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CLINICAL INVESTIGATION **Brain**

SPOT-SCANNING-BASED PROTON THERAPY FOR EXTRACRANIAL CHORDOMA

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Purpose: To evaluate effectiveness and safety of spot-scanning-based proton-radiotherapy (PT) for extracranial chordomas (ECC).

Methods and Material: Between 1999–2006, 40 patients with chordoma of C-, T-, and L-spine and sacrum were treated at Paul Scherrer Institute (PSI) with PT using spot-scanning. Median patient age was 58 years (range, 10–81 years); 63% were male, and 36% were female. Nineteen patients (47%) had gross residual disease (mean 69 cc; range, 13–495 cc) before PT, and 21 patients (53%) had undergone prior titanium-based surgical stabilization (SS) and reconstruction of the axial skeleton. Proton doses were expressed as Gy(RBE). A conversion factor of 1.1 was used to account for higher relative biological effectiveness (RBE) of protons compared with photons. Mean total dose was 72.5 Gy(RBE) [range, 59.4–75.2 Gy(RBE)] delivered at 1.8–2.0 Gy(RBE) dose per fraction. Median follow-up time was 43 months.

Results: In 19 patients without surgical stabilization, actuarial local control (LC) rate at 5 years was 100%. LC for patients with gross residual disease but without surgical stabilization was also 100% at 5 years. In contrast, 12 failures occurred in 21 patients with SS, yielding a significantly decreased 5-year LC rate of 30% ($p = 0.0003$). For the entire cohort, 5-year LC rates were 62%, disease-free survival rates were 57%, and overall survival rates were 80%. Rates were 100% for patients without SS. No other factor, including dosimetric parameters (V95, V80) were predictive for tumor control on univariate analysis.

Conclusion: Spot-scanning-based PT at PSI delivered subsequently to function-preserving surgery for tumor debulking, decompression of spinal cord, or biopsy only is safe and highly effective in patients with ECC without major surgical instrumentation even in view of large, unresectable disease.

Proton radiotherapy, Chordoma, Radiotherapy, Paraspinal tumors.

INTRODUCTION

The majority of chordomas are low-grade malignancies with relatively low metastatic potential. Arising from remnants of the embryonal notochord, they can originate along the axial skeleton between the clival bone of the skull base superiorly and the coccyx inferiorly. The annual incidence rate is low at approximately 0.1 in 100,000 (1). Because of their central location, chordomas develop in proximity to critical anatomical structures. For spinal locations (including sacrum and coccyx), critical structures are spinal cord, cauda equina, nerve roots, kidneys, and bowel. Local tumor control is the prerequisite for cure. Complete, microscopic surgical resection remains often elusive. This is reflected by the limitations of surgery as sole treatment modality in accomplishing long-term disease free survival. Chugh *et al.* (2) have provided an excellent review on this topic.

Radiation therapy is recommended postoperatively in cases of gross residual disease or for positive margins following maximum resection and frequently as definitive treatment following recurrence.

Chordomas, analogous to the majority of mesenchymal tumors, are not particularly sensitive to radiation treatment, requiring radiation doses >70 Gy for gross disease at conventional fractionation schemas. Historic results after conventional radiotherapy to doses ranging between 50 and 60 Gy resulted in poor local control rates below 25% (3, 4). Best reported local control rates with photons based on modern, fractionated stereotactic radiation therapy for lesions in the skull base revealed 5-year actuarial local control rates of approximately 50% (5). Over the years, two potential strategies have been further explored: radical en bloc surgical resection and radiation dose escalation. For radiation therapy, an early publication by Pearlman *et al.* (6) suggested a possible dose–response effect. Although it has been established that increasing radiation doses (in the range of and in excess of 70 Gy) will lead to long-term tumor control, delivery of radiotherapy represents a challenge for conventional

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radiation treatment modalities because of nearby critical neurologic structures with tolerance dose levels significantly below a tumoricidal dose (7, 8).

At present the most promising results in the treatment of chordomas have been reported by particle therapy for the skull-base—in general combining maximal surgical tumor resection with adjuvant high-dose particle therapy. This approach has been pioneered at Massachusetts General Hospital in collaboration with the Harvard Cyclotron Laboratory (9, 10). As for extracranial locations, initial publications have also documented substantial improvements n outcome (11).

