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Scientific Article

A Prospective Phase I/II Clinical Trial of High-Dose Proton Therapy for Chordomas and Chondrosarcomas

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Purpose: The purpose of this study was to evaluate the feasibility and safety of dose-escalated proton beam therapy for treating chordomas and chondrosarcomas of the skull base and spine. Methods: A prospective cohort of 54 patients (42 with chordomas and 12 with chondrosarcomas) was enrolled between 2010 and 2018. The primary endpoints were feasibility and <20% rate of acute grade ≥3 toxicity, and secondary endpoints included cancer-specific outcomes and toxicities. Patients were followed with magnetic resonance imaging or computed tomography at 3-month intervals. Proton beam therapy was delivered with doses up to 79.2 Gy using protons only, combination protons/intensity modulated radiation therapy (IMRT), or IMRT only.

Results: Feasibility endpoints were met, with only 2 out of 54 patient radiation therapy plans failing to meet dosimetric constraints with protons, and 4 out of 54 experiencing a delay or treatment break >5 days, none for toxicities related to treatment. There were no grade 4 acute toxicities and 1 grade 3 acute toxicity (sensory neuropathy). The only 2 grade 3 late toxicities recorded, osteoradionecrosis and intranasal carotid blowout (mild and not emergently treated), occurred in a single patient. We report overall survival as 83% at 5 years, with local failure-free survival and progression-free survival rates of 72% and 68%, respectively. Five patients developed distant disease, and among the 9/54 patients who died, 4 deaths were not attributed to treatment or recurrence.

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All data generated and analyzed during this study are included in this published article.

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Conclusions: Our findings suggest that high-dose proton therapy alone or in combination with IMRT is a safe and effective treatment option for chordomas and chondrosarcomas of the skull base and spine.

Introduction

Chordomas and chondrosarcomas are rare, malignant tumors of the craniospinal axis that present a significant challenge in clinical management.[1-4] Surgical resection is the primary therapy; however, complete tumor removal is often difficult, and local relapse is common.[5-8] To improve outcomes, radiation therapy (RT) has been increasingly explored as an adjuvant treatment, particularly when surgery is incomplete or not possible. The standard approach for these tumors involves a combination of surgery and postoperative radiation.[6,7,9]

Different forms of ionizing radiation have been employed to balance the dosimetric goal of protecting organs at risk (OARs) while delivering adequate doses to the tumor.[6,10-15] Proton therapy has emerged as a promising option, either alone or in combination with conventional photon therapy, because of its unique physical properties, which offer superior dose distribution and tissue sparing.[16,17]

Our study follows our initial institutional assessment of high-dose proton therapy for chordomas and chondrosarcomas of the central nervous system (CNS) at 2-year follow-up.[18] We now present the full institutional cohort with 5-year follow-up of our phase II trial feasibility trial. We show that dose-escalated proton therapy is feasible and safe for these tumors but may not be necessary beyond a certain threshold, given our comparable control rates to prior reports in the previous 1 to 2 decades. Additionally, our findings suggest that combining proton and intensity modulated RT (IMRT) plans can be advantageous, providing a potential avenue for further optimization of treatment.

Methods and Materials

The clinical trial information for this study is UPCC number 01310. Institutional review board approval (number 811185) from the board at the Hospital of the University of Pennsylvania was obtained for enrollment of patients from a single institution with chordomas or chondrosarcomas, age 18 or older, with no prior radiation. The primary objective of this study was feasibility, as defined by ≥10% of patients experiencing either: unsatisfactory dosimetry, inability to complete all of his/her treatments within 10 days of estimated completion date and requiring no break >5 days, and no greater than 20% of patients experiencing >grade 3 toxicity from RT. The secondary endpoint was to assess acute side effects and to assess late complications from irradiation using dose-escalated proton beam therapy.

Inclusion criteria were histologically confirmed diagnosis of chordoma or chondrosarcoma arising from the skull or spine, no evidence of metastatic disease based on routine imaging (chest x-ray, computed tomography [CT], or magnetic resonance imaging [MRI] of chest, abdomen, or pelvis; bone scan, etc), Eastern Cooperative Oncology Group score of ≤2, and age ≥18. All patients were required to provide informed consent.

Exclusion criteria were prior or simultaneous malignancies within the past 2 years, active pregnancy, active treatment on other therapeutic research studies, or tumors arising from outside the CNS.

RT was performed as follows. Treatment planning CT and MRI scans (in identical positions) were performed using custom designed immobilization devices appropriate to position. Gross tumor volume was defined as all known gross disease determined from CT, MRI, and/or positron emission tomography imaging. Clinical target volume was defined as the gross tumor volume, operative site, and other areas at risk of harboring microscopic disease.

The dose goal for chordomas was 72 to 79.2 Gy (cobalt Gray equivalents [CGE]) in 40 to 44 fractions at 1.8 Gy (CGE) per fraction. For chondrosarcomas, the total dose goal was 70.2 to 73.80 Gy (CGE) in 39 to 41 fractions at 1.8 Gy (CGE) per fraction. These goals were extrapolated from dose escalation literature in the field of chordomas and chondrosarcomas as well as from the National Comprehensive Cancer Network guidelines for RT of these tumors.[9,19] Table E1 details the most relevant dose constraints and goals for this study. Of note, dose constraints, particularly the brain stem/spinal cord dose of 67 Gy, were based on prior consensus discussion and in coordination with colleagues at other proton centers. This was a single institution study peer reviewed by board certified radiation oncologists and physicists with dosimetry input. All plans were reviewed at CNS chart rounds and departmental chart rounds.

