). Moreover, there was a significant difference in median OS between clival (23.8 years, range, 0.07–34.6 years), vertebral (9.3 years, range, 0.3–25.1 years), and sacral (6.5 years, range, 0.3–7.4 years) tumor locations (p = .0424) (Fig. 5). Similarly, median PFS was significantly higher in the clival cohort (21.8 years, range, 0.5–23.5 years), compared to the vertebral (3.3 years, range, 0.2–9.0 years), and sacral (1.1 years, range, 1.1–1.1 years) tumor locations (p = .0438). There was no significant correlation between tumor location and EOR for all tumor locations.

The median OS was significantly decreased in patients that underwent STR only (6.0 years, range, 0.07–14.4 years) compared to patients that underwent initial STR and adjuvant RT (23.8 years, range, 0.2–25.6 years) (p = .0206) (Fig. 5). In contrast, there was no significant difference in median OS of patients that underwent GTR only (34.6 years, range, 2.8–34.6 years) when compared to patients that underwent initial GTR and adjuvant RT (15.9 years, range, 0.3–18.6 years) (p = .1396). However, median OS was significantly higher for patients that under-

went GTR only when compared to patients who underwent initial STR and adjuvant RT (p = .0421).

There was a significantly lower OS in patients with postoperative Frankel grade D or less (10.5 years, range, 0.07–25.3 years) as compared to patients with postoperative Frankel grade E (25.6 years, range, 0.2–34.6 years) (p = .0062). However, there was no significant difference in median OS for patients with recurrent disease who underwent re-resection (11.6 years, range, 5.7–25.6 years) compared to those who did not undergo repeat resection (4.0 years, range, 1.4–16.5 years) (p = .2205).

Two patients (5.4%), 1 clival and 1 sacral chordoma patient, underwent excisional biopsy without resection, followed by RT as the primary treatment. The patient with sacral chordoma later experienced metastasis to the thoracic spine and underwent resection of the metastatic lesion given neurological compromise. The median OS for the nonsurgical patients was 7.0 years, compared to a median OS of 9.3 years for the surgical cohort.

The median follow-up period for all patients was 1731 days (range, 13–9319 days). As of November 2023, 17 patients had died among the overall cohort. Causes of death included cardiac arrest, sepsis, and cancer related complications.

Discussion

Chordomas are rare bone tumors that arise from the remnants of the embryonic notochord and account for approximately 1% to 4% of all primary bone tumors, 17% of primary bone tumors of the spine, and 0.2% of tumors of the skull base [2,18–20]. They have an annual incidence of 0.08 per 100,000 population in the US and are more common in males and Caucasians in the 5th or 6th decade of life [21]. In our cohort, male patients accounted for 59.5% and the mean age (SD) at diagnosis was 46.0 ± 20.8 years. Although rare, chordomas can occur in young patients [20]. Our cohort included 2 pediatric patients –a 7-year-old male and a 17-year-old female patient.

Epidemiologically, the most common sites of occurrence of chordomas include the sacrum (29%–50%), clivus (32%–40%) and mobile spine (10%–20%) [2,8,10,22]. In contrast, in our cohort, clival chordomas accounted for 56.8% of the total patients, followed by chordomas of the mobile spine (27%), and the sacrum (10.8%). Chordomas of the sacrococcygeal region tend to occur in older patients compared to tumors in other locations (peak age ~60 years) and clival chordomas tend to occur slightly more frequently in females [2,21]. This was similarly observed in our series, with the mean age (SD) of sacral chordoma patients (61.8 ± 10.3 years) over a decade older than the clival (42.8 ± 21.4 years) and vertebral chordoma patient population (46.3 ± 21 years) and females accounting for most of the clival chordoma subgroup (52.6%).

Histologic appearance and molecular features

The histology of chordomas was erroneously first described by Virchow in the 1800's as "ecchondrosis physalifora spheno-occipitali", characterizing the vacuolated cells that are typically seen in chordomas as originating from cartilaginous tissue [23]. Microscopically, these tumors are composed of cells with abundant eosinophilic cytoplasm and intracytoplasmic vacuoles embedded in a chondroid or myxoid stroma [19]. This histology, however, is not pathognomonic and can be present in other primary bone tumors such as osteosarcomas, chondrosarcomas, Ewing sarcomas, and clival metastasis [24].

There are 4 distinct histologic subtypes of chordoma, including conventional chordoma, chondroid chordoma, dedifferentiated chordoma and SMARCB1 (IN1) deficient poorly differentiated chordoma (Fig. 4) [25,32]. Microscopically, conventional and chondroid chordomas are resistant to radiation treatment and show a low-grade histopathology characterized by cords of tumor cells arranged into discrete lobules, separated by fibrous septa and embedded in a myxoid matrix [26–29]. In contrast, dedifferentiated and poorly differentiated chordomas show a more solid pattern of epithelioid to rhabdoid tumor cells arranged in a less prominent chondroid or myxoid matrix and have a more aggressive clinical course from time of diagnosis [19,30,31] (Fig. 4).

