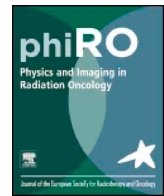




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Original Research Article

Robustness of elective lymph node target coverage with shrinking Planning Target Volume margins in external beam radiotherapy of locally advanced cervical cancer

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ABSTRACT

Background and purpose: Image-Guidance decreases set-up uncertainties, which may allow for Planning Target Volume (PTV) margins reduction. This study evaluates the robustness of the elective lymph node target coverage to translational and rotational set-up errors in combination with shrinking PTV margins and determines the gain for the Organs At Risk (OARs).

Material and methods: Ten cervix cancer patients who underwent external beam radiotherapy with 45 Gy/25Fx were analysed. Daily Image-Guidance was based on bony registration of Cone Beam CT (CBCT) to planning CT (pCT) and daily couch correction (translation and yaw). On each pCT, four Volumetric Modulated Arc Therapy dose-plans were generated with PTV margins of 0, 3, 5 and 8 mm. The elective clinical target volume (CTV-E) was propagated from daily CBCTs to the pCT to evaluate daily CTV-E dose. Additional systematic translational isocenter shifts of 2 mm were simulated. D98% (dose received by 98% of the volume of interest) and D99.9% were extracted from each CTV-E for all dose-plans and scenarios. Total dose was accumulated by Dose-Volume Histogram addition. The dosimetric impact of PTV margin reduction on the OARs was evaluated through V30Gy (volume included within the 30 Gy isodose), V40Gy and body V43Gy.

Results: When decreasing the PTV margin from 5 to 0 mm, bowel V30Gy was decreased by 13% (from 247 cm³ to 214 cm³), body V43Gy by 19% (from 1462 cm³ to 1188 cm³) and PTV by 39% (from 1416 to 870 cm³). The dosimetric impact of combined systematic shifts and residual rotations on the elective target with a 0 mm PTV margin was a decrease of D98% (mean ± SD) from 44.1 Gy ± 0.4 Gy to 43.7 Gy ± 0.8 Gy and a minimum of 42.4 Gy.

Conclusion: PTV margin reduction from 5 to 0 mm induced significant OARs dosimetric gains while elective target coverage remained robust to positioning uncertainties.

1. Introduction

External Beam Radiotherapy (EBRT) with concomitant chemotherapy and image-guided brachytherapy is standard treatment for locally advanced cervical cancer (LACC) patients [1]. The EBRT target includes tissue related to the primary tumour and the lymph nodes (LN). The nodal Clinical Target Volume (CTV) includes the draining nodal regions as well as metastatic LNs, which can be targeted with an additional boost. The primary tumour target related to cervix, vagina and uterus is highly mobile while the LN target is subject to less internal movement and deformation because of its relation to the bony structure. In order to secure the dose coverage of CTVs against set-up and

patient positioning uncertainties, safety margins are applied to arrive at an expanded volume called the Planning Target Volume (PTV) [2,3].

Since the introduction of modern EBRT techniques such as Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), the conformity of the dose distribution to the target has significantly improved [4–6]. With increased conformality, the target position across treatment fractions is more crucial. Image-Guided Radiotherapy (IGRT) reduces set-up uncertainties and has potential to allow for PTV margin reduction. Reducing the volume of healthy tissue irradiated is of major importance as the adverse side effects for the patients are related to dose and irradiated volume [7–10].

For LACC patients, image guided patient set-up is based on bony

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anatomy in order to align the elective lymph node target. In many centers, Cone Beam CT (CBCT) is used with the advantage of providing soft tissue contrast which can be used to evaluate the coverage of the primary tumour target [11–13]. The improvement in accuracy caused by IGRT use has been demonstrated in several studies [14,15]. However, even after IGRT, residual set-up errors may still be present. This is the case for instance when the rotations of the anatomy cannot be compensated by the degrees of freedom of the couch. Furthermore, systematic or random translational set-up uncertainties will be present due to mismatch between CBCT isocenter and gantry isocenter, Multi Leaf Collimator misalignment, as well as couch misalignment during couch correction. The magnitude of residual errors still present after IGRT use has been quantified for patients with pelvic tumors [16–18]. These studies reported on geometrical mismatches and not dosimetric consequences of these. As delivered dose is a primary endpoint of radiotherapy, the translation of geometric uncertainties into dosimetric uncertainties is crucial to understand implications of margin reduction as well as robustness of treatment delivery.

The purpose of this study was to evaluate, after CBCT-IG, the dosimetric impact of residual rotations as well as translational set-up errors in combination with shrinking PTV margins on the elective LN target and to evaluate the magnitude of dose reductions to Organs At Risk (OARs) with shrinking margins.

