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Original Article

# Clinical Outcome of Sacral Chordoma Patients Treated with Pencil Beam Scanning Proton Therapy

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## Abstract

*Aims:* Sacral chordomas are locally aggressive, radio-resistant tumours. Proton therapy has the potential to deliver high radiation doses, which may improve the therapeutic ratio when compared with conventional radiotherapy. We assessed tumour control and radiation-induced toxicity in a cohort of sacral chordoma patients treated with definitive or postoperative pencil beam scanning proton therapy.

*Methods and materials:* Sixty patients with histologically proven sacral chordoma treated between November 1997 and October 2018 at the Paul Scherrer Institute with postoperative ($n = 50$) or definitive proton therapy ($n = 10$) were retrospectively analysed. Only 10 (17%) patients received combined photon radiotherapy and proton therapy. Survival rates were calculated using the Kaplan–Meier actuarial method. The Log-rank test was used to compare different functions for local control, freedom from distant recurrence and overall survival. Acute and late toxicity were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

*Results:* The median follow-up was 48 months (range 4–186). Local recurrence occurred in 20 (33%) patients. The 4-year local control, freedom from distant recurrence and overall survival rates were 77%, 89% and 85%, respectively. On univariate analysis, subtotal resection/biopsy ($P = 0.02$), tumour extension restricted to bone ($P = 0.01$) and gross tumour volume >130 ml ($P = 0.04$) were significant predictors for local recurrence. On multivariate analysis, tumour extension restricted to bone ($P = 0.004$) and gross total resection ($P = 0.02$) remained independent favourable prognostic factors for local recurrence. Twenty-four (40%), 28 (47%) and eight (11%) patients experienced acute grade 1, 2 and 3 toxicities, respectively. The 4-year late toxicity-free survival was 91%. Two patients developed secondary malignancies to the bladder 3–7 years after proton therapy.

*Conclusions:* Our data indicate that pencil beam scanning proton therapy for sacral chordomas is both safe and effective. Gross total resection, tumour volume <130 ml and tumour restricted to the bone are favourable prognostic factors for local tumour control.



*Key words:* Local tumour control; pencil beam scanning; prognostic factors; proton therapy; sacral chordoma

## Introduction

Chordomas are rare bone tumours, with an incidence of about 0.8–1 per million per year [1] arising from remnants of the chorda dorsalis. They arise equally distributed along the vertebral column from the skull base to the sacro-coccygeal region [2]. Although usually described as slow-growing tumours with low metastatic potential, they show aggressive local growth, leading to impaired neurological symptoms, which can ultimately lead to death [3]. The treatment strategy usually consists of maximal tumour debulking that leaves the patients functionally intact with, if necessary, sequential staged surgical procedures. Total resection can often only be achieved at a high functional cost. As such, less radical surgery that results in tumour debulking and adjuvant radiation treatment is an appropriate strategy if the patients want to minimise post-operative adverse events and late sequelae. After surgery

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alone, dependent on surgical margins, which were shown to be an important prognostic factor [4–7], recurrence rates are high [7–11], which has a negative impact on the survival of these patients with these challenging tumours. The addition of adjuvant systemic treatment did not improve the prognosis [12], nor did radiation therapy, with moderate doses up to 60 Gy delivered to these radio-resistant tumours [13]. Only with the administration of high radiation therapy doses (i.e. in the range of 70–78 Gy) can this treatment modality result in improved local tumour control and overall survival rates for skull base and extracranial chordoma patients alike [14,15]. The high radiation conformity and the reduction of the integral dose by the use of protons has made proton therapy the standard radiation modality for the management of these tumours, with increased tumour control and reduced toxicity rates [16–18]. At the Paul Scherrer Institute (PSI), pencil beam scanning (PBS) proton therapy was developed and delivered for routine clinical use; since 1996 more than 1500 patients [19] have been treated with this delivery technique. Preliminary results of patients with extracranial chordomas and chondrosarcomas treated with PBS proton therapy at our institution have been published [20–23]. This study was an update of these series, with a focus on the chordomas of the sacrococcygeal region only, with a long-term follow-up and an increased patient number.