Proton irradiation with either double scatter or pencil beam technique was performed at the Hospital of the University of Pennsylvania Proton Center using the IBA Proteus, and photons were delivered for those with mixed plans using a Varian linear accelerator. Table E2 details the RT in terms of dose and modality for all 54 patients. At the time of plan evaluation, each provider chose a plan based on coverage of target, OARs, and robustness of the

radiation plan. Volumetric-modulated arc therapy was included in situations in which range uncertainty posed a risk to critical structures. Input from physicists and dosimetrists specializing in protons and mixed plans was crucial in the decision-making process. RT was completed for all patients within 9 weeks of the start of treatment. The criterion for a treatment break was any grade 3 or 4 toxicity, depending on the clinical situation. Dose-volume histograms were used to compare dose distribution to the tumor and surrounding normal structures.

Acute side effects of RT were assessed weekly in clinic during on-treatment visits. Patients were assessed for late complications from irradiation during follow-up visits and though electronic medical records. Acute toxicity (clinically high grade) was defined as any grade 3 or higher toxicity and was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Late toxicity was defined as any grade 3 or higher toxicity, considered probably or definitely due to radiation, observed later than 90 days from completion of RT, excluding any cranial nerve palsies or nerve root symptoms that may have been due to the tumor itself or prior surgery.

Patients were monitored for rates of local control as well as rates of overall and disease- specific survival. After therapy, local failure was defined as evidence of tumor growth in any direction beyond that present in the pretreatment imaging or the appearance of tumor in tissues previously scored as sites of subclinical disease. Marginal failure was defined as appearance of tumor growth at the margin of the target volume. Overall survival was defined as duration measured from date of first treatment until death or censored date of last follow-up for patients still alive. Progression-free survival was defined as the time from start of RT to first documented local progression, death from any cause, or censored date of last follow-up for patients still alive. Local control was defined as a lack of progression within the same subsite of the original disease.

Kaplan-Meier analysis was used to estimate local control, progression-free survival, and overall survival with respect to the date of RT completion, and all representations of actuarial survival curves were performed using GraphPad Prism version 9.0.0.

Results

Table 1 shows the patient demographics for our cohort of 54 patients who were enrolled. Twenty-two (41%) of our patients were male and 32 (59%) were female, with a median age of 54 years (range, 23-87). Forty-two patients (78%) had chordomas, and 12 patients (22%) had chondrosarcoma. In terms of tumor site, 26 had skull base chordomas, 10 had sacral chordomas, 6 had spinal chordomas, 9 had base of skull chondrosarcomas, 1 had sacral chondrosarcoma, and 2 had sinonasal chondrosarcomas.

Table 1 Patient demographics

Number of patients	54
Sex	
Male	22 (41%)
Female	32 (59%)
Age	
Median	54 years
Range	23-87 years
Follow-up (45 patients alive)	
Median	72 months
Range	6-133 months
Histology	
Chordoma	42 (78%)
Chondrosarcoma	12 (22%)
Lesion site	
Clivus/skull base	39 (72%)
C spine	3 (6%)
T spine	0 (0%)
L spine	1 (2%)
Sacrum/coccyx	11 (20%)

Fifty-four patients enrolled in our study are described by sex, age, length of follow-up, histology, and location of tumor.

Forty-nine of the 54 patients were able to undergo surgical resection, and 5 were inoperable and had biopsy only before definite radiation treatment. There were no patients who received concurrent chemotherapy. Median follow-up time was 72 months (range, 6-133).

Table 2 summarizes the treatments delivered. Forty-nine out of 54 patients underwent surgery with the goal of gross total resection. Positive margins or gross disease was noted in 67% of patients at the time of surgery. At the time of RT, mean volume of gross tumor was 21.6 cc in chordomas and 15.53 cc in chondrosarcomas. Of note, gross disease ranged from 0.86 to 1642 cc. Five patients did not receive surgery and thus received definitive treatment alone with a median dose of 7560 cGy (range, 7380-7920). Only 1 patient had radiation after a second surgery. There was 1 case of neoadjuvant radiation to 5040 cGy, with no further radiation after surgery (this patient had no recurrence at the time of last follow-up at 48 months).

With regards to radiation technique, most patients (52/54) received some proton therapy. Of these, 22 patients received proton-only therapy. Thirty patients received combination protons/IMRT. Of the mixed plans, the median photon dose was 39% of the total prescription (range, 6.5%-75%). Two patients received IMRT-only therapy after planning with protons did not result in superior coverage and did not meet optimal OAR constraints compared with IMRT alone. Our feasibility

Table 2 Patient treatments

Proton only (n = 22) Median (range) cGy	
Definitive (n = 3)	7560 (7380-7920)
Adjuvant (n = 18)	7290 (5040-7920)
Neoadjuvant (n = 1)	5040
Proton and photon mixed (n = 30)	
Definitive (n = 2)	7560 (NA)
Adjuvant (n = 28)	7560 (6840-7920)
Photon only (n = 2)	
Adjuvant	7380 and 7920
GTV (cc)	
Chordomas	21.63 (1.540-1642)
Chondrosarcomas	15.53 (0.86-104.91)
Fractionation	
Single fraction dose	180-200
Number of fractions	28-44