2. Materials and methods

2.1. Materials and target delineations:

Eleven consecutive patients with LACC without para-aortic irradiation were reviewed for this study. The patients were treated from 12-2015 until 06-2016. One patient with a metal hip was excluded leaving ten patients for analysis.

The CTV-High-Risk (CTV-HR) was composed of the Gross Tumor Volume (GTV-T) and the remaining cervix. Together with the entire uterus, the parametria, and 2 cm of the upper vagina, it formed the CTV-Low-Risk (CTV-LR) [19,20]. The ITV-T included the CTV-HR and CTV-LR with an individualised margin added accounting for internal motion. The elective nodal target volume (CTV-E) was delineated following the relevant vessels with a margin of 7 mm as a starting point and excluding bone and uninvolved muscle/fascia (detailed explanations can be found in the EMBRACE II protocol for all lymph node regions [19]). The pelvic LN regions included parametrial, internal iliac, external iliac, presacral and iliaca communis. The cranial limit of the CTV-E was located at the aortic bifurcation in all the analysed patients. CTV-E also included metastatic nodes when present (CTV-N). ITV-45 was formed by the fusion of ITV-T and CTV-E.

2.2. Dose-planning and Image-Guidance procedure:

The planning aim dose and fractionation schedule for the ITV-45 was 45 Gy in 25 fractions. Two patients had two metastatic LNs at diagnosis that were targeted with 55 Gy with simultaneous integrated boost.

Patients were positioned in supine position using knee fixation. One treatment planning scan (pCT) was acquired, as well as CBCT for daily IGRT at each fraction delivery. The CBCT images were used to apply couch corrections according to bony fusion with the three translational directions and yaw (rotation around the antero-posterior axis) while pitch and roll were not compensated for. Pitch is the rotation around the right-left axis and roll around the cranio-caudal axis (Appendix 1, Fig. 1). The radiation technologists assessed residual deviations between pCT and CBCT bony anatomy in the cranial part of the CBCT. If deviations would exceed 5 mm after couch shift, the patient was repositioned and a new CBCT was acquired. The number of fractions that required repositioning was counted for each patient.

Rectum, bladder, sigmoid, and outer contour of bowel were

delineated according to the EMBRACE-II protocol [19]. In addition, sacrum was contoured. Dose-planning and image registrations were performed using the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). Four 3-arc VMAT dose-plans, complying with the EMBRACE-II constraints [19], were created per patient on the pCT-scans with variable ITV45-to-PTV-45 margins: 0, 3, 5 and 8 mm. The ITV-45 which includes CTV-E had to be entirely covered by $\geq 95\%$ of the dose (42.8 Gy). The PTV had a “relaxed” coverage criterion, which allowed up to 5% of its volume to receive $\leq 95\%$ of the dose ($V95\% > 95\%$) making a collapse of the 95% isodose into the PTV possible.

2.3. Simulation and evaluation of set-up uncertainties

The dosimetric impact of daily positioning uncertainties (pitch and roll) alone and combined with systematic translational shifts was evaluated. As daily CBCT-IG corrected for three translational directions and yaw, patient positioning uncertainties were assumed to include only residual roll and pitch. Additional systematic translational shifts were imposed to represent uncertainties related to linac, couch and imaging system.

Residual rotations were determined through two steps of registration. First, the CTV-E contour on the pCT was propagated to the CBCT images to match with the daily corresponding anatomy (Fig. 1). For this step, a 6-degrees-of-freedom registration was performed based on bony fusion between the pCT and each CBCT. Parts of the CTV-E outside the CBCT Field of View (FOV) were not cropped. The CTV-E is not perfectly rigid and there may be local deviations in the CTV-E contours after the 6-degrees-of-freedom registrations. If the 6-degrees-of-freedom registration did not lead to satisfying results (local deviations of > 2 mm), manual adaptation of the CTV-E structure was performed. Once the CTV-E was transferred to the CBCT, a second registration was performed to transfer it back to the pCT, but this time, according to the daily “online CBCT-pCT match” which defines the couch correction imposed during each treatment fraction. This second fusion re-achieves the in-room patient position (Fig. 1). In this way, 25 CTV-E contours were propagated to the pCT representing the daily positions of the CTV-E.

Additionally, systematic geometric set-up uncertainties were simulated through isocenter shifts on the pCT and combined with residual rotations. Systematic isocenter shifts of 2 mm were performed on pCT in six directions with the 0 mm margin dose-plan: right, left, cranial, caudal, anterior and posterior in order to represent uncertainties related to linac, couch and imaging system. In our institution, a tolerance of ≤ 1 mm is used for alignment of CBCT isocenter and gantry isocenter as well as couch correction. Therefore 2 mm is a conservative estimate of deviations. The dose was recalculated after each shift was performed. The dosimetric impact of translational shifts in the 0 mm PTV margin scenario is a “worst case” as the impact of translational shifts will be smaller for PTV margins > 0 mm. Therefore, translational shifts were only simulated in the 0 mm PTV margin scenario.

