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EXTRACRANIAL CHORDOMA: OUTCOME IN PATIENTS TREATED WITH FUNCTION-PRESERVING SURGERY FOLLOWED BY SPOT-SCANNING PROTON BEAM IRRADIATION

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Purpose: To evaluate the use of postoperative proton therapy (PT) in extracranial chordoma.
Patients and Methods: Twenty-six patients were treated. Gross total resection was achieved in 18 patients. Nine patients had cervical, 2 had thoracic, 8 had lumbar, and 7 had sacro-coccygeal chordomas. Thirteen patients had implants. PT was administered after function-preserving surgery, using a gantry and spot scanning, without or with intensity modulation (IMPT; 6 patients), and/or photon-based radiotherapy (RT, 6 patients). Median total dose was 72 cobalt Gray equivalent (CGE; range, 59.4–74.4), with means of 70.5 and 73.2 CGE for patients with and without implants. Median follow-up time was 35 months (range, 13–73 months). Adverse events were scored using the Common Terminology Criteria for Adverse Events grading system (version 3.0).
Results: At 3 years, actuarial overall survival (OS) and progression-free survival (PFS) rates were 84% and 77%, respectively. One patient each died of local failure (LF), distant failure (DF), suicide, and secondary tumor. We observed 5 LFs and 3 DFs; 3-year LF-free and DF-free survival rates were 86%. We observed four radiation-induced late adverse events (Grade 2 sensory neuropathy; Grade 3 subcutaneous necrosis, and osteonecrosis; and Grade 5 secondary cancer). In univariate analysis, implants were associated with LF ($p = 0.034$). Gross residual tumor above 30 mL was negatively associated with OS ($p = 0.013$) and PFS ($p = 0.025$).
Conclusions: Postoperative PT for extracranial chordomas delivered with spot scanning offers high local control rates. Toxicity was acceptable. Implants were significantly associated with LF. Residual tumor above 30 mL impacted negatively on OS and PFS. © 2007 Elsevier Inc.

Chordoma, Proton beam therapy, Spot scanning, Extracranial tumors.

INTRODUCTION

Chordomas originate in the skull base as well as in extracranial sites: in the entire spine, the sacrum, and the coccyx. They arise from remnants of the embryonic notochord (1, 2). The annual incidence rate is low, approximately 0.1/100,000 (3). Chordomas consequently develop in close contact with important anatomic structures, such as the optical apparatus, brainstem, spinal cord, and cauda equina, lungs, and bowels. Complete resection is extremely challenging, and chordomas are not particularly sensitive to radiation treatment (4). After photon-based radiotherapy (RT) with doses up to 40–60 Gy, reported 5-year local control rates remained below 20% (5–9). To improve these unacceptable results, several strategies have been proposed, such as radical en bloc resection for extracranial tumors (10, 11) as well as radiation dose escalation, because of a known dose–response effect (12, 13).

Treatments with hadrons, using protons, helium, carbon, or neon ions, are distinctly more target-selective than RT as a result of the physical properties of charged particle beams, which end in a Bragg peak. Hadron beams are characterized by depth dose distributions having a low-dose entrance region, a region of homogeneous high dose at the target volume followed by a steep fall-off to no measurable dose. This allows for the delivery of higher doses to the target volume, because nontarget volumes are spared effectively. The use of proton therapy (PT) for chordoma has been pioneered at the Massachusetts General Hospital in Boston, using the Harvard Cyclotron Laboratory for beam delivery (14–16). PT and other hadron beams have also been used at

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Table 1. Overview of outcome of high-dose charged particle radiation treatment for chordoma (≥60 CGE); Surgical treatments varied widely

Study First author, year (ref.)	Patients included	Type of irradiation	Dose* CGE	Local control (%) 3-year	(%) 5-year	(%) 10-year
Skull-base and proximal cervical spine						
Castro, 1994 (17)	53	Helium, Neon	65		63	
Terahara, 1999 (18)	115	PT, RT	69		59	44
Hug, 1999 (19)	58	PT, RT	71	67	59	
Noel, 2003 (20)	67	PT, RT	67	71		
Schulz-Ertner, 2003 (21)	67	Carbon, RT	60	87		
Igaki, 2004 (22)	13	PT, RT	72	67	46	
Weber, 2005 (23)	18	PT, RT	74	87		
Mobile spine, sacrum and coccyx						
Schoenthaler, 1993 (24)	14	Helium, Neon	76		55	23

Abbreviations: PT = proton beam therapy; RT = conventional photon radiotherapy.

* Doses indicated are medians or means as indicated by the authors, depending on the study. We accepted estimates of relative biologic effectiveness of hadron beams as applied by the authors. Doses of treatments with heavy charged particles (carbon, helium, neon ions) are not corrected for dose per fraction, which varied. We use cobalt Gray equivalent (CGE) to express the cumulative doses of proton beam therapy, intensity-modulated proton beam therapy, and RT in this study.

several other centers in California, Europe, and Japan (17–24). The use of hadron beams for radiation therapy allowed substantial improvements in outcome at the skull base, as well as extracranial chordomas in the proximal cervical spine, sacrum, and coccyx (Table 1).

Based on these findings and availability of a gantry with a novel spot-scanning system at our institute (25), we started a program of PT for cranial (23) and extracranial chordomas. The goals of the present study were to analyze outcomes of the latter tumors and acute and late toxicity after PT using spot scanning, with or without intensity modulation (IMPT). RT was selectively used as a result of the schedule constraints at Paul Scherrer Institute or because of referrals after initiation of RT. As a rule, we aimed at avoiding RT, however.

PATIENTS AND METHODS

Patients

Between October 1999 and December 2003, 26 cases were treated at Paul Scherrer Institute using dynamic spot scanning. Patients were referred after surgery from 19 centers in Europe. Eight patients had residual chordoma masses smaller than 500 mL that were deemed not to be amenable to further resection (range, 13–433). Two patients were also treated with palliative intent for nonresectable tumors larger than 1000 mL. However, they are not part of this analysis. No patient was referred with a mass between 500 and 1000 mL. Median age was 49 years (range, 10–81 years). Children able to fully cooperate were accepted. Three children aged 10, 11, and 14 years were treated. All but 1 patient had typical chordoma. The remaining patient had a chondroid chordoma, a less malignant subtype (26). Additional patient characteristics are shown in Table 2. Informed consent was obtained from all patients. Legal representatives gave consent for children.

Surgery

Maximally possible tumor removal without damaging the spinal cord or cauda equina was recommended. Resection was macroscopically complete in 18 patients and subtotal in 8 (Table 2). In 2 of these 8 cases, the remaining gross tumor volume (GTV) was small (≤30 mL; namely, 13 and 25 mL, respectively) and large in 6 (>30 mL; range, 34–433). All patients were referred after their last surgery. Implants were used for stabilization after extensive resections in 13 of the 26 patients (50%). Three patients respectively have had surgeries for 1, 2, and 3 local recurrences after surgical treatment alone, before they were referred for PT.

Patient positioning, volume definitions, and radiotherapy planning

Patients were positioned in individually tailored whole body vacuum casts. For treatment in the cervical region, patients were positioned in the supine position, with a vacuum-bite block, like the patients treated for a lesion in the skull base (23), otherwise in the

Table 2. Patient characteristics

	Male	Female	Total
Gender	14	12	26
Chondroid subtype	1	0	1
Gross total resection	9	9	18
Minor residual macroscopic disease (≤30 mL)	2	0	2
Large macroscopic disease (>30 mL; range, 34–433)	3	3	6
Implants	6	7	13
Age younger than 40 y	2	6	8
Age younger than 20 y	1	2	3
Surgery for recurrence (prior to PT, IMPT, RT)	0	3	3
Location			
Cervical spine	2	7	9
Thoracic spine	2	0	2
Lumbar spine	4	4	8
Sacrum and coccyx	5	2	7

Abbreviations: PT = proton beam therapy; IMPT = intensity-modulated PT; RT = conventional photon radiotherapy.

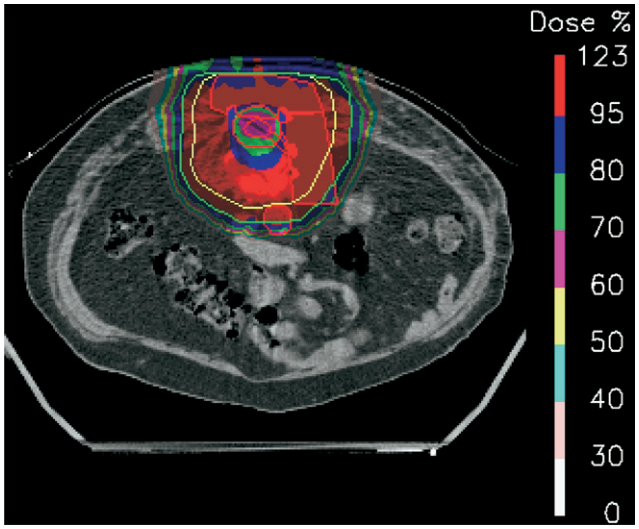

Fig. 1. Midplane dose distribution of a case irradiated postoperatively for lumbar chordoma. Prescribed dose (100%) corresponds to 45.5 CGE which was delivered in fractions of 2.0 CGE (conventional proton therapy) and 2.5 CGE (intensity-modulated proton therapy) with selective sparing of the cauda equina. Dose per fraction to the cauda never was higher than 2.1 CGE. The remainder of the treatment was delivered with radiotherapy for reasons detailed in the text. The green line outlines the planning target volume, and the yellow line the clinical target volume. Red lines mark anatomic structures, technical volumes, and a volume drawn manually to compensate for artifacts in the planning computed tomography.

prone position, as described previously (27). The patient-positioning verification relies on computed tomographic (CT) images performed outside the treatment room before every daily treatment. These CT images are made in topogram mode (scout view). These CT data are then transferred to an in-house algorithm developed at Paul Scherrer Institute and compared with the planning images which are used as references. With the immobilization devices implemented at our institution, it is possible to have a positioning reproducibility within 1–3 mm for the cervical spine and 3–8 mm for thoracic/abdominal/pelvic cases, respectively (Alessandra Bolsi, unpublished data).

The GTV was defined as the macroscopic residual tumor for subtotally resected patients ($n = 8$). The presurgery tumor bed with (subtotal resection, $n = 8$) or without GTV (total resection, $n = 18$) plus the dorsal surgical pathway, but not the transabdominal pathway, was defined as the clinical target volume (CTV). It comprised tissues in contact with chordoma, and volumes occupied by implant material, where present. The planning target volume (PTV) was defined as the CTV plus a margin of 5–10 mm in three dimensions for noncervical chordomas. For cervical chordomas, a margin of 3–5 mm was implemented.

Implant-associated CT artifacts were corrected manually as previously described (27); anatomic structures were outlined and assigned an estimated density in Hounsfield units. A representative case is shown in Fig. 1. Implants also cause difficulties in treatment planning and unavoidably, inhomogeneities—in other words, hot spots and cold spots (27).

Proton therapy and IMPT planning was performed with "PSIplan", a software developed at our institute and previously described (23, 27, 28). RT planning (6 patients, Table 3) was performed by the referring institution.

Radiation modalities

All patients were treated with PT. Six patients received IMPT to improve target dose coverage for targets with challenging geometrics or penetrated by an organ at risk. RT was acceptable for a part of the treatment if it was unavoidable, *i.e.*, for patients who were referred late (RT had already been started at the referring institution), or if the annual accelerator shutdown at Paul Scherrer Institute obliged us to complement PT with RT. Six patients hence were treated with RT; 20 patients hence received PT alone, with or without IMPT (Table 3). For PT, only part of the fractionated treatment was delivered using IMPT. For the 6 IMPT patients, the median dose delivered with this technique was 45 CGE (range, 37.5–54). The remainder of the treatment was delivered with PT (5 cases) and PT and RT combined (1 case).

Units, doses, fractions

With international agreements on proton beam dose description still pending, we express proton doses in ^{60}Co Gy equivalents (CGE; 1 CGE = 1 Gy × 1.1) (29, 30). RT doses are given in Gy, cumulative doses in CGE (1 Gy = 1 CGE). We aimed at 72–74 CGE delivered in 36–37 fractions of 2 CGE, 4 PT fractions per week owing to limited beam availability; 5 weekly fractions of 2 Gy were delivered in RT. Where bones or implants caused hot spots above 120% of the reference dose, we treated in fractions of 1.8 CGE, and up to 72 CGE (40 fractions), as described (27). One case, however, was treated with 4 fractions of 2 CGE and 15 fractions of 2.5 CGE because of imminent annual accelerator shutdown. When the PTV was treated with 2.5 CGE/fractions in this case, the dose to the center of the cauda equina was restricted to 2 CGE/fractions using IMPT (Fig. 1). Treatment was subsequently completed with RT at the referring institution (26 Gy, 13 fractions), to a total dose of 71.5 CGE.

Table 3. Uses of conventional radiotherapy for the treatment of extracranial chordoma. RT was used for various reasons, specifically, due to late referral (five cases) and because of annual accelerator shutdown (one case)

RT before PT, IMPT (doses, Gy)	PT (doses, CGE)	IMPT (doses, CGE)	RT after PT, IMPT (doses, Gy)	Total doses* (CGE)
20 × 2 = 40	11 × 2	no	no	62
27 × 2 = 54	11 × 1.8	no	no	73.8
24 × 2 = 48	12 × 2, 2 × 1.5	no	no	71
27 × 2 = 54	12 × 2	no	no	72
10 × 2 = 20	27 × 2	no	no	74
no	4 × 2	15 × 2.5	13 × 2	71.5

Abbreviations: RT = radiotherapy; PT = proton therapy; IMPT = intensity-modulated proton therapy.
* We use CGE to express the cumulative doses of PT, IMPT, and RT in this study.

