Single-institution clinical experience using robust intensity modulated proton therapy in chordoma and chondrosarcoma of the mobile spine and sacrum: feasibility and need for plan adaptation

Kroesen, M.; Miladinovic, V.; Hutschemaekers, S.A.J.; Jacobs, J.; Vos, C. van der; Wolf, A.L.; ... ; Krol, A.D.G.

Radiotherapy and Oncology 166 (2022) 58–64

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Single-institution clinical experience using robust intensity modulated proton therapy in chordoma and chondrosarcoma of the mobile spine and sacrum: Feasibility and need for plan adaptation

Michiel Kroesen [a,b,c,*], Vesna Miladinovic [a,b,d], Stefan A.J. Hutschemaekers [a], Jenneke Jacobs [a], Charlotte van der Vos [a], Anne Lisa Wolf [a], Mischa S. Hoogeman [a,c], Marco van Vulpen [a], Johan L. Bloem [d], Sander P.D.S. Dijkstra [e], Wilco C. Peul [f], Joan J. Penninkhof [c], Augustinus D.G. Krol [a,b]

[a] HollandPTC, Delft; [b] Department of Radiation Oncology, Leiden University Medical Center; [c] Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam; [d] Department of Radiology; [e] Department of Orthopaedic Surgery, Leiden University Medical Center; and [f] University Neurosurgical Center Holland, LUMC, HMC & HAGA, Leiden-The Hague, The Netherlands

ARTICLE INFO

Article history:
Received 4 May 2021
Received in revised form 11 September 2021
Accepted 21 November 2021
Available online 26 November 2021

Keywords:
Chordoma
Chondrosarcoma
Intensity modulated proton therapy
Pencil beam scanning
Robust planning

ABSTRACT

Background: Due to its specific physical characteristics, proton irradiation is especially suited for irradiation of chordomas and chondrosarcoma in the axial skeleton. Robust plan optimization renders the proton beam therapy more predictable upon individual setup errors. Reported experience with the planning and delivery of robustly optimized plans in chordoma and chondrosarcoma of the mobile spine and sacrum, is limited. In this study, we report on the clinical use of robustly optimized, intensity modulated proton beam therapy in these patients.

Methods: We retrospectively reviewed patient, treatment and acute toxicity data of all patients with chordoma and chondrosarcoma of the mobile spine and sacrum, treated between 1 April 2019 and 1 April 2020 at our institute. Anatomy changes during treatment were evaluated by weekly cone-beam CTs (CBCT), supplemented by scheduled control-CTs or ad-hoc control-CTs. Acute toxicity was scored weekly during treatment and at 3 months after therapy according to CTCAE 4.0.

Results: 17 chordoma and 3 chondrosarcoma patients were included. Coverage of the high dose clinical target volume was 99.8% (range 56.1–100%) in the nominal and 80.9% (range 14.3–99.6%) in the voxel-wise minimum dose distribution. Treatment plan adaptation was needed in 5 out of 22 (22.7%) plans. Reasons for plan adaptation were either reduced tumor coverage or increased dose to the OAR.

Conclusions: Robustly optimized intensity modulated proton beam therapy for chordoma and chondrosarcoma of the mobile spine is feasible. Plan adaptations due to anatomical changes were required in approximately 23 percent of treatment courses.

Chordomas (CH) and chondrosarcomas (CS) located in the axial skeleton are malignant neoplasms of bone [1]. These tumors are locally aggressive, with vertebral bone invasion causing potential neurological compromise, and in contrast have a relatively low tendency to metastasize [2]. CH is a primary malignant bone tumor occurring in the clivus, vertebral column and the sacral bone arising from remnants of the embryonal notochord [3]. CH has an incidence rate of approximately 0.8 per million per year [4,5]. CH tumors show a high tendency for local recurrence; the 5-year local control for spinal CH tumors is around 60% [6–10]. CS has an incidence of 10 per million per year, and 10% and 5% arise in the mobile spine and sacrum, respectively [11]. To maximize the local control of CH and CS tumors, optimal surgery is a prerequisite and high dose radiation is often indicated [5]. Proton therapy is well suited to deliver a high dose radiation to the target, while sparing the neurological structures and organs at risk (OAR) nearby from exposure to mid- or low-dose radiation [12].

Proton irradiation for CH and CS is mostly delivered using a Planning-Target-Volume (PTV)-based treatment planning and a pencil beam scanning (PBS) technique [7,13,14]. With PBS, a uniform target coverage can be achieved by optimizing the energy, lateral position, and weights of the individual pencil beams [15]. This is also denoted as Intensity Modulated Proton Therapy (IMPT). However, the IMPT dose distribution is sensitive to range and setup errors, leading to dose degradation due to the misalignment of the

* Corresponding author at: Holland Particle Therapy Center Huismansingel 4 2629JH Delft The Netherlands.
E-mail addresses: m.kroesen@hollandptc.nl (M. Kroesen), a.d.g.krol@lumc.nl (A.D.G. Krol).

https://doi.org/10.1016/j.radonc.2021.11.020
0167-8140/

pencil beams [14,16–19]. For CH and CS, the proton specific sensitivity to errors is a real concern, because the target prescription dose exceeds by far the maximum tolerable doses of nearby critical structures, such as the spinal cord, cauda equina and bowel.

