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Scientific Article

Impact of Dosimetric Compromises on Early Outcomes of Chordomas and Chondrosarcomas Treated With Image-guided Pencil Beam Scanning Proton Beam Therapy

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Purpose: To critically review the clinical factors, dosimetry, and their correlation with early outcomes in patients with chordomas and chondrosarcomas treated with pencil beam scanning (PBS) proton beam therapy (PBT).

Methods and Materials: Consecutive 64 patients diagnosed with chordoma or chondrosarcoma treated at our center were studied. Patient, tumor, and treatment-related factors including dosimetry were captured. Early and late toxicities and early outcomes were evaluated and correlated with clinical and dosimetric factors using standard statistical tools.

Results: The median age of patients was 39 years (range, 4-74 years), and most common site was skull base (47%), followed by sacrum (31%) and mobile spine (22%). The median prescription dose to the high-risk clinical target volumes for chordoma and chondrosarcoma was 70.4 cobalt gray equivalent (CGE) and 66 CGE at 2.2 CGE per fraction, respectively. At presentation, 55% presented after a recurrence/progression of which 17% had received previous radiation and 32% had a significant neural compression. At the time of PBT, 25% of patients had suboptimal neural separation. Three-fourths of patients had at least an acceptable target coverage. Although 11% had a tier 1 compromise (gross tumor volume [GTV] D98 < 90%), 14% had a tier 2 compromise (GTVD98 < 59 CGE). With a median follow-up of 27.5 months, 2-year local control and progression-free survival was 86.7% and 81.8% for chordomas and 87.5% and 77.1% for chondrosarcomas, respectively. Residual GTV of >25 cm^3 and a tier 2 compromise were associated with inferior local control (hazard ratio [HR], 0.19; P = .019; HR, 0.061; P = .022, respectively) and progression-free survival (HR, 0.128; P = 0.014; HR, 0.194; P =.025, respectively) on multivariate analysis. Despite multiple surgeries, a majority presented with recurrent disease and previous radiations and grade 3 acute and late toxicities were limited and comparable with others in the literature.

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Conclusions: Despite multiple surgeries, adequate neural separation was challenging to achieve. Severe dosimetric compromise (GTV D98 < 59 CGE) led to inferior early outcomes. Adequate neural separation is key to avoiding dosimetric compromise and achieving optimal local control.

Introduction

Chordomas and chondrosarcomas of the skull base and spine are relatively rare malignant bone tumors with varying biology and outcomes.[1] Chordomas arise from the transformed undifferentiated notochordal remnants, whereas chondrosarcomas arise from the cartilage cells.[2] They have distinctive pathologic features, and their outcomes vary significantly because 5-year local control rates of appropriately treated chondrosarcomas and chordomas are 75% to 99% and 53% to 81% respectively.[3]

Despite the differences in biology and behavior, their outcomes are often reported together given similar anatomic location, clinical presentation, radiologic characteristics, and treatment principles.[4] En bloc resection, which is considered the gold standard for most malignant bone tumors, is difficult to achieve because of their location and proximity to critical structures such as the brainstem, spinal cord, cranial/spinal nerves, and vessels.[5,6] Most patients undergo R2 resections, and despite multiple surgeries, there is often residual disease very close to or abutting neural structures. Therefore, radiation therapy is also challenging given the proximity to radiosensitive serial structures and the need for relatively large doses (>66-76 Gy) to achieve long-term tumor disease control. In view of frequent local recurrences, reirradiation is also a challenge. Proton beam therapy (PBT) because of its unique physical and biological properties can be exploited to deliver highly conformal and higher physical doses to achieve better local control.[7] Several retrospective studies have shown superior local control rates with PBT compared with conformal photon-based techniques in chordomas and chondrosarcomas.[8-10]

In the last decade, owing to the emergence of pencil beam scanning (PBS), the availability of modern dose calculation algorithms (eg, Monte Carlo algorithms) and routine availability of image guidance has enabled significantly improved quality of PBT plans for the treatment of these patients. Image guidance, especially volumetric imaging with cone beam computed tomography (CBCT) with modern PBT systems, ensures crisp treatment margins, conformity of dose distributions to the clinical target volumes (CTVs), and evaluation of daily dose deposition triggering plan adaptation when required.

However, despite the use of conformal radiation therapy techniques including PBT, often dosimetric compromises are made to respect the tolerance of neural structures. It has been reported that one-third of recurrences occur in regions where dosimetric compromises were made.[11] This study aimed to critically review our patient cohort, dosimetry of our intensity modulated proton therapy (IMPT) plans, and preliminary clinical outcomes in 64 patients of skull base, spinal, and sacral chordomas and chondrosarcomas treated consecutively at our center.

Methods and Materials

Consecutive 64 patients of histologically proven chordoma and chondrosarcoma of skull base, spine, and sacrum treated with image-guided PBS PBT from January 2019 to March 2023 at our institution with a minimum follow-up of 6 months were retrospectively analyzed. The study reports the patient, tumor, and treatment-related parameters of the cohort (Table 1). Important dosimetric parameters including dosimetric compromises made to the target coverage were reviewed. In addition, early clinical response and toxicities related to PBT were analyzed and reported. The study was approved by the institutional ethics committee.

