

High-dose carbon-ion based radiotherapy of primary and recurrent sacrococcygeal chordomas: Long-term clinical results of a single particle therapy center.

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Abstract

Background

This study aimed to analyze the oncological long-term results and late toxicity of carbon ion-based radiotherapy (RT) of patients with sacral chordoma and to identify potential prognostic factors for local control (LC) and overall survival (OS).

Methods

A total of 68 patients with sacral chordoma (median age 61 years, range 34 - 84 years) treated at the Heidelberg Ion Beam Therapy Center were included in this study. Of these 52 patients (77%) received a primary RT and 16 patients (23%) received a RT in a recurrent situation. All patients were treated with carbon ion RT, either in combination with photons or as a monotherapy, with a median radiation dose of 66 Gy RBE (range 60 - 74 Gy). In 40 patients (59%), RT was performed in the postoperative situation. Postoperative care included regular MRI scans, which were performed in 3-month intervals in the first year and in 6-month intervals in the following years. Local progression was defined as an enlargement of the maximum tumor diameter by 10% or a new tumor growth within the planning target volume (PTV). LC and OS were determined using the Kaplan-Meier method. Furthermore, the relevance of various prognostic factors for LC and OS was assessed by univariate and multivariate analysis.

Results:

The median follow-up period was 60 months (range 1 - 96 months). The 5-year rates for LC, metastasis-free and disease-free survival and OS were 43%, 82%, 44% and 82%, respectively. Local recurrence was observed in 31 patients (46%), occurring after a median follow-up time of 24 months (range 2 – 72 months). Only 10% of local recurrences occurred later than 5 years after RT. The univariate analysis showed a statistical significance for the initial macroscopic tumor volume (GTV) and a strong trend for the therapy situation (primary vs. recurrence situation) to predict a local tumor recurrence. In the log-rank test and univariate analysis, the age of patients, size of the GTV and PTV were identified as strong predictors of OS after RT of sacral chordoma. In the multivariate testing, borderline significance was evident for the therapeutic situation (primary vs. recurrence situation) to predict local tumor recurrence, while none of the tested factors were significant for the prediction of OS after RT.

The incidence of late toxicity \geq III° according to CTCAE v5.0 was 21%. Sacral insufficiency fractures occurred in 49% of patients (maximum III°: 16%) and were thus by far the most frequent late side effect in our analysis. Radiogenic damage to the peripheral nerves, intestinal tract and skin was observed in only 9% (\geq III°: 5%), 3% (all II°) and 9% (all I°) of patients.

Conclusion

Our analysis showed only moderate long-term local control rates after carbon ion-based RT, with sacral chordomas having a particularly poor prognosis in the recurrent situation. A recent study (ISAC) evaluates

the safety and effectiveness of further dose escalation and hypofractionation of proton and carbon ion therapy in sacral chordoma. Here, the potential benefits of dose escalation must be weighed against the possible side effects.

Background

Chordomas are rare primary osseous malignant tumors that originate from remnants of the chorda dorsalis, but this process and its reasons are not yet understood [1]. Expression of the brachyury gene, localized on 6q27, has been identified as a diagnostic marker of chordoma [2]. Furthermore, germ line duplication of brachyury has been found in families with chordomas [3]. Therefore, the transcription factor T (brachyury) could play an important role in the development of chordomas. As a result of their origin, almost all chordomas arise along the craniospinal axis, mainly in the skull base and sacrum [4]. With a proliferation index of < 5% -10%, the vast majority of chordomas are slowly growing tumors. De-differentiated chordomas are extremely rare and characterized by a more aggressive clinical course than conventional chordomas with higher rates of local and distant tumor recurrences [5].

The treatment of sacral chordoma is a multidisciplinary task and, despite all the progress made in recent years, remains a great challenge. Because the symptoms are initially only minor, early diagnosis is very rare, so that the tumors are often very large and characterized by locally aggressive growth when they are diagnosed. Surgical resection is regarded as a mainstay of therapy. However, as sole treatment modality it is associated with relatively high locoregional recurrence rates, whereby the size of the tumors, incomplete tumor resections and tumor recurrences seem to have a negative effect on local control (LC) [6–9]. Pathologically complete resections can only be achieved in about 50% of the cases, although the question of the required safety margins is still subject to discussion [9–11]. Therefore, postoperative radiotherapy (RT) is generally recommended to improve LC, even after pathologically complete tumor resections [12]. A further major problem after sacrectomy is the resulting large bone soft tissue defect, which is associated with considerable morbidity and often requires costly surgical measures to cover the defect. High sacrectomies (above the level S2/3) carry the highest risk for postoperative side effects including protracted wound healing disorders, restricted mobility and complete paralysis of the bladder and rectum [12].

Due to the risks of surgery, some patients reject surgical procedures. Other patients experience inoperable recurrences or are not operable because of their comorbidities. For all those patients, definitive RT with particles is an alternative and at least an equivalent option to primary surgical resection with less side effects [8].

However, only a few long-term study data are available regarding response and toxicity after particle-based irradiation of sacral chordoma [8, 13].