The histology of chordomas may also vary based on their location of origin, as noted by Che et al. Clival chordomas are characterized by diffuse growth patterns in an abundant chondroid matrix whereas spinal and sacral chordomas typically have a lobulating pattern in a nonchondroid, myxoid matrix [33]. On gross pathology, chordomas may appear on radiologic imaging as a gelatinous, lobulated mass with regions of necrosis and hemorrhage along with nodes of calcifications and bone fragments [34] (Fig. 3).

On immunohistochemical staining, these tumors express nuclear brachyury, cytokeratins, S100, and epithelial membrane antigen (EMA) [19]. The combined expression of cytokeratin and brachyury is a relatively specific method to differentiate chordoma from other primary bone malignancies, and was the primary method used to confirm diagnosis of chordoma for all 37 patients in our series. Elevated levels of brachyury, a transcription factor involved in notochord development, have been linked to familial cases of chordomas and is currently being used as a potential site of targeted therapy for chordomas [31,35,36,37].

Radiological features

Radiological diagnosis of chordomas is often challenging as these tumors show overlapping imaging features with various spinal tumors and biopsy is often required for confirmation of tissue diagnosis [24]. Typically, chordomas present as midline, locally aggressive osteolytic lesions with associated soft-tissue masses on radiographs, given their notochordal origin [24]. Further evaluation with computed tomography (CT) typically shows well-circumscribed osteolytic bony changes with rare marginal sclerosis and associated regions of irregular calcification, thought to represent sequestered normal bone [24,38,39]. CT imaging, although necessary, must be supplemented with MRI to evaluate nearby critical neural elements and adjacent viscera. T1-weighted MRI often displays low to moderate signal intensity with rare small foci of hyperintensity due to intratumoral hemorrhage and/or increased proteinaceous contents, while T2-weighted MRI shows marked hyperintensity due to the presence of vacuolated cellular components which contain high fluid contents [21,24,38–41] (Fig. 3). On gadolinium-enhanced T1-weighted MRI, these tumors show a heterogenous enhancement with a honeycomb appearance and there is an inverse correlation between MRI contrast-enhancement intensity and prognosis [41,42].

As chordomas are often found at the midline and are locally highly aggressive, these tumors may encase or invade adjacent critical neurovascular structures, which indicates further workup with CT and MR angiograms [24]. Functional imaging workup with bone scan or positron emission tomography (PET) is often limited to chordoma patients with metastatic disease.

In our cohort, radiological diagnosis of chordoma was accurately made preoperatively in 18 patients (48.6%). Other differential diagnosis considered include meningioma (2 patients), primary bone tumor (2 patients), metastases (1 patient), paraganglioma (1 patient), and a range of nonspecific diagnoses (Table 1).

Clinical presentation

The presentation of chordomas is highly variable depending on the location of the tumor. Clival or skull base chordomas often present as extradural mass lesions with bony erosion and can reach sizeable dimensions prior to symptom onset [39]. When symptomatic, tumors in this region often present with cranial nerve palsies (typically CN VI), headaches, and brainstem dysfunction with truncal ataxia and bulbar palsy [26,39]. In our cohort of clival chordoma patients, cranial nerve palsy (71.4%) was the leading presentation followed by symptoms of headache (10%) (Table 1). Similarly, spinal and sacral chordomas often present with symptoms attributable to compression of neural ele-

