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FULL PAPER

Variation in patient position and impact on carbon-ion scanning beam distribution during prostate treatment

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Objective: We assessed the impact of changes in patient position on carbon-ion scanning beam distribution during treatment for prostate cancer.

Methods: 68 patients were selected. Carbon-ion scanning dose was calculated. Two different planning target volumes (PTVs) were defined: PTV1 was the clinical target volume plus a set-up margin for the anterior/lateral sides and posterior side, while PTV2 was the same as PTV1 minus the posterior side. Total prescribed doses of 34.4 Gy [relative biological effectiveness (RBE)] and 17.2 Gy (RBE) were given to PTV1 and PTV2, respectively. To estimate the influence of geometric variations on dose distribution, the dose was recalculated on the rigidly shifted single planning CT based on two dimensional-three dimensional rigid registration of the orthogonal radiographs before and after treatment for the fraction of maximum positional changes.

Results: Intrafractional patient positional change values averaged over all patients throughout the treatment course were less than the target registration error = 2.00 mm and angular error = 1.27°. However, these maximum positional errors did not occur in all 12 treatment fractions. Even though large positional changes occurred during irradiation in all treatment fractions, lowest dose encompassing 95% of the target (D_{95})-PTV1 was >98% of the prescribed dose.

Conclusion: Intrafractional patient positional changes occurred during treatment beam irradiation and degraded carbon-ion beam dose distribution. Our evaluation did not consider non-rigid deformations, however, dose distribution was still within clinically acceptable levels.

Advances in knowledge: Inter- and intrafractional changes did not affect carbon-ion beam prostate treatment accuracy.

The depth dose distribution for a charged particle beam exhibits a Bragg peak at the end of range, which is particularly sensitive to variation in tissue density along its path length. For this reason, changes in patient position perturb charged particle beams more strongly than photon beams.¹ Of the two major treatment uncertainties, intrafractional motion and interfractional changes, treatment accuracy for the prostate appears more strongly affected by interfractional changes.^{2–7} Clinical protocols now incorporate several approaches to overcoming these uncertainties, including acquisition of radiographs or cone beam CT images.

However, despite these technical solutions to intra- and interfractional changes and improvements in patient positional accuracy during the patient set-up procedure, treatment accuracy may also be affected by positional changes during treatment. Most treatment centres do not check patient positional accuracy after treatment beam irradiation, because approaches to adjusting distribution in the next fraction to compensate for under-/overdosage in the preceding

have not been developed and because patient position is assumed not to change during treatment. Our hospital has been providing carbon-ion scanning beam treatment since 2011.⁸ The average time from complete patient set-up to complete beam irradiation was 2.6 min. Although this is relatively short, we have no quantitative data on the effect of patient positional change on carbon-ion scanning dose distribution.

In this study, we evaluated patient positional change during treatment and its impact on carbon-ion scanning dose distribution in treatment of the prostate.

METHODS AND MATERIALS

Patients and image acquisition

The study was conducted in 68 patients randomly selected from among patients with prostate cancer (68.2 ± 4.0 years) undergoing carbon-ion scanning beam treatment at our hospital. The number of treatment fractions was 12, delivered with 2 beam angles using horizontal beam ports and rotation of the treatment couch to 180° [International

Electrotechnical Commission (IEC) definition: θ rotation⁹]. The treatment beam was irradiated from a single beam angle per day.

All patients were fixed by immobilization with a shell device, which covered the patient and was affixed with tape to the bottom of the table to improve the positional reproducibility of the patient. These immobilization devices were constructed of a relatively thick shell (3-mm) made of a low-temperature thermoplastic (Shellfitter; Kuraray Co. Ltd, Osaka, Japan) and contained a hydraulic urethane resin inner lining (MOLDCARE®; Alcare Co., Ltd, Tokyo, Japan).