Therefore, we have updated the data of a previously published patient cohort in order to assess long-term tumor response and late toxicities after high-dose, heavy ion-based RT [14].

Patients And Methods

Patients

This retrospective analysis comprised 68 patients with histologically proven sacrococcygeal chordoma who received high-dose carbon-ion based RT at the Heidelberg ion therapy facility in the time period between November 2009 and December 2013. The independent ethics committee of the Heidelberg University Medical Faculty approved this retrospective study (S-165/2012).

Treatment

Patients were assigned to radiation treatment either with carbon ions alone or combined photons and carbon ions after treatment planning with CT and pelvic MRI scans. The majority of patients (n = 52; 77%) received a primary treatment, whilst the remaining patients were treated in the recurrence situation. Target volumes and organs at risk were contoured using the Siemens Oncologist software tools (Siemens, Erlangen, Germany). Macroscopic tumor volume based on MRI was defined as the gross tumor volume (GTV). For the primary plan, the clinical target volume (CTV2) comprised not only the GTV or tumor bed but also an extended safety margin usually including the whole sacrum to account for the typical ways of locoregional tumor dissemination. In more than half of the patients (n = 40; 59%) a shrinking field technique was used to deliver a radiation boost; therefore, the target volume was reduced to the GTV and/or the tumor resection cavity with an additional small safety margin of 3–5 mm (CTV1). Furthermore, the clinical target volumes (CTV1 and CTV2) were expanded by 3–7 mm to generate the planning target volumes (PTV1 and PTV2). The study patients were either treated with carbon ions alone or bimodal radiation treatment including a combination of photons (primary plan) and carbon ions (boost plan) (see Fig. 1).

Follow up examinations

The follow up examinations included regular MRI scans of the pelvis, which were performed at 3-monthly intervals in the first year after RT and at 6-monthly intervals in the following years. For this analysis the follow-up was carried out until the 1st of January 2018. Local progression was defined as an increasing maximum tumor diameter of at least 10% or development of new tumor formations within the irradiated region based on analysis of MR images by a board-certified radiologist (TB). LC, progression-free survival (PFS), metastasis-free survival (MFS) and overall survival (OS) were assessed. Late toxicities were analyzed descriptively.

Statistics

Statistical analysis was performed with the R environment of statistical computing (version 3.5.1, R Core Team 2018, Vienna, Austria). A p-value of $p < .05$ was considered statistically significant. The survival time after RT was plotted according to the Kaplan-Meier method. Log-rank testing was applied to analyze univariate group differences in the survival after RT. Furthermore, multiple continuous potentially

prognostic factors of survival and local tumor control were evaluated using univariate and multivariate Cox regression models.

Results

Follow-up

The median follow-up time after radiation treatment was 59.5 months (range 1–96 months). Overall, 72% of the patients were followed-up for at least 5 years or until death. The lost to follow-up rate after 1, 2 and 5 years amounted to 3% (2 patients), 7% (5 patients) and 15% (10 patients), respectively. The baseline characteristics of the study population are listed in Table 1.

Table 1
Patients' properties

Characteristics	Value	%
Age (years)	61	
- Median	34–84	
- Range		
Gender (n)	22	32.6
- Female	46	67.4
- Male		
Resection status (n)	28	41.2
- Biopsy	26	38.2
- R2	14	20.6
- R0/1		
Treatment (n)	52	76.5
- Primary	16	23.5
- Recurrent		
Most cranial level of tumor (n)	7	10.3
- L4/5	12	17.7
- S1	23	33.8
- S2	14	20.6
- S3	5	7.4
- S4	4	5.9
- S5	3	4.4
- Os coccygeum		

Characteristics	Value	%
GTV (ml)	182	
- Median	0–1727	
- Range	263	
CTV1 (ml)	0–1743	
- Median	938	
- Range	60–2577	
CTV2 (ml)	414	
- Median	0–2325	
- Range	1109	
PTV1 (ml)	84–3138	
- Median		
- Range		
PTV2 (ml)		
- Median		
- Range		
Radiation dose ED ₂ Gy	16	23.5
Carbon ion only: ($\alpha/\beta = 2$)	2	2.9
- 60 Gy/3 Gy (RBE) 75.0 Gy	14	20.6
- 63 Gy/3 Gy (RBE) 78.8 Gy	14	20.6
- 66 Gy/3 Gy (RBE) 82.5 Gy	1	1.5
- 64 Gy/4 Gy (RBE) 96.0 Gy	1	1.5
IMRT + carbon ion boost	20	29.4
- 50 Gy/2 Gy + 15 Gy/3 Gy (RBE) 68.8 Gy		
- 50 Gy/2 Gy + 18 Gy/3 Gy (RBE) 74.5 Gy		
- 50 Gy/2 Gy + 24 Gy/3 Gy (RBE) 80.0 Gy		

