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Long-term outcomes of high dose carbon-ion radiation therapy for unresectable upper cervical (C1-2) chordoma

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Abstract

Background: Chordoma is a rare, locally invasive neoplasm of the axial skeleton. Complete resection is often difficult, especially for the upper-cervical (C1-2) spine. We evaluated the efficacy and safety of carbon-ion radiotherapy (CIRT) for unresectable C1-2 chordoma.

Methods: Patients with C1-2 chordoma treated with definitive CIRT (60.8 Gy [RBE] in 16 fractions) were retrospectively analyzed. We evaluated OS, LC, PFS, and toxicity.

Results: Nineteen eligible patients all completed the planned course of CIRT. With the median follow-up 68 months (range: 29–144), median OS was 126 months (range: 36-NA). Five-year OS, LC, and PFS were 68.4% (95% CI, 42.8%–84.4%), 75.2% (46.1%–90.0%), and 64.1% (36.3%–82.3%), respectively. Regarding acute toxicity of grade ≥3, there was only one grade 3 mucositis. Late toxicity included radiation-induced myelitis (grade 3 in 1 patient; 5.3%), and compression fractures ($n = 5$; 26.3%).

Conclusions: High-dose CIRT is a promising treatment option for unresectable upper cervical chordoma.

KEYWORDS

carbon-ion radiation therapy, cervical spine, chordoma, myelitis, vertebral compression fractures

1 | INTRODUCTION

Chordoma is a rare, low-grade but locally aggressive tumor that arises in notochordal remnants in the midline from the skull base to the sacrum, with an overall incidence of <1 in 1 000 000 persons per year.[1–3] The most common tumor sites are the sacrum (50%–55%), followed by the skull base (30%–35%) and mobile spine (10%–20%,

Abbreviations: AE, adverse events; CI, confidence interval; CIRT, carbon-ion radiation therapy; CT, computed tomography; CTV, clinical target volume; GTV, gross tumor volume; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky performance status; LC, local control; MRI, magnetic resonance imaging; OAR, organ at risk; OS, overall survival; PFS, progression-free survival; PTV, planning target volume; RBE, relative biological effectiveness; RECIST, the Response Evaluation Criteria in Solid Tumors; VCF, vertebral compression fractures.

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of which the cervical spine accounts for approximately 5%).[4–6]

Surgery has been the standard treatment for the control of chordoma, and cases involving the mobile spine are ideally managed via en bloc resection.[2,5,7,8] However, in the cervical spine, the extent of surgery is severely limited by the risk of neurological morbidities, and especially upper cervical localization makes en bloc resection impossible in most cases.[6,7,9–12]

In patients who receive radiation therapy (RT), the dose is also severely limited by the spinal cord, nerves, and visceral tolerance. Due to these dose constraints and the radioresistance of the tumor, RT had not been expected to play a decisive role in the treatment of chordomas, but is commonly utilized for patients with a positive surgical margin after surgery, and was reported to contribute to their increased survival.[6,13–16] To improve the dose distribution, several new radiation modalities, such as intensity-modulated radiation therapy (IMRT) and particle therapy including proton and carbon ion radiation therapy (CIRT), have been introduced in recent decades. Among them, CIRT is expected to provide conformal dose distribution and a high biological effect.[13,14,17–21] This study evaluated the long-term outcomes of patients with inoperable upper cervical chordoma who received high-dose CIRT.

2 | MATERIALS AND METHODS

2.1 | Patient eligibility

Patients with unresectable upper cervical chordoma that was treated with definitive CIRT at our institution between April 2005 and December 2014 were retrospectively analyzed. All patients included in this study were prescribed 60.8 Gy (relative biological effectiveness [RBE]) in 16 fractions.

The main eligibility criteria for this study were as follows: (a) histologically confirmed chordoma from the upper cervical spine (C1-2), (b) grossly measurable tumor, (c) no distant metastasis, (d) age 15 years or older, (e) an Eastern Cooperative Oncology Group performance status score ≤2, (f) medically inoperable tumor or refusal of surgery, and (f) no serious medical or psychological conditions precluding the safe administration of treatment. Patients who previously underwent irradiation for the same lesion were excluded.

Patients provided their informed consent, which authorized the use of their personal information for research purposes. This retrospective study was reviewed and approved by the Institutional Ethical Committee on Human Clinical Research (17-023) and was carried out in accordance with the Declaration of Helsinki. This trial was registered with UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm, identification number UMIN 000029380).

2.2 | Carbon-ion radiation therapy

During both the planning computed tomography (CT) and CIRT, patients were positioned in customized cradles and immobilized by a thermoplastic shell. Three-dimensional treatment planning was performed using the HIPLAN (National Institute of Radiological Sciences, Chiba, Japan) or Xio-N (ELEKTA, Stockholm, Sweden and Mitsubishi Electric, Tokyo, Japan) software programs.

