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Urethra-sparing stereotactic body radiotherapy for prostate cancer: how much can the rectal wall dose be reduced with or without an endorectal balloon?

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Abstract

Background: This is a dosimetric comparative study intended to establish appropriate low-to-intermediate dose constraints for the rectal wall (R_{wall}) in the context of a randomized phase-II trial on urethra-sparing stereotactic body radiotherapy (SBRT) for prostate cancer. The effect of plan optimization on low-to-intermediate R_{wall} dose and the potential benefit of an endorectal balloon (ERB) are investigated.

Methods: Ten prostate cancer patients, simulated with and without an ERB, were planned to receive 36.25Gy (7.25Gy \times 5) to the planning treatment volume (PTV) and 32.5Gy to the urethral planning risk volume (uPRV). Reference plans with and without the ERB, optimized with respect to PTV and uPRV coverage objectives and the organs at risk dose constraints, were further optimized using a standardized stepwise approach to push down dose constraints to the R_{wall} in the low to intermediate range in five sequential steps to obtain paired plans with and without ERB (Vm_1 to Vm_5). Homogeneity index for the PTV and the uPRV, and the Dice similarity coefficient (DSC) for the PTV were analyzed. Dosimetric parameters for R_{wall} including the median dose and the dose received by 10 to 60% of the R_{wall} , bladder wall (B_{wall}) and femoral heads (F_{Heads}) were compared. The monitor units (MU) per plan were recorded.

Results: Vm_4 reduced by half $D_{30\%}$, $D_{40\%}$, $D_{50\%}$, and D_{med} for R_{wall} and decreased by a third $D_{60\%}$ while HI_{PTV} , HI_{uPRV} and DSC remained stable with and without ERB compared to Vm_{ref} . HI_{PTV} worsened at Vm_5 both with and without ERB. No statistical differences were observed between paired plans on R_{wall} , B_{wall} except a higher $D_{2\%}$ for F_{Heads} with and without an ERB.

Conclusions: Further optimization to the R_{wall} in the context of urethra sparing prostate SBRT is feasible without compromising the dose homogeneity to the target. Independent of the use or not of an ERB, low-to-intermediate doses to the R_{wall} can be significantly reduced using a four-step sequential optimization approach.

Keywords: Stereotactic body radiotherapy, Endorectal balloon, Dosimetric optimization, Prostate cancer, Urethra sparing

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Background

Stereotactic body radiotherapy (SBRT) for prostate cancer is emerging as a safe treatment option for patients with localized disease [1]. Clinical interest in extreme hypofractionated treatments results from estimated low α/β ratio values for prostate tumors (i.e. ≈ 1.5 Gy) compared with the nearby organs at risk (OAR); rectum, urethra and bladder, with α/β values of 3–5 Gy [2, 3]. A treatment strategy, such as intentionally under-dosing areas of potentially lower tumor burden, for example the periurethral transitional zone of the prostate, may be used to reduce the risk of radiation induced urinary toxicity [4–6]. However, the risk of rectal toxicity is a major concern when designing prostate dose-escalation studies. Both conventionally fractionated radiotherapy and SBRT studies have shown that higher dose to the rectum correlates with increased rectal toxicity [7]. Minimizing the dose to the rectum, over the whole range from low to high doses, could impact the quality of life [8].

Guidelines for dose constraints for OAR for prostate SBRT are either inexistent or not well established. For the most widely used SBRT schedule (7.25 Gy, 5 fractions), recommended dose constraints have been published by King et al. [1]. These are the constraints that have been adopted by the *Novalis Circle Phase II Trial* ([ClinicalTrials.gov Identifier NCT01764646](https://clinicaltrials.gov/ct2/show/study/NCT01764646)). Dose to the rectum can be reduced by using either a software-based technique i.e. dosimetry plan optimization with the goal of reducing the dose to the rectal wall (R_{wall}) [9], and/or gadget-based techniques, such as the use of an inflated endorectal balloon (ERB) [10] or prostate-rectal spacers [11–13].

We aimed to perform a dosimetric comparative study undertaken in the context of a randomized phase-II trial on urethra-sparing SBRT for prostate cancer. The principal goal of the study was to determine the optimal strategy for minimizing the low-to-intermediate-dose regions of the R_{wall} , with the secondary goal of assessing the potential dosimetric benefit for the R_{wall} of using an ERB compared to no-ERB.

Methods

Ten prostate cancer patients (cT1-3a N0 M0, Roach index for lymph-node involvement < 20%), treated between February 2013 and June 2014, were selected for the study. They were part of a population of 170 patients recruited in nine countries as part of a prospective multicentric randomized phase-II trial of short vs. protracted urethral-sparing SBRT for localized prostate cancer. This study concerns the first 10 consecutive patients recruited in one of the institution. They were all simulated, planned, and treated with an ERB inflated with 100 ml air [14].

For each patient, a first computed tomography simulation scan (CT_{sim}) was acquired with an ERB, followed by

a second CT_{sim} without the ERB. Planning CTs were acquired with axial slices of 2-mm thickness. A pediatric urinary catheter was introduced for accurate urethra delineation. A rigid registration with a pelvic magnetic resonance imaging (MRI) acquired on a flat table with the patient in the same treatment position and with an ERB was performed for definition of clinical target volume (CTV) and urethra in the CT_{sim} dataset acquired with ERB. On the other hand, the diagnostic MRI, realized without ERB, was used for contouring purposes for the second CT_{sim} dataset acquired without ERB.

A rectal enema was performed at home or in the clinic, based on patient preference, at the CT_{sim} and during the treatment course prior to insertion of the ERB (6 times in total). The enema was well tolerated overall and if necessary a second enema was performed if the rectum was not completely emptied. Patients were positioned in the supine position and immobilized with the *Combifix™* system. They were instructed to drink 600–700 mL of water one hour before the procedure, immediately after emptying their bladders. Three to four fiducials were implanted transrectally in the prostate under ultrasound guidance by an experienced uro-radiologist a minimum of seven days prior to the CT_{sim} acquisition for image-guidance.

The planning risk volume for the urethra (uPRV) consisted of the urethra plus a surrounding isotropic expansion of 3 mm inside the transitional zone (maximum axial uPRV size 1 cm). The CTV included the prostate, with or without the seminal vesicles (6 and 4 patients, respectively). The planning target volume (PTV) was defined as the CTV plus a 5 mm isotropic expansion in all directions except posteriorly, where a 3 mm expansion was used, excluding the uPRV. The absolute volumes of the PTV with and without ERB were similar for each patient: median 96.4 cm³ (range, 68.0–143.6) with the ERB and 92.4 cm³ (range 57.0–131.7) without. A 3 mm thick R_{wall} was defined on each CT from the lowest level of the ischial tuberosities to the rectosigmoid flexure. A 5 mm thick bladder wall (B_{wall}) and both proximal femurs (F_{heads}) were contoured on the corresponding CT axial slices. All contours were drawn in the Eclipse (Varian Medical Systems, Palo Alto, USA) treatment planning system (TPