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Organ motion in gynecological RT

Impact of organ shape variations on margin concepts for cervix cancer ART

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ABSTRACT

Background and purpose: Target and organ movement motivate adaptive radiotherapy for cervix cancer patients. We investigated the dosimetric impact of margin concepts with different levels of complexity on both organ at risk (OAR) sparing and PTV coverage.
Material and methods: Weekly CT and daily CBCT scans were delineated for 10 patients. The dosimetric impact of organ shape variations were evaluated for four (isotropic) margin concepts: two static PTVs (PTV_{6mm} and PTV_{15mm}), a PTV based on ITV of the planning CT and CBCTs of the first treatment week ($PTV_{ART\ ITV}$) and an adaptive PTV based on a library approach ($PTV_{ART\ Library}$).
Results: Using static concepts, OAR doses increased with large margins, while smaller margins compromised target coverage. ART PTVs resulted in comparable target coverage and better sparing of bladder (V40 Gy: 15% and 7% less), rectum (V40 Gy: 18 and 6 cc less) and bowel (V40 Gy: 106 and 15 cc less) compared to PTV_{15mm}. Target coverage evaluation showed that for elective fields a static 5 mm margin sufficed.
Conclusion: $PTV_{ART\ Library}$ achieved the best dosimetric results. However when weighing clinical benefit against workload, ITV margins based on repetitive movement evaluation during the first week also provide improvements over static margin concepts.

State-of-the-art radiotherapy of cervix cancer is based on combined external beam radiotherapy (EBRT) and brachytherapy, involving complex techniques and technologies in both steps [1], together with concomitant chemotherapy. For EBRT, intensity modulated radiotherapy (IMRT) with image guidance and reduced margins is increasingly being used to optimise organs-at-risk (OAR) sparing in order to decrease the risk of side effects (gastrointestinal, genitourinary or haematologic) [2,3]. Through the use of IMRT and VMAT, the high grade OAR complications (G3 and G2) decreased [2]. However, 60–70% of the patients still experienced early lower grade (G1–2) OAR side effects, of which 30% developed into late morbidity [4].

Despite significantly improved dose distributions, optimised OAR sparing and target coverage are impaired by the motion of target structures and surrounding OARs. Cervix tumour and uterus shapes and their topographic positions can change daily because of variations in bladder and rectum fillings [5–9].

To overcome the fact that the pelvic anatomy at the time of imaging for treatment planning is not necessarily representative throughout the whole EBRT course, adaptive radiotherapy (ART) might be a solution. Since automated on-line planning and delineation are not yet available, pre-planned off-line strategies are currently the best choice. Recent studies showed that plan library approaches based on pre-processed plans, which are selected according to the daily anatomy, can considerably reduce radiation induced complications to normal tissue while still maintaining target coverage [10–13]. For cervix cancer, those plan libraries rely on an empty and a full bladder scan to obtain the range of bladder volume changes and corresponding cervix-uterus motion. Through correlated motion between bladder and cervix-uterus, ITVs are defined [14]. This method requires multiple CT scans before treatment, subsequent image analysis and the creation of multiple treatment plans. Another possible approach can be obtaining motion information from CBCT scans acquired during the first week of treatment with reduced imaging burden to the patient and less pre-treatment planning time.

Most studies documented in the literature were concerned with the dosimetric evaluation of different ART strategies evaluated on off-line (weekly) MRI or CT scans [10,11,13,15] or limited CBCT data [16]. To the authors' knowledge, this is the first study investigating the plan library method described by Heijkoop et al. [14] for

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supine positioning. Furthermore we compared this method that requires sophisticated scanning and planning techniques to another strategy with reduced workload. The aim of this study was to evaluate the dosimetric impact on OAR sparing and PTV coverage using fixed and adaptive margin concepts with different levels of complexity and workload.