The gross tumor volume (GTV) was defined using CT (slice thickness: 2.0–2.5 mm) and magnetic resonance imaging (MRI) images with contrast medium. The clinical target volume (CTV) had margins of 5–8 mm added around the GTV and included the entire vertebral body if possible. The CTV margin was adjusted as needed when the tumor was in close proximity to or invaded a critical organ at risk (OAR), such as the spinal cord and mucosa of the pharynx. The planning target volume (PTV) had 2-mm margins added around the CTV.

The target reference point dose was defined as the isocenter. The treatment plans were made to cover the GTV with >95% of the prescribed dose and the PTV with >90% of the prescribed dose.

The dose limits for critical normal tissues were defined as a maximum point dose of 30 Gy (RBE) for the spinal cord and brain stem. If the tumor was close to the spinal cord, it was acceptable if the minimum dose to 1 cc of the most irradiated volume (D1cc) of the spinal cord and brain stem was <30 Gy (RBE). The dose limits of the cord were given priority over PTV coverage. A typical dose distribution is shown in Figure 1.

The prescribed dose was 60.8 Gy (RBE) in 16 fractions with four fractions per week. Carbon-ion doses were expressed as photon-equivalent doses in Gy (RBE) and were defined as the physical dose multiplied by the carbon-ion RBE.

2.3 | Follow-up and statistical analyses

The initial imaging examination (MRI or CT) was performed when the patient completed all CIRT sessions. After that, follow-up examinations were conducted at intervals of 3–6 months within the first 5 years, and 6–12 months thereafter; including physical examinations, blood examinations, CT, and MRI. If continuous examinations at our hospital were difficult, the latest medical reports and diagnostic images were sent to us.

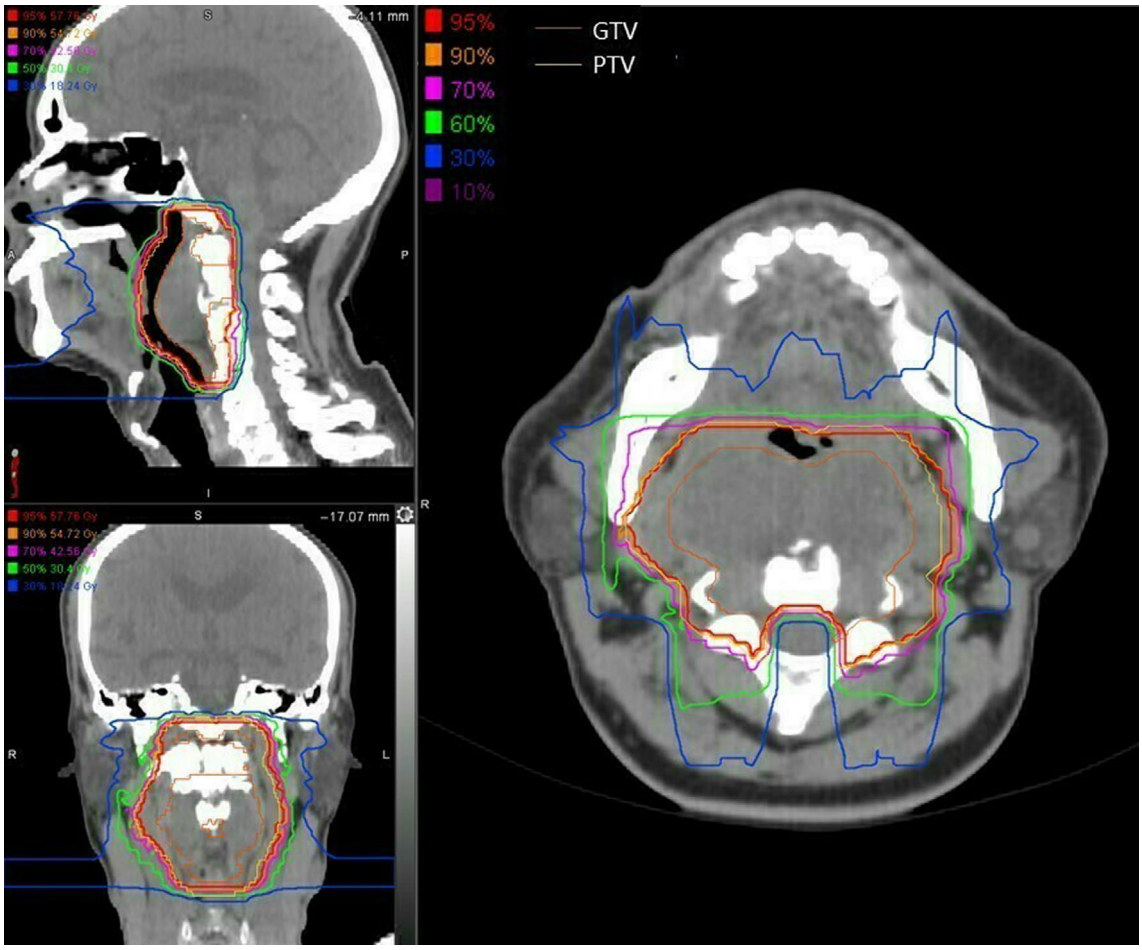

FIGURE 1 Radiation dose distribution of CIRT for C1-2 chordoma. The thin orange line represents the GTV and the thin yellow line represents the PTV. [Color figure can be viewed at wileyonlinelibrary.com]

