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Clinical Investigation

Long-Term Outcomes and Prognostic Factors After Pencil-Beam Scanning Proton Radiation Therapy for Spinal Chordomas: A Large, Single-Institution Cohort

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Summary

Extracranial/spinal chordoma remains a rare but challenging disease that demands maximal safe resection and high-dose adjuvant radiation therapy to achieve local control. At Paul Scherrer Institute, 100 patients have been treated for spinal chordoma with pencil-beam scanning proton therapy over the last 20 years. We report long-term results after safe, accurate delivery

Purpose: To evaluate the efficacy and safety of high-dose pencil-beam scanning proton therapy (PBS-PT) in the adjuvant treatment of spinal chordomas.

Methods and Materials: Between 1997 and 2015, 100 patients with spinal chordomas (median age, 56 years; range, 25-81 years) were treated with adjuvant PBS-PT at the Paul Scherrer Institute: cervical (n = 46), thoracic (n = 4), lumbar (n = 12), and sacral (n = 38). The majority (88%) received PBS-PT alone rather than combined photon−proton therapy. The median radiation therapy dose prescribed was 74 Gy (relative biological effectiveness [RBE]) (range, 59.4-77 Gy [RBE]). Thirty-nine patients (39%) had undergone surgical stabilization, primarily with titanium hardware, before radiation therapy.

Results: With a median follow-up of 65 months (range, 13-175 months), 5-year local control, disease control, and overall survival rates were 63% (95% confidence interval [CI] 57.7-68.7%; median, 103 months), 57% (95% CI 50.9-62.1%; median, 82 months), and 81% (95% CI 76.8-85.6%; median, 157 months), respectively. On univariate and multivariate analyses, the presence of surgical stabilization was highly prognostic for worsened outcomes. Multivariate analysis also revealed the extent of treatment volumes

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of high-dose radiation therapy, despite the usual close proximity of tumor to critical structures in this disease setting.

and presence of gross residual disease to be important in predicting outcomes. High-grade (grade ≥3) toxicities were rare in both the acute (8%) and late (6%) settings. **Conclusion:** For spinal chordomas, PBS-PT remains a highly effective and safe method for delivery of dose-escalated adjuvant radiation therapy. The presence of metallic surgical stabilization prognosticates for worsened outcomes. Further investigation is warranted to characterize ideal treatment volumes and effect of surgical stabilization on therapy for these challenging tumors.

Introduction

Chordomas are rare tumors arising from notochordal remnants, with an incidence estimated at 0.08 per 100,000 individuals per year (1, 2). Although they exhibit potential for distant metastasis, their locally malignant characteristics near central critical structures make them particularly challenging (3). They arise approximately equally in the skull base, mobile spine, and sacrum (2).

Although en bloc resection is generally indicated, the site, size, and infiltrative nature of this tumor complicate this approach (4-7). Estimates of successful oncologic gross total resection range from 50% downward (1, 6, 8, 9).

After maximal resection, radiation therapy has demonstrated the potential to improve long-term local control (LC) and overall survival (OS) (10-13). Initial efforts with 40- to 60-Gy photon radiation therapy proved relatively ineffective (14-16). Chordomas exhibit a steep dose−response curve, requiring at least 60 to 65 Gy for significant effect (12, 13, 17-22). Particle therapy, most often proton radiation therapy, has been used to achieve doses in the range of 70 to 74 Gy (relative biological effectiveness [RBE]) (uniformly adjusted for RBE 1.1 of protons). Proton therapy allows for dose escalation without frequent complication, despite low tolerances in nearby organs at risk (11, 23-25). Recent series have noted significantly improved outcomes with these doses, achieving LC in two-thirds of patients and OS of approximately 80% at 5 years (10-13, 26).

At the Paul Scherrer Institute Center for Proton Therapy (PSI), pencil-beam scanning proton radiation therapy (PBS-PT) was developed and initiated for clinical use in 1996, with approximately 1300 patients treated to date (27). Chordomas continue to be among the most commonly treated entities at the center. Outcomes for skull base tumors have recently been published (21). Previous formal reports of extracranial chordomas and chondrosarcomas encompassed 26 and 40 total patients, respectively (12, 13). The purpose of the present study was to update this series with a significantly expanded patient experience and long-term follow-up, as well as to assess independent predictors for tumor control.

Methods and Materials

Patients

Between 1997 and 2015, 100 patients with extracranial chordoma arising from the cervical/thoracic/lumbar (C/T/L) spine or sacrum were treated with PBS-PT at PSI. This series was retrospectively reviewed on an ethics committee−approved protocol (EC Nr. EKNZ 2015-443). Patients with base of the skull lesions and pediatric (<18 years) patients were excluded. Pathologic analyses were commonly, but not uniformly, reviewed at a local institution if there was indeterminate or incomplete (eg, brachyury) testing. Median patient age was 55.5 years (range, 25-81 years), including 57 men (57%) and 43 women (43%) (Table 1).

