Evaluation of Dosimetric Robustness of Carbon Ion Boost Therapy for Anal Carcinoma

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Abstract

Purpose: The radiation therapy treatment outcome of human papillomavirus–negative anal carcinoma may be improved by the biological effectiveness of carbon ions. However, abdominal tissue motion can compromise the precision of carbon ion therapy. This work aims to evaluate the dosimetric feasibility of carbon ion boost (CIB) therapy for anal carcinoma.

Materials and Methods: An algorithm to generate computed tomographies based on daily magnetic resonance imaging data and deformable image registration was developed. By means of this algorithm, fractional computed tomography data for 54 treatment fractions for 3 different patients with anal carcinoma were derived. The dose for a sequential CIB (CIBseq) treatment plan was recalculated on the fractional computed tomography data and accumulated over the number of fractions. The resulting dose distributions were compared to standard intensity-modulated radiation therapy treatment with an integrated photon boost.

Results: For the investigated patient cases, similar dosimetric results for CIBseq treatment and for intensity-modulated radiation therapy with an integrated photon boost were found. For CIBseq treatment, bladder-filling variation had the strongest influence on the dose distribution. However, the detrimental effects on the mean target dose remained below 1 Gy (RBE) as compared to photon therapy.

Conclusion: This study shows the dosimetric feasibility of CIB therapy for anal carcinoma for the first time and gives reason for clinical exploitation of the enhanced biological effect of carbon ions for patients with human papillomavirus–negative anal cancer.

Keywords: carbon ion therapy; anal carcinoma; magnetic resonance–guided radiation therapy; magnetic resonance image–based treatment planning

Introduction

The occurrence of anal carcinoma (AC) is associated with the presence of human papillomavirus in more than 80% of patients [1]. However, positive human papillomavirus status in combination with the overexpression of cyclin-dependent kinase inhibitor 2A (p16INK4a) yields improved treatment outcome...
On the other hand, human papillomavirus–negative tumors are associated with reduced local recurrence control rates and overall survival [5].

Radiation therapy using carbon ions offers precise dose shaping to the tumor while sparing healthy surrounding tissue together with an enhanced relative biological effectiveness (RBE) in the tumor, compared to photons. This makes carbon ion therapy most beneficial for radioresistant tumors and those situated close to critical healthy organs. The advantages of carbon ions were investigated not only for head and neck tumors but also for numerous abdominal and pelvic tumors [6].

In the case of AC, significant tissue motion caused by variable bladder and rectum fillings and tissue displacements due to variable positioning can be observed. This can lead to severe misdosage. This work aims to answer the question of whether or not tissue motion is a real obstacle for carbon ion boost (CIB) treatment of anal cancer. As a current standard, computed tomography (CT) image data are used for radiation therapy treatment planning. Magnetic resonance imaging (MRI) comes along with an enhanced soft tissue contrast as compared to CTs. Here, MRIs provide the anatomic information of the current treatment fraction. Several methods exist to generate electron density data required for dose calculation using MRIs. These comprise bulk density assignment [7–10], atlas mapping [11–13], or voxelwise conversion of image intensities [14–18]. Density assignment requires segmentation, and the resulting intensity distinction might be insufficient for particle therapy dose calculation. On the other hand, atlas mapping relies on the accuracy of image registration. This comes along with an increased sensitivity of MRI atlas mapping for patients with an atypical anatomy [19]. So far, voxelwise density conversion often requires ultrafast echo time imaging sequences to overcome the problem of a very low bone signal in MRI. Another challenge of this method may be variation in image intensities and intensity uniformity, when voxelwise intensity conversion using a classification approach is applied [19].

In this work, we focus on the impacts of motion on the dose distribution. Therefore, a workflow for generation of CT data, required for dose calculation and based on MRIs and image registration, is presented. Using these data for dose accumulation over a treatment course, we aim to answer the question of whether radiation therapy with a sequential CIB for AC is feasible from a dosimetric point of view.