Simulation

Patients with skull base and upper cervical tumors were immobilized with thermoplastic face mask and customized neck rest on a base of skull base frame. Patients with dorsolumbar and sacral tumors were immobilized with vacuum cushion in preferably in prone or occasionally in customized lateral position. These patients were simulated with an empty bladder protocol after adequate bowel preparation. A simulation computed tomography (CT) of the region of interest with 2-mm slice thickness was acquired as per standard institutional protocol. All patients also underwent a planning multiparametric magnetic resonance imaging (MRI) preferably in the treatment position. Patients with metal implants underwent simulation imaging (both CT and MRI) with metal artifact reduction algorithms. All patients with metal implants additionally underwent megavoltage CT on the Radixact (Accuray) machine and orthogonal digital radiographs to qualitatively assess the dimensions and shape of the metal implant. CT myelography was performed if spinal cord visualization on MRI was difficult owing to implant-related MRI artifacts. A detailed information regarding the type, content, and actual dimensions of the metal implant was acquired before simulation.

Table 1 Patient, tumor, and treatment characteristics

Parameter	Skull base	Cervicodorsolumbar	Sacral	Total
No. (%)	30 (47)	14 (22)	20 (31)	64 (100)
Age (y), median (range)	35 (4-67)	39 (15-61)	58 (28-74)	39 (4-74)
Histology, n (%)				
Chordoma	24 (37.5)	12 (22.2)	18 (28.1)	54 (84.3)
Chondrosarcoma	6 (9)	2 (3.1)	2 (3.1)	10 (15.7)
Recurrent, n (%)	21 (32.8)	7 (10.9)	7 (10.9)	35 (54.6)
Reirradiation, n (%)	7 (10.9)	1 (1.5)	3 (4.6)	11 (17.1)
Brain stem compression during PBT, n (%)	9 (14)	0	0	9 (14)
Optic apparatus compression during PBT, n (%)	2(3.1)	0	0	2(3.1)
Spinal cord compression during PBT, n (%)	0	5 (7.8)	0	5 (7.8)
Neural structure compression during PBT, n (%)	11 (17.1)	5 (7.8)	0	16 (25)
No. surgeries (before PBT), n (%)				
No surgery	0	0	8 (12.5)	8 (12.5)
1 time	12 (22.2)	7 (10.9)	6 (9.3)	25 (39)
2 times	14 (21.8)	5 (7.8)	3 (4.6)	22 (34.3)
3 times	2 (3.1)	1(1.5)	1 (1.5)	4 (6.2)
>3 times	2 (3.1)	1(1.5)	2 (3.1)	5 (7.8)
Gross residual at PBT, n (%)	17 (30.9)	4 (7.2)	20 (36.3)	41 (74.5)
GTV (mL), median (range)	12.75 (0.19-132)	36.85 (0.83-9)	395 (36.1-1345)	35.85 (0.19-1345)
	Ch-15.75 (0.19-132)	Ch: 41 (0.83-110)	Ch: 432.5 (36.1-1345)	Ch: 41 (0.19-1345)
	ChSa: 6.95 (0.28-22.1)	ChSa: 5.23 (1.4-9)	ChSa: 111.6 (39.6-183.7)	ChSa: 9.45 (0.28-183.7)
Technique	SFO, MFO	MFO	SFO, MFO	
Median dose in CGE (range)				
Chordoma (in 32 fractions)	70 (66-70.4)	70.4 (68.2-70.4)	70.4 (66-70.4)	70.4 (66-70.4)
Chondrosarcoma (in 30 fractions)	65.8 (63-68)	66	68 (67.8- 68.2)	66 (63-68.2)

Abbreviations: CGE = cobalt gray equivalent; Ch = chordoma; ChSa = chondrosarcoma; GTV = gross tumor volume; MFO = multifield optimization; PBT = proton beam therapy; SFO = single field optimization.

Target delineation

The gross tumor volumes (GTVs) encompassed any gross residual disease as defined on CT and/or MRI. Clinical target volumes-high risk (CTV-HR) encompassed entire GTV with a small margin (typically 3 mm and rationalized) along with the adjacent areas harboring direct microscopic infiltrations at risk of recurrence as judged by treating physician. Clinical target volumes-low risk (CTV-LR) was defined by growing additional margins (typically a margin of 1 cm for skull base, cervical, and dorsolumbar tumors and 1.5-3 cm for sacral tumors) over CTV-HR and included regions of usual infiltrations or routes of spread. Bilateral cavernous sinuses were included if involved partially by infiltration. Similarly, CTV-LR for clival lesions almost always included entire clivus and prevertebral regions upto C1 or C2 vertebra. For spinal tumors, CTV-LR included the entire vertebral body (if the respective vertebra was involved partially) and included the paravertebral regions generously. Wherever possible, surgical tracts, biopsy sites, and scars were included in the CTV-LR.

Dose prescription

Doses were prescribed in relative biological effectiveness (RBE)-weighted physical doses. The RBE for proton radiation was set to 1.1. Thus the dose unit, GyRBE (or CGE) was the physical dose in Gy × 1.1. In patients with chordomas, CTV-HR was prescribed a dose of 70.4 CGE in 32 fractions (EQD 2-74 Gy, α/β 2) at 2.2 CGE per fraction, whereas dose to CTV-LR was individualized, which ranged from 54 to 64 CGE (54-56 CGE for skull base and spinal tumors and 60-64 CGE for sacral tumors). For chondrosarcoma, CTV-HR was prescribed a dose of 66 CGE/30 to 33 fractions, and CTV-LR was prescribed a dose of 54 CGE.

