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Scientific Article

Intensity Modulated Carbon Ion Radiation Therapy Using Pencil Beam Scanning Technology for Patients With Unresectable Sacrococcygeal Chordoma

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Purpose: To investigate the safety and efficacy of intensity modulated carbon ion radiation therapy (IM-CIRT) using pencil beam scanning technology for patients with unresectable sacrococcygeal chordoma (SC).

Methods and Materials: A total of 35 patients with unresectable SC were retrospectively analyzed, including 54.3% (19/35) recurrent cases. In 68.6% (24/35) cases, tumor was located in S2 or above, and all cases were treated with hypofractionated IM-CIRT. The median dose was 70.4 Gy (range, 69-80 Gy) (relative biologic effectiveness) in 16 fractions (range, 16-23 fractions), typically delivered over 5 fractions per week.

Results: The 3-year overall survival, cause-specific survival, progression-free survival, locoregional progression−free survival, and distant metastasis−free survival rates with a median follow-up time of 42 months (range, 12-91 months) for the entire cohort were 93.2%, 96.3%, 61.8%, 80%, and 77.3%, respectively. Multivariate analysis revealed that gross tumor volume (hazard ratio, 3.807; 95% CI, 1.044-13.887; $P = .043$) was the only significant prognostic factor for progression-free survival and the dose for the gross tumor volume ≥70.4 Gy (relative biologic effectiveness) was relevant with significantly better locoregional progression−free survival (hazard ratio, 0.190; 95% CI, 0.038-0.940; $P = .042$). No significant prognostic factor for overall survival, cause-specific survival, and distant metastasis−free survival and no severe (ie, grade ≥3) acute toxicity were identified. Severe late toxicities occurred in 3 patients (8.57%): pain (1 patient), motor neuropathy (1 patient), and skin ulcer (1 patient). Furthermore, no severe toxicity related to urinary function or defecation was observed following IM-CIRT. Pain grades improved or remained unchanged in 85.7% of patients.

Conclusions: IM-CIRT produced acceptable 3-year outcomes without substantial late adverse effects, especially urinary and anorectal complications for SC, and did not appear to increase pain. IM-CIRT at high doses using hypofractionated radiation therapy may improve outcomes for local control and seems to be feasible even for postoperative recurrent SC.

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Introduction

Sacrococcygeal chordoma (SC) constitutes 60% of all chordomas originating from the residual embryonic notochord. Both National Comprehensive Cancer Network (NCCN) guidelines and the Chordoma Global Consensus Group (CGCG)[1-3] suggested that surgery is the main treatment strategy for curative intent. However, owing to the pathologic, physiological, and anatomic characteristics, complete resection with sufficient margins is only achieved in approximately 50% of patients with SC. Moreover, surgical resection for tumors above the level of S3 is highly challenging because the bilateral S1/S2 nerve roots responsible for bladder and rectal function were susceptible to be injured, which might induce serious neurologic sequelae and affect patients' quality of life.[1,2] Radiation therapy (RT) is an alternative treatment option for these patients. But owing to the limit of adjacent critical organs at risk (OARs; eg, bowel and rectum), the dose of conventional photon RT is not sufficient to control the tumor.[4] Highly conformal treatment techniques such as carbon ions and protons are recommended for the SC.[1,3,5]

The rationale for carbon ion RT (CIRT) is that administering a high linear energy transfer (LET) irradiation would translate to a higher biological effective dose (BED) delivered to the tumor. The relative biologic effectiveness (RBE) ratio of carbon ion may correspond to approximately 2 to 3:1 compared with photon and proton.[6] Theoretically, the more precise intensity modulated CIRT (IM-CIRT) may provide improved toxicity profile and disease control compared with photon RT.[7] Results of retrospective studies[4,8-22] demonstrated that IM-CIRT is the most promising definitive RT option for primary and recurrent SC (Table E1). In order to improve the management of this rare disease, the publication of more information about IM-CIRT for SC is essential. In the present study, we present the results of patients with SC treated in a uniform fashion with IM-CIRT using pencil beam scanning (PBS) technology in our center.

Methods and Materials

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board (230619WXP-01) of the Shanghai Proton and Heavy Ion Center (SPHIC), and all patients provided written informed consent for medical research prior to initial treatment.

Patients' characteristics

Between June 2015 and March 2023, 52 consecutive patients with SC were treated in SPHIC. Eligibility criteria included histologically confirmed SC, no distant metastases, no prior sacrococcygeal RT, Eastern Cooperative Oncology Group performance status of 0 to 2, measurable tumors (R1/2 resection or only biopsy), definitive IM-CIRT, follow-up of ≥12 months, and no active concomitant malignancy. After exclusion, the remaining 35 patients with unresectable SC were evaluated in this study (Table 1).