Recently, robust optimization and evaluation methods have become available in clinical treatment planning systems. In robust treatment planning, in addition to the standard situation (nominal scenario), error scenarios are taken into account in the optimization and evaluation of a treatment plan. How robustness evaluation can be applied in clinical practice for IMPT is described in detail by Korevaar et al. [16]. Despite the robustness of the treatment plan, it is still possible that shape and position of target and nearby critical structures change during the treatment course, which may result in underdosing and/or overdosing of the target and OAR.

Considering the before mentioned conceptual drawbacks of PTV-based proton planning, robust optimization and evaluation of the target and OAR doses was implemented at our institution from the outset. In this report, we analyzed the feasibility, need for plan adaptation, and acute toxicity using robust IMPT in patients with a CH and CS of the mobile spine and sacrum. To our knowledge, this is the first report on clinical use of robust IMPT planning in these patients.

Materials and methods

Patient inclusion

The research protocol for this retrospective study was approved by the medical ethics committee of Leiden University Medical Centre (G19.118). Patients included had a histologically confirmed CH or CS of the mobile spine or sacrum and were staged using MRI and chest-CT. Patients were treated with a radical dose, either pre- and/or postoperative when surgery was possible or definitive when inoperable/irresectable. Intention was to give pre-operative proton beam therapy at the level of cauda equina, while when spinal cord compression above L1 was present, proton beam was applied postoperatively. The inclusion period was from 1 April 2019 until 1 April 2020. The time between the planning-CT/ MRI and start of radiotherapy treatment was between 2-4 weeks. In the postoperative setting, the start of radiotherapy was aimed for between 8-12 weeks post-surgery.

Radiotherapy preparation, target definition and radiation doses

CT (Siemens Healthineers, Erlangen, Germany) and 3T MRI (Philips, Best, Netherlands) scans were acquired in treatment (supine head first) position and fused for contouring. CT-scans were performed using a 120 kVp energy setting, 3 mm slice thickness, 1 s rotation time and a reconstruction diameter of 600 mm over a 512 × 512 image matrix. MRI scans were acquired according to the following protocol: *survey turbo field echo (TFE) in three orthogonal planes; coronal and axial T1-weighted turbo spin echo (TSE), with echo times (TE 10–20 ms) and repetition times (TR 600–700 ms); axial T2-weighted TSE mDIXON with echo times (TE 60–80 ms), repetition times (TR 2500–5000 ms) and with water, fat, and in phase reconstructions; axial dynamic sequence including T1 map TFE; coronal and axial Gd-chelate enhanced fat suppressed spectral presaturation with inversion recovery (SPIR) T1-weighted TSE*. Gadolinium-chelate contrast agent (Dotarem®, Guerbet, Villepinte, France) was administrated using a Medard power injector at 0.2 mL per kilogram of bodyweight with 2 mL/s flow.

Both CT and MRI scans were performed with the patient in head first supine position, on a base-of-skull (BoS) carbon fibre table insert (kVue BoS insert, Qfix, Avondale, PA, USA) and using a knee wedge (Qfix) for fixation. Spinal and sacral chordoma patients were treated in supine position without fixation. In individual cases a thin mattress (Softouch, Qfix, water equivalent thickness 1 mm) or grip ring (Qfix) was used for patient comfort.

Pre- and postoperatively, 50 Gy(RBE) in 25 fractions and 24 Gy (RBE) in 12 fractions was prescribed to the target, respectively. In case of definitive radiotherapy, the GTV/high dose CTV was treated to a total dose of 74 Gy(RBE) in 37 fractions for CH and 70 Gy(RBE) in 35 fractions for CS, whereas the elective CTV was treated to a total dose of 59.2 Gy(RBE) in 37 fractions for CH and 59.5 Gy (RBE) in 35 fractions for CS using a simultaneous integrated boost technique [4]. In one patient a deviant dose was applied; 68 Gy(RBE)/57.5 Gy(RBE) in 34 fractions. For postoperative radiation, the high dose area consisted of the surgical bed and any remnant disease. For CH of the sacrum, the contouring guidelines of the SACRO trial (www.clinicaltrials.gov; NCT02986516) and Radaelli et al. were adhered to [20]. In brief, for CH of the mobile spine and sacrum, contouring for the elective target volume was performed with at least one to two vertebrae cranial and caudal of the tumor or surgical bed.

Radiotherapy planning

RayStation (version 7.0.0.19, RaySearch Laboratories, Stockholm, Sweden) was used for treatment planning. A typical beam setup consisted of 3 posterior beams, radiating through the carbon fiber table and the robotic table onset. The 6.8 cm thick robotic table onset, consisting of a carbon support frame with an inner foam core, was modelled in RayStation using material overrides to a total water-equivalent thickness of 0.68 cm. Available energies ranged from 70 MeV to 250 MeV and range shifters with physical thicknesses of 3 or 5 cm were used for superficially located targets. A Monte Carlo algorithm for dose calculation was used with a grid spacing of 5 mm.