Material and methods

Ten cervix cancer patients were included in this institutional board (IBR) approved study (Table 1). All patients were treated with EBRT to a total dose of 45 Gy consisting of 1.8 Gy per fraction, 5 times/week and received concomitant chemotherapy (40 mg/m^2 cisplatinum weekly). Treatment planning was performed in supine position using the ProSTEP system (Elekta, Germany). The planning-CT scan (Siemens MultiSlice CT Somatom Plus 4 Volume Zoom, Germany) was performed with oral (Scannotrast) and intravenous contrast, a slice thickness of 4 mm, in-plane resolution 512 × 512 pixels and voxel size 0.98 × 0.98 × 4 mm^3. The same imaging protocol was used for weekly repeated CT-scans without oral and IV contrast. CBCTs were performed 3–5 times per week using the Elekta XVI™ system (Elekta, UK) with an optimised protocol (using M15 filter) to have a longitudinal scan length encompassing the pelvis region (26 cm). To minimise the amount of scatter radiation, we chose a transversal field of view of 41 × 41 cm^2, a bow-tie filter, 120 kV and 1040 mAs. Patients were asked to have a full bladder for the scans and treatments, but this was neither protocolled nor verified, resulting in a range of bladder fillings in the planning CT scan and during treatment. In total, 205 image data sets were analysed.

A single experienced radiation oncologist (PG, 10 years of experience) manually delineated all planning-CT, weekly CT and available CBCT-scans according to contouring guidelines [17]. The CTV-T represented the target CTV, which included the primary tumour, uterus, parametria and proximal third of the vagina in the cases of no vaginal involvement. In the cases of vaginal involvement, the CTV-T was contoured 2 cm below the distal tumour extension. The CTV-E represented the elective nodal region, which included relevant nodal draining groups (common, internal and external iliac, obturator and presacral lymph nodes).

The following OARs were considered: bladder from its base to the dome, rectum inferiorly starting from the anorectal junction and superiorly extending up to the beginning of the sigmoid at the rectosigmoid junction. Finally, the bowel bag was defined as the whole potential pelvic space of bowel with exclusion of the rectum, up to 2 cm above the cranial end of the clinically used PTV [18].

Table 1
Patient overview and characteristics.

	Maximum top of uterus motion (cm)	Notes	FIGO stage
P1	3	<200 ml difference bladder volume	IIIB
P2	5		IIB
P3	4	<200 ml difference bladder volume	IIB
P4	5	In week 4 uterus moved ventrally	IIB
P5	2–3	In 3 fractions uterus flipped backwards	IIIB
P6	7	Position uterus reversed with bladder volume, in one fraction, uterus moved dorsally	IIB
P7	3	In week 4 uterus moved dorsally	IIIB
P8	8		IIB
P9	3–4	In a few fractions uterus moved dorsally	IB
P10	2–3		IB

In this dataset, only one planning CT scan was available and no range of different bladder volume scans was made on the same day. Nevertheless, using the weekly CT scans with smallest and largest bladder volumes, which were available in the dataset, bladder filling-based cervix/uterus motion models could be constructed for all but one patient.

Empty and full organ structures (bladder and cervix-uterus) were registered using an in-house developed MATLAB program that was based on the continuous point drift code package (CPD2) [19] to obtain the range of bladder motion. Through correlated motion with the cervix-uterus, the position of the cervix-uterus for a half–full bladder was determined.

We determined volume changes of all organs using CBCT information over time in relation to the planning scans and the weekly CT-scans. This allowed us to estimate how representative the plan was compared to those made during the treatment, including target volume changes over time.

To assess the appropriateness of PTV concepts for different levels of adaptation, the dosimetric impact of the actual organ positions measured with the CBCTs was calculated for different dose distributions based on:

a. PTV_{6mm}: CTV-T from the planning CT scan with the clinically used margin of 5 or 6 mm.
b. PTV_{15mm}: CTV-T from the planning CT scan with a 15 mm margin.
c. $PTV_{ART\ ITV}$: a static PTV based on an ITV of the planning CT and all CBCT scans from the first treatment week with a 5 mm margin. To exclude the CBCT scans used to generate the model, for dosimetric evaluation, the dosimetric parameters for first week of treatment were set equal to PTV_{15mm}.
d. $PTV_{ART\ Library}$: two PTVs based on a two-stage plan library approach [14] that consists of an empty–half full bladder ITV and a half full–full bladder ITV, both with a 5 mm margin. Plan selection was based on the position of the uterus in the CBCT scans within the 95% isodose line of one of the two dose distributions. In a case where the bladder was small, but the uterus still fitted within the 95% isodose of the half–full–full plan, that plan was chosen above the half–full–empty plan because of a more favourable dose distribution for bladder.

