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ORIGINAL ARTICLE

Reduction of PTV margins for elective pelvic lymph nodes in online adaptive radiotherapy of prostate cancer patients

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ABSTRACT

Background: Cone beam CT (CBCT) based online adaptive radiotherapy (oART) is a new development in radiotherapy. With oART, the requirements for planning target volume (PTV) margins differ from standard therapy because motion occurs during a session. In this study, we aim to evaluate a margin reduction for locally advanced prostate patients treated with oART.

Material and methods: Intrafraction motion of the elective pelvic lymph nodes was evaluated by two radiation therapists (RTTs) for 150 fractions from 10 prostate patients treated with oART. PTV margins of 3, 4 and 5 mm where added to these lymph nodes for all patients. The seven first patients were treated with 5 mm PTV margin, while the last three patients were treated with 4 mm margin. After treatment, the RTTs reviewed the verification CBCTs and evaluated whether the various PTV margins would have covered the adapted clinical target volume, scoring each fraction as approved, inconclusive or rejected. Couch shifts corresponding to the rigid prostate match between the CBCTs were analyzed with respect to the RTT evaluation.

Results: The RTTs approved a 4 mm margin in 95% of the fractions, while 2% of the fractions were rejected. For a 3 mm margin, 57% of the fractions were approved, while 5% were rejected. The scoring from the two RTTs was consistent; e.g., for 3 mm, one RTT approved 58% of the fractions, while the other approved 55%. If the couch was moved less than 2 mm in any direction, 70% of the fractions were approved for a 3 mm margin, compared to 32% for shifts greater than 2 mm.

Conclusion: It is safe to reduce the PTV margin from 5 to 4 mm for the elective pelvic lymph nodes for prostate patients treated with oART. Further margin reductions can be motivated for patients presenting little intrafraction motion.

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KEYWORDS
Margins; online adaptive; prostate cancer; pelvic lymph nodes; aRT

Introduction

For patients with high-risk prostate cancer with increased risk for lymph node metastases irradiation of the pelvic lymph nodes, in addition to the prostate and seminal vesicles, is a common practice to reduce the risk of loco-regional disease progression [1,2]. Elective lymph node irradiation recently led to both higher disease-free and higher distant metastasis-free survival at 5 years by the POP-RT trial [3]. This treatment may, however, increase the risk of bowel-related side effects [4]. Contributing to the risk of bowel toxicity is the independent motion of the prostate in relation to the pelvic lymph nodes, which need to be incorporated into the planning target volume (PTV) [5].

To circumvent the challenge of independent motion patterns of the treatment targets, we and others have explored different mitigation measures such as multileaf collimator tracking [6], sequential delivery of prostate boost to reduce systematic errors [7] and adaption through plan selection [8]. The recent introduction of MR linear accelerator (MR linac) and cone beam CT (CBCT) based adaptive system (Ethos^{TM}) offers new possibilities to daily adapt to the anatomical changes present between and even within treatment fractions and thereby reduce margins from the clinical target volume (CTV) to the PTV [9,10]. Furthermore, with online adaptive radiotherapy (oART), the requirements for margin expansion differ from standard therapy because contouring and organ shape changes are addressed at each fraction. The errors due to target delineation are therefore to a larger degree subject to random variation, instead of being solely systematic preparation errors as in conventional image-guided radiotherapy (IGRT).

While several different studies have already analyzed the necessary margins for the prostate during conventional and adaptive treatment, the necessary margins for the elective lymph nodes are not so well documented [11–15]. In this study, we aim to evaluate the consequences of reducing PTV margins of the pelvic lymph nodes for locally advanced prostate patients when treated with oART, compared to margins used in conventional IGRT.

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Material and methods

Patient material and treatment delivery

Ten patients with locally advanced prostate cancer treated with oART using Ethos™ in 2022–2023 at Haukeland University Hospital (HUH) were included in the study. This quality assurance project was approved by the Data Protection officials at HUH (https://eprotokoll.ihelse.net/home, eProtokollnr: 3982) and complied with Norwegian directives for processing personal data. All patients were treated in 25 fractions with differential prescription; 2.0 Gy/fx to the pelvic lymph nodes, 2.4 Gy/fx to the proximal 1.5–2.0 cm of seminal vesicles, 2.7 Gy/fx to the prostate, and if indicated 2.9 Gy/fx simultaneous integrated boost to the localized prostate tumor. Not all patients received all 25 fractions as oART and only fractions delivered with oART were analyzed in the study. More details on this and the fractionation is given in Table 1.