Robust multi-scenario optimization was performed using the RayStation built-in functionality, including the nominal scenario and 5 mm shift in the 6 principal directions, for a density uncertainty of 0%, +3% or −3%, resulting in a total of 21 scenario's. Both target coverage and critical serial organs were robustly optimized. Highest priority was given to the cost functions belonging to the target volumes. OAR dose parameters were evaluated in the nominal scenario as well as in the individual treatment scenario dose distributions. Robustness evaluation was performed following the Dutch consensus of robustness evaluation [12], evaluating scenario doses shifted on the principal directions and vertices, with a positive and negative range error. Scenario dose distributions were reduced to voxel-wise minimum (Vxmin) and maximum (Vxmax) dose distributions, for evaluation of CTV coverage and hot spots respectively. As Vxmin and Vxmax dose evaluations lack information about the number of scenarios involved, clinical evaluation included a report on the number of scenarios in which dose constraints were violated. Dose constraints to the OAR used are listed in Suppl. Table 1. Dose to the OAR was kept within constraints in the nominal plan. When constraint doses exceeded 100%/102%/110% in more than 12/8/0 scenarios, re-optimization was performed using OAR dose parameters as robust cost functions, thereby compromising robust target coverage.

If possible, non-tissue materials from surgery (metal, carbon, cement) were avoided and/or addressed by range adapted CTVs, by adding an extra margin to the distal and/or proximal part of the CTV in the beam direction. In cases where foreign materials of high density or unknown composition could not be avoided, the dose for extremes in range uncertainty was evaluated. Plans were recalculated with material overrides on the implant (e.g. water, titanium) for the possibility of getting an unacceptable dose, especially for spots with end of range in critical OAR (e.g. bowel).

Table 1
Patient and treatment characteristics. 20 patients having in total 22 radiotherapy treatment courses (2 pre- and postoperatively), were included. IQR = Interquartile range.

Characteristic	Categories	Value
Patients (*n* = 20)		
Age (years)	Median (IQR)	63 (52–73.75)
Sex	Male	17 (85.0%)
	Female	3 (15.0%)
Diagnosis	Chordoma	17 (85.0%)
	Chondrosarcoma	3 (15.0%)
Presentation	Primary	17 (85.0%)
	Recurrent	3 (15.0%)
Grade chondrosarcoma	Grade I	0
	Grade II	3 (100%)
	Grade III	0
Tumor site	Thoracic spine	6 (30.0%)
	Lumbar spine	3 (15.0%)
	Sacral bone	11 (55.0%)
Spinal tumors (*n* = 9)	Yes	3 (33.3%)
Clinical spinal cord compression	No	6 (66.6%)
Sacral bone tumors (*n* = 11)	S2	3 (15.0%)
Highest level of nerve root involvement	S3	2 (10.0%)
	S4	2 (10.0%)
	S5	1 (5.0%)
	Unknown	3 (15.0%)
Treatment courses (*n* = 22)		
Sequence radiotherapy course	Preoperative	5 (22.7%)
	Definitive	8 (36.4%)
	Postoperative	9 (40.9%)
Fixation material for spinal reconstruction	None	17 (77.3%)
	Titanium	2 (9.1%)
	Carbon	2 (9.1%)
	Titanium and Carbon	1 (4.5%)

Table 2
Treatment course details, plan evaluations and adaptations. Treatment course details of the 22 proton beam treatment courses. *Elective dose of simultaneous integrated boost plan.

Characteristic	Number of evaluable plans	Categories	Number of plans (%)
Number of beam positions	22	3	20 (90.9%)
		4	1 (4.0%)
		5	1 (4.0%)
Prescription dose Elective CTV (Gy)	18	50	2 (11.1%)
		57.8*	1 (5.6%)
		59.2*	12 (66.7%)
		59.5*	3 (16.7%)
Prescription dose High Dose CTV (Gy)	20	24	3 (15.0%)
		68	1 (5.0%)
		70	4 (20.0%)
		74	12 (60.0%)
Number of evaluation CTs	22	0	7 (31.8%)
		1	7 (31.8%)
		2	3 (13.6%)
		More than 2	5 (22.7%)
Number of plan adaptations during RT course	22	0	17 (77.3%)
		1	5 (22.7%)
Reason plan adaptation	5	Target coverage	3 (60.0%)
		Dose to OAR	2 (40.0%)

All clinical treatment plans are independently verified in an RW3 slab phantom, using a Matrixx PT (IBA dosimetry, Schwarzenbruck, Germany) 2D ion chamber array detector, with an action threshold of 90% of measured points passing a gamma criteria of 2%/2mm.

Radiotherapy treatment setup

Patients were treated with the Varian Probeam pencil beam scanning proton system (Varian Medical Systems, Palo Alto, CA, USA). Patient setup was performed using orthogonal X-ray imaging, or cone beam CT (CBCT) when soft tissue matching or anatomical monitoring was required. For each fraction, online corrections were performed to account for both translational and rotational