At Paul Scherrer Institute, the concept of spot-scanning-based proton therapy delivery has been pioneered (12) and was introduced in the clinic in 1996. Chordomas at cranial and extracranial locations were selected as one of the first indications, and preliminary results have been published previously (13, 14). Rutz *et al.* (14), for the Paul Scherrer Institute group, reported on 26 patients with extracranial chordomas and median follow-up period of 35 months after photon therapy (PT). A 3-year disease-free survival of 77% was documented.

The aim of the present study was to analyze long-term outcomes data for this tumor entity and to evaluate the long-term safety of spot-scanning-based proton radiotherapy in these anatomic locations.

METHODS AND MATERIAL

Patients

Between October 1999 and December 2006, 40 patients with extracranial chordomas of C-, T-, L-spine, and sacrum underwent proton therapy (PT) at PSI. Median age of all patients was 58 years (range, 10–81 years, including 3 pediatric patients aged <18 years) (see Table 1).

For purpose of this analysis the patient cohort was separated into a "No-GTV group" (GTV = gross tumor volume) and a "GTV group" according to absence or presence of radiographic gross residual disease at time of PT. Twenty-one patients (No-GTV group = 53%) had no identifiable gross residual tumor at time of referral, whereas 19 of 40 patients (GTV group = 47%) had gross residual disease deemed not to be suitable for further resection. GTV ranged between 13 and 495 cc (mean, 69.13 cc).

Twenty-one patients (21 of 40 = 53%) had undergone prior surgical stabilization (SS) of the axial skeleton. Extensive, combined ventral and dorsal titanium-based instrumentation, *i.e.,* reconstruction of vertebral body plus posterior stabilization, had been performed in 13 of 21 patients with SS. Eight of 21 patients with SS had undergone Harms' titanium cage placement for vertebral body reconstruction only. Patients with combined dorsal and ventral instrumentation (with or without Harms' titanium cage) were defined as patients with "complex SS."

Informed consent was obtained from all patients. Legal representatives gave consent for children. Patient, tumor, and treatment characteristics are summarized in Table 1.

Table 1. Patient-, tumor-, and treatment-related characteristics of 40 chordoma patients treated with spot-scanning-based PT at the Paul Scherrer Institute

Characteristics	No. of patients
Sex	
Total	40
Male	25
Female	15
Age at time of PT (years)	
<18 years	3
Median 58 (range, 10–81)	
>18 years	37
Tumor status	
Primary disease	32
Recurrent disease	8
Presence or absence of gross residual disease (GTV) before PT	
No GTV	21
GTV	19
Anatomic location	
Cervical spine	16
Thoracic spine	04
Lumbar spine*	10
Sacrum (± coccyx)	11
Surgical stabilization	
No	19
Yes	21
IMPT	
No	21
Yes	19
RT modality	
Protons only	31
Mixed protons/photons	9
Administered dose (photons)	Mean 41.8 Median 43.2 (range, 20.0–54)
Dose prescription Gy(RBE)†	Mean 72.5 Median 74 (range, 59.4–75.2)

Abbreviations: GTV = gross tumor volume; IMPT = intensity-modulated proton therapy; PT = proton therapy; RBE = relative biological effectiveness.

* One patient with a thoracic-lumbar chordoma.

† Delivered at 1.8–2 Gy(RBE) dose per fraction.

Volume definitions and treatment planning

All patients were immobilized using combination of body cast, vacuum-assisted bite-block system, or thermoplastic mask for precise positioning depending on anatomic tumor location. On the basis of the planning CT scan in immobilized treatment position, GTV was defined as evidence of macroscopic tumor on radiographic images (CT/MRI) at the time of referral. The presurgical tumor extension plus the dorsal surgical pathway, but not the transabdominal pathway (where applicable), were defined as the clinical target volume (CTV). In addition, surgical instrumentations were included in the CTV definition. CT artifacts from titanium implants were compensated manually and assigned soft tissue and bone-equivalent Hounsfield units for dose calculation.

The planning target volume (PTV) was defined as target volume plus a margin of 5–10 mm in all three dimensions for all locations except cervical spine (Fig. 1). For cervical chordomas, PTV margins of 3–5 mm were implemented. Treatment planning was performed using the in-house "PSI-plan" as previously described (13, 15, 16).

RT planning with photons (9 patients, see Table 1) was performed in collaboration with the referring institutions.

