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Original Article

Hypofractionated proton and carbon ion beam radiotherapy for sacrococcygeal chordoma (ISAC): An open label, randomized, stratified, phase II trial

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ABSTRACT

Introduction: Sacrococcygeal chordomas have high recurrence rates and are challenging to treat.
Methods: In this phase II prospective, randomized, stratified trial, the safety and feasibility of hypofractionated ion radiation therapy were investigated. The primary focus was monitored through the incidence of Grade 3–5 NCI-CTC-AE toxicity. Secondary endpoints included local progression-free (LPFS) and overall survival (OS).
Results: The study enrolled 82 patients with primary (87 %) and recurrent (13 %) inoperable or incompletely resected sacral chordomas from January 2013 to July 2022, divided equally into proton therapy (Arm A) and carbon ion beam therapy (Arm B) groups, each receiving a total dose of 64 Gy (RBE) in 16 fractions, 5–6 fractions per week. Overall 74 % of patients received no previous surgery and 66 % of tumors were confirmed by a brachyury staining. The mean and median Gross Tumor Volume at the time of treatment (GTV) was 407 ml and 185 ml, respectively. The median follow-up of the surviving patients was 44.7 months, and the 2-year and 4-year OS rates were 96 % and 81 %, respectively. Factors such as smaller GTV and younger age trended towards better OS. The LPFS after 2-year and 4-year was 84 % and 70 %, respectively. Male gender emerged as a significant predictor of LPFS. There was no significant difference between the treatment groups. We observed five grade 4 wound healing disorders (6 %).
Conclusion: The initial response rates were promising; however local control was not sustained. More comparative research on fractionation schemes is essential to refine treatment approaches for inoperable sacral chordoma.

Introduction

Sacral chordoma, a rare and malignant bone tumor, poses a significant challenge in oncological treatment due to its aggressive nature and complex anatomical location [1]. Chordomas arise from remnants of the notochord, occurring predominantly in the skull base, mobile spine and the sacrococcygeal region. These slow-growing neoplasms are characterized by a high rate of local recurrence and a tendency for late

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metastatic spread [2,3]. The management of sacral chordomas is complicated by the common proximity to critical structures like the lumbosacral plexus [3].

Surgery is the mainstay treatment for sacral chordoma [3]. However, especially after intralesional or marginal resection, high local recurrence rates are common [4], and a significant number of tumors cannot be surgically addressed. The advent of particle therapy, particularly proton and carbon ion beam therapy, has broadened the treatment options for sacral chordoma.

Proton beam therapy is increasingly favored for treating chordoma due to its dosimetric advantages, resulting in improved local control rates and acceptable toxicity profiles [5]. Carbon ion beam therapy offers additional benefits, such as higher linear energy transfer (LET) leading to greater biological damage within tumor cells, potentially yielding higher local control rates and improved overall survival. Additionally, carbon ions are less susceptible to radio-resistance mechanisms, making them effective against hypoxic tumor cells [6–8]. Despite these advantages, challenges persist, including the high cost and limited availability of particle therapy centers, especially carbon ion facilities. Recent research has focused on optimizing particle therapy for sacral chordoma, exploring dose escalation and hypofractionation schedules.

In this study, we present the outcomes of a phase II trial, exploring the feasibility and safety of proton and carbon ion beam radiation therapy for the treatment of sacrococcygeal chordoma.

Materials and methods

This phase II pilot study was a prospective, randomized, stratified, open trial designed to evaluate the safety and feasibility of hypofractionated radiation therapy with ions (protons or carbon ions) using raster-scan technique for primary treatment of sacrococcygeal chordoma, as well as in adjunctive therapy following R2 resection. The trial protocol has been previously published [9].

The study primarily aimed to assess the safety and feasibility of the treatment regimen. This was evaluated by monitoring Grade 3–5 NCI-CTC-AE (version 4.0) toxicity incidence up to 12 months after treatment and instances of discontinuation of planned therapy for any reason. Secondary endpoints included local progression-free survival (LPFS), overall survival (OS), and quality of life (QoL).

A total of 100 patients were planned to be enrolled, with 50 patients in each treatment arm. Inclusion criteria were histologically confirmed chordoma, a Karnofsky index of $\geq$70 %, age between 18 and 80 years, macroscopic tumor evidence on MRI and written informed consent. Exclusion criteria included distant metastases, absence of macroscopic tumor evidence on MRI and prior pelvic radiation therapy.