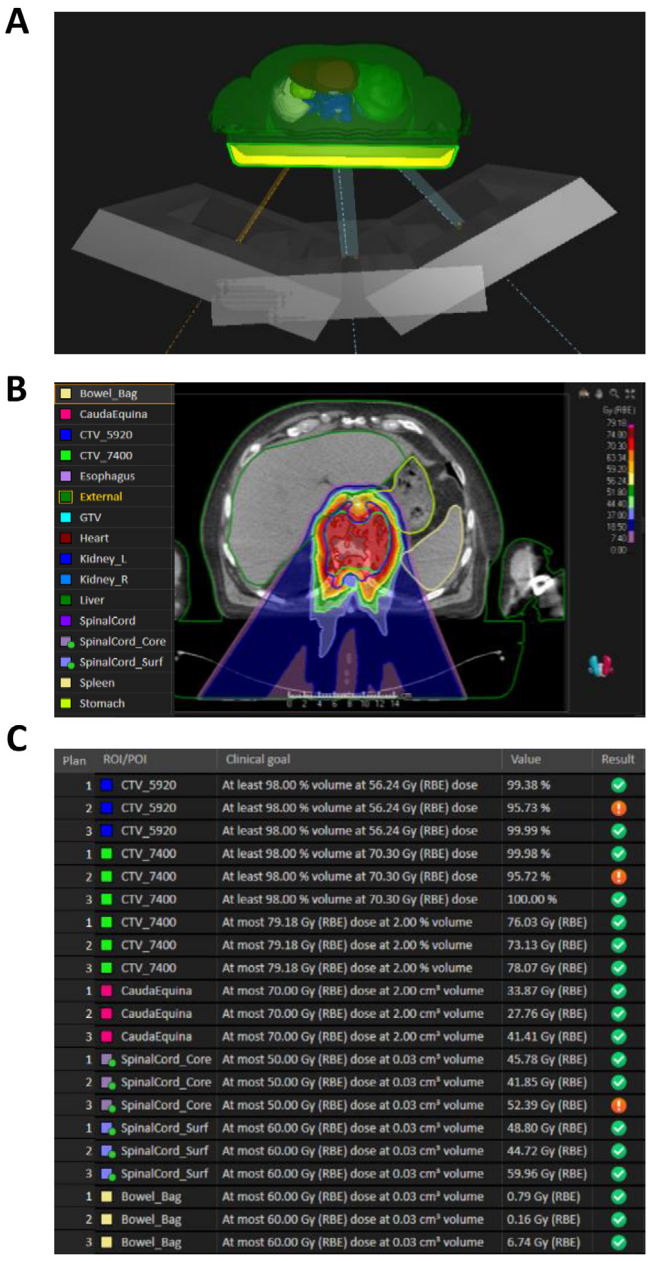

Fig. 1. Representative example of treatment plan. Representative example of a patient with a chordoma of the thoracic spine. Beam setup using 3 posterior beams (A), nominal plan (B) and target and OAR dose parameters for nominal plan as well as Vxmin and Vxmax dose distributions (C) are shown.

setup errors. Post-fraction kV imaging was performed each fraction to evaluate intra fraction motion; residual errors larger than 2 mm and/or 1 degree were reported to the treating physician. Analysis of residual errors after online set up correction and intra fraction motion showed that a robustness margin of 5 mm was sufficient for systemic and random post-fraction errors measured (data not shown).

Dose recalculation and plan adaptation

In all patients, a weekly post-fraction CBCT was made to evaluate any changes in the anatomy. For patients with an anticipated positional change of the organs nearby the target, a standard weekly control-CT was performed. In addition, whenever alterations in the target or OARs were observed on the weekly CBCT, a control-CT was planned ad-hoc. Every control-CT was automatically matched with the initial planning CT and CTVs and OAR were transferred either rigidly or deformable to the new CT and checked by the treating physician. A dose recalculation was performed by forward recalculation and evaluation of the initial plan using robustness settings of 2 mm setup and 3% range uncertainty. The robustness setting for setup error during evaluation is smaller than during optimization and accounts for the maximum residual setup error after an online setup correction. The decision to initiate a plan adaptation was discussed during regular team meetings, but ultimately left at the discretion of the treating physician.

Data collection and statistical analysis

Patient characteristics, planning parameters, treatment parameters and acute toxicity data were extracted from the patient's files and the treatment planning system. Acute toxicity was scored weekly during treatment, at end of treatment and 3 months after treatment according to CTCAE v4.0. Patient data were anonymized, stored in a web-based database (Castor EDC) and analyzed using SPSS (version 26.0) statistical analysis software. Only descriptive analyses were performed.

Results

General characteristics of patients and treatments

General patient and treatment characteristics are listed in Table 1. Within the inclusion period, 20 patients received in total 22 radiotherapy courses (two patients had both pre- and postoperative proton beam therapy). One patient received preoperative photon therapy previously and was now referred for postoperative proton therapy. The majority of patients (17/20) was male. 17/20 patients presented with CH and 3/20 patients with CS. In eight patients en-bloc surgery would result in major loss of neurological functions and patients chose, in a process of shared decision making, for definitive radiotherapy with protons. These patients were defined as having "irresectable" tumors. Three patients were treated for a recurrent tumor. Five patients needed spinal reconstruc-

Table 3
Proton beam plan parameters. CTV volumes and dose parameters from treatment plans are listed as well as aims or dose constraints at our institute. IQR = Interquartile range. D0,03 cc = highest dose in 0,03 cc of OAR volume. D2cc = highest dose in 2 cc in OAR volume. V45 = volume receiving 45 Gy(RBE) or more.

