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Intensity-modulated radiotherapy for the management of primary and recurrent chordomas: a retrospective long-term follow-up study

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ABSTRACT

Background: Chordomas have a high risk of recurrence. Radiotherapy (RT) is required as adjuvant therapy after resection. Sufficient radiation doses for local control (LC) can be achieved using either particle therapy, if this technology is available and feasible, or intensity-modulated radiotherapy.

Materials and methods: 57 patients (age, 11.8–81.6 years) with chordomas of the skull base, spine and pelvis who received photon radiotherapy between 1995 and 2017 were enrolled in the study. Patients were treated at the time of initial diagnosis (68.4%) or during recurrence (31.6%). 44 patients received adjuvant radiotherapy and 13 received definitive radiotherapy. The median total dose to the physical target volume was 70 Gy equivalent dose in 2 Gy fractions (EQD2) (range: 54.7–82.5) in 22–36 fractions.

Results: LC was 76.4%, 58.4%, 46.7% and 39.9% and overall survival (OS) was 98.3%, 89%, 76.9% and 47.9% after 1, 3, 5 and 10 years, respectively, with a median follow-up period of 6.5 years (range, 0.5–24.3 years). Age, dose and treatment concept (post-operative or definitive) were significant prognostic factors for OS. Primary treatment, macroscopic tumour at RT and size of the irradiated volume were statistically significant prognostic factors for LC.

Conclusion: Photon treatment is a safe and effective treatment for chordomas if no particle therapy is available. The best results can be achieved against primary tumours if the application of curative doses is possible due to organs at risk in direct proximity. We recommend high-dose radiotherapy, regardless of the resection status, as part of the initial treatment of chordoma, using the high conformal radiation technique if particle therapy is not feasible.

Key words: chordoma; radiotherapy; photon; long-term follow-up

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Introduction

The overall incidence of chordoma is 8.4 per 10 million people, according to the Surveillance, Epidemiology, and End Results database [1]. Chordomas are rare malignant bone tumours that originate from notochordal remnants. Therefore, chordomas are usually located along the neuroaxis [2]. No risk factors for the development of chordoma have been identified. Chordomas are usually low-grade tumours that grow locally and aggressively, with very high recurrence rates [1, 3]. Chordomas are pathologically classified into classic, chondroid and dedifferentiated subtypes [4]. The dedifferentiated subtype is associated with the worst prognosis, and the chondroid subtype has the best prognosis [5, 6]. Dedifferentiated chordoma patients present with significantly higher rates of both synchronous and metachronous metastases and have shorter overall survival (OS) rates compared to conventional chordoma patients [7]. Despite the low potential for metastasis in classic and chondroid subtypes [8, 9], local control (LC) is the most important prognostic factor for survival [10]. Surgical margins are the most significant prognostic factor for local and distant recurrence, and the combined surgical approach (anterior/posterior) is associated with local recurrence [11]. Because chordomas are rare, the available evidence is insufficient to indicate if the addition of radiotherapy improves survival in patients with sacral and spinal chordomas after gross total resection [12]. Furthermore, little well-founded knowledge concerning individualized prediction and prognostic factors for survival is available. Huang et al. developed a nomogram that may provide prognostic predictions for patients with spinal chordomas; the nomogram includes tumour diameter, metastasis and resection status that divide patients into risk groups and support the development of personalized treatments [13].

Complete surgical removal is the cornerstone of treatment for chordomas. However, complete resection is often difficult to achieve with acceptable functional outcomes due to locally invasive growth patterns and directly adjacent structures/organs at risk (e.g. nerves or blood vessels in the skull base). Hence, macroscopic residual tumour often remains after surgery, resulting in insufficient tumour control with a worse overall outcome [14]. Therefore, radiotherapy is recommended as adjuvant or additive therapy after function-conserving tumour resection. A dose escalation of at least 70 gray (Gy) [relative biological effectiveness (RBE)] appears to be necessary for sufficient LC of 74% after 5 years [15].

High conformal techniques, such as proton or carbon ion beam therapy, are better for applying sufficiently high radiation doses, due to the critical structures next to the irradiated tumours [16, 17]. Nevertheless, due to surgical stabilization factors [depth dose equivalent variation, artefacts in magnetic resonance and computed tomography (CT)-based planning], health insurance status, or lack of capacity, proton or carbon ion beam therapy cannot be performed in some cases. Although conventional irradiation can achieve good palliation, residual tumours are rarely cured with conventional photon irradiation due to low dose conformity and coverage of the target volume. Patients receiving more than 55 Gy or a time, dose and fractionation factor of 90 were free from local progression for five or more years [18, 19]. Treatment of chordomas shifted to highly specialized particle therapy radiation centres and intensity-modulated radiation therapy (IMRT) as the first-line therapy has become rare. Therefore, in this study, a historical cohort with a long follow-up is compared with curative conventional treatments if particle therapy is not available.