Participants were split into two groups: proton beam therapy and carbon ion beam therapy. Both groups received a total dose of 64 GyRBE in 16 fractions (4.0 GyRBE per fraction, administered 5–6 times per week). Randomization was done in a 1:1 ratio using block randomization, with stratification based on tumor size (clinical target volume, CTV, greater or less than 1000 ml) at the time of randomization.

Survival data of those lost to follow-up were updated using information from the German Cancer Registry. Overall survival (OS) was the time from treatment start to any-cause death. Local progression-free survival (LPFS) and distant progression-free survival (DPFS) measured time from therapy start to progression of the primary lesion and distant metastases, respectively. Survival analysis for each endpoint utilized Kaplan-Meier curves, log-rank tests as well as univariate Cox regression analyses. Stratified Kaplan–Meier curves were plotted for binary subgroup factors. Variables at a p-value below 0.05 were considered significant. Hazard ratio (HR) with 95 % Wald CI is provided together with the p-value of the log-rank test.

The Gross Tumor Volume (GTV) was determined using T2-weighted and contrast-enhanced T1-weighted MRI sequences with fat saturation. The CTV margin of 2 cm was added in both bone and soft tissues and adjusted to non-infiltrated organs at risk. The Planning Target Volume (PTV) included an additional margin of 7 mm in the beam direction and 5 mm in the remaining directions. Carbon ions RBE-weighted dose was calculated with the local effect model 1 (assuming an alpha/beta value of 2 Gy) while protons dose predictions assumed a fix RBE of 1.1.

The patients were treated in prone or supine position mostly depending on patient comfort or physician preference. Treatment planning was performed using two posterior beams at the gantry or with two horizontal beams. Plans were calculated with Syngo RT Planning (Siemens) or RayStation (RaySearch) (Fig. 1).

Patient cohort

In this prospective, randomized phase II trial, we investigated the characteristics and treatment outcomes of 82 patients diagnosed with sacral chordomas, evenly divided between two treatment arms: carbon ion radiotherapy (^{12}C) and proton therapy, with 41 patients (50 %) in each group. Treatment was administered between January 2013 and July 2022. One patient was excluded from survival analysis. Upon progression, the pathological diagnosis was revised to neuroendocrine carcinoma.

Initially, we planned to enroll a total of 100 patients. However, due to two consecutive grade 4 wound healing complications and complex postoperative issues in a patient who underwent unplanned surgery shortly after radiotherapy, we opted to terminate the study prematurely after consulting with the data safety monitoring board (DSMB). The latter patient was excluded from local control analysis. One patient discontinued treatment after 15 fractions due to a non-treatment-related myocardial infarction followed by pneumonia. He passed away during intensive care treatment at the age of 78 years.

The cohort was predominantly male (62 %), with a median age of 63.5 years at therapy onset. Treatment at initial diagnosis was administered to 87 % of patients, a partial resection before radiotherapy in 26 %. The brachyury staining was available in 66 % of patients. One patient had a poorly differentiated chordoma with loss of INI-1 and Ki-67 of 50 %. Patient characteristics were evenly distributed between the two treatment modalities (Table 1). The median GTV for the cohort was 185 ml, the mean GTV was 407 ml. The CTV and PTV had median values of 930.50 ml and 1260 ml, respectively.

Survival outcomes

Sixty patients (73 %) of the total cohort were alive or censored at the time of last follow-up. The median follow-up time until censoring of the surviving patients was 44.7 months (range 1.3–124). The overall survival rate of the whole cohort at two and four years was 96 % and 81 % (Fig. 2). We did not observe a significant difference between the carbon ion and proton group (HR [95 % CI]: 1.67 [0.697–4.025], p = 0.242). A GTV smaller than the median GTV (<185 ml) and younger age (<63.5 years) trended towards better OS on univariate Kaplan Meier-analysis (HR [95 % CI]: 2.36 [0.95–5.83], p = 0.056 and HR [95 % CI]: 2.97 [1.20–7.36], p = 0.013, respectively). Gender, recurrence vs. initial diagnosis as well as prone position vs. supine position were not significant.