Contour and (dose) parameter	Number of evaluable plans	Value		Aim or Constraint
Volume Elective CTV (cm^3)	18	762.8 (328.4–1661.1)	Median (IQR)	
Volume High Dose CTV (cm^3)	20	162.8 (59.8–463.3)	Median (IQR)	
Coverage elective CTV Nominal plan (percent V95% prescription dose)	18	99.8 (82.7–100)	Median (range)	>98%
Coverage elective CTV Voxel wise minimum plan (percent V95% prescription dose)	18	96.5 (72.8–99.6)	Median (range)	>98%
Coverage high dose CTV Nominal plan (percent V95% prescription dose)	20	99.1 (56.1–100)	Median (range)	>98%
Coverage high dose CTV Voxel wise minimum plan (percent V95% prescription dose)	20	85.0 (14.3–99.6)	Median (range)	>98%
Spinal Cord Surface D0.03 cc Nominal plan (Gy(RBE))	10	47.1 (10.0–50.0)	Median (range)	D0.03 cc $\leq$ 60 Gy(RBE)
Spinal Cord Surface D0.03 cc Voxel wise maximum plan (Gy(RBE))	10	52.9 (16.0–61.0)	Median (range)	D0.03 cc $\leq$ 60 Gy(RBE)
Spinal Cord Core D0.03 cc Nominal plan (Gy(RBE))	10	41.8 (7.0–50.0)	Median (range)	D0.03 cc $\leq$ 50 Gy(RBE)
Spinal Cord Core D0.03 cc Voxel wise maximum plan (Gy(RBE))	10	48.5 (13.0–56.0)	Median (range)	D0.03 cc $\leq$ 50 Gy(RBE)
Cauda Equina Dmean Nominal plan (Gy(RBE))	16	16.7 (0.2–59.3)	Median (range)	Dmean $\leq$ 60 Gy(RBE)
Cauda Equina D2cc Nominal plan (Gy(RBE))	16	59.7 (0.7–69.3)	Median (range)	D2cc $\leq$ 70 Gy(RBE)
Cauda Equina D2cc Voxel wise maximum plan (Gy(RBE))	16	61.8 (1.9–72.4)	Median (range)	D2cc $\leq$ 70 Gy(RBE)
Bowel Bag Dmean Nominal plan (Gy(RBE))	16	0.64 (0.0–5.8)	Median (range)	Dmean $\leq$ 30 Gy(RBE)
Bowel Bag D0.03 cc Nominal plan (Gy(RBE))	16	55.4 (0.2–60.3)	Median (range)	D0.03 cc $\leq$ 60 G(RBE)
Bowel Bag D0.03 cc Voxel wise maximum plan (Gy(RBE))	16	60.0 (1.1–66.2)	Median (range)	D0.03 cc $\leq$ 60 G(RBE)
Skin D1cc Nominal plan (Gy(RBE))	19	60.90 (16.1–70.1)	Median (range)	
Skin V45 Nominal plan (cm^3)	14	3.5 (1.4–5.8)	Median (IQR)	

tion of which three received at least partly carbon pedicle screws and vertebral cages instead of titanium, to allow for a safer proton beam treatment (Table 1).

Proton beam plan characteristics, evaluations and adaptations

The 22 radiotherapy course details are listed in Table 2 and one representative treatment plan is shown in Fig. 1. The median coverage of the elective and high dose CTV in the nominal plan were 99.8% (range 82.7–100) and 99.1% (range 56.1–100), respectively. Dose constraints to OAR were always respected in the nominal plan, however, dose outliers were accepted in individual patients and scenarios, leading to outliers in Vxmax doses exceeding constraints (Table 3). For example, dose to the spinal cord was accepted as high as 56 Gy(RBE) in Vxmax dose distributions (Table 3).

In 7/22 radiotherapy courses no control-CTs were made at all during the whole treatment course. On the contrary, in 5/22 courses at least two control-CTs were acquired during the treatment course. In 5/22 (22.7%) of treatment courses a plan adaptation was performed; in 2/5 because of increased dose to the OAR and in 3/5 because of reduced tumor coverage (Table 2). In both cases in which OAR dose was exceeded, the OAR involved was the bowel bag. For the cases of which the plan was adapted, the dose parameters before adaptation, upon evaluation and after plan adaptation are shown in Suppl. Fig. 1. A visual example of movement of the small bowel towards the high dose area in a patient treated postoperative for a chondrosarcoma is shown in Fig. 2.

Acute toxicity

One patient was excluded from the toxicity analysis because of sudden death during radiotherapy treatment neither related to the oncological condition, nor to radiotherapy. Hence 19 patients receiving 21 radiotherapy courses were included for the toxicity analysis. Toxicity at baseline, end of treatment and at three months after treatment for the 21 treatment courses is listed in Table 4. Grade II radiotherapy induced toxicity was paresthesia in 1/21 (4.8%) courses, fatigue in 3/21 (14.3%), dermatitis in 5/21 (23.8%), dysphagia in 1/21 (4.8%) and anal pain in 1/21 (4.8%). In 1/21 (4.8%) courses a grade III dermatitis was present at the end of treatment. No grade IV or V radiotherapy induced toxicity was observed (Table 4).

