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# Proton beam therapy for bone sarcomas of the skull base and spine: A retrospective nationwide multicenter study in Japan

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## Key words

Multicenter study, proton beam therapy, sarcoma, skull base, spine

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We conducted a retrospective, nationwide multicenter study to evaluate the clinical outcomes of proton beam therapy for bone sarcomas of the skull base and spine in Japan. Eligibility criteria included: (i) histologically proven bone sarcomas of the skull base or spine; (ii) no metastases; (iii)  $\geq 20$  years of age; and (iv) no prior treatment with radiotherapy. Of the 103 patients treated between January 2004 and January 2012, we retrospectively analyzed data from 96 patients who were followed-up for  $>6$  months or had died within 6 months. Seventy-two patients (75.0%) had chordoma, 20 patients (20.8%) had chondrosarcoma, and four patients (7.2%) had osteosarcoma. The most frequent tumor locations included the skull base in 68 patients (70.8%) and the sacral spine in 13 patients (13.5%). Patients received a median total dose of 70.0 Gy (relative biological effectiveness). The median follow-up was 52.6 (range, 6.3–131.9) months. The 5-year overall survival, progression-free survival, and local control rates were 75.3%, 49.6%, and 71.1%, respectively. Performance status was a significant factor for overall survival and progression-free survival, whilst sex was a significant factor for local control. Acute Grade 3 and late toxicities of  $\geq$ Grade 3 were observed in nine patients (9.4%) each (late Grade 4 toxicities [ $n = 3$  patients; 3.1%]). No treatment-related deaths occurred. Proton beam therapy is safe and effective for the treatment of bone sarcomas of the skull base and spine in Japan. However, larger prospective studies with a longer follow-up are warranted.

**B**one sarcomas (BSs) are extremely rare, accounting for  $<0.2\%$  of newly diagnosed malignant tumors in the United States each year.<sup>(1)</sup> The primary definitive treatment for BSs is surgical resection. However, BSs of the skull base (SB) and spine are often difficult to resect completely. Radiotherapy is an option for unresectable or partially resectable tumors, although the majority of BSs are resistant to conventional photon radiotherapy. Therefore, photon radiotherapy has traditionally been used in a neoadjuvant or adjuvant setting.<sup>(2, 3)</sup>

The efficacy of proton beam therapy (PBT) for BSs (primarily chordomas and chondrosarcomas [CSs]) of the SB and spine has been reported since the 1980s.<sup>(4–28)</sup> Photons emit maximal energy near the body surface; this energy gradually decreases at deeper points in the body. In contrast, charged particles (e.g., protons and carbon ions) deposit a relatively low-dose near the body surface and emit their maximum energy just before they stop inside the body (the Bragg peak effect). The Bragg peak effect may be spread out according to the location and size of the tumor,<sup>(29,30)</sup> making it possible to deliver high-dose radiation to the tumor, whilst limiting the

dose delivered to the organs at risk. The biological effects of protons are almost identical to the biological effects of photons (relative biological effectiveness [RBE], 1.1).<sup>(31)</sup>

Much evidence concerning the effectiveness of PBT for BSs of the SB and spine has been reported from Western countries, whereas only a limited number of small studies<sup>(7, 17, 22, 28)</sup> have been published from Japan, even Asia. As of March 2012, six PBT centers treated BSs in Japan since. These include the Hyogo Ion Beam Medical Center, University of Tsukuba, Shizuoka Cancer Center Hospital, National Cancer Center Hospital East, Southern Tohoku General Hospital, and Fukui Prefectural Hospital.

We conducted a retrospective, nationwide multicenter study to evaluate the clinical outcomes of PBT for BSs of the SB and spine in Japan.

## Materials and Methods

**Study design and patients.** We conducted a retrospective, nationwide multicenter study across six PBT centers in Japan. All patients provided written informed consent. The study

protocol was approved by the appropriate Institutional Review Board committee of each center. Research was conducted in accordance with the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). Eligibility criteria included: (i) histologically proven BSs of the SB or spine; (ii) no metastases; (iii)  $\geq 20$  years of age; and (iv) no previous radiotherapy. Of the 103 patients treated between January 2004 and January 2012, we retrospectively analyzed data from 96 patients (93.2%) who were followed-up for  $>6$  months or had died within 6 months.