Serial pelvic MRIs were available for 78 patients. The median follow-up time until censoring of those without local progression was 45.4 (8.7–108). The LPFS after 2 years and 4 years was 84 % and 70 % respectively and did not differ significantly between the carbon ion and the proton group (HR [95 % CI]: 0.80 [0.36–1.72], p = 0.57) (Figure 1). The median time until local progression was 42.5 months (8–108). Male gender was a significant predictor of superior LPFS on univariate analysis (HR [95 % CI]: 0.39 [0.18–0.82], p = 0.01), while prone vs. supine position, the GTV size above or below the median and recurrence vs. first diagnosis were not significant.

Thoracic CT screening was available for 53 patients. In total 14 patients developed distant metastases, 9 in the proton arm and 5 in the

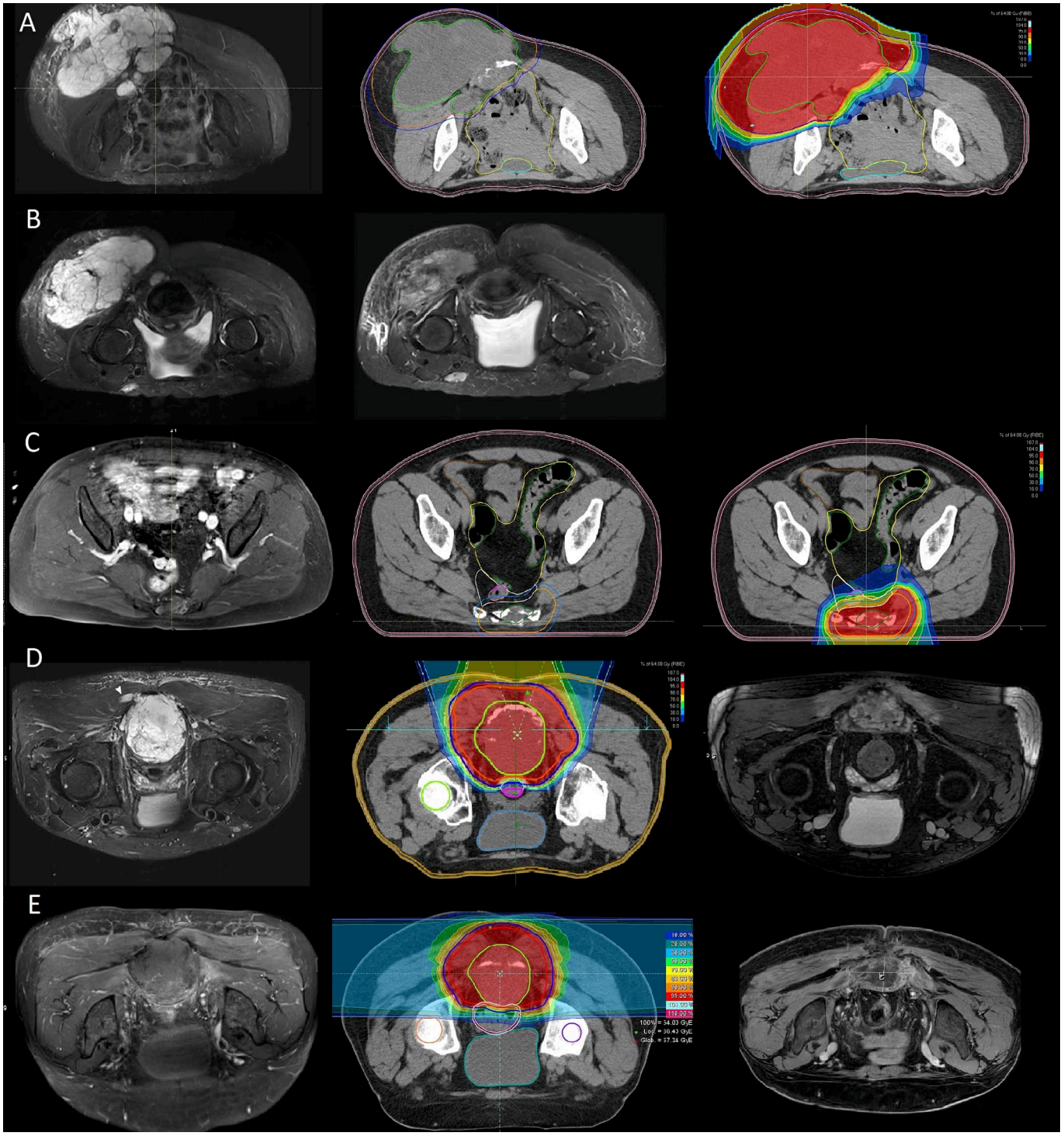

Fig. 1. Positioning, Immobilization, Treatment Planning and Follow-Up of Patients with Sacrococcygeal Chordoma. (A) Treatment planning for a patient with sacral chordoma treated with active scanned protons in the prone position using two posterior beams at the gantry: T2 TIRM-weighted MRI and CT images showing target volume and OAR contours. The GTV is displayed in green, the CTV in orange/red, and the PTV in blue. PTV coverage was adjusted to spare the small bowel. Note the tumor infiltration into the skin. (B) Follow-up MRI of the same patient shows a significant reduction in tumor size (right) compared to the planning MRI (left). (C) Treatment planning for a male patient treated with carbon ions in the supine position using two posterior beams at the gantry. Patients experiencing tumor-related pain were treated in the prone position using a vacuum mat to avoid pain caused by the supine position. Other patients were treated in the supine position, immobilized with a ProSTEP as shown. (D) Male patient with sacral chordoma treated with protons in the prone position using two posterior beams at the gantry. Proton and carbon ion beam plans were optimized to the same constraints. Treatment planning was performed with SyngoRT Planning (Siemens) or RayStation (RaySearch). Follow-up MRI (right) shows a significant