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Original article

# The impact of interfractional anatomical changes on the accumulated dose in carbon ion therapy of pancreatic cancer patients

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*Background and purpose:* We evaluated the robustness of carbon ion therapy for pancreatic cancer patients by investigating the impact of interfractional anatomical changes on the accumulated dose when using bony anatomy- and fiducial marker-based position verification.

*Material and methods:* Carbon ion treatment plans were created for 9 patients in this retrospective planning study. The planning CT was deformably registered to each daily cone-beam CT (CBCT). The gastrointestinal gas volume visible on each CBCT was copied to these deformed CT images. Subsequently, the fraction doses were calculated by aligning the treatment plan according to a bony anatomy- and a fiducial marker-based registration.

We compared the accumulated fraction doses with the planned dose using dose–volume histograms (DVHs) of the internal gross tumour volume (iGTV), internal clinical target volume (iCTV), duodenum, stomach, liver, spinal cord and kidneys.

*Results:* iCTV coverage ($D_{98\%}$) was on average reduced from 98.6% as planned to 81.9% and 88.6% for the bony anatomy- and marker-based registrations, respectively. DVHs of the duodenum showed large differences between the planned and accumulated dose.

*Conclusions:* Severe reductions in dose coverage of the target due to interfractional anatomical changes were observed in both position verification methods.



Pancreatic cancer is one of the most common causes of cancer-related deaths. Surgical resection is considered the treatment option of choice in this patient group, but preoperative radiochemotherapy has the potential to increase complete tumour resectability [1]. However, radiotherapy of pancreatic cancer is very toxic due to the high dose to surrounding organs-at-risk (OARs) such as the stomach and duodenum. Compared with radiotherapy using photons, charged particle radiotherapy using carbon ions is characterized by a more conformal dose distribution, due to the sharp dose fall-off around the target volume [2–4]. Therefore, a high dose can be delivered to the tumour, while at the same time the healthy organs located in close proximity to the tumour can be spared. Promising improvements in overall survival after radiotherapy using carbon ions in pancreatic cancer patients have been reported from Japanese clinical trials [3].

During radiotherapy, pancreatic tumours show considerable movement due to respiration [5,6] and changes in gastrointestinal filling [7]. Besides these movements, anatomical deformations such as changing body contours and gastrointestinal gas volumes are observed over the course of treatment. These deformations have a random character and can greatly influence the penetration depth of carbon ions and, hence, increase toxicity and reduce the effectiveness of the treatment [8]. To enable corrections for these random changes, daily imaging just prior to treatment is required. In photon therapy, cone-beam CT (CBCT) imaging is widely available on linacs nowadays. In carbon ion therapy, however, imaging on the treatment machine is most often based on 2D orthogonal X-ray images [9]. Consequently, anatomical changes cannot be visualized in 3D at the time of treatment and the effect on the dose delivery remains unclear.

The purpose of this collaborative study is to investigate the impact of interfractional anatomical changes in pancreatic cancer patients on the accumulated fraction doses when using carbon ion therapy. Additionally, the effect of different position verification methods (i.e. based on bony anatomy or on fiducial markers

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[7,10]) on the accumulated dose is evaluated. To this end, a retrospective treatment planning study was performed at the Gunma University Heavy Ion Medical Center (GHMC) using CT and daily CBCT imaging data obtained from pancreatic cancer patients treated at the Academic Medical Center (AMC).

## Materials and methods

### *Patients and imaging*

Nine consecutive patients with a tumour in the pancreatic head, treated using photon radiotherapy at the AMC between July 2013 and October 2014, were included in this planning study (Table 1). Patients were enrolled in the PREOPANC study [11] and informed consent was available for all patients.

Patients received either a 3D-CT exam (patient 1) or a 4D-CT exam consisting of 10 respiratory phases, of which the average scan was used for treatment planning (LightSpeed RT16 scanner, General Electric Company, Waukesha, WI, USA). Intratumoural gold fiducial markers (2–4 per patient, Visicoil, 0.35 mm diameter, IBA Dosimetry GmbH, Schwarzenbruck, Germany) were implanted under endoscopic ultrasound guidance to enable position verification using CBCT [7,10].

The clinical delineations, performed by an experienced radiation oncologist, were used; the stomach and duodenum were delineated for the purpose of this study. The internal gross tumour volume (iGTV) was defined as the gross tumour volume (GTV) including lymph nodes and fat infiltration on each phase of the 4D CT scan. In case only a 3D scan was available, only the GTV was defined. The iGTV (or GTV) was expanded using a 5 mm margin to create the internal clinical target volume (iCTV) [12]. The duodenum, stomach, kidneys, liver and spinal cord were delineated on the average CT scan, including all 4D-CT phases. During the delineation process, all phases of the 4D-CT and a contrast-enhanced fast CT scan were available.

CBCT images were acquired at the treatment machine (Synergy platform, Elekta AB, Stockholm, Sweden) prior to each treatment fraction (Table 1). Patients breathed freely in supine position during all imaging.