Local control

Local recurrence was observed in 31 patients (46%), occurring after a median follow-up time of 24 months (range 2–72 months). The majority of local relapses (22/31 patients; 71%) occurred within the

first 3 years after primary treatment, but in 3 patients (10%) local relapse was observed later than 5 years after irradiation. For the overall study population, the 2-, 3- and 5-year probabilities for local tumor control were 75%, 61% and 43%. The majority of patients with local relapses received systemic therapy, re-irradiation and/or surgical resection; only 4 patients decided for a wait-and-see approach. Amongst the tested prognostic factors, only the GTV proved to be statistically significant in the univariate testing ($p = 0.02$). However, in the multivariate analysis, the GTV was insignificant for prediction of local tumor relapse (see Table 2). To further analyze the influence of tumor volume prior to RT, study patients were stratified into 2 risk groups (i.e., no residual macroscopic tumor vs. macroscopic tumor prior to RT). The subgroup of patients with no residual macroscopic tumor (R0/1 situation, 14/68 patients) had 2-, 3- and 5-year LC rates of 92%, 67% and 40% after surgical resection and adjuvant RT; the rest of the study patients with incomplete tumor resection and additive RT or definitive RT (R2 situation, status post biopsy) reached 2-, 3- and 5-year LC rates of 71%, 61% and 44%, respectively.

Table 2
Analysis of prognostic factors related to local control after palliative RT.

Parameter	Univariate testing			Multivariate testing		
	p-value	HR	95% CI	p-value	HR	95% CI
EQD2 (Gy)	0.67	0.986	0.927–1.05	0.88	1.006	0.934–1.08
Recurrent tumor	0.05	2.099	0.985–4.47	0.07	2.149	0.952–4.85
GTV (ml)	0.02	2.812	1.16–6.84	0.97	0.986	0.417–2.33

Besides GTV, borderline significance was evident when comparing primary and recurrent tumors (see Table 2). For patients with a primary disease, local tumor control after 2, 3 and 5 years was 85%, 74% and 53%. In patients with recurrent chordomas, the 2-, 3- and 5-year LC rates reached only 40%, 27% and 9%, respectively.

In contrast, applied cumulative equivalent radiation dose (EQD2) was statistically insignificant for LC in both the univariate and multivariate analyses (see Table 2).

Distant metastases

Six patients (9%) developed distant metastasis, half of which were located in the pelvis. Extra-pelvic metastases manifested in the autochthonous back muscles of the thoracic and lumbar spine (2 patients) and in the lungs (1 patient). In all patients, local relapse was diagnosed prior to (2 patients) or concomitant to metastatic spread (4 patients). The median time until first distant failure of the disease was 42 months (range 12–67 months) after carbon-ion based RT. Distant metastases were treated with surgical resection and/or systemic therapy (e.g. tyrosin kinase inhibitors). The 2-, 3- and 5-year probabilities for MFS were 97%, 92% and 82%, respectively.

Survival

Twenty-three patients (34%) died during follow-up. In 17 of those 23 patients (74%), local relapse and/or distant metastases have been diagnosed before death. After a follow-up period of 2, 3 and 5 years, PFS was 75%, 64% and 44%, while the OS rates amounted to 97%, 93% and 82%, respectively. After local relapse or distant metastasis, the 3-year OS rates amounted to 42% and 50%, respectively. In comparison, patients without disease failure exhibited a 3-year OS of 84%.

Univariate log-rank tests found statistically significant associations of the patient's age at diagnosis group, GTV group and the PTV2 (primary plan) group with OS after RT of sacral chordomas ($p = 0.01$, $p = 0.003$ and $p = 0.0001$), see Figs. 2–4. Further tested factors including the patients' gender, the radiation dose, the localization of the tumor, the CTV1 (boost plan), CTV2 (primary plan) and PTV1 (boost plan) were not statistically significant for survival prediction after RT in the log-rank test. We also found no statistically significant difference in OS when comparing patients with a primary disease and a recurrent disease ($p = 0.3$, log-rank test).

In univariate Cox models for continuous predictors, patients' age at the beginning of RT, PTV1 and PTV2 were found to have statistically significant associations with OS after RT (p -values 0.01, 0.04 and 0.002; see Table 3); furthermore, borderline significance was found for the GTV ($p = 0.06$). The 5-year OS rates amounted to 45% for the elderly patients (age ≥ 70 years) and 77% for the residual younger patients (age < 70 years), respectively. For patients with a PTV2 ≥ 1109 ml the 5-year OS was 62%, while patients with a PTV2 < 1109 ml had a 5-year OS rate of 86% (see Fig. 4). There was no significant prognostic factor for OS in the multivariate analysis (Table 3).

Table 3
Analysis of prognostic factors related to overall survival after palliative RT.