reduction in tumor size and compression of the rectum. Note the treatment-associated T2-weighted changes of the gluteal musculature. (E) Horizontal beam plan for a male patient with sacral chordoma treated with two opposing beams and protons. Generally, gantry plans were favored over horizontal plans due to increased conformity. Horizontal plans were used when the gantry was not fully operational e.g. during maintenance or repairs. Note the initial tumor size (left) and the regression of the tumor during follow-up on T1-weighted contrast enhanced MRI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Patient and treatment characteristics.

	Entire patient cohort	C12	Protons
N	82 (100)	41 (50)	41 (50)
Sex (N, %)			
- Male	51 (62.2)	27 (65.9)	24 (58.5)
- Female	31 (37.8)	14 (34.1)	17 (41.5)
Age at therapy (years)			
- Median (Range)	63.5 (25–80)	65 (25–79)	62 (27–80)
Time biopsy to radiotherapy (months)			
- Median (Range)	2 (0–112)	2 (0–100)	2 (0–112)
Primary vs. Recurrence (N, %)			
- Primary	71 (86.6)	35 (85.4)	36 (87.8)
- Recurrence	11 (13.4)	6 (14.6)	5 (12.2)
Biopsy vs. Resection (N, %)			
- Biopsy	61 (74.4)	32 (78)	29 (70.7)
- Resection	21 (25.6)	9 (22)	12 (29.3)
Brachyury-Status (N, %)			
- positiv	54 (65.9)	26 (63.4)	28 (68.3)
- negativ	0 (0)	0 (0)	0 (0)
- missing	28 (34.1)	15 (35.6)	13 (31.7)
Volume in ml (Median, Range)			
- GTV	184.8 (1.7–3169.2)	144.6 (1.7–3169.2)	214.3 (2.6–1341.8)
- CTV	930.5 (252.4–5262.6)	917.5 (252.4–5515)	957.5 (255.9–3665)
- PTV	1260 (388.7–6402.2)	1212 (388.7–6402.2)	1320 (410.4–4208)
GTV (N, %)			
- GTV < 1000 ml	73 (89)	35 (85.4)	38 (92.7)
- GTV > 1000 ml	9 (11)	6 (14.6)	3 (7.3)
GTV Median (N, %)			
- GTV < Median	41 (50)	22 (53.7)	19 (46.3)
- GTV > Median	41 (50)	19 (46.6)	22 (53.7)
Gantry vs. horizontal Beam (N, %)			
- Gantry	70 (85.4)	36 (87.8)	34 (82.9)
- Horizontal	12 (14.6)	5 (12.2)	7 (17.1)
Supine vs. prone treatment position (N, %)			
- Supine	19 (23.2)	9 (22)	10 (24.4)
- Prone	63 (76.8)	32 (78)	31 (75.6)
Insufficiency fractures (N, %)			
- no	46 (59.7)	25 (64.1)	21 (55.3)
- yes	31 (40.3)	14 (35.9)	17 (44.7)
Time to fracture (months)			
- Median (Range)	19.5 (0–116)	19 (0–116)	20 (4–108)