The elective volumes (CTV-E) were not adapted and stayed constant for all scenarios. For all above-mentioned PTVs, a union was made with PTV-E (=CTV-E with 5 mm margin), resulting in PTV_{45Gy}.

For one patient with lymphocells, a new CTV-E was created at week 4 when the volume remained constant.

Treatment planning was done in Monaco® (Elekta, version 3.3). The same planning template was used for all plans. Fine-tuning was performed only if one of the planning constraints could not be met. For all plans and CBCTs, the coverage of the CVT-T and CVT-E for 42.75 Gy (95% of the prescribed dose of 45 Gy) and 40 Gy (which is the lower limit for low risk uterus irradiation) was calculated. For the OARs, we calculated the relative volume receiving more than 30 Gy for bladder and the absolute volume receiving more than 40 Gy for rectum and bowel.

For the dosimetric evaluation, no deformable registration was used. All CBCT contours were projected rigidly to the planning CT scan using matching of the bony structures. Acceptable target coverage was reached if the volume receiving less than 42.75 Gy was less than 5%. for more than half of the fractions. Dose volume parameters could only be analysed for each fraction separately, as reliable volumetric non-rigid dose deformation algorithms were not available for these, sometimes very large, deformations. Summed DVH parameters are given to indicate differences

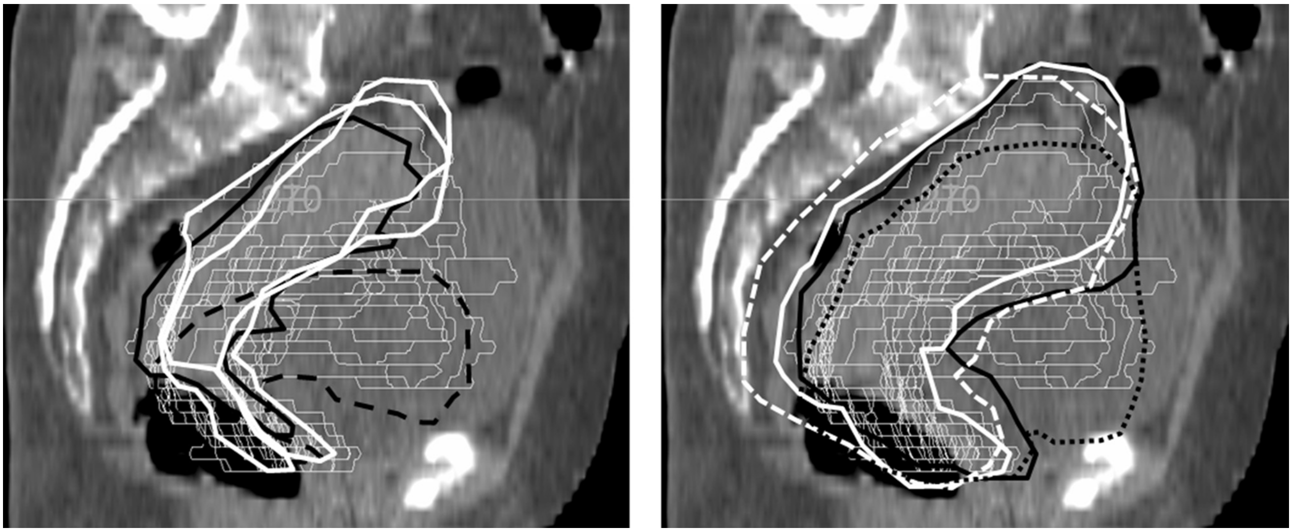

Fig. 1. Example of the different uterus positions and corresponding PTVs. Left panel: black solid line: full bladder target position, black dashed line: empty bladder target position, white: target positions in the first week of treatment, thin grey lines: CBCT uterus positions. Right panel: black solid line: half–full–full $PTV_{ART\ Library}$, black dotted line: half–full–empty $PTV_{ART\ Library}$, white dashed line: PTV_{15mm}, white solid line: $PTV_{ART\ ITV}$.

between the methods, although dose accumulation was unavailable.

Once a week, an extra CBCT scan was acquired after the radiotherapy fraction so that intra-fraction motion of the bony anatomy surrounding the pelvic organs could be assessed.