Planning dose constraints and treatment goals are summarized in Table 2. Based on GTV D98, patients

Table 2 Treatment goals and important organs at risk dose constraints

Parameter	Treatment goal	
GTV	98% volume to receive 98% of prescription dose	
Dose tiers based on GTVD98		
Ideal	D98% ≥ 98%	
Optimal	D98 at least 95% but <98%	
Acceptable	D98% at least 90% but <95%	
Tier 1 compromise	D98% <90%, but >59 CGE	
Tier 2 compromise	D98% < 59 CGE	
CTV-HR	D95% ≥ 95%	
CTV-LR	D95% ≥ 95%	
Site	OAR	Constraint
Skull base	Brainstem surface D0.03 cm^3	<63 CGE
	Brainstem core D0.03 cm^3	<54 CGE
	Optic apparatus* D0.03 cm^3	<54 CGE
	Spinal cord D0.03 cm^3	<45 CGE
Cervicodorsolumbar	Spinal cord D0.03 cm^3 (cervical)	<54 CGE
	Spinal cord D0.03 cm^3 (dorsolumbar)	<45 CGE
Sacral	Sigmoid V70 (cm^3)	0
	Sigmoid V65 (cm^3)	<2
	Sigmoid V63 (cm^3)	<5
	Rectum V70 (cm^3)	0
	Rectum V65 (cm^3)	<2
	Bowel bag V15 (cm^3)	<120

Abbreviations: CGE = cobalt gray equivalent; CTV = clinical target volume; GTV = gross target volume; HR = high risk; LR = low risk; OAR = organs at risk.
*Optic apparatus includes right and left optic nerves and optic chiasm.

were stratified into 5-dose tiers in accordance with our institutional protocol for these tumors (Table 2). In patients undergoing reirradiation, the constraints were individualized based on previous radiation details.

Treatment planning

Treatment planning for IMPT was performed on RayStation treatment planning system (RaySearch Laboratories) using Monte Carlo algorithm for dose optimization and calculation. The beam arrangement varied depending on the target volume geometry and dose limits to neighboring organs at risk (OARs). Typically, beam arrangement consisted of 4 beams for skull base chordomas (2 anterior oblique and 2 posterior oblique) and 3 beams for spinal and sacral chordomas (2 posterior obliques and 1 noncoplanar inferior oblique). During planning, individual factors such as patient positioning reproducibility were considered while choosing beam angles for optimal target coverage. Proton plans were generated either with multifield optimization techniques, which were robust to range and setup uncertainties. A pretreatment patient-specific quality assurance (QA) was performed to verify the approved plan before treatment was implemented.

Treatment delivery, image guidance, QA imaging, and plan adaptation

Patients were set up for the treatment on the basis of anatomic landmarks, and markings applied on the patients or immobilization devices. The setup was verified on a daily basis with the help of orthogonal KV-x-rays and volumetric CBCT imaging. Appropriate couch corrections were applied before the treatment. Intrafraction motion was monitored using surface guidance (AllignRT; VisionRT). A significant deformation of the anatomy or weight loss as visualized on CBCT triggered a QA CT scan. The treatment imaging was audited daily. Most patients additionally underwent periodic QA CT scans in the treatment position with varying frequency (1-3 weekly). The original plan was overlaid on the QA CT scans to evaluate the proton dose perturbation and the need for plan adaptation as per the treating physician.

Patients were evaluated by the physician weekly for treatment-related toxicities as per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. After completion of the treatment, patients were followed up every 3 monthly for 6 months and 6 monthly thereafter. At each follow-up, patients were evaluated clinically for toxicities and imaging response as per multiparametric MRI of the local site along with spinal screening and CT scan of thorax.

Statistical analyses were performed using t tests to compare means, whereas categorical variables ware analyzed using χ^2 tests. Survival analyses were conducted using Kaplan-Meier curves, with differences in survival distributions assessed through log-rank tests. Univariate analyses were performed to identify potential associations, and variables with significance were further evaluated in multivariate analyses using Cox-proportional hazards models. All statistical tests were 2 sided, and a significance level of 0.05 was applied.

Results

Patients and tumor characteristics of the 64 patients are listed in Table 1. A total of 56 patients (88%) underwent surgery at least once before PBT, 31 (48%) and 9 (14%) patients underwent surgery at least twice and thrice before they were planned for PBT, respectively. At presentation, 22 patients (34%) had their tumor abutting or compressing serial neural structures (Fig. 1). All these patients were considered for resurgery and the same was done in 20 of the 22 patients. Of these 20 patients, resurgery was able to achieve optimal neural separation in 6 patients.

At the time of PBT planning, 16 patients (25%) had their tumors abutting neural structures, 35 patients (55%) patients had recurrent disease and 11 patients (17%) had a previous course of radiation; 75% (41/64) patients had a gross residual tumor at the time of planning PBT (despite the multiple surgical procedures) with a median GTV of 35.8 cm^3 (range, 0.19-1345 cm^3). Sacral tumors had the largest GTV among all patients with a median GTV of 395 cm^3 (range, 36-1345 cm^3). Among the 11 patients who received PBT as part of reirradiation, 2 patients received PBT as third course of radiation.

A majority of patients had classical or chondroid chordoma, whereas 3 patients had poorly differentiated chordoma and 1 had dedifferentiated chordoma. Similarly, most patients with chondrosarcomas had low-grade histology, whereas 3 patients had high-grade histology.