### Materials and Methods

#### Patient Data

For each patient a planning CT was acquired. In the scope of the magnetic resonance–guided radiation therapy study, performed at our institute [20], additional T2-weighted MRIs were acquired for each day of treatment and were used in this study. For this purpose, the patients were transferred between the MRI scanner and the linear accelerator via an air-based shuttle system (Zephyr System, Diacor, Salt Lake City, Utah) within several minutes to assure almost identical positioning for both procedures. In this work, 54 fractions of 3 patients with AC were studied in total. Patient data are summarized in Table 1. Patient (Pat) 1 and Pat3 are male, Pat2 is female. For Pat2 a vaginal plug was used for imaging as well as for radiation therapy treatment to reduce the toxicity of the frontal part of the vagina. For all other patients no auxiliary means were used for imaging and no specific bladder or rectum-emptying protocol was applied. We tried to keep the rectum filling as low as possible. All patients had a T2M0-staged tumor. Lymph nodes were affected in all patients. The number of planned treatment fractions was 25 for each patient; however, not for all treatment days are MRIs available owing either to technical service of the MR scanner or to unsuitable image quality for further processing. The number of available fractional images is also indicated in Table 1. In total, image data of 54 treatment fractions could be processed.

The extent of motion was quantified by means of structure contours. The bladder and boost target volume were delineated and clinically approved on the planning CT. These structures were propagated to the single fractions by image transformation derived from image registration as described below. The volume of the bladder and boost volume were

| Patient | Gender | Age (y) | Staging | Histology | No. of image fractions used |
|---------|--------|---------|---------|-----------|-----------------------------|
| Pat1    | M      | 72      | T2N3M0  | AIN III   | 21                          |
| Pat2    | F      | 51      | T2N2M0  | SSC       | 19                          |
| Pat3    | M      | 72      | T2N1M0  | SSC       | 14                          |

Abbreviations: Pat, patient; AIN, anal intraepithelial neoplasia; SSC, squamous cell carcinoma.
calculated for each fraction as well as the maximum diameters in superior-inferior, anterior-posterior, and left-right directions. The greatest influence on tissue displacement is due to bladder-filling variation. For Pat1, bladder filling varied between 206 and 239 mL; for Pat2, between 60 and 338 mL; and for Pat3, between 100 and 254 mL. The boost volume thus varied in correspondence to the bladder shrinkage and expansion. However, it should be noted that the method of motion evaluation relies on the transformed and manually corrected contours, which might be associated with geometric inaccuracy due to the registration. **Supplementary Figure 1** visualizes the motion over the course of used image fractions for all 3 patients.

Each patient received intensity-modulated radiation therapy (IMRT) with a simultaneous integrated boost (SIB). Forty-five Gy delivered in 25 fractions was prescribed to the planning target volume (PTV) and 55 Gy to the boost volume. For the considerations in this study, only the primary tumor and, for Pat1, the pararectal lymph nodes, were taken into account. For each patient a clinically approved IMRT SIB treatment plan was calculated by using an in-house treatment planning software [21–23]. For sequential CIB therapy (CIB_seq), a photon IMRT plan with 45 Gy prescribed to the PTV and the boost volume was optimized on the planning CT and an additional CIB treatment plan with a prescribed dose of 10 Gy (RBE) to the boost volume was calculated. For the purpose of this study, the CIB radiation dose was planned to be delivered in 5 treatment fractions. For the considerations here, the first 5 available imaging fractions were chosen for each patient. In an initial therapeutic setting we could think of applying carbon ion therapy in the beginning so that the major part of the boost volume could benefit. The motion study as depicted in **Supplementary Figure 1** reveals that with regard to tumor (boost) volume, no systematic change could be noted. The bladder-filling variation had the largest influence on the target motion and is not dependent on the treatment fraction. Thus, no systematic overestimation or underestimation of motion is expected by the choice of imaging fractions for the evaluation of CIB treatment.

Following the method published in the study of Wilkens and Oelfke [24], tabulated α depth curves were calculated by using the local effect model to account for the biological effect of carbon ions. These were based on a fixed photon radiosensitivity with $\alpha = 0.1 \text{ Gy}^{-1}$ and $\beta = 0.05 \text{ Gy}^{-2}$ for photons.

### Dose Accumulation Software

A software was developed that has to fulfill 3 requirements:

1. generate fractional CT data suitable for treatment planning
2. accumulate the dose of all treatment fractions
3. provide the possibility for treatment plan adaptation.