Material and methods

All patients with chordoma of the skull base, spine, or pelvis who were not suitable for proton or carbon ion beam therapy and who were exclusively treated with photons between 1995 and 2017 at the university hospital of Heidelberg were included in the current analysis. All patients were followed for at least 6 months. Patients with previous radiotherapy and patients who received combined modality treatments (especially with particle therapy boost) were excluded from the analysis. IMRT was delivered with a 6/15 MV linear accelerator (Siemens AG, Erlangen, Germany). Treatment plans were created using inverse treatment planning. CT images were transferred to a Siemens oncologist workstation for contouring. Inverse treatment planning was performed on a tomotherapy planning workstation. Demarcation of organs at risk

and target volume definition were based on CTs and magnetic resonance imaging (MRI) scans. Gross tumour volumes (GTV) (as an indication of the entire initial or residual tumour size) were rare and depended on tumour location and the presence of macroscopic tumours. In some cases, a clinical target volume (CTV) with an individual safety margin based on surgical and histological reports and MRI images was created to account for subclinical disease. The margin depended on tumour localization and was 1–2 mm for the skull base and 5 mm–2 cm for the mobile spine. In most cases, only the physical target volume (PTV) was contoured. If a CTV was present, a PTV margin of 3–5 mm was chosen, considering the patient fixation and the irradiated region. Only PTV was used to compare target volumes. A comparison of the tumour sizes was not feasible due to missing or contradicting data.

The main endpoint of this retrospective analysis was LC. Secondary endpoints were OS and treatment outcome/prognostic factors. After approval from the ethics committee at the University of Heidelberg, all accessible patients were contacted for informed consent and received a follow-up information sheet regarding the current retrospective analysis and questionnaires concerning their side effects and tumour status. We also evaluated all medical records and contacted other treating physicians or registration offices to assess patient vital status. If available, follow-up MRI scans were evaluated to determine the tumour status.

The Kaplan-Meier method was used for statistical analysis to assess LC and OS. The 10-year follow-up was divided into 5 periods: baseline, 0 to 1 year, 1 to 3 years, 3 to 5 years and 5 to 10 years. Age, PTV (deviating from the median), macroscopic tumour, sex, dose and time of treatment were tested for prognostic significance using log-rank tests. The survival function was estimated using the Kaplan–Meier product-limit method and significance was assessed using log-rank tests. Standard errors for 95% confidence intervals (95% CI) were calculated based on the asymptotic variance (20). The level of significance was $p < 0.05$.

Results

Patient characteristics are summarized in Table 1. Between 1995 and 2017, 57 patients with histologically proven chordomas were treated with IMRT at our institution. The mean age at the start of radiotherapy was 57.9 years (range, 11.8–81.6 years). The male-female ratio was 56.1% to 43.9% (32:25 patients). Most primary tumours

Table 1. Patient characteristics

	All patients	
	n = 57	%
Follow up [years] Median (range)	6.5 (0.5–24.3)	
Age (therapy) Median (range)	57.9 (11.8–81.6)	
Gender		
Male	32	56.1
Female	25	43.9
Tumour site		
Brain/base of skull	15	26.3
Cervical spine	16	28.1
Thoracic spine	9	15.8
Lumbar spine	12	21.1
Pelvis	5	8.8
Resection status		
R0	5	11.4
Rx	10	22.7
R1	2	4.5
R2	24	54.5
Missing	3	6.8
Only tumour biopsy	13	
Radiation concept		
Additive/Adjuvant	44	77.2
Definitive	13	22.8
Metastasis during follow-up		
Yes	6	10.5
No	51	89.5
Missing	0	–
Local control during follow–up		
Yes	34	59.7
No	20	35.1
Missing	3	5.3
Radiotherapy schedule		
70 Gy in 35Fx	43	75.4
66 Gy in 22 Fx	3	5.3
Other	11	19.3
Median (range)	70 Gy (57.6–70.0) 35 fractions (22.0–36.0)	

→

Table 1. Patient characteristics

	All patients	
	n = 57	%
Target volume [mL]		
≥ 400	26	35.6
< 400	30	52.6
Missing	1	1.8
Median (range)	361.7	(28.3–4628.7)
Primary treatment	39	68.4
Treatment of recurrence	18	31.6
Planning on Myelo-CT		
Yes	26	45.6
No	31	54.4
Metal image artefacts in PTV		
Yes	28	49.1
No	29	50.9
Macroscopic tumour at RT		
Yes	39	68.4
No	14	24.6
Unknown	4	7.0

Myelo-CT — computed tomography after conventional myelography; PTV — planning target volume; RT — radiotherapy

were located in the skull base and cervical spine (54.4%), followed by the lumbar spine and pelvis (29.9%). Eighteen patients (31.6%) were treated for recurrent tumours after multiple resections, and 39 patients (68.4%) were treated for primary tumours. Post-operative radiotherapy was administered in 44 patients (77.2%), and 13 patients (22.8%) were treated with primary radiotherapy after biopsy alone. The time between surgery and the start of additive/adjuvant RT was < 6 months in all cases. Only 5 patients had complete resections. In 39 patients (68.4%), no macroscopically residual tumour was detected at the time of radiotherapy. In 13 patients (29.5%), the resection status could not be determined (Rx or missing data). In 28 patients (49.1%), metal artefacts after surgical stabilization were detected in the planning CT adjacent to the irradiated target volume. For treatment planning, 26 patients (45.6%) received CT after conventional myelography (Myelo-CT). Data about asymptomatic lung and/or bone metastases before starting radiotherapy treatment was insufficient.