All CTVs were defined by senior oncologists in the planning CT. The pelvic lymph nodes CTV followed the RTOG prostate cancer lymph node delineation recommendation [16] and included the external iliac lymph nodes with lower limitation at the top of the femoral heads, the internal iliac lymph node, the obturator lymph nodes with lower limitation at top of the symphysis pubis, the presacral lymph nodes in the level of S1–S3 and the common iliac lymph nodes up to mid-L5. The first seven patients were treated with a PTV expansion of 5 mm around the pelvic lymph node CTV, equal to conventional IGRT routines, while the last three patients were treated with 4 mm PTV expansion, following updated adaptive routines at our institution.

Radiation therapists (RTTs) performed the treatment, with an oncologist present for the first 2–5 fractions. After this, oncologists reviewed the treatments weekly. For each oART session, an initial CBCT was first taken. Here, important organs for the co-registration (prostate, seminal vesicles, rectum and bladder) were delineated, and CTVs were subsequently generated based on a structure-guided deformable registration of the planning CT and the CBCT. The CTVs were reviewed and edited if necessary by the RTTs. An adaptive plan was then generated, and before treatment delivery, a second CBCT (verification CBCT) was acquired to verify patient anatomy and correct for possible intrafraction motion occurring when constructing the oART plan. A rigid soft-tissue prostate match was performed between this verification CBCT and the first CBCT (Figure 1(a)). If the verification CBCT violated the tolerance demand, i.e., the CTV was outside the

Table 1. Fractionation and treatment times for the included patients.

Patient	Fractionation PTVp/PTVp + sv/ PTVln [Gy/fraction]	PTVln margin [mm]	Number of adaptive fractions	Average (std) time between CBCT1 and CBCT2 [min]	Average (std) time between CBCT1 and completed delivery [min]
1	2.7*/ 2.4/ 2.0	5	25	15 (3)	22 (3)
2	2.7/ 2.4/ 2.0	5	25	19 (3)	24 (3)
3	2.7/ 2.4/ 2.0	5	18	17 (3)	22 (3)
4	2.7*/2.4/2.0	5	3	21 (2)	27 (2)**
5	2.7*/2.4/2.0***	5	17	19 (2)	25 (3)
6	2.7*/ 2.4/ 2.0	5	9	15 (2)	18 (2)
7	2.7*/ 2.4/ 2.0	5	25	15 (2)	20 (2)
8	2.7*/ 2.4/ 2.0	4	12	17 (3)	25 (3)**
9	2.7*/ 2.4/ 2.0	4	8	18 (4)	25 (4)
10	2.7*/ 2.4/ 2.0	4	8	16 (1)	24 (2)

Abbreviations. Standard deviation (std), prostate PTV (PTVp), prostate and seminal vesicles PTV (PTVp + sv), elective lymph nodes PTV (PTVln), first CBCT (CBCT1) and verification CBCT (CBCT2).
*Boost of 2.9 Gy/fraction to the localized prostate tumour.
**One fraction corrected for the time spent while the patient was releasing bowel gas.
***Boost of 2.4 Gy/fraction to malignant lymph node.