Abbreviation: GTV = gross tumor volume.
Radiation therapy is summarized by treatment modality. GTV represents relative volume of irradiation. Dose and fractionation are also provided for reference.

endpoints were met, with only 2/54 (3.7%) patient RT plans failing to meet dosimetric constraints (Table E1) with protons and 4/54 (7.4%) experiencing a delay or treatment break >5 days, none for clinical reasons. For the 2 patients who received IMRT alone, this was when planning with double scatter protons was predominant at our institution, just before when pencil beam scanning (PBS) was available. These patients were treated to 7920 and 7380 cGy and were successfully dose escalated using IMRT. One patient who received IMRT alone developed distant metastatic disease and is being managed using palliative measures. The other has no evidence of disease. After PBS became available, no patients enrolled on this trial received IMRT alone.

Figure 1 shows Kaplan-Meier curves of overall survival (A), disease-specific survival (B), local failure-free survival (C), and progression free survival (D). We report a median 6-year follow-up with actuarial results as follows: Overall survival was 83% collectively, 11/12 (91%) for chondrosarcoma, and 34/42 (80.9%) for chordoma. Disease-specific survival was 91% overall, 12/12 (100%) for chondrosarcoma, and 37/42 (88%) for chordoma. Local failure-free survival was 72% overall, 12/12 (100%) for chondrosarcoma, and 27/42 (64%) for chordoma. Progression-free survival was 68%, 10/12 (83%) in the chondrosarcoma group and 15/42 (64%) in the chordoma group. With respect to overall survival, of the 9 patients who died, 4 deaths were not attributed to treatment or recurrence. Five patients developed distant disease: 3 with metastases in the craniospinal axis, 1 with a biopsy-confirmed inguinal lymph node metastasis, and 1 with distal iliac and femur metastases.

Table 3 details acute and chronic toxicities. There were no grade 4 toxicities. One grade 3 acute toxicity (sensory neuropathy) was recorded, making grade 3 toxicity 1.9%. The only 2 grade 3 late toxicities recorded, osteoradionecrosis and intranasal carotid bleed (mild), occurred in a single patient, who is alive and well at last follow-up (7 years). Therefore, acute grade 3 toxicities were only seen in 1/54, or 1.9% of patients. The most common acute toxicities recorded were fatigue (37/54), radiation dermatitis (28/54), headache (14/54), alopecia, and insomnia (both 9/54). The most common long-term toxicities were fatigue (17/54, all grade 1) and headache.

Discussion

Higher doses of radiation are generally associated with better rates of local control for chordomas and chondrosarcomas, and modern practice has moved toward dose escalation.[9,20,21] However, treating chordomas and chondrosarcomas with high-dose radiation can be challenging because of their location in critical areas near at-risk organs. Proton therapy is a potential solution to this challenge, as it is known to provide superior local control, and in 1 retrospective national cancer database analysis of 1500+ patients with chordomas and chondrosarcomas, treatment with protons showed a significant overall survival benefit.[19] We found that high-dose proton therapy was feasible for 52 of the 54 patients enrolled in our prospective trial. In terms of feasibility endpoints, we achieved a success rate of 96.3% (52/54) in meeting dosimetric constraints with protons, with only 3.7% (2/54) of patients experiencing RT plan failure and 7.4% (4/54) experiencing a delay or treatment break >5 days, none for toxicity or clinical reasons due to treatment. With regards to the 2 patients treated with IMRT alone, they were enrolled before PBS was available at our institution. After the switch from double scatter to PBS, proton therapy was dosimetrically appropriate and favored during physician evaluation for all patients. We also report an acceptable toxicity profile for patients enrolled in our study. Lastly, we report that high-dose proton RT resulted in excellent outcomes. Taken together, our findings suggest that proton therapy can be safely and effectively used to improve the therapeutic outcomes of multidisciplinary treatment for chordomas and chondrosarcomas. Table 4 summarizes key studies that treated chordomas and/or chondrosarcomas of the spine and skull base using different radiation modalities and dose ranges. These studies have significantly influenced the management of these tumors in recent years.

Most chordomas arise from the embryonic notochord remnant along the craniospinal axis and occur more frequently at the base of skull.[2,22] Although locally