### *Carbon ion treatment planning*

Carbon ion treatment plans were created using XiO-N (collaborated product of Elekta AB, Stockholm, Sweden and Mitsubishi Electric Corporation, Tokyo, Japan) [13]. The average 4D-CT was used for planning without any density override to gastrointestinal gas volumes. A passive scattering technique using 4 beams (angles: 0°, 90°, 180° and 270°) was applied. A margin of 3 mm was added to the iCTV to account for range uncertainties and penumbra effects; the stomach and duodenum were excluded from this planning target volume (PTV). Each beam was optimized separately to enclose the PTV with the 95% isodose surface. The field boundary was defined using a multileaf collimator (MLC), which enclosed the PTV with an additional 5 mm margin. To account for patient setup errors, a smearing technique using a factor of 3 mm was applied to create the beam-specific compensating bolus [8]. Treatment plans were generated to deliver at least 95% of the prescribed dose (36 GyE in 12 fractions) to 99% of the PTV ($V_{95\%} \geqslant 99\%$). PTV coverage was allowed to be compromised slightly in favour of OAR sparing if the coverage of the iCTV was not compromised ($V_{95\%} \geqslant 99\%$). To calculate the dose in GyE (Cobalt Gray Equivalent) [14], the relative biological effectiveness (RBE) was included in the absorbed dose using a Spread Out Bragg Peak (SOBP) concept [4].

**Table 1**
Patient characteristics.

| Patient | Planning CT | Number of available CBCTs[a] | iCTV volume (ml) |
|---|---|---|---|
| 1 | 3D-CT | 15 | 155.7 |
| 2 | 4D-CT | 15 | 53.9 |
| 3 | 4D-CT | 15 | 63.6 |
| 4 | 4D-CT | 15 | 163.7 |
| 5 | 4D-CT | 14[b] | 58.5 |
| 6 | 4D-CT | 15 | 151.3 |
| 7 | 4D-CT | 13 | 105.1 |
| 8 | 4D-CT | 15 | 199.3 |
| 9 | 4D-CT | 15 | 186.0 |

[a] One RT fraction per treatment day (15 × 2.4 Gy or 13 × 3.0 Gy).
[b] For one CBCT, artefacts prevented reliable image registration.

### *Calculating accumulated dose*

CBCT images are not directly suitable for dose calculations, because CBCT Hounsfield units (HU) are inaccurate [15]. To enable fractional dose calculations, for each patient the planning CT was deformably registered to each of the first 12 CBCT images (Velocity, version 3, Varian Medical Systems, Inc., Palo Alto, CA, USA) [15]. To only take the gastrointestinal gas volumes of one fraction into account, the gastrointestinal gas as visualized on the deformed planning CT had to be removed, while the gas volumes on each CBCT had to be defined. Therefore, prior to registration, all voxels in the CT with a value of less than −150 HU were assigned a value 0 HU. Next, on each CBCT, the gastrointestinal gas was automatically delineated using a threshold of −550 HU. This delineation was then copied to the corresponding deformed CT image and in the planning system a density override of 0.01 was applied to these volumes for dose calculation.

As part of the AMC online position verification protocol, the CBCT images were registered to the planning CT, first using the bony anatomy, followed by a registration using the fiducial markers (XVI, version 4.5, Elekta AB, Stockholm, Sweden) [7]. To evaluate the difference in position verification method, fraction doses were calculated for both of these methods by aligning the plan isocenter to each deformed CT image according to the corresponding registration.

Typically in Japan, when using passive scattering carbon ion therapy, one beam is delivered per treatment day. The clinical beam schedule (12 fractions: beam angle 0°, 90°, 270°, 0°, 90°, 270°, 0°, 90°, 270°, 180°, 180°, 180°) was used for the dose calculations on the deformed CT images as well.

The fraction doses can be accumulated either deformably or rigidly. Dose deformation requires a voxel-by-voxel deformable image registration accuracy [16], which cannot be guaranteed in this study due to the limited soft-tissue contrast in the CBCTs. Therefore, the calculated fraction dose distributions for both position verification methods were rigidly summed to acquire the accumulated dose distribution and, consequently, organ deformations were not taken into account.

### *Data analysis*

The volume of the gastrointestinal gas delineations on CT and CBCT was evaluated. Vector distances between the bony anatomy- and marker-based registrations were calculated as the 3D vector displacement [7].

For all dose distributions (i.e. planned, bony anatomy- and marker-based accumulated), dose–volume histograms (DVHs) were calculated for the iGTV, iCTV, duodenum, stomach, kidneys, liver and spinal cord. For each patient, the dose to 98% of the volume ($D_{98\%}$) and to 2% of the volume ($D_{2\%}$) [17] were calculated for the iGTV and iCTV; the dose to 2*cc* of the volume ($D_{2cc}$) was evaluated for the OARs [18]. The mean dose ($D_{mean}$) and equivalent uniform dose (EUD) were calculated for all volumes. EUD values were

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