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Adoptive radiotherapy

An adaptive radiotherapy planning strategy for bladder cancer using deformation vector fields

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A B S T R A C T

Purpose: Adaptive radiotherapy (ART) has considerable potential in treatment of bladder cancer due to large inter-fractional changes in shape and size of the target. The aim of this study was to compare our clinically applied method for plan library creation that involves manual bladder delineations (Clin-ART) with a method using the deformation vector fields (DVFs) resulting from intensity-based deformable image registrations (DVF-based ART).
Materials and methods: The study included thirteen patients with urinary bladder cancer who had daily cone beam CTs (CBCTs) acquired for set-up. In both ART strategies investigated, three plan selection volumes were generated using the CBCTs from the first four fractions; in Clin-ART boolean combinations of delineated bladders were used, while the DVF-based strategy applied combinations of the mean and standard deviation of patient-specific DVFs. The volume ratios (VRs) of the course-averaged PTV for the two ART strategies relative the non-adaptive PTV were calculated.
Results: Both Clin-ART and DVF-based ART considerably reduced the course-averaged PTV, compared to non-adaptive RT. The VR for DVF-based ART was lower than for Clin-ART (0.65 vs. 0.73; $p < 0.01$).
Conclusions: DVF-based ART for bladder irradiation has a considerable normal tissue sparing potential surpassing our already highly conformal clinically applied ART strategy.

Radiotherapy (RT) of bladder cancer is characterised by large inter-fractional changes in shape and size of the target, leading to the use of wide margins (in the 15–25 mm range) to ensure target coverage throughout the course of treatment [1]. RT of this tumour site has therefore been associated with relatively high rates of severe radiation-induced morbidity [2–4].

The findings of repeat imaging studies with CT – and later with cone-beam CT (CBCT) – have documented a clear need to adapt to the daily anatomical changes [5]. Adaptive RT (ART) is a technique where the soft tissue information from daily imaging (in this study CBCT) is used in a systematic manner to adapt the treatment to the patient anatomy, in particular in order to account for inter-fractional anatomy changes [6–9]. For patients with urinary bladder cancer and for other pelvic treatment sites random anatomical changes are dominating [10,11] and this makes plan selection from a library of treatment plans an appealing strategy. We have recently implemented clinically an adaptive daily plan selection protocol [12]. Among several challenges of such strategies is the dependence of manual contouring on the CBCTs that are used as image input for planning. Intensity-based deformable image registration (DIR) algorithms (such as Thirions Demons algorithm) can alleviate this dependence as they do not depend on manually delineated contours [13–15]. Indeed, the deformation vector fields (DVFs) obtained from DIRs between the planning CT (pCT) and repeat CBCTs carry detailed information about the anatomical changes from the planning geometry to these repeat observations, ideally linking the geometry of the organs in the planning CT to the geometries in the CBCT.

As an attempt to improve the ART planning process, we have therefore explored the use of DVFs for the creation of the plan library in a daily plan selection strategy for bladder cancer. The specific aim of the study was to compare the resulting conformity of ART plans derived using patient-specific DVFs from intensity-based DIRs (DVF-based ART) relative to our current clinically applied method for creation of plan libraries (Clin-ART).

Materials and methods

Patients and delivered RT

The study included thirteen patients with muscle-invasive urinary bladder cancer treated with RT in our institution in the period

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from November 2011 to May 2013. Five of the patients were treated with non-adaptive RT (Group A) while eight patients were treated with the Clin-ART strategy (Group B) [16,8]. The male/female ratio was 11/2. During the actual treatment and in this study, the CTV was defined as the whole bladder and any tumour visible on the treatment planning CT scan (pCT). All patients were CT-scanned and treated with a voided bladder. Patients in group A was treated using population-based margins of 2 cm anterior and superior, 1.5 cm posterior and 1 cm in the other directions [1]. The additional margin for setup was 8 mm superior-inferior and 5 mm in the other directions, to generate the PTV_{nonART}. In group B, the patients received daily feedback on which ART plan had been delivered. During treatment, patients were set-up on a daily basis using cone-beam CT (CBCT; OBI, Varian Medical Systems, Palo Alto, CA), with the CBCTs matched to the pCT according to pelvic bony anatomy. In this study, the daily CBCT scans were used to evaluate and compare the two alternative ART planning strategies.

Generation of plan selection volumes for the clinically applied ART strategy

Our current Clin-ART strategy involves manual delineation of the CTV (bladder and any visible tumour) in the CBCTs from the first four fractions, following the same outlining protocol as for the pCT. The CTVs from the CBCTs were copied to the pCT using the clinically applied online rigid registrations. Based on these five bladder contours (pCT and four CBCTs), the small-size plan selection volume (PSV_{Small}) was defined as the volume contained in at least two out of the five bladder volumes, while the medium-size PSV was created as the union of all five volumes (PSV_{Medium}) [8]. An isotropic margin of 3 mm to account for residual uncertainties in registrations and delineations was added to generate the PSVs. A further 5 mm isotropic margin was added to account for intra-fractional motion to generate the corresponding PTVs (Supplementary Fig. 1). The margins used on the large-size PTV were equal to our standard PTV margins prior to the clinical introduction of ART [1].