Local control (LC) was basically defined as no increase in tumor size in PTV on consecutive CT/MRI studies according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[22] LC, overall survival (OS), and progression-free survival (PFS) were calculated from the initiation of CIRT using the Kaplan–Meier method; the log rank test was used for group comparisons. Acute (within 90 days of CIRT initiation) adverse events (AEs) were evaluated according to the Radiation Therapy and Oncology Group scoring system.[22] Late (after 90 days) AEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (United States National Cancer Institute, Bethesda, MD).[23] Risk factors for vertebral compression fractures (VCFs) were assessed using the chi-squared test. Univariate descriptive statistical analyses, Kaplan–Meier survival estimates, and log-rank tests were performed using EZR version 1.54 which is a graphical interface for R (The R Foundation for Statistical Computing).[24] A confidence interval of 95% was chosen (95% confidence interval [CI]), and *p*-values of <0.05 were considered to indicate statistical significance.

3 | RESULTS

A total of 20 consecutive patients were identified and 19 were included in the study. One patient was excluded from this analysis due to a lack of imaging examinations from the start of the irradiation. All patients completed the planned CIRT: 60.8 Gy (RBE) in 16 fractions. The median duration of treatment was 28 days (range: 25–31 days). In all cases, radical resection was judged to be anatomically difficult and the patients were referred to our hospital. Two patients underwent surgery as pretreatment for radiation therapy (laminectomy, $n = 1$; posterior fusion, $n = 1$). No patients received chemotherapy. The patient and tumor characteristics are shown in Table 1.

The median observation time from the initiation of CIRT was 68 months (range: 29–176 months). The

TABLE 1 Patient and tumor characteristics

Patient characteristics		$n = 19$
Age (years)		63 (26–81)
Male/female		13/6
KPS		80 (70–90)
Primary/recurrent		17/2
Symptoms at diagnosis	Yes/no	19/0
Main occupation of tumor	C1	3
	C2	16
Tumor diameter (mm)		49 (20–70)
Spinal canal invasion	Yes/no	10/9
Nerve root compression	Yes/no	6/13
Distance from the cord	0 mm	3
	1–3 mm	13
	4–9 mm	3
GTV (cc)		39.3 (9.11–117.93)
PTV (cc)		123.6 (48.8–287.90)
GTV mean (Gy [RBE])		59.97 (58.53–65.54)
GTV min (Gy [RBE])		27.75 (0.46–47.61)
PTV mean (Gy ([RBE])		59.67 (57.84–65.22)
PTV min (Gy [RBE])		21.24 (4.7–39.77)

Abbreviations: C, cervical spine; GTV, gross tumor volume; KPS, Karnofsky performance status; *n*, number; PTV, planning tumor volume; RBE, relative biological effectiveness.