Discussion

The dose distribution of proton beam therapy is more sensitive to patient setup errors compared to photon therapy [13,21]. In our clinical practice, we therefore use robustly optimized treatment plans to account for setup errors in addition to range uncertainties. Our analysis showed that out of 22 treatment courses 5 unique plan adaptations were required, which were caused by anatomical changes. We conclude that robustly optimized intensity modulated proton beam therapy is feasible, as long as the dosimetric impact of anatomical changes is monitored, for example by control-CT or CBCT scanning.

Robust optimization and evaluation seems more suitable for proton beam therapy planning, compared to PTV-based planning, because of the higher sensitivity of protons to density changes [14,16]. Still, there is currently no evidence that PTV-based planning in proton beam therapy is clinically inferior to robust planning [15]. We did not compare PTV-based versus robust planning, which is a limitation of our study. There are however several studies that have reported on the comparison between both planning strategies, for example in skull base chordoma and head and neck cancer, showing increased coverage and lower OAR doses for robust planning compared to PTV based planning [18,22].

Although recalculation of the dose on control-CTs during radiotherapy treatment was most often reassuring, for selected patients we observed a clinically significant decrease in target coverage or increase in dose to OAR (5/22 radiotherapy courses). From Suppl. Fig. 1 it is clear that the change in dose to OAR due to anatomical variation could be substantial and warrant close monitoring of the anatomy during treatment. The results in Suppl. Fig. 1 also show that treatment plan adaptation could almost completely recover the initial values of the dosimetric parameters. Due to the fixed nature of CH and CS tumors of the spine and sacrum, we did not

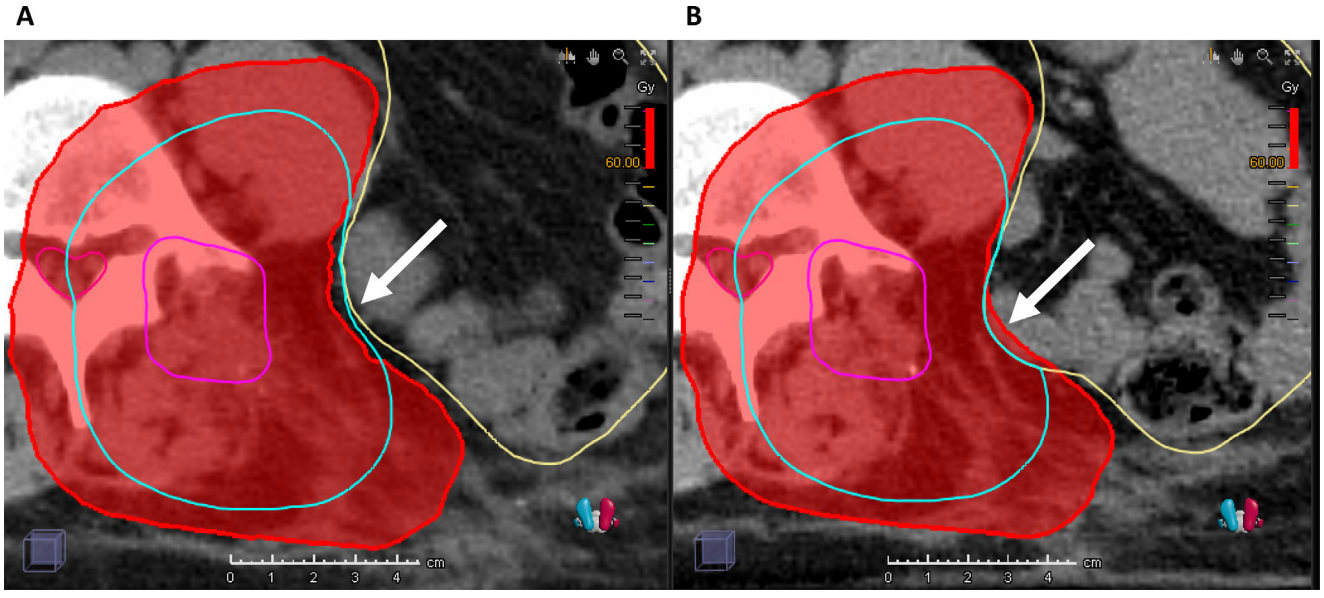

Fig. 2. Example of overdose to bowel on control CT. Vxmax scenarios of the original plan (A) and recalculated plan on the control-CT (B) for a chondrosarcoma patient in postoperative setting. On the control-CT, CTV and bowel contouring were adjusted because of a reposition of the small bowel, replacing the retroperitoneal space. Red area: 60 Gy (RBE) isodose line. Pink contour: surgical bed. Blue contour: CTV (GTV + 2 cm margin or boundary retroperitoneal space). Yellow contour: small bowel. Arrow: area of overdose (>60 Gy (RBE)) to small bowel on control-CT.

Table 4
Toxicity at baseline, end of radiotherapy and 3 months following radiotherapy.