This dataset allowed us to confirm the 1D top of bladder/bladder volume model as proposed by Bondar et al. [20] and shows that this model is also applicable to data of other centres and for patients in supine position, even under the circumstances that the full and empty bladder scans are not made on the same day (See Supplementary material).

Results

In the studied patient group, the bladder filling and uterus position varied largely. Although the aim of this study was to quantify the dosimetric impact of organ motion on different approaches, the first part of the results contains also information about bladder volume changes that are specific for this patient group and their influence on the corresponding uterus positions. This knowledge is of importance for understanding the dosimetric outcome that is described later in this section (see Fig. 1).

For the bladder, both the average volume and the variation in volume decreased over treatment. The bladder volume in the planning-CT was never representative of the bladder volume during the treatment for three of the 10 patients; the volumes differed by more than 200 ml for all fractions. For four other patients, the bladder volume in the planning-CT was only representative for the actual bladder volume during a part of the treatment (less than 200 ml difference in 6–80 percent of the scans, depending on the patient).

The upper panel of Fig. 2 shows examples of the variation in bladder volumes and uterus positions for all patients. The patients are arranged in order of the difference of the bladder volume between the planning CT and the average during treatment. Uterus motion varied between 2.5 and 8 cm. In some cases, the pattern of bladder-uterus correlation changed during some stage of treatment (Table 1).

The dosimetric effect of organ motion on the different PTV concepts is shown in the lower panels of Fig. 2. In general, the plans with the clinically applied margin resulted in less target coverage for the CTV-T compared to the other plans, indicating that this small margin, without the incorporation of any motion estimate, was not feasible. A margin of 15 mm resulted in better coverage for almost all patients at the cost of increased doses to rectum, bladder and bowel. Both the ART PTVs resulted in acceptable target coverage and better sparing of bladder (V40 Gy: 15% and 7% less), rectum (V40 Gy: 18 cc and 6 cc less) and bowel (V40 Gy: 106 and 15 cc less) compared to PTV_{15mm} for $PTV_{ART\ Library}$ and $PTV_{ART\ ITV}$, respectively. In general, the ART concept resulted in the lowest doses to both rectum and bowel.

For patient 6, with pronounced uterus motion, the variation in bladder volume in the CT scans was not large enough to construct an ART model. For patient 8, whose uterus position varied largely during the treatment, $PTV_{ART\ Library}$ resulted in a higher dose to the bladder compared to PTV_{15mm} and $PTV_{ART\ ITV}$. However, for those two PTV concepts, target coverage was insufficient.

For the eight patients (P1, 3, 5–19) that had normally sized lymph nodes, the volume of the elective nodal region outside the PTV_{45Gy} was smaller than 2% in 83% of all fractions; and for 96% of the fractions, the exceeding volume stayed below 3%. Dosimetrically, the effect of residual lymph node motion was even smaller (Fig. 3) with the volume receiving less than 42.75 Gy staying below 3% for all fractions and below 1% for 80% of the fractions.

Patient 4 had surgical staging of lymph nodes and had lymphoceles after that. At the beginning of radiotherapy she had drains bilaterally and therefore the volume of CTV-E was small. Then the volume increased during the first part of the treatment and remained constant after that. The average volume outside the 5 mm PTV based on the planning-CT was 14.3 ± 0.6% for the CBCTs of week 4–6, (the time period in which the nodal volume was constant), resulting in 8% of the volume receiving less than 42.75 Gy and 6% receiving less than 40 Gy. When at week 4 a new PTV-E would have been constructed, the volume outside the PTV_{45Gy} would have dropped to 1.5 ± 0.5% which would have ensured good dosimetric coverage. For this patient, with a top of uterus motion of 5 cm and who had a large decrease in bladder volume throughout the treatment, the dosimetric effect of the motion was smaller than expected because of considerable overlap between PTV-E and PTV-T resulting in less steep dose gradients in the direction of the motion.