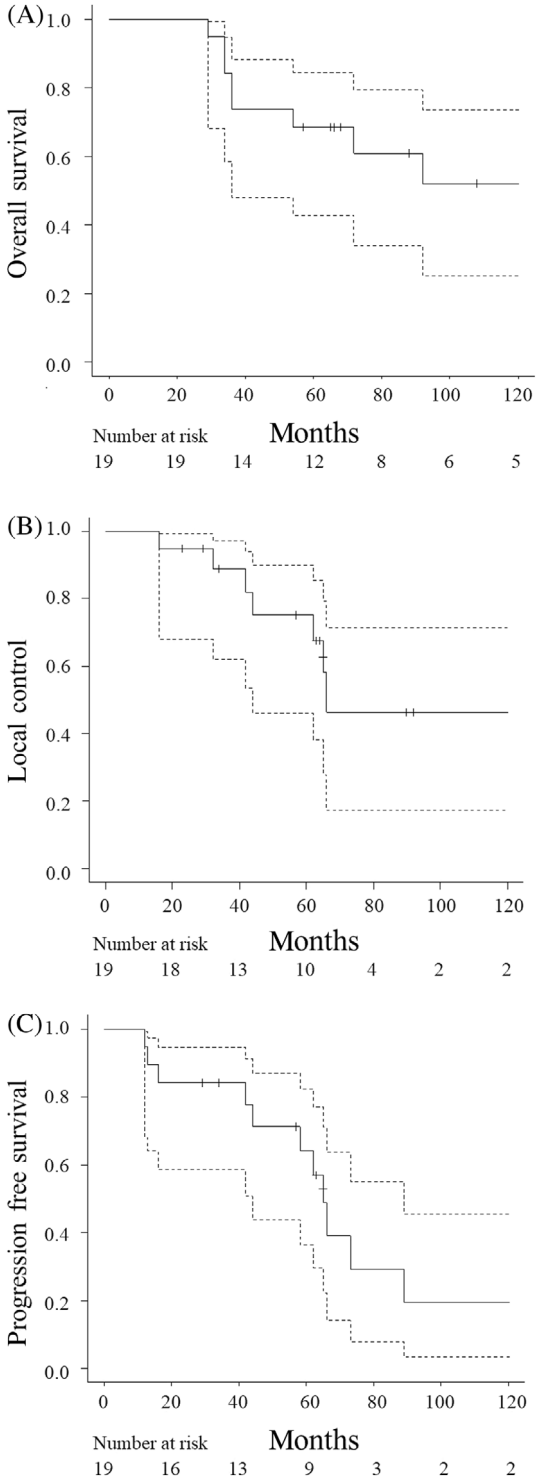

FIGURE 2 Kaplan–Meier curves for (A) overall survival, (B) local control, and (C) progression-free survival in the whole cohort

2-year, 5-year, and 10-year OS rates were 100%, 68.4% (95% CI, 42.8%–84.4%), and 52.1% (95% CI, 25.2%–73.5%), respectively (Figure 2A). Of the 9 patients who died during the course, 6 died of chordoma and the remaining three died of other diseases (one heart failure and two unspecified) with no recurrence of chordoma. The 2-year, 5-year and 10-year LC rates were 94.7% (95% CI, 68.1%–99.2%), 75.2% (95% CI, 46.1%–90.0%), and 46.4% (95% CI, 17.2%–71.5%), respectively. During the follow-up period, local recurrences, or recurrences within the PTV, were detected in 7 patients (37%), and 3 of them (43%) were occurred ≥5 years after irradiation (Figure 2B). Two of the local recurrences were confined to the marginal area close to the spinal cord, suggesting an association with dose reduction due to the restriction to the spinal cord. Of these 7 local recurrences, 6 were treated with salvage mass reduction and 1 with re-irradiation after fully explaining the risks.

The 2-year, 5-year and 10-year progression free survival rates were 84.2% (95% CI, 58.7%–94.6%), 64.1% (95% CI, 36.3%–82.3%), and 19.5% (95% CI, 3.4%–45.6%), respectively (Figure 2C). In total, five patients developed distant metastasis (lower cervical spine [$n = 3$], paratracheal lymph nodes [$n = 1$], and lung [$n = 1$]). Three of the five patients (60%) also had local recurrence before or after distant metastasis. Salvage surgery was performed in the three cases of recurrence in the lower

TABLE 2 Univariate analysis of local control and overall survival rates

		LC		OS	
	No. of patients	**5y LC**	***p*-value**	**5y OS**	***p*-value**
Sex			0.54		0.55
Male	13	74.6%		66.7%	
Female	6	75.0%		69.2%	
Age (years)			0.094		1.00
>70	5	100%		60.0%	
≤70	14	68.1%		71.4%	
KPS			0.98		0.33
90–100	9	85.7%		55.6%	
≤80	10	67.5%		80.0%	
Tumor status			0.39		0.35
Initial	17	71.5%		64.7%	
Recurrent	2	100%		100%	
GTV (cc)			0.40		0.042*
>40	9	58.3%		50.0%	
≤40	10	88.9%		88.9%	
Spinal cord compression			0.43		0.91
Yes	3	64.3%		70.0%	
No	16	88.9%		66.7%	
Minimum dose of GTV [Gy (RBE)]			0.43		0.95
>30	8	87.5%		75.0%	
≤30	11	67.5%		63.6%	

Abbreviations: 5y, 5 year; GTV, gross tumor volume; KPS, Karnofsky performance status; LC, local control; n, number; OS, overall survival; RBE, relative biological effectiveness.

cervical spine. The remaining two distant metastases (lung and lymph node) were treated only with palliative therapy and no definitive local therapy.

The factors predicting OS and LC are summarized in Table 2. The univariate analysis of prognostic factors for OS revealed that a GTV of >40 cc was significant prognostic factor ($p = 0.042$). The 5-year OS of patients with GTV of >40 cc was 50.0% and with GTV of <40 cc was 89.9%. In contrast, sex, age, Karnofsky performance status (KPS), tumor status (initial or recurrent), spinal cord infiltration, and minimum dose of GTV were not statistically significant factors. With regard to LC and PFS, the univariate analysis indicated no statistically significant differences among these factors.