Proton treatment regimen

Proton doses D_{RBE} were expressed as Gy(RBE). A conversion factor of 1.1 was used to account for higher relative biological

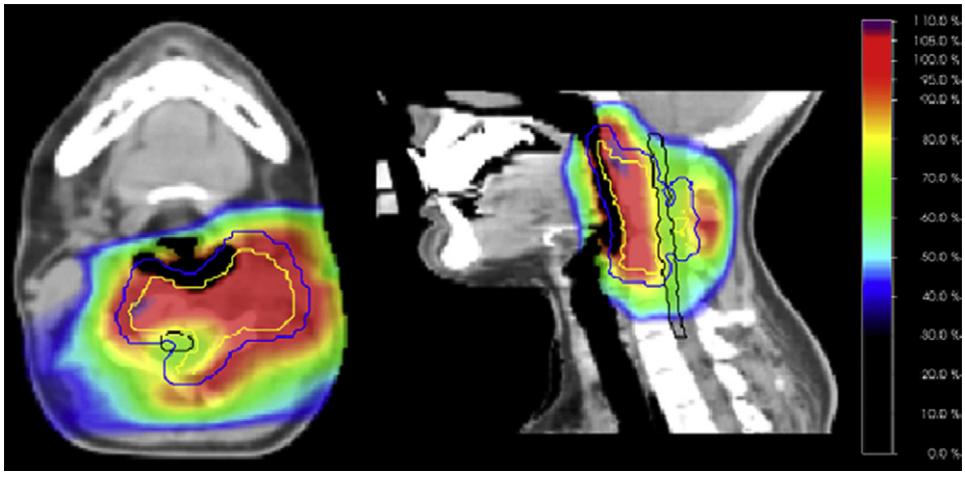

Fig. 1. Axial and sagittal slice and dose distribution of a patient with a cervical chordoma. Outer blue line: planning target volume 1 (PTV 1) = CTV + 5 mm. Inner yellow line: planning target volume 2 (PTV 2) = GTV+5mm. Black line: spinal cord.

effectiveness (RBE) of protons compared with photons. A standard dose per fraction of 1.8–2 Gy(RBE) was employed. In general, 4 proton fractions per week at 2 Gy(RBE) per fraction were delivered because of limited beam time availability at the time. Dose per fraction was reduced to 1.8 Gy(RBE), when bones or implants caused hot spots above 120% of the reference dose. This has been described previously (14).

Intensity-modulated proton therapy (IMPT) was introduced during this treatment period by Lomax *et al.* (16) and applied as part of treatment planning in 19 patients (48%). Analogous to IMRT for photons, IMPT with an inverse planning algorithm is used to optimize target dose coverage while complying with constraints imposed by organs of risk (OAR). OAR dose constraints were defined as 63 Gy(RBE) to spinal cord surface (similar to brainstem surface constraints established previously in the treatment of skull base tumors) (13) and 54 Gy(RBE) to the center of spinal cord (17). Caudally to the fifth lumbar vertebra (L_5), full dose was permitted.

The mean prescription dose $D_{(RBE)}$ was 72.5 Gy(RBE) (range, 59.4–75.2). Thirty-seven patients (93%) received ≥70 Gy (RBE) and 38 patients ≥69 Gy(RBE). The entire treatment course was delivered with protons exclusively in 31 of 40 patients (78%); 9 of 40 patients (22%) were treated with combined photons and protons. Mean photon dose in patients with mixed photon/proton RT was 41.8 Gy ranging between 20 and 54 Gy. Two patients received <69 Gy(RBE): initial photon RT (with protons reserved as boost) delivered at an outside institution restricted in one patient with cervical chordoma the total dose to 62 Gy(RBE) because of spinal cord constraints. The spinal cord had already received 40 Gy. In another patient, an unexpected equipment failure in 2002 required a prolonged treatment shut down for repair. The decision was made to terminate the patient's treatment at 59.4 Gy(RBE).

Follow-up

Patients underwent repeat radiological examinations. In general, spinal MRIs and CT scans were obtained at 6 weeks after PT, every 6 months for the first 2 years, and annually thereafter.

No patient was lost to follow-up. Acute adverse events were defined as symptoms occurring during or within 90 days of PT. Adverse events >90 days were censored as late events. Adverse events were scored according to the U.S. National Institutes of Health Common Terminology Criteria for Adverse Events grading system CTCAE v3.0.

Median follow-up time was 43 months (range, 24−91). Minimum follow-up was 24 months, *i.e.,* 2 years. Observation times were 180 patient years for overall survival (OS) and 159 for local control (LC).

Statistical analysis

Kaplan-Meier curves (18) with log-rank tests were used for times-to-event analyses calculated from the beginning of PT until the date of last follow-up or date of the event, whichever occurred first. The following events were considered: all causes of death for overall survival (OS), the length of time after treatment that a patient survived with no sign of disease progression (DFS), and local failure, defined as radiographically documented tumor progression at the irradiated site on two consecutive examinations. Date of failure was censored as date of radiographic progression or onset of clinical symptoms. Statistical analysis was performed with the Stata 9.1 software (StataCorp, College Station, TX). We analyzed the following covariables for clinical endpoints: gender, GTV, presence of surgical implants, and total prescription dose.

The effects of SS on dose coverage in patients with extracranial chordoma were analyzed in 31 patients treated with PT exclusively and quantified according to the following dosimetric values: V95 and V80 (percentage of the target volume receiving 95% and 80% of the dose).

RESULTS

Local control

Thirteen patients developed local failure resulting in actuarial 5-year local control rate of 62% for the entire cohort (Fig. 2). All 19 patients without SS had local tumor control at 5 years (100%). Subsequently, one patient without SS failed locally at 71 months. In contrast, 12 of 13 local failures occurred in 21 patients with SS, yielding a 5-year LC rate of only 30%. The difference of 5-year LC rates for patient with versus patients without SS was highly statistically significant (p = 0.0003). The extent of SS (complex vs. noncomplex SS) did not influence local control probability (p = 0.698).

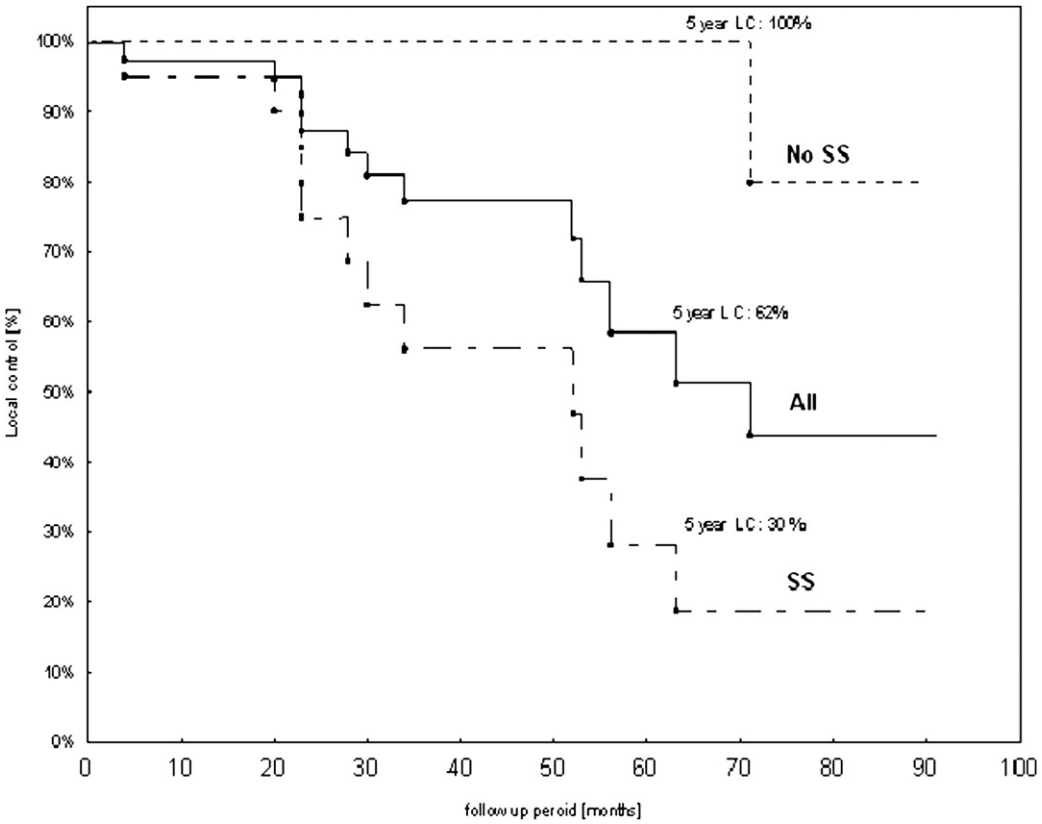

Fig. 2. Local tumor control (LC) probability in 40 patients with extracranial chordoma following spot-scanning-based proton therapy. SS = surgical stabilization.

Nineteen patients underwent proton therapy for gross residual disease (GTV group) and 8 patients experienced local failure, resulting in a 5-year LC rate of 47%. Of note, in 8 of 19 patients with GTV but without SS, actuarial 5-year LC was 100%; only one patient failed late at 71 months. Compared with the GTV group, 5-year LC rates were 66% for the No-GTV group (5/21 patients with local failure). The difference of 47% vs. 66% was statistically significant ($p = 0.048$).

Investigating a possible interconnectivity between gross residual disease and surgical stabilization, we correlated those parameters with local control: 11 of 19 patients with gross residual tumor had SS. Of those 11 patients with both GTV and SS, 7 patients experienced local failure, yielding a 5-year local control rate of 27%. The comparison with the subgroup of 8 patients with GTV without SS (100% 5-year LC) reached statistically significant difference ($p = 0.019$).

Five of 13 local failures occurred in 8 patients with recurrent disease, yielding a 5-year LC rate of 24% in patients with recurrent disease vs. 86% in patients without recurrent disease ($p = 0.039$). Seven of eight patients with recurrent disease had SS. All patients with recurrent disease and local failure (5/8) had SS.

Although the small number of patients in each subgroup did not permit a multivariate analysis, these differences indicate interdependence between SS and presence of GTV; for example, a subtotal resection was accomplished despite extensive surgery requiring SS. This would likely indicate a more advanced infiltrative tumor stage or more aggressive natural history of disease.

A summary of prognostic factors for local control is shown in Table 2. Anatomic location, use of IMPT, gender, and protons only vs. mixed proton/photon regimen did not yield statistically significant differences.

Disease-free survival

The actuarial 5-year DFS rate for all 40 patients was 57% (Fig. 3). According to DFS criteria, we observed 15 events: 13 patients developed local failure. One additional patient died from leiomyosarcoma of the urinary bladder (discussed subsequently). Another patient with a chordoma of the cervical spine developed a second focus of chordoma in the vicinity of the initial tumor site. The epicenter of this new focus was outside of the irradiated planning target volume. The distance between the peripheral border of initial tumor site and the second focus of the chordoma was approximately 25–30 mm.

Disease-free survival was significantly reduced in patients with SS ($p = 0.011$). The actuarial 5-year DFS was 86% in patients without SS and 30% in patients with SS, with the majority of failures occurring in the GTV group. Hence, 5-year DFS was reduced in patients with gross residual tumor ($p = 0.032$). Five-year DFS was 40% in patients with residual tumor compared with 68% in patients without residual

Table 2. Impact of various potential prognostic factors on the likelihood of achieving LC, DFS, and OS after proton therapy in 40 patients with extracranial chordoma

Characteristics	Patient *n*	Local Failure (*n*)	5-year LC (%)	*p* value	Any failure (*n*)	5-year DFS (%)	*p* value	Death (*n*)	5-year OS (%)	*p* value
Total	40	13	62		15	57		6	80	
Sex										
Female	15/40	5	60	0.987	6	56	0.818	5	62	0.015
Male	25/40	8	59		9	54		1	92	
Surgical stabilization										
Yes	21/40	12	30	0.0003	12	30	0.011	4	75	0.381
No	19/40	1	100		3	86		2	86	
Gross residual tumor										
Yes	19/40	8	47	0.048	10	40	0.032	4	66	0.141
No	21/40	5	66		5	68		2	89	

Abbreviations: DFS = disease-free survival; LC = local control; OS = overall survival.

tumor. All patients without gross residual disease and without SS remained free of disease progression. Gender did not influence DFS ($p = 0.818$). A summary of prognostic factors for DFS is shown in Table 2.

Overall survival

Actuarial 5-year OS for 40 patients was 80% (Fig. 3). Death occurred in 6 of 40 patients (15%), and all deaths were related to disease. Five patients (13%) died either of local failure (3/40) or a combination of local failure and distant metastasis (2/40). This included one patient who committed suicide 32 months after PT. This patient had experienced local failure in the lumbar spine causing paralysis and distant metastatic disease at various sites including bones and lungs. We classified this death as disease-related because the patient was terminally ill from metastatic disease. Gross residual tumor did not significantly affect 5-year OS rates ($p = 0.141$), although four of six deaths occurred in patients with gross residual tumor. The 5-year OS rate was 66% in patients with gross residual tumor and 89% in patients without gross residual tumor. SS did not affect 5-year OS, although 4 of 6 deaths occurred in the SS group ($p = 0.381$). The 5-year OS rate was 75% in patients with SS compared with 86% in patients without SS.