## Materials and Methods

### *Patient and Tumour Characteristics*

Between November 1997 and October 2018, 60 (median age 59 years; range 28–82) adult patients (male, $n = 41$; 68%) with histologically proven sacral chordoma were treated at PSI with PBS proton therapy. Only 10 (17%) patients received combined photon radiotherapy and proton therapy, mainly for logistical reasons. Patients' characteristics are summarised in Table 1. Inoperable, incompletely (R1 or R2) or completely resected (R0) patients with close margins were included into the study cohort. Most patients ($n = 47$; 78%) were treated upfront with surgery and adjuvant proton therapy (Table 1). The extent of surgical resection was categorised according to the definition of La Corte *et al.* [24] for chordomas as gross total resection if 100% of the chordoma was removed, subtotal resection if the removed tumour amount was between 99% and 85% and partial resection if it was <85%. Fifty (83%) patients underwent surgery and 10 (17%) had a biopsy only. For those undergoing resection, 33 (66%) underwent gross total resection. Twelve patients had two or three surgeries (Table 1). Only one (2%) patient had metal implants for stabilisation. This analysis was approved by the Northwest and Central Switzerland Ethics Committee (EKNZ-2018-01156).

### *Treatment Characteristics*

For treatment planning, computed tomography was carried out and all patients were immobilised with a body cast. Preoperative and postoperative magnetic resonance images (MRI) were usually fused with the planning computed tomography scan. The gross tumour volume (GTV) included the resection cavity, gross residual tumour if any. The clinical target volume (CTV1) defining the first dose level encompassed the GTV, surgical tract and areas of microscopic tumour spread. CTV1 was expanded by 1 cm to the GTV adapted to anatomical borders. The CTV2 included the GTV and was treated as the boost volume either in a sequential ($n = 51$, 85%) or a simultaneous integrated boost (SIB; $n = 9$, 15%) delivery paradigm. The planning target volume included a 7 mm margin to account for set-up/range uncertainty. In-house planning software (PSIplan) was used for treatment planning, as described previously [14]. Patients received definitive or adjuvant radiation therapy to total doses ranging from 60.0 to 77.0 Gy(RBE) (median 74) with single-fraction doses from 1.8 to 3.0 Gy(RBE) (median 2) (see Supplementary Table S1 for fractionation details). For logistical reasons, some patients received combined photon–proton radiation therapy ($n = 10$, 17%). More specifically, most ($n = 6$; 60%) cases were referred to PSI in order to deliver only the radiation boost with protons. Two patients were treated with photons as no immediate proton treatment slots were available. In another two patients it was necessary to treat a small number of fractions with photons due to a proton therapy interruption caused by a major technical issue with the cyclotron. As such, the range of total photon doses delivered to these patients was indeed very different (2–54 Gy). For proton therapy, PBS proton therapy only was delivered. Five (8%) patients with large inoperable tumours received concomitant hyperthermia up to 6 weekly sessions. We reported these results and the treatment details recently [25]. During the median overall treatment time of 49 days (range 41–67), all patients received the total dose prescribed.

### *Follow-up*

Follow-up was carried out by PSI and/or the referring physicians with clinical and MRI controls every 6 months within the first 2 years after proton therapy and then yearly thereafter. Patient data were reviewed regularly by the entire clinical team to characterise disease status as well as toxicity in a weekly follow-up meeting. Acute toxicities were defined as those adverse events that occurred from the first day to day 90 after treatment, and all side-effects occurring from day 90 onwards were defined as late toxicities. Adverse events were graded based on the US National Institutes of Health CTCAE grading system v5.0 [26].