As for grade ≥3 acute AEs, one patient developed grade 3 mucositis (5%), but no grade ≥4 acute AEs. Regarding late AEs (excluding compression fractures, which are discussed below), there was no case of grade 4 or higher, but two cases (11%) of grade 3. One of them was a case of dysphagia, which resolved with only conservative palliative therapy. The other case was radiation myelitis. In all, five patients (26.3%) experienced radiation-induced encephalomyelitis; 3 (60%) of these cases were classified as grade 1, with only imaging findings and no clinical symptoms. One of the remaining two complained of neck pain (grade 2). The other developed numbness and difficulty moving their limbs (grade 3). In the grade 3 case, there was no intrathecal invasion (tumor-spinal distance, 6 mm), and the maximum dose and D1cc of the spinal cord were 41.8 Gy (RBE) and 20.5 Gy (RBE), respectively.

Regarding VCF, 4 patients already had a VCF before irradiation due to tumor infiltration. Post-irradiation VCFs occurred in 5 additional patients (median, 20 months) during follow-up. Three of these patients underwent posterior spinal fusion. As previously reported,[25,26] patients with VCF after CIRT tended to have higher Spinal Instability Neoplastic Score (SINS) values ($p = 0.07$). When the 4 cases with pretreatment

TABLE 3 Baseline SINS classification according to VCF status

SINS component	SINS	VCF all; $n = 9$ (VCF AE; $n = 5$)	No VCF; $n = 10$
Location			
Junctional (O-C2; C7-T2, T11-L1; L5-S1)	3	9 (5)	10
The others (mobile spine, semirigid, rigid)	0–2	0	0
Pain			
Mechanical	3	6 (2)	2
Occasional and nonmechanical	2	0	4
Pain free	1	3 (3)	4
Bone lesion			
Lytic	2	7 (4)	6
Mixed	1	2 (1)	3
Blastic	0	0	1
Radiographic spinal alignment			
Subluxation or translation	4	4 (2)	0
Kyphosis or scoliosis	2	4 (2)	3
Normal	0	1 (1)	7
Vertebral body collapse			
>50%	3	6 (2)	2
<50%	2	3 (3)	7
No collapse with >50% body involved	1	0	1
None of the above	0	0	0
Posterolateral involvement			
Bilateral	3	6 (2)	2
Unilateral	1	3 (3)	6
None of the above	0	0	2
SINS classification			
Unstable (score of 13–16)		7 (3)	1
Potentially unstable (7–12)		2 (2)	9
Stable (0–6)		0	0

Abbreviations: AE, adverse event; *n*, number; SINS, Spinal Instability Neoplastic Score; VCF, vertebral compression fracture.

VCF were considered together, the frequency of VCF was as high as 50%, further emphasizing the relationship with the SINS ($p = 0.0055$) (Table 3).

4 | DISCUSSION

To our knowledge, this is the first study to report the long-term results of high-dose CIRT for upper cervical spine chordoma. There are few published series focusing on CIRT for cervical chordoma, especially in the upper cervical region, probably due to its rarity. However, the research on chordoma in the upper cervical spine, a rare site with the most severe anatomical conditions, will be helpful for revealing the characteristics and treatment of this tumor.[5,6,13,16,27–29]

4.1 | Comparison with surgical treatment

Several reports have focused on surgical management for cervical spine chordoma; however, these were either mixed studies or they did not mention the methods or modalities of adjuvant radiation therapy.[7,8,13,15,18,30,31] Wang et al. reported analyzed 14 consecutive patients with primary chordoma of the cervical spine who underwent surgery and postoperative RT.[30] With a mean follow-up time of 58.6 months, the 1- and 5-year OS rates were 92.9% and 85.7%, respectively. They also reported that an upper cervical tumor location was significantly associated with a high rate of tumor recurrence ($p = 0.019$). Guan et al. reported the preliminary results of adjuvant proton and CIRT for 91 patients with skull base or cervical spine chordoma and chondrosarcoma (6 of whom had cervical tumors).[18] With a median follow-up time of 28 months, the 2-year LC, PFS and OS rates were reported to be 86.2%, 76.8%, and 87.2%, respectively.

The long-term prognosis was not significantly inferior when the results of CIRT were compared to these surgical data. Given that all cases were inoperable, it can be said that definitive CIRT for unresectable upper cervical chordoma provided satisfying results.

4.2 | Comparison with radiation therapy of the other modalities

While chordomas have traditionally been recognized as radioresistant tumors, their therapeutic effect is known to be dose-dependent.[13,14,32] Previous reports showed that conventional RT at a dose of up to 50–60 Gy was insufficient for long-term control of chordoma, even as a postoperative adjuvant therapy.[33] With advances in radiation technology, effective RT doses have become relatively safely delivered.[14,17–21] Recent reports have shown that advanced RT with total doses of >65 Gy improved

survival in comparison to patients treated with low doses.[16] Beams using proton or carbon ion offer improved conformal dose distribution in comparison to conventional photon radiotherapy.[34–37] Moreover, carbon ions have a biological advantage due to their increased RBE through double-stranded breaks in DNA in comparison to protons and photons,[38–40] which may provide better tumor control.