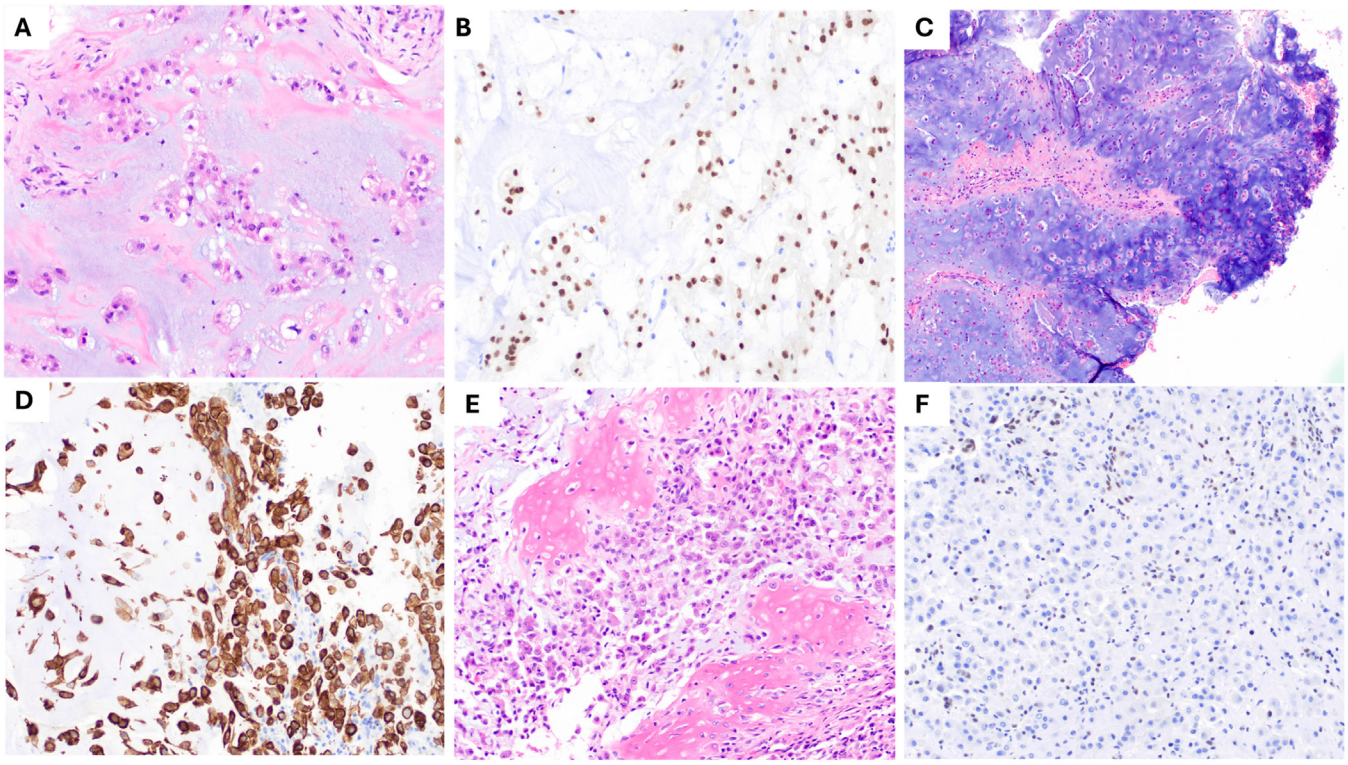

Fig. 4. (A) H&E, 200x magnification: Conventional chordoma with nests and cords of tumor cells embedded within a myxoid matrix. A subset of cells have vacuolated, bubbly cytoplasm (physaliphorous cells). (B) Brachyury immunohistochemical stain, 200x: The neoplastic cells show nuclear expression of brachyury. (C) H&E, 100x magnification: Chondroid subtype of chordoma containing abundant extracellular matrix resembling hyaline cartilage. (D) Pankeratin immunohistochemical stain, 200x magnification: Chondroid chordoma with neoplastic cells embedded in extracellular matrix resembling hyaline cartilage expressing pankeratin, which would typically be negative in cartilage. (E) H&E, 200x magnification: Poorly differentiated chordoma composed of tumor cells with a more epithelioid to rhabdoid appearance within a variably myxoid background. (F) INI1 immunohistochemical stain, 200x: Poorly differentiated chordoma with loss of nuclear expression of INI1 within tumor cells and preservation of nuclear expression within internal control (endothelial cells of vessels).

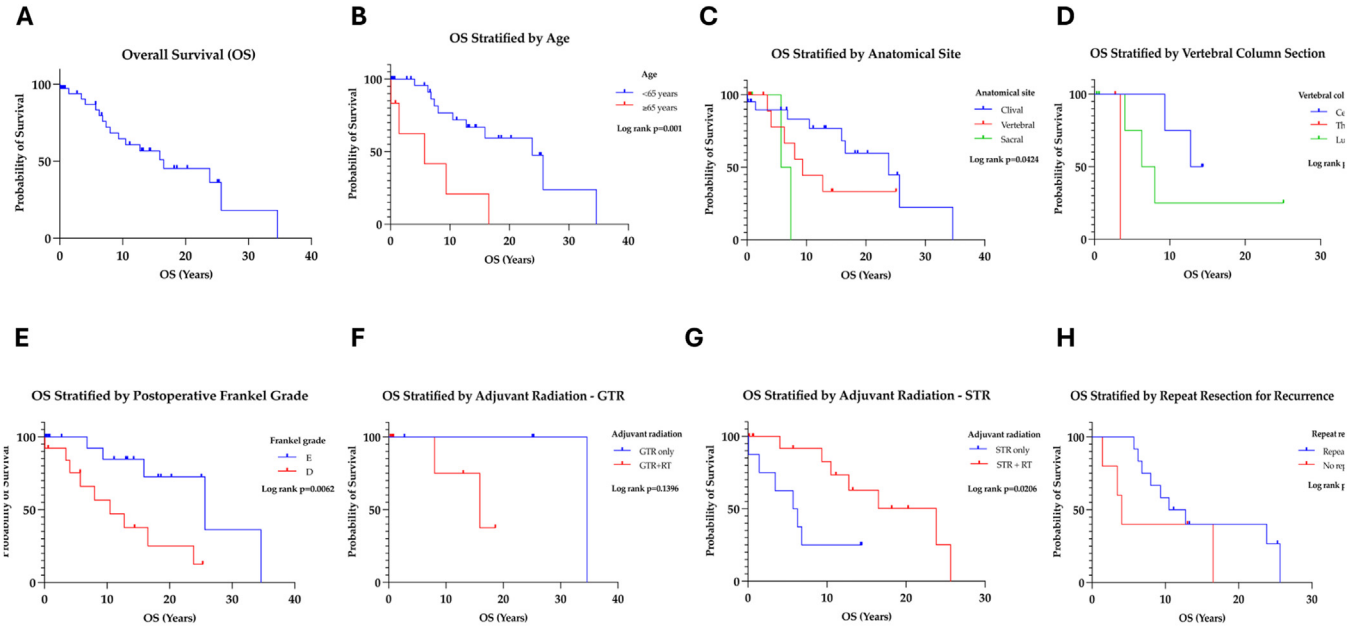

Fig. 5. Kaplan Meier survival curves. Overall survival (A) in patients with a diagnosis of skull base and spinal chordomas. Overall survival as stratified by the following: age (B), anatomical site (C), vertebral column section (D), Post operative Frankel grade (E), adjuvant RT in the GTR setting (F), adjuvant RT in the STR setting (G). Abbreviations: gross total resection (GTR); radiotherapy (RT); subtotal resection (STR).