Median GTV D98 was 65.5 CGE (range, 37.8-70.3 CGE). The median CTV-HR D98 and CTV-LR D95 were 66.1 CGE (range, 37.1-70.3 CGE) and 56.5 CGE (range, 37.6-65 CGE). Hard OAR dose constraints to serial neural structures were achieved in all patients with or without dosimetric compromise to the target coverage. On the nominal plans, GTV D98 was ideal, optimal, and acceptable in 24, 10, and 14 patients, respectively (Fig. 2). In 16 of the 64 patients (25%), the coverage was below acceptable range. All these 16 patients had suboptimal neural separation at the time of PBT planning. Of these patients with dosimetric compromise, 9 patients (14%) had a tier 2 dosimetric compromise and 7 patients (11%) a tier 1 compromise. Among the 16 patients, gross tumor was abutting the brain stem in 9 patients, optic apparatus in 2

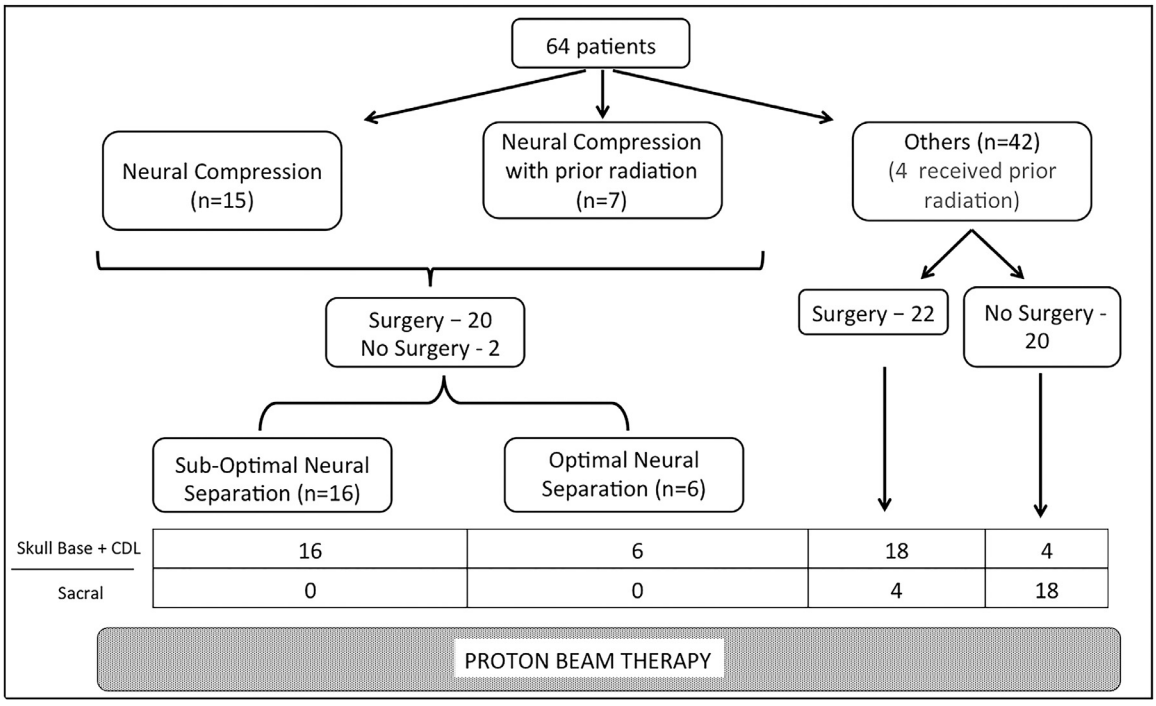

Figure 1 Consort diagram stratifying patients based on neural compression at presentation, neural separation before proton therapy, and tumor location.

patients, spinal cord in 5 patients, and multiple structures in 1 patient.

Four patients of cervical chordomas and 1 patient with clival chordoma underwent decompressive surgeries with fat placement between spinal cord/brainstem and the tumor, and all these patients received at least acceptable dose coverage to GTV D98. Thirteen patients (20%) had metal implants, and all these patients underwent proton-photon combination treatments. The median percentage of total dose delivered with photons (Helical Tomotherapy) was 25%.

Three patients (2 patients of spinal chordoma and 1 patient of sacral chordoma) underwent plan adaptation during the treatment. The plan adaptation was triggered on the CBCT scan because of tissue loss in 2 patients and rectal deformation in 1 patient, which resulted in increased dose to OAR in 2 patients and target dose compromise in 1 patient. Two patients underwent the plan adaptation in week 4 and 1 patient in week 3.

All patients completed their treatment without any major interruptions. All acute toxicities are listed in Table 3. Four patients (6.2%) had acute grade 3 reactions. Specifically, 2 patients developed radiation dermatitis: 1 reported mucositis, and 1 experienced pain. Skin toxicity was the most common acute toxicity noted in patients irrespective of the site of the disease. For patients of clival and cervical chordomas, the second most commonly reported toxicity was oropharyngeal mucositis, whereas for patients with dorsolumbar and sacral lesions, it was pain.

Late toxicities

Grade 3 toxicity was noted in 1 patient (1.5%) who developed cerebrospinal fluid leak 7 months posttherapy (a patient of cervical chordoma underwent multiple surgeries before PBT), which may or may not be directly related to the PBT. Grade 2 toxicities were noted in 9 patients (14%). Five patients had grade 2 neuropathic pain. One patient each developed temporal lobe necrosis and transient optic neuritis requiring steroid and supportive medications. Both the abovementioned neurologic toxicities were noted in patients who had a history of radiation therapy. Two patients had treatment-induced hypothyroidism, which mandated hormone replacement. Sacral insufficiency fracture (grade 1) was noted in 4 patients, implant-related pain and stiffness were noted in one patient, and mild sensorineural hearing loss was noted in 3 patients.