4.3 | Comparison with chordomas of the other sites

It has been reported that the prognosis of chordoma differs depending on the tumor site, and the prognosis of mobile spine tumors, especially cervical spine tumors is poor.[5,6,27,28,41] Among them, higher levels of cervical chordoma have been demonstrated to be associated with a worse prognosis,[11,12,30] probably in association with the difficulty of surgery with a sufficient margin.[6,30] Wang et al. argued in their paper that clear exposure in the upper cervical region was more challenging than in the lower cervical region, and complete resection of the tumor tissue could be very difficult due to the complicated nearby structures.[30]

The same is true for radiation therapy. While many reports have described using doses of >70 Gy for the sacral spine,[42–45] cervical spine lesions require relatively low doses.[13,17–20,45] Moreover, dose constraints on important OARs (e.g., the spinal cord and brainstem) could result in insufficient radiation doses to parts of the tumors.[46]

Our institution has separated protocols for bone and soft tissue tumors above and below C2: 60.8 Gy (RBE) in 16 fractions for C2 and above and 64–70.4 Gy (RBE) in 16 fractions for below C2. These doses were determined through clinical trials conducted at our hospital.[20,43,46]

In 2016, the clinical results of CIRT using 64–73.6 Gy (RBE) for sacral chordoma were reported from our hospital.[43] According to the paper, with a median follow-up of 62 months, the 5-year LC, OS rates were 77.2% and 81.1%, respectively. As in previous reports of sacral chordoma, the tumor volume was larger than that of the upper cervical spine, but the tumor control was more favorable, probably due in part to the prescribed dose.

On the other hand, we reported the results of CIRT using 60.8 Gy (RBE) for skull base chordoma in 2020.[46] With a median follow-up period of 108 months, the 5- and 9-year LC rates were 76.9% and 69.2%, respectively. The 5- and 9-year OS rates were 93.5% and 77.4%, respectively. Despite the same dose regimen, CIRT for the skull base was associated with significantly better results in comparison to the upper cervical spine in terms of both LC and OS, probably due in part to the smaller size of the GTV (18.7 cc; range: 1.5–126.7) and the relative simplicity of the anatomy.

4.4 | Predictors

With regard to the prognostic analysis, a GTV of >40 cc was the only significant predictor of OS (Table 2). This prognostic factor is well-known and has been validated by many previous reports on chordoma.[8,27,46–49] Currently, we are working on the development of more conformal treatment using a technique called "scanning,"[50] and we are trying to apply higher dose in cases with tumor volumes ≥35 cc based on the analysis of our clinical results of skull base chordoma.[46]

Distance to the spinal cord and minimum dose of tumor have also been reported as prognostic factors,[15,17,51] although no difference was found in the present study due to insufficient number of cases. As one way to improve dose distribution, especially for tumors bordering the spinal cord, Matsumoto et al.[52] have reported the hopeful outcome of pre-CIRT separation surgery for primary spinal/para-spinal tumor; which provides a small spinal margin of 2–3 mm, thereby enabling a full radiation dose to be delivered to the entire tumor volume. We may need to positively consider pre-irradiation surgical pretreatment for cases with spinal canal infiltration.

The SINS values originally made for bone metastases helped to predict VCFs in cervical chordomas. However, in our subjects, VCFs occurred at similar frequency before and after CIRT. In other words, in cervical chordoma, VCF is often caused by vertebral instability caused by the tumor itself, not only as post-CIRT AEs. For patients with high SINS values, we should recognize the risk of VCF (and associated neurological symptoms) from the time of the diagnosis, and consider posterior fixation after irradiation as needed.

4.5 | Limitations

The present study was associated with several limitations. Primarily, it was conducted at a single institution and was retrospective in nature. Therefore, a degree of intrinsic bias may remain. Second, the small number of patients may have limited the statistical power of the results. Moreover, it is still difficult to compare data between institutions because dose prescriptions have not been widely established. In the future, nationwide multi-institutional research will be required to explore the role of CIRT and appropriate dose administration methods in the treatment of upper cervical chordoma.

5 | CONCLUSION

The present study suggested that definitive CIRT represented a promising alternative treatment for patients with unresectable upper cervical spine chordoma. The accumulation of further cases and the analysis of detailed data are required.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This retrospective study was reviewed and approved by the Institutional Ethical Committee on Human Clinical Research (17-023).