Dose constraints

Applicable dose constraints were 63 CGE to surface brainstem in patients irradiated in the upper cervical spine, as in treatment for skull base chordomas (23), and 54 and 64 CGE, respectively, for center spinal cord and center cauda equina, based on estimates for RT-associated risks (31). Caudally to the fifth lumbar vertebra (L_5), full dose delivery was allowed. Other dose constraints were not applicable in our cohort, because of the steep lateral and distal dose gradients and small volumes of other organs at risk that were irradiated.

Follow-up evaluation

Patients had clinical and radiologic examinations 6 weeks after RT and at 3-month to 6-month intervals for 2 years, yearly thereafter or as clinically indicated. Follow-up was carried out by the referring physicians. The observation period for this report ended on October 5, 2005. No patient was lost to follow-up.

Statistical analysis

Kaplan-Meier curves (32) with log–rank tests and univariable Cox proportional hazard models were used for times-to-event analyses calculated from the beginning of PT until the date of last follow-up or the date of the event, whichever occurred first. The following events were considered: all causes of death for overall survival (OS); death or progressive disease for progression-free survival (PFS); local failure (LF) defined as radiologically documented tumor progression at the irradiated site on two consecutive examinations or as documented progression causing clinical symptoms; and distant failure (DF), defined as radiologically documented appearance of metastatic disease. We had also included marginal failure, recurrence at the rim of the PTV, in our initial analysis. However, we were unable to identify even one such event and concluded that implant-associated artifacts in CT and MRI may have severely interfered with the capacity to detect small marginal failures without clinical impact, before they would extend toward the PTV, manifesting clinically as LF.

Acute adverse events were defined as symptoms occurring during or within 90 days of RT; later events 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 (33).

Statistical analysis was performed with Stata 9.1 software (Stata Corp., College Station, TX). With only 26 patients studied, multivariable models were not feasible. We analyzed the following co-variables for clinical endpoints: gender, age above vs. below 40 years, GTV above vs. below 30 mL, PTV above vs. below 615 mL, total dose above vs. below 71 CGE, and the presence vs. the absence of implants.

RESULTS

Target volumes, doses

Planning target volumes ranged from 11.4 to 1900.9 mL (median, 615 mL). Mean PTV was 943 mL in the patients with an implant (range, 23.4–1900.9) and 823 mL in patients without (range, 11.4–1271.8). Median delivered dose was 72 CGE (range, 59.4–74.4). Prior RT or hotspots of proton dose in the spinal cord restricted the total combined radiation dose that could be delivered to less than 70 CGE in 3 cases (59.4, 62.0, and 69.4 CGE) because the dose constraints to the spinal cord were reached. All 3 patients had implants. The other 23 patients were treated to at least 70 CGE, 97.2% of 72 CGE. Mean total doses were 70.5 and 73.2 CGE in patients with and without implants, respectively. Implant-associated hot spots in the center of the spinal cord as well as prior RT were the reasons for lower total dose.

Outcomes

Median follow-up time for all patients was 35 months (range, 13–72 months), 49 months for patients treated without IMPT (range, 19–72 months), and 24 months with IMPT (range, 13–35). Median follow-up time was also 49 months for patients with and without implants.

Four patients have died: 1 patient died of LF in the upper cervical spine 22 months after PT, and 1 patient of distant metastasis, without an LF component 26 months after PT. One patient committed suicide 32 months after PT. This patient had presented with an LF in the lumbar spine and was consequentially paralyzed, as well as with DF at various sites. One of them, a painful lesion in the tibia and right below the knee, was managed surgically before the onset of paralysis. We classified this death as disease-related because we judged the patient to be terminally ill from her metastatic disease. Finally, 1 patient died of treatment-induced metastatic secondary cancer, a leiomyosarcoma of the urinary bladder, diagnosed 49 months after combined RT/PT irradiation for a sacral chordoma. A dose of 50.4 Gy had been delivered with RT, followed by 24 CGE delivered with PT. We therefore also classified this death as disease-related, death from secondary cancer—a Grade 5 adverse event. Of note, the PT dose delivered to the bladder of this last patient was well below 1%. Therefore, we concluded that this event was probably caused by RT, rather than PT, although it is known that even small radiation doses may cause cancer. The actuarial 3-year OS was 84% (95% confidence interval [CI], 67–100).