The dosimetric impact on the CTV-E of residual rotations alone and of residual rotations combined with systematic shifts was evaluated by extracting D98% (dose received by 98% of the volume of interest) and D99.9% for each fraction in the described scenarios. Fractional Dose-Volume Histogram (DVH) parameters were added across all fractions to estimate accumulated dose. “DVH addition” can be considered a worst-case scenario for dose accumulation as it tends to under/over estimate the delivered dose in low/high dose regions [21]. Dose calculation was performed on the pCT anatomy, and changes in anatomy such as weight loss, tumour shrinkage or organ filling were not taken into account.

2.4. Evaluation of dosimetric impact of PTV margin

For all dose-plans, V30Gy (volume of the organ within the 30 Gy isodose) and V40Gy were extracted for rectum, bladder and bowel on

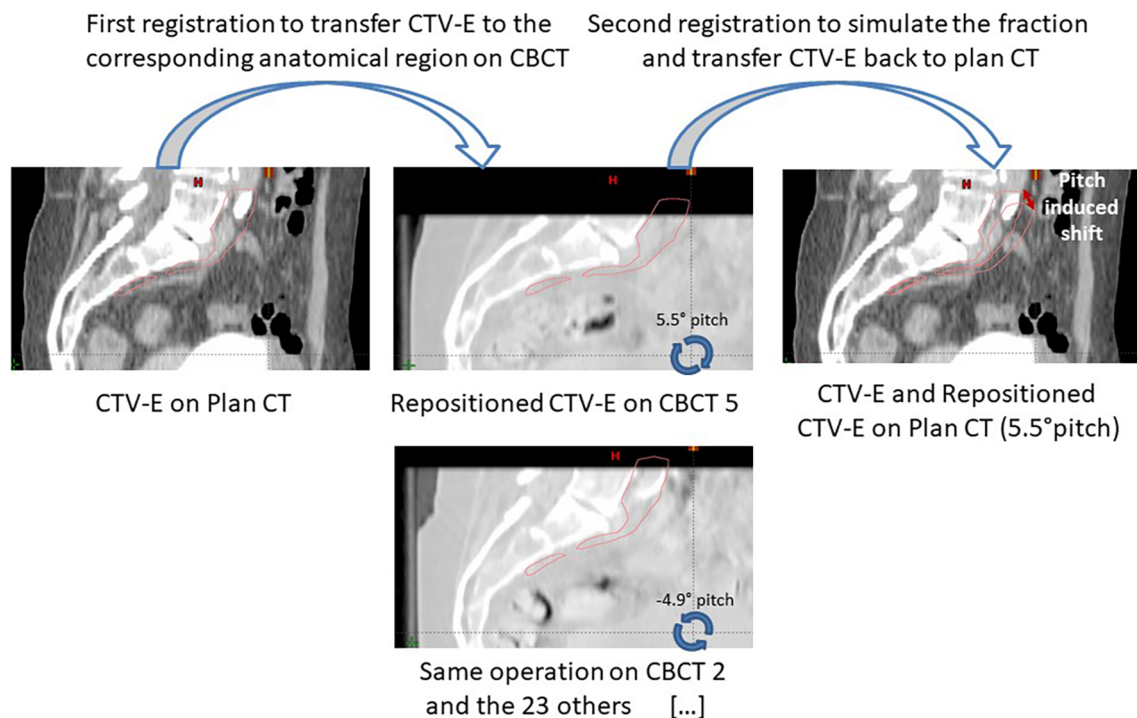


Fig. 1. Diagram illustrating the registration steps performed to propagate the CTV-E of each treatment fraction to the pCT (taking into account residual rotations).

pCT. D50% was extracted for os sacrum. Body V43Gy was extracted to assess the overall treated volume. To compare OAR DVH parameters for margins ≥ 3 mm to the 0 mm scenario, paired t-tests were used and p-values < 0.05 were considered statistically significant. Prior to using t-tests, normality of the distributions was evaluated and confirmed by Shapiro-Wilk tests and a threshold p-value of 0.05.

2.5. Evaluation of residual rotations

The average of the absolute yaw, pitch and roll of the 6-degrees-of-freedom registrations was calculated per patient. The pitch (θ) and the distance (R) between the isocenter and the anterior-cranial edge of CTV-E were used to calculate the pitch induced shift (d) in this region (illustrated in Fig. 1) using the formula: $d = R \cdot \tan(\theta)$. The shifts were calculated for all fractions, their absolute values evaluated and averaged per patient.