Treatment with IM-CIRT

All patients underwent IM-CIRT using PBS technology. Briefly, after immobilizing the patients using an individual vacuum bag and a body mask, computed tomography (CT) without contrast enhancement in the treatment position for planning (2-mm slice thickness) and contrast-enhanced magnetic resonance imaging (MRI) were performed. The fusion technique was used to accurately delineate the gross tumor volume (GTV) including the visible tumor and OARs using the Siemens Syngo RT planning system (Siemens Healthcare). The GTV plus a 5-mm margin was defined as the clinical target volume (CTV) for the boost dose (CTVboost), and CTVboost plus a 5-mm margin was established as the CTV. The CTV plus a margin of 5 to 10 mm, accounting for setup variability and an internal margin where necessary, was defined as the planning target volume. Multifield scanning beams techniques was used depending on the depth of the tumor bed, target volume coverage, and OARs irradiated (eg, bladder/small bowel). As shown in Table 1, the median prescribed dose to CTVboost was 70.4 Gy (RBE) (range, 69-80 Gy [RBE]) (defined as carbon ion physical dose multiplied by RBE value) in 16 fractions (range, 16-23 fractions), typically delivered over 5 fractions per week, and 99% of the dose of CTV prescribed to the 99% isodose line. The dose constraints were D-max (maximum dose) <55 Gy (RBE) on the bowel and D-max <66 Gy (RBE), V60 [volume receiving ≥ 60 Gy (RBE)] <3 mL, V50 <7 mL, and V30 <25% on the rectum. Figure 1 shows MRI of tumor before and after RT as well as the applied IM-CIRT plan with the dose-volume histogram for a representative case.

Follow-up

For all patients, follow-up was every 3 to 4 monthly for the first 2 years after treatment and every 6 monthly for 2 additional years thereafter and then on. Medical history and physical examination, routine MRI/CT scan of the sacropelvic region, and CT of chest were performed at each follow-up session.

Adverse effects

Acute and late toxicities from RT were graded according to the Common Terminology Criteria for Adverse

Table 1 Characteristics of 35 patients with sacrococcygeal chordoma

Characteristic	Total (N = 35)	Patients with primary disease (n = 16)	Patients with recurrent disease (n = 19)	*P* value (2-sided)
Gender				.739
Male	21	9	12	
Female	14	7	7	
Age (y)				
Median (range)	62 (29-84)	64 (33-84)	53 (29-78)	.095
<69	26	9	17	.050
≥69	9	7	2	
Performance status* (n)				.922
0	15	7	8	
1/2	20	9	11	
GTV volume (mL)				
Median (range)	213.96 (16.27-2892.96)	254.56 (16.27-2026.84)	178.47 (71.13-2892.96)	.974
<210.8	17	7	10	.600
≥210.8	18	9	9	
No. of surgeries before CIRT				**.000**
0	13	13	0	
1	13	3	10	
2	7	0	7	
3	2	0	2	
Targeted therapy (n)				.109
No	31	16	15	
Yes	4	0	4	
Total dose of CIRT, Gy (RBE)				.818
Median (range)	70.4 (69-80)	70.4 (69−74.8)	70.4 (69-80)	
Fractionated dose of CIRT, Gy (RBE)				.442
Median (range)	4.4 (3-4.4)	4.4 (3-4.4)	4.4 (3-4.4)	
BED, Gy (RBE)				.818
Median (range)	225.28 (172.5-240)	225.28 (172.5-239.36)	225.28 (172.5-240)	
Metal implants (n)				**.009**
No	28	16	12	
Yes	7	0	7	
Cranial extension (n)				.716
S2 or above	24	6	5	
Below S2	11	10	14	

Abbreviations: BED = biological equivalent dose; CIRT = carbon ion radiation therapy; GTV = gross tumor volume; RBE = relative biologic effectiveness.
*Performance status was based on the scale of the Eastern Cooperative Oncology Group.
P value < 0.05 was considered statistically significant.

Events, version 4.0.3. The change in pain grades was evaluated between the initiation of IM-CIRT and the last follow-up or until recurrence. The sacral insufficiency fractures (SIFs)[12,23] were reviewed by a board-certified radiologist in a blinded manner based on MRI data and were defined as fracture lines with strongly decreased signal on T1- and T2-weighted images and surrounding medullary edema with decreased signal on T1-weighted