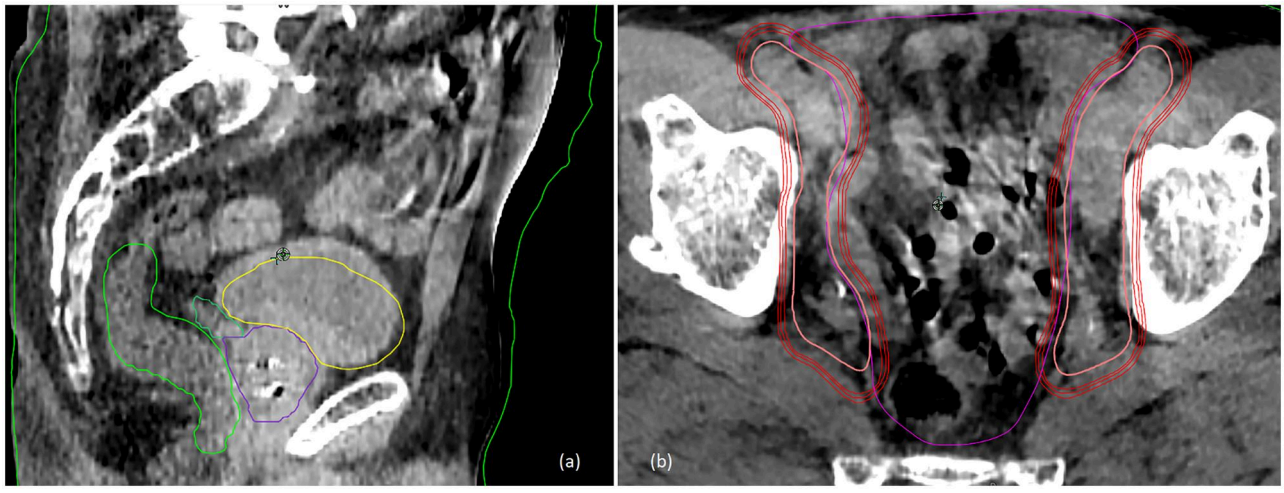

Figure 1. Illustration of the motion between the initial CBCT and the verification CBCT with organ delineations (bladder in yellow, rectum in light green, prostate in purple and seminal vesicles in dark green) from the initial CBCT overlaid on the verification CBCT (a), and of the PTV expansions of the pelvic lymph nodes with CTV in pink and PTV with 3, 4 and 5 mm margin in red (b).

PTV on the verification CBCT, the patient had to, e.g., release bowel gas, before a new verification CBCT was taken. If this solved the problem, the patient would be treated with the derived oART plan, else the patient would have to start the adaptive process from the beginning.

Post-treatment analysis

Margins for pelvic lymph nodes CTV were evaluated retrospectively on CBCT images. The intrafraction motion of the pelvic lymph nodes was estimated from the time points where the two CBCTs were acquired. In the following, when referring to a specific PTV, it is always the PTV of the elective lymph nodes. The pelvic lymph node CTV was expanded with 3, 4 and 5 mm isotropic PTV margins for the analysis (Figure 1(b)).

After treatment, the RTTs reviewed the verification CBCTs of all fractions and evaluated in every transversal slice whether a 3, 4 or 5 mm PTV margin covered the CTV. This was done independently by two RTTs for 150 fractions from the 10 prostate patients. Each fraction was scored as approved, inconclusive or rejected based on geometric evaluation of the CTV and the different PTV expansions, as given in Table 2. The criteria of the scoring were agreed upon by the interdisciplinary team performing oART before any scoring was made. The size and direction of couch shifts corresponding to the rigid match between the first and the second CBCT were then analyzed with respect to the RTT evaluation of each PTV margin. Finally, the time points of the first CBCT, the verification CBCT and the end of treatment were retrieved.

Dosimetric analysis

To evaluate the impact of margin reduction on dose to the bowel bag (defined by the RTOG contouring atlas [17]), treatment plans for three example patients (patients 2, 3 and 5 in Table 1) were created using respectively 0, 3, 4, 5 and 10 mm PTV margins. The dose to the bowel bag was analyzed for the mean dose and volume of the bowel bag that received more than 40 Gy (V_{40Gy}). In addition, for all patients, the mean dose and V_{40Gy} at planning were compared to the planned dose with oART. This was done to evaluate the consistency of bowel bag doses in the original plan on the planning CT as compared to that during treatment.

Table 2. Evaluation criteria for PTV margin evaluation.