All patients were treated using a photon IMRT technique; 3D-CRT was performed if IMRT failed for technical reasons. Hypofractionated radiation therapy was applied to three patients at the discretion of the physicians. The median total dose to the target volume (PTV) was 70 Gy (range, 57.6–70 Gy) equalling 70 Gy equivalent dose in 2 Gy fractions (EQD2) (range, 54.7–82.5) in a median of 35 fractions (range 22–36) over 6–7 weeks. The median PTV volume was 361.7 ml (range, 28.3–4628.7 ml). The volume was more than 400 ml in 26 patients (35.6%). Regular follow-up included radiological (CT/MRI) and clinical examinations were carried out in institutes close to the patient's home. Follow-up examinations were performed at 6 weeks, 3 months, 6 months and every year after radiotherapy if possible. Long-term toxicity was measured using specifications in medical records and questionnaires. Side effects were not documented according to the Common Toxicity Criteria. Due to the retrospective analysis without baseline performance and questionnaires from only seven patients, the performance and side effects could not be evaluated.

The median follow-up period was 6.5 years (range, 0.5–24.3 years). LC was 39.9% and OS 47.9% after 10 years. LC was 76.4%, 58.4% and 46.7% after 1, 3 and 5 years, respectively. OS was 98.3%, 89 % and 76.9% after 1, 3, and 5 years, respectively. Five patients were lost to follow-up concerning LC and clinical outcome and were only taken into account when determining the survival data. The Kaplan–Maier plots for LC, progression-free survival and OS are shown in Figure 1A, B and C, respectively. The local 5-year progression-free survival for patients who received 70 Gy EQD2 or more (n = 43) was 50.0% (95% CI: 30.9–66.4%), and the 5-year progression-free survival for all patients (n = 52) was 46.7% (95% CI: 28.7–62.8%). Six patients (10.5%) developed distant metastases (half in bone, a third in the lung), and 20 patients (35.1%) developed local recurrences during follow-up.

Considering the missing data in five patients, we suspect significant differences regarding patient characteristics. Age ≤ 58 years (p = 0.0334), total dose ≥ 70 Gy EQD2 (p = 0.0012) and an additive/adjuvant radiation concept (p = 0.0047) were significant prognostic factors for better OS. Primary treatment with IMRT at the initial date of diagnosis independent of surgery (p = 0.0436), macroscopic tumour at RT (p = 0.0467) and PTV size < 400 mL (p = 0.0004) were significant prognostic factors

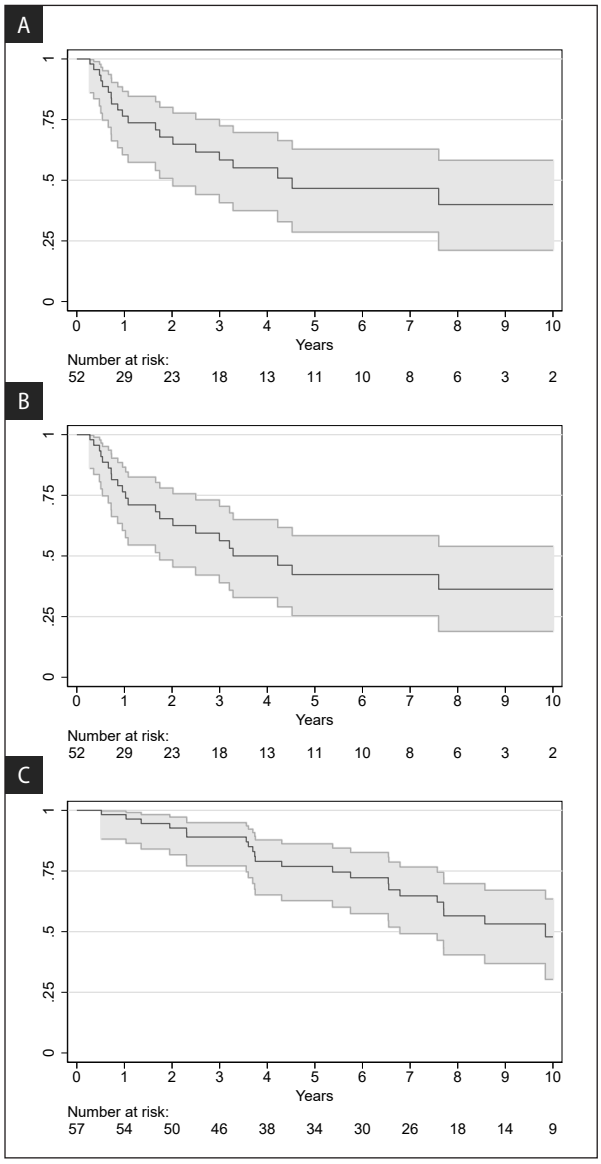

Figure 1. A. Duration of local control (LC): all patients (missing data: 5 patients lost of follow-up); **B.** Progression-free survival (PFS): all patients (missing data: 5 patients lost of follow-up)**; C.** Overall survival (OS): all patients

for LC. The Kaplan-Maier plots and p-values are shown in Figure 2.