The representative PBT planning procedure was as follows. Radiation treatments were planned using a computed tomography-based three-dimensional treatment planning system. Each patient was immobilized using a custom-made thermoplastic cast and computed tomography and magnetic resonance imaging were performed. The target volumes and organs at risk were delineated on computed tomography-magnetic resonance imaging fusion images. The clinical target volume was defined as the gross tumor volume plus a 5.0-mm basic margin, and the adjacent structures were included in selected patients. The planning target volume was defined as the clinical target volume plus a setup margin and an internal margin where necessary.

The reported dose of PBT was calculated by multiplying the physical dose by the RBE of the protons (1.1). Since various dose fractionations were adopted, the antitumor effects of PBT were compared on the basis of a biologically effective dose, alpha/beta ratio of 10.0 Gy ( $BED_{10}$ ). It is important to note that although the alpha/beta ratios for BSs may be  $<10.0$  Gy, the precise alpha/beta ratios for chordomas, CSs, and osteosarcomas have yet to be determined. Therefore, we adopted an alpha/beta ratio of 10.0 Gy that has been commonly used for antitumor effects.  $BED_{10}$  was calculated as follows:

$$BED_{10}(\text{Gy}[\text{RBE}]) = \text{total dose}(\text{Gy}[\text{RBE}]) \times \left\{ \frac{1 + \text{dose per fraction}(\text{Gy}[\text{RBE}])}{10(\text{Gy}[\text{RBE}])} \right\}$$

The following are examples of dose constraints in a 32-fraction protocol: brainstem, optic nerve, and spinal cord (cauda equina not included), maximum dose of  $\leq 48.0$  Gy (RBE); small intestine, maximum dose of  $\leq 52.0$  Gy (RBE); large intestine, maximum dose of  $\leq 57.0$  Gy (RBE); and rectum, volume receiving  $\geq 65.0$  Gy (RBE) of  $\leq 17.0\%$  and volume receiving  $\geq 40.0$  Gy (RBE) of  $\leq 35.0\%$ .

Representative treatment plans for PBT in patients with BSs of the SB and spine are represented in Fig. 1.

Toxicities were evaluated using the Common Terminology Criteria for Adverse Events, version 4.0.

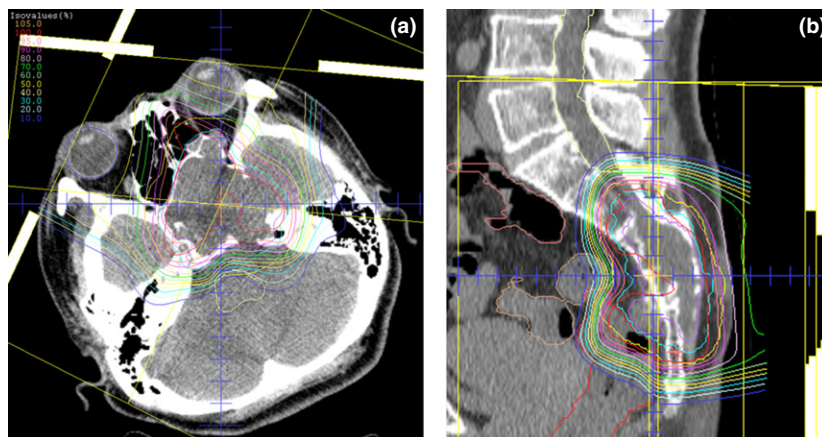
**Statistical analyses.** Continuous variables are presented as medians and ranges and categorical variables are presented as frequencies and percentages. Overall survival (OS), progression-free survival (PFS), and local control (LC) curves were estimated using the Kaplan–Meier method and compared by the log-rank test. Variables with a  $P < 0.05$  from the univariate analysis were included in the multivariate analysis, using a Cox proportional hazards model. All statistical analyses were conducted using Statistical Package for the Social Sciences for Windows, software version 23 (IBM Corp., Armonk, NY, USA). A two-sided  $P < 0.05$  was considered statistically significant.