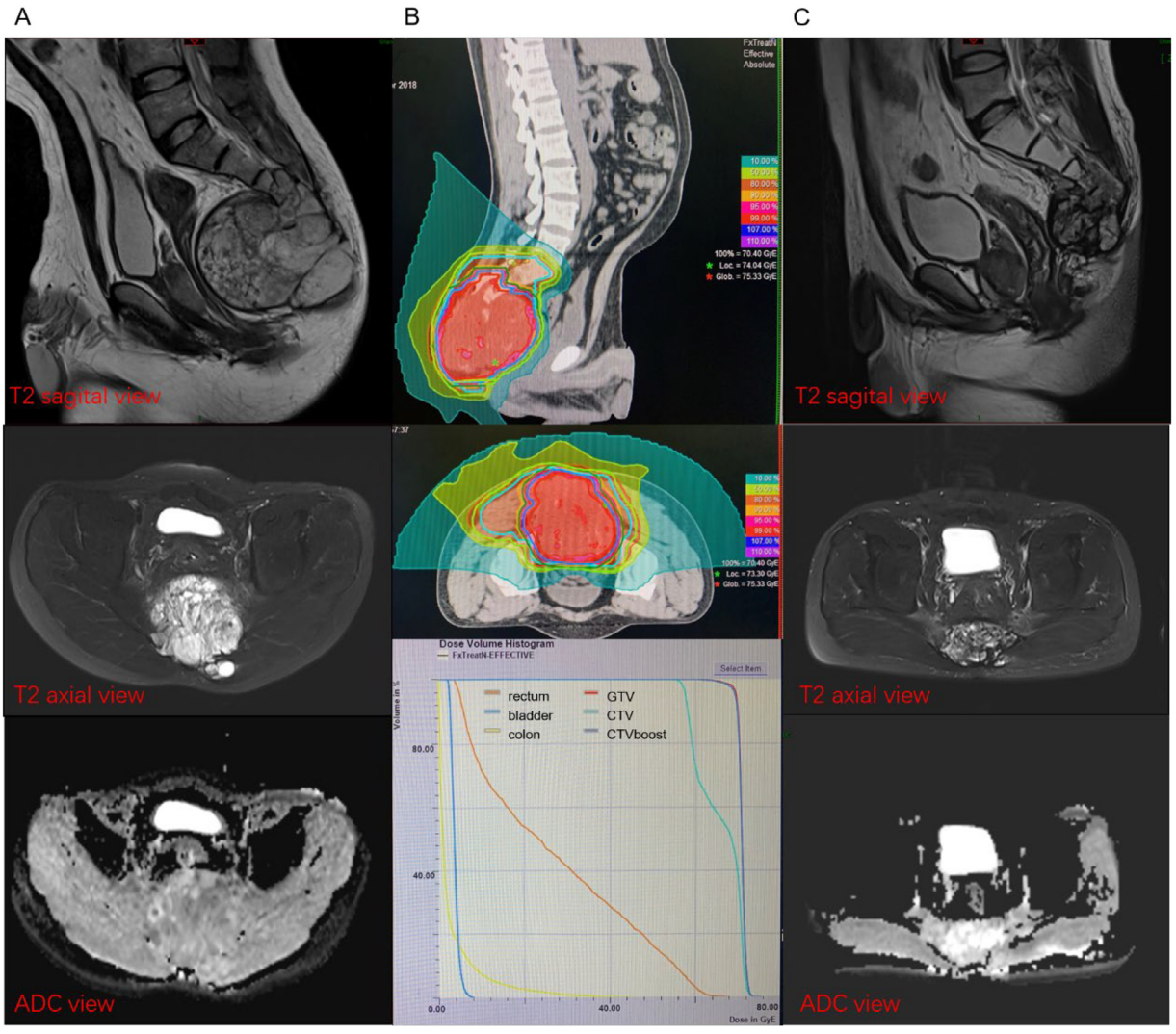

Figure 1 Carbon ion treatment and follow-up magnetic resonance imaging (MRI) of a 36-year-old patient with sacrococcygeal chordoma. (A) Pretreatment MRI. (B) Dose distribution of a carbon ion plan with 70.4 Gy (relative biologic effectiveness) in 16 fractions. (C) MRI of 28 months after treatment, showing marked tumor regression.
Abbreviations: CTV = clinical target volume; CTVboost = clinical target volume for the boost dose; GTV = gross tumor volume.

images and increased signal on T2-weighted images. Based on the previous study,[23] only patients who had underwent MRI in our hospital and have been followed up for more than 2 years (or until fracture or death) were included into the SIF analysis. Medical records were reviewed for correlation of SIFs with associated clinical symptoms.

Statistical analysis

Associations between categorical variables were tested using the χ^2 or Fisher exact test. Continuous variables were analyzed using the Student *t* test if normal distribution was met; otherwise, the Mann-Whitney *U* test was used. To evaluate the efficacy of IM-CIRT, overall survival (OS), cause-specific survival (CSS), progression-free survival (PFS), locoregional progression−free survival (LRFS), and distant metastasis−free survival (DMFS) were evaluated. Time to locoregional failure and distant metastasis was calculated from completion of RT until documented treatment failure. Treatment failure, as defined by Aibe et al,[9] included local progression (recurrence or regrowth in the local region regardless of extent) and distant metastasis (recurrence outside of the local region). OS was calculated from completion of RT until death or last follow-up date. The cutoff value for survival analysis was determined by evaluating the receiver operating characteristic curve specifically for progressive disease at the last follow-up time. The optimal cutoff value was determined using the Youden J index. For age and GTV, cutoff values of 69 years and 210.8 mL were selected, respectively. The impact of age, gender (male or female), recurrence status, performance status, GTV volume,