This was a retrospective study; therefore, the results were difficult to interpret due to the heterogeneity of the study population. This study also included two younger patients. An eleven-year-old girl with clivus chordoma and a nineteen-year-old boy with chordoma of the thoracic vertebrae. Both had curative post-operative radiotherapy and OS and LC was 24 years for the girl and 32 months for the boy. Table 2 shows the OS of specific populations according to tumour location (brain/base of skull, spine, pelvis) in 48 patients who received total doses of 68 Gy EQD2. No significant differences in OS were detected. Concerning LC, outcomes were significantly better in patients with primary tumours compared with outcomes in patients with recurrent tumours ($p = 0.02$).

Discussion

We report consistent rates of LC and OS for chordoma following high-dose photon linear accelerator IMRT. The advantage of IMRT is that the beam can be modulated to shape the radiation dose distributions with steep dose fall-off at the borders between the tumour and organs at risk. In combination with sufficient image guidance, millimetric delivery precision can be achieved, allowing minimisation of the PTV margins. Because of the higher integral dose with photons rather than protons, tumour control may be affected by a higher potential for adverse effects. Hence, the significance of high-dose photon-based versus proton radiation is controversial. Conventional radiation is limited to palliative treatment because of the lower LC rates [21].

Because of the limitations in dose escalation using conventional radiation, treatment of chordomas shifted to highly specialized particle therapy radiation centres. The advantage of particle therapy lies in the predictable dose deposition at a given depth, allowing for maximal dosing at the tumour/OAR interface and dose escalation within the tumour [22]. Therefore, higher doses can be delivered with particle therapy than possible with conventional radiation. Consequently, the results are more favourable compared with conventional radiation [23]. Thus, particle therapy is the gold standard for treating chordomas. Nevertheless, in some cases (due to surgical stabilization, health insurance status, or lack of capacity), proton or carbon ion beam therapy could not be performed and photon IMRT was used instead. In most patients in the current analysis (49.1%), metal artefacts after surgical stabilization were the reason for the treatment with photons. Metallic implants complicate MR and even CT-based planning of local radiation therapy, because they induce uncontrollable dose-modulating effects in adjuvant radiotherapy, especially if charged particles are used [24].

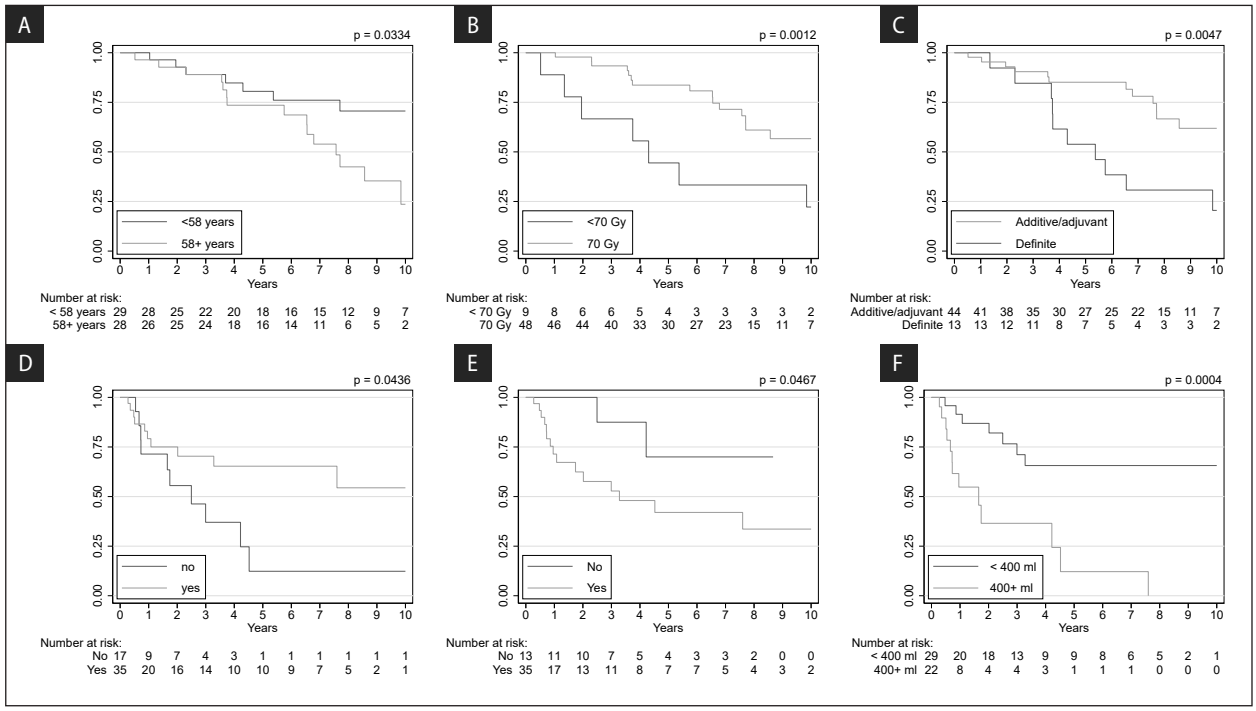

Figure 2. A. Overall survival (OS) according to age: median was 58 years (p = 0.0334); **B.** OS according to total dose: < 70 Gy EQD2 *vs*. at least 70 EQD2 (p = 0.0012); **C.** OS according to radiation concept: postoperative *vs*. definite (p = 0.0047); **D.** Duration of local control (LC) by primary treatment (yes) *vs*. recurrence (no) (p = 0.0436); **E.** Duration of LC by macroscopic tumor at radiotherapy (RT) start (yes) (p = 0.0467); **F.** Duration of LC by irridiated target volume: median was about 400 mL (p = 0.0004)

Table 2. Overall survival (OS) and local control (LC) by tumor location [total dose > 68 Gy equivalent dose in 2 Gy fractions (EQD2)]

Tumour location	Brain/base of skull			Spine			Pelvis		
	n	Median (range)	p-value	n	Median (range)	p-value	n	Median (range)	p-value
OS [years]	9	5.8 (2.1–11.5)		36	7.6 (0.5–18.3)		3	2.3 (0.7–3.7)	< 0.001
Treatment concept									
Definite	3	6.6 (5.7–10.8)	0.844	3	7.3 (3.7–12.2)	0.764	2	3.0 (2.3–3.7)	NA
Additive/Adjuvant	6	4.5 (2.3-11.5)		33	7.6 (0.5–18.3)		1	0.7	
Treatment situation									
Recurrence	1	5.2	0.605	13	7.6 (3.0–18.3)	0.728	0		NA
Primary treatment at the time of diagnosis	8	6.1 (2.3–11.5)		23	7.6 (0.5–9.7)		3	2.3 (0.7–3.7)	

In patients who were not suitable for particle therapy, LC was 39.9% and OS was 47.9% after 10 years (median follow-up, 6.5 years). Even if the Kaplan-Meier 10-year estimates were less reliable, these data are consistent with expected outcomes following proton and previous photon therapy [25–29]. The 10-year LC rates were 54% after irradiation with carbon ions in patients with skull base chordomas, whereas a 10-year OS rate of 75% was already reported [17].

Because chordomas are rare and particle therapy is now state of the art, the sample size was small. The median time of follow-up (6.5 years) ranged from six months to 24.3 years. Furthermore, the distribution between adjuvant/additive and definitive RT (44 patients *vs*. 13 patients) and be-

tween primary treatment and treatment of recurrent tumours (39 patients *vs*. 18 patients) were not equal. Skull base and spine tumour sites were more common than tumours at the sacrum or pelvis sites. In a 2010 report, about 34 patients with sacral chordoma were treated with IMRT, the 5-year LC was 27% (29). In another study, Lu et al. reported on patients with sacral chordoma who were treated with IMRT (n = 48) or gamma knife (n = 26). The reported LC-rates after 5 years were 70.9 % and 18.3 %, respectively [30]. Chordomas of the skull base, spine and pelvis/sacrum behave very differently (metastasis rate, clinical presentation); furthermore, the oncological management is different for the different tumour locations (treatment-related complications, target margins). Because of these limitations and the retrospective character of the study, creating homogenous groups was difficult. Due to the small subgroups, significant differences were rare. The insignificant results of subgroup analyses can be found in the Supplementary File and Table 2.

Long-term (up to 30 years) follow-up data concerning clinical outcomes (performance status, side effects) are lacking. Furthermore, some clinical data, including follow-up imaging, medical reports about further treatment and pathological findings, are collected by other institutions. We invited all survivors of this cohort for an interview. Unfortunately, only 7 patients replied. All responding patients mentioned no or only low-grade late toxicities (data not shown). Performance and side effects could not be evaluated.

Histological reports are also lacking. Only 21 of 57 patients had detailed histological reports, including immunohistology. Thus, diagnoses were uncertain for some patients. Patients may have also had chondrosarcomas that were incorrectly identified (brachyury had not been established as a specific marker). Statistical outliers may be explained by misdiagnoses. A table with detailed histology findings is included in the Supplementary File — Table S1.

Despite all the inadequacies of this retrospective analysis, we found significant differences in LC and OS dependent on the time of treatment (primary *vs*. recurrent treatment), treatment concept (adjuvant *vs*. definitive), macroscopic tumour, target tumour volume, age and applied dose. Due to missing data (GTV, CTV, margins), only PTV close to the median volume (361 mL) was chosen to categorize the groups. A PTV < 400 mL was associated with better LC. No PTV cut-offs are known prognostic factors but PTV is probably related to prognostic factors such as tumour size and toxicity [15, 31]. Staab et al. [32] also reported better OS of male patients with proton therapy. The results from Hyogo Ion Beam Medical Center and carbon ion therapy at the Heidelberg Ion-Beam Therapy Center showed longer progression-free survival in male patients [33, 34]. In our analyses, no gender-specific differences in LC and OS were detected.