### *Statistical Analysis*

Actuarial time to event rates were calculated using the Kaplan–Meier method. The time to local failure, distant metastasis, date of death and toxicity higher than grade 2 were determined from the first day of proton therapy. The first imaging or biopsy showing local or distant recurrence was the event for local control or distant metastasis, and death was the event defining overall survival. The date of

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**Table 1**
Patient and disease characteristics ($n = 60$)

| | |
|---|---|
| Age at start of proton therapy (years) | |
| Median (range) | 59 (28–82) |
| Gender | *n* (%) |
| Female | 19 (32) |
| Male | 41 (68) |
| Treatment | *n* (%) |
| Primary | 47 (78) |
| For recurrent disease | 13 (22) |
| Type of surgery | *n* (%) |
| Gross total resection | 33 (55) |
| Subtotal resection | 17 (28) |
| None (biopsy only) | 10 (17) |
| Tumour extension | *n* (%) |
| Restricted to bone | 11 (18) |
| Into bone and soft tissue | 49 (82) |
| Number of surgeries before proton therapy | *n* (%) |
| 0 | 10 (17) |
| 1 | 38 (63) |
| 2 | 7 (12) |
| 3 | 5 (8) |
| Metal implants | *n* (%) |
| Yes | 1 (2) |
| No | 59 (98) |
| Proton therapy | *n* (%) |
| Definitive | 10 (17) |
| Postoperative | 50 (83) |
| Treatment modality | *n* (%) |
| Proton only | 50 (82) |
| Proton and photon mixed | 10 (17) |
| Proton therapy combined with hyperthermia | *n* (%) |
| Yes | 5 (8) |
| No | 55 (92) |
| Delivered dose in Gy(RBE) | Median (range) |
| Total dose | 74 (60–77) |
| Single fraction dose | 2 (1.8–3) |
| Fractions | 37 (20–41) |
| Irradiated volume (ml) | 191 (0–1141) |

examination during follow-up revealing no toxicity higher than grade 2 determined freedom from high-grade toxicity-free survival. The Log-rank test was used to evaluate the event end points for local control, freedom from distant metastases, overall survival and freedom from grade 3 toxicity. A $P < 0.05$ was considered statistically significant. Multivariate analyses were carried out using Cox proportional hazards models in variables with a $P$ value $<0.1$ revealed in univariate analyses. A stepwise backward selection method (criterion for removal: $P < 0.05$) was applied. Analyses were carried out with JMP (version 14.0.2; SAS Institute, Cary, NC, USA).

## Results

### *Control Rates*

After a median follow-up time of 48 months (range 4–186), 20 (33%) recurrences were observed. Noteworthy was that seven (35%) patients failed after 5 years and two other treatment failures were observed 10 and 12 years after proton therapy. Local recurrence/progression only and distant failure only were observed in 12 and two patients, respectively. For the remaining eight patients, two local recurrence occurred before distant, and two distant recurrences occurred before local recurrence, whereas for four other patients, treatment failure was concomitant locally and distantly (Table 2). Distant metastases occurred in the lung in eight of 10 patients (Table 2). The median time to local and distant failure was 48 months (range 2–146) and 48.5 months (range 8–186), respectively. The 4-year local control and DMFS were 77% (95% confidence interval 63–88) (Figure 1) and 89% (95% confidence interval 75–95), respectively.

Six patients (10%) died of tumour progression and four other patients (7%) died of non-chordoma-related causes (i.e. bladder carcinoma, other unknown malignancy, myocardial infarction and complications of an orchitis or concomitant to this illness). The 4-year overall survival was 85% (95% confidence interval 70–93).

### *Prognostic Factors*

On univariate analysis, a significantly improved rate of local control was associated with gross total resection ($P = 0.02$, hazard ratio 0.33; 95% confidence interval 0.13–0.85), no tumour extension beyond the bone ($P = 0.013$, hazard ratio 0.11; 95% confidence interval 0.01–0.85) (Figure 2) and GTV smaller than 130 ml ($P = 0.04$, hazard ratio 2.59; 95% confidence interval 0.99–6.77). On multivariate analysis, tumour restricted to bone ($P = 0.0035$) and gross total resection (0.018) were the only significant independent factors associated with a significant improved local tumour control (Table 3). No significant factors were identified for freedom from distant metastases and overall survival. A trend towards statistical significance for overall survival was observed for gross total resection versus subtotal resection or biopsy ($P = 0.052$, hazard ratio 0.28; 95% confidence interval 0.07–1.11), tumour restricted to bone ($P = 0.052$) and GTV smaller than 130 ml ($P = 0.07$, hazard ratio 2.97; 95% confidence interval 0.86–10.3) (Table 3). Of note, there was a suggestion of better local control with hypofractionation, although this did not reach statistical significance ($P = 0.07$).