Five patients developed an LF. No recurrence was observed in any surgical pathway. All 5 patients with an LF had titanium implants ($p = 0.034$, Table 4). Two of them were treated with less than 70 CGE (62.0 and 69.4, respectively) and had an LF at 56 and 63 months, respectively. Three other patients developed LF at 4, 20, and 24 months of follow-up and were treated with high radiation doses (74, 72, and 72.8 CGE, respectively). Within the observation period, 3 of these 5 patients have developed paraplegia or tetraplegia resulting from the LF. Of note, the third patient treated with a dose below 70 CGE/Gy had no failure for up to 37 months (dose: 59.4 CGE). Estimated 3-year PFS and local control (LC) rates were 77% (95% CI, 59–95) (Fig. 2) and 86% (95% CI, 62–95), respectively. Remarkably, 3-year LC was 100% for the patients without an implant (95% CI, not applicable) and 69% (95% CI, 30–89) for the patients with an implant (Fig. 3), respectively. On univariate analysis, only implants (yes vs. no) ($p = 0.03$; Table 4) were a significant predictor for LF.

Noteworthy, all patients without an LF maintained their full independent status. Specifically, they retained control over bladder and anal sphincter functions, which remained stable after recovery from surgery, and they were able to

Table 4. Univariate analyses (log–rank test)

	Location HR (95% CI)	Gender male vs. female HR (95% CI)	GTV > 30 mL HR (95% CI)	PTV > 615 mL HR (95% CI)	Age <40 years HR (95% CI)	Total dose* >71 CGE HR (95% CI)	Implants yes *vs.* no HR (95% CI)
OS	NA	0.22 (0.022–2.1)	10 (1.1–98)	1.1 (0.15–7.7)	3.1 (0.43–22)	NA	1.2 (0.16–8.3)
4 events	$p = 0.87$	$p = 0.15$	**$p = 0.013$**	$p = 0.93$	$p = 0.24$	$P = 0.094$	$p = 0.89$
PFS	NA	0.75 (0.15–3.8)	6.1 (1.01–36)	2.2 (0.40–11)	1.4 (0.3–7.7)	3.6 (0.40–32)	2.2 (0.40–12)
7 events	$p = 0.48$	$p = 0.72$	**$p = 0.025$**	$p = 0.36$	$p = 0.71$	$P = 0.23$	$p = 0.36$
LF	NA	0.88 (0.12–6.4)	1.8 (0.16–19)	1.1 (0.16–8.1)	2.8 (0.38–21)	1.9 (0.18–20)	NA
5 events	$p = 0.13$	$p = 0.90$	$p = 0.64$	$p = 0.90$	$p = 0.29$	$P = 0.58$	**$p = 0.034$**
DF	NA	0.37 (0.033–4.1)	1.8 (0.16–19)	2.4 (0.22–27)	1.4 (0.13–16)	NA	2.2 (0.20–25)
3 events	$p = 0.37$	$p = 0.39$	$p = 0.64$	$p = 0.46$	$p = 0.79$	$P = 0.25$	$p = 0.50$

Abbreviations: HR = hazard ratio; CI = confidence interval; GTV = gross tumor volume; PTV = planning target volume; OS = overall survival; PFS = progression-free survival; LF = local failure; DF = distant failure; NA = not assessable (HR estimation impossible due to missing events in one group).

Significant p values are shown in boldface.

* We use cobalt Gray equivalent (CGE) to express the cumulative doses of proton therapy, intensity-modulated proton therapy, and radiotherapy in this study.

walk and use their arms and hands without significant functional impasse. The GTV in the 5 patients with an LF was 0 mL in 3 cases and 13 and 34 mL, respectively, in the remaining 2 cases. GTV was not associated with LF (hazard ratio 1.8; 95% CI, 0.16–19.0; $p = 0.64$, Table 4). GTV (≤30 mL vs. >30 mL), however, influenced OS and PFS (Table 4). The 3-year OS and PFS rates were 92% (95% CI, 54–99) and 87% (95% CI, 56–96) in the ≤30 mL volume group vs. 53% (95% CI, 7–86) and 67% (95% CI, 19–90) in the >30 mL volume group ($p = 0.01$ for OS and $p = 0.03$ for PFS, respectively).

Three patients presented with DF, both with ($n = 2$) or without ($n = 1$) a LF component. The three-year DF-free survival rate was 86% (95% CI, 76–100), corresponding to a metastasis incidence of 14% (95% CI, 0–24). No DF was observed later than after 3 years.

Tumor location ($p = 0.13$), gender ($p = 0.9$), PTV ($p = 0.34$), and age ($p = 0.29$) were not significantly associated with LF. Similarly, tumor location ($p = 0.9$ for OS and $p = 0.5$ for PFS), gender ($p = 0.2$ for OS and $p = 0.7$ for PFS), PTV ($p = 0.9$ for OS and $p = 0.4$ for PFS), age ($p = 0.2$ for OS and $p = 0.7$ for PFS), total dose ($p = 0.2$ for PFS)