Evaluation score	Criteria
Rejected	CTV not covered by PTV in >1 transversal slice
Inconclusive	CTV borderline to PTV in > 1 transversal slice and/or CTV not covered by PTV in 1 transversal slice
Approved	CTV in all transversal slices covered by PTV

Results

Margin analysis

The RTTs approved 98% and 95% of the fractions with 5 and 4 mm PTV margins, respectively (Figure 2). Only 2% of the fractions were rejected in both cases, and 9 of the 10 investigated patients had no fractions rejected. For a 4 mm margin, 93% of the fractions were approved by both RTTs and the RTTs rejected the same fractions (Figure 3). For a 3 mm margin, 57% of the fractions were approved, while 5% were rejected. Here, 39% of the fractions were deemed inconclusive (Figure 2). Six of the ten investigated patients had no fractions rejected. The scoring from the two RTTs was slightly less consistent for a 3 mm margin (Figure 3).

Couch shift analysis

The mean couch shift and the standard deviation were 0.11 ± 0.13 cm, 0.03 ± 0.11 cm and 0.04 ± 0.10 cm in the anterior, superior and right directions, respectively. In 65% of the fractions, the couch movement was less than 0.20 cm in any direction (Figure 3). If the couch was moved by less than 0.20 cm in any direction, a 3 mm margin was approved for 70% of the fractions (74% by RTT_1 and 64% by RTT_2), compared to 32% of the fractions (28% by RTT_1 and 36% by RTT_2) if the couch was moved more than 0.20 cm.

The average time between the first CBCT and the verification CBCT was 17 min, ranging from 11 to 37 min, while the time between the verification CBCT and the end of delivery was 5 min, ranging from 3 to 10 min. These times were

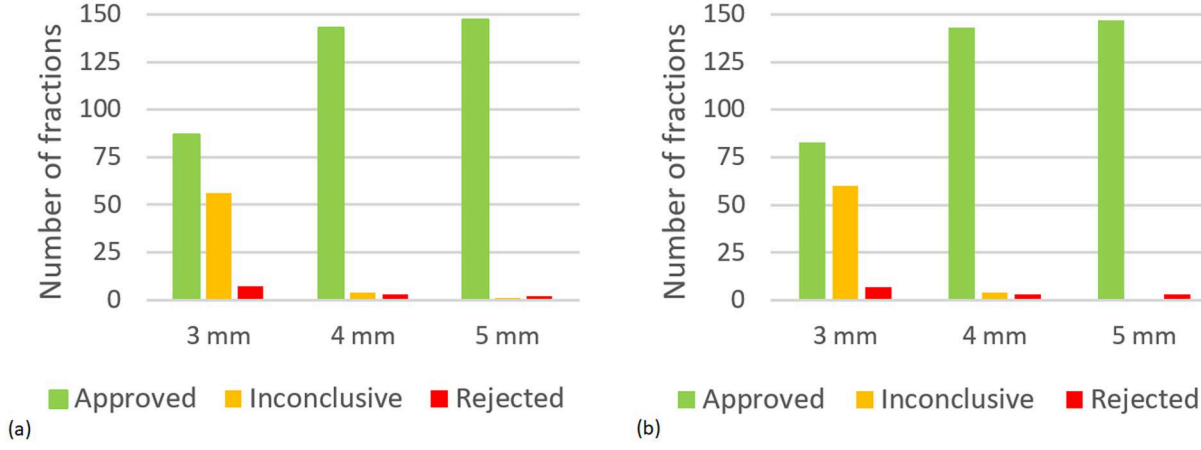

Figure 2. Scoring of fractions (colour-coded) with, respectively, 3, 4 and 5 mm PTV margin by RTT_1 (a) and RTT_2 (b).