Post-operative radiotherapy of chordoma, regardless of the resection status, improved OS compared with patients with no partial or total resection within six months before RT (p = 0.0047). RT has been shown to improve LC after complete or incomplete resection and in salvage treatment [19, 35]. In proton therapy, macroscopic residual tumours in patients with extracranial chordoma were identified as a significant factor affecting LC and OS. However, the significant disadvantage of extended resection associated with surgical stabilization was discussed [32]. Our data showed no significant results on this issue (p = 0.0691) but a clear trend was observed for better LC with no stabilization or no Myelo-CT treatment planning (p = 0.0502). Graphs are shown in the Supplementary File. In photon radiotherapy of chordoma of the spine, LC might be limited by a worse dose coverage of the target volume in proximity to the spinal cord.

Significantly better LC was observed in patients who underwent RT as a primary treatment concept (p = 0.04). Researchers at The Massachusetts General Hospital reported significantly better LC and OS rates in patients who were treated after surgery for primary versus recurrent tumours [36]. Higher local failure rates were observed in recurrent chordoma patients (p = 0.04). This suggests a higher biological aggressiveness of recurrent tumours and needs further investigation. High charged particle therapy may have more biological effects in recurrent tumours [34]; however, this issue required further investigation. In 2017, high-dose (re)irradiation with curative intent was recommended by the Chordoma Global Consensus Group for recurrent chordomas [37]. However, no significant differences in OS were observed between patients

with LC versus progressive disease. Nevertheless, adjuvant radiotherapy may also prolong survival when adequate radiation doses are applied. Furthermore, Bergh et al. reported that local failure was significantly associated with an increased risk of metastasis and tumour-related death. In our study, 6 patients developed distant metastasis; 3 of these patients had LC when metastases were detected and local progression was detected in all 6 patients. As already mentioned, LC was not a prognostic factor for OS (p = 0.216) [38]. Graphs are shown in the Supplementary File.

Our results demonstrated significantly better LC and OS rates in patients who were treated with photons using doses greater than 70 Gy EQD2. In a 2010 report about 34 patients with sacral chordoma, LC was significantly better after IMRT in patients treated for primary tumours and using doses greater than 60 Gy. Actuarial LC rates were 79%, 55% and 27% and OS rates were 97%, 91% and 70% after 1, 2 and 5 years, respectively [29]. Napieralska et al. reported on 23 patients with chordomas of the skull base and upper spine who were treated with hyprofractionated stereotactic radiotherapy and a median dose of 52 Gy. LC after five years was 43% [39]. In 2022, in another report of 15 patients with sacral, lumbar, neck and skull base chordoma, 5-year survival for patients receiving a high RT dose was 72% and the cumulative 5-year incidence of local failure was 48% [40]. This is in line with our results for OS (98.3%, 89% and 76.9% after 1, 3 and 5 years) and LC (76.4%, 58.4% and 46.7% after 1, 3 and 5 years) demonstrating a higher and probably more accurate LC and OS rate at 5 years. At 5 years of follow-up, 11 and 34 patients were at risk for LC and OS, while only 3 patients were at risk left for LC and OS in the previously mentioned study [29].

Conclusion

Despite particle therapy being the current gold standard for adjuvant treatment of chordoma, photon IMRT improved LC if used as adjuvant therapy. If particle therapy is not possible, photon IMRT is the next best alternative for the adjuvant treatment of chordoma.

Conflict of interest

None declared.

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Additional notes

Author responsible for statistical analysis: Prof. Dr. Volker Winkler (e-mail: volker.winkler@urz.uni-heidelberg.de).

Employment or leadership position: Prof. Debus is CEO of Heidelberg Ion Beam Therapy Center (HIT).

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

References

1. Smoll NR, Gautschi OP, Radovanovic I, et al. Incidence and relative survival of chordomas: the standardized mortality ratio and the impact of chordomas on a population. Cancer. 2013; 119(11): 2029–2037, doi: 10.1002/cncr.28032, indexed in Pubmed: 23504991.
2. Salisbury JR, Deverell MH, Cookson MJ, et al. Three-dimensional reconstruction of human embryonic notochords: clue to the pathogenesis of chordoma. J Pathol. 1993; 171(1): 59–62, doi: 10.1002/path.1711710112, indexed in Pubmed: 8229458.
3. Walcott BP, Nahed BV, Mohyeldin A, et al. Chordoma: current concepts, management, and future directions. Lancet Oncol. 2012; 13(2): e69–e76, doi: 10.1016/S1470-2045(11)70337-0, indexed in Pubmed: 22300861.
4. Chugh R, Tawbi H, Lucas DR, et al. Chordoma: the nonsarcoma primary bone tumor. Oncologist. 2007; 12(11): 1344–1350, doi: 10.1634/theoncologist.12-11-1344, indexed in Pubmed: 18055855.
5. Jian BJ, Bloch OG, Yang I, et al. Adjuvant radiation therapy and chondroid chordoma subtype are associated with a lower tumor recurrence rate of cranial chordoma. J Neurooncol. 2010; 98(1): 101–108, doi: 10.1007/s11060-009-0068-1, indexed in Pubmed: 19953297.
6. Mitchell A, Scheithauer BW, Unni KK, et al. Chordoma and chondroid neoplasms of the spheno-occiput. An immunohistochemical study of 41 cases with prognostic and nosologic implications. Cancer. 1993; 72(10): 2943–2949, doi: 10.1002/1097-0142(19931115)72:10<2943::aid-cncr2820721014>3.0.co;2-6, indexed in Pubmed: 7693324.
7. Nachwalter RN, Rothrock RJ, Katsoulakis E, et al. Treatment of dedifferentiated chordoma: a retrospective study from a large volume cancer center. J Neurooncol. 2019; 144(2): 369–376, doi: 10.1007/s11060-019-03239-3, indexed in Pubmed: 31338785.
8. Chambers PW, Schwinn CP. Chordoma. A clinicopathologic study of metastasis. Am J Clin Pathol. 1979; 72(5): 765–776, doi: 10.1093/ajcp/72.5.765, indexed in Pubmed: 389031.
9. Eriksson B, Gunterberg B, Kindblom LG. Chordoma. A clinicopathologic and prognostic study of a Swedish national series. Acta Orthop Scand. 1981; 52(1): 49–58, doi: 10.3109/17453678108991758, indexed in Pubmed: 7211316.