The correlation between absolute average pitch, roll and accumulated D99.9% was tested for each margin using Pearson correlation. Pitch induced shifts were also correlated to D99.9% using the same statistical test. P-values < 0.05 were considered statistically significant.

The anatomical location of the CTV-Es outside the 95% isodose due to residual rotations was visually evaluated on pCT by a physicist.

3. Results

The planned PTV and OARs dose-volume parameters as well as their significance level in margins ≥ 3 mm differing from the 0 mm margin are reported in table 1. When decreasing the PTV margin from 5 to 0 mm, average bowel V30Gy was decreased by 13% from 247 (± 63) cm^3 to 214 (± 56) cm^3 , body V43Gy by 19% from 1462 (± 262) cm^3 to 1188 (± 235) cm^3 and PTV volume by 39% from 1416 (± 217) cm^3 to 870 (± 166) cm^3 . V40Gy was decreased by 6% from 52% ($\pm 14\%$) to 49% ($\pm 13\%$) for bladder, 17% from 60% ($\pm 12\%$) to 50% ($\pm 7\%$) for rectum and 18% for bowel from 91 (± 49) cm^3 to 75 (± 45) cm^3 .

The 6-degree rigid registration between pCT and CBCT fractions was with local deviations of ≤ 1 mm in 88% of registrations. For one patient, given the fact that the CTV-E region is not perfectly rigid,

mismatches of 1–2 mm occurred during six fractions in the region of L4-L5 vertebra. One patient with CTV-E cranial border at the top of L4, had mismatch of 1–2 mm in 21 fractions and 3–4 mm in three fractions in the region of L4-L5 vertebra. For the three fractions with mismatches of 3–4 mm, the CTV-E contours transferred to CBCTs were manually adapted using the delineations tools available in the Treatment Planning System.

CTV-E coverage increased with PTV margin increase. With only residual rotations considered and PTV margin of 0 mm, the most degraded accumulated D99.9% dropped from 43.4 Gy to 39.2 Gy (90% of the planned dose) and D98% from 44.1 Gy to 43.5 Gy (99% of planned dose) as shown in Fig. 2.

On average, 2.3 fractions per patient necessitated the use of the repositioning strategy. While, for two patients this strategy was not employed, the highest number was reached for one patient with six fractions that necessitated a repositioning.

The CTV-E cranial border was located at L5 (2 patients), L4-L5 (6 patients), L4 (1 patient), and L3-L4 (1 patient). The distance from image isocenter to cranial-anterior edge of CTV-E ranged from 4 to 15 cm with an average of 10 cm. This distance is the lever that transforms pitch error into a pitch-induced shift. The average absolute pitch and roll per patient, ranged from 0.5° to 2.3° and 0.5° to 2°, respectively. Average pitch induced shifts per patient at the cranial anterior edge of CTV-E ranged from 1 to 4.3 mm. Fractional pitch induced shifts ranged from -7.8 to 7.7 mm. Average absolute pitch induced shift correlated with D99.9% degradation with all PTV margins in Pearson correlation as shown in Fig. 3 (p-values < 0.05).

When systematic 2 mm isocenter shifts were combined with residual rotational errors in 0 mm PTV margin plans, the accumulated D98% and D99.9% further decreased as shown in Fig. 4. Of the 60 scenarios (6 directions for 10 patients), all led to accumulated D98% $\geq 95\%$ (42.75 Gy) of prescription dose except from two scenarios, where D98% dropped to 42.5 Gy and 42.4 Gy with a caudal and a posterior isocenter shift, respectively, in two different patients. The overall D99.9% average was 40.7 ± 1.6 Gy and minimum 35 Gy.

The posterior isocenter shift, in the 0 mm PTV margin scenario, led to a mean \pm SD accumulated dose degradation by $0.9\% \pm 0.8\%$ for

Table 1

Average, standard deviation (SD) of volumes (OARs, PTV, V43Gy) of planning data and statistical significance level of the difference to 0 mm marked by * as well as planned doses (CTV-E D99.9%, D98%) for each dose-plan with specific PTV margin.