ments and/or spinal instability [38,43]. The most common presentations include mechanical pain, neurological deficit, bladder/bowel dysfunction, radiculopathy, and a palpable mass, which were also reflected in our cohort (Table 1) [38,43]. Given the typical indolent growth pattern of sacral chordomas, these patients present with relatively larger tumors and a longer interval from symptom onset to clinical presentation (Fig. 3) [10,43]. Similarly in our cohort, the mean time to presentation for sacral chordomas (11.3 months ± 16.8 months) was slightly longer than the time to presentation of clival and vertebral tumor locations (9.7 months ± 14.3 months and 9.9 months ± 11.6 months, respectively).

Management and long-term outcomes

The gold-standard treatment for chordomas is an en bloc gross total resection of tumor tissue with circumferential tumor free margin [44–47]. However, given the notochordal origins of these tumors, predilection to the axial skeleton, and proximity to critical neurovascular structures, en bloc resection with tumor free margins is difficult to achieve. Often, this results in intralesional curettage and subtotal resection of tumor tissue or gross total resection without tumor free margins, resulting in patients being predisposed to an increased risk of local recurrence, leading to a decrease in progression free survival and overall survival rates [1,7,8,26,48,49]. It has been shown in prior studies that local recurrence is the most important prognostic factor in progression free survival in patients with chordomas [7,49,50].

In epidemiological studies dating back 30 years, the mean overall survival for patients with chordoma was reported to be around 6.29 years, with 67.6% surviving at 5 years, 39.9% at 10 years and 13.1% at 20 years [3]. More recently, with more aggressive surgery and adjuvant treatments, 10-year overall survival rates of 95% (skull base chordomas) and 58–100% (sacral and spinal chordomas) have been reported [51–53]. Comparably in our series, the median OS for all patients was 16.5 years (range, 0.07–34.6 years) with a 5-year survival rate of 86.2% and a 10-year survival rate of 62.96%. When stratified by tumor location, there was a significant difference in median OS between clival (23.8 years, range, 0.07–34.6 years), vertebral (9.3 years, range, 0.3–25.1 years), and sacral (6.5 years, range, 0.3–7.4 years) tumor locations ($p = .0424$). The improved OS of clival chordoma patients as compared to spinal and sacral tumor location has been previously reported in other series [54,55]. There was no significant correlation between tumor location, age, sex, EOR, post op neurological status and adjuvant RT treatment. Given that EOR is the most important predictor of OS, the difference in median OS seen based on tumor locations may be due to differences in tumor biology and inherent aggressiveness in tumors arising from different locations [21]. Other factors noted to significantly affect median OS in our series included: older age (≥65) (5.7 years) compared to patients <65 (23.8 years) ($p = .001$) and lower postoperative Frankel grade (postoperative Frankel grade D or less [10.5 years] compared to patients with postoperative Frankel grade E [25.6 years]) ($p = .0062$).

Postoperatively, all patients maintained or had an improvement in their preoperative neurological function as quantified by Frankel grade and the median postoperative KPS (90) trended higher when compared to preop (80) ($p = .0911$). More importantly, a higher postoperative Frankel grade was associated with increased OS ($p = .0062$), suggesting that improvements in neurological status are associated with improved patient survival.

Clinical outcomes by extent of resection and re-resection

The importance of achieving wide margins in chordoma resection has been corroborated in previous studies [45–47]. A recent meta-analysis by Yu et al. showed significantly lower recurrence and mortality rates in patients with sacral chordomas undergoing wide margin excision as compared to those with subtotal debulking [51]. This strong correlation between EOR and OS has also been reported in spinal and clival chordoma patients [22,39,51]. Similarly in our cohort, median OS for GTR patients was significantly higher when compared to patients that underwent STR and adjuvant RT ($p = .0421$). Though there was no correlation between EOR and tumor location in our series, EOR was noted to have a higher impact on OS in patients with spinal tumor locations when compared to clival and sacral tumors, highlighting the importance of a more aggressive surgical approach with tumors in this location. This could be accounted for by the presence of critical neurovascular structures in close proximity to the tumor bed, likely limiting the maximal dose of RT that can be safely delivered, though it's difficult to make definite conclusions given the small sample size in each cohort. Controversially, Dennis et al. recently reported that en bloc resection may not be necessary if intralesional debulking and separation surgery was followed by stereotactic body RT [14]. It's important to note however that this is a single institutional study and long-term follow-up with a multi-institutional cohort is needed prior to validation of this data.