10. Noël G, Feuvret L, Ferrand R, et al. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. Neurosurgery. 2004; 55(6): 1252–60; discussion 1260, doi: 10.1227/01.neu.0000143330.30405.aa, indexed in Pubmed: 15574207.
11. Kerekes D, Goodwin CR, Ahmed AK, et al. Local and Distant Recurrence in Resected Sacral Chordomas: A Systematic Review and Pooled Cohort Analysis. Global Spine J. 2019; 9(2): 191–201, doi: 10.1177/2192568217741114, indexed in Pubmed: 30984500.
12. Yolcu Y, Wahood W, Alvi MA, et al. Evaluating the Role of Adjuvant Radiotherapy in the Management of Sacral and Vertebral Chordoma: Results from a National Database. World Neurosurg. 2019; 127: e1137–e1144, doi: 10.1016/j.wneu.2019.04.070, indexed in Pubmed: 30995559.
13. Huang Z, Fan Z, Zhao C, et al. A Novel Nomogram for Predicting Cancer-Specific Survival in Patients With Spinal Chordoma: A Population-Based Analysis. Technol Cancer Res Treat. 2021; 20: 15330338211036533, doi: 10.1177/15330338211036533, indexed in Pubmed: 34382474.
14. Tzortzidis F, Elahi F, Wright D, et al. Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. Neurosurgery. 2006; 59(2): 230–7; discussion 230, doi: 10.1227/01.NEU.0000223441.51012.9D, indexed in Pubmed: 16883163.
15. Gatfield ER, Noble DJ, Barnett GC, et al. Tumour Volume and Dose Influence Outcome after Surgery and High-dose Photon Radiotherapy for Chordoma and Chondrosarcoma of the Skull Base and Spine. Clin Oncol (R Coll Radiol). 2018; 30(4): 243–253, doi: 10.1016/j.clon.2018.01.002, indexed in Pubmed: 29402600.
16. Schulz-Ertner D, Karger CP, Feuerhake A, et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. Int J Radiat Oncol Biol Phys. 2007; 68(2): 449–457, doi: 10.1016/j.ijrobp.2006.12.059, indexed in Pubmed: 17363188.
17. Uhl M, Mattke M, Welzel T, et al. Highly effective treatment of skull base chordoma with carbon ion irradiation using a raster scan technique in 155 patients: first long-term results. Cancer. 2014; 120(21): 3410–3417, doi: 10.1002/cncr.28877, indexed in Pubmed: 24948519.
18. Fuller DB, Bloom JG. Radiotherapy for chordoma. Int J Radiat Oncol Biol Phys. 1988; 15(2): 331–339, doi: 10.1016/s0360-3016(98)90012-8, indexed in Pubmed: 2457005.
19. Romero J, Cardenes H, la Torre A, et al. Chordoma: results of radiation therapy in eighteen patients. Radiother Oncol. 1993; 29(1): 27–32, doi: 10.1016/0167-8140(93)90169-9, indexed in Pubmed: 8295984.
20. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. 2nd ed. Wiley Series in Probability and Statistics 2002.
21. Catton C, O'Sullivan B, Bell R, et al. Chordoma: long-term follow-up after radical photon irradiation. Radiother Oncol. 1996; 41(1): 67–72, doi: 10.1016/s0167-8140(96)91805-8, indexed in Pubmed: 8961370.
22. Amichetti M, Amelio D, Minniti G, et al. Proton therapy in chordoma of the base of the skull: a systematic review. Neurosurg Rev. 2009; 32(4): 403–416, doi: 10.1007/s10143-009-0194-4, indexed in Pubmed: 19319583.
23. Sahgal A, Chan MW, Atenafu EG, et al. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes. Neuro Oncol. 2015; 17(6): 889–894, doi: 10.1093/neuonc/nou347, indexed in Pubmed: 25543126.
24. Müller BS, Ryang YM, Oechsner M, et al. The dosimetric impact of stabilizing spinal implants in radiotherapy treatment planning with protons and photons: standard titanium alloy vs. radiolucent carbon-fiber-reinforced PEEK systems. J Appl Clin Med Phys. 2020; 21(8): 6–14, doi: 10.1002/acm2.12905, indexed in Pubmed: 32476247.
25. Bostel T, Mattke M, Nicolay NH, et al. High-dose carbon-ion based radiotherapy of primary and recurrent sacrococcygeal chordomas: long-term clinical results of a single particle therapy center. Radiat Oncol. 2020; 15(1): 206, doi: 10.1186/s13014-020-01647-8, indexed in Pubmed: 32831113.
26. Combs SE, Laperriere N, Brada M. Clinical controversies: proton radiation therapy for brain and skull base tumors. Semin Radiat Oncol. 2013; 23(2): 120–126, doi: 10.1016/j.semradonc.2012.11.011, indexed in Pubmed: 23473689.
27. Förander P, Bartek J, Fagerlund M, et al. Multidisciplinary management of clival chordomas; long-term clinical outcome in a single-institution consecutive series. Acta Neurochir (Wien). 2017; 159(10): 1857–1868, doi: 10.1007/s00701-017-3266-1, indexed in Pubmed: 28735379.
28. Youn SH, Cho KHo, Kim JY, et al. Clinical outcome of proton therapy for patients with chordomas. Radiat Oncol J. 2018; 36(3): 182–191, doi: 10.3857/roj.2018.00164, indexed in Pubmed: 30309209.
29. Zabel-du Bois A, Nikoghosyan A, Schwahofer A, et al. Intensity modulated radiotherapy in the management of sacral chordoma in primary versus recurrent disease. Radiother Oncol. 2010; 97(3): 408–412, doi: 10.1016/j.radonc.2010.10.008, indexed in Pubmed: 21056488.
30. Lu S, Peng X, Zou B, et al. Adjuvant gamma knife surgery and image-guided, intensity-modulated radiation therapy for the treatment of sacral chordomas. Rep Pract Oncol Radiother. 2019; 24(1): 74–79, doi: 10.1016/j.rpor.2018.10.007, indexed in Pubmed: 30505236.
31. Chen YL, Liebsch N, Kobayashi W, et al. Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. Spine (Phila Pa 1976). 2013; 38(15): E930–E936, doi: 10.1097/BRS.0b013e318296e7d7, indexed in Pubmed: 23609202.
32. Staab A, Rutz HP, Ares C, et al. Spot-scanning-based proton therapy for extracranial chordoma. Int J Radiat Oncol Biol Phys. 2011; 81(4): e489–e496, doi: 10.1016/j.ijrobp.2011.02.018, indexed in Pubmed: 21497457.
33. Toyomasu Y, Demizu Y, Matsuo Y, et al. High-dose proton therapy and carbon-ion therapy for stage I nonsmall cell lung cancer. Cancer. 2010; 116(10): 2476–2485, doi: 10.1002/cncr.24998, indexed in Pubmed: 20225229.
34. Uhl M, Welzel T, Jensen A, et al. Carbon ion beam treatment in patients with primary and recurrent sacrococcygeal chordoma. Strahlenther Onkol. 2015; 191(7): 597–603, doi: 10.1007/s00066-015-0825-3, indexed in Pubmed: 25737378.
35. York JE, Kaczaraj A, Abi-Said D, et al. Sacral chordoma: 40-year experience at a major cancer center. Neurosurgery. 1999; 44(1): 74–9; discussion 79, doi: 10.1097/00006123-199901000-00041, indexed in Pubmed: 9894966.