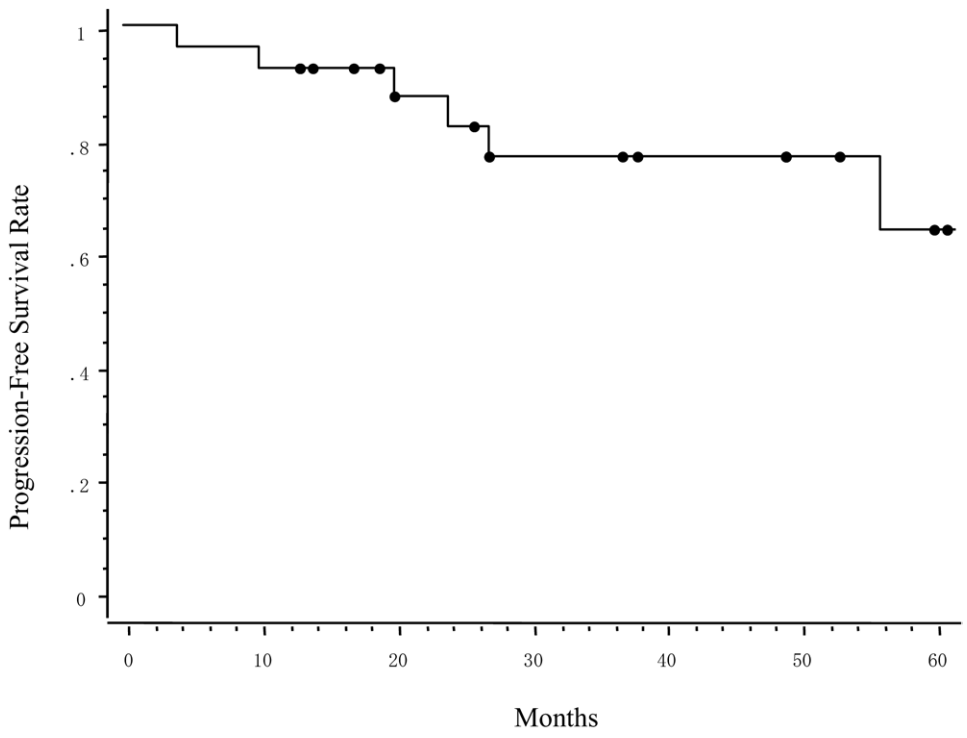

Fig. 2. Progression-free survival of 26 patients who underwent optimal resection preserving the spinal cord and cauda equina functions followed by proton therapy, with or without intensity-modulated proton therapy/radiotherapy.

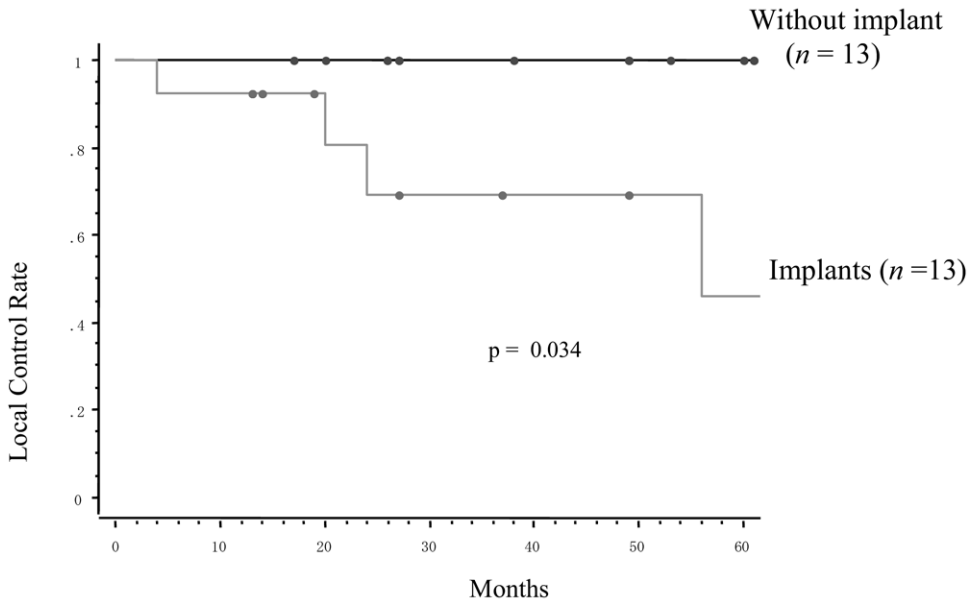

Fig. 3. Local control in patients with an implant as compared to without implant in patients who underwent optimal, spinal cord, and cauda equina preserving resection of chordoma followed by postoperative proton therapy. A total of 5 local failures was observed in this cohort (1 last failure after 63 months is not shown). All failures occurred in patients with an implant ($p = 0.034$).

and implants ($p = 0.9$ for OS and $p = 0.4$ for PFS) were not significantly associated with OS or PFS (Table 4). Noteworthy, total dose was of borderline significance for OS ($p = 0.09$). None of the studied co-variables was associated with the risk of distant metastasis (Table 4).