Similarly, EOR has also been shown to correlate with PFS, irrespective of tumor location [22,39,51]. This was replicated in our cohort, where there was either a trend towards significance or significance in the increased risk of tumor progression/recurrence in patients that underwent STR when compared to patients that underwent GTR for clival and spinal tumor locations ($p=0.0886$, 0.0001 respectively).

Thirteen surgically managed patients (37.14%) required re-resection due to local tumor recurrence with the highest recurrence rate among spinal chordoma patients (41.7%). In patients that underwent repeat tumor debulking/resection, there was an improvement/trend of an improvement in median OS when compared to patients that underwent nonsurgical treatment with adjuvant RT only (clival: 23.8 years vs 16.5 years [$p = .2614$], spinal: 8.0 years vs 4.0 years [$p = .062$]). This finding was also previously corroborated by Goumenos et al. and Noya et al. in their review of patients with clival and sacral chordomas, respectively [38,39].

Clinical outcomes by modality of radiation therapy

Traditionally, chordomas were considered a radioresistant tumor with older studies reporting poor results when conventional RT was used as adjuvant treatment in the setting of subtotal tumor resection or debulking [56–58]. More recently, however, with the advent of RT techniques, several clinical studies have shown significant improvement in disease-free survival when adjuvant RT was used following STR [44,59,60]. Modern advances in RT techniques such as intensity-modulated radiotherapy (IMRT), PBRT, carbon ion radiotherapy (CIRT) and stereotactic radiotherapy (SRT) allow for an extremely precise delivery of high dose of radiation to the post-surgical tumor bed, resulting in a much-improved local tumor control rates and overall survival [52,54,55,61].

In our series, twenty-two patients (62.9%) received adjuvant radiotherapy treatment following initial resection. Similar to prior series, the median OS was significantly lower in patients that underwent STR only when compared to patients that underwent STR and adjuvant RT ($p = .0206$). However, there was no significant difference in median OS of patients that underwent GTR only when compared to patients that underwent GTR and adjuvant RT ($p = .1396$). This was recently corroborated by Yolcu et al. in a review of the National Cancer Database, which showed adjuvant RT had no additional benefit in OS in patients when GTR of the tumor was achieved [17]. Similarly, Julian et al. systematic review of the literature revealed no additional benefit for adjuvant RT in the setting of GTR of clival chordomas [16]. However, a single institutional series by Olabisi et al. showed some improvement in OS with the use of RT in the setting of GTR of skull base chordomas [15,16]. Given the heterogeneous findings in the literature and the non-negligible risks associated with RT, the risk-benefit ratio in individual patients needs to be considered prior to tailoring of adjuvant treatment decisions, especially in the setting of GTR of tumor tissue.

Among patients that received RT, standard XRT was used in 2 patients, HD-FSRT was used in 16 patients and PBT was used in 4 pa-

tients. Similar to prior reports, there was a trend toward improved median OS in patients that underwent STR and received adjuvant RT with proton beam, followed by standard XRT and HD-FSRT (p = .0901) [52,54,55,61]. Moreover, in line with prior literature, the median OS was not significantly different between RT modalities in patients that underwent GTR (p = .179).

Interestingly, a recent prospective phase II study showed significant improvement in recurrence-free survival when spinal chordoma patients received preoperative and postoperative PBT as compared to only postoperative RT treatment [62]. This was also previously reported by Rotondo et al. and is likely accounted for by the decreased seeding of viable tumor tissue focally and along the resection tract that occurs with preoperative RT [63]. These encouraging results show that the timing of RT may have an important role in reducing recurrence rates. More research is needed into whether preoperative RT (in addition to postoperative RT) is beneficial in preventing long-term recurrence of this rare tumor.

Limitations

This institutional review was a retrospective study that included a limited number of patients from a single center. Given the rarity of the pathology and expected single institutional limited number of patients, we reviewed the literature extensively to further strengthen our recommendations, however, the small sample size may limit the accuracy of comparative conclusions. The change over time in surgical and radiation oncological techniques and procedures may additionally introduce bias to the treatment comparisons in our study, as it spans 40 years. The retrospective and nonrandomized nature of this work also decreases its level of evidence.

Conclusion

Our results further reaffirm the role of targeting GTR in surgical management of chordoma patients, as this has the best long-term overall survival and outcome. Consistent with the literature, patients with sacral chordoma had the lowest OS, followed by vertebral and clival chordoma patients. Interestingly, postoperative neurological function was shown to impact median OS with patients with postoperative Frankel grade E experiencing significantly better survival rates over patients with Frankel grade D or less. This further validates the importance of maximal but safe resection of tumor, while ensuring no new onset of neurological deficit ensues. While the role of adjuvant RT in improving median OS of patients with STR was unequivocal, further studies are warranted before recommending postoperative RT treatment in the GTR setting. Furthermore, proton beam-based RT modality was noted to have the best tumor control rates with markedly improved OS rates when compared to HD-SRT and standard XRT, though the role of preoperative PBT remains to be clearly elucidated.