After the patient entered the treatment room, orthogonal flat panel detector (FPD) images were acquired (CXDI-55C; Canon Inc., Tokyo, Japan) for the patient set-up procedure, which was performed using two dimensional–three dimensional (2D-3D) auto registration software.¹⁰ This process calculated positional error between the current position and planning CT, which was acquired under free-breathing conditions using a large-bore 16-slice CT (Aquilion™ LB; Toshiba Medical Systems Corporation, Tokyo, Japan). The next position was sent to the robotic arm treatment couch system, and orthogonal FPD images were again acquired to verify patient position. This process was repeated until the patient position achieved a clinically acceptable level. The tumour was then irradiated with carbon-ion beam, after which orthogonal FPD images were again acquired at the same patient position.

In 2013, treatment room occupation time averaged over all patients was 12.2 min [entry = 3.6 min, patient set-up = 5.4 min, preparation for irradiation = 1.0 min (movement of therapists from the treatment room to the control room), treatment beam irradiation = 1.6 min, exit = 0.6 min]. Average time from the completion of patient set-up to completion of beam irradiation was 2.6 min (maximum = 3.7 min, minimum = 2.1 min).

Data analysis

To calculate positional error (three translations: Δx , Δy and Δz , and three rotations: $\Delta\psi$, $\Delta\phi$ and $\Delta\theta$, defined in IEC;⁹ where ψ , ϕ and θ were rotation along the x -, y - and z -axis, respectively), FPD images before (final patient set-up) and after irradiation were compared with those of planning CT, separately using the 2D-3D auto registration software. Interfractional positional errors for the respective treatment fractions were expressed as the target registration error (TRE) and angular error (AE), calculated using the following equations:

$$\text{TRE}_{\text{inter}} = \sqrt{\Delta x^2 + \Delta y^2 + \Delta z^2}$$

$$\text{AE}_{\text{inter}} = \sqrt{\Delta\psi^2 + \Delta\phi^2 + \Delta\theta^2}$$

Figure 1. Results for interfractional positional error before and after irradiation, as a function of treatment fraction number (Patient 1) for (a) target registration error ($\text{TRE}_{\text{inter}}$) and (b) angular error (AE_{inter}).

By comparing positional errors before and after irradiation (intrafractional positional error), the magnitude of intrafractional positional errors during irradiation was expressed as:

$$TRE_{intra} = \sqrt{(\Delta x_{after} - \Delta x_{before})^2 + (\Delta y_{after} - \Delta y_{before})^2 + (\Delta z_{after} - \Delta z_{before})^2}$$

$$AE_{intra} = \sqrt{(\Delta \psi_{after} - \Delta \psi_{before})^2 + (\Delta \varphi_{after} - \Delta \varphi_{before})^2 + (\Delta \theta_{after} - \Delta \theta_{before})^2}$$

Treatment planning

Radiation oncologists input prostate, seminal vesicle and rectum contours on the CT image manually. MRI images were used to clearly image these organs. The clinical target volume (CTV) was defined as the prostate and the seminal vesicle. Two planning target volumes (PTVs) were defined. The first PTV (PTV1) was the CTV plus 10 mm to the anterior/lateral sides and 5 mm to the posterior side. These margins account for set-up errors and interfractional positional changes (= internal margin). The second PTV (PTV2) was the same as PTV1, but without the 5 mm to the posterior side to minimize excessive dose to the rectum.¹¹

Treatment was delivered using the hybrid depth carbon-ion scanning dose calculation.¹² Beam weight maps for the PTVs were optimized using the relative biological effectiveness (RBE)-weighted absorbed dose. The total prescribed dose of 51.6 Gy (RBE) [= 4.3 Gy (RBE) per fraction from 90° or 270°] was given

as 34.4 Gy (RBE) to PTV1 and 17.2 Gy (RBE) to PTV2. Treatment planning parameters were optimized using planning CT data. To estimate the influence of the geometric variations on dose distribution, the dose was recalculated on the rigidly shifted planning CT based on the 2D-3D rigid registration of the orthogonal radiographs before and after treatment for the fraction of maximum positional changes. Since we evaluated patient positional errors throughout the treatment course, accumulated dose distribution could be calculated by summing dose distributions with positional variations at respective treatment fractions. Since it requires man-hours to calculate dose distributions in all treatment fractions and sum them up, we instead calculated dose distributions with maximum positional changes during treatment course to reflect conditions under a worst-case scenario.