36. Park L, Delaney TF, Liebsch NJ, et al. Sacral chordomas: Impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. Int J Radiat Oncol Biol Phys. 2006; 65(5): 1514–1521, doi: 10.1016/j.ijrobp.2006.02.059, indexed in Pubmed: 16757128.
37. Stacchiotti S, Gronchi A, Fossati P, et al. Best practices for the management of local-regional recurrent chordoma: a position paper by the Chordoma Global Consensus Group. Ann Oncol. 2017; 28(6): 1230–1242, doi: 10.1093/annonc/mdx054, indexed in Pubmed: 28184416.
38. Bergh P, Kindblom LG, Gunterberg B, et al. Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. Cancer. 2000; 88(9): 2122–2134, doi: 10.1002/(sici)1097-0142(20000501)88:9<2122::aid-cncr19>3.0.co;2-1, indexed in Pubmed: 10813725.
39. Napieralska A, Blamek S. Intracranial chordoma: radiosurgery, hypofractionated stereotactic radiotherapy and treatment outcomes. Rep Pract Oncol Radiother. 2021; 26(5): 764–772, doi: 10.5603/RPOR.a2021.0097, indexed in Pubmed: 34760311.
40. Chen AT, Hong CB, Narazaki DK, et al. High dose image-guided, intensity modulated radiation therapy (IG-IMRT) for chordomas of the sacrum, mobile spine and skull base: preliminary outcomes. J Neurooncol. 2022; 158(1): 23–31, doi: 10.1007/s11060-022-04003-w, indexed in Pubmed: 35451720.