Parameter	Univariate testing			Multivariate testing		
	p-value	HR	95% CI	p-value	HR	95% CI
Patients' age (y)	0.01	1.055	1.013–1.10	NA	NA	NA
EQD2 (Gy)	0.48	0.971	0.895–1.05	0.533	0.975	0.899–1.06
Level of proximal invasion \geq S2	0.21	1.765	0.725–4.30	NA	NA	NA
Recurrent tumor	0.31	1.593	0.654–3.88	0.36	1.539	0.628–3.77
GTV (ml)	0.06	1.001	1.00–1.00	NA	NA	NA
PTV1 (ml)	0.04	1.001	1.00–1.00	NA	NA	NA
PTV2 (ml)	0.002	1.001	1.00–1.00	NA	NA	NA

Toxicity

At baseline, most patients had tumor- or operation-related complaints, with pain, sensitivity and bladder emptying disorders being the most common impairments; other initial complaints were motor deficits,

rectal disorders and urinary and fecal incontinence (see Table 4). The operated patients had considerably more neurological impairments than the patients without surgery (bladder emptying disorders: 48% vs. 29%, rectal disorders: 23% vs. 18%, urinary and fecal incontinence: 18% vs. 11%, sensitivity disorders: 35% vs. 21% and motor deficits: 8% vs. 0%). Furthermore, 6 patients had an enterostoma, all affected patients had a sacral chordoma at level S1–3 and 5 patients had a previous surgery.

Table 4
Late morbidities (CTCAE v5.0) after carbon-ion based radiotherapy for primary and recurrent sacral chordoma

Grade	0	1	2	3	4
Skin	62	6	0	0	0
Gastrointestinal tract	66	0	2	0	0
Peripheral nerves	62	1	2	1	2
Sacral insufficiency fractures	35	21	1	11	0
The values given are patient numbers.					

After RT, 40 patients (59%) developed radiogenic late toxicities, which affected the bone and nerve tissues, the gastrointestinal tract and the skin (see Table 4). The incidence of late toxicities \geq grade 3 was 21% (14 of 68 patients). Of the 14 patients with severe radiogenic late toxicities, 12 received a radiation dose of at least 80 Gy (EQD2). Sacral insufficiency fractures (SIFs) were by far the most common late side effect in our analysis accounting for 49% of the patients (33 of 68 patients). Of these, 36% (12 of 33 patients) were symptomatic with considerable impairments in everyday life and severe pain requiring multiple pain medications as well as intensive care by a pain specialist. The median time until diagnosis of SIFs was 12 months (range 1–62 months), whereby the majority of SIFs occurred within the first 2 years after RT (85%, 28 of 33 patients).

Radiogenic damage to the peripheral nerves, intestinal tract and skin was much less frequently observed with an incidence of 9% (6 patients), 3% (2 patients) and 9% (6 patients), respectively (see Table 4).

Discussion

In our analysis, 46% of the study patients experienced a local relapse after a median follow-up period of 24 months (range 2–72 months). The majority of local relapses (90%) occurred in the first 5 years after primary therapy including heavy ion-based irradiation, resulting in a 5-year LC rate of 43%, which is in line with other retrospective studies [10, 15, 16]. In contrast to the frequent local recurrences, distant metastases were relatively rare. In only 9% of our study patients metastases were diagnosed in the follow-up imaging after a median follow-up of 42 months (range 12–67 months), with half of these lesions being localized outside the pelvis. Other studies reported higher metastasis rates in the range between 19 and 40% [8, 17–19].

In our analysis, 94% of patients suffered from pain and/or neurological deficits prior to RT. The most serious impairments were observed in patients who had previously had a sacrectomy, including chronic pain, bladder/rectum disorders and urinary and fecal incontinence.

In contrast, the tolerability of the radiation treatment in our study was relatively good. None of the study patients developed urinary or fecal incontinence, severe gastrointestinal toxicity or permanent severe skin damage. In 21% of our study patients, late toxicities \geq grade 3 were observed affecting the bone and nerve tissues (3 patients with neuropathy, 11 patients with SIFs; see Table 4), and 86% of those patients received a dose of at least 80 Gy (EQD2). Overall, SIFs were by far the most common late toxicity, affecting 49% of the study patients. However, only one third of these fractures (36%) were clinically symptomatic, with severe pain being the main complaint. To this date, there are only 2 other retrospective studies that have specifically investigated the occurrence of sacral fractures after high-dose irradiation of chordomas and reported similar fracture rates [20, 21]. In our analysis, most fractures (85%) occurred within the first 2 years after RT.

During follow-up, 34% of our study patients died. Of these, 74% had a local and/or distant tumor relapse prior to death. For the entire study population, the 5-year PFS, MFS and OS rates were 44%, 82% and 82% after a median follow-up period of 60 months, respectively. In the multivariate analysis we could not identify any significant prognostic factor for LC. However, borderline significance was evident for treatment in the event of locoregional relapse (p-value = 0.07). Irradiation within the primary therapy resulted in 5-year LC rates of 53% compared to 9% when RT was performed in the relapse situation. In line with our results, researchers at the Massachusetts General Hospital (MGH) reported significantly worse LC rates and OS rates when therapy was given in the relapse situation compared to the primary situation [22].