Cervical (n = 46) and sacral (n = 38) lesions were most common, although thoracic (n = 4) and lumbar (n = 12) tumors were also encountered. Seventy patients (70%) were treated at initial presentation, and 30 (30%) at recurrence. Two included patients were subsequently treated for metachronous distant spinal lesions with long-term control. The presence of gross residual disease at the time of radiation therapy was common (n = 60; 60%) in

Table 1 Patient, tumor, and treatment characteristics

Characteristic	No. of cases (%)
Sex	
Male	57 (57)
Female	43 (43)
Median (range) age (y)	55.5 (25-81)
Median (range) total dose (Gy[RBE])	74 (59.4-77)
Treatment setting	
Initial presentation	70 (70)
Recurrence	30 (30)
Gross residual tumor	
Present	60 (60)
Absent	40 (40)
Spinal level	
Cervical	46 (46)
Thoracic	4 (5)
Lumbar	12 (12)
Sacral	38 (37)
Surgical stabilization	
Present	39 (39)
Absent	61 (61)
Treatment era	
Focal volume	44 (44)
Comprehensive volume	56 (56)
Modality	
PBS-PT alone	88 (88)
Photon−PBS-PT Combined	12 (12)

Abbreviation: PBS-PT = pencil-beam scanning proton therapy.
Values are number (percentage) except where otherwise noted.

this experience, with only 40 patients (40%) exhibiting no visualized residual tumor. Thirty-nine patients (39%) were irradiated with spinal surgical stabilization (SS) in place.

Patients were also prestratified for analysis by era of treatment. Before this review it was noted that treatment volumes were comprehensively larger after 2008 at PSI. After review of early treatment outcomes, institutionally standardized clinical target volumes (CTVs) were expanded in size in an effort to address a trend of marginal failures. Forty-four patients (44%) in the present series were treated in the earlier, "focal" volume era, and the remaining 56 (56%) were treated with more "comprehensive" volumes (Table 1).

Treatment

For computed tomography (CT) simulation/treatment, all patients were immobilized with a body cast, thermoplastic mask, and/or vacuum-assisted, table-mounted bite-block, according to disease site. As available, preoperative and postoperative magnetic resonance (MR) images were fused for delineation. Any present SS and associated CT artifacts were contoured and Hounsfield units overridden to adjust to appropriate stopping power. Residual gross tumor volume and the preoperative extent were contoured. The CTV1 for the initial 54 Gy (RBE), in most cases, was highly individualized before 2008. In later years this encompassed the gross tumor, surgical bed, and partial surgical tract and involved vertebral body/site, as well as 1 or more vertebral bodies above/below. The CTV2 was drawn to include gross disease, postoperative bed with margin, and the entire extent of preoperative tumor. This volume was treated to the prescription dose, most commonly 74 Gy (RBE).

The planning target volumes (PTVs) included a 5- to 10-mm margin to account for setup/range uncertainty. In-house planning software (PSIplan) was used for all treatment planning. Patients received adjuvant radiation therapy to doses ranging from 59.4 Gy (RBE) to 77 Gy (RBE) (median, 74 Gy[RBE]; mean, 73.4 Gy[RBE]). Eighty-two patients (82%) received $>$73 Gy (RBE), and 95 patients (95%) received $\geq$70 Gy (RBE). In the earlier years, some patients were treated with combined photon–proton radiation therapy (n = 12, 12%). The most common fractionation schedule was 1.8-2 Gy (RBE) per day.

Most phases of treatment used 2-4 fields, although gantry angles were regularly varied between treatment phases to reduce systematic uncertainties (Fig. 1). For proton therapy, PBS-PT alone was delivered. Treatment plans commonly started with a single-field optimization approach for the initial 30-36 Gy (RBE) to improve robustness of target coverage, followed by intensity modulated proton therapy to optimally spare organs at risk (28).

Fields were generally arranged posteriorly in the sacrum, T-spine, and L-spine, with the patient prone to avoid traversing the table. The C-spine was often treated supine with 2 anterior and 2 posterior obliques. Patients underwent CT scout imaging before fractions to verify positioning.

Standardized institutional dose constraints were used for the MR T2-delineated spinal cord (D2% $<$ 64 Gy[RBE]). The center of the cord (automatically generated circular contour with 2- to 3-mm diameter at geometric center of cord) was constrained to 54 Gy (RBE). Dose constraints to the cauda equina and sacral nerve roots were applied on a case-by-case basis, depending on tumoral proximity or involvement.