Abbreviations: GTV (macroscopic tumor volume), CTV (clinical target volume), PTV (planning target volume), *N* (number), C12 (carbon ions).

carbon ion arm. The median distant progression free survival (DPFS) after 2y and 4y was 76 % and 69 %, respectively (Fig. 2). The most common location of metastasis was the lung. The distant control of patients treated with protons was significantly inferior to patients treated with carbon ions (83 % vs. 48 % after 4 years, (HR [95 % CI]: 0.28 [0.09– 0.94], p = 0.028). A GTV smaller than the median was associated with an improved distant control (HR [95 % CI]: 4.44 [1.19–16.57], p = 0.016).

Toxicity

Insufficiency fractures were a complication for 31 of 77 patients with available local information. The median time to fracture occurrence was 19.5 months across both groups, with no significant difference between the two. The occurrence of an insufficiently fracture was associated with a trend toward improved overall survival (HR [95 % CI]: 0.41 [0.16–1.06], p = 0.057). The fractures that occurred were often associated with pain. Partly, these led to hospitalization. In many cases, opioid substances and co-analgesics were used. However, the medication was not systematically recorded.

Skin toxicity was common. At the end of radiotherapy 45 % of patients reported grade 1 and 4 % grade 2 radiation dermatitis. After twelve months, observed skin toxicity was mostly grade 1 (45 %) and grade 2 (9 %). We observed n = 4 (5 %) grade 4 wound healing disorders in the time frame of 12 months and one additional after 12 months, n = 5 in total (three in the proton arm and two in the carbon ion arm). Of those, one patient had an additional rectal fistula which communicated with the wound healing disorder and required a Hartmann's procedure.

We observed an increase in grade 1 pain at the end of radiotherapy compared to baseline (39 % vs. 60 %). After 12 months the rates of grade 2 and grade 3 pain increased, the rates were higher compared to the baseline (35 % and 15 %, respectively).

In regards to motor and sensory neuropathy, we observed an increase of grade 1 and 2 toxicity after 12 months. At baseline, motor neuropathy grade 1 and 2 was present 7 % and 8 % of patients, respectively. At 12 months motor neuropathy rose to 28 % (grade 1) and 16 % (grade 2). Grade 1 sensory neuropathy was reported in 13 % of cases at baseline and grade 2 in 16 %. It increased to 43 % (grade 1) and 21 % (grade 2). An extract of the relevant toxicities is presented in Tables 2 and 3.

Gastrointestinal and genitourinary toxicity was overall limited. We observed no higher grade (grade 3–4) diarrhea, enteritis, cystitis or urinary retention. After 12 months one additional case of grade 3 proctitis and one additional case of grade 3 urinary incontinence occurred.

Discussion

In this report, we present the results of a prospective phase II study on hypofractionated radiation therapy for sacral chordoma with protons or carbon ions, marking the first study of its kind. Although the findings regarding local control fell short of our expectations, the study remains valuable for its unique insights into the treatment of this challenging condition and for setting a foundation for future research in this field.

A retrospective study at the Hyogo Ion Beam Medical Center, Japan, from July 2005 to June 2011, assessed carbon ion (CIRT) and proton therapies for primary sacral chordomas in 23 patients. Treatment involved either 70.4 Gy (RBE) in 16 or 32 fractions, with 16 receiving CIRT and 7 proton therapy. After a median 38-month follow-up, high rates of local control (94 %), overall survival (83 %), and progression-free survival (68 %) were observed at three years. The 32-fraction protocol notably reduced severe toxicities compared to the 16-fraction protocol, both initially and at later stages [10].