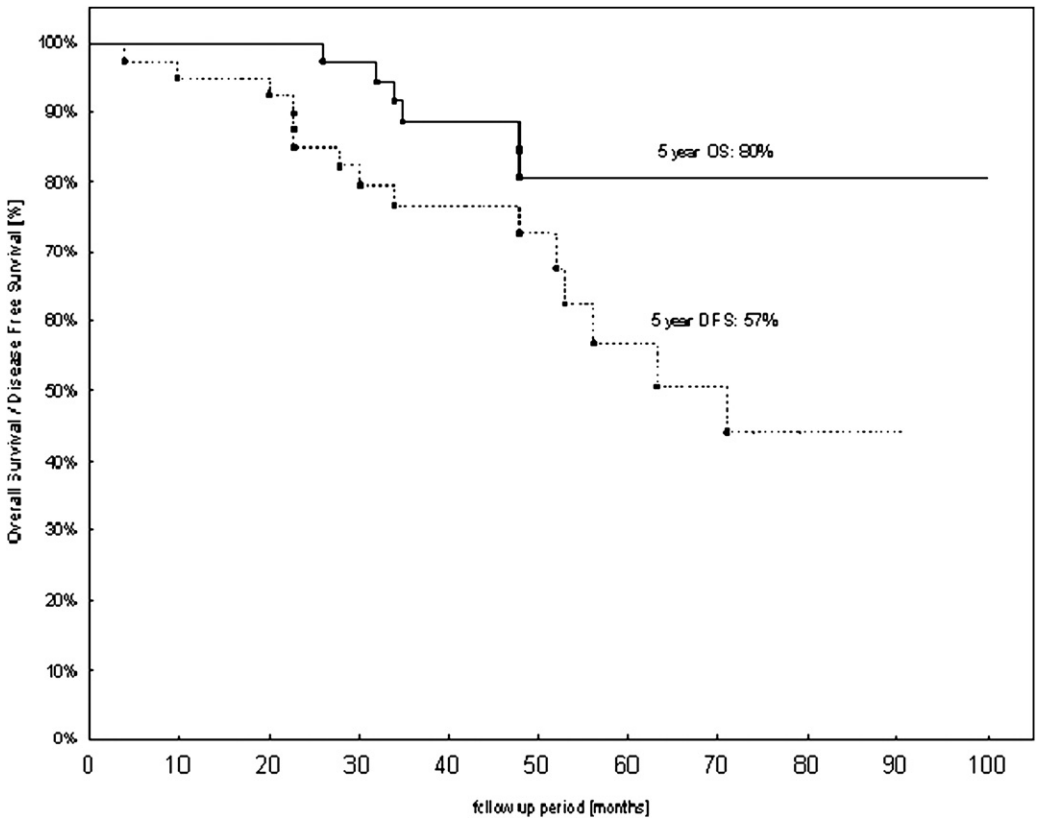

Fig. 3. Overall survival (OS) and disease-free survival (DFS) in 40 patients with extracranial chordoma following spot-scanning-based proton therapy.

Gender affected 5-year OS. Five of six deaths occurred in female patients. Five-year OS in female patients was 62% and significantly lower compared with male patients (92%; $p = 0.015$).

Dosimetric characteristics

The dosimetric characteristics of the entire patient cohort are summarized in Table 3. The mean administered total dose was 72.5 Gy(RBE). All patients were treated with single doses per fraction of 1.8 or 2 Gy(RBE). The administered mean dose in patients without surgical stabilization was 73.4 Gy(RBE) and 71.8 Gy(RBE) in patients with surgical stabilization and did not differ significantly ($p = 0.160$). The administered dose in patients with complex SS did also not differ significantly ($p = 0.914$) compared with patients with either ventral or dorsal instrumentation only. There was no evidence of significantly reduced prescription dose in patients with local failure compared with patients without local failure ($p = 0.234$).