Follow-up

For the majority of patients, spinal MR imaging was acquired at 6 weeks after completion of PBS-PT and approximately every 6 months for several years. At PSI, follow-up radiographic examinations are reviewed by the entire clinical team in weekly conference. Clinical records regarding toxicity are also obtained from referring physicians and reviewed with prospective identification of toxicities. All summaries from these conferences, as well as internal and external progress reports, were retrospectively reviewed for this analysis.

Patients with at least 1 year of follow-up were included in this analysis. Acute adverse events were defined as those occurring within 90 days of start of therapy, with late effects after 90 days. Adverse events were graded

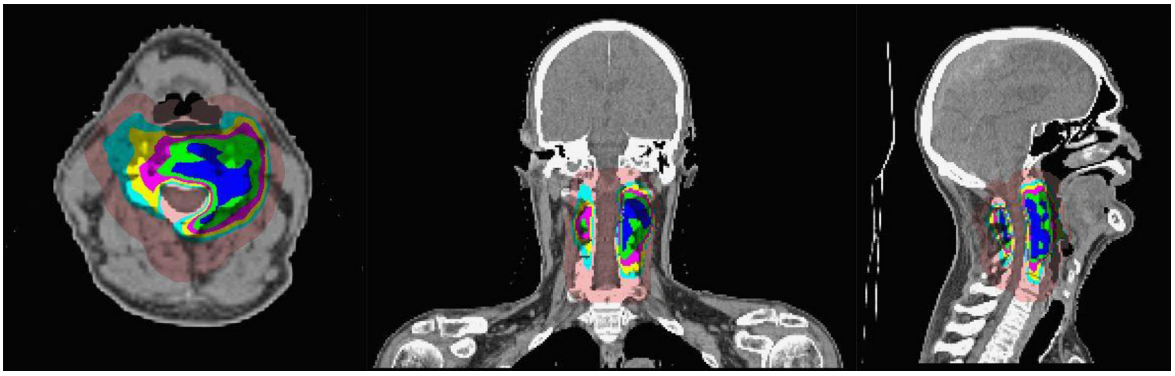

Fig. 1. Example pencil-beam scanning proton therapy dose distribution (74 Gy) for a cervical spine chordoma centered on the left neural foramen.

according to the US National Institutes of Health Common Terminology Criteria for Adverse Events grading system, version 4.0.

Patterns of failure

All locoregional treatment failures were reviewed by the medical and physics team at PSI. All available posttreatment imaging and follow-up information was used to map treatment failures against PBS-PT field design and dose distributions by direct comparison or by fusion of the diagnostic MR imaging, when possible, with the planning CT. Failure patterns were defined as follows: cord-sparing donut: recurrence deemed centered within the spinal canal at a vertebral level of high-dose treatment; high-dose region: centered within region receiving prescription dose; marginal: centered outside of the approximately 80% isodose line for PTV1 (<45 Gy) but receiving dose; marginal to PBS-PT boost: centered outside of the approximately 80% isodose for PTV2 (<60 Gy) but within PTV1; low-dose region: fully within PTV1 outside of PTV2. Patients with and without SS were compared in a preplanned analysis to examine the role of SS in potential PBS-PT dose perturbation and consequent failures.

Outcomes and statistical analysis

Local control, disease control (DC), and OS were assessed for all patients. Local failure was defined as confirmed radiographic or clinical progression/recurrence dated to the first imaging (usually MR) clearly demonstrating treatment failure. Disease progression was defined as clinical or radiographic evidence of local, regional, or distant recurrence/progression. Survival was identified as confirmed date of death or last follow-up. Local control, DC, and OS were measured from start of radiation therapy to date of first respective event or until last date of follow-up.

Statistical analysis was performed using the SPSS Statistics software package (IBM, Armonk, NY). The following covariates were analyzed for relationship to the clinical outcomes cited above: patient age, gender, total radiation therapy dose, treatment of initial or recurrent disease, presence of gross residual disease, proton therapy alone or combined photon−proton therapy, craniocaudal length of CTV1 in millimeters, spinal region (C, T, L, sacrum), PTV1 volume (cm^3), PTV2 volume (cm^3), presence of SS, and treatment volume era (focal vs comprehensive). Kaplan-Meier log-rank and Cox regression univariate analyses were performed for each endpoint. Factors at or below the 0.2 significance level were allowed to progress to regression multivariate analysis.