Toxicity	Toxicity Grade	Baseline	End of Treatment	3 months
Tumor Pain	0	16 (76.2%)	16 (76.2%)	16 (76.2%)
	1	2 (9.5%)	3 (14.3%)	4 (19.0%)
	2	3 (14.3%)	2 (9.5%)	1 (4.8%)
Fecal Incontinence	0	18 (85.7%)	18 (85.7%)	18 (85.7%)
	1	2 (9.5%)	2 (9.5%)	2 (9.5%)
	2	1 (4.8%)	1 (4.8%)	1 (4.8%)
Diarrhea	0	21 (100%)	21 (100%)	20 (95.2%)
	1	0	0	1 (4.8%)
	2	0	0	0
Urinary Incontinence	0	19 (90.5%)	19 (90.5%)	20 (95.2%)
	1	0	0	1 (4.8%)
	2	2 (9.5%)	2 (9.5%)	0
Urinary Retention	0	19 (90.5%)	20 (95.2%)	18 (81.0%)
	1	0	0	1 (4.8%)
	2	2 (9.5%)	1 (4.8%)	2 (9.5%)
Erectile dysfunction	0	11 (52.4%)	11 (52.4%)	7 (33.3%)
	1	0	0	1 (4.8%)
	2	2 (9.5%)	2 (9.5%)	0
	Not applicable	3 (14.3%)	3 (14.3%)	3 (14.3%)
	Unknown	5(23.8%)	5(23.8%)	10 (47.6%)
Peripheral motor neuropathy	0	20 (95.2%)	20 (95.2%)	20 (95.2%)
	1	0	0	1 (4.8%)
	2	1 (4.8%)	1 (4.8%)	0
Peripheral sensory neuropathy	0	19 (90.5%)	19 (90.5%)	19 (90.5%)
	1	0	1 (4.8%)	1 (4.8%)
	2	2 (9.5%)	1 (4.8%)	1 (4.8%)
Paresthesia	0	21 (100%)	20 (95.2%)	19 (90.5%)
	1	0	0	1 (4.8%)
	2	0	1 (4.8%)	1 (4.8%)
Fatigue	0	14 (66.7%)	7 (33.3%)	13 (61.9%)
	1	7 (33.3%)	11 (52.4%)	6 (33.3%)
	2	0	3 (14.3%)	1 (4.8%)
	3	0	0	1 (4.8%)
Dermatitis	0	21 (100%)	9 (42.9%)	19 (90.5%)
	1	0	6 (28.6%)	2 (9.5%)
	2	0	5 (23.8%)	0
	3	0	1 (4.8%)	0
Dysphagia	0	21 (100%)	20 (95.2%)	21 (100%)
	1	0	0	0
	2	0	1 (4.8%)	0
Anal Pain	0	21 (100%)	20 (95.2%)	21 (100%)
	1	0	0	0
	2	0	1 (4.8%)	0

anticipate the relatively high frequency of plan adaptations (22.7%) [13]. The necessity of plan adaptation is well-known for treatment sites where anatomical changes are observed more often, such as head and neck or lung [17,23]. Ideally, the plan adjustment should be performed immediately before the fraction dose delivery. This could enable reduction of setup robustness values and potentially also dose escalation. However, daily adaptation is not a clinical reality in proton therapy yet, but is currently under development [24,25].

We observed a mild acute toxicity profile from the proton beam therapy. The highest radiotherapy related toxicity observed was grade III dermatitis in one patient. Toxicity was scored using predefined forms and at scheduled time points, according to the CTCAE4.0. Our acute toxicity rates are in line with previously reported –low– toxicity rates from proton beam therapy for spinal and sacral CH [7,13]. The combined grade III and IV late toxicity following proton beam therapy for CH and CS of the mobile spine and sacrum is reported with an incidence of around 5 percent [7,13,26–28]. The incidence of late toxicity in our cohort has to be awaited.

In 5 out of 20 of patients in our cohort, surgical stabilization material was present. In a large cohort of vertebral and sacral CH patients treated at the Paul Scherrer Institute, surgical stabilization using titanium fixation material was an independent negative predictor for local control, but there may be a bias for more aggressive biology and larger tumors requiring surgical stabilization [7]. The dose calculation in patients with titanium implants was reported to remain accurate as well [20]. Since the introduction of proton therapy in The Netherlands, referring neurosurgeons have started to also use Carbon implants in selected cases to stabilize the spine. Carbon implants do not cause streak artefacts on CT images and do not have to be avoided by the proton beam. Of note, the Leiden Medical University Centre (LUMC) is the center of preference for bone tumors, including CS and CH in The Netherlands.

Limitations of our study are the small patient numbers and the retrospective data collection. In addition, although we show herein that we robustly optimize for critical OAR and actively monitor the dose in the OAR during the treatment course, the long-term toxicity in our patient cohort has to be awaited.

To our knowledge, this is the first report on the clinical use of robustly optimized IMPT treatment for CH and CS of the mobile spine and sacrum. The results of our study indicate that a workflow for robust and adaptive scanning proton therapy is feasible. We also conclude that, although robustly planned, monitoring of target and OAR volume, shape and position is warranted throughout treatment. We will continue to prospectively monitor treatment results and late effects in our patients.

Conflict of interest statement

None of the authors on this manuscript have any conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.11.020.