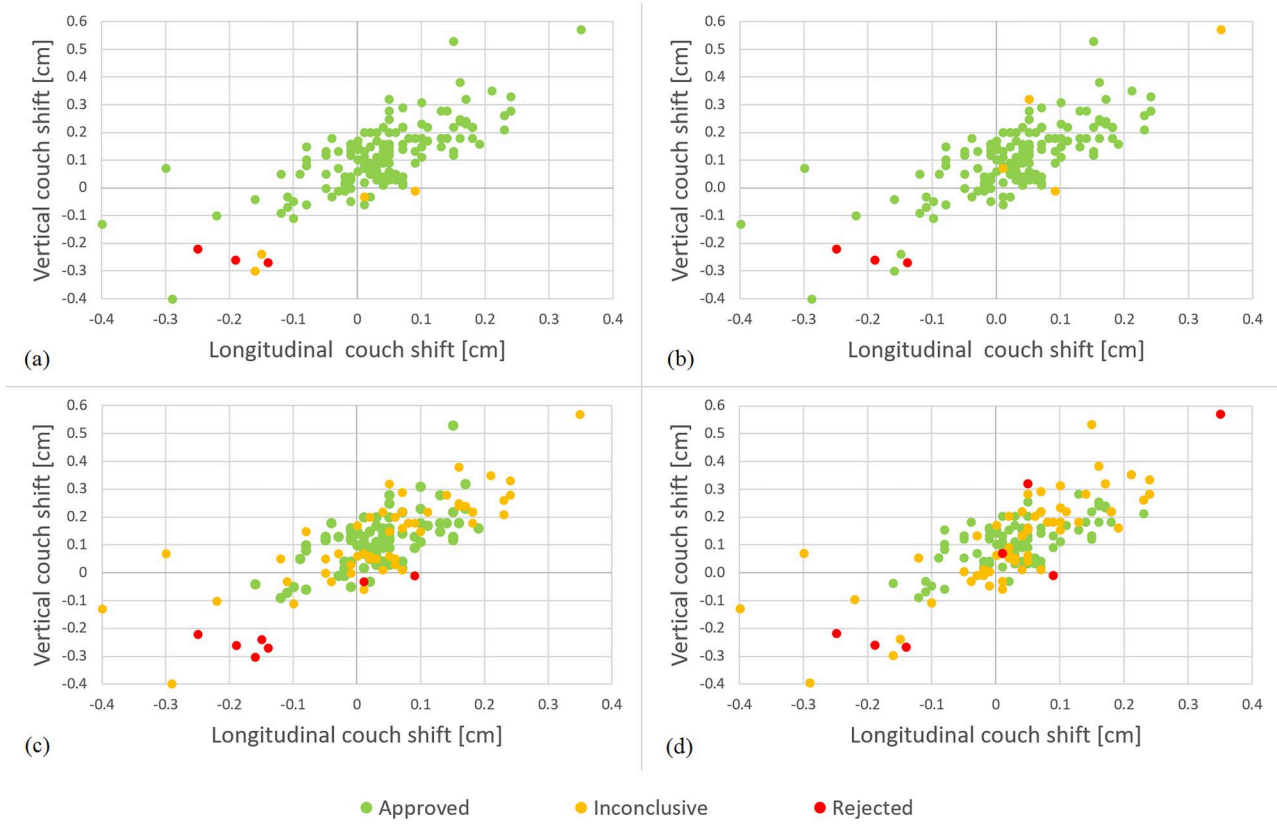

Figure 3. Couch movement between initial and verification CBCT represented by the prostate match in vertical and longitudinal directions for each scored fraction (colour-coded), displayed for the 4 mm margin with scoring by RTT_1 (a) and RTT_2 (b), and for 3 mm margin with scoring by RTT_1 (c) and RTT_2 (d).