PTV margin	0 mm	3 mm	5 mm	8 mm
PTV volume (cm ³)	870 ± 166	1207 ± 193 *	1416 ± 217 *	1740 ± 250 *
V43Gy (cm ³)	1188 ± 235	1269 ± 195 *	1462 ± 262 *	1788 ± 271 *
D99.9% (Gy)	43.4 ± 0.2	43.7 ± 0.3	44.3 ± 0.2	44.5 ± 0.4
D98% (Gy)	44.2 ± 0.4	44.7 ± 0.1	44.9 ± 0.1	44.9 ± 0.3
Bowel V30Gy (cm ³)	214 ± 56.3	224 ± 57.1	247 ± 63.3 *	303 ± 79.7 *
Bowel V40Gy (cm ³)	75.2 ± 45.2	81.9 ± 45.4 *	91.4 ± 49.1 *	133.7 ± 57.6 *
Bladder V30Gy (%)	73.5 ± 14.3	75.1 ± 14.3	74.5 ± 13.4	80.8 ± 12.8 *
Bladder V40Gy (%)	49.3 ± 13.3	51.0 ± 12.8	52.4 ± 14.1 *	59.2 ± 14.0 *
Rectum V30Gy (%)	76.9 ± 8.0	77.8 ± 7.9 *	81.4 ± 6.3 *	84.9 ± 6.3 *
Rectum V40Gy (%)	49.8 ± 7.1	54.2 ± 8.1 *	60.3 ± 12.4 *	71.0 ± 10.6 *
Sacrum D50% (Gy)	31.0 ± 1.4	31.8 ± 1.5 *	33.9 ± 2.4 *	37.5 ± 1.2 *

D98% and reached at worst 2.4% compared to accumulated dose without shift. For D99.9% the dose was degraded by $2.9\% \pm 1.23\%$ compared to accumulated dose without shift and reached at worst 4.9%.

For all patients, repeated dose degradations induced by residual rotations only occurred at the level of the promontorium or above, up to L4-L5 regions as depicted for one patient in Fig. 5.

4. Discussion

The PTV volume and the V43Gy volume were significantly reduced through margin reduction. In particular, V43Gy was reduced by 274 cm³ (19%) from 1462 to 1188 cm³ when the PTV margin was reduced from 5 to 0 mm. In general, the PTV volume was reduced by ~100 cm³ per mm of PTV margin reduction. The same trend was observed for V43Gy for margins ≥ 3 mm. A PTV margin decrease from 5 to 0 mm also induced considerable advantages for OARs, e.g. with reductions of V40Gy of 6–18% for bowel, bladder and rectum. For all patients and all margins, residual rotational errors did not decrease

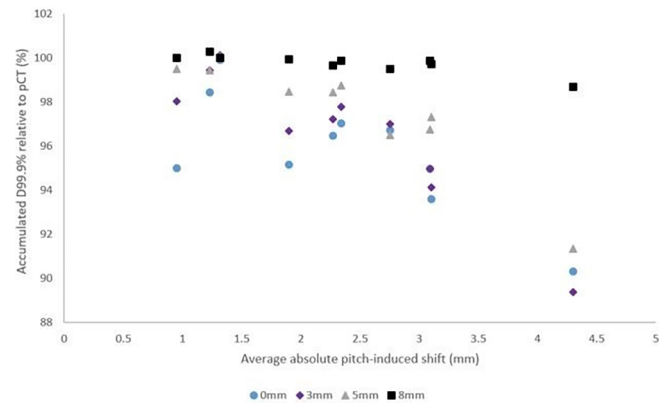


Fig. 3. Accumulated D99.9% dose degradation relative to planned dose (%) as a function of average absolute pitch induced shift (mm) for the four ITV-to-PTV margins.