RESULTS

Patient positional error

The single case with the largest intrafractional patient positional error between before and after irradiation (TRE_{intra} and AE_{intra}) (Patient 1, second treatment fraction) is introduced here. Maximum positional error differences before and after irradiation were $TRE_{intra} = 2.00$ mm and $AE_{intra} = 0.96^\circ$ throughout the treatment course (Figure 1). Positional error average values after irradiation were increased by $TRE_{intra} = 0.79$ mm and $AE_{intra} = 0.41^\circ$ during irradiation ($TRE_{inter} = 0.37 \pm 0.11$ mm and $AE_{inter} = 0.10 \pm 0.06^\circ$ before irradiation; and $TRE_{inter} = 0.95 \pm 0.45$ mm and $AE_{inter} = 0.45 \pm 0.18^\circ$ after irradiation).

Figure 2. Interfractional positional errors averaged for all patients before and after irradiation for (a) target registration error (TRE_{inter}) and (b) angular error (AE_{inter}). deg, degree; max, maximum; SD, standard deviation.

Table 1. Interfractional (before and after irradiation) and intrafractional patient positional errors for all patients

Metrics	Δx (mm)	Δy (mm)	Δz (mm)	$\Delta\psi$ (°)	$\Delta\phi$ (°)	$\Delta\theta$ (°)	Target registration error (mm)	Angular error (°)
Interfractional positional error								
Before irradiation								
Mean	0.00	0.00	-0.04	0.07	0.01	0.01	0.36	0.18
SD	0.23	0.22	0.24	0.16	0.13	0.08	0.18	0.15
Median	0.00	0.00	-0.02	0.03	0.00	0.00	0.34	0.14
min.	-1.21	-0.80	-1.16	-0.67	-0.40	-0.43	0.00	0.00
max.	0.94	0.86	0.94	1.08	0.76	0.30	1.31	1.09
After irradiation								
Mean	0.01	-0.10	-0.16	0.09	0.00	0.00	0.55	0.26
SD	0.40	0.31	0.33	0.25	0.16	0.12	0.31	0.20
Median	0.00	-0.08	-0.15	0.08	0.00	0.00	0.50	0.22
min.	-2.16	-1.30	-1.53	-1.11	-0.89	-0.56	0.00	0.00
max.	1.83	1.22	1.26	1.35	0.84	0.48	2.20	1.38
Intrafractional positional error								
Mean	0.00	-0.10	-0.11	0.02	0.00	-0.01	0.40	0.21
SD	0.30	0.19	0.28	0.20	0.14	0.10	0.26	0.16
Median	0.00	-0.10	-0.11	0.03	0.00	0.00	0.34	0.17
min.	-1.50	-1.11	-1.11	-0.99	-0.90	-0.74	0.00	0.00
max.	1.35	1.08	1.32	1.01	0.48	0.48	2.00	1.27

max., maximum; min., minimum; SD, standard deviation.

Interfractional patient positional error for all patients throughout the treatment course is visualized as a histogram in Figure 2. Before irradiation, patient positional errors averaged over all patients were $TRE_{inter} = 0.36 \pm 0.18$ mm (median, 0.34 mm; maximum, 1.31 mm) and $AE_{inter} = 0.18 \pm 0.15^\circ$ (median, 0.14°; maximum, 1.09°). Interfractional positional errors after irradiation were slightly increased, to $TRE_{inter} = 0.55 \pm 0.31$ mm (median, 0.50 mm; maximum, 2.20 mm) and $AE_{inter} = 0.26 \pm 0.20^\circ$ (median, 0.22°; maximum, 1.38°). While intrafractional positional error for all patients throughout the treatment course was less than $TRE_{intra} = 2.00$ mm and $AE_{intra} = 1.27^\circ$. Results are summarized in Table 1.