### *Toxicities*

Acute grade 3 skin toxicity with moist desquamation in non-skin folds was observed in four (7%) patients. No acute grade $\geq$4 toxicities were observed. Late grade 3 toxicity was observed in five (5%) patients: sacral insufficiency fractures and neuropathic pain interfering with activities of daily life were observed in two and one patients, respectively. Two (3%) patients developed secondary malignancies (grade 4, $n = 1$; grade 5, $n = 1$) in the bladder, 3 and 7 years after the completion of radiation therapy. Of note, both patients received a combination of photon and proton therapy (Table

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**Table 2**
Characteristics of patients with recurrent disease

| RN Patient | Concomitant recurrence | Local failure | Onset (months) | Distant failure | Onset (months) | Location of distant failure |
|---|---|---|---|---|---|---|
| 1 | Yes | Yes | 42 | Yes | 42 | Bone, lung |
| 2 | No | Yes | 69 | Yes | 57 | lung |
| 3 | No | Yes | 122 | No | - | - |
| 4 | No | Yes | 43 | No | - | - |
| 5 | Yes | Yes | 37 | Yes | 37 | Bone, liver, lung |
| 6 | No | Yes | 24 | No | - | - |
| 7 | No | Yes | 56 | No | - | - |
| 8 | No | Yes | 29 | Yes | 71 | Lung, soft tissue |
| 9 | No | Yes | 17 | No | - | - |
| 10 | No | Yes | 71 | No | - | - |
| 11 | No | Yes | 41 | No | - | - |
| 12 | Yes | Yes | 55 | Yes | 55 | Lung |
| 13 | No | Yes | 53 | No | - | - |
| 14 | No | Yes | 2 | No | - | - |
| 15 | No | Yes | 18 | Yes | 15 | Liver, lung |
| 16 | No | Yes | 76 | No | - | - |
| 17 | No | Yes | 146 | No | - | - |
| 18 | Yes | Yes | 80 | Yes | 80 | Bone, liver, lung |
| 19 | No | Yes | 19 | No | - | - |
| 20 | Yes | Yes | 81 | Yes | 81 | Lung |
| 21 | No | No | - | Yes | 4 | Skin |
| 22 | No | No | - | Yes | 26 | Bone |

4). The 4-year toxicity-free survival was 91% (95% confidence interval 79–97) (Figure 3).

## Discussion

High-dose particle therapy combined with surgery, when functionally feasible, is considered as standard treatment for sacral chordoma, based on published results from various institutions worldwide. With particle therapy, safe dose escalation is feasible while sparing pelvic critical structures and therefore minimising the likelihood of radiation-induced toxicity. The present study reported a 4-year local control rate of 77% after proton therapy in a cohort comprising 45% of patients with inoperable or subtotal resected sacral chordoma treated at diagnosis or for recurrent disease (Table 1). These outcomes are in line with other publications using protons [15,16]. Sacral chordoma treated with adjuvant proton therapy after gross total resection showed a significantly better local control rate than those in inoperable patients or those with subtotal resection and partial resection (Table 4). As such, it would be recommended to pursue aggressive surgical management, with staged surgery procedures, prior to proton therapy. It has been PSI's management policy to propose re-intervention if the tumour geometry and/or the residual tumour is too large. We need to convince our surgical colleagues, neurosurgeons and orthopaedists alike to consider additional surgical staged procedures for what is perceived in the surgical community as a 'benign' disease. However, we have been only partially successful, as attested