In summary, the main challenge in the treatment of sacral chordoma is to achieve permanent local control after primary treatment. Compared to our results, other particle centers reported better LC rates. The MGH, for example, reported 5-year LC rates of 60% after high-dose, proton-based irradiation with or without surgery after a median follow-up of 41 months [7]. The Nationale Institute of Radiological Sciences (NIRS) in Chiba, Japan could show even better results than the MGH with 5-year LC rates of 77% [8]; in this study, patients received primary hypofractionated heavy ion therapy with a median dose of 70,4 Gy in 16 fractions over 4 weeks. The median follow-up period was 62 months. In total, 29% of local recurrences occurred later than 5 years after irradiation. As in our study, there was no statistically significant prognostic factor for a local relapse in this study.

However, the comparison of previous study results is complicated by the differences in radiation modalities, doses and fractionation, biological models, the populations studied (primary vs. relapse situation, definitive vs. postoperative situation), tumor volumes and target volume definitions, follow-up periods and local relapse definition. In our study 81% of the patients had a macroscopic tumor (median volume 243 ml) and 24% of the patients were irradiated in the local relapse situation. Therefore, our study

population represents rather an unfavourable collective compared to many other retrospective studies [8, 23, 24].

Due to the fact that chordomas grow slowly, long follow-up periods are necessary; local recurrences often occur later than 5 years after primary therapy and even after 10 years of follow-up no plateau of local recurrence rates is reached [12]. Therefore, when comparing studies, the follow-up time must be taken into account.

A further problem is that there is no uniform definition of local relapse. In many studies there is no detailed information on this or reference is made only to the radiologist's assessment [7, 8, 24]; Chen et al. defined the local recurrence as an increase in size of chordomas in 2 consecutive follow-up examinations [23]. In another study the modified Response Evaluation Criteria in Solid Tumors (RECIST) and volumetric analysis were used to evaluate the tumor response to RT [13].

Another critical point is the definition of the clinical target volume, which differed significantly between our study and other retrospective studies. In our study the CTV of the basic plan usually included the entire sacrum and in the boost plan this was reduced to a small GTV-CTV safety margin of 3–5 mm. This field shrinkage technique was also used in the MGH studies [7, 22]. In contrast, In the NIRS and HIMBC studies only one CTV was generated for the entire irradiation series by adding a small safety margin to the GTV (as it was done in our study for the boost plan), i.e. often the entire sacrum was not included in the target volume [8, 24]. Consequently, in many other studies sacral tumor recurrences could only have been classified as locoregional recurrences if they were out-of-field or at the edge of the field, whereas in our study they were always classified as local recurrences. Therefore, PFS may be a better comparison parameter than LC when comparing the results of different retrospective series. For instance, LC in the NIRS patient collective was almost twice as high as in our collective (5-year LC 43% vs. 77%), while PFS and OS rates were similar (5-year PFS 44% vs. 50%, 5-year OS 82% vs. 81%) [8]. In this study, univariate analysis found that the patient's age and the PTV were strong prognostic factors for the OS. However, none of these factors reached statistical significance in the multivariate testing.

A further problem are the different models in Europe and Japan for prescribing the dose of carbon ion therapy, which makes it difficult to compare the doses applied in the various retrospective studies [25]. Therefore, another possible explanation for the better LC rates of the NIRS study could be the higher cumulative equivalent radiation dose applied (64.0–73.6 Gy RBE). However, the radiation dose was no significant predictor for LC in our analysis.

Our study has several limitations. First, the data set was collected retrospectively. The main problem for conducting prospective studies in sacral chordoma is the rarity of the disease, which is why there are only retrospective studies on this topic so far. Secondly, the number of patients in our study is limited, which is also explained by the rarity of the disease; however, there are only a few studies with more patients than in our study [6–8]. Thirdly, the median follow-up time of about 5 years is sufficient for many tumors to collect long-term oncological data, but it is not sufficient for sacral chordomas, as these grow slowly and local recurrences therefore often occur later than 5 years after primary therapy [6]. Therefore, we intend to

further observe this patient collective and to republish the collected data again. In addition, a randomized phase 2 study is currently underway at the Heidelberg Ion Therapy Center (ISAC), which compares hypofractionated proton and heavy ion therapy in sacral chordoma patients with a dose of 64 Gy RBE in 16 fractions in both therapy arms; the results are still pending [26].

Conclusion

Our analysis showed only moderate long-term LC rates after carbon-ion based RT, whereby sacral chordomas have a particularly poor prognosis in the recurrence situation. Future studies should take further dose escalation into account to improve LC and PFS. However, possible benefits of dose escalation must be weighed against the risks of treatment. In our study, 21% of the patients experienced severe late toxicities with SIFs being the main clinical problem.

List Of Abbreviations

LC Local control

RT Radiotherapy

CT Computed tomography

MRI Magnetic resonance imaging

GTV Gross tumor volume

CTV Clinical target volume

PTV Planning target volume

PFS Progression-free survival

MFS Metastasis-free survival

OS Overall survival

SIF(s) Sacral insufficiency fractures (SIFs)

MGH Massachusetts General Hospital

NIRS Nationale Institute of Radiological Sciences

RBE Relative biological effectiveness

Declarations

Ethics approval and consent to participate

The Heidelberg Ethics Committee approved this study on 7th August 2012 (S-165/2012). Due to the retrospective design, informed consent was not required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TB and MU developed and planned the retrospective analysis. DW is responsible for statistical considerations/basis of the analysis. MM, NHN, TW, SA, AM, TS, JD and MU participated in data collection and/or interpretation of the results. TB wrote the manuscript. All authors read and approved the final manuscript.