Adverse events

All patients completed treatment as intended. Acute side effects included Grade 1 to 4 skin reactions (Grade 4, 1 case), as well as Grade 1 to 3 mucosal reactions in the 7 patients treated in the proximal cervical spine. One patient treated in the cervical region developed moderate Lhermitte's sign 4 weeks after PT. It persisted for a few weeks, then spontaneously resolved (Grade 1). No other acute adverse event was reported, except mild (Grade 1) fatigue.

Treatment-related late adverse events were reported in 4 cases. One patient (73.8 CGE) required surgery for necrotic subcutaneous tissue (Grade 3) at 18 months after PT; 1 patient (71 CGE) required surgery for osteonecrosis (Grade 3) of irradiated lumbar vertebrae at 26 months after PT. One patient irradiated in the cervical spine (74 CGE) developed sensory neuropathy in the left arm and mild skin fibrosis 17 months after PT (Grade 2 and 1 events, respectively). One patient succumbed to treatment-induced secondary cancer in the urinary bladder, where it had been irradiated with photons, clearly outside the proton field (Grade 5).

DISCUSSION

Radiotherapy with hadrons occupies a pivotal role in the treatment of chordomas. The results of the present study, which is limited however by small numbers and short follow-up, suggest that postoperative spot-scanning PT, without or with IMPT, achieves high tumor control rates for extracranial chordomas. The 3-year local control rate of 86% observed in our cohort is considerably higher than any previously published LC rates after RT alone or surgery with or without postoperative RT, for this tumor entity. The preliminary estimates after 5 years are 69% for LC (data not shown), 100% in patients without an implant (Fig. 3). These are also encouraging: All nonhadron series report 5-year LC rates below 20% (5–9). In patients treated with stereotactic RT in the skull base and proximal cervical spine with a median dose of 67 Gy, LC after 5 years was 50% (13) in a German series. This is comparable to the estimated LC rate we found in patients with surgical implants (46%, Fig. 3). However, our median follow-up time is only 35 months and any 5-year estimate therefore remains highly provisional. The findings (LC of 86%) compare favorably to previously published 3-year results of hadron therapy for chordoma located in the skull base and proximal cervical spine, sacrum, and coccyx, which are in the range of 67–87% (Table 1).

The toxicity associated with postoperative PT using spot scanning was acceptable. Although the administered doses were high (median dose, 72 CGE), treatment was well tolerated. Two Grade 3 late adverse events were observed (subcutaneous, and bone necrosis) in this series, which were successfully managed with surgery. Neurologic symptoms (sensitive neuropathy Grade 2) developed in 1 case, suggesting that the center of the spinal cord and cauda equina dose constraints applied here are reasonably safe. Marucci *et al.* recently reported that dose constraints of 55 to 58 CGE in the center of the cervical spinal cord are safe (31), which is just above our slightly more conservative constraint of 54

CGE for the entire cord. Marucci *et al.* made a point that this tolerance is dependent on a significant sparing at the distal edge of the cord. This was not a factor studied here.

In this small series, surgical implants were a significant ($p = 0.034$) risk factor for LF (Fig. 3). It is noteworthy that the follow-up of patients with and without implants were essentially the same (median, 49 months), avoiding a lead-time bias in the analysis. Surgical implants hence appear to be associated with an inordinately high rate of LF. This observation raises some interesting technical issues. Several factors may contribute to an increased risk of failure in patients with an implant. These include but are not limited to: (*1*) biologically more aggressive nature or more advanced initial clinical presentation of tumors requiring vertebral resection and implant material for stabilization; (*2*) technical difficulties in removing tumor tissue, while sparing spinal cord and cauda equina, followed by the installation of implant material; (*3*) artifacts in CT and magnetic resonance imaging datasets, with difficulties to plan radiation treatment, including target definition, as well as dose delivery; (*4*) dose inhomogeneities caused by implants; and (*5*) reduced dose per fraction (1.8 CGE instead of 2.0 CGE) and total doses (means, 70.5 vs. 73.2 CGE) due to implant-associated hot spots; (*6*) implant-associated cold spots.

Our major concern is that tissue inhomogeneities and artifacts in the CT dataset used in planning, such as those induced by implants, modify the proton range and could cause serious underdosage of the PTV as well as to hot spots in critical structures. The ability to accurately map these density heterogeneities is thus of paramount importance. As for planning of three-dimensional conformal treatments, CT data are an essential prerequisite in PT. For planning purposes, a conversion of CT numbers (Hounsfield units) to electron density must be performed. If this conversion is perverted by major artifacts, the range-modifying effects of inhomogeneities become a real issue. Although PT is the optimal treatment for chordoma, this technique has a number of potential shortcomings for patients with implants that must be carefully considered.