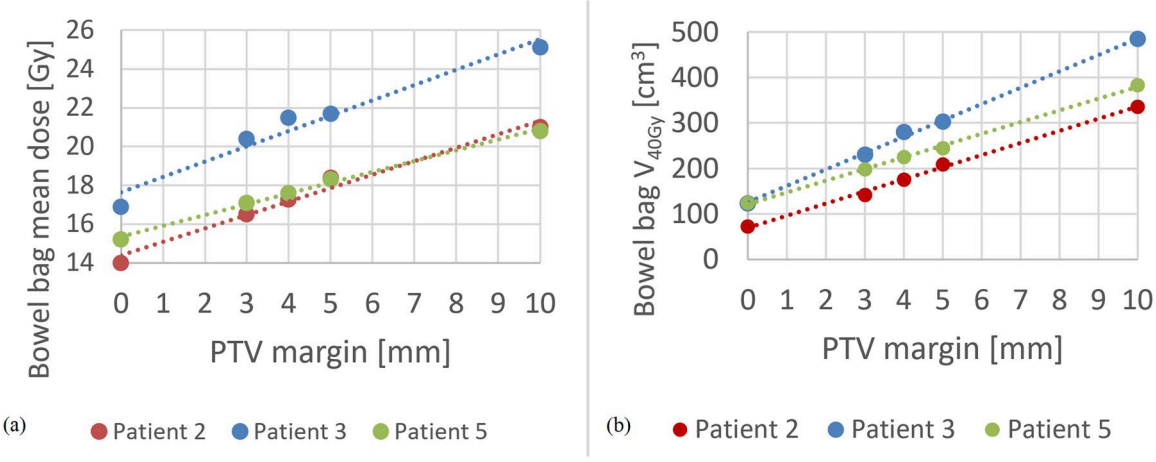

Figure 4. Mean dose to the bowel bag (a) and volume of bowel bag that receives more than 40 Gy (b) for three example patients planned with different margins for the pelvic lymph nodes. Patient numbers are according to Table 1.

similar for oART fractions delivered with a 4 and 5 mm margin. Details for each patient are given in Table 1.

Dosimetric consequences for the bowel bag

Both the mean dose and V_{40Gy} to the bowel bag were reduced when decreasing the PTV margins (Figure 4). The mean dose to the bowel bag was reduced with 0.6–0.8 Gy per millimeter PTV margin reduction, and the V_{40Gy} was reduced with 26–36 cm^3 per millimeter PTV margin reduction, according to the slopes of the linear fits of the data in Figure 4.

For the seven patients treated with oART using 5 mm margins, the difference between the original plan and the mean bowel dose with oART delivery was always less than 0.4 Gy whereas it was less than 0.3 Gy for patients treated with 4 mm margins.

Discussion

In this study, we evaluated the PTV margin for the elective lymph nodes for locally advanced prostate patients undergoing oART. Based on the results from the first seven

patients, a 4 mm margin expansion was implemented into our clinical oART routine. A further reduction to 3 mm needs more careful consideration. Although, six of the investigated patients had no fractions rejected with a 3 mm margin, a greater number of fractions were evaluated as inconclusive (Figure 3). We therefore analyzed if couch movement between the first and second CBCT could serve as an indication of the need to increase from a 3 mm margin expansion selectively to patients, but found no definitive answer.

Others investigating PTV margins for oART of prostate cancer have mainly focused on treatments without nodal involvement. Christiansen et al., however, also analyzed reduction of the nodal CTV, when treating adaptively with an MR linac [12]. They investigated a 2 mm expansion of the elective CTV in addition to reduced margins for the primary target and found satisfactory dose coverage as well as reduced dose to the bowel cavity as compared to their margins for conventional IGRT. For prostate with/without seminal vesicle involvement, oART has been found to safely enable PTV margin reductions around the prostate for the vast majority of the investigated patients without compromising target coverage [14,15,18]. Along with these studies on the prostate, our study for the pelvic lymph nodes, therefore, agrees that oART, as compared to conventional IGRT, can be used with smaller PTV margins since only intra-fractional movements of the prostate and the pelvic lymph nodes, respectively, need to be compensated for. Other aspects that should be incorporated into the margin may, however, not be reduced by oART.

Our evaluations were based on CBCTs taken prior to treatment. Intra-fraction motion occurs both during the oART planning phase and during dose delivery (beam-on). A limitation of the study is that we only have measured two time points, and not continuous tracking of the motion between these times. A comparison with a post-treatment CBCT would have had a better correspondence with the time of an entire treatment. However, the majority of the time the patient is lying on the couch between the two CBCTs before treatment (Table 1), and the main difference in couch shift is assumed to originate from the patient relaxing in the initial part of the fraction. This assumption is partly supported by data from Budiharto et al. who analyzed intrafraction motion for prostate cancer extending up to 10 min [11]. They found that during the first 2.5 min after online set-up, the margin needed to cover 95% of the motion was 6.1 mm, while after 5 min and 10 min, this margin was only increased further by 0.1 mm and 2.6 mm, respectively. The assumption has also been confirmed for breast cancer, where Svestad et al. showed that surface shift in the vertical direction for right-sided breast was mainly caused by a movement that occurred during the first minute after setup [19].