References

[1] Board WCoTE, *Soft tissue and bone tumours*. 2020: International Agency for Research on Cancer.
[2] Whelan JS, Davis LE. Osteosarcoma, chondrosarcoma, and chordoma. J Clin Oncol 2018;36:188–93.
[3] Sciubba DM, Cheng JJ, Petteys RJ, Weber KL, Frassica DA, Gokaslan ZL. Chordoma of the sacrum and vertebral bodies. J Am Acad Orthop Surg 2009;17:708–17.
[4] Stacchiotti S, Sommer J, G. Chordoma Global Consensus. Building a global consensus approach to chordoma: a position paper from the medical and patient community. Lancet Oncol 2015;16:e71–83.
[5] Sahyouni R, et al., A historical recount of chordoma. J Neurosurg Spine, 2018;28(4): 422-28.
[6] Bakker SH, Jacobs WCH, Pondaag W, Gelderblom H, Nout RA, Dijkstra PDS, et al. Chordoma: a systematic review of the epidemiology and clinical prognostic factors predicting progression-free and overall survival. Eur Spine J 2018;27:3043–58.
[7] Snider JW, Schneider RA, Poelma-Tap D, Stieb S, Murray FR, Placidi L, et al. Long-term outcomes and prognostic factors after pencil-beam scanning proton radiation therapy for spinal chordomas: a large, single-institution cohort. Int J Radiat Oncol Biol Phys 2018;101:226–33.
[8] Demizu Y, Imai R, Kiyohara H, Matsunobu A, Okamoto M, Okimoto T, et al. Carbon ion radiotherapy for sacral chordoma: A retrospective nationwide multicentre study in Japan. Radiother Oncol 2021;154:1–5.
[9] Murray FR, et al., Prognostic factors for spinal chordomas and chondrosarcomas treated with postoperative pencil-beam scanning proton therapy: a large, single-institution experience. J Neurosurg Spine, 2020: 1-10.
[10] Indelicato DJ, Rotondo RL, Begosh-Mayne D, Scarborough MT, Gibbs CP, Morris CG, et al. A prospective outcomes study of proton therapy for chordomas and chondrosarcomas of the spine. Int J Radiat Oncol Biol Phys 2016;95:297–303.
[11] Stuckey RM, Marco RA. Chondrosarcoma of the mobile spine and sacrum. Sarcoma 2011;2011:274281.
[12] Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. Neurosurg Rev 2009;32:403–16.
[13] Aibe N, Demizu Y, Sulaiman NS, Matsuo Y, Mima M, Nagano F, et al. Outcomes of patients with primary sacral chordoma treated with definitive proton beam therapy. Int J Radiat Oncol Biol Phys 2018;100:972–9.
[14] Unkelbach J, Alber M, Bangert M, Bokrantz R, Chan TCY, Deasy JO, et al. Robust radiotherapy planning. Phys Med Biol 2018;63:22TR02.
[15] Lomax AJ, Pedroni E, Rutz HP, Goitein G. The clinical potential of intensity modulated proton therapy. Z Med Phys 2004;14:147–52.
[16] Korevaar EW, Habraken SJM, Scandurra D, Kierkels RGJ, Unipan M, Eenink MGC, et al. Practical robustness evaluation in radiotherapy - A photon and proton-proof alternative to PTV-based plan evaluation. Radiother Oncol 2019;141:267–74.
[17] Kraan AC, van de Water S, Teguh DN, Al-Mamgani A, Madden T, Kooy HM, et al. Dose uncertainties in IMPT for oropharyngeal cancer in the presence of anatomical, range, and setup errors. Int J Radiat Oncol Biol Phys 2013;87:888–96.
[18] Liu W, Mohan R, Park P, Liu Z, Li H, Li X, et al. Dosimetric benefits of robust treatment planning for intensity modulated proton therapy for base-of-skull cancers. Pract Radiat Oncol 2014;4:384–91.
[19] Unkelbach J, Paganetti H. Robust proton treatment planning: physical and biological optimization. Semin Radiat Oncol 2018;28:88–96.
[20] Dietlicher I, Casiraghi M, Ares C, Bolsi A, Weber DC, Lomax AJ, et al. The effect of surgical titanium rods on proton therapy delivered for cervical bone tumors: experimental validation using an anthropomorphic phantom. Phys Med Biol 2014;59:7181–94.
[21] Unkelbach J, Bortfeld T, Martin BC, Soukup M. Reducing the sensitivity of IMPT treatment plans to setup errors and range uncertainties via probabilistic treatment planning. Med Phys 2009;36:149–63.
[22] Liu W, Frank SJ, Li X, Li Y, Zhu RX, Mohan R. PTV-based IMPT optimization incorporating planning risk volumes vs robust optimization. Med Phys 2013;40:021709.
[23] van der Laan HP, Anakotta RM, Korevaar EW, Dieters M, Ubbels JF, Wijsman R, et al. Organ sparing potential and inter-fraction robustness of adaptive intensity modulated proton therapy for lung cancer. Acta Oncol 2019;58:1775–82.
[24] Jagt TZ et al. Online-adaptive versus robust IMPT for prostate cancer: How much can we gain? Radiother Oncol 2020;151:228–33.
[25] Albertini F et al. Online daily adaptive proton therapy. Br J Radiol 2020;93:20190594.
[26] Pennicooke B, 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): S186-92.
[27] Kabolizadeh P, Chen Y-L, Liebsch N, Hornicek FJ, Schwab JH, Choy E, 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;97:254–62.
[28] Rutz HP, Weber DC, Sugahara S, Timmermann B, Lomax AJ, Bolsi A, et al. Extracranial chordoma: outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation. Int J Radiat Oncol Biol Phys 2007;67:512–20.