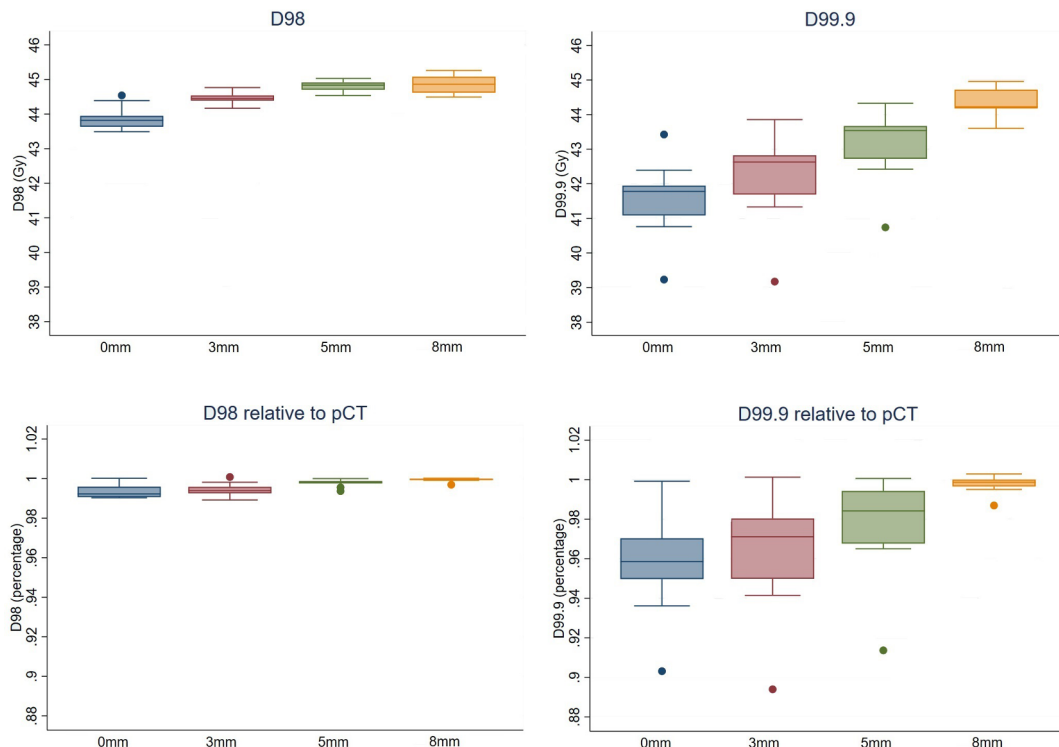


Fig. 2. Accumulated CTV-E D99.9% and D98% in absolute values (Gy) as well as relative to pCT (%). In these plots the impact of residual rotations, only, is displayed.

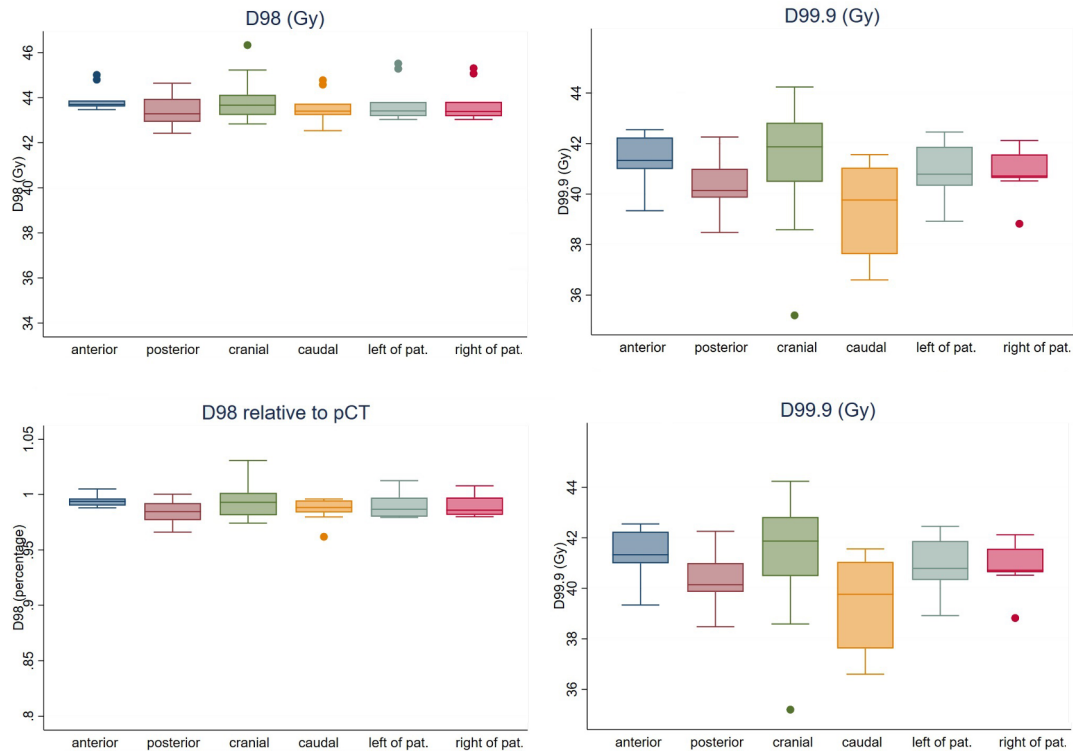


Fig. 4. Accumulated CTV-E D99.9 and D98% in absolute values (Gy) as well as relative to pCT (%). These plots display the dose degradation in the 0 mm PTV margin scenario with systematic isocenter shift combined with residual rotations.

D98% below 95% of prescribed dose. The dosimetric impact of combined systematic shifts and residual rotations on CTV-E D98% was also limited: D98% was below 95% of dose prescription in only two scenarios out of 60 and dropped at worst to 42.4 Gy.