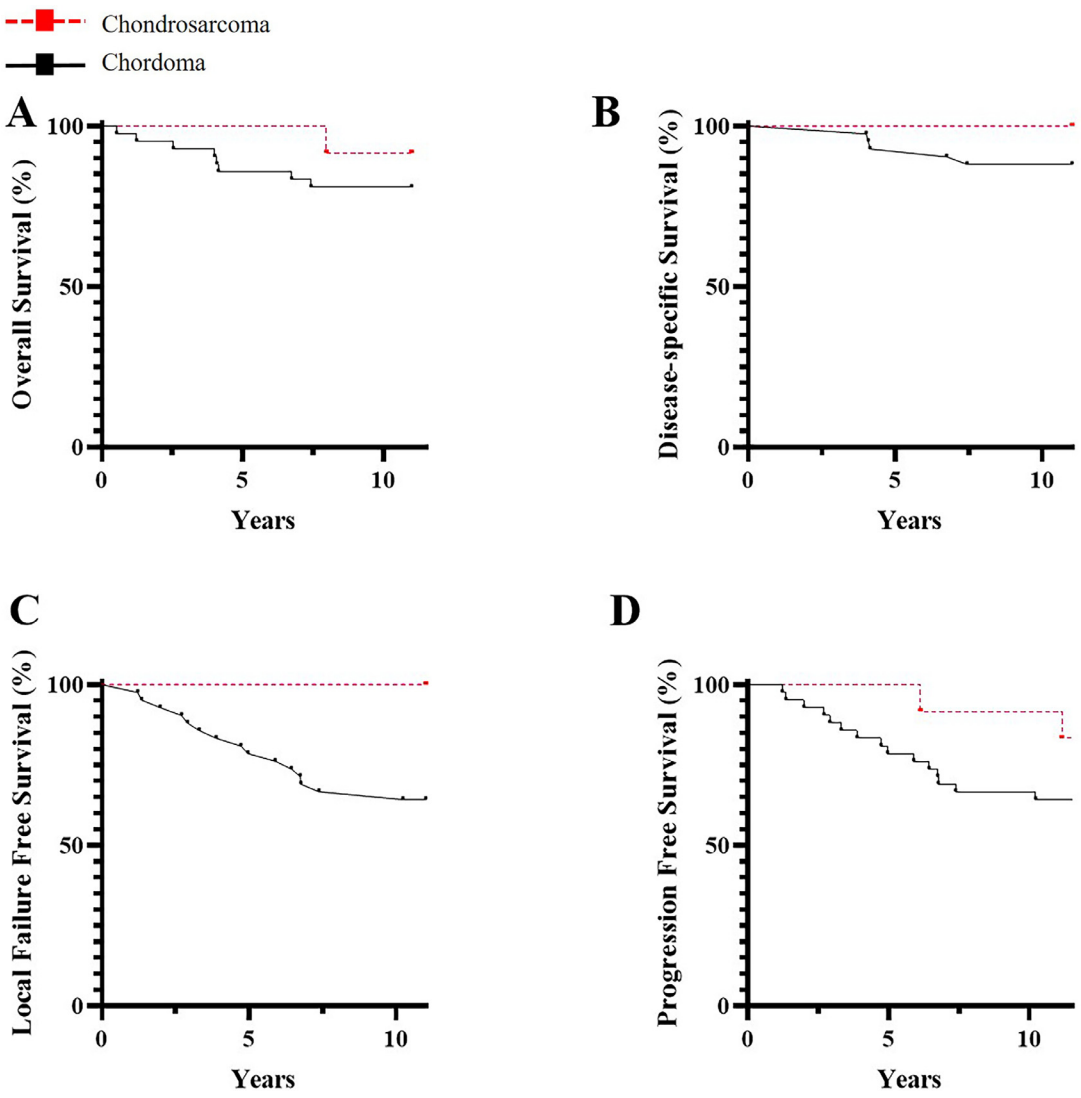

Figure 1 Actuarial outcomes. Kaplan-Meier curves show survival for chordoma (black-solid) and chondrosarcoma (red-dashed) overall with a median follow-up of 72 months. (A) Overall survival. (B) Disease-specific survival. (C) Local failure-free survival. (D) Progression-free survival.

malignant, 10% to 25% of cases may result in metastasis.[23,24] Among our cohort, 26 chordomas were located at the base of the skull, with 16 patients experiencing local failure and 12 of those failures involving the base of the skull. We observed a 54% rate of local failure at 6+ years median follow-up, comparable to similar studies reporting local control rates ranging from 50% to 81%.[3,7,17,25-27] We report our 5-year overall survival rates of chordomas of the base of skull to be 80%, consistent with previous findings of Hug et al,[28] who reported 79% 5-year overall survival for these tumors in patients who underwent proton RT of the skull base.

Chordomas of the spine and sacrum chordomas showed improved actuarial outcomes compared with chordomas of the base of skull within our cohort. Of note, all of our patients with chondrosarcoma had grade 2 to 3 chondrosarcomas, as reported by our pathologist. Grade 1 chondrosarcomas are typically observed given extremely slow growth. At 5 years, there were 4 chordoma failures of the spine/sacrum, equivalent to a 25% failure rate. We had 3 deaths within the cohort (2 sacral and 1 mobile spine), resulting in an overall survival rate of 81% (13/16) for spine/sacral chordomas. Our results were slightly better than those reported by Stacchiotti et al,[16] who reported a 5-year overall survival of 50% to 80% and local control of 50% to 65% for spine/sacrum. Indelicato et al[29] reported a 54% local control rate for 34 chordomas of the spine using protons (mean, 70.2 Gy; range, 64.2-75.6 Gy). It is possible that our higher control rate may be attributed to the smaller number of patients in our series as well as potentially dose escalation of up to 79.2 Gy; however, larger prospective studies are necessary.