Results

For the 100 patients included in the study, median follow-up was >5 years (65 months; range, 13-175 months). Local control, DC, and OS rates at 5 years for the entire cohort were 63% (95% confidence interval [CI] 57.7-68.7%), 57% (95% CI 50.9-62.1%), and 81% (95% CI 76.8-85.6%), respectively. In total, at time of analysis, 37 patients had experienced local failure, 42 any failure, and 26 died. Median follow-up for patients treated in the focal era (initiating PBS-PT before 2008) (n = 44) was 89 months (range, 26-175 months), whereas those treated comprehensively (n = 56) were followed for a median of 51.5 months (range, 13-92 months).

Local control

Cox regression univariate and multivariate analyses (Tables 2 and 3) were performed to correlate patient and treatment factors with LC. On univariate analysis, the presence of SS ($P = .01$) and larger PTV1s (continuous) ($P = .048$) were found to correlate with worsened LC. Patients with SS demonstrated significantly worse LC by Kaplan-Meier analysis (Fig. 2). Five-year LC rates were 76% and 46% without and with SS, respectively. Of note, neither stratification of spinal region (C/T/L/Sacrum, $P > .48$; or C/T/L vs sacrum, $P = .86$) was significantly correlated with LC.

In addition, on univariate analysis, treatment stratified by volume era was marginally predictive for LC in the entire cohort ($P = .10$; Table 2). Actuarial LC at 5 years numerically improved from 57% to 70% in the later, comprehensive era (Fig. 3). Of note, despite a relative balance of vertebral levels of disease between the 2 eras (C/T/L/S for 2007 and prior: 18/2/9/15; 2008 and later: 28/2/3/23), PTV1s and PTV2s (available values) were on average larger in the comprehensive volume era than in the focal volume era: respective PTV1s of 1061 and 802 cm^3 (30% increase); respective PTV2s of 698 and 554 cm^3 (24% increase). On multivariate analysis, only smaller PTV1 (hazard ratio [HR] 1.08/100 cm^3, $P = .005$) and absence of SS (HR 0.287, $P = .002$) held as prognostic for improved LC.

Locoregional patterns of failure

Of the 37 patients with local failure, 33 (89%) had sufficient imaging and records available to accurately determine the relationship of the failure to the treatment fields and dose distribution. This included 19 patients (58%) with SS and 14 (42%) without. The most prevalent pattern of failure in patients with SS was within the cord-sparing "donut" of dose falloff toward the spinal cord (n = 8, 42%). Failures in the high-dose region were less common in patients with SS: 4 of 19 (21%) high dose, 3 of 19 (16%) marginal, 2 of 19 (10.5%) marginal to PBS-PT boost after XRT, and 2 of 19 (10.5%) in the low-dose PBS-PT region. Instead, failure clearly within the high-dose region was more prevalent among patients without SS (11 of 14, 79%)—marginal 2 of 14 (14%) and in the cord-sparing region 1 of 14 (7%).

Table 2 Univariate analyses for local control (LC), disease control (DC), and overall survival (OS)

Characteristic	No. of cases (%)	5-y LC (%)	LC *P*	5-y DC (%)	DC *P*	5-y OS (%)	OS *P*
Sex			.62		.78		.47
Male	57 (57)	62.1		55.5		84.7	
Female	43 (43)	65.0		58.7		76.7	
Age (range, 25-81 y)							
Continuous variable			.29		.16		.02*
Median							
<55.5 y	50 (50)	66.1		61.7		85.7	
≥55.5 y	50 (50)	59.6		50.1		76.5	
Total RT dose (range, 59.4-77 Gy[RBE])							
Continuous variable			.84		.95		.69
Median							
<74 Gy (RBE)	34 (34)	62.2		59.3		81.7	
≥74 Gy (RBE)	66 (66)	63.7		55.3		80.7	
Treatment setting			.43		.18		.24
Initial presentation	70 (70)	63.4		61.1		80.5	
Recurrence	30 (30)	61.8		47.4		81.8	
Gross residual tumor			.45		.13		.05*
Present	60 (60)	59.7		50.5		76.4	
Absent	40 (40)	68.9		65.9		87.9	
Surgical stabilization			.01*		.003*		.01*
Present	39 (39)	45.9		33.6		73.1	
None	61 (61)	75.6		72.4		87.3	
Treatment era			.10		.07		.01*
Focal volume	44 (44)	57.2		48.5		70.5	
Comprehensive volume	56 (56)	70.0		65.9		94.5	
Median CTV-1 craniocaudad length (mm) (range, 18-318 mm)							
Continuous variable			.16		.17		.83
Median							
<106 mm	47 (47)	70.3		62.8		86.8	
≥106 mm	50 (50)	52.0		45.5		74.3	
UTA	3 (3)						
Median PTV1 (cm^3) (range, 42.3-4023.96 cm^3)							
Continuous variable			.05*		.19		.22
Median							
<699.95 cm^3	44 (44)	71.5		61.1		84.2	
≥699.95 cm^3	44 (44)	46.9		43.0		76.6	
UTA	12 (12)						
Median PTV2 (cm^3) (range, 24.7-3749.0 cm^3)							
Continuous variable							
Median			.29		.49		.84
<402.01 cm^3	44 (44)	67.1		56.1		80.0	
≥402.01 cm^3	44 (44)	53.8		49.9		81.8	
UTA	12 (12)						
Modality			.49		.87		.77
PBS-PT alone	88 (88)	61.0		53.1		80.8	
Photon-PBS-PT combined	12 (12)	75.0		75.0		83.3	