In a retrospective nationwide multicenter study, a total of 219 patients who underwent CIRT for sacral chordoma at institutions across Japan between December 2003 and July 2014 were included. The results showed a 5-year overall survival (OS) rate of 84 %, progression-free

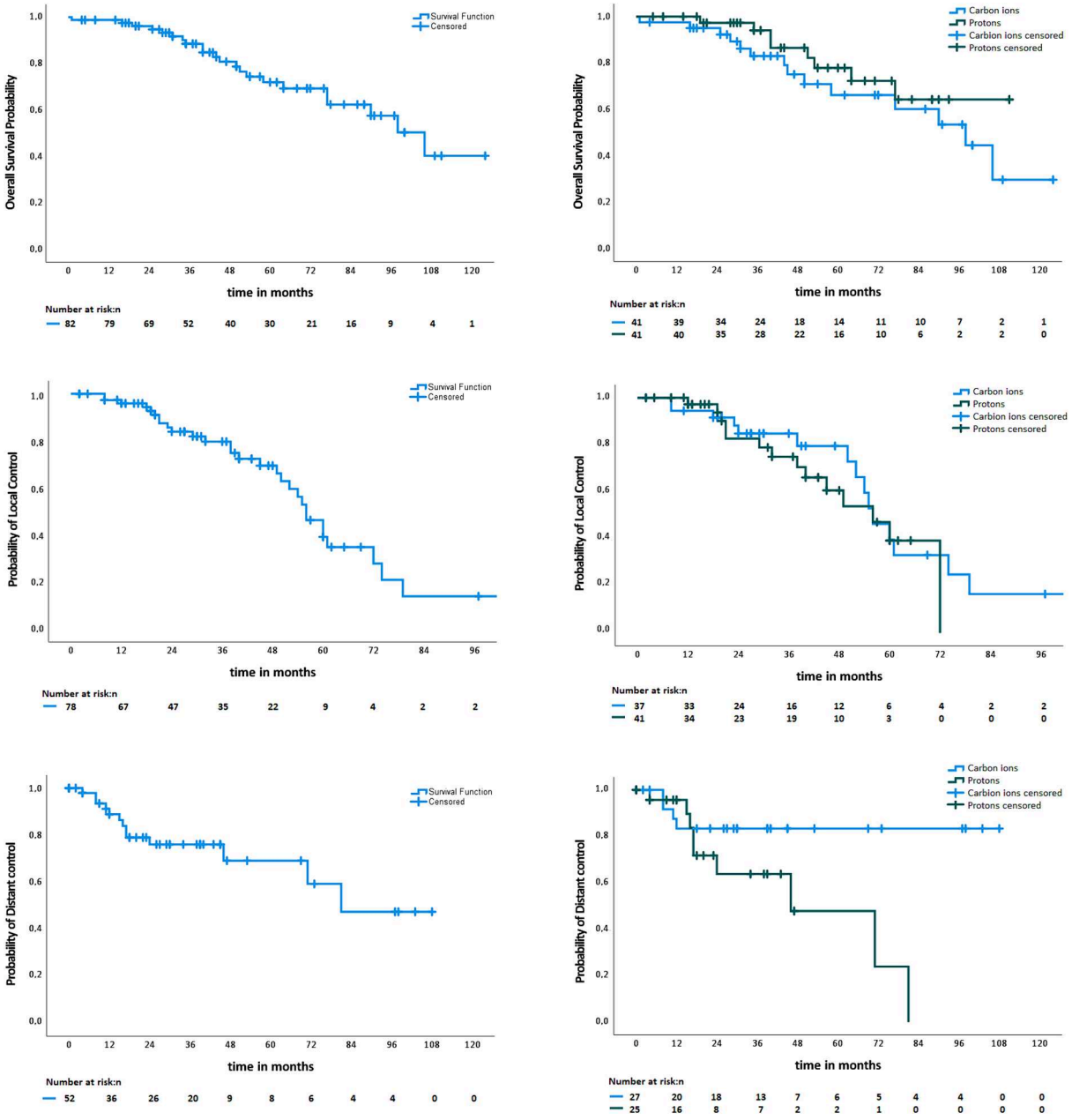

Fig. 2. Kaplan-Meier Analysis of OS, LPFS, and DPFS. The figure displays Kaplan-Meier curves for Overall Survival (OS), Local Progression-Free Survival (LPFS), and Distant Progression-Free Survival (DPFS). The left side presents results for the entire cohort, while on the right results are separated by treatment type: protons and carbon ions.

survival (PFS) rate of 48 %, and a local control (LC) rate of 72 %. The incidence of acute and late grade 3 toxicities was observed in 4 % and 6 % of patients respectively [11]. In our study, a higher weekly fraction dose was given, with 5–6 fractions per week, compared to the Japanese institutions' approach of 16 fractions usually administered at 4.2–4.6 GyRBE, but only 4 fractions per week.