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Figures

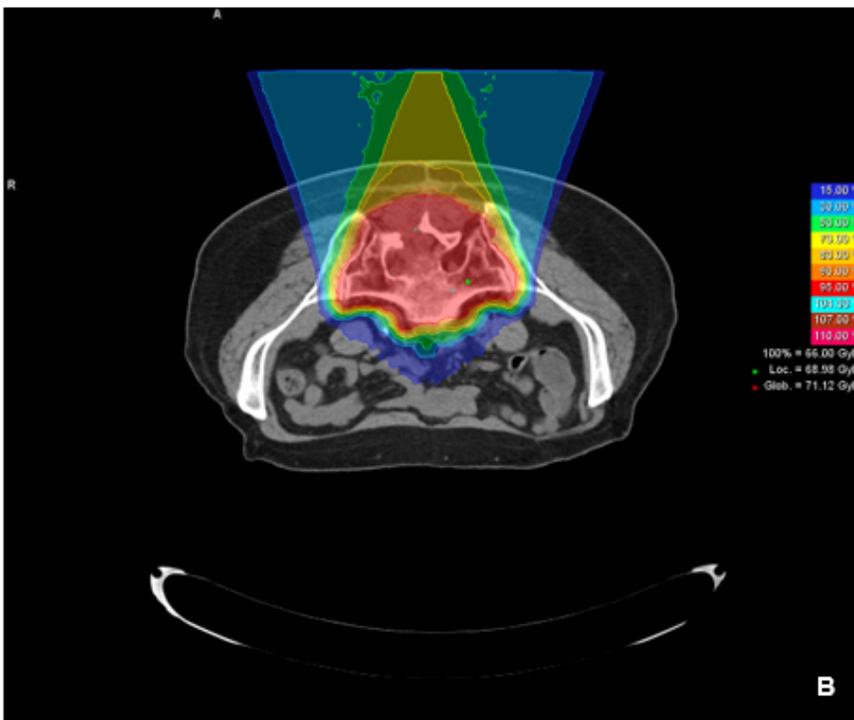


Figure 1

Typical dose distribution of a carbon ion plan with 66 Gy (RBE) total dose (A: Sagittal plane, B: Axial plane).