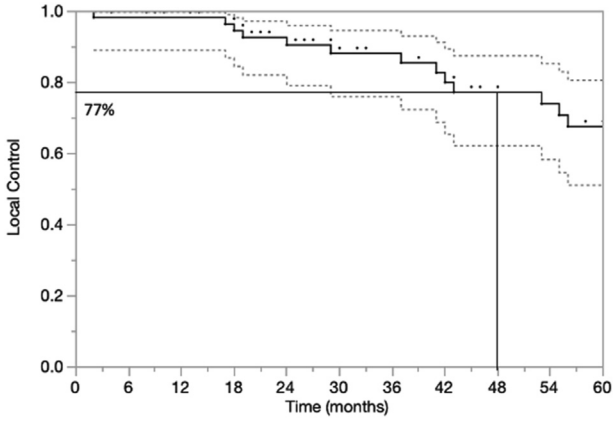


**Fig 1.** Local control in sacral chordoma patients ($n = 60$).

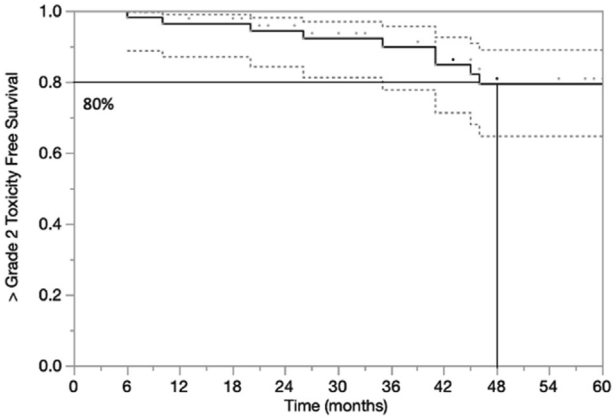


**Fig 2.** Four-year >grade 2 toxicity rate.

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**Table 3**
Univariate and multivariate analysis