In a first step, the fractional MR data providing excellent morphologic information are used to generate CT data that are required for dose calculation. To generate fractional CT data, a rigid image registration between the measured planning CT—also called reference CT ($r\text{CT}_m$)—and the reference MRI ($r\text{MRI}_m$), both successively acquired on the day of treatment planning without repositioning of the patient, is performed. The resulting deformation vector field is then applied to the $r\text{MRI}_m$ and the transformed MRI is then called $r\text{MRI}_2\text{CT}$. This is followed by image registration between the $r\text{MRI}_2\text{CT}$ and the current fractional MRI. Each registration procedure is divided into an automatic rigid registration followed by elastic 3-dimensional registration. Both rigid registrations that are performed are based on fiducial markers. A rigid marker system consisting of a polymethylmethacrylate frame around the patient with imbedded contrast agent–filled hoses was used [20]. Subsequently, automatic 3-dimensional deformable image registration, based on b-spline deformation offered by plastimatch [25], is performed. In cases where large bladder expansion was noticed, additional anatomic landmarks were chosen to yield a better registration result. The quality of image registration is evaluated by visual control to assure correct physiological motion depicted by the resulting vector fields. Then, the transformation is applied to the $r\text{CT}_m$ as well as to the structure contours. Thus, the resulting image provides anatomic information of the current fraction. The whole process flow is visualized in **Figure 1**. Subsequently, the inverse transformation is calculated, which is later used to map the dose calculated on the artificially generated fractional CT back to the $r\text{CT}_m$. Thereby, the doses of all fractions are accumulated on the $r\text{CT}_m$.

Extensive evaluation of this method is beyond the scope of this article and is described in Kraus et al [26]. The main findings will be summarized here. In a phantom study where measured CT data and CT data computed with the method described above were compared, we found mean absolute errors in the range of 29.9 HU and 66.6 HU for individual tissue types. The largest deviation was found for bone. Deviations in the image intensities lead to differences in dose volume parameters (D98, D50, D2) below 1.6% and 3.2% for photon IMRT and proton therapy, respectively. For the phantom, the
effect for proton irradiation is expected to be comparable to that for carbon ions, since the range in tissue is influencing the result most.

Since for dose accumulation the inverse vector field is used, the inverse consistency (IC) of the vector fields is checked for each fraction. Inverse consistency is calculated by the Euclidean difference of each voxel and the voxel transformed by forward and reverse transformation. Only pixels inside the body contour cut cranially to a region relevant for radiation therapy of the actual case are considered. The mean IC and its standard deviation over the number of fractions are reported, as well as IC maps for single selected cases.

Dose Accumulation

To accumulate dose over the number of treatment fractions, radiation therapy treatment plans had to be calculated. In preparation of this study, the beam angle configuration was evaluated and the best-suited beam angle configuration was chosen. Three different ion beam arrangements including 1 or 2 beams were tested. For the here evaluated patient cases, beam configurations using 2 posterolateral (120°, 240°) or lateral (90°, 270°) beam angles were found to provide the optimal compromise between target volume dose coverage, sparing of organs at risk, and interfractional dose variation. For Pat1, 2 lateral beams (90°, 270°) were chosen for the following considerations and for Pat2 and Pat3, 2 beams coming from 120° and 270°, where 0° is defined as anterior of the isocenter in supine position. Dose prescription is described in detail in the “Patient Data” section.

For the 2 different scenarios (SIB and CIBseq), treatment plans were optimized on the basis of rCTm. The dose is recalculated on each fractional CT generated with the algorithm described above. Subsequently, the dose is mapped to the rCTm and summed over the number of treatment fractions. Missing fraction data as described above were replaced by data from previous fractions to yield comparable results for all patients. The photon doses were accumulated over 25 fractions and the sequential CIB doses, over 5 fractions.
Results

Evaluation of Image Registration

The mean IC and its standard deviation over the number of fractions are reported. For all patients the mean IC is below 3 mm. For Pat1, IC amounts to 0.82 mm ± 0.22 mm, which corresponds to a maximum bladder volume variation of only 33 mL. For Pat2 where the bladder volume varies by up to 278.4 mL in between fractions, IC is increased to 2.93 mm ± 0.9 mm. For Pat3, IC amounts to 2.28 mm ± 1.2 mm.

Supplementary Figure 2 shows the fractional MR image as well as the transformed MR image after deformable image registration overlaid in different colors. Where images match, the colors cancel out to gray. In the transversal image slices, the matching of most shown pixels can be seen. Small differences can be seen at the edges of the body contours for all patients. For Pat2 and Pat3, small deviations can be noticed in the rectal and prostate region for Pat3. Additionally, Supplementary Figure 2 shows the IC for the corresponding MR images on the right. Since the parameters for image registration were optimized to gain the best result in the target region, IC is increased at the edges of the body contours. This is mainly due to an abrupt change from moving to nonmoving pixels. For Pat2, for whom strong intra-abdominal motion was observed, IC is also increased inside the body contour.