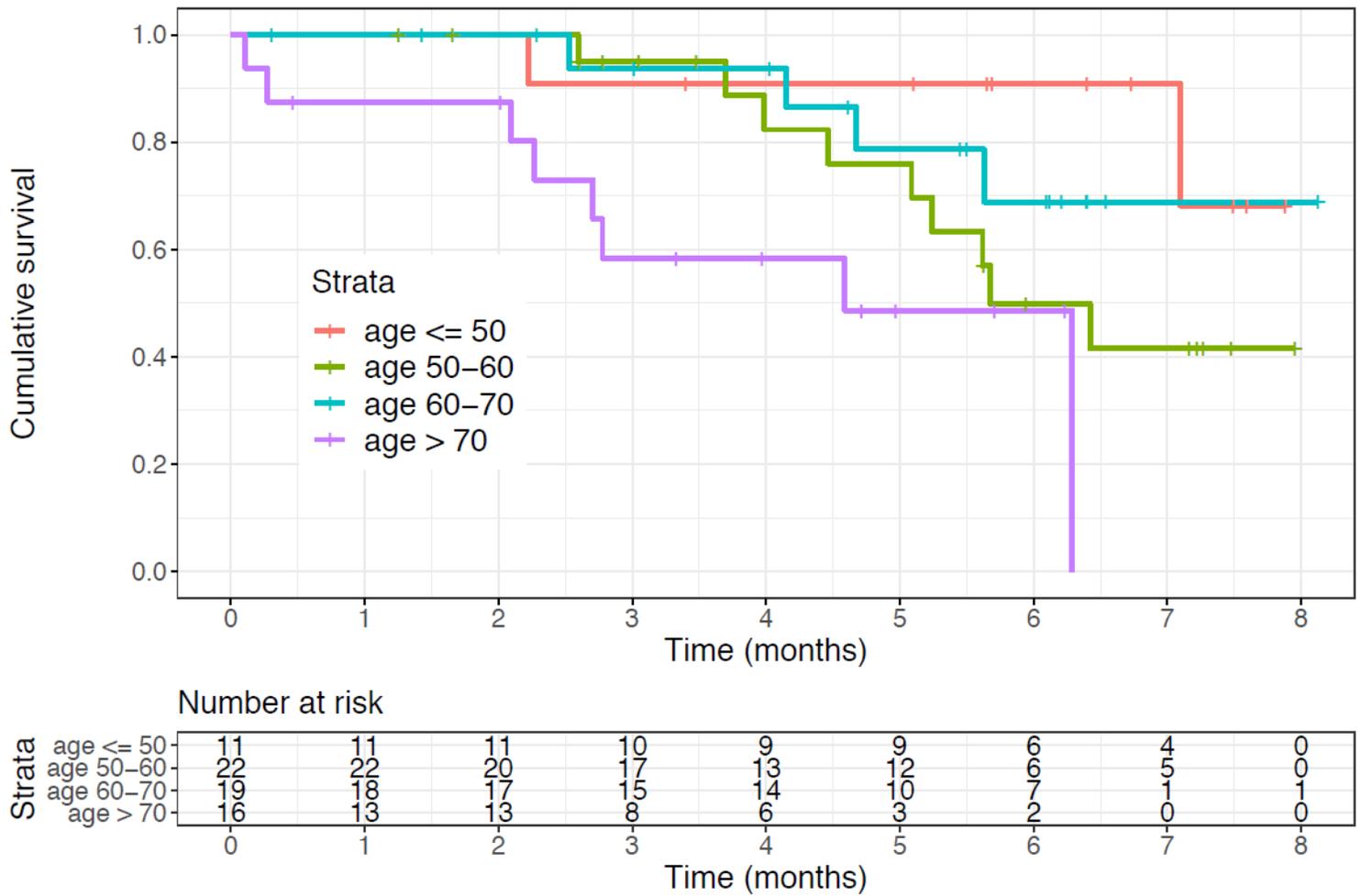


Figure 2

After stratification of patients into 4 age groups a comparison was made between them regarding the overall survival ($p = 0.01$, log-rank test).