| Univariate analysis | | Local control | | FFDR | | Overall survival | |
|---|---|---|---|---|---|---|---|
| | | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age in years (median = 59) | >65 | 0.75 (0.22–2.66) | 0.67 | 1.13 (0.23–5.52) | 0.88 | 2.10 (0.54–8.21) | 0.27 |
| | >50 | 1.15 (0.46–2.84) | 0.77 | 1.29 (0.36–4.66) | 0.70 | 1.98 (0.51–7.68) | 0.31 |
| | >40 | 1.08 (0.36–3.29) | 0.89 | 2.32 (0.29–18.5) | 0.41 | 1.01 (0.21–4.77) | 0.99 |
| Sex | male versus female | 1.09 (0.43–2.74) | 0.86 | 1.37 (0.35–5.32) | 0.65 | 0.69 (0.19–2.47) | 0.57 |
| Oncologic surgery prior PT | yes versus no | 1.24 (0.16–9.84) | 0.83 | 0.53 (0.06–4.81) | 0.57 | 0.32 (0.04–2.78) | 0.28 |
| Total no. surgeries | >median_(>1) | 1.36 (0.53–3.46) | 0.52 | 1.13 (0.29–4.43) | 0.86 | 0.97 (0.25–3.81) | 0.97 |
| Interval 1st surgery to PT | >median_(5 months) | 1.46 (0.58–3.69) | 0.42 | 1.48 (0.40–5.56) | 0.56 | 0.91 (0.26–3.19) | 0.88 |
| | >2 months | 1.02 (0.13–7.92) | 0.98 | n/a | 0.48 | n/a | 0.46 |
| | >12 months | 1.77 (0.68–4.61) | 0.24 | 1.35 (0.33–5.46) | 0.73 | 1.43 (0.40–5.15) | 0.58 |
| Interval last surgery to PT | >median_(>4 months) | 1.37 (0.54–3.52) | 0.51 | 0.93 (0.25–3.47) | 0.91 | 1.40 (0.39–5.02) | 0.60 |
| | >2 months | 0.77 (0.25–2.37) | 0.65 | 0.69 (0.14–3.37) | 0.64 | 0.91 (0.19–4.31) | 0.90 |
| | >12 months | 2.68 (0.75–9.64) | 0.12 | 1.44 (0.17–12.0) | 0.73 | 0.81 (0.10–6.44) | 0.84 |
| Gross total resection | yes versus STR or biopsy | **0.33 (0.13–0.85)** | **0.0210*** | 0.34 (0.09–1.24) | 0.09 | 0.28 (0.07–1.11) | 0.05 |
| Biopsy only | yes versus GTR or STR | 0.81 (0.10–6.41) | 0.84 | 1.87 (0.21–16.8) | 0.57 | 3.10 (0.36–26.7) | 0.28 |
| Tumour extension restricted to bonyee | yes versus no | **0.11 (0.01–0.85)** | **0.013*** | 0.22 (0.03–1.84) | 0.13 | n/a | 0.05 |
| PT treatment for a recurrence | yes versus no | 2.09 (0.83–5.25) | 0.11 | 1.85 (0.51–6.62) | 0.34 | 2.09 (0.60–7.29) | 0.24 |
| PT with hyperthermia | yes versus no | n/a | 0.53 | n/a | 0.66 | n/a | 0.88 |
| PT with photons mixed | yes versus no | 1.02 (0.33–3.11) | 0.98 | n/a | 0.10 | 1.46 (0.37–5.67) | 0.59 |
| Hypofractionated PT | yes versus no | 2.84 (0.88–9.09) | 0.07 | 1.25 (0.15–10.6) | 0.83 | 3.12 (0.63–15.6) | 0.14 |
| GTV | >130 ml = mean | **2.59 (0.99–6.77)** | **0.04*** | 2.93 (0.81–10.6) | 0.09 | 2.97 (0.86–10.3) | 0.07 |
| | >0 ml = median | 2.17 (0.85–5.53) | 0.10 | 2.59 (0.73–9.26) | 0.13 | 2.09 (0.59–7.43) | 0.24 |
| | >200 ml | 1.86 (0.66–5.25) | 0.24 | 2.19 (0.56–8.58) | 0.25 | 1.70 (0.43–6.66) | 0.44 |
| | >300 ml | 1.27 (0.36–4.43) | 0.71 | 1.64 (0.34–7.82) | 0.53 | 1.50 (0.31–7.20) | 0.61 |
| *Multivariate analysis (backwards elimination)* | | | | | | | |
| Model 1: Tumour extension restricted to bone | | | | | | | |
| Hypofractionated PT | yes versus no | 1.15 (0.26–5.13) | 0,86 | n/a | | n/a | |
| Tumour extension restricted to bonyee | yes versus no | **0.11 (0.01–0.85)** | **0.0035*** | n/a | | n/a | |
| Model 2: Gross total resection | | | | | | | |
| Hypofractionated PT | yes versus no | 1.69 (0.49–5.80) | 0,75 | n/a | | n/a | |
| Gross total resection | yes versus no | **0.33 (0.13–0.85)** | **0.0181*** | n/a | | n/a | |
| Model 3: GTV | | | | | | | |
| Hypofractionated PT | yes versus no | 1.07 (0.22–5.13) | 0.94 | n/a | | n/a | |
| GTV | >130 ml = mean | 2.59 (0.99–6.77) | 0.06 | n/a | | n/a | |

CI, confidence interval; FFDR, freedom from distant recurrence; GTR, gross total resection; GTV, gross tumour volume; HR, hazard ratio; PT, proton therapy; STR, subtotal resection.
* Statistically significant.

by the small number of staged surgical procedures (Table 1). Similar results were reported from the Boston group [15]. The 5-year local tumour control rate in their series of primarily operated and adjuvant irradiated patients with R0/1 was 86%, whereas the patients treated with radiation therapy alone had a local control rate of only 50%. Additionally, in a later study, the same group analysed the outcome in a larger cohort of operated patients where they observed a trend towards improved local control in R0/1 compared with R2 margin status [27]. They correlated *en bloc* resection with a higher probability of gross total tumour removal, leading to significantly better 5-year local control rates with this procedure than in patients with an intralesional operation. Our investigation analysing the extension of the tumour discriminating between restriction of the chordoma to the bone and an additional extraosseous component with or without infiltration into surrounding tissue and organs led to significant differences in local control rates in multivariate analysis (Table 4). The analysis of dependence of tumour volume affecting local control rate showed that the GTV is a significant prognostic factor for local control, with a cut-off of 130 ml (Table 3) on univariate analyses. Other groups have also shown that tumour size is a predictor for better overall survival [18,27]. Of note, the observed suboptimal local tumour outcome for large/inoperable tumours led to a change in our proton treatment fractionation for these challenging tumours. We implemented a SIB concept with hypofractionation based on the excellent tumour control rates in other published studies using hypofractionation with protons as well as with heavy ions [18,28]. Retrospective data of 23 patients of primary and recurrent macroscopic tumours treated at Hyogo Ion Beam Medical Center in Japan with