Abbreviations: CTV1 = clinical low-risk treatment volume; PBS-PT = pencil-beam scanning proton therapy; PTV1 = planning low-risk treatment volume; PTV2 = planning high-risk/gross disease treatment volume; RBE = relative biological effectiveness; UTA = unable to assess, insufficient data.
* Statistically significant.

Disease control

Disease control was similarly analyzed by univariate, multivariate, and Kaplan-Meier approaches (Figs. 2 and 3). Because most disease failures were local, similar factors were found to be significant/marginal on univariate analysis (Table 2): volume era ($P = .075$) and the presence of SS ($P = .003$). On multivariate analysis, the presence of SS prognosticated for much worsened DC at 5 years (72% SS absent vs 34% SS present; HR 0.344, $P = .003$). Increasing

Table 3 Multivariate analyses for local control, disease control, and overall survival

Endpoint and characteristic	Hazards ratio	*P*
Local control		
PTV1 (cm^3)	1.08/100 cm^3	.005
Surgical stabilization*	0.29	.002
Disease control		
CTV1 craniocaudad length (mm)	1.10/10 mm	.008
Surgical stabilization*	0.34	.003
Volume era†	0.53	.075
Gross residual disease‡	0.62	.18
Overall survival		
Volume era†	0.15	.007
Age§	1.03	.06
Gross residual disease‡	0.27	.007

* Favors lack of surgical stabilization.
† Favors comprehensive volume era.
‡ Favors lack of gross residual disease.
§ Favors younger age.

craniocaudal length of CTV1 also diminished DC (HR 1.10/10 mm, $P = .008$). A trend toward statistical significance was observed with the comprehensive volume era and improved 5-year DC (66% vs 49%; HR 0.525, $P = .075$). The presence of gross residual disease failed to predict for worsened DC (HR 0.62, $P = .18$).

Overall survival

Univariate and multivariate Cox regression (Tables 2 and 3) analyses were computed for OS, as were Kaplan Meier curves (Figs. 2 and 3). On univariate analysis, advancing age ($P = .018$), presence of SS ($P = .01$), and focal volume era ($P = .01$) each correlated with worsened OS. Only treatment in the comprehensive era (HR 0.148, $P = .007$) and the absence of gross residual disease (HR 0.274, $P = .007$) held as prognostic for improved survival on multivariate analysis (Table 3). Advancing patient age ($P = .06$) was marginally significant for worsened survival.

Toxicity

Serious early and late toxicities were rarely encountered. Eleven patients (11%) experienced high-grade (grade $\geq$3) toxicities. Eight patients (8%) had acute grade 3 toxicities: moist desquamation in non-skin folds (n = 6), mucositis (n = 2), and dysphagia (n = 1) (including 1 patient with both mucositis and dermatitis). No acute grade $\geq$4 toxicities were noted. Five patients (5%) (including 3 also with acute grade 3 toxicity) experienced late grade 3 toxicity: vertebral/sacral insufficiency fracture (n = 3), aspiration pneumonia (n = 1), and esophageal stenosis requiring dilation (n = 1). One patient (1%) developed a second malignancy (grade 4), rhabdomyosarcoma of the bladder, approximately 3 years after completion of radiation therapy for a sacral chordoma. It should be noted that this patient received combined photon–proton therapy (54 Gy photon; 19.8 Gy (RBE) proton); in review of the patient's PBS-PT plan, there was minimal contribution of dose from the proton therapy boost. In total, this constitutes an actuarial 5-year freedom from grade $\geq$3 toxicity survival rate of 89% (95% CI 85.5-91.9%). Five-year freedom from grade $\geq$3, long-term or persistent toxicity (n = 6) was 94% (95% CI 88.6-98.6%).