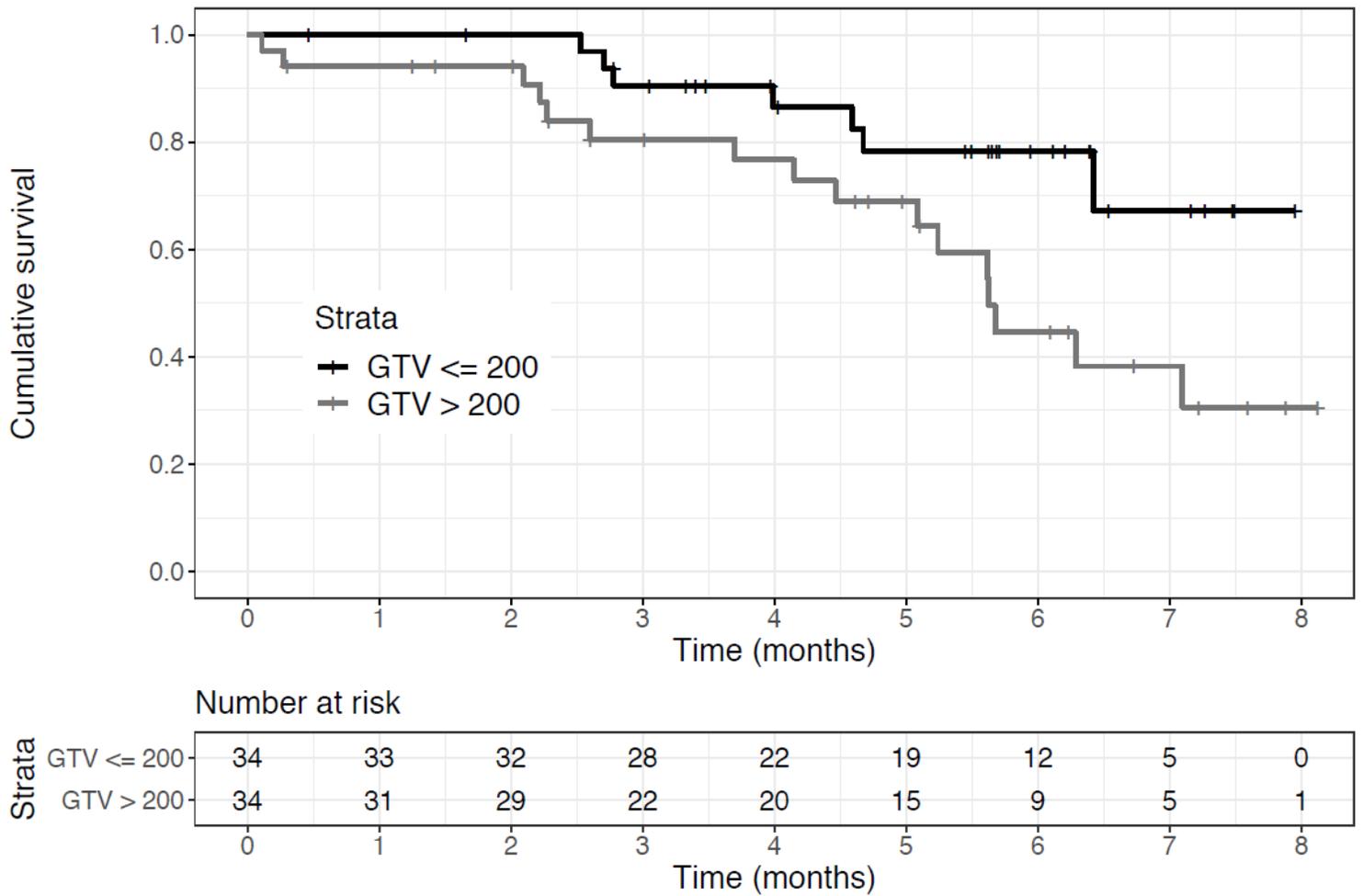


Figure 3

Overall survival (OS) was estimated using the Kaplan - Meier method. Comparison was made between patients with a gross tumor volume (GTV) of > 200 ml vs. ≤ 200 ml ($p = 0.003$, log-rank test).

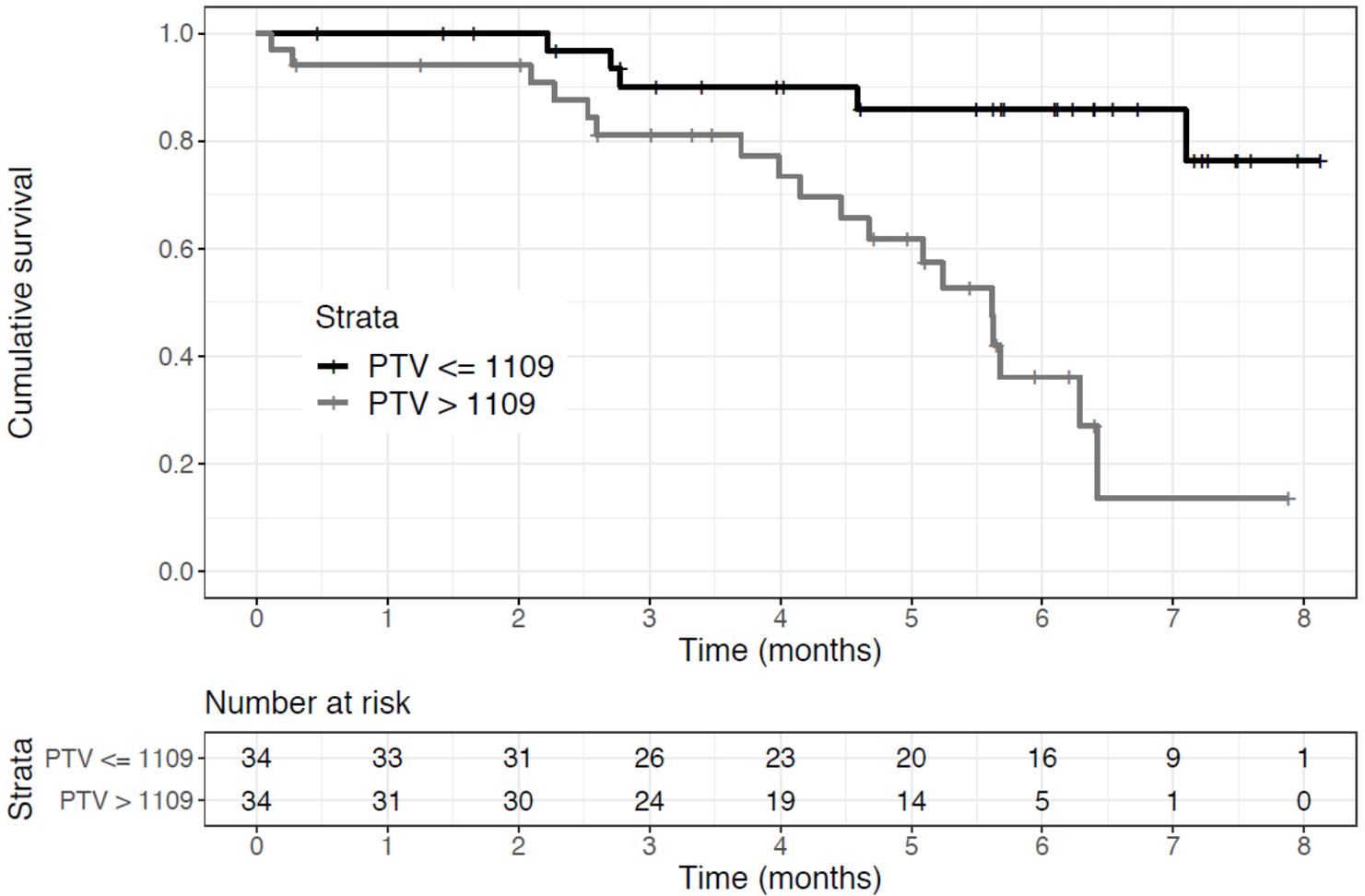


Figure 4

Overall survival (OS) was estimated using the Kaplan - Meier method. Comparison was made between patients with a planning target volume (PTV) of > 1109 ml vs. ≤ 1109 ml ($p = 0.0001$, log-rank test).