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REFERENCES

1. Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer*. 2013;49:684-695.
2. Stacchiotti S, Sommer J, Chordoma Global Consensus Group. Building a global consensus approach to chordoma: a position paper from the medical and patient community. *Lancet Oncol*. 2015;16:e71-e83.
3. Smoll NR, Gautschi OP, Radovanovic I, Schaller K, Weber DC. Incidence and relative survival of chordomas: the standardized mortality ratio and the impact of chordomas on a population. *Cancer*. 2013;119:2029-2037.
4. Bjornsson J, Wold LE, Ebersold MJ, Laws ER. Chordoma of the mobile spine. A clinicopathologic analysis of 40 patients. *Cancer*. 1993;71:735-740.
5. Pan Y, Lu L, Chen J, Zhong Y, Dai Z. Analysis of prognostic factors for survival in patients with primary spinal chordoma using the SEER registry from 1973 to 2014. *J Orthop Surg Res*. 2018;13:76.
6. Zuckerman SL, Bilsky MH, Laufer I. Chordomas of the skull base, mobile spine, and sacrum: an epidemiologic investigation of presentation, treatment, and survival. *World Neurosurg*. 2018;113:e618-e627.
7. Pham M, Awad M. Outcomes following surgical management of cervical chordoma: a review of published case reports and case series. *Asian J Neurosurg*. 2017;12:389-397.
8. Boriani S, Bandiera S, Biagini R, et al. Chordoma of the mobile spine: fifty years of experience. *Spine (Phila PA 1976)*. 2006;31(4):493-503.
9. Alan O, Akin Telli T, Ercelep O, et al. Chordoma: a case series and review of the literature. *J Med Case Reports*. 2018;12:239.
10. Wasserman JK, Gravel D, Purgina B. Chordoma of the head and neck: a review. *Head Neck Pathol*. 2018;12:261-268.
11. Jiang L, Liu ZJ, Liu XG, et al. Upper cervical spine chordoma of C2–C3. *Eur Spine J*. 2009;18:293-298; discussion 298–300.
12. Konieczkowski DJ, DeLaney TF, Yamada YJ. Radiation strategies for spine chordoma: proton beam, carbon ions, and stereotactic body radiation therapy. *Neurosurg Clin N Am*. 2020;31:263-288.
13. Zabel-du Bois A, Nikoghosyan A, Schwahofer A, et al. Intensity modulated radiotherapy in the management of sacral chordoma in primary versus recurrent disease. *Radiother Oncol*. 2010;97:408-412.
14. De Amorim BK, DeLaney T. Chordomas and chondrosarcomas—the role of radiation therapy. *J Surg Oncol*. 2016;114:564-569.
15. Dial BL, Kerr DL, Lazarides AL, et al. The role of radiotherapy for chordoma patients managed with surgery: analysis of the National Cancer Database. *Spine (Phila PA 1976)*. 2020;45(12):E742-E751.
16. Iannalfi A, D'Ippolito E, Riva G, et al. Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy. *Neuro Oncol*. 2020;22:1348-1358.
17. Seidensaal K, Harrabi SB, Uhl M, Debus J. Re-irradiation with protons or heavy ions with focus on head and neck, skull base and brain malignancies. *Br J Radiol*. 2020;93:20190516.
18. Guan X, Gao J, Hu J, et al. The preliminary results of proton and carbon ion therapy for chordoma and chondrosarcoma of the skull base and cervical spine. *Radiat Oncol*. 2019;14:206.
19. Mizoe JE, Hasegawa A, Takagi R, Bessho H, Onda T, Tsujii H. Carbon ion radiotherapy for skull base chordoma. *Skull Base*. 2009;19:219-224.
20. Kamada T, Tsujii H, Blakely EA, et al. Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience. *Lancet Oncol*. 2015;16:e93-e100.
21. Matsufuji N. Selection of carbon beam therapy: biophysical models of carbon beam therapy. *J Radiat Res*. 2018;59:i58-i62.
22. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31:1341-1346.
23. Common Terminology Criteria for Adverse Events (CTCAE). Vol. 4.03: US National Cancer Institute, Division of Cancer Treatment & Diagnosis, Cancer Therapy Evaluation Program; 2010.
24. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48:452-458.
25. Matsumoto Y, Shinoto M, Endo M, et al. Evaluation of risk factors for vertebral compression fracture after carbon-ion radiotherapy for primary spinal and paraspinal sarcoma. *Biomed Res Int*. 2017;2017:9467402.