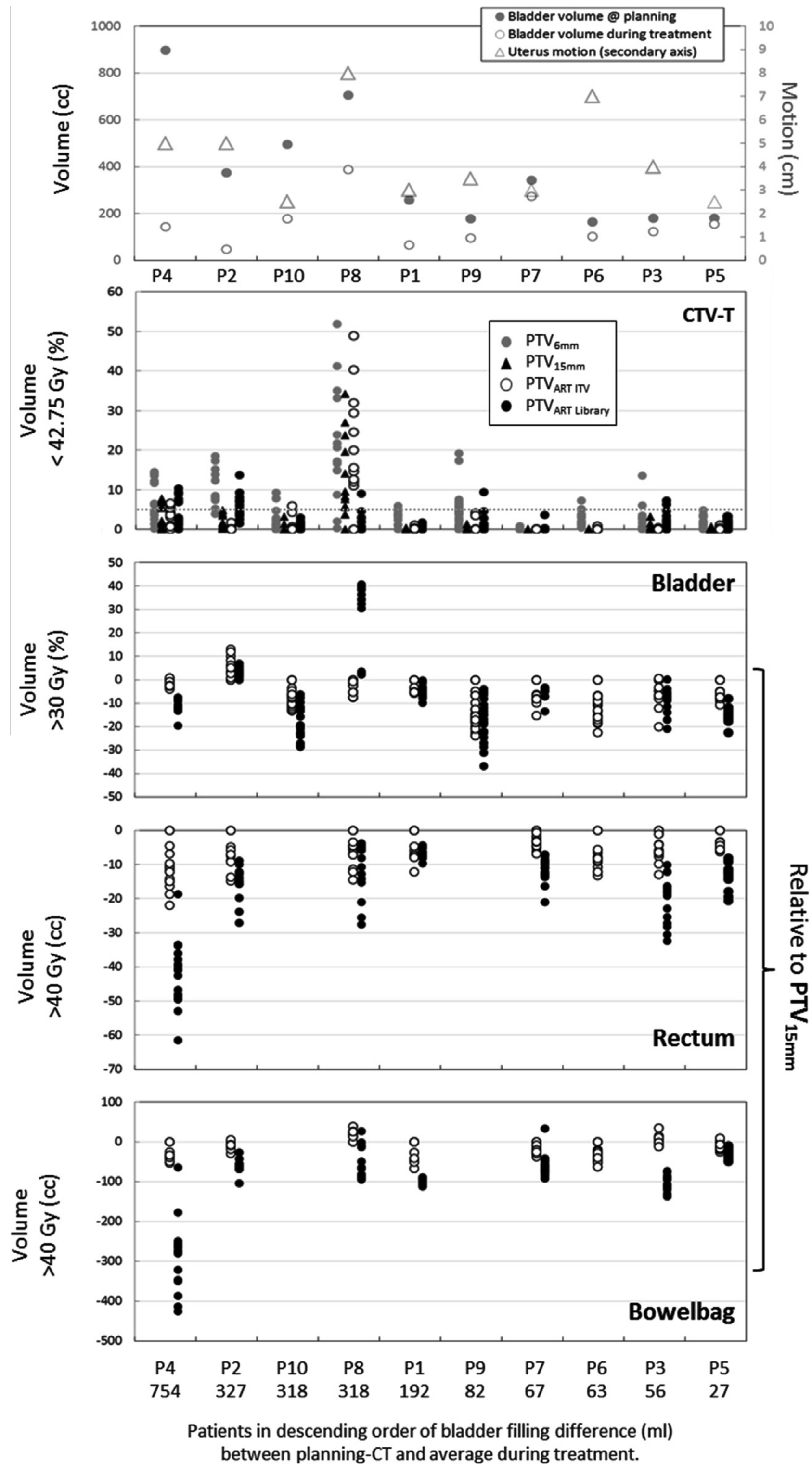

Fig. 2. Geometrical data (top graph) and dose–volume parameters for different PTV concepts for CTV, bladder, rectum and bowel volumes calculated for all CBCTs (lower panels). For the OARs the data is presented relative to PTV_{15mm}. The dosimetric data for the clinical plan was omitted because target coverage was not sufficient. Two-tailed paired t-tests (reference plan is PTV_{15mm}) showed that all differences in the graphs are statistically significant.

For Patient 2, the enlarged parts of the elective nodal region moved with variations in bladder volume causing a larger part to be systematically outside the PTV_{45Gy} (on average 2.7%, maximum 4.6%) resulting in 2% of the CTV-E receiving less than 42.75 Gy on average and 1% receiving less than 40 Gy (which could be quite a large volume in absolute terms depending on the CTV-E volume).