With a median follow-up of 27.5 months (range, 9-53 months), 8 patients (12.5%) had local progression of disease after a median duration of 11 months. Six patients developed distant metastases at a median of 13.5 months, of which 3 patients died of metastatic chordoma. Two-year local control and progression-free survival (PFS) were 86.7% and 81.8% for chordoma and 87.5% and 77.1% for chondrosarcomas, respectively (Fig. 3). On univariate analysis (Table 4), GTV of the residual disease >25 cm^3 at the time of PBT and previous radiation were associated with poor 2-year local control and PFS. Tier 2 dosimetric compromise was also associated with inferior

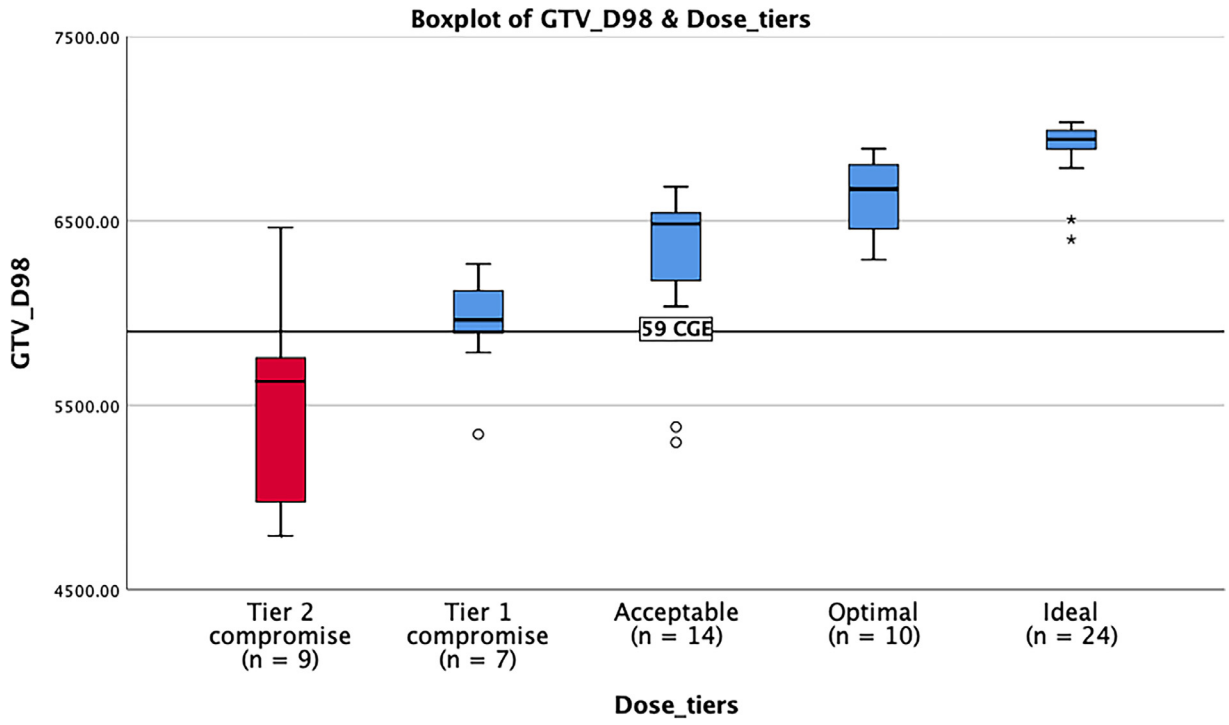

Figure 2 GTV98 as a function of dose tiers.

2-year local control and PFS, although local control was statistically significant (Fig. 4). On multivariate analysis (Table 5), residual GTV > 25 cm^3 and tier 2 dosimetric compromise were associated with poor 2-year local control and PFS.

Discussion

The study critically evaluated our initial experience of patients with chordomas and chondrosarcomas treated with mildly hypofractionated IMPT. Our early experience consisted of a large proportion of patients with recurrent disease (56%), including 17% of patients with a history of radiation therapy. At the time of PBT, owing to either suboptimal neural separation and/or previous radiation, one-quarter of the PBT plans had a dosimetric compromise (GTV D98 < 90%) of which 14% had a tier 2 compromise (GTV D98 < 59 CGE). Early disease trend in this cohort suggests that patients with residual GTV of >25 cm^3 and those who had tier 2 dosimetric compromise (GTV D98 < 59 CGE) had significantly inferior 2-year local control and PFS (Tables 4 and 5).

Our dosimetric evaluation criteria for chordomas and chondrosarcomas, although arbitrary, are based on our standard practice for other sites. On nominal plans, the usual treatment goal is to achieve CTV-HR D98 of ≥98% of the prescription dose and to achieve at least D95 of ≥95% in worst-case scenario on robust evaluation (usually for 3-mm setup and 3.5%-4% range uncertainty). In certain challenging scenarios when dosimetric compromises have to be made, the institutional practice is to accept a D98 of at least >90% of the prescribed dose. Therefore, D98 < 90% was considered as compromised dosimetry for this study, and the same was stratified into tier 1 and 2 based on previous studies that showed that the disease outcomes were inferior if the GTV D98 was <59 CGE.[3,12]

At presentation, 22 patients (34%) had neural structures compression with (7 patients) or without (15 patients) a history of radiation. All of them were recommended for further surgery/targeted debulking; 20 of the 22 patients underwent surgery, and 6 patients achieved adequate neural structure decompression/separation. For the rest (25%) with suboptimal separation surgeries, the tumor location was skull base in 11 patients (17%), cervical in 3 patients (4.5%), and dorsolumbar in 2 patients (3%).