## Results

**Patients.** Patient characteristics are summarized in Table 1. Seventy-two patients (75.0%) had chordoma, 20 patients (20.8%) had CS, and four patients (4.2%) had osteosarcoma. The most frequent tumor location was the SB in 68 patients (70.8%), followed by the sacral spine in 13 patients (13.6%). Therefore, the most frequent combinations of histological subtypes and tumor locations were chordoma of the SB ( $n = 53$  patients; 55.2%), CS of the SB ( $n = 15$  patients; 15.6%), and chordoma of the sacrum ( $n = 12$  patients; 2.5%). Pre-PBT, 68 patients (70.8%) underwent surgical resection. Fifty-five (80.9%) of 68 patients with a tumor of the SB and 11 (73.3%) of 15 patients with a tumor of the spine underwent surgical resection, whereas only two (15.4%) of 13 patients with a tumor of the sacrum underwent surgical resection. Four patients (4.2%; osteosarcoma [ $n = 2$  patients], CS [ $n = 1$  patient], and chordoma [ $n = 1$  patient]) received chemotherapy pre-PBT.

Patients received a median total dose of 70.0 Gy (RBE) ( $BED_{10}$ , 86.0 Gy [RBE]). Three patients (3.1%) were treated with combined PBT and photon radiotherapy (12.5–44.0 Gy in 5–22 fractions). Accelerated hyperfractionation (60.5–77.4 Gy [RBE] in 50–64 fractions, twice daily) was administered to 20 patients (20.8%).

**Survival and local control.** The median follow-up was 52.6 (range, 6.3–131.9) months. The 5-year OS, PFS, and LC rates for all 96 patients were 75.3% (95.0% confidence interval [CI]: 65.7%–84.9%), 49.6% (95.0% CI: 38.6%–60.6%), and 71.1% (95.0% CI: 60.1%–82.1%), respectively (Fig. 2–3). The 5-year OS, PFS, and LC rates for chordoma patients ( $n = 72$ ) were 75.5% (95.0% CI: 63.9%–87.1%), 45.6% (95.0% CI: 32.7%–58.5%), and 68.4% (95.0% CI: 55.1%–81.7%), respectively. The 5-year OS, PFS, and LC rates for CS patients ( $n = 20$ ) were 83.5% (95.0% CI: 66.3%–100.0%), 72.2%



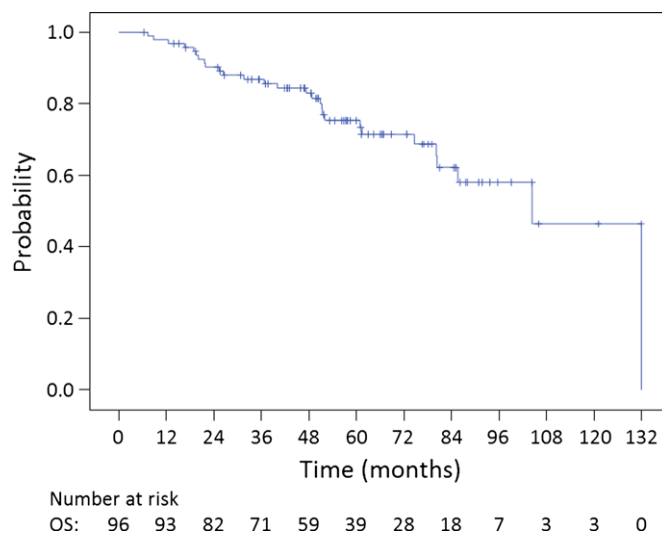
**Fig. 1.** Representative treatment plans for proton beam therapy in (a) a 45-year-old female with skull base chordoma (65.0 Gy [relative biological effectiveness] delivered in 26 fractions) and (b) a 53-year-old female with sacral chordoma (70.4 Gy [relative biological effectiveness] delivered in 32 fractions).