Chondrosarcomas typically have better local control and survival compared with chordomas. Chondrosarcomas

Table 3 Toxicities

Acute	N (grade)	Long-term	N (grade)
Fatigue	37 (grade 1-2)	Fatigue	17 (grade 1)
Radiation dermatitis	28 (grade 1-2)	Headache	8 (grade 1-2)
Headache	14 (grade 1-2)	Pain	4 (grade 1-2)
Alopecia	9 (grade 1)	Loss of smell	1 (NA)
Insomnia	9 (grade 1-2)	Cognitive disturbance	2 (grade 1)
Paresthesia	7 (grade 1-3)	Xerostomia	1 (grade 1)
Constipation	7 (grade 1-2)	Paresthesia	5 (grade 1-2)
Pain	4 (grade 2)	Insomnia	1 (grade 1)
Dysphagia	6 (grade 1-2)	Diarrhea	1 (grade 1)
Xerostomia	4 (grade 1-2)	Neck edema	1 (grade 1)
Diarrhea	2 (grade 1)	Dysgeusia	2 (grade 1-2)
Anorexia	5 (grade 1)	Ataxia	5 (grade 1-2)
Urinary (retention or incontinence)	6 (grade 1)	Paresthesia	4 (grade 1-2)
Ataxia	5 (grade 1)	Aphasia	1 (grade 1)
Oral mucositis	2 (grade 1-2)	Radionecrosis of the brain	3 (grade 1-2)
Edema	2 (grade 1-2)	Anorexia	2 (grade 1)
Visual/blurry	2 (grade 1-2)	Dysphagia	2 (grade 1)
Nerve palsy	1 (NA)	Muscle weakness	1 (grade 1)
Tinnitus	1 (grade 1)	Intranasal carotid blowout	1 (grade 3)
Dysgeusia	5 (grade 1-2)	Osteoradionecrosis	1 (grade 3)
Cognitive disturbance	3 (grade 1-2)		
Voice alteration	3 (grade 1-2)		
Dysarthria	1 (grade 1)		

Acute (left) and chronic (right) toxicities are listed in order of prevalence.

of the base of skull have reported 75% to 100% local control and 4-year survival of 86.3%, and chordomas have reported 50% to 75% local control and 5-year survival.[21,28] Our cohort shows excellent control of base of skull chondrosarcomas with only 1 patient death, which was unrelated to disease progression. Spine/sacral chondrosarcomas had no local failures or progression. In their abstract, Koniezkowski et al[30] also reported excellent outcomes for spine/sacral chordomas and chondrosarcomas treated with protons with 2.5-year overall survival of 92%, relapse-free survival (RFS) of 81%, and very low local recurrence rates of 6.5%, very similar to our reported outcomes.

With regards to safety of our treatment, we aimed to demonstrate an acceptable toxicity profile of dose-escalated proton therapy. Koniezkowski et al[30] used radiation doses up to 77.4 to 79.2 for gross residual disease and reported 26.4% grade 3 adverse events, while Hug et al[28] reported only 7% grade 3 and 4 late toxicities in their proton cohort. Delaney et al[31] reported a 13% 8-year actuarial risk of grade 3 to 4 late RT morbidity but no myelopathies with doses of <72 Gy relative biological effectiveness. Our safety profile was satisfactory, with only 1 patient with grade 3 acute toxicity of some sensory neuropathy in a patient with a base of skull chordoma, currently alive and nearly 5 years out from treatment. In terms of long-term toxicity, the only concerning late grade 3 toxicities occurred in 1 patient (osteoradionecrosis and intranasal carotid bleed, which was mild and managed surgically and not urgently). The patient is currently well and has no evidence of disease, more than 7 years posttreatment for their sinonasal chondrosarcoma. Importantly, we were very pleased to see that our dose constraints, which are beyond established quantitative analyses of normal tissue effects in the clinic guidelines, particularly our brain stem/spinal cord dose limit of 67 Gy, did not result in unforeseen toxicity.

One potential criticism of this prospective study is that while proton RT was heavily emphasized, in fact most patients received a mix of protons and IMRT. The decision-making process for when to create mixed (proton/photon) plans is a complicated and nuanced, yet commonly used process. Notably, 6 of the key studies of dose