The dosimetric characteristics (V80% and V95%) of 31 patients treated with protons exclusively are summarized in Table 3. In this cohort, prescribed dose was not significantly reduced in patients with SS ($p = 0.215$). None of the parameters studied, *i.e.,* neither V95 nor V80, were significantly different in patients with SS compared with patients without SS.

Adverse events

Acute: All patients completed treatment as intended. One patient treated for cervical spine chordoma developed moderate Lhermitte's sign 4 weeks after PT. It resolved spontaneously after several weeks. No other unexpected and no high-grade acute adverse events were observed.

Late: No high-grade (≥ Grade 3, CTCAE v3.0) neurotoxicity, kidney, or bowel toxicities were observed. Two Grade 3 late adverse events occurred: one patient with extensive surgical resection and insertion of surgical stabilization had received 71 Gy(RBE) postoperatively. He developed osteonecrosis (Grade 3) of an irradiated lumbar vertebra at 13 months and required surgical intervention. At the time of analysis, this patient had no neurological deficits, was free of disease, and was able to conduct daily activities.

A second patient with a large sacral chordoma experienced >3 years after PT a subcutaneous fistula in the sacral region and required several wound debridements. The patient died at 4 years from a treatment-induced second malignancy. He developed a leiomyosarcoma of the urinary bladder diagnosed 49 months after mixed photon/proton therapy for a sacral chordoma. A dose of 50.4 Gy had been delivered with photon RT, followed by 24 Gy(RBE) proton boost. The bladder had been included in most of the photon fields and had received approximately 40 to 50 Gy photon RT. The contribution to bladder dose by protons was comparably small—<1% of the prescription dose, or <0.24 Gy(RBE). Overall, we concluded that this event was most likely due to RT rather than PT, although we are aware that even small radiation doses may induce malignancy. Ultimately we classified this death as therapy-related death from second malignancy.

Table 3. Prescribed dose, V95 (%), V80 (%) of 31 chordoma patients treated with spot-scanning-based proton therapy exclusively at Paul Scherrer Institute

Characteristics	All	No SS	SS	*p* value
Total	31	14	18	
Prescribed dose				
Mean	72.8	73.5	72.2	0.215
Median	74.0	74.0	73.5	
Range	59.4–75.2	70.0–74.0	59.4–75.2	
V95 (%)				
Mean	79.4	79.3	79.4	0.936
Median	80.8	81.7	78.4	
Range	54.4–97.1	55.5–96.2	54.4–97.1	
V80 (%)				
Mean	94.8	95.1	94.5	0.704
Median	95.9	95.3	96.2	
Range	81.0–100	88.2–99.9	81.0–100.0	

Abbreviation: SS = surgical stabilization.

DISCUSSION

High-dose proton radiotherapy in a multidisciplinary approach can accomplish tumor control in a high proportion of patients with extracranial chordomas. In our series, PT yielded best results (100% local control at actuarial 5 years) in the following subgroups of patients:

1. patients with or without prior resection but without SS or major reconstruction.
2. the subgroup of patients with evidence of gross disease before PT but without a surgical approach requiring SS. These patients may or may not have had prior tumor resection for purposes of debulking or decompression.

Surgical resection resulting in the need to stabilize the spine by use of multiple instrumentations yielded less favorable results, even when gross total tumor resection was accomplished.

Our results (14) are consistent with the experience at Massachusetts General Hospital (MGH). De Laney *et al.* (11) reported a 5-year actuarial LC of 78% for patients with spinal and paraspinal sarcomas (29/50 patients with chordoma).

Because of the higher RBE compared with protons, there is also a strong interest in using carbon ions in treatment of paraspinal sarcomas. Kamada *et al.* (19) reported on 19 patients with unresected bone and soft-tissue sarcomas treated with carbon ions at National Institute of Radiological Sciences, Japan (NIRS), Japan. Local control rates in patients receiving ≥64 GyE were significantly higher than rates for those receiving 52.8–57.6 GyE (84% at 3 years vs. 53% at 3 years, respectively). In 17 patients treated up to 73.6 Gy(RBE), no acute adverse events were observed except Grade 3 skin toxicity in seven patients. Comparing carbon-ion with proton therapy

data, the overall 3-year LC rates of 73% at the NIRS facility with carbon ions are similar to our outcomes data of 75% obtained with spot-scanning based protons.