The intra-fraction motion of the bony anatomy surrounding the pelvic organs was Σ = 0.8 mm, 0.5 mm and 0.4 mm in LR, PA and SI

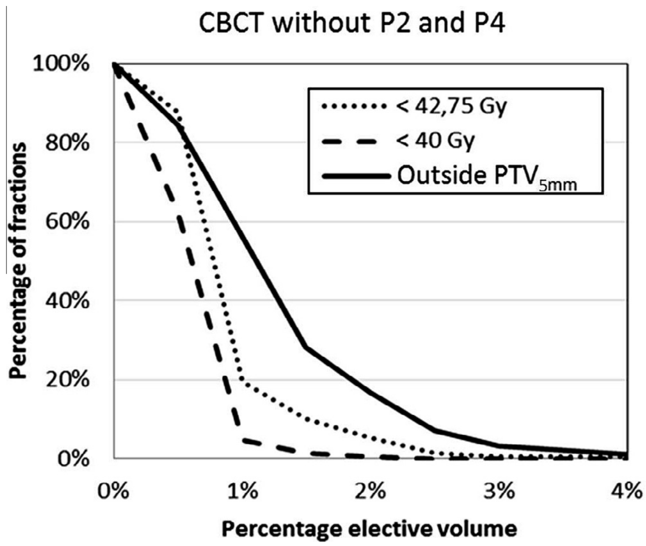

Fig. 3. Histogram of volume percentage of lymph nodes outside a 5 mm PTV and dosimetric results. Patients 2 and 4 were excluded due to enlarged lymph nodes.

directions, respectively and σ = 1.3 mm, 1.3 mm and 1.4 mm in LR, PA and SI respectively.

Discussion

An extensive dataset consisting of 205 CT- and CBCT-scans was manually contoured and analysed, showing organ shape and topography variations for 10 cervix cancer patients. This set enabled us to combine different aspects that play a role in ART; for example, how daily changing of patient anatomy can influence treatment quality for different degrees of plan adaptation.

Using a snapshot planning CT with 15 mm PTV margin resulted in better target coverage for almost all fractions at the cost of higher doses to OARs, especially for rectum and bowel.

Previous studies implemented and developed a sophisticated ART concept with a two stage library approach [14], correlating target position with bladder filling and the direction of the target motion using daily CBCT data for the treatment plan selection process [9]. Our data verified that this is indeed feasible, with the remark that model-predicted cervix-uterus shapes based on a set of planning-CTs can change in the course of therapy. In this case, re-planning based on CBCT scans, that gradually become available during the treatment, can improve the results. Therefore, daily CBCTs should not only be used for on-line plan selection at the linac, but should also be analysed after treatment to confirm the cervix-uterus prediction model or to verify that the magnitude of the uterus motion does not change throughout the treatment. The intra-fraction motion of the bony anatomy surrounding the pelvic organs was small and comparable to Heijkoop et al. [21]. This means that one can rely on the patient position during the fraction once the patient is adequately set-up.

For elective nodal regions without enlarged lymph nodes, the target coverage evaluation showed that a 5 mm PTV margin seemed to be sufficient with the dose-gradients that are characteristic for this treatment. This is in contrast to other studies [22,23], where somewhat larger variation was found in weekly MR/repeat CT scans. The impaired visibility of lymph nodes on CBCT-scans might be an explanation for this. On the other hand, the lymph node volumes in our dataset were delineated according to delineation guidelines with a large GTV to CTV margin to account for these uncertainties [17]. When a patient has enlarged lymph nodes that were found to be more mobile, contouring of a nodal GTV should be considered and consequently more frequent imaging and updating of the nodal PTV margins is recommended.

In conclusion, due to the daily random organ motion that is often present in cervix cancer patients, VMAT plans for PTVs based on a snapshot CT scan with fixed margins did not perform well in terms of primary target coverage. Two adaptive PTV scenario's: one simple ITV strategy (based on one week of CBCT imaging, requiring no extra imaging) versus a more complex and workload-intensive library approach (based on full and empty bladder scan), both perform better in terms of target coverage. Especially for the patients with large organ motion, the library strategy resulted in lower dose to the OARs.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.08.004.

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