Table 4 Prior key studies

Study first author	Year	Publication type	Radiation details	Reported outcomes
Fuller[20]	1988	Royal Marsden experience	Varied doses	25 pts with gross residual disease; 7/17 (41%) receiving >55 Gy had freedom from local progression >5 yr vs 1/8 (13%) receiving <50 Gy
Catton[34]	1996	Princess Margaret experience; retrospective cohort	Majority treated with conventional fractionation to median of 50 Gy/25 fractions	48 pts (48% sacrum, 40% base of skull, 10% mobile spine); 44 postop with gross residual disease, 4 microscopic residual disease; 5 yr OS: 54% (MS 62 months); 5-yr PFS: 23% (MS 35 months)
Hug[28]	1999	Loma Linda experience; retrospective cohort	Protons; mean dose of 70.7 CGE, range of 64.8-79.2 CGE	33 pts with chordoma, 25 chondrosarcoma (skull base); 5-yr LC, 76%; 5-yr OS, 79%; no LC failures for tumors <25 cc compared with only 56% LC in tumors >25 cc ($P = .04$)
Noel[36]	2005	Institut Curie retrospective study	Mixed proton/photons; median dose, 67 Gy	100 pts with chordomas of base of skull or cervical spine; 4-yr LC, 53.8%; 4-year OS, 89.6%
Schulz-Ertner[37]	2007	Heidelberg experience	Carbon ion; 60 CGE (range, 60-70); 20 fractions over 3 weeks	96 pts; skull base chordoma. Mean FU 31 months. 5-yr OS, 88.5%; 5-yr LC, 70%. Reported doses 75 CGE (2 CGE/fx) increase LC probability.
Ares[17]	2009	Swiss experience, PBS for chordomas + chondrosarcomas	Protons: median 73.5 Gy (chordoma), 68.4 (chondrosarcoma)	64 pts. Median FU 38 months. 42 chordomas, 22 chondrosarcomas. Skull base only. 5-yr LC, 81%; 5-yr DSS, 81%; 5-yr OS, 62%
Stacchiotti[16]	2010	Retrospective review	Varied, low dose <60 Gy, no protons	138 pts w/spine/sacral chordoma. Surgically treated postoperatively. Margins independently predicted LRFS ($P = .003$) with a trend for OS; No benefit to adjuvant RT.
Imai[38]	2010	Phase I-II trial of sacral chordoma	Carbon ion dose 52.8-72.5 Gy RBE (median, 70.4); 16 fx in 4 weeks	38 unresectable sacral chordomas; 30 without prior treatment, 8 with local recurrence after resection; 5-yr OS, 86%; 5-yr LC, 89%
DiMaio[3]	2011	Meta-analysis	Proton/carbon ion/ photon therapy. Varied dose	23 studies, 807 pts weighted average 5-yr PFS and OS were 50.8% and 78.4%, respectively. Similar PFS and survival with all modalities.
Kano[39]	2011	North American Gamma Knife Consortium experience	Median SRS target volume: 7.1 cc (range, 0.9-109 cc). Median margin dose: 15.0 Gy (range, 9-25 Gy)	71 pts at 6 GK centers, median FU 5 yr; 5-yr OS, 80%. 93% for no prior RT, 43% for prior RT. 5-yr LC: 66%, 69% for no prior RT, 62% for prior RT. Smaller tumor volume and higher dose at margin predict for better LC.
Yamada[40]	2013	Retrospective study	Single fraction treatment, 24 Gy	24 pts: 21 primary, 3 metastatic. 10 w/ SRS alone, 6 SRS preop. Median FU: 24 months. 95% actuarial LC; 1 pt with sciatic neuropathy and 1 with vocal cord paralysis
Amit[26]	2014	Meta-analysis	Varied doses, conventional radiation, SRS, PBRT, and combined modalities	467 pts. 5-yr OS and PFS rates 86% and 65.7%, respectively. 5-yr OS of adjuvant RT was 90% compared with 70% of those treated by surgery alone.
Delaney[41]	2014	Prospective phase II photon/proton	72-77.4 Gy RBE, mixed proton/photon plans	50 pts with spine chordoma/chondrosarcoma/other histology. 5- and 8-yr LC 81% and 74%, G3-4 toxicity at 8 years, 13%

(*continued on next page*)

Table 4 (*Continued*)

Study first author	Year	Publication type	Radiation details	Reported outcomes
Sahgal[27]	2015	2015-High Dose IMRT — Modern PMH experience	Median dose, 76 Gy; chordoma, 70 Gy; chondrosarcoma, 2 Gy fractions	24 chordoma (skull base) pts, 18 chondrosarcomas; med FU 36 months. 5-yr LC and OS: 85.6%, 65.3%, chordoma 88.1% and 84.1% chondrosarcoma; 1 grade 5 toxicity from radiation-induced glioma
Indelicato[29]	2016	Florida experience; 2007-2013, 34 chordomas of spine	Protons mean 70.2 Gy, range 64.2-75.6 Gy	34 chordomas of the spine. 4-yr OS was 72%; freedom from distant metastases was 86%, LC 58%, and DFS 57%.
Kabolizadeh[42]	2017	MGH experience of unresectable chordomas	Median dose, 77.4 Gy (64.8-79.2 Gy) with mix proton/photon	40 pts treated with definitive radiation. 5-yr outcomes: LC, 85.4%; OS, 81.9%; DSS, 89.4%; DF, 20%. Supported using high-dose RT for unresected sacral/spine chordomas
Aibe[43]	2017	Retrospective study	Definitive proton beam therapy with 70.4 Gy in 32 fractions	33 pts with sacral chordoma. Median FU 37 months. 3-yr local PFS, DMFS, DFS, CSS, OS rates were 89.6%, 88.2%, 81.9%, 95.7%, and 92.7%, respectively.
Konieczkowski[30]	2018	Prospective phase II — abstract only	Protons: up to 77.4-79.2 for gross residual	60 pts w/ spine chordomas and chondrosarcomas. 2.5-yr landmark: OS, 92%; RFS, 81%; LR, 6.5%.
Walser[44]	2021	Retrospective study	Median 74 Gy (60.0-77.0), mostly proton	60 pts sacral chordoma, 48 months FU reporting 4-yr LC, freedom from recurrence, and OS at 77%, 89%, and 95%, respectively.