26. Fourney DR, Frangou EM, Ryken TC, et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *J Clin Oncol*. 2011;29:3072-3077.
27. Bergh P, Kindblom LG, Gunterberg B, Remotti F, Ryd W, Meis-Kindblom JM. Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. *Cancer*. 2000;88:2122-2134.
28. Pennicooke B, Laufer I, Sahgal A, et al. Safety and local control of radiation therapy for chordoma of the spine and sacrum: a systematic review. *Spine (Phila PA 1976)*. 2016;41(Suppl 20): S186-S192.
29. Ruggieri P, Angelini A, Ussia G, Montalti M, Mercuri M. Surgical margins and local control in resection of sacral chordomas. *Clin Orthop Relat Res*. 2010;468:2939-2947.
30. Wang Y, Xiao J, Wu Z, et al. Primary chordomas of the cervical spine: a consecutive series of 14 surgically managed cases. *J Neurosurg Spine*. 2012;17:292-299.
31. Molina CA, Ames CP, Chou D, et al. Outcomes following attempted en bloc resection of cervical chordomas in the C-1 and C-2 region versus the subaxial region: a multiinstitutional experience. *J Neurosurg Spine*. 2014;21:348-356.
32. Kano H, Niranjan A, Lunsford LD. Radiosurgery for chordoma and chondrosarcoma. *Prog Neurol Surg*. 2019;34:207-214.
33. Tai PT, Craighead P, Bagdon F. Optimization of radiotherapy for patients with cranial chordoma. A review of dose-response ratios for photon techniques. *Cancer*. 1995;75:749-756.
34. Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. *J Clin Oncol*. 2007;25:953-964.
35. Trifiletti DM, Brown PD. Proton and carbon ion therapy for skull base chordomas. *Neuro Oncol*. 2020;22:1241-1242.
36. Yu Z, Hong Z, Zhang Q, et al. Proton and carbon ion radiation therapy for locally advanced pancreatic cancer: a phase I dose escalation study. *Pancreatology*. 2020;20:470-476.
37. Chen YL, Liebsch N, Kobayashi W, et al. Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. *Spine (Phila PA 1976)*. 2013;38(15):E930-E936.
38. Wambersie A, Gahbauer AR, Menzel GH. RBE and weighting of absorbed dose in ion-beam therapy. *Radiother Oncol*. 2004; 73(Suppl 2):S176-S182.
39. Lazar AA, Schulte R, Faddegon B, Blakely EA, Roach M 3rd. Clinical trials involving carbon-ion radiation therapy and the path forward. *Cancer*. 2018;124:4467-4476.
40. Saager M, Glowa C, Peschke P, et al. Fractionated carbon ion irradiations of the rat spinal cord: comparison of the relative biological effectiveness with predictions of the local effect model. *Radiat Oncol*. 2020;15:6.
41. Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. *Int J Radiat Oncol Biol Phys*. 1995;33:579-584.
42. Rotondo RL, Folkert W, Liebsch NJ, et al. High-dose proton-based radiation therapy in the management of spine chordomas: outcomes and clinicopathological prognostic factors. *J Neurosurg Spine*. 2015;23:788-797.
43. Imai R, Kamada T, Araki N, Working Group for Bone and Soft Tissue Sarcomas. Carbon ion radiation therapy for unresectable sacral chordoma: an analysis of 188 cases. *Int J Radiat Oncol Biol Phys*. 2016;95:322-327.
44. Bostel T, Mattke M, Nicolay NH, et al. High-dose carbon-ion based radiotherapy of primary and recurrent sacrococcygeal chordomas: long-term clinical results of a single particle therapy center. *Radiat Oncol*. 2020;15:206.
45. Demizu Y, Imai R, Kiyohara H, Matsunobu A, Okamoto M, Okimoto T. Carbon ion radiotherapy for sacral chordoma: a retrospective nationwide multicentre study in Japan. *Radiother Oncol*. 2021;154:1-5.
46. Koto M, Ikawa H, Kaneko T, Hagiwara Y, Hayashi K, Tsuji H. Long-term outcomes of skull base chordoma treated with high-dose carbon-ion radiotherapy. *Head Neck*. 2020;42:2607-2613.
47. Fung V, Calugaru V, Bolle S, et al. Proton beam therapy for skull base chordomas in 106 patients: a dose adaptive radiation protocol. *Radiother Oncol*. 2018;128:198-202.
48. Ares C, Hug EB, Lomax AJ, Bolsi A, Timmermann B, Rutz HP. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. *Int J Radiat Oncol Biol Phys*. 2009;75:1111-1118.
49. McDonald MW, Linton OR, Moore MG, Ting JY, Cohen-Gadol AA, Shah MV. Influence of residual tumor volume and radiation dose coverage in outcomes for clival chordoma. *Int J Radiat Oncol Biol Phys*. 2016;95:304-311.
50. Furukawa T, Inaniwa T, Sato S, et al. Performance of the NIRS fast scanning system for heavy-ion radiotherapy. *Med Phys*. 2010;37:5672-5682.
51. Kabolizadeh P, Chen YL, Liebsch N, et al. Updated outcome and analysis of tumor response in mobile spine and sacral chordoma treated with definitive high-dose photon/proton radiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;97: 254-262.
52. Matsumoto Y, Matsunobu A, Kawaguchi K, et al. Clinical results of carbon-ion radiotherapy with separation surgery for primary spine/paraspinal sarcomas. *Int J Clin Oncol*. 2019;24: 1490-1497.

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