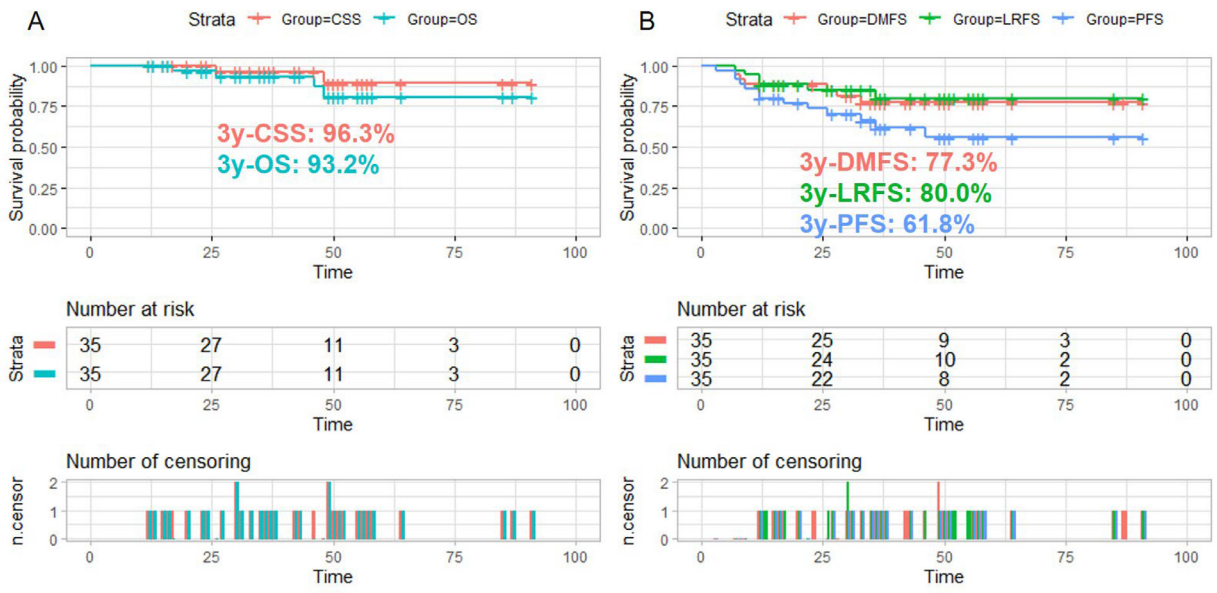

Figure 2 Kaplan-Meier curves for (A) overall survival (OS) and cause-specific survival (CSS) and (B) progression-free survival (PFS), locoregional progression−free survival (LRFS), and distant metastasis−free survival (DMFS) of all 35 patients after intensity modulated carbon ion radiation therapy treatment are shown.

systemic therapy or surgery, GTV dose, fractionated dose, BED, metal implants, and cranial extension on OS, CSS, PFS, LRFS, and DMFS were evaluated in univariate analyses using the Kaplan-Meier (KM) method. Fracture-free survival (FFS) was depicted using KM plots, and comparison between treatment groups was conducted using the log-rank test. Multivariate analyses employed Cox proportional hazards models for variables with a P value <.2 from univariate analyses. Stepwise forward LR selection method (criterion for removal, $P < .05$) was used. To facilitate comparability, 3-year survival rates were extrapolated from KM curves using Engauge Digitizer version 4.1 (https://digitizer.sourceforge.net) and are summarized in Table E1. Statistical analyses were conducted and survival curves were generated using SPSS (Version 19.0. IBMCorp., Armonk, N.Y., USA) and R software (version 4.0.3, R Core Team, 2020). A 2-sided P value <.05 was considered statistically significant.

Results

Table 1 presents the characteristics of 35 patients. Median follow-up was 42 months (range, 12-91 months), with a median age of 62 years. Sixteen patients had primary disease, while 19 received salvage IM-CIRT for recurrent tumors. Among them, 22 patients (62.9%) underwent 1 to 3 surgeries. The most common dose fractionation was 70.4 Gy (RBE) in 16 fractions (n = 22; 62.9%). All patients had tumor extension involving soft tissue, with a median GTV volume of 213.96 mL (range, 16.27-2892.96 mL) at treatment initiation. Additionally, 24 patients (68.6%) had tumors located in S2 or above. Only 4 patients had received targeted therapy (imatinib for 3 cases and anlotinib for 1 case) before and/or concurrent with IM-CIRT. The patients with recurrent disease were younger ($P = .05$), had undergone more surgeries ($P < .001$), and had more metal implants ($P = .009$) compared with those with primary disease. Four patients treated with definitive IM-CIRT were deceased. The 3-year OS, CSS, PFS, LRFS, and DMFS rates for the entire cohort (Fig. 2) were 93.2%, 96.3%, 61.8%, 80%, and 77.3%, respectively.

Patterns of failure

During the entire follow-up period, 11 patients (3 with primary tumors and 8 with recurrent tumors) developed failure (Table 2), including isolated locoregional progression (n = 4), locoregional progression with distant metastasis (n = 2), and distant metastasis (n = 5). Among those with locoregional progression, 4 and 2 patients's locoregional failure occurred within and adjacent to the GTV, respectively. Distant metastases were observed in bones (n = 6), liver (n = 1), lungs (n = 4), and pericardium (n = 1).