Dose calculation

Dose distributions were evaluated for the two cases with the largest patient positional errors.

For the first case, the planned dose distribution satisfactorily delivered over 95% of the prescribed dose to the PTV1 (= 98.8%) and PTV2 (= 95.3%) (Patient 1; Figure 3a). The dose-volume histogram for PTV1, PTV2 and rectum is shown in Figure 4a. Since patient positional error was not particularly large, the dose distribution difference provided a clearer understanding of distribution than did observation of dose distributions before and after irradiation. Dose distribution differences for before and after irradiation are shown in Figure 3b,c, respectively. Since interfractional patient positional errors before irradiation was mostly

shifted to the inferior direction [Δx (mm), Δy (mm), Δz (mm), $\Delta\psi$ (°), $\Delta\phi$ (°), $\Delta\theta$ (°)] = (-0.10, -0.29, -0.05, 0.00, 0.00, 0.00) at the second treatment fraction, positive and negative dose differences were observed around the apex and base of the prostate, respectively. Prostate dose before irradiation was therefore slightly decreased compared with that for treatment planning (Figure 4a). Lowest dose encompassing 95% of the target (D_{95}) values were almost the same as those for the planned dose (98.8% and 95.6% for PTV1 and PTV2, respectively).

The magnitude of dose differences was <1.8 Gy (RBE). Interfractional patient positional error after irradiation was [Δx (mm), Δy (mm), Δz (mm), $\Delta\psi$ (°), $\Delta\phi$ (°), $\Delta\theta$ (°)] = (-1.60, -0.34, 1.26, -0.85, 0.12, -0.45) at the second treatment fraction, indicating that additional anterior and left side shifts occurred during treatment beam irradiation. These in turn resulted in large negative and positive dose differences [<8 Gy (RBE)] at the anterior and posterior aspects, respectively (Figure 3c), and rectum dose was consequently higher than the planned dose and before irradiation (Figure 4a).

For the next case (Patient 2), interfractional patient positional errors were [Δx (mm), Δy (mm), Δz (mm), $\Delta\psi$ (°), $\Delta\phi$ (°), $\Delta\theta$ (°)] = (0.10, -0.02, -0.71, 0.59, 0.24, 0.15) and (-1.26, -0.02, -1.53, 1.35, 0.28, 0.01) before and after irradiation, respectively. The magnitude of the positional errors increased from before to after irradiation. D_{95} values for both PTV1 and PTV2 were

Figure 3. (a) Carbon-ion beam dose distribution for the planned dose for Patient 1. Dose distribution differences for (b) the dose before irradiation minus planned dose and (c) the dose after irradiation minus planned dose. Interfractional patient positional errors [x (mm), y (mm), z (mm), ψ ($^\circ$), ϕ ($^\circ$), θ ($^\circ$)] were $(-0.10, -0.29, -0.05, 0.00, 0.00, 0.00)$ and $(-1.60, -0.34, 1.26, -0.85, 0.12, -0.45)$ for before and after irradiation at the second treatment fraction, respectively. The yellow line and light blue line within the yellow line are planning target volume (PTV)1 and PTV2, respectively. The second light blue line is the rectum. RBE, relative biological effectiveness. For colour images see online.

decreased in the order of planned dose, and before and after irradiation (Figure 4b). Nevertheless, D_{95} values for PTV1 were $>98\%$ (98.8% for the plan, 98.4% before irradiation and 98.1% after irradiation) throughout treatment. D_{95} values for PTV2 were 93.8% for the planned dose, 91.3% before irradiation and 87.5% after irradiation. Since the patient was shifted 0.71 and 1.53 mm in the posterior direction before and after irradiation, respectively, rectal doses were decreased in the order of the plan, before and after irradiation (Figure 4b).

DISCUSSION

We quantified patient positional changes during treatment beam irradiation in carbon-ion scanning treatment for prostate cancer. Positional change values averaged over all patients were less than $TR_{intra} = 2.00$ mm and $AE_{intra} = 1.27^\circ$ throughout the treatment course. Even though this large positional change would occur in all treatment fractions, dose assessment showed that it was clinically acceptable.