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**Table 4**
Tumour morbidity and toxicity*

| | | Tumour morbidity | Acute toxicity | Late toxicity |
|---|---|---|---|---|
| | | *n* (%) | *n* (%) | *n* (%) |
| Tumour mass swelling | | 5 (9) | na | na |
| Pain/sensoric/motoric | | 6 (10) | 9 (17) | 12 (20) |
| Gastrointestinal | | 7 (12) | 10 (18) | 7 (12) |
| Genitourinary | | 6 (10) | 4 (7) | 0 (0) |
| General condition | | na | 2 (4) | 0 (0) |
| Dermatitis | | na | 51 (94) | 0 (0) |
| Fibrosis | | na | na | 10 (17) |
| Pigmentation | | na | na | 10 (17) |
| Bone fracture | | na | na | 5 (8) |
| Second malignancy | | | | 2 (3) |
| **Grade** | 0 | na | 1 (2) | 26 (43) |
| | 1 | na | 22 (37) | 12 (20) |
| | 2 | na | 26 (43) | 18 (30) |
| | 3 | na | 6 (10) | 3 (5) |
| | 4-5† | | | 2 (3)† |
| Missing | | na | 5 | 0 |

* According to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.
† Second malignancy grade 4 in one and 5 in another patient.

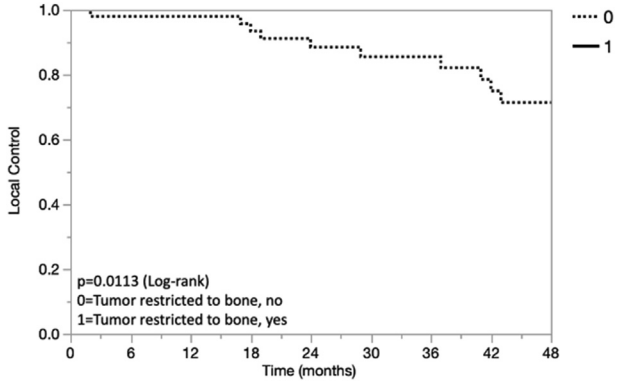


**Fig 3.** Tumour extension regarding restriction to bone (yes versus no).

protons and carbon ion showed a 3-year local control rate of 94% delivering 70.4 Gy(RBE) in either 16 or 32 fractions. Likewise, NIRS in Chiba published data of 188 patients irradiated for medically unresectable chordoma in 16 fractions to total doses of 64.0–70.4 Gy(RBE). The 5-year local control rate was 77.2%. At the Heidelberg Ionbeam-Therapy Center, the carbon ion treatment of 56 patients with sacral chordoma was retrospectively analysed [29]. Thirty-three patients received carbon ion only with single doses of 3 Gy(RBE) up to total doses of 60–66 Gy(RBE). The other 23 patients received a carbon ion boost of 15–24 Gy(RBE) with single doses of 3 Gy(RBE) after normofractionated intensity-modulated radiotherapy of 50–52 Gy. The local control rate after 3 years was 53%. There was no significant difference in local control regarding dose or fractionation scheme. The nine patients in our study who were treated with a SIB concept received single doses of either 3 Gy(RBE) up to 60 Gy(RBE) or 2.5 Gy(RBE) to 70 Gy(RBE). The five most recently treated patients received additional hyperthermia therapy combined with hypofractionated proton therapy [25]. On univariate analysis, we observed a trend towards better local control for patients treated with hypofractionation compared with normofractionated regimens in patients with unresectable disease. The use of moderate hypofractionation did not result in a significantly higher toxicity rate, regarding gastrointestinal or neurotoxicity (Table 3). The grade 3 toxicity observed in 2/8 patients treated with hypofractionation as well as the grade 4 skin toxicity reported from NIRS in their analysis highlight that the use of hypofractionation has to be well assessed and caution is warranted in the delivery of higher daily fractions. The rate of higher-grade toxicities in our cohort overall was moderate and comparable with the rates in other studies using normofractionated proton therapy. Higher-grade acute toxicity was limited to grade 3 skin toxicity in three patients (5%).