Discussion

High-dose proton therapy remains a highly effective and safe adjuvant therapy for spinal chordomas. Long-term follow-up of the experience at PSI has confirmed the significant improvements in LC that proton therapy offers over historical photon techniques. This series has demonstrated rates of LC, DC, and OS consistent with experiences of Massachusetts General Hospital, MD Anderson Cancer Center, and the University of Florida (10, 26, 29). Of note, these institutions never reported the precise pattern of failures of these challenging spinal tumors, and we believe this analysis brings significant input to the radiation therapy community.

Pencil-beam scanning proton therapy has offered comparatively high rates of LC with good tolerability and very limited high-grade toxicity. Despite regular utilization of spinal cord constraints of D2% of 64 Gy (RBE) to the surface and 54 Gy (RBE) to the center, no clinical myelopathies were encountered in 18 years of experience with a median >5-year follow-up. A report of PSI's spinal cord dose constraints and experience, including spinal chondrosarcomas, has been presented separately (25).

The presence of SS remains prognostic for worsened LC and DC on multivariate analysis. This result confirms trends seen in early experience at PSI (12, 13). It should be noted that rates of LC, DC, and OS in this series are nearly identical to those from institutions that use combined-modality (photon–proton) treatments to mitigate the effect of SS on dose delivery (29).

The causation for the prognostic impact of reconstructive hardware remains complex. We have demonstrated previously that PBS-PT plans are remarkably robust to the presence of SS when utilizing either single-field optimization or intensity modulated proton therapy (30). Surgical stabilization may be a proxy of the inherent biological aggressiveness and/or preoperative size of the chordoma. Of note, though SS is generally more common in the C/T/L spine than in the sacrum, as was the case in this series, there was no noted correlation between spinal region and outcomes. Possible explanations for the observed differential prognosis include imbalances with respect to uncharacterized baseline prognostic factors, statistical chance, or a true surgical hardware effect. The unique, detailed patterns of failure mapping within this effort is limited in sample size but shows no convincing evidence of clinically meaningful PBS-PT dose perturbation by the SS. To the contrary, failures clearly within the intended high-dose region were more common among patients without SS.

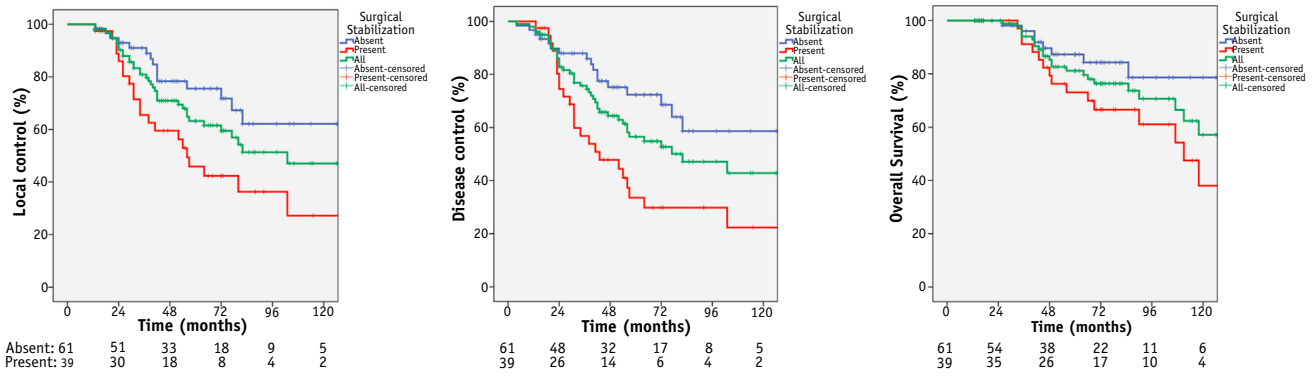

Fig. 2. Local control, disease control, and overall survival stratified by presence or absence of surgical stabilization.

Instead, recurrences within the unavoidable low-dose region near the spinal cord were most prevalent among patients with SS. Nevertheless, SS and associated artifacts undeniably complicate visualization of the tumor bed and its consequential delineation process, require density override for dose calculation, and challenge imaging follow-up, all of which may contribute to worsened outcomes. Alternatives to titanium SS should be sought for these reasons, but in the interim, PBS-PT seems safe and robust for treatment amidst metallic SS when necessary.

Improvement in outcomes in patients in the later treatment era, and especially in those with SS, may be possibly attributable to more comprehensive target volumes utilized at our institution since 2008. This may mitigate the effect of more extensive local disease that is poorly visualized or obscured by SS. However, there may be a number of contributing/confounding factors not captured in the multivariate analysis: improved relationships with multidisciplinary teams, greater insistence on maximal safe resections, improved systemic therapies, and improved/widened use of MR imaging. Additionally, increased PTV1 (cm^3) prognosticated for worsened LC on multivariate analysis. Unfortunately, this parameter represents a balance between larger initial disease/postoperative bed and more generous contouring.