Prognostic factors

Univariate analysis (Table 3) showed that older age (≥69 years) was significantly associated with worse OS ($P = .001$) and CSS ($P = .021$), respectively. Patients with recurrent disease ($P = .045$) and those who had undergone prior surgery ($P = .019$) exhibited significantly better OS. Higher BED (≥225.28 Gy) and greater GTV dose (≥70.4 Gy [RBE]) were significantly linked to improved CSS ($P = .015$ and $P = .042$, respectively). Larger GTV (≥210.8

Table 2 Details of the 11 patients who developed failures

Gender/age (y)	GTV (mL)	Cranial extension	Nature of disease	Treatment	Dose fractionation (Gy [RBE]/fx)	Patterns of failure (mo)	Salvage treatment at failure	Final status (last follow-up time [mo])
F/70	2026.84	S1	Primary	CIRT	69/23	DM (26)	None	DOD (26)
F/77	213.96	S2	Primary	CIRT	69/23	LR (12) + DM (28)	TT + BRT	DOD (48)
F/33	376.12	S2	Primary	S ×1 + CIRT	70.4/16	DM (8)	S	AWD (52)
F/55	309.06	S1	Recurrent	S ×1 + CIRT	69/23	LR (7)	S	AWD (42)
M/78	2892.96	S2	Recurrent	S ×2 + CIRT	69/23	LR (36)	S	AWD (87)
M/43	512.74	S2	Recurrent	S ×1 + CIRT	72/18	DM (7)	TT	AWD (30)
F/62	473.24	S1	Recurrent	S ×3 + CIRT	74.8/17	DM (33)	None	AWD (55)
M/53	166.25	S3	Recurrent	S ×2 + CIRT	70.4/16	LR (22)	S	AWD (23)
F/29	230.74	S2	Recurrent	S ×2 + TT + CIRT	70.4/16	DM + RR (9)	TT	AWD (24)
M/67	125.3	S1	Recurrent	S ×1 + CIRT	70.4/16	RR (12)	TT + AHK ×4	AWD (49)
M/69	71.13	S2	Recurrent	S ×1 + CIRT	70.4/16	DM (3)	Unknown	AWD (13)

Abbreviations: AHK = argon helium knife; AWD = alive with disease; BRT= brachytherapy; CIRT = carbon ion radiation therapy; DM = distant metastasis; DOD = death from disease; F = female; fx = fraction; GTV = gross tumor volume; LR = local recurrence; M = male; RBE = relative biologic effectiveness; RR = regional recurrence; S = surgery; TT = target therapy.

mL) (Fig. 3) was associated with worse PFS (P = .029), while GTV dose ≥70.4 Gy (RBE) (Fig. 3) was associated with better LRFS (P = .022). Additionally, larger GTV (≥210.8 mL) and tumors located at S2 level or above were more likely to result in distant failure (both P = .047).

Multivariate analysis (Table 4) revealed that GTV (hazard ratio, 3.807; 95% CI, 1.044-13.887; P = .043) was the only significant prognostic factor for PFS, while GTV dose ≥70.4 Gy (RBE) was associated with significantly better LRFS (hazard ratio, 0.190; 95% CI, 0.038-0.940; P = .042). However, no significant prognostic factor was identified for OS, CSS, and DMFS.

Adverse effects

In our study, grade 1 and 2 acute toxicities included leucopenia (grade 1, 3/35), neutropenia (grade 1, 2/35), thrombocytopenia (grade 2, 1/35), and radiation dermatitis (grade 1, 13/35). No patients with grade 3 or 4 acute toxicity were observed. The rate of severe late toxicities (grade ≥3) was only 8.57% (Tables 5 and E2), which included pain (2.86%), motor neuropathy (2.86%), and skin ulcer (2.86%). Moreover, severe toxicity of urinary function and defecation secondary to IM-CIRT was not observed. The pain grades were improved, unchanged, or deteriorated in 10 (28.6%), 20 (57.1%), and 5 (14.3%: 4 patients with tumor located in S2 or above and 1 patient with recurrent tumor after 2 surgeries located in S3 and who received CIRT with 80 Gy [RBE]) patients, respectively. Thirteen patients, who have undergone MRI in our hospital and had been followed up for more than 2 years (or until fracture or death), were included to analyze the frequency and clinical relevance of SIFs after IM-CIRT of SC (Table E3 and Fig. E1). Median follow-up was 28 months (range, 16-49 months). SIFs were diagnosed in 5 (38.4%) of 13 patients, and most sacral fractures (80%) occurred within 3 years after CIRT. The FFS probability of the 13 patients amounted to values of 0.923 after 2 years and 0.462 after 3 years. No significant difference regarding the fracture rates between patients who received a CIRT after previous surgeries and patients treated with CIRT alone was found. Approximately 20% of patients with SIFs (1 of 5 patients) had associated pain (grade 2). The FFS probability of the males was better than that of females (P = .025).