Generation of plan selection volumes for the DVF-based ART strategy

For the generation of plan libraries in the DVF-based ART strategy, rigid registrations (allowing for translations and rotations) were initially performed on pelvic bony anatomy between the pCT and each of the four initial CBCTs. Subsequently, DIRs from the pCT to the four CBCTs were performed using a rectangular region of interest covering the small pelvis and the intensity-based Thirions demons algorithm (SmartAdapt; Varian Medical Systems, Palo Alto, CA) [17]. The registrations were completed within around 2 min. Using the pCT and the related structure file together with the four DVFs resulting from the DIRs, the mean DVF (mDVF) and the related standard deviation (sdDVF) were calculated for each patient. The small size volume (PSV_{Small}) was generated applying the DVF corresponding to the 33% percentile (i.e., mDVF-0.43·sdDVF) to the CTV in the pCT. Likewise, the 67% percentile (i.e., mDVF + 0.43·sdDVF) was applied to the same CTV to generate the medium sized volume (PSV_{Medium}). Finally, to generate the large size volume, the 99.9% percentile (i.e., mDVF + 3·sdDVF) was applied to the CTV. Finally, a 3 mm margin was added in the PSVs, to account for residual uncertainties in image registration. Like for the Clin-ART strategy, the three corresponding PTVs were created by adding a 5 mm isotropic margin to the PSVs, to account for intra-fractional changes.

Daily plan selection with the two ART strategies

In the simulation of daily plan selection with the two ART strategies, all patients were considered treated with non-adaptive RT during the first week of treatment. For fractions 6–30 the CBCT of the day was matched to the planCT prior to delivery using bony match with visual inspection of the bladder. First, the PSV_{small} for the respective strategy overlaid on the CBCT was evaluated and if the bladder was covered with this PSV, the patient was assumed treated with the small sized treatment plan. Otherwise, the PSV_{medium} was evaluated and if the bladder was covered by this volume, the medium sized plan was selected. If neither of these two PSVs covered the bladder, the large sized treatment plan was chosen. In very few occasions, the bladder was not covered by the PTV_{large} and in a clinical setting the patient would have been asked to empty the bladder before a new CBCT acquisition was performed.

The above procedure was simulated for both ART strategies using the online bony anatomy match overlaying the PSVs on the CBCT. For each patient and ART strategy, the weighted average of the volume of the PTV used throughout the course of ART was calculated (referred to as the course-average PTV) and the ratio of this volume relative to the non-adaptive PTV was calculated.

We also performed a further comparison of the two planning strategies, assessing the bladder delineated on weekly CBCTs of all patients. The Dice index [18] as well as the false positive ratio (i.e., ratio of volume covered by the PSV and not the bladder relative to the bladder volume) between the bladder and the selected PSV were calculated.

Statistics and analysis

To assess whether the sample of 30 deformation vectors was normally distributed, a Shapiro–Wilk test was used on each voxel inside the non-adaptive PTV for each patient; this analysis was performed in MATLAB (version R2011a, The Mathworks, Inc., Natick, MA, USA) [19]. The DVFs were derived following the same procedure as for the four CBCTs used in the plan creation process, using SmartAdapt to perform a rigid registration on pelvic bony anatomy followed by an intensity-based DIR.

A Wilcoxon-signed rank test was used to test for a difference in volume ratio between the two plan selection strategies for all patients and then within the two patient groups. This analysis was performed using the STATA statistical software package (Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

Overall, the PSVs resulting from the Clin-ART strategy was found to have a larger degree of spatial irregularity than the PSVs resulting from the DVF-based approach. An example of the three PSVs for the two strategies for one of the patients is shown in the Supplementary material.

The DVF-based strategy had generally smaller PTVs, in particular for the large size PTV (Fig. 1). In patient group A (that were actually treated with non-adaptive RT) there were fractions where the bladder extended outside even the largest PSV for either of the strategies (Fig. 2). In the patient group B there were very few fractions not covered by the PSVs. The patient where this occurred most often (four times, patient 8B) had a diverticulum (of 1.5–2 cm size) in the posterior part of the bladder.

Both ART strategies resulted in a considerable reduction in the course-averaged PTV. However, the DVF-based strategy performed better than Clin-ART for all but one patient, with a larger reduction in the ratios of the course-averaged PTV for ART relative to non-ART (VR) (Fig. 3). The overall mean VR was 0.73 for Clin-ART and