High-dose radiation therapy of extracranial chordoma with spot-scanning-based protons was well tolerated. During long-term follow-up, we did not observe any late neurologic adverse events. This is consistent with the MGH experience. Using similar dose constraints to spinal chord surface of 63 Gy(RBE) and to the spinal cord center of 54 Gy(RBE), DeLaney *et al.* (11) did not report any high-grade spinal cord late toxicities. However, they did observe Grade 3 nerve root toxicities in the sacrum in patients treated at doses of 77.12–77.4 Gy(RBE) and calculated a high-grade toxicity threshold dose of >70.2 Gy(RBE) to nerve roots. We did not observe any nerve root toxicity in our cohort, which received a slightly lower median prescribed dose of 74 Gy(RBE) compared with the MGH series, which received 76.6 Gy(RBE). Our data are consistent with prior work by Pieters *et al.* (20) evaluating cauda equina tolerance at the MGH.

The amount of unresected residual tumor volume in patients with skull-base chordoma before the start of PT has been found to be of prognostic value (10, 21).

In our series of extracranial chordomas, the presence of gross residual disease before PT has also been identified as a prognostic factor for LC. Eight failures were diagnosed in 19 patients with residual disease prior to PT resulting in 5-year actuarial LC rate of 47%. However, seven of these eight patients with local failure and residual disease had additional SS. Eight patients with residual disease had no additional surgical stabilization, and only one patient had a local failure after 71 months. None of the patients with GTV but without SS had failed at actuarial 5 years. Although residual tumor size might be an influence, our numbers indicate excellent LC even in view of large residual disease. This raises the question of benefit of additional surgery, if such surgery would require insertion of SS.

Overall, we found a reduced LC rate in patients with SS. Twelve failures in 21 patients with SS resulted in a 5-year actuarial LC rate of 30%. Nonetheless, we could achieve an extremely high 5-year LC rate of 100% in patients without SS and gross residual disease. Despite the inability to perform multivariate analysis, our findings indicate a relationship between surgical stabilization and the probability of recurrence of extracranial chordomas following PT.

A higher rate of local recurrence in patients with metallic, spine-stabilizing implants was also reported by the MGH group (11), although the difference did not reach statistical significance. In this series, 5 of 16 patients (31%) with spine stabilization hardware suffered local recurrences vs. 4 of 34 (12%) patients without such hardware. According to the authors, 15 of 16 patients (11) with metallic implants had tumors at the thoracic or lumbar level where the proximity of the spinal cord and cauda might make wide resection and radiation delivery more challenging than in the sacrum. Hence, DeLaney *et al.* (11) contributed the difficulties to plan and deliver radiation treatment in patients with SS to the anatomical level of disease.

The presence of titanium-based metal inside the target volume can potentially affect various levels of accuracy—for example, the physician's ability to delineate accurately the target volume because of artifacts and for the treatment plan to accomplish the goals of homogeneous target coverage. We were not able to identify a difference in target dose or target coverage based on dose–volume histogram analysis depending on presence or absence of metal.

As to other potentially prognostic factors, the role of patient's sex in the prognosis of chordomas remains unclear. The MGH series (22) revealed a better 5-year local control for male compared with female patients with skull-base chordomas. In our previous publication on skull base chordomas, we observed a insignificant trend for decreased local control in women (21). In our present series, sex did not influence 5-year LC and DFS. However, in our series of extra-cranial chordomas, sex did affect 5-year OS. In our series of extracranial chordomas, 5 female and 8 male patients developed a local failure. Four of five female patients with local failure died from local tumor progression, whereas none of the male patients died from local tumor progression or metastatic disease. Therefore, 5-year OS in female patients (62%) was significantly lower compared with male patients (92%). At present, we cannot explain this difference. Ultimately, it is expected that the majority of patients with local failure will succumb to their disease, in which case there will be no statistically significant gender difference. Halperin *et al.* (23) suspected that sexual hormone receptors might be an influencing factor in adults with chordomas and that genetic factors could play a role in clinical outcome.

CONCLUSION

Five-year results of this study indicate the safety and efficacy of spot-scanning-based PT for paraspinal tumors—specifically, extracranial chordomas. Actively scanned proton delivery achieves high rates of local tumor control in patients with extracranial chordomas even in view of large, unresectable disease. Local control was significantly better in patients without SS. It is hoped that further analysis based on additional patients and longer follow-up will clarify whether SS is indeed an independent prognosticator or a surrogate for more advanced disease.

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