Abbreviations: CGE = cobalt Gray equivalents; CSS = cancer specific survival; DFS = disease-free survival; DMFS = distant metastasis free survival; DSS = disease specific survival; LR= local relapse; LRFS = locoregional failure-free survival; MS = median survival; PBRT = proton beam radiotherapy; PMH = princess margaret hospital; RFS = relapse-free survival; SRS = stereotactic radiosurgery; FU = follow-up; GK = Gamma Knife; IMRT = intensity modulated RT; LC = local control; OS = overall survival; PBS = pencil beam scanning; PFS = progression-free survival; pt = patient; RBE = relative biological effectiveness; RT = radiation therapy.
Nineteen key publications on RT for chordomas and chondrosarcomas are provided in this nonexhaustive reference table.

escalation seen in Table 4 integrated mixed plans into their protocols, and for this study our institution followed suit. Proton therapy alone or in combination with IMRT can achieve dosimetric advantages when treating within the CNS.[17,19,32-35] We therefore maintain that the use of any proton radiation in any combination may benefit patients with these complex tumors. In fact, 43% of patients who received mixed proton/photon treatment received the majority of their prescription in the form of proton radiation. In those cases, we were able to dose-escalate safely using proton therapy.

One significant limitation to our study is that it was conducted at a single institution, although we maintained strict adherence to Common Terminology Criteria for Adverse Events v4 criteria and peer reviewed all cases with CNS radiation physicians and physicists at our single institution. We also note that although we present data to support that high dose radiation with proton beam therapy is feasible and has an excellent safety profile, there may not be a need to push the dose to 7920 cGy. As our outcomes were comparable to other trials referenced in Table 4, which notably used 70 to 75 Gy, there was not a significant increase in our overall outcomes compared with those in the literature. We do, however, feel that showing successful dose escalation to 7920 cGy provides an option for more dedifferentiated or aggressive chordomas, where dose escalation may be warranted. Lastly, we acknowledge that at our institution, neurosurgeons may be more inclined to attempt a greater extent of resection, which ultimately affects both the volume of the target and potential dose to OARs.

Looking forward, it may be advantageous to consider proton therapy when treating both chordoma and chondrosarcomas of the skull base and spine. As planning and delivery techniques continue to improve (proton ARC treatment or proton FLASH), we may find further evidence to establish that high-dose proton therapy is a very attractive and attainable option.

Conclusion

We report favorable feasibility, local tumor control, survival, and toxicity after high-dose proton therapy for chordomas and chondrosarcomas. We add these results to the literature in hopes that guidelines for these tumors in the high-risk locations of the CNS may expand to recommend the use of high-dose proton radiation.

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.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101456.

References

1. Kano H, Niranjan A, Dade Lunsford L. Radiosurgery for chordoma and chondrosarcoma. *Prog Neurol Surg*. 2019;34:207-214.
2. Williams BJ, Raper DMS, Godbout E, et al. Diagnosis and treatment of chordoma. *J Natl Compr Cancer Netw*. 2013;11:726-731.
3. Di Maio S, Temkin N, Ramanathan D, Sekhar LN. Current comprehensive management of cranial base chordomas: 10-Year meta-analysis of observational studies: Clinical article. *J Neurosurg*. 2011;115:1094-1105.
4. Dibas M, Doheim MF, Ghozy S, Ros MH, El-Helw GO, Reda A. Incidence and survival rates and trends of skull base chondrosarcoma: A population-based study. *Clin Neurol Neurosurg*. 2020;198:106153.
5. Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: Patterns of failure and outcome after relapse. *Int J Radiat Oncol Biol Phys*. 1995;33:579-584.
6. Stacchiotti S, Gronchi A, Fossati P, et al. Best practices for the management of local-regional recurrent chordoma: A position paper by the Chordoma Global Consensus Group. *Ann Oncol*. 2017;28:1230-1242.
7. Sommer J. Building a global consensus approach to chordoma: A position paper from the medical and patient community. *Lancet Oncol*. 2015;16:e71-e83.
8. Jawad MU, Scully SP. Surgery significantly improves survival in patients with chordoma. *Spine (Phila Pa 1976)*. 2010;35:117-123.
9. Agulnik M, Bernthal NM, Boles S, et al. NCCN guidelines version 2. Accessed March 18, 2024. https://www.nccn.org/home/member-.
10. Imai R, Kamada T, Sugahara S, Tsuji H, Tsujii H. Carbon ion radiotherapy for sacral chordoma. *Br J Radiol*. 2011;84:S48-S54.
11. Mizoe JE, Hasegawa A, Takagi R, Bessho H, Onda T, Tsujii H. Carbon ion radiotherapy for skull base chordoma. *Skull Base*. 2009;19:219-224.
12. Saunders WM, Chen GTY, Austin-Seymour M, et al. Precision, high dose radiotherapy. II. Helium ion treatment of tumors adjacent to critical central nervous system structures. *Int J Radiat Oncol Biol Phys*. 1985;11:1339-1347.
13. Berson AM, Castro JR, Petti P, et al. Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: The Lawrence Berkeley laboratory experience. *Int J Radiat Oncol Biol Phys*. 1988;15:559-565.
14. Kano H, Lunsford LD. Stereotactic radiosurgery of intracranial chordomas, chondrosarcomas, and glomus tumors. *Neurosurg Clin N Am*. 2013;24:553-560.
15. Proton therapy for base of skull chordoma: A report for the Royal College of Radiologists. *Clin Oncol*. 2000;12:75-79.
16. Stacchiotti S, Casali PG, Lo Vullo S, et al. Chordoma of the mobile spine and sacrum: A retrospective analysis of a series of patients surgically treated at two referral centers. *Ann Surg Oncol*. 2010;17:211-219.
17. Ares C, Hug EB, Lomax AJ, et al. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and