We found that dosimetric coverage to the GTV was compromised in 25% (16/64) of patients, and 11% had a tier-1 dosimetric compromise whereas 14% had a tier 2 compromise. All these patients had neural structure compression before PBT and did not achieve optimal neural structure separation. Additionally, 4 patients had a history of radiation therapy to a median dose of 60 CGE (range, 41.4-66 CGE). One-third of patients in tier 2 dosimetric compromise had a history of radiation therapy. Of these tier 2 patients, tumors were located in the skull base in 6 patients, cervical in 2 patients, and dorsal spine in 6 patients. The 2-year local control in patients with tier 2

Table 3 Acute toxicities

Toxicity (CTCAE v4.0)	Skull base (n)	Cervicodorsolumbar (n)	Sacral (n)	n (%)
Skin (n = 64)				
Grade 1	27	6	11	44 (68.7)
Grade 2	2	1	7	10 (15.6)
Grade 3	0	0	2	2 (3.1)
Oropharyngeal mucositis (n = 37)				
Grade 1	8	2	0	10 (27)
Grade 2	8	1	0	9 (24.3)
Grade 3	1	0	0	1 (2.7)
Pain (n = 64)				
Grade 1	2	4	4	10 (15.6)
Grade 2	0	0	2	2 (3.1)
Grade 3	0	0	1	1 (1.5)
Gastrointestinal (n = 27)				
Grade 1	0	0	9	9 (33.3)
Grade 2	0	0	5	5 (18.5)
Grade 3	0	0	0	0
Genitourinary (n = 27)				
Grade 1	0	0	13	13 (48.1)
Grade 2	0	0	3	3 (11.1)
Grade 3	0	0	0	0

Oropharyngeal mucositis was calculated for all skull base lesion + 7 cervical lesions (30+7). Gastrointestinal and genitourinary toxicities were calculated for all sacral + 7 dorsolumbar lesions (20+7).
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

dosimetric compromise was significantly worse compared with the rest of the cohort (Fig. 4). This underscores the importance of separation surgeries in limiting the dosimetric compromises and possibly early local failures in patients with neural structure compression. None of the 5 patients who underwent placement of fat between the neural structure and the residual tumor during the separation surgeries had a dosimetric compromise. Patients with fat spacer completed the treatment within 3 months of surgery and did not have any major deformation of the

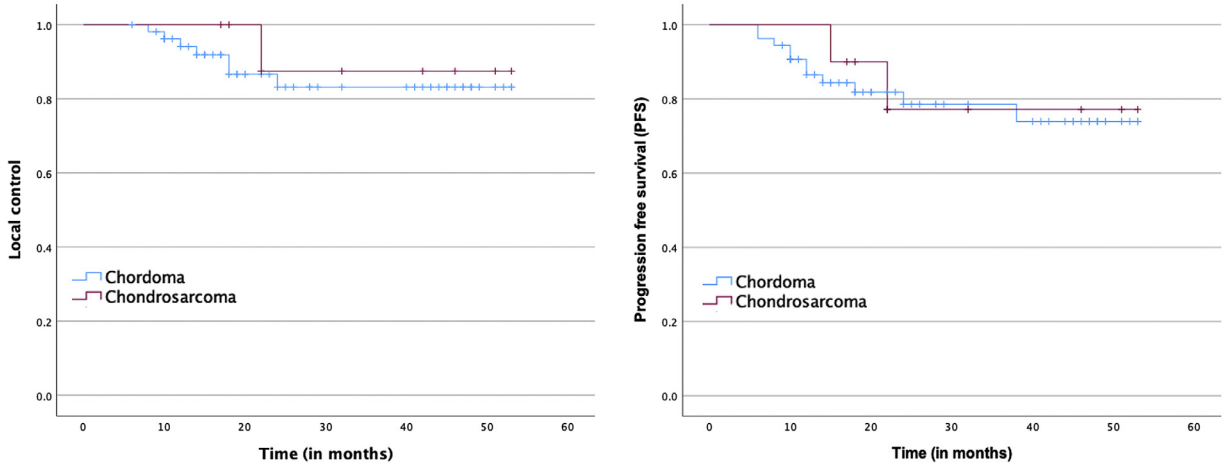

Figure 3 Kaplan-Meier curves for local control (A) and progression-free survival (B) for chordomas and chondrosarcomas.

Table 4 Univariate analyses

		Local control		PFS	
Clinical outcome	**No. (%)**	**2 y (%)**	***P***	**2 y (%)**	***P***
Total cohort	64	86.5		80.6	
Diagnosis					
Chordoma	54 (84)	86.7	.652	81.8	.352
Chondrosarcoma	10 (16)	87.5		77.1	
Presentation					
De novo	29 (45)	90.1	.951	81.7	.573
Recurrent	35 (55)	82.6		73.1	
Dosimetry					
Atleast acceptable	48 (75)	89.1	**.046**	82.8	.351
Tier 1 compromise	7 (11)	100		87.5	
Tier 2 compromise	9 (14)	57.1		57.1	
Residual GTV volume (cm^3)					
<25	26 (41)	94.7	**.045**	90.9	**.021**
>25	38 (59)	81		73.5	
Location					
Skull base and mobile spine	44 (69)	85.9	.776	84.4	.22
Sacral	20 (31)	88.8		74.3	
Prior radiation					
Yes	11 (17.1)	64.8	**.038**	60.6	**.009**
No	53 (83.9)	90.8		84.9	

Abbreviations: GTV = gross tumor volume; PFS = progression-free survival.
p value: significant at <0.05 level (Bold).

spacer mandating adaptive replanning. Fat globules could serve as a relatively safe and cost-effective option in these patients wherever feasible (Fig. 5). Other studies have also noted similar results with spacers.[13,14]