In a retrospective study comparing CIRT with en bloc resection, 911 patients were analyzed from two institutional cohorts and the National Cancer Database. The data revealed no significant difference in OS between the groups, with CIRT showing a median OS of 68.1 months versus 58.6 months for the en bloc resection cohort. CIRT was associated with reduced peripheral motor neuropathy rates [12].

Our institution assessed carbon ion beam therapy, either alone (68 %) or combined with IMRT (32 %), in 68 sacral chordoma patients. The median total dose administered was 66 Gy (range: 60 to 74 Gy; RBE), with a median follow-up of 60 months, showing 5-year LC and OS rates of 53 % and 74 %, respectively. Local recurrence occurred in 46 % of patients, mainly within 25 months [13,14]. Sacral insufficiency fractures were diagnosed in 29 patients (52 %), with 79 % occurring within 2 years post-RT. Fracture rates did not significantly differ between patients who underwent surgery with postoperative RT and those receiving definitive RT. Approximately one-third of patients with sacral insufficiency fractures (34 %) experienced clinical symptoms, primarily pain [15].

In contrast to the scheme of 22 × 3 Gy (RBE), 16 × 4 Gy (RBE) represents a dose escalation. Interestingly, this dose escalation and hypofractionations does not necessarily translate into an improvement in local control. The suboptimal local control observed in this study may stem from several factors. Tumors treated were notably large and deemed inoperable, suggesting a challenging patient cohort. The utilization of X-ray-based image guidance, along with weekly computed tomography scans and a demand-based adaptive protocol, may have

Table 2
Toxicity graded by CTCAE version 4 –whole cohort.

(N, %)	Baseline	End of treatment	12 months
- **Skin:**	**77**	**78**	**76**
- 0	76 (99)	40 (51)	29 (38)
- 1	1 (1)	35 (45)	34 (45)
- 2	0 (0)	3 (4)	7 (9)
- 3	0 (0)	0 (0)	2 (3)
- 4	0 (0)	0 (0)	4 (5)
- Missing	5	4	5
Pain:	**77**	**78**	**78**
- 0	18 (23)	15 (19)	7 (9)
- 1	30 (39)	46 (60)	31 (40)
- 2	23 (29)	16 (21)	27 (35)
- 3	6 (8)	1 (1)	12 (15)
- 4	0 (0)	0 (0)	1 (1)
- Missing	5	4	4
Motor neuropathy:	**76**	**77**	**76**
- 0	64 (84)	65 (84)	42 (55)
- 1	5 (7)	8 (10)	21 (28)
- 2	6 (8)	4 (5)	12 (16)
- 3	1 (1)	0 (0)	1 (1)
- 4	0 (0)	0 (0)	0 (0)
- Missing	6	5	6
Sensory neuropathy:	**77**	**77**	**77**
- 0	54 (70)	46 (60)	27 (35)
- 1	10 (13)	23 (30)	33 (43)
- 2	12 (16)	7 (9)	16 (21)
- 3	1 (1)	1 (1)	1 (1)
- 4	0 (0)	0 (0)	0 (0)
- Missing	5	5	5

resulted in less-than-ideal dose coverage of the PTV, particularly in the anterior aspect of the tumor towards the small pelvis. In this anatomical region, the need to moderate radiation dose to safeguard critical organs at risk could further hinder achieving optimal dose delivery.

The definition of local progression varies widely across studies, often lacking detailed explanation. In our study, local progression may have been assessed with heightened sensitivity, preceding the fulfillment of RECIST 1.1 criteria [16]. Irradiated chordomas usually do not completely regress but instead decrease in size, and in instances of recurrence, they may grow slowly over several months. Consequently, depending on the stringency of the criteria used, such progression can be identified either earlier or later in its course.

In our study, we conducted an indirect comparison between the proton and carbon ion arms and found no discernible differences in their outcomes. This suggests that both ion types exhibit comparable efficacy when utilized in the specific fractionation scheme of our study. The observed lack of superiority of carbon ions over protons could potentially be explained by the application of the LEM-1 in our dosimetric planning. LEM-1, known for its conservative dose estimation, particularly in the beam's entrance region for posterior beams or in the middle of the target for opposite beams, may lead to a lower dose delivery [17,18].