Evaluation of Dose Accumulation

The dose was accumulated over 25 treatment fractions for SIB and CIB\textsubscript{seq} treatment and compared with the planned dose distribution calculated on a static CT. The results are summarized in Table 2 and visualized for the boost volume in Figure 2. Also, the results for CIB without photon treatment are listed. The largest motion-caused effects were observed for the D\textsubscript{98} of the PTV, which was reduced by 9.4 and 7.6 Gy (RBE) when the dose was accumulated over all fractions for Pat2, compared to static dose delivery for SIB and CIB\textsubscript{seq} treatment, respectively. For the boost volume, dose reduction of 1.1 and 0.7 Gy (RBE) was observed for D\textsubscript{98} for Pat2 for SIB and CIB\textsubscript{seq}, respectively, when the dose was accumulated. The reduced doses are due to the large intra-abdominal motion for Pat2, mainly caused by large bladder-filling variations. Also, for Pat2 a vaginal plug was used for imaging, which is displaced by bladder expansion and shrinkage, resulting in shifted target volumes. In Figure 3A and 3B an overlay of the rCT\textsubscript{m} and the fxCT\textsubscript{art} (artificial fractional computed tomography) shows the different bladder fillings and resulting tissue displacements for imaging fraction 5 for Pat2. An example of the resulting dose distribution is also shown, where the boost volume is shifted relative to the pelvis bones. In this case, this leads to a greater amount of high-density tissue material within the beam’s path as visible in Figure 3D, compared to the planned dose distribution shown in Figure 3C.

When sequential CIB dose delivery was added to IMRT photon delivery, abbreviated CIB\textsubscript{seq}, the dose deviations from the static case were comparable to those of SIB dose delivery, both including dose accumulation. A general trend of a more
Conformal dose distribution to the boost volume for CIBseq treatment could be observed for all patients and are visualized in terms of dose-volume histograms in Figure 4. This is due to a more conformal static dose distribution for carbon ions and due to the sequential boost dose delivery concept. Again, the largest impacts were seen for Pat2; however, rather to the PTV than to the boost volume. For Pat3 a general trend of higher doses was noted for dose accumulation for both scenarios (SIB and CIBseq) compared to static dose delivery. The D98 of the PTV was increased by almost 5 Gy (RBE) for Pat2 for CIBseq, compared to SIB treatment for the accumulated dose. The smallest effect of dose increase within the boost volume was noticed for Pat2 again. Here, the D98 was only increased by 1 Gy (RBE) for CIBseq compared to SIB treatment.

**Discussion**

To find a valid statement on the effects caused by tissue displacement, the dose for an entire treatment course had to be summed. In this work, we first generated suitable CT data from MRIs providing the morphologic information of each treatment session. We applied rigid as well as deformable image registration between the MRI acquired on the day of treatment and the fractional MRIs. This method is similar to the one used by ViewRay, which also relies on image registration [27]. Clearly, a good match between the rMRm and the rCTm is the prerequisite for correct propagation of the MR-based transformations to the CTs. For the here used patient cases almost negligible position variations could be observed. The process flow includes deformable image registration to account for tissue expansion and shrinkage. However, deformable image registration lacks a ground truth in many cases [28]. At the moment, we think that a visual check of the registration result should not be abandoned. More important than a perfect match of registered images seems a vector field giving physiologically correct motion. Atlas-based methods, also using image registration, might be prone to errors for patients showing an atypical anatomy [19]. The method introduced here is patient specific; however, it requires the acquisition of at least 1 CT scan. The registration results were optimized by the use of additional anatomic landmarks in cases where huge bladder-filling variations lead to unsatisfying registration results. This is crucial to yield anatomically and physiologically reasonable results, since the vector fields are used for dose mapping and accumulation. For this purpose, the inverse transformation between the fractional MRI and the rMRI_{m} has been derived. This may cause slightly different transformations as result from forward image registration. For the patients studied here, the ICs of the applied vector fields have been evaluated. Mean IC is below 3 mm for all cases;
within the irradiated region, IC is even smaller. Inverse consistency is increased, localized at the body contour edges, where
the image intensity abruptly changes. For the considerations in this study, these effects are not expected to influence the
dosimetric results strongly, since only very small doses are reached at the body contours. Furthermore, all of the performed
dose accumulations are based on the same transformations for SIB and CIB\textsubscript{seq} treatment. Thus, the comparability of the 2
treatment scenarios is not influenced by the IC.