The median residual GTV volumes were 12.75 cm^3 (range, 0.19-132 cm^3), 36.85cm^3 (range, 0.83-9 cm^3), and 395 cm^3 (range, 36.1-1345 cm^3) for skull base, mobile spinal, and sacral tumors, respectively. Patients with larger residual GTV could have a better GTV D98 owing to a relatively smaller proportion of their volume getting underdosed compared with patients with smaller residual GTV (assuming the residual GTV to be close to neural

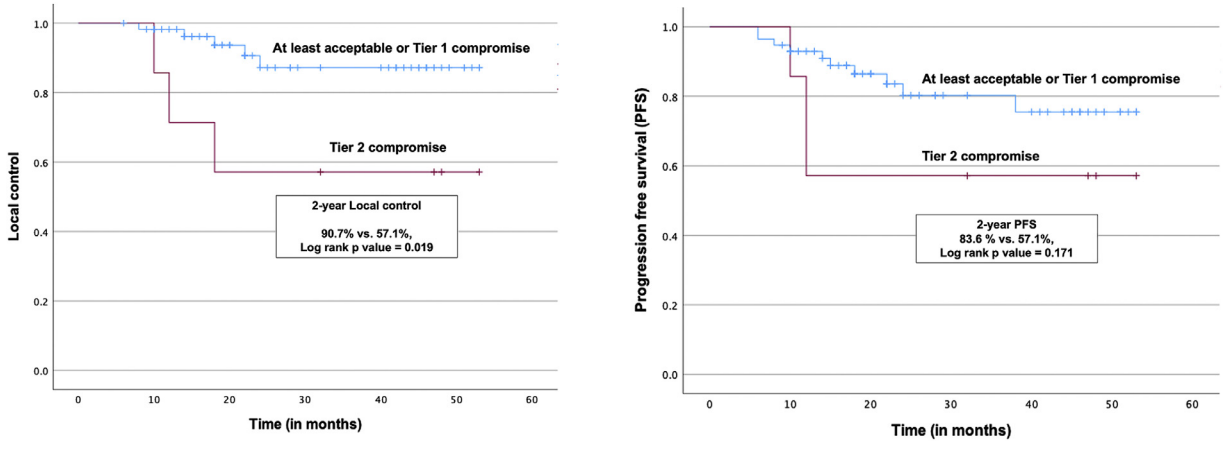

Figure 4 Kaplan-Meier curves for local control (A) and progression-free survival (B) with respect to dose tiers.

Table 5 Multivariate analysis

	Local control		PFS	
Prognostic factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
GTV residual >25 vs <25 cm^3	0.026 (0.001-0.547)	**.019**	0.128 (0.025-0.662)	**.014**
Tier 2 vs acceptable/tier1 compromise	0.061 (0.006-0.664)	**.022**	0.194 (0.046-0.814)	**.025**
Recurrent vs de novo presentation	0.620 (0.069-5.53)	.669	0.798 (0.265-2.409)	.689
Chordoma vs chondrosarcoma	0.432 (0.034-5.529)	.519	0.483 (0.08-2.752)	.410
Skull base and mobile spine vs sacral	0.865 (0.042-17.6)	.925	0.688 (0.182-2.6)	.581
Upfront radiation vs reirradiation	0.977 (0.047-20.41)	.988	0.635 (0.074-5.418)	.678

Abbreviations: GTV = gross tumor volume; HR = hazard ratio; PFS = progression-free survival.
p value: significant at <0.05 level (Bold).

structures). However, in the study, smaller residual GTV was associated with better outcomes. Therefore, disease outcomes are possibly influenced by a complex array of factors including treatment volume, residual size of the GTV, and extent of the dosimetric compromise, apart from the other treatment-related factors (location of tumor, extent of surgery—en bloc vs gross total vs debulking surgeries; primary vs reirradiation) and tumor biology. For example, in our cohort, despite significantly larger residual GTVs (because of less frequent surgeries), the local control and PFS of sacral tumors were similar compared with those of the rest of the cohort. This possibly underscores the fact that the outcomes were more dependent on the dosimetric compromise than on the residual GTV.

With a median follow-up of 27.5 months, 2-year local control and PFS in our cohort was 86.7% and 81.8% for chordoma and 87.5% and 77.1% for chondrosarcoma, respectively. The results seem contradictory to most studies in the literature reporting higher local control and PFS for chondrosarcoma than those for chordoma.[3,15] A small patient number of chondrosarcomas could have skewed the results in our cohort. Among the 10 patients of chondrosarcoma, only 1 patient had a local progression, while 3 patients had systemic progression; 2 of these patients had grade 2 chondrosarcoma and the other had multiple enchondromatosis with a malignant transformation of a distant site enchondroma.