We are currently looking into whether correcting densities improves this problem and, more importantly, what cutoff Hounsfield units values should be implemented for the stopping power of titanium. Yet, to break new ground, alternative strategies are probably required for these patients. First, preoperative PT could be recommended to patients with large tumors requiring potential surgical implants. This strategy obviates the need to correct the CT densities during the PT planning and would possibly allow for reduced CTVs (and consequentially, PTVs) as the potential tumor-seeding by the surgeon would be less of an issue. Second, if preoperative PT is not feasible, the use of megavoltage CT could indeed reduce the reconstruction artifacts associated with implants (34), when compared with diagnostic (kV) CT. A potential disclaimer, however, is the low detective quantum efficiency which leads to poor low contrast resolution and high image noise. This consequentially makes the identification of normal tissues and identification of tumor (residual chordoma) volume more difficult, although it may be less difficult in the vicinity of nontarget structures with lower or higher densities (35), such as chordomas abutting the spinal axis. Last, there is an urgent need to implement image fusion in the planning process, specifically, with magnetic resonance imaging and positron emission tomography data.

On univariate analysis, residual tumor volume was a significant prognostic variable for PFS and OS (Table 4). GTV >30 mL was associated with a significant risk of DF ($p = 0.025$) or death ($p = 0.013$). GTV is considered a major prognostic factor for skull base chordoma in several series from the United States (19, 36) and Japan (22). We did not find gender (Table 4) a significant outcome factor. This is possibly simply the result of the small number of patients included in this study, allowing only major outcome differences (*i.e.*, implants, Fig. 3; GTV >30 mL, Table 4) to be recognized as risk factors by statistical analysis.

Currently, we consider the concomitant use of PT with a molecularly targeted inhibitor (*e.g.*, imatinib) of the platelet-derived growth factor receptor to improve tumor control in patients with implants and GTV above 30 mL. The platelet-derived growth factor receptor is a promising target frequently overexpressed in chordoma (37) although the overexpression of this tyrosine kinase receptor gene in chordomas has recently been challenged (38). Imatinib for metastatic and nonresectable chordoma is under ongoing clinical scrutiny (http://www.clinicaltrials.gov; NCT00150072).

The metastasis incidence of 14% in this cohort is higher than in the cohort treated for skull base chordoma at our institute, where no distant metastasis was observed (23), but it was the same as in the study of Schoenthaler *et al.*, who reported on the treatment of sacral chordoma (24). Three patients experienced DF; 2 of them had metastasis with concurrent LF. If this high rate of distant metastasis for extracranial chordoma becomes confirmed in our continuously growing cohort, it may reflect that extracranial chordomas are prone to distant metastasis, when compared with its intracranial counterpart. If this propensity for metastasis proves to be correct (at 3 years, the incidence rate for DF was 14% (95% CI, 0–24), this observation should be an incentive to conduct prospective trials with concomitant or adjuvant targeted agents after PT.

One patient developed a fatal radiation-induced secondary cancer, a leiomyosarcoma of the urinary bladder, most likely as a result of the use of RT. He was treated postoperatively with RT (54 Gy) for sacral chordoma. The resulting approximate dose to the bladder was 15–20 Gy. The patient subsequently was treated with a PT boost (11×1.8 CGE) at Paul Scherrer Institute to a total target dose of 73.8 CGE. However, PT completely spared the bladder (less than 1% of the PT dose), and the use of spot scanning to deliver PT results in a minimized risk for treatment-induced secondary cancer from secondary neutrons (39). Permanent control of the chordoma for the survival time of the patient (49 months), however, was achieved. Yet, this patient died of metastatic secondary cancer. This illustrates aptly why the exclusive use of PT has additional advantages over the com-

bination of PT with RT (40, 41). The Massachusetts General Hospital group recently reported an excellent local control rate of 91% at 5 years for primary sacral chordoma treated with or without surgery and high-dose PT/RT treatment, as well as a strikingly high incidence of distant failure (42).

CONCLUSIONS

A high local control rate was achieved after function-sparing surgery for extracranial chordoma followed by PT, delivered at a gantry with spot-scanning capacity. All LFs occurred in patients with surgical implants, and GTV volumes above 30 mL were negatively associated with OS and PFS. A substantial number of patients failed distantly. One patient presented with a radiation-induced tumor after combined photon-proton irradiation. Although the follow-up is short, no patient presented with a secondary neoplasm after PT only, and spinal cord and cauda equina function was maintained in all patients without an LF. The use of a radiosensitizer to improve outcome in patients at high risk for failure is an area of future investigation.

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