The analysis from Boston with proton therapy and Heidelberg with heavy ions both showed worse outcome regarding local control in recurrent sacral chordomas [15,29]. Thirteen (22%) of our patients were treated after local recurrence of the chordoma. Twelve of these patients were reoperated on (seven with one and five with two reoperations). In our analysis there was no significant difference regarding local control for these patients ($P = 0.11$).

Regarding treatment technique, it is advisable to irradiate sacral chordomas exclusively with a posterior beam arrangement with two to three fields. This guarantees the highest plan robustness conditions and avoidance of dose in pelvic organs (i.e. over-shooting). However, this results in an increase in the integral dose in the skin and the soft tissue covering the sacral region. Higher-grade skin toxicity was also reported in the abovementioned high dose hypofractionated particle series [16,18,28]. Regarding late higher-grade toxicities observed at PSI, two (3%) patients developed fractures of involved bone requiring

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surgical intervention after proton therapy. In the analysis of the irradiated sacral chordoma patients from the Boston group, a substantial rate of sacral insufficiency fractures was also reported [30]. Importantly, bladder cancer was diagnosed 3 and 7 years after the completion of proton therapy in our series. Of note, both had combined photon/proton treatment with photon doses of 45 Gy and 54 Gy. One patient died as a result of his secondary malignancy. Different studies have investigated the rate of occurrence of bladder carcinoma and other second malignancies after photon therapy to the pelvis. Of prime interest are the studies where only radiation therapy and no chemotherapy was used, as in prostate cancer treatment. In their review, Suriano *et al.* [31] showed the results from different studies investigating the occurrence of bladder cancer after radiation therapy for prostate cancer and found an elevated risk. Interestingly, Weber *et al.* [32] has shown that most of the diagnosed secondary malignancies that occur in the gastrointestinal tract in irradiated prostate cancer patients develop in areas that receive below the Gy unit. Although the occurrence of a secondary malignancy by a solid tumour 3 years after radiation therapy in our patient is early, in the study of Shirodkar *et al.* [33] the mean latency from radiation to diagnosis of bladder cancer was 5.5 years. Regarding the fact that all criteria for a radiation-induced malignancy in our two patients were fulfilled [34], we considered these two cancers to be radiation-induced.

Finally, it is noteworthy that a fair percentage of patients (35%) failed after 5 years and treatment failures were observed 10 and 12 years after PBS proton therapy in two patients. For clinical follow-up, these results are important, and they indicate a non-trivial level of recurrence in a population in which only a minority of patients receive follow-up by a specialist. As such, long-term clinical and imaging follow-up is needed. At PSI, we recommend annual MRIs for 5 years (every 6 months within the first 2 years after proton therapy) after PBS. From this time point until 10 years we recomment a MRI every two years (individual discussions with patients thereafter) after the management of chordoma, bearing in mind that this follow-up strategy would not have detected one (5%) recurrence in our cohort.

## Conclusions

The results of this retrospective analysis of patients with resectable and non-resectable sacral chordomas treated with high dose PBS proton therapy is encouraging, with good tumour control and a low probability of late high-grade radiation-induced toxicity in most chordoma patients. Both the gross total resection and the tumour restricted to the bone were independent predictors of local tumour control. There was a suggestion of better local control with hypofractionation, with or without hyperthermia, although this did not reach statistical significance, in large inoperable sacral chordomas. This strategy will be pursued in a multi-institutional pilot study involving the USA, the Netherlands and Switzerland.

## Conflicts of Interest

The authors declare no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2021.07.012.

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