Despite 55% of our chordoma cohort being recurrent, our 2-year local control and PFS is comparable with other published results.[16-18] In a recently published Proton Collaborative Group (PCG) prospective registry trial, with a median follow-up of 22 months, the authors reported a 2-year local control of 97% and PFS of 89%. Our results were comparable, especially in patients with de novo presentation (90% and 82%, respectively) and without a history of irradiation (91% and 85%, respectively). The abovementioned prospective study only included two-

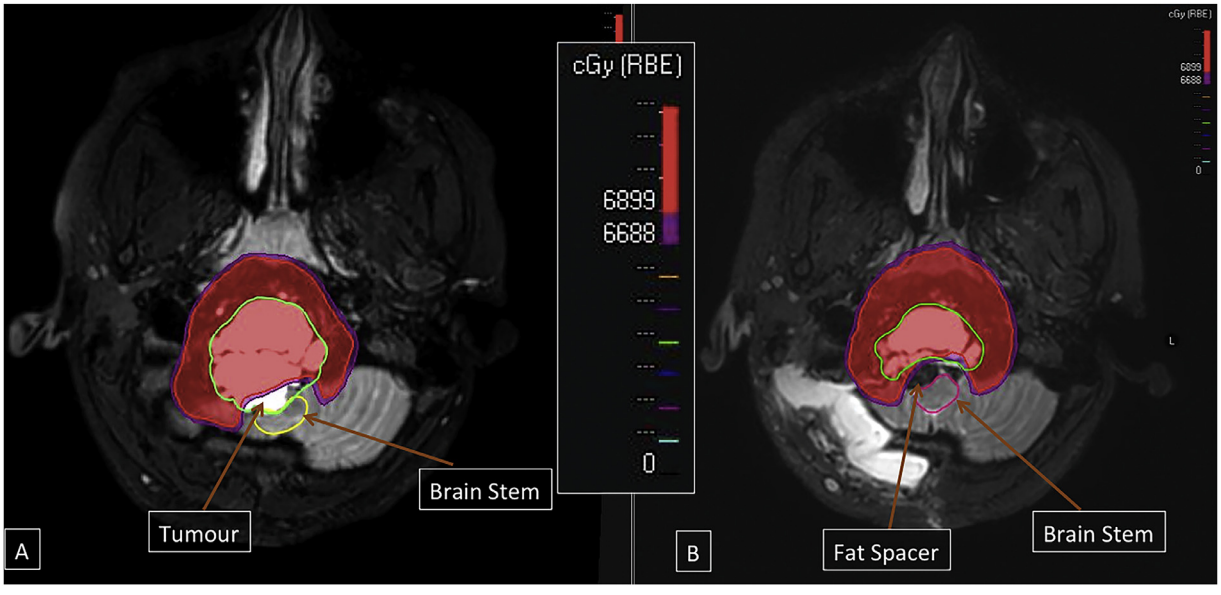

Figure 5 Impact of fat spacer on target coverage in a 7-year-old child with clival chordoma: (A) at presentation; (B) after fat spacer placement.

thirds of the total treated patients who had adequate follow-up, whereas ours included all consecutively treated patients.

We did not find any statistically significant difference between de novo and recurrent patients (90% vs 82%). Possibly, longer follow-up could result in a larger difference between these patients. However, we found a significant local control and PFS difference between patients without and with a history of irradiation (local control: 90.8% vs 64.8%; $P = .038$; PFS: 84.9% vs 60.6%; $P = .009$). Similar results were reported by Holliday et al[19] (2-year local control of 80% vs 46% for upfront vs recurrent, respectively) and Indelicato et al[20] (4-year local control of 71% vs 19% for upfront radiation vs reirradiation for recurrence, respectively). However, McDonald et al[21] demonstrated that high doses were feasible in the reirradiation setting with PBT because they reported 85% 2-year local control in a cohort consisting of 16 patients with chordoma treated with a median reirradiation dose of 75.6 CGE.[21]

Despite the high percentage of patients with recurrent disease, a history of multiple surgeries, large volumes of irradiation, and challenging location, the acute and late toxicities were limited in our cohort of patients: 15.6% and 3.1% of our patients had grade 2 and 3 acute skin toxicity, respectively. Moreover, 3.1% (n = 2) of patients with acute grade 3 skin toxicities were noted in first 32 patients compared with none in the later half. This is similar to our experience for patients treated for other sites as well. Several steps have been taken by our department to reduce the acute skin toxicities such as skin-sparing techniques (institutional protocol), which has resulted in a reduction in grade 3 acute skin toxicities.[22] Grade 3 late toxicities were noted in 1 patient, and grade 2 were noted in 14%, which is comparable with the PCG prospective registry data despite our cohort including relatively large number of recurrent and reirradiations.[21] Although certain grade 2 late toxicities were noted, most of these were anticipated (eg, because of location, volume of disease, reirradiation setting, and young age), which led to early detection of these toxicities and faster subsequent recovery of these patients. With more prolonged follow-up, late toxicities such as peripheral neuropathy, insufficiency fractures, hearing loss, and hormonal disturbances, are likely to increase.

Although this study reports early outcomes of a relatively uniform patient cohort with standardized treatment philosophy and protocols including target delineation, PBT planning, plan evaluation, treatment delivery, and follow-up, there are certain limitations. Retrospective study, relatively shorter follow-up for outcomes, and late toxicities limit this study's ability to make any firm conclusions about the same. However, the standardized treatment protocol used in this study as well as the dosimetric outcomes achieved in this study can serve as a guide for implementing or modifying image-guided IMPT protocols. The outcomes in this study are also useful to inform patients and their families regarding early outcomes with aggressive treatment protocols for these relatively rare tumors.

Conclusions

The study reports early outcomes in a uniformly treated cohort of consecutive patients of skull base, spinal, and sacral chordomas and chondrosarcomas. Among this cohort that consisted of a large percentage of recurrent disease and reirradiations, despite multiple surgeries (including targeted separation surgeries), optimal neural separation was not achieved and that led to dosimetric compromise in one-fourth of patients. We also noted that GTV D98 of <59 CGE was associated with inferior 2-year local control. This study highlights the importance of dose to the coolest GTV (not merely high physical dose to the majority of GTV) and the need for separation surgeries in patients with neural compression to achieve optimal disease control.

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.

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