Discussion

Locoregional recurrence was approximately 50% in patients with SC after macroscopic complete resection with or without RT.[3,14] In the past decade, several studies showed that RT offers the chance for durable radiologic local control (LC) with acceptable toxicity in either primary or recurrent SC[4,9,11,12,15,17,18,20,21,24] (Table E1), while proton or CIRT seems to have better LC than photon RT. The rationale of CIRT is administering potential

Table 3 Univariate analyses for survival outcomes

Variables	OS	CSS	PFS	LRFS	DMFS
Gender (female vs male)	0.198	0.108	0.213	0.532	0.093
Age (<69 vs ≥ 69 y)*	**0.001**	**0.021**	0.115	0.711	0.287
Nature of disease (primary vs recurrent)	**0.045**	0.150	0.376	0.105	0.826
PS (0 vs 1/2)	0.071	0.196	0.262	0.515	0.972
GTV (<210.8 vs ≥210.8 mL)*	0.060	0.178	**0.029**	0.390	**0.047**
Surgery (no vs yes)	**0.019**	0.095	0.326	0.236	0.523
Targeted therapy† (no vs yes)	0.516	0.653	0.680	0.574	0.841
GTV dose (<70.4 vs ≥ 70.4 Gy [RBE])	0.227	**0.015**	0.200	**0.022**	0.551
Fractionated dose (<4.4 vs ≥4.4 Gy [RBE])	0.115	0.070	0.215	0.277	0.502
BED‡ (<225.28 vs ≥225.28 Gy [RBE])	0.064	**0.042**	*0.097*	0.182	0.362
Metal implants (no vs yes)	0.375	0.530	0.769	0.281	0.672
Cranial extension (below S2 vs S2 or above)	0.643	0.304	0.057	0.313	**0.047**

Abbreviations: BED = biological effective dose; CSS = cause-specific survival; DMFS = distant metastasis–free survival; GTV = gross tumor volume; LRFS = locoregional progression–free survival; OS = overall survival; PFS = progression-free survival; PS = performance status; RBE = relative biologic effectiveness.

*The cutoff value for the survival analysis was selected on the basis of the receiver operating characteristic curve for progressive disease at the last follow-up. The optimal cutoff value was determined using the Youden J index. For age and GTV, we selected 69 years and 210.8 mL as the cutoff values, respectively.

†Target therapy before radiation therapy and/or concurrent target therapy.

‡$\alpha/\beta = 2$.

P value < 0.05 was considered statistically significant.

higher biological effects than those by proton RT. Hence, a randomized phase II trial of patients with SC treated by hypofractionated proton versus CIRT (the Ion Irradiation of Sacrococcygeal Chordoma trial) is ongoing.[25] For patients with unresectable disease, NCCN guidelines[5] and CGCG[1,3] recommend that high-dose RT (specialized

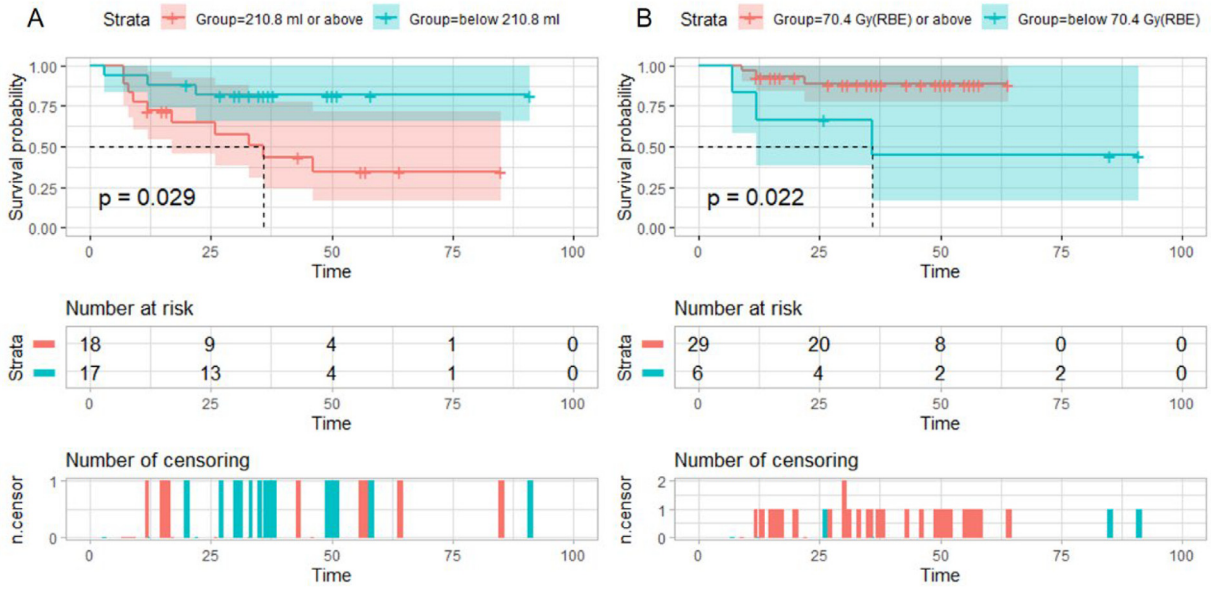

Figure 3 Univariate analysis using the log-rank test. (A) Progression-free survival of patients with sacrococcygeal chordoma treated with intensity modulated carbon ion radiation therapy stratified by gross tumor volume (<210.8 mL vs ≥210.8 mL; $P = .029$). (B) Locoregional progression–free survival of patients with sacrococcygeal chordoma treated with intensity modulated carbon ion radiation therapy stratified by gross tumor volume dose (<70.4 vs ≥70.4 Gy relative biologic effectiveness [RBE]; $P = .022$).