In contrast to some experiences and in agreement with others, treatment at initial presentation or at disease recurrence did not seem to significantly affect outcomes in the present series (10, 19, 29, 31-34). This factor, however, may be highly confounded by various treatment parameters. In particular, the indications utilized by surgeons for radiation referral vary widely, and the closeness of collaboration between the surgeon and radiation oncologist is key in producing the best outcomes. Patients with recurrent disease likely not only possess a more aggressive biology of disease, but also their risk of unresectability, tumoral seeding, and tumor bed hypoxia are substantially higher. Multidisciplinary management, including radiation consultation, should be standard at initial diagnosis for patients with chordoma.

In addition, young age no longer correlated with increased local failure, although pediatric patients were excluded from this series (13, 29). Advancing age, as expected, correlated with shortened survival. The presence of gross residual disease at the time of proton therapy remains an important prognostic factor, and the importance of complete surgical resection should not be underestimated.

Sufficient power to perform a formal multivariate analysis, including the above parameters, in the setting of patients treated for chordoma, represents a particular strength of this effort. However, this report has several limitations. The retrospective nature of the review lends toward certain biases. Although promising in the setting of PBS-PT, this experience did not incorporate the use of passive scattering and only limitedly used combined-modality therapy, which are commonly used approaches at this juncture. The extent of initial disease and postoperative residual gross tumor could not be quantified because of variable contouring

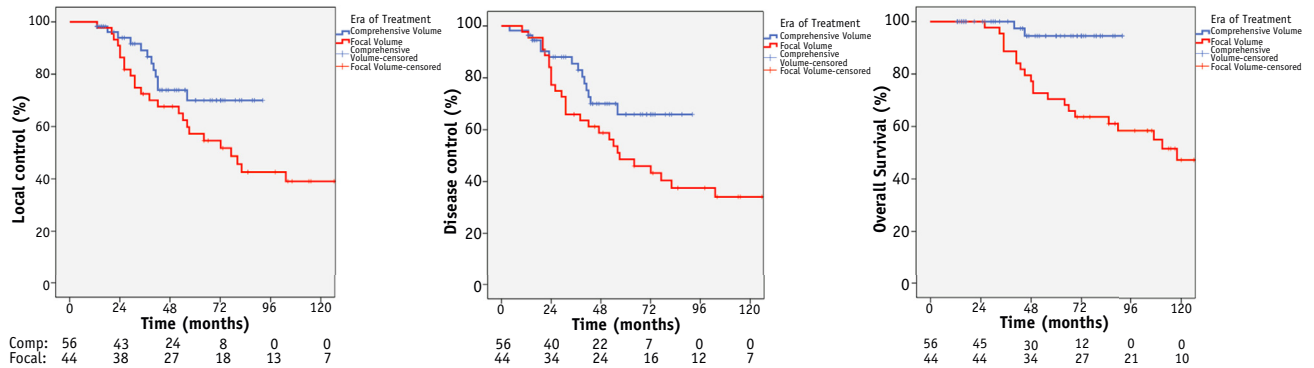

Fig. 3. Local control, disease control, and overall survival stratified by era of treatment (focal vs comprehensive).

practices and/or inadequate imaging data, although surrogates in target volumes and the presence of gross residual disease were incorporated.

Nevertheless, this analysis stands as one of the largest to date, especially with long-term follow-up. It includes an important multivariate analysis for prognostic factors for outcomes in this rare disease entity and the results of extensive experience with proton therapy alone with and without SS.

Conclusions

Pencil-beam scanning proton therapy remains a highly effective method for delivery of dose-escalated adjuvant radiation therapy in the treatment of spinal chordomas. Metallic SS continues to prognosticate for worsened outcomes, although results with PBS-PT alone mirror those with combined-modality therapy overall. More comprehensive treatment volumes are likely indicated for treatment of this tumor entity.