Financial Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Short Summary: Gross total resection of skull base and spinal chordomas is associated with improved long-term survival outcomes independent of adjuvant radiotherapy, while adjuvant radiotherapy is associated with improved survival outcomes in subtotal resection

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number [UL1TR002537]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

[1] Ruggieri P, Angelini A, Ussia G, Montalti M, Mercuri M. Surgical margins and local control in resection of sacral chordomas. Clin Orthop Relat Res 2010;468(11):2939–47. doi:10.1007/s11999-010-1472-8.
[2] van Wulfften Palthe ODR, Tromp I, Ferreira A, et al. Sacral chordoma: a clinical review of 101 cases with 30-year experience in a single institution. Spine J 2019;19(5):869–79. doi:10.1016/j.spinee.2018.11.002.
[3] McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973-1995. Cancer Causes Cont 2001;12(1):1–11. doi:10.1023/a:1008947301735.
[4] Xiao Y, Yu W, Zheng J, et al. Bibliometric insights in advances of chordoma: global trends and research development in the last decade. Orthop Surg 2023;15(10):2505–14. doi:10.1111/os.13831.
[5] Sciubba DM, Chi JH, Rhines LD, Gokaslan ZL. Chordoma of the spinal column. Neurosurg Clin North Am 2008;19(1):5–15. doi:10.1016/j.nec.2007.09.006.
[6] Bailey CS, Fisher CG, Boyd MC, Dvorak MF. En bloc marginal excision of a multilevel cervical chordoma. Case report. J Neurosurg Spine 2006;4(5):409–14. doi:10.3171/spi.2006.4.5.409.
[7] Wolf RJ, Winkler V, Mattke M, Uhl M, Debus J. Intensity-modulated radiotherapy for the management of primary and recurrent chordomas: a retrospective long-term follow-up study. Rep Pract Oncol Radiother 2023;28(2):207–16. doi:10.5603/RPOR.a2023.0022.
[8] Zhou Y, Hu B, Wu Z, Cheng H, Dai M, Zhang B. The clinical outcomes for chordomas in the cranial base and spine: a single center experience. Medicine (Baltimore) 2019;98(23):e15980. doi:10.1097/md.0000000000015980.
[9] Lee IJ, Lee RJ, Fahim DK. Prognostic factors and survival outcome in patients with chordoma in the united states: a population-based analysis. World Neurosurg 2017;104:346–55. doi:10.1016/j.wneu.2017.04.118.
[10] Ahmed R, Sheybani A, Menezes AH, Buatti JM, Hitchon PW. Disease outcomes for skull base and spinal chordomas: a single center experience. Clin Neurol Neurosurg 2015;130:67–73. doi:10.1016/j.clineuro.2014.12.015.
[11] Walcott BP, Nahed BV, Mohyeldin A, Coumans JV, Kahle KT, Ferreira MJ. Chordoma: current concepts, management, and future directions. Lancet Oncol. 2012;13(2):e69–76. doi:10.1016/s1470-2045(11)70337-0.
[12] Stener B, Gunterberg B. High amputation of the sacrum for extirpation of tumors. Principles and technique. Spine (Phila Pa 1976) 1978;3(4):351–66. doi:10.1097/00007632-197812000-00009.
[13] Austin JP, Urie MM, Cardenosa G, Munzenrider JE. Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. Int J Radiat Oncol Biol Phys 1993;25(3):439–44. doi:10.1016/0360-3016(93)90065-4.
[14] Lockney DT, Shub T, Hopkins B, et al. Spinal stereotactic body radiotherapy following intralesional curettage with separation surgery for initial or salvage chordoma treatment. Neurosurg Focus 2017;42(1):E4. doi:10.3171/2016.9.Focus16373.
[15] Sanusi O, Arnaout O, Rahme RJ, Horbinski C, Chandler JP. Surgical resection and adjuvant radiation therapy in the treatment of skull base chordomas. World Neurosurg 2018;115:e13–21. doi:10.1016/j.wneu.2018.02.127.
[16] Gendreau JL, Hameed NUF, Jimenez A, Chakravarti S, Mehkri Y, Mukherjee D. Fractionated radiotherapy after gross total resection of clival chordoma: a systematic review of survival outcomes. Neurosurgery 2023;93(2):257–66. doi:10.1227/neu.0000000000002418.
[17] Yolcu Y, Wahood W, Alvi MA, et al. Evaluating the role of adjuvant radiotherapy in the management of sacral and vertebral chordoma: results from a national database. World Neurosurg 2019;127:e1137–44. doi:10.1016/j.wneu.2019.04.070.
[18] Barber SM, Sadrameli SS, Lee JJ, et al. Chordoma-current understanding and modern treatment paradigms. J Clin Med 2021;10(5):1054. doi:10.3390/jcm10051054.
[19] Karpathiou G, Dumollard JM, Dridi M, et al. chordomas: a review with emphasis on their pathophysiology, pathology, molecular biology, and genetics. Pathol Res Pract. 2020;216(9):153089. doi:10.1016/j.prp.2020.153089.
[20] Lau CS, Mahendraraj K, Ward A, Chamberlain RS. Pediatric chordomas: a population-based clinical outcome study involving 86 patients from the surveillance, epidemiology, and end result (seer) database (1973-2011). Pediatr Neurosurg 2016;51(3):127–36. doi:10.1159/000442990.
[21] George B, Bresson D, Herman P, Froelich S. Chordomas: a review. Neurosurg Clin N Am 2015;26(3):437–52. doi:10.1016/j.nec.2015.03.012.
[22] D'Amore T, Boyce B, Mesfin A. Chordoma of the mobile spine and sacrum: clinical management and prognosis. J Spine Surg. 2018;4(3):546–52. doi:10.21037/jss.2018.07.09.
[23] Sahyouni R, Goshtasbi K, Mahmoodi A, Chen JW. A historical recount of chordoma. J Neurosurg Spine 2018;28(4):422–8. doi:10.3171/2017.7.Spine17668.
[24] Lee SH, Kwok KY, Wong SM, Chan CXJ, Wong YT, Tsang ML. Chordoma at the skull base, spine, and sacrum: a pictorial essay. J Clin Imaging Sci 2022;12:44. doi:10.25259/jcis_62_2022.
[25] Anderson WJ, Doyle LA. Updates from the 2020 World Health Organization Classification of soft tissue and bone tumours. Histopathology 2021;78(5):644–57. doi:10.1111/his.14265.