Compared to the dose levels of the Japanese clinical trial utilizing their own biological model (modified microdosimetric kinetic model, mMKM), a difference in dose prediction of approximately −10 % to 20 % is expected with LEM-1 [18]. Consequently, other centers employing LEM-1 tend to administer higher doses per fraction based on the Japanese experience, with doses reaching up to 73.6 (RBE) in 16 fractions [19,20]. However, simply scaling up the mean prescribed dose using LEM-1 to match the Japanese mMKM prescribed dose does not resolve the underdosage when calculating with mMKM an optimized plan with LEM-1. Therefore, investigations into alternative models, akin to

Table 3
Toxicity graded by CTCAE version 4 by study arms.

(N, %)	Carbon ions			Protons		
	Baseline	End of treatment	12 months	Baseline	End of treatment	12 months
Skin:	**39**	**40**	**36**	**38**	**38**	**40**
- 0	38 (97)	26 (65)	22 (61)	38 (100)	14 (37)	7 (18)
- 1	1 (3)	14 (35)	11 (31)	0 (0)	21 (55)	23 (58)
- 2	0 (0)	0 (0)	2 (6)	0 (0)	3 (8)	5 (13)
- 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)
- 4	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	3 (8)
- Missing	2	1	5	3	3	1
Pain:	**39**	**40**	**37**	**38**	**38**	**41**
- 0	12 (31)	10 (25)	6 (16)	6 (16)	5 (13)	1 (3)
- 1	16 (41)	24 (60)	17 (46)	14 (37)	22 (58)	14 (34)
- 2	8 (21)	6 (15)	8 (22)	15 (39)	10 (26)	19 (46)
- 3	3 (8)	0 (0)	6 (16)	3 (8)	1 (3)	6 (15)
- 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
- Missing	2	1	4	3	3	0
Motor neuropathy:	**39**	**39**	**35**	**37**	**38**	**41**
- 0	31 (79)	33 (85)	24 (69)	33 (89)	32 (84)	18 (44)
- 1	2 (5)	3 (8)	7 (20)	3 (8)	5 (13)	14 (34)
- 2	6 (15)	3 (8)	3 (9)	0 (0)	1 (3)	9 (22)
- 3	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)
- 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- Missing	2	2	6	4	3	0
Sensory neuropathy:	**39**	**39**	**36**	**38**	**38**	**41**
- 0	26 (67)	24 (62)	14 (39)	28 (74)	22 (58)	13 (32)
- 1	7 (18)	11 (28)	16 (44)	3 (8)	12 (32)	17 (41)
- 2	5 (13)	4 (11)	5 (14)	7 (18)	3 (8)	11 (27)
- 3	1 (3)	0 (0)	1 (3)	0 (0)	1 (3)	1 (2)
- 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- Missing	2	2	5	3	3	0

Japanese mMKM [17], are underway at our institution. Lastly, the enhanced distant control with carbon ions could be linked to their high LET, as potential inductor of abscopal effect [21]. Subsequent ad-hoc studies from the ISAC trial will aim to characterize in depth potential implications of several parameters, such as biological models, LET or beam orientations, in the patient's outcome (toxicity and tumor/distant control). Further studies are deemed necessary to guide future strategies, including beam orientation, prescribed dose levels, and fractionation schemes, to mitigate toxicity and improve local control.

Conclusion

The ISAC study revealed that hypofractionation with 16 fractions of 4 GyRBE single doses can yield promising response rates, however, local control was not sustained. Certainly, further studies, especially comparative ones in the European context, are necessary to identify an optimal dose and fractionation scheme for the treatment of inoperable sacral chordoma.

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CRediT authorship contribution statement

Katharina Seidensaal: Writing – original draft, Project administration, Investigation, Formal analysis, Data curation. **Andreas Froehlke:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Adriane Lentz-Hommertgen:** Supervision, Data curation. **Burkhard Lehner:** Writing – review & editing, Investigation, Conceptualization. **Andreas Geisbuesch:** Writing – review & editing, Investigation. **Jan Meis:** Writing – review & editing, Formal analysis, Conceptualization. **Jakob Liermann:** Writing – review & editing, Investigation. **Andreas Kudak:** Data curation. **Katharina Stein:** Data curation. **Matthias Uhl:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Thomas Tessonnier:** Writing – original draft, Formal analysis. **Andrea Mairani:** Writing – review & editing, Formal analysis. **Juergen Debus:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Klaus Herfarth:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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