Table 4 Multivariate analyses of progression-free survival and locoregional progression−free survival

Endpoint	Variables	Multivariate analyses	
		HR (95% CI)	*P* value
PFS	GTV volume (<210.8 vs ≥210.8 mL)*	3.807 (1.044-13.887)	**.043**
LRFS	GTV dose (<70.4 vs ≥70.4 Gy)	0.190 (0.038-0.940)	**.042**

Abbreviations: GTV = gross tumor volume; HR = hazard ratio; LRFS = locoregional progression−free survival; PFS = progression-free survival.
*The cutoff value for the survival analysis was selected on the basis of the receiver operating characteristic curve for progressive disease at the last follow-up. The optimal cutoff value was determined using the Youden J index. For GTV, we selected 210.8 mL as the cutoff value.
P value < 0.05 was considered statistically significant.

techniques including protons and heavy ions) is a primary treatment option. The CGCG also recommended a dose of 74 Gy (RBE) delivered in conventional fractionation for proton, or 66-70.4 Gy (RBE) using moderate hypofractionation (3-4.4 Gy [RBE]) for CIRT, in the setting of macroscopic residual disease.[1,3] Likewise, the NCCN guidelines recommended[5] a final target dose of 70 Gy and 72 to 78 Gy for patients who received postoperative RT after R1 and R2 resection with resectable disease and >70 Gy for patients with unresectable disease. In our study, we studied 35 unresectable SCs treated with high-dose (70.4 Gy [RBE]; range, 69-80 Gy [RBE]) IM-CIRT using PBS technology. Although 62.9% (19/35) of patients presented with recurrent tumors, the 3-year OS (93.2%), CSS (96.3%), PFS (61.8%), LRFS (80%), and DMFS (77.3%) rates for the entire cohort were marvelous.

LC by RT for SC is a function of radiation dose. Previous study showed that visible residual chordoma is infrequently cured with conventional photon-based RT (dose, <60 Gy).[26] A study[4] from University Hospital Heidelberg presented retrospective data of 34 patients with sacral chordomas (50% recurrent cases) who received intensity modulated RT: the 5-year actuarial LRFS was only 27%. Such poor outcome might be due to the lower dose (median dose, 66 Gy) and low LET beam.[27] Lu et al[19] showed that patients with primary disease received intensity modulated RT using higher doses (70-74 Gy) had better 5-year LRFS rate (70.9%). Compared with photon RT,[6] particle RT (proton or carbon ions) may favor higher dose and/or dose escalation to improve LC. Recent studies from Hyogo Ion Beam Medical Center (HIBMC)[9] and Massachusetts General Hospital[15] demonstrated that proton RT contributed to high 5-year LC rate (81.8%) for patients with unresected primary tumors. There is a trend toward better PFS with doses of >78 Gy (RBE) of definitive proton-based RT for unresectable disease.[15] Bostel et al[12] in Heidelberg Ion Beam Therapy Center (HIT) reported that 3-year LC rates were 77% and 27% for 68 patients with primary or recurrent disease who were treated with high-dose CIRT (median dose, 66 Gy [RBE]; range 60−74 Gy [RBE]) using active raster scanning. Demizu et al[17] in Japan Carbon-Ion Radiation Oncology Study Group (J-CROS) summarized that the 3- and 5-year LC rate of 219 patients with primary disease treated with CIRT (most common dose fractionation, 67.2 Gy [RBE] in 16 fractions) using passive scattering technique was 88.8% and 72% for all patients, which were consistent with the results reported by Imai et al[18,24] in National Institute of Radiological Sciences (NIRS). In our study, the 3-year LRFS rates were 93.8% and 66.6% for patients with primary and recurrent disease after CIRT, respectively. Multivariate analysis revealed that GTV dose ≥70.4 Gy (RBE) was the only factor related to better LRFS (P = .042) for patients with unresectable disease. All[13,24] indicated that IM-CIRT at high doses (≥70.4 Gy [RBE]) using hypofractionated RT may improve outcomes for LC and seems to be workable even after repeated resections of recurrent tumor.