The clinical implications of dose degradation in any target depend on the risk of disease failure in the given target and on the steepness of the dose-effect curve [22]. Nomden et al. reported that 6% of LACC patients had a nodal failure in the pelvis, 8% in the para-aortic region and 1.3% in the inguinal region. The risk of nodal failure decreased with increasing distance from the primary target as 41% of patients with nodal failure had a component in the external/internal iliac nodes whereas 27% had one in the common iliac region. Furthermore, Nomden et al reported that of the patients with nodal failure, 41% were

located outside the elective target (39% Para-aortic), 40% inside the elective target and 35% inside the nodal boost target. Similar findings were reported by Beadle et al [23]. The control of microscopic disease within the elective target is therefore high. Also, Nomden et al. reported that patients with pelvic nodes at diagnosis treated with para-aortic prophylactic treatment had less para-aortic nodal failures compared to those without para-aortic radiotherapy and this effect was even more pronounced for the subgroup of patients with positive common iliac nodes. Focus for improvement of nodal control through radiotherapy is therefore currently on risk adapted elective target selection with increased administration of para-aortic irradiation to avoid para-aortic failures, as well as intensification of the boosting of pathologic LNs [20].

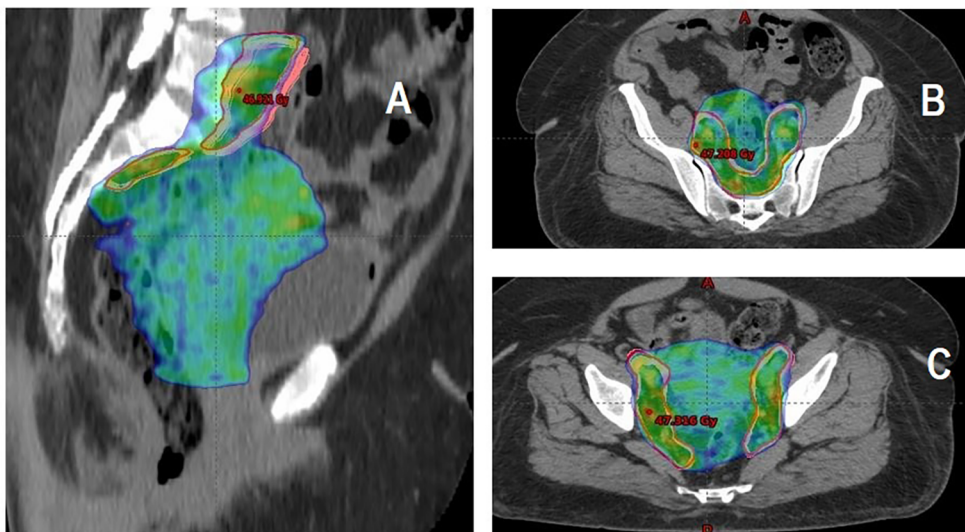


Fig. 5. Transverse (B, C) and sagittal (A) slices showing the 42.8 Gy (95%) isodose as well as the planning CTV-E structure (red) and 25 superimposed CTV-Es resulting from the residual rotation errors of the 25 fractions. Dose colour wash indicates doses between 42.8 Gy and 48.1 Gy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

This study demonstrated that the CTV-E “cold spot” below 95% of prescription dose was most often located at the cranial/anterior border in the common iliac region, which is the CTV-E region with least risk of nodal failure [24]. Furthermore, the dose-effect relationship for disease control in an elective target is likely to be shallow due to absence of GTV. Therefore, we hypothesise that a drop to a minimum of 42.4 Gy in 98% of the CTV-E and to 35 Gy at worst in 2% of the elective volume is not likely to cause an increased incidence of LN recurrences. As compared to the positional uncertainties analysed in this paper, inter-observer variations in delineations and the target selection uncertainties (definition of CTV-E upper border) are altogether of larger magnitude [25–27], of larger dosimetric consequence and with more significant clinical implications (failure outside the CTV-E).

Laursen et al. already investigated residual rotations in cervix patients and their results were comparable with the ones of this study in particular with regard to pitch induced shifts [17]. Shifts related to rotation have been reported to be larger (up to 15 mm) in prone patients positioned with a belly-board [28]. Residual rotational errors after translational couch corrections were found to be of $\Sigma = 5.1/5.5$ mm in the AP direction in the L4/L5 region in a study by Ahmad et al [16]. When using a 6-degrees-of-freedom couch, this error was reduced to $\Sigma = 2.7/2.2$ mm. For prostate patients, Kershaw et al. [18], found a maximum systematic or random translational error of 2 mm for the lymphatic regions with a 3-degree-of-freedom couch and 1 mm with a 6-degrees-of-freedom couch but did not evaluate the dosimetric consequences. Another study on prostate patients by Thörnqvist et al. with prostate IGRT, found that a 5 mm margin around the elective target was sufficient for 17/19 patients to reach D99 > 95% [29].