References

1. Walcott BP, Nahed BV, Mohyeldin A, et al. Chordoma: Current concepts, management, and future directions. *Lancet Oncol* 2012;13:e69-e76.
2. McMaster ML, Goldstein AM, Bromley CM, et al. Chordoma: Incidence and survival patterns in the United States, 1973-1995. *Cancer Causes Control* 2001;12:1-11.
3. Sundaresan N. Chordomas. *Clin Orthop Relat Res* 1986;204:135-142.
4. Hsieh PC, Xu R, Sciubba DM, et al. Long-term clinical outcomes following en bloc resections for sacral chordomas and chondrosarcomas: A series of twenty consecutive patients. *Spine* 2009;34:2233-2239.
5. 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.
6. Tzortzidis F, Elahi F, Wright D, et al. Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. *Neurosurgery* 2006;59:230-237; discussion: 230-237.
7. Samson IR, Springfield DS, Suit HD, et al. Operative treatment of sacrococcygeal chordoma. A review of twenty-one cases. *J Bone Joint Surg Am* 1993;75:1476-1484.
8. Jawad MU, Scully SP. Surgery significantly improves survival in patients with chordoma. *Spine* 2010;35:117-123.
9. Boriani S, Bandiera S, Biagini R, et al. Chordoma of the mobile spine: Fifty years of experience. *Spine* 2006;31:493-503.
10. Holliday EB, Mitra HS, Somerson JS, et al. Postoperative proton therapy for chordomas and chondrosarcomas of the spine: Adjuvant versus salvage radiation therapy. *Spine* 2015;40:544-549.
11. 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.
12. Staab A, Rutz HP, Ares C, et al. Spot-scanning-based proton therapy for extracranial chordoma. *Int J Radiat Oncol Biol Phys* 2011;81:e489-e496.
13. Rutz HP, Weber DC, Sugahara S, et al. Extracranial chordoma: Outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation. *Int J Radiat Oncol Biol Phys* 2007;67:512-520.
14. Romero J, Cardenes H, la Torre A, et al. Chordoma: Results of radiation therapy in eighteen patients. *Radiother Oncol* 1993;29:27-32.
15. Catton C, O'Sullivan B, Bell R, et al. Chordoma: Long-term follow-up after radical photon irradiation. *Radiother Oncol* 1996;41:67-72.
16. Debus J, Schulz-Ertner D, Schad L, et al. Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. *Int J Radiat Oncol Biol Phys* 2000;47:591-596.
17. Pearlman AW, Friedman M. Radical radiation therapy of chordoma. *Am J Roentgenol Radium Ther Nucl Med* 1970;108:332-341.
18. Igaki H, Tokuuye K, Okumura T, et al. Clinical results of proton beam therapy for skull base chordoma. *Int J Radiat Oncol Biol Phys* 2004;60:1120-1126.
19. Noel 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* 2005;44:700-708.
20. Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Results of carbon ion radiotherapy in 152 patients. *Int J Radiat Oncol Biol Phys* 2004;58:631-640.
21. Weber DC, Malyapa R, Albertini F, et al. Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy. *Radiother Oncol* 2016;120:169-174.
22. 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;45:351-358.
23. Chowdhry VK, Liu L, Goldberg S, et al. Thoracolumbar spinal cord tolerance to high dose conformal proton-photon radiation therapy. *Radiother Oncol* 2016;119:35-39.
24. Marucci L, Niemierko A, Liebsch NJ, et al. 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;59:551-555.
25. Stieb S, Snider JW, Placidi L, et al. Long-term clinical safety of high-dose proton radiation therapy delivered with pencil beam scanning technique for extracranial chordomas and chondrosarcomas in adult patients: Clinical evidence of spinal cord tolerance. *Int J Radiat Oncol Biol Phys* 2018;100:218-225.
26. 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;23:788-797.
27. Pedroni E, Bacher R, Blattmann H, et al. The 200-MeV proton therapy project at the Paul Scherrer Institute: Conceptual design and practical realization. *Med Phys* 1995;22:37-53.
28. Lomax A. Intensity modulation methods for proton radiotherapy. *Phys Med Biol* 1999;44:185-205.
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. Dietlicher I, Casiraghi M, Ares C, et al. The effect of surgical titanium rods on proton therapy delivered for cervical bone tumors: Experimental validation using an anthropomorphic phantom. *Phys Med Biol* 2014;59:7181-7194.
31. Rombi B, Ares C, Hug EB, et al. Spot-scanning proton radiation therapy for pediatric chordoma and chondrosarcoma: Clinical outcome of 26 patients treated at paul scherrer institute. *Int J Radiat Oncol Biol Phys* 2013;86:578-584.
32. Naka T, Boltze C, Samii A, et al. Skull base and nonskull base chordomas: Clinicopathologic and immunohistochemical study with special reference to nuclear pleomorphism and proliferative ability. *Cancer* 2003;98:1934-1941.
33. 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.
34. Almefty K, Pravdenkova S, Colli BO, et al. Chordoma and chondrosarcoma: Similar, but quite different, skull base tumors. *Cancer* 2007;110:2457-2467.