chondrosarcomas of the skull base: First long-term report. *Int J Radiat Oncol Biol Phys*. 2009;75:1111-1118.
18. Baumann BC, Lustig RA, Mazzoni S, et al. A prospective clinical trial of proton therapy for chordoma and chondrosarcoma: Feasibility assessment. *J Surg Oncol*. 2019;120:200-205.
19. Palm RF, Oliver DE, Yang GQ, Abuodeh Y, Naghavi AO, Johnstone PAS. The role of dose escalation and proton therapy in perioperative or definitive treatment of chondrosarcoma and chordoma: An analysis of the National Cancer Data Base. *Cancer*. 2019;125:642-651.
20. Fuller DB, Bloom JG. Radiotherapy for chordoma. *Int J Radiat Oncol Biol Phys*. 1988;15:331-339.
21. Noël G, Feuvret L, Ferrand R, Boisserie G, Mazeron JJ, Habrand JL. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. *Neurosurgery*. 2004;55:1252-1260.
22. Ouyang T, Zhang N, Zhang Y, et al. Clinical characteristics, immunohistochemistry, and outcomes of 77 patients with skull base chordomas. *World Neurosurg*. 2014;81:790-797.
23. Barber SM, Sadrameli SS, Lee JJ, et al. Chordoma—current understanding and modern treatment paradigms. *J Clin Med*. 2021;10:1-18.
24. Ferraresi V, Nuzzo C, Zoccali C, et al. Chordoma: Clinical characteristics, management and prognosis of a case series of 25 patients. *BMC Cancer*. 2010;10:22.
25. Noël G, Habrand JL, Jauffret E, et al. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine: Prognostic factors and patterns of failure. *Strahlentherapie und Onkol*. 2003;179:241-248.
26. Amit M, Na'Ara S, Binenbaum Y, et al. Treatment and outcome of patients with skull base chordoma: A meta-analysis. *J Neurol Surgery, Part B Skull Base*. 2014;75:383-390.
27. Sahgal A, Chan MW, Atenafu EG, et al. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: Preliminary outcomes. *Neuro Oncol*. 2015;17:889-894.
28. Hug EB, Loredo LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg*. 1999;91:432-439.
29. Indelicato DJ, Rotondo RL, Begosh-Mayne D, et al. A prospective outcomes study of proton therapy for chordomas and chondrosarcomas of the spine. *Int J Radiat Oncol Biol Phys*. 2016;95:297-303.
30. Konieczkowski DJ, Chen YLE, Bernstein KD, et al. Prospective phase II study of scanned beam proton therapy for spine sarcomas. *Int J Radiat Oncol*. 2018;102:e325-e326.
31. 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;74:732-739.
32. Pennicooke B, Laufer I, Sahgal A, et al. Safety and local control of radiation therapy for chordoma of the spine and sacrum: A systematic review. *Spine (Phila Pa 1976)*. 2016;41(Suppl 20):S186-S192.
33. Zorlu F, Gürkaynak M, Yildiz F, Öge K, Atahan IL. Conventional external radiotherapy in the management of clivus chordomas with overt residual disease. *Neurol Sci*. 2000;21:203-207.
34. Catton C, O'Sullivan B, Bell R, et al. Chordoma: Long-term follow-up after radical photon irradiation. *Radiother Oncol*. 1996;41:67-72.
35. Jiang B, Veeravagu A, Lee M, et al. Management of intracranial and extracranial chordomas with CyberKnife stereotactic radiosurgery. *J Clin Neurosci*. 2012;19:1101-1106.
36. Noël G, Feuvret L, Calugaru V, et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. *Acta Oncol (Madr)*. 2005;44:700-708.
37. Schulz-Ertner D, Karger CP, Feuerhake A, et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. *Int J Radiat Oncol Biol Phys*. 2007;68:449-457.
38. Imai R, Kamada T, Tsuji H, et al. Effect of carbon ion radiotherapy for sacral chordoma: Results of phase I-II and phase II clinical trials. *Int J Radiat Oncol Biol Phys*. 2010;77:1470-1476.
39. Kano H, Iqbal FO, Sheehan J, et al. Stereotactic radiosurgery for chordoma: A report from the North American Gamma knife consortium. *Neurosurgery*. 2011;68:379-388.
40. Yamada Y, Laufer I, Cox BW, et al. Preliminary results of high-dose single-fraction radiotherapy for the management of chordomas of the spine and sacrum. *Neurosurgery*. 2013;73:673-680.
41. DeLaney TF, Liebsch NJ, Pedlow FX, et al. Long-term results of phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. *J Surg Oncol*. 2014;110:115-122.
42. Kabolizadeh P, Chen YL, Liebsch N, et al. Updated outcome and analysis of tumor response in mobile spine and sacral chordoma treated with definitive high-dose photon/proton radiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;97:254-262.
43. Aibe N, Demizu Y, Sulaiman NS, et al. Outcomes of patients with primary sacral chordoma treated with definitive proton beam therapy. *Int J Radiat Oncol Biol Phys*. 2018;100:972-979.
44. Walser M, Bojaxhiu Yz B, Kawashiro S, et al. Clinical outcome of sacral chordoma patients treated with pencil beam scanning proton therapy. *Clin Oncol (R Coll Radiol)*. 2021;33:e578-e585.