[26] Wang K, Xie SN, Wang L, et al. Natural growth dynamics of untreated skull base chordomas in vivo. World Neurosurg 2020;136:e310–21. doi:10.1016/j.wneu.2019.12.164.
[27] Aydemir E, Bayrak OF, Sahin F, et al. Characterization of cancer stem-like cells in chordoma. J Neurosurg 2012;116(4):810–20. doi:10.3171/2011.12.Jns11430.
[28] Owen JH, Komarck CM, Wang AC, et al. UM-Chor1: establishment and characterization of the first validated clival chordoma cell line. J Neurosurg. 2018;128(3):701–9. doi:10.3171/2016.10.Jns16877.
[29] Rosenberg AE, Brown GA, Bhan AK, Lee JM. Chondroid chordoma–a variant of chordoma. A morphologic and immunohistochemical study. Am J Clin Pathol 1994;101(1):36–41. doi:10.1093/ajcp/101.1.36.
[30] Wasserman JK, Gravel D, Purgina B. Chordoma of the head and neck: a review. Head Neck Pathol 2018;12(2):261–8. doi:10.1007/s12105-017-0860-8.
[31] Yamaguchi T, Imada H, Iida S, Szuhai K. Notochordal tumors: an update on molecular pathology with therapeutic implications. Surg Pathol Clin. 2017;10(3):637–56. doi:10.1016/j.path.2017.04.008.
[32] Shih AR, Cote GM, Chebib I, et al. Clinicopathologic characteristics of poorly differentiated chordoma. Mod Pathol. 2018;31(8):1237–45. doi:10.1038/s41379-018-0002-1.
[33] Cha YJ, Suh YL. Chordomas: histopathological study in view of anatomical location. J Korean Med Sci 2019;34(13):e107. doi:10.3346/jkms.2019.34.e107.
[34] Tenny S, Varacallo M. Chordoma. 2023 Aug 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 28613596.
[35] Vujovic S, Henderson S, Presneau N, et al. Brachyury, a crucial regulator of notochordal development, is a novel biomarker for chordomas. J Pathol. 2006;209(2):157–65. doi:10.1002/path.1969.
[36] Yang XR, Ng D, Alcorta DA, et al. T (brachyury) gene duplication confers major susceptibility to familial chordoma. Nat Genet. 2009;41(11):1176–8. doi:10.1038/ng.454.
[37] Otani R, Mukasa A, Shin M, et al. Brachyury gene copy number gain and activation of the PI3K/Akt pathway: association with upregulation of oncogenic Brachyury expression in skull base chordoma. J Neurosurg 2018;128(5):1428–37. doi:10.3171/2016.12.Jns161444.
[38] Goumenos S, Kakouratos G, Trikoupis I, et al. Clinical outcome after surgical treatment of sacral chordomas: a single-center retrospective cohort of 27 patients. Cancers (Basel) 2024;16(5):973. doi:10.3390/cancers16050973.
[39] Noya C, D'Alessandris QG, Doglietto F, et al. Treatment of clival chordomas: a 20-year experience and systematic literature review. Cancers (Basel) 2023;15(18):4493. doi:10.3390/cancers15184493.
[40] Erdem E, Angtuaco EC, Van Hemert R, Park JS, Al-Mefty O. Comprehensive review of intracranial chordoma. Radiographics 2003;23(4):995–1009. doi:10.1148/rg.234025176.
[41] Santegoeds RGC, Temel Y, Beckervordersandforth JC, Van Overbeeke JJ, Hoeberigs CM. State-of-the-art imaging in human chordoma of the skull base. Curr Radiol Rep 2018;6(5):16. doi:10.1007/s40134-018-0275-7.
[42] Lin E, Scognamiglio T, Zhao Y, Schwartz TH, Phillips CD. Prognostic implications of gadolinium enhancement of skull base chordomas. AJNR Am J Neuroradiol. 2018;39(8):1509–14. doi:10.3174/ajnr.A5714.
[43] Baig Mirza A, Bartram J, Okasha M, et al. Surgical management of spinal chordoma: a systematic review and single-center experience. World Neurosurg. 2021;156:e111–29. doi:10.1016/j.wneu.2021.09.001.
[44] York JE, Kaczaraj A, Abi-Said D, et al. Sacral chordoma: 40-year experience at a major cancer center. Neurosurgery 1999;44(1):74–9 discussion 79-80. doi:10.1097/00006123-199901000-00041.
[45] Atalar H, Selek H, Yildiz Y, Sağlik Y. Management of sacrococcygeal chordomas. Int Orthop. 2006;30(6):514–18. doi:10.1007/s00264-006-0095-x.