Treatment-induced toxicities and complications remain a challenge in the treatment of SC. In our study, no severe (ie, grade ≥3) acute toxicity was observed, while severe late toxicities rate was 8.57%, including pain (1 patient), motor neuropathy (1 patient), and skin ulcer (1 patient). For all cases, after IM-CIRT, the pain grades improved or unchanged in most (∼86%) patients. Only 1 patient with large GTV (837.41 mL) and S2 extension presented with grade 3 pain secondary to CIRT (2.86%), which was lower than the previous results (Table E1) of patients treated by proton RT from Curie Institute (14%)[21] and HIBMC (6%).[9] High doses (>73 Gy [RBE][28]) may be the only factor of neural injury, and the dose constraint of sciatic nerve for hypofractionation with carbon ions was dose to 10 (D10) cm of the sciatic nerve <70 Gy (RBE).[1,29] In our study, the patient who had S2 extension and soft tissue invasion, underwent 2 prior surgeries, and received anlotinib after salvage IM-CIRT with 70.4 Gy (RBE) in 16 fractions subsequently experienced grade 3 motor neuropathy (2.86%), which was comparable with the previous results of patients treated by CIRT from NIRS (3.2%)[18] and HIT (5%).[12] Skin dose should also be considered with caution before high-dose CIRT: dose constraints of skin for hypofractionation with carbon ions was D2 cm^2 < 60 Gy (RBE).[1,30] A 84-year-old patient (2.86%) with suspicious skin involvement treated by IM-CIRT using 74.8 Gy (RBE) in 17 fractions presented with skin ulcer in our center. The incidence rate was lower than that observed in the NIRS' study[18] and J-CROS

Table 5 Details of the 3 patients who experienced late toxicities (grade 3)

Gender/age (y)	Toxicity (grade 3)	GTV (mL)	Cranial extension	Tumor extension	Complication	Nature of RT	Treatment received	Dose fractionation (Gy [RBE]/fx)
F/77	Pain	837.41	S2	Sacrococcygeal vertebrae, right iliac bone, gluteus maximus, and erector spinalis	Diabetes	Primary	CIRT	72/18
M/84	Skin ulcer	295.15	S5	Suspicious skin involvement	Postoperative prostate cancer	Primary	CIRT	74.8/17
F/29	Motoric neuropathy	230.74	S2	Sacrococcygeal vertebrae, left iliac bone, and gluteus maximus	Postoperative liver metastasis of chordoma (margin negative)	Salvage	S ×2 + TT + CIRT	70.4/16

Abbreviations: CIRT = carbon ion radiation therapy; F = female; fx = fraction; GTV = gross tumor volume; M = male; RT = radiation therapy; S = surgery; TT = target therapy; RBE = relative biologic effectiveness.

study,[17] which used passive application techniques. The reasons might be PBS technology application in our study, which contributes to improve conformality of the high dose to the target volume and results in a lower skin dose compared with the passive application techniques.[31,32] Additionally, European doses of optimally matched plans using local effect model were approximately 5% to 15% greater than the Japanese ones using microscopic kinetic model[33] and the RBE-weighted doses in our center were too conservative compared with those in Japanese institutes.[34] Moreover, severe toxicity of urinary function and defecation secondary to CIRT was not observed in our study. For patients with SC, especially those with tumor levels located above S3 level, CIRT might contribute to better quality of life and relatively low urinary-anorectal toxicity compared with radical resection,[35] which could induce complete urinary and bowel incontinence in at least 80% of the patients.[1-3] SIFs were diagnosed in 38.4% (5/13) patients, which is consistent with the previous study.[23,36] The FFS probability of the males was better than that of females (P = .025), presumably because age-related osteopenia is less common among male patients than among women.[37]

Several pitfalls need to be addressed. First, this is only a retrospective study to address the CIRT of unresectable SC using PBS technology. Further investigation, preferably in prospective fashion, is warranted to optimize the dosage and confirm the efficacy of CIRT in the treatment of SC. Second, the limited details in pathology reports for distinguishing chordoma subtypes might affect the analysis of clinical outcomes in CIRT. Previous studies[38] have shown that the histotype of dedifferentiated and/or poorly differentiated chordoma is associated with a particularly aggressive clinical behavior and worse prognosis. Third, the 3-year DMFS rate was 77.3% in our study, and a more effective strategy for improving DMFS is needed. Fourth, we found that GTV volume was the only significant prognostic factor for PFS. Recent studies[39-41] showed that outcomes for patients with unresectable SC receiving CIRT can be improved by modulating the dose-averaged LET (LETd) within the GTV. We have preliminarily found that the LETd of CTV and/or GTV using 2 fields (45° direction) is 10% to 20% higher than LETd under laterolateral directions (Table E4). Last but not the least, we could only report the 3-year outcomes with confidence because the follow-up period of 42 months was relatively short. The median time to locoregional progression was 12 months (range, 7-36 months), which was shorter than the 28 months (range, 7-46 months) for patients with primary disease reported by Aibe et al[9] in spite of their follow-up time being calculated from the initiation of RT. Bostel et al[12] suggested that the majority of local relapses (71%) occurred within the first 3 years after primary treatment, but only 10% local relapse was observed later than 5 years after RT.

Conclusions

IM-CIRT using PBS technology produced acceptable 3-year outcomes without substantial late adverse effects, especially urinary and anorectal complications for SC localized above S3, and has the potential to reduce pain. IM-CIRT at high doses (≥70.4 Gy [RBE]) using hypofractionated RT may improve outcomes for LC and seems to be workable and safe even after repeated resections of recurrent tumor, but the sciatic nerve and skin need to be contoured and respected during treatment planning.

Disclosures

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101558.

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