In addition to movement, there are uncertainties in target delineation. Lawton et al. investigated delineation of the pelvic lymph nodes using contouring performed by 11 radiation oncologists [20]. Delineation uncertainties were considerable, with at most moderate agreement between radiation oncologists. In part, the poor agreement resulted from disagreement of definitions on the extension of the pelvic lymph node CTV, leading to the development of consensus guidelines, e.g., [16, 21]. In our oART procedure, an oncologist is present only during the 2–5 first fractions of oART, when a consensus on target extensions and possible volumes of special interest is agreed upon for the specific patient. Thereafter specifically trained RTTs are responsible for editing CTVs with the oncologist available for calling and for weekly offline review of the oART fractions. With this procedure, we aim to limit delineation uncertainties resulting from differences in definitions of the elective target. Our choice of having RTTs evaluate CTV coverage in this study is therefore a reflection of our clinical procedure for the majority of the fractions using oART. A strength of our study is that we included evaluations from two RTTs in order to incorporate variation in the assessment of CTV coverage. The assessments showed a high degree of consistency. The RTTs together reviewed the six cases for a 3 mm margin where only one of them had rejected the fraction. They came to an agreement that four fractions should be classified as rejected and two fractions should be classified as inconclusive. This did not make any significant difference in the overall results. After this agreement, the resulting 5% rejection rate for the 3 mm margin was still unchanged for both RTTs.

The PTV margin should also consider the machine precision of the linear accelerator. The discrepancy between imaging isocenter and irradiation isocenter, inaccuracies in couch shifts, gantry angles and collimators could lead to both systematic and random errors [22–26]. In the commonly applied van Herk derivation of margins, the penumbra compensates for some of the uncertainties [26]. We based our analysis purely on geometric agreement between two sets of contours and not the van Herk method, since the latter is not considering shape changes of the target. In our study, a 4 mm or larger margin expansion was needed to fulfill our geometric criterion, i.e., the PTV should cover the CTV, in 90% of the fractions. When evaluating necessary margin expansions with the van Herk method, 90% of the patients should receive at least 95% of the prescribed dose of the CTV [26]. Ideally, the criteria for the geometric evaluation in Table 2 should be coupled to dosimetric consequences, but due to the limited patient data available and the different fractionations applied to the patients this was not feasible. Another alternative would be to evaluate dosimetric consequences directly using, e.g., 95%-isodose lines in respect to the CTV. Dosimetric information on the verification CBCT is, however, not accessible on the Ethos-system unless the verification CBCT is used as input to a second adaption. Although not as informative as a dosimetric analysis, our criterion is closer to clinical oART applications with Ethos where it could be used to support planning decisions.

Our initial experience from the clinical implementation of 4 mm margin to the pelvic lymph nodes indicates that this is feasible without demanding further revision of our oART procedure. With the margin reduction, we kept the tolerance demands for patient repositioning and emptying of gas from the rectum that requires a second verification CBCT as before the PTV reduction. A concern was therefore that the smaller margins would lead to an increased frequency of patient

repositioning or emptying of the rectum. Although data is still limited, a second verification CBCT was required in 1 out of the 122 oART fractions using 5 mm margin, and 1 out of the 28 fractions using a 4 mm margin. In these cases, the patient had to release bowel gas; however, none of these instances required a second adaptive plan to be created.

Reducing the PTV margin to the pelvic lymph nodes reduces the dose to the bowel bag. However, we found the bowel bag doses to be highly patient dependent. Given these large variations, the potential for bowel sparing with different oART margins shown in this study should only be used as an indication of what can be achieved. For each patient, the bowel bag dose seen on the original planning CT was consistent with the delivered oART dose, possibly enabling improved decision making for dose response. Whether the bowel bag dose sparing achievable through margin reductions with oART has clinical relevance needs to be established through clinical studies.

Conclusion

In conclusion, it is safe to have a 4 mm PTV margin around the elective pelvic lymph nodes for prostate patients treated with oART. This can reduce the dose received by the bowel. Experience from clinical implementation of a 4 mm margin as standard routine for treating prostate patients with oART reveals it is feasible with our existing procedure.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

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