**Table 1. Patient characteristics**

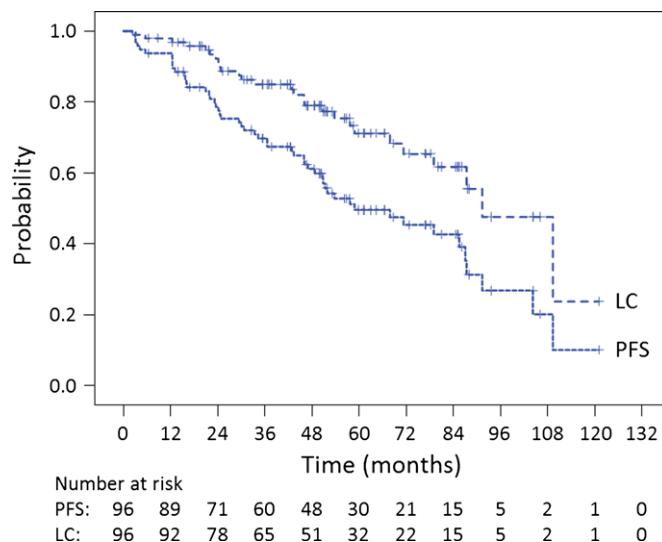
Characteristic	Patients (n = 96)
Age, years	
Median (range)	56 (20–80)
<60	55 (57.3)
≥60	41 (42.7)
Sex, n (%)	
M	51 (53.1)
F	45 (46.9)
PS, n (%)	
0	39 (40.6)
1	50 (52.1)
2	5 (5.2)
3	2 (2.1)
Histological subtype, n (%)	
CH	72 (75.0)
CS	20 (20.8)
OSA	4 (4.2)
Tumor location, n (%)	
SB	68 (70.8)
Cervical spine	8 (8.3)
Lumbar spine	5 (5.2)
Lumbosacral spine	2 (2.1)
Sacral spine	13 (13.6)
Tumor status, n (%)	
Primary	73 (76.0)
Recurrent	23 (24.0)
Surgery, n (%)	
Pre-PBT	68 (70.8)
Post-PBT	2 (2.1)
None	26 (27.1)
Chemotherapy, n (%)	
Pre-PBT	4 (4.2)
Post-PBT	0 (0.0)
None	92 (95.8)
PTV, mL	
Median (range)	72 (9–1,984)
≤70	48 (50.0)
>70	48 (50.0)
Radiotherapy, n (%)	
PBT alone	93 (96.9)
PBT + photon radiotherapy	3 (3.1)
Total dose, Gy (RBE)†	
Median (range)	70 (50–84)
≤70	50 (52.1)
>70	46 (47.9)
BED <sub>10</sub> , Gy (RBE)†	
Median (range)	86 (60–103)
≤85	49 (51.0)
>85	47 (49.0)

†The sums of the photon dose/BED<sub>10</sub> and proton dose/BED<sub>10</sub> were used for patients treated with PBT + photon radiotherapy. BED<sub>10</sub>, biologically effective dose, alpha/beta = 10 Gy; CH, chordoma; CS, chondrosarcoma; F, female; M, male; OSA, osteosarcoma; PBT, proton beam therapy; PS, performance status; PTV, planning target volume; RBE, relative biological effectiveness; SB, skull base.

(95.0% CI: 51.2%–93.2%), and 82.2% (95.0% CI: 63.8%–100.0%), respectively. The 5-year OS, PFS, and LC rates for patients with tumors of the SB (n = 68) were 77.6% (95.0% CI: 66.6%–88.6%), 57.0% (95.0% CI: 44.3%–69.7%), and 76.2% (95.0% CI: 64.4%–88.0%), respectively. The 5-year OS, PFS, and LC rates for patients with tumors of the spine



**Fig. 2.** Kaplan–Meier curve of overall survival (OS) for all 96 patients with bone sarcoma of the skull base and spine.



**Fig. 3.** Kaplan–Meier curves of local control (LC) and progression-free survival (PFS) for all 96 patients with bone sarcoma of the skull base and spine.

(n = 28) were 70.7% (95.0% CI: 51.7%–89.7%), 30.7% (95.0% CI: 11.1%–50.3%), and 55.6% (95.0% CI: 30.3%–80.9%), respectively. The 5-year OS, PFS, and LC rates for patients with chordoma of the SB (n = 53) were 74.6% (95.0% CI: 61.3%–87.9%), 52.8% (95.0% CI: 38.1%–67.5%), and 73.8% (95.0% CI: 59.9%–87.7%), respectively.