The inverse transform was calculated to gain the most accurate registration result to deform the dose to the reference CT
data, at the cost of an increased IC. To improve ICs, one could also think of using directly inverted vector fields or self-
consistent deformable image registration algorithms.

Other methods applied for generation of CT data either require image registration, such as atlas-based MR-CT density
mapping \cite{11,29}, or rely on bulk electron density assignment, where no vector fields required for dose accumulation are
generated \cite{7–10,15,30,31}. Here, the dose was mapped by image transformation. Energy-mass mapping has been shown to
improve the registration results for lung cases \cite{32}. In the pelvic region, less density variation is expected. Here, a relative
comparison of dose distributions has been presented; therefore, the detrimental effects caused by image registration are
deemed not to devaluate the results regarding the comparability of CIB and SIB therapy for anal cancer.

Comparison of SIB and CIB\textsubscript{seq} dose delivery over the course of the treatment showed remarkably small dose deviations for
the cases investigated here. The accumulated dose distribution for CIB dose delivery without photon irradiation was
compromised by up to 1.9 Gy (RBE), compared to static dose delivery. This largely averaged out when IMRT photon
irradiation was added, as was noticed for Pat2, for whom the intra-abdominal tissue motion was largest and the bladder
volume varied between 60 to 338 mL between treatment fractions. Clearly, there may be patients with exceedingly different
anatomy; however, in this work 54 different fractional image data sets were evaluated such that a wide spectrum of possible
interfractional anatomic motion is covered.
In this study, the same target volume concepts for carbon ion treatment were chosen as are applied for photon IMRT. These could be adapted for CIB therapy taking the precise dose delivery into account, potentially influencing the results for dose accumulation. Application of motion mitigation techniques such as described in the study of Rietzel and Bert [33] could further improve the dosimetric result for the boost volume. Expected quantifiable range uncertainties could be taken into consideration for motion-specific margin design and thus could be used to make the dose distribution more robust against motion.

Contour data were also transformed, visually approved, and manually corrected where necessary. Thereby, deviations from the original delineation may have occurred and have influenced the dose distribution for the individual structure. All of the drawbacks associated with image registration clearly influence the absolute dose values; however, the relative comparability of SIB and CIBseq treatment is not affected, which was the focus of this work.

In this study, no specific requirements for bladder filling were applied. This led to strong intraindividual bladder-filling variations. For Pat2 these resulted in dosimetric mismatch for individual fractions for CIB treatment. Most of the detrimental effects could be averaged out by dose accumulation and additional photon therapy. However, the results might be more reproducible if a bladder-drinking/bladder-emptying protocol was followed. This should be considered in the future to ensure a safe application of CIBseq to AC.

Carbon ions have proven their physical and biological potential for many abdominal and pelvic tumors as summarized by Schlaff et al [6]. Rather radioresistant rectal cancer has also attracted notice for carbon ion therapy [34–36]. These and the results gained in this study encourage us to advance CIB treatment of anal cancer. Even though the prognosis of most patients with anal cancer is good, carbon ions with their increased biological effectiveness could improve the therapeutic outcome for patients with human papillomavirus–negative anal cancer with a dismal prognosis.

To our knowledge, up to date no study has been published that evaluates the exploitation of carbon ions for AC treatment based on daily anatomic data. In this work, we demonstrated that the sharp local dose deposition of carbon ions, in combination with interfractional pelvic and abdominal motion, is not an obstacle for CIB therapy together with photon IMRT of anal cancer.

Conclusion

In this work we examined the dosimetric feasibility of CIB therapy for anal cancer. We found CIBseq dose distributions comparable with those delivered by standard SIB radiation therapy for anal cancer treatment. Influences on the dose distribution caused by interfractional tissue motion were rather small and could be largely averaged out by additional photon IMRT. These promising results give reason for further physical and clinical exploitation of CIBseq treatment of anal cancer with a poor response to photon radiation therapy treatment.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflict of interest to disclose.

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**Ethics Approval and Consent to Participate:** Patient data were acquired within a clinical study protocol [20], which was approved by the ethics committee of the medical faculty of Heidelberg, votum number S-144/2013.

**Consent for Publication:** All patients have given written consent for the utilization of anonymized imaging data for research purposes.

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