The clinical acceptability of this positional change largely resulted from the very short time from the start of the patient set-up procedure to the completion of beam irradiation, namely an average of 2 min. Nevertheless, any prolongation of this time might lead to a larger difference in positional change. Several factors impact patient positional change, including rotation of the foot, sliding of the waist, relaxation of psoas/hip muscle tone etc. Of note, none of these causes can be identified in FPD images.

Recent patient set-up in photon beam therapy is performed by registration of target position or marker seeds rather than bony anatomical structures. It is not, however, suitable for particle therapy, because particle beam is strongly affected on tissue density variations along a given ray, especially in prostate treatment, such as a high-density object such as femur bone. Therefore, if patient set-up is performed by registration of target position or marker seeds in particle therapy, particle

Figure 4. Dose-volume histograms for the planned dose, and doses before and after irradiation for the first planning target volume (PTV), second PTV and rectum. (a) Patient 1. (b) Patient 2.

beam could not stop at the desired position. Our treatment centre, therefore, registers bony anatomical structures and interfractional prostate positional was minimized by the pre-operation described later.

This study evaluated the impact of patient positional changes on dose distribution in prostate treatment. The influence of respiration suggests that positional changes would be larger in the thoracic and abdominal regions than in the pelvic region, and dose distribution might accordingly be more strongly degraded than in prostate treatment. Moreover, given that patient respiratory pattern is not always reproducible,¹³ scanning dose conformation to a moving target under irregular breathing conditions might be degraded if rescanning and/or gating etc. techniques are not adapted. These considerations are beyond the scope of the present study and will be evaluated in future studies.

A few limitations of this study warrant mention. First, although a single treatment planning CT was used to estimate interfractional positional errors before and after irradiation, variables of organ and gas bowel position at planning CT acquisition and before/after irradiation were not precisely the same, because it is based on the rigid shift of planning CT instead of an actual control CT neglecting all non-rigid deformations taking place. Dose assessments therefore likely included small errors. Previous publications introduced intrafractional prostate motion during several seconds to a few minutes. Most of them evaluated prostate motion in two dimensions, however, Kitamura et al¹⁴ reported that the average prostate motion in three dimensions was $TRE_{intra} = 0.52$ mm [0.3 mm in anteroposterior (AP), left-right (LR) and superior-inferior (SI) directions], it was larger than our results ($TRE_{intra} = 0.40$ mm). While average interfractional

prostate motion was also previously reported that TRE_{inter} values were 3.7 mm (2.7 mm in AP, 2.4 mm in LR and 1.0 mm in SI)¹⁵ and TRE_{inter} values were 4.3 mm (2.7 mm in AP, 2.7 mm in LR and 2.0 mm in SI).¹⁶ These results were also larger than our results ($TRE_{inter} = 0.36$ and 0.55 for before and after irradiations, respectively). The prostate protocol at our institution aims to provide consistent tumour positioning and to minimize dose variation between planning and actual treatment delivery by starting treatment after approximately 1 h of urination and emptying the rectum voluntarily or with a laxative or enema before planning CT as well as for each treatment stage. Bladder volume and gas bowel positional differences therefore likely had less impact than did patient positional errors. Furthermore, our use of this protocol ensures that our results closely reflect clinical conditions.

Second, since our evaluation was based on orthogonal two-dimensional images not serial CT images in the respective treatment fractions due to the limitation of CT radiation exposure, anatomical structure deformations were not considered. The rigid 2D-3D registration might also be affected by registration uncertainty owing to missing three-dimensional information. Patient deformation changes were minimized by using immobilization shell for improved positional and soft-tissue thickness reproducibility and for managing bladder volume and gas bowel. This limitation may only have little effect on the dose assessment.

In conclusion, we found that intrafractional patient positional changes occurred during treatment beam irradiation, and that these changes degraded carbon-ion beam dose distribution. Our evaluation did not consider non-rigid deformations, however, dose distribution was still within clinically acceptable levels.

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