This study considered the dose degradation on the CTV-E, which is a structure relatively rigid as it is well related to bony anatomy. The primary target, is on the contrary subject to motion and in particular in between fractions [30]. Therefore it needs an appropriate ITV margin which might also be buffered by the current PTV margin standard. Monitoring of the primary target during radiotherapy, allows for individualised ITV margins [11]. By use of replanning or plan-selection strategies, target coverage of individuals with unanticipated motion can be ensured [12].

Moving from 3 to a 0 mm PTV margin decreased the PTV by 337 cm³ from 1207 to 870 cm³ and V43Gy by only 81 cm³ from 1269 to 1188 cm³. This may be explained by the combination of dose constraints to the ITV45 and PTV. The PTV coverage criterion allowed 5% of the PTV to receive $\leq 95\%$ of the dose. However, because ITV45 needs to be entirely covered by 95% of the dose, this advantage became limited with small or no margins. As it is not possible to achieve perfect conformality for the ITV-45 with 0 mm margin, regions with dose > 95% around the ITV-45 cannot be avoided leading to V43Gy increase.

This combination of constraints to the ITV45 and PTV is justified by the more likely presence of ITV45 in its planning position than towards

edges of PTV. The concept of integrating coverage probability into dose optimisation was introduced by Baum et al [31]. This approach was first clinically implemented for LN boosting in LACC by Ramlov et al [32] and later in the EMBRACE-II protocol [20]. Ramlov et al used a similar combination of dose constraints: > 100% to the nodal GTV and 90% at the edge of the nodal PTV [32]. Similar to our study, Ramlov et al found that dose de-escalation at the nodal PTV edges allowed for advantages for OARs and without compromising target coverage. Early clinical outcome of dose administration with lowered PTV edge dose for both elective and pathologic LN targets has been reported [20,33] and long term clinical outcome is currently being collected in the EMBRACE-II study.

The rigid propagation of CTV-E was verified visually to be anatomically acceptable in the vast majority of cases. However, anterior bending of L4-L5 caused uncertainties in CTV-E definition in this region for some patients (which were however corrected when > 2 mm). When applying a systematic 2 mm posterior isocenter shift with a 0 mm PTV, D98% and D99.9% were degraded by maximum 2.4% and 4.9%, respectively, compared to accumulated dose without shift. This indicates that the dosimetric impact of these uncertainties would be limited.

A limitation of our study was that some CTV-Es exceeded the CBCT cranio-caudal extension (16 cm) by a few centimeters (up to 2.7 cm). The anatomy present on CBCT was assumed to be representative of the motion of the missing parts. In addition, this study analysed only pelvic patients, and conclusions drawn in this study cannot be extended to patients with pelvic plus para-aortic irradiation. Also, 10 patients is a limited cohort, but considering that a repositioning strategy was applied if deviations > 5 mm, it is not expected that much wider deviations would occur if a larger population had been observed.

Considerable reductions in irradiated volumes, made possible by advanced radiotherapy technologies, have been gradually implemented in clinical practice over the last decade. The clinical outcome of such volume reductions has to be first evaluated as for example in EMBRACE-II with IMRT/VMAT and 5 mm PTV margins. Provided that the impact of reduced margins on the clinical outcome is not detrimental, further PTV margin reduction to e.g. 0 mm could be considered.

To conclude, PTV margin reduction induces considerable OAR dosimetric gains. Pelvic elective target coverage with daily CBCT-IG is robust to residual rotational uncertainties alone or when combined with 2 mm systematic shifts. CTV-E coverage is very robust to set-up uncertainties when PTV margins of 5 mm are applied and further margin reduction could be considered.

Declaration of Competing Interest

This study was supported by Varian Medical System through an unrestricted research grant.

Appendix 1

Fig. A1.

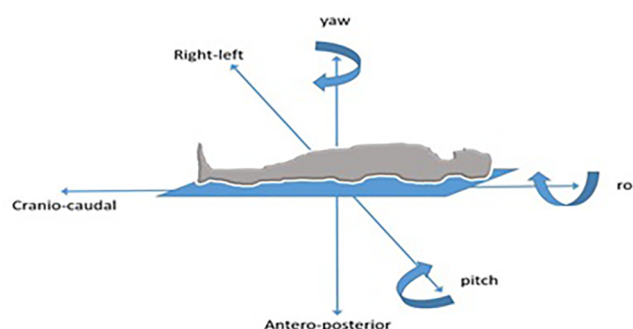


Fig. A1. Visual illustration of the angles pitch, yaw and roll for a patient lying on a couch.

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