[46] Kaiser TE, Pritchard DJ, Unni KK. Clinicopathologic study of sacrococcygeal chordoma. Cancer 1984;53(11):2574–8. doi:10.1002/1097-0142(19840601)53:11<2574::aid-cncr2820531136>3.0.co;2-5.
[47] Samson IR, Springfield DS, Suit HD, Mankin HJ. Operative treatment of sacrococcygeal chordoma. a review of twenty-one cases. J Bone Joint Surg Am. 1993;75(10):1476–84. doi:10.2106/00004623-199310000-00008.
[48] Choy W, Terterov S, Kaprealian TB, et al. Predictors of recurrence following resection of intracranial chordomas. J Clin Neurosci. 2015;22(11):1792–6. doi:10.1016/j.jocn.2015.05.024.
[49] Yang Y, Li Y, Liu W, Xu H, Niu X. The clinical outcome of recurrent sacral chordoma with further surgical treatment. Medicine (Baltimore) 2018;97(52):e13730. doi:10.1097/md.0000000000013730.
[50] 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):2122–34. doi:10.1002/(sici)1097-0142(20000501)88:9<2122::aid-cncr19>3.0.co;2-1.
[51] Yu X, Kou C, Bai W, et al. Comparison of wide margin and inadequate margin for recurrence in sacral chordoma: a meta-analysis. Spine (Phila Pa 1976) 2020;45(12):814–19. doi:10.1097/brs.0000000000003386.
[52] Marucci L, Niemierko A, Liebsch NJ, Aboubaker F, Liu MC, Munzenrider JE. Spinal cord tolerance to high-dose fractionated 3D conformal proton-photon irradiation as evaluated by equivalent uniform dose and dose volume histogram analysis. Int J Radiat Oncol Biol Phys 2004;59(2):551–5. doi:10.1016/j.ijrobp.2003.10.058.
[53] Houdek MT, Rose PS, Hevesi M, et al. Low dose radiotherapy is associated with local complications but not disease control in sacral chordoma. J Surg Oncol Jun 2019;119(7):856–63. doi:10.1002/jso.25399.
[54] Terahara A, Niemierko A, Goitein M, et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. Int J Radiat Oncol Biol Phys 1999;45(2):351–8. doi:10.1016/s0360-3016(99)00146-7.
[55] DeLaney TF, Liebsch NJ, Pedlow FX, et al. Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. Int J Radiat Oncol Biol Phys 2009;74(3):732–9. doi:10.1016/j.ijrobp.2008.08.058.
[56] Cummings BJ, Hodson DI, Bush RS. Chordoma: the results of megavoltage radiation therapy. Int J Radiat Oncol Biol Phys. 1983;9(5):633–42. doi:10.1016/0360-3016(83)90228-6.
[57] Rich TA, Schiller A, Suit HD, Mankin HJ. Clinical and pathologic review of 48 cases of chordoma. Cancer 1985;56(1):182–7. doi:10.1002/1097-0142(19850701)56:1<182::aid-cncr2820560131>3.0.co;2-j.
[58] Catton C, O'Sullivan B, Bell R, et al. Chordoma: long-term follow-up after radical photon irradiation. Radiother Oncol. 1996;41(1):67–72. doi:10.1016/s0167-8140(96)91805-8.
[59] Azzarelli A, Quagliuolo V, Cerasoli S, et al. Chordoma: natural history and treatment results in 33 cases. J Surg Oncol. 1988;37(3):185–91. doi:10.1002/jso.2930370311.
[60] Zhou H, Jiang L, Wei F, et al. Prognostic factors in surgical patients with chordomas of the cervical spine: a study of 52 cases from a single institution. Ann Surg Oncol. 2017;24(8):2355–62. doi:10.1245/s10434-017-5884-5.
[61] Zabel-du Bois A, Nikoghosyan A, Schwahofer A, et al. Intensity modulated radiotherapy in the management of sacral chordoma in primary versus recurrent disease. Radiother Oncol 2010;97(3):408–12. doi:10.1016/j.radonc.2010.10.008.
[62] Konieczkowski DJ, Chen YLE, Bernstein KD, et al. Prospective phase II study of scanned beam proton therapy for spine sarcomas. Int J Radiat Oncol Biol Phys 2018;102(3):e325–6. doi:10.1016/j.ijrobp.2018.07.1005.
[63] Rotondo RL, Folkert W, Liebsch NJ, et al. High-dose proton-based radiation therapy in the management of spine chordomas: outcomes and clinicopathological prognostic factors. J Neurosurg Spine. 2015;23(6):788–97. doi:10.3171/2015.3.Spine14716.