During follow-up, 27 (28.1%) and 19 patients (19.8%) experienced local (in-field) or regional/distant (out-of-field) recurrences, respectively. Frequent sites of out-of-field recurrence included regional (n = 8 patients; 8.3%) and bone metastases (n = 4 patients; 4.2%).

A performance status (PS) of 0–1 was associated with a significantly longer OS (log-rank test, *P* < 0.001; Table 2). PS (0–1; *P* < 0.001), tumor location (SB; *P* = 0.019), and planning target volume (≤70.0 mL; *P* = 0.026) were associated

Table 2. Log-rank test results

Variable	Patients (n = 96)	P-value		
		OS	PFS	LC
Age, years				
<60	55			
≥60	41	0.167	0.455	0.380
Sex				
M	51			
F	45	0.606	0.455	0.041*
PS				
0–1	89			
2–3	7	<0.001*	<0.001*	0.066
Histological subtype				
CH	72			
Other	24	0.773	0.194	0.169
Tumor location				
SB	68			
Spine	28	0.524	0.019*	0.176
Tumor status				
Primary	73			
Recurrent	23	0.393	0.077	0.067
Surgery				
Pre-PBT	68			
Post-PBT/none	28	0.241	0.537	0.971
Chemotherapy				
Pre-PBT	4			
Post-PBT/none	92	0.065	0.117	0.880
PTV, mL				
≤70	48			
>70	48	0.056	0.026*	0.154
Radiotherapy				
PBT alone	93			
PBT + photon radiotherapy	3	0.280	0.145	0.193
BED <sub>10</sub> , Gy (RBE)				
≤85	49			
>85	47	0.250	0.240	0.637

\* $P < 0.05$ . BED<sub>10</sub>, biologically effective dose, alpha/beta = 10 Gy; CH, chordoma; F, female; LC, local control; M, male; OS, overall survival; PBT, proton beam therapy; PFS, progression-free survival; PS, performance status; PTV, planning target volume; RBE, relative biological effectiveness; SB, skull base.

with a significantly longer PFS, while female sex was associated with a significantly improved LC rate ( $P = 0.041$ ). Histological subtype, surgery, and BED<sub>10</sub> were not associated with OS, PFS, or LC.

The Cox proportional hazards model revealed that only a PS of 0–1 was associated with a significantly longer PFS ( $P < 0.001$ ), whilst tumor location (SB) exhibited a trend towards a longer PFS ( $P = 0.053$ ; Table 3).

**Toxicities.** Grade 3 acute toxicities occurred in nine patients (9.4%). The most frequent toxicity was dermatitis in four patients (4.2%). All patients completed the planned radiotherapy and subsequently recovered from their reactions. No acute toxicities of ≥Grade 4 occurred.

Late toxicities of ≥Grade 3 occurred in nine patients (9.4%). Grade 3 late toxicities included musculoskeletal and connective tissue disorders in three patients (3.1%; deformity [ $n = 2$ ] and necrosis [ $n = 1$ ]), eye disorders in one patient (1.0%; blurred vision and pain), middle ear inflammation in one

Table 3. Cox proportional hazards model results

Covariate	Patients (n = 96)	PFS	
		95% CI	P-value
PS			
0–1	89		
2–3	7	0.071–0.441	<0.001*
Tumor location			
SB	68		
Spine	28	0.992–3.283	0.053
PTV, mL			
≤70	48		
>70	48	0.890–2.859	0.116

\* $P < 0.05$ . CI, confidence interval; PFS, progression-free survival; PS, performance status; PTV, planning target volume; SB, skull base.

patient (1.0%), and pain in one patient (1.0%). Grade 4 late toxicities included tissue necrosis in two patients (2.1%) and a brainstem infarction in one patient (1.0%). The patient suffering from a brainstem infarction received a high-dose (maximum, 65.3 Gy [RBE] with a mean of 46.7 Gy [RBE]) to the brainstem. No treatment-related deaths occurred.

## Discussion

Our study is the first to evaluate PBT for BSs of the SB and spine on a nationwide multicenter basis in Japan. To the best of our knowledge, this study comprises the largest cohort of patients among reports published from Asia. Our findings are promising given that BSs of the SB and spine are difficult to resect completely. Recently, reports regarding particle therapy, including PBT and carbon ion radiotherapy,<sup>(32–36)</sup> for BSs of the SB and/or spine have been increasing rapidly, especially between 2014 and 2016. The results of recent studies, from 2011 to 2016, are summarized in Table 4. With respect to histological subtype, CS patients were generally associated with more favorable outcomes compared to chordoma patients. Weber *et al.*<sup>(25)</sup> demonstrated in a multivariate analysis that CS patients had a significantly improved OS and LC rate compared to chordoma patients. In our study, histological subtype was not a significant factor for OS, PFS, or LC. Regarding the comparison between PBT and carbon ion radiotherapy, there appears to be no apparent differences between these two treatment modalities. Mima *et al.*<sup>(22)</sup> published the results of particle therapy using carbon ions or protons as a definitive treatment for primary sacral chordoma patients and reported that there were no significant differences between the two ion types. Although a randomized controlled trial is needed to validate this finding, a German group is conducting a phase II trial of PBT and carbon ion radiotherapy for chordomas of the SB, CSs of the SB, and sacrococcygeal chordomas.<sup>(37–39)</sup>

In the present study, univariate and multivariate analyses revealed that a PS of 0–1 was associated with a significantly longer OS ( $P < 0.001$ ) and PFS ( $P < 0.001$ ), whereas female sex was associated with a significantly improved LC rate ( $P = 0.041$ ). To the best of our knowledge, this is the first report to identify PS as a significant prognostic factor, although most previously published reports did not include PS as a variable in the prognostic analyses. The statistical significance of PS may be due to chance alone since it was highly unbalanced between the two groups (0–1:  $n = 89$  vs. 2–3:  $n = 7$ ). However, it is logical that PS would affect survival.

**Table 4.** Recent studies of particle therapy for bone sarcomas of the skull base and/or spine

Author(s)	Year	Patients	Histological subtype	Tumor location	Therapy	OS	LC
Staab <i>et al.</i> <sup>(18)</sup>	2011	40	CH	Spine	P ± X ± S	80% (5y)	62% (5y)
Fuji <i>et al.</i> <sup>(17)</sup>	2011	16	CH/CS	SB	P ± S	100%	100% (CH), 86% (CS) (3y)
Matsumoto <i>et al.</i> <sup>(32)</sup>	2013	47	CH/CS/OSA/Other	Spine	C ± S	52% (5y)	79% (5y)
Uhl <i>et al.</i> <sup>(33)</sup>	2014	155	CH	SB	C ± S	85% (5y)	72% (5y)
Uhl <i>et al.</i> <sup>(34)</sup>	2014	79	CS	SB	C ± S	96% (5y)	88% (5y)
DeLaney <i>et al.</i> <sup>(20)</sup>	2014	50	CH/CS/Other	Spine	X + P ± S	84% (5y)	81% (5y)
Deraniyagala <i>et al.</i> <sup>(21)</sup>	2014	33	CH	SB	P ± S	92% (2y)	86% (2y)
Mima <i>et al.</i> <sup>(22)</sup>	2014	23	CH	Sacrum	C or P	83% (3y)	94% (3y)
Rotondo <i>et al.</i> <sup>(23)</sup>	2015	126	CH	Spine	X + P ± S	81% (5y)	62% (5y)
Hohl <i>et al.</i> <sup>(35)</sup>	2015	56	CH	Sacrum	C ± IMRT	52% (5y)	79% (5y)
Holliday <i>et al.</i> <sup>(24)</sup>	2015	19	CH/CS	Spine	S + P	93% (2y)	58% (2y)
Weber <i>et al.</i> <sup>(25)</sup>	2016	222	CH/CS	SB	S + P	86% (5y)	81% (5y)
Imai <i>et al.</i> <sup>(36)</sup>	2016	188	CH	Sacrum	C	81% (5y)	77% (5y)
Feuvret <i>et al.</i> <sup>(26)</sup>	2016	159	CS	SB	S + P	96% (5y)	95% (5y)
Indelicato <i>et al.</i> <sup>(27)</sup>	2016	51	CH/CS	Spine	P ± S	72% (4y)	58% (4y)
Hayashi <i>et al.</i> <sup>(28)</sup>	2016	19	CH	SB	S + P	83% (5y)	75% (5y)
Current study	2016	96	CH/CS/OSA	SB, Spine	P ± S	75% (5y)	71% (5y)

C, carbon ion; CH, chordoma; CS, chondrosarcoma; IMRT, intensity modulated radiotherapy; LC, local control; OS, overall survival; OSA, osteosarcoma; P, proton; S, surgery; SB, skull base; X, photon; y, year.

Staab *et al.*<sup>(18)</sup> and Mima *et al.*<sup>(22)</sup> reported that male chordoma patients had a significantly longer OS and PFS than female chordoma patients. Conversely, in the present study comprising 72 chordoma patients (75.0%), female sex was associated with a significantly improved LC rate. Several hypotheses have been proposed to explain the possible influence of sex on the treatment outcome of chordoma patients, as reviewed by Halperin.<sup>(40)</sup> For instance, sex hormone receptors may represent an influential factor in adult chordoma patients and genetic factors may also play a role in determining clinical outcomes. Although not statistically significant overall, a planning target volume of ≤70.0 mL was associated with a significantly longer PFS in the univariate analysis ( $P = 0.026$ ), but not the multivariate analysis ( $P = 0.116$ ), and exhibited a trend towards a longer OS ( $P = 0.056$ ). Several other studies<sup>(11,15,18,25,41)</sup> have demonstrated that tumor volume is a significant prognostic factor.

Proton beam therapy-related acute and late toxicities appeared to be tolerable. Grade 3 acute toxicities were reversible and did not influence treatment schedules. Nine patients (9.4%) experienced ≥Grade 3 late toxicities with a median follow-up of 52.6 months. However, the tumors were close to the affected organs and the events were considered to be unavoidable in all cases. Grade 4 brainstem infarction occurred in a patient with CS of the SB. Information concerning radiation-associated toxicities is very limited in the literature, most probably because most published series are retrospective studies that extend back several decades to accumulate an adequate number of patients. In such a scenario, two long-term studies of PBT for BSs of the SB or spine<sup>(20, 25)</sup> have been published. DeLaney *et al.*<sup>(20)</sup> reported Grade 3/4 late toxicities in 10.0% and 13.0% of spinal chordoma, CS, and other sarcoma patients at 5 and 8 years, respectively, whereas Weber *et al.*<sup>(25)</sup> reported Grade 3/4 late toxicities in 8.1% of SB chordoma and CS patients with a median follow-up of 50.0 months. Our results are comparable with the findings of these two studies. Despite high doses to treatment volumes, accompanying toxicities were relatively low, even though the majority of tumors were

located in regions adjacent to the organs at risk (i.e., the brainstem, optic nerve, and spinal cord), because the precise dose distribution of PBT could limit doses to critical structures.

This study has three important limitations. The foremost are its retrospective design and the relatively low impact of the statistical analyses. However, many previously published studies have also used a retrospective design, which is likely related to the difficulty of performing a prospective study given the rarity of the disease. Second, the follow-up period was relatively short (median, 52.6 months) and the major histological subtypes (chordoma and CS) in this study are slow growing with the potential for recurrence 5 years post-PBT. Therefore, we will continue to monitor these patients with the intention of being able to report on follow-up data. Finally, PS was highly unbalanced between the two groups (0–1:  $n = 89$  vs. 2–3:  $n = 7$ ), and thus, the statistical significance of this variable may have occurred by chance alone. However, we identified no biased estimates with unstable standard errors in our multivariate analysis.

In conclusion, we are the first to demonstrate the safety and efficacy of PBT for BSs of the SB and spine in a retrospective, nationwide multicenter study in Japan. Larger prospective studies with a longer follow-up are required to validate these findings.

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### Disclosure Statement

The authors have no conflict of interest.

## Abbreviations

BED <sub>10</sub>	biologically effective dose, alpha/beta ratio of 10.0 Gy
BS	bone sarcoma
CI	confidence interval
CS	chondrosarcoma
LC	local control

OS	overall survival
PBT	proton beam therapy
PFS	progression-free survival
PS	performance status
RBE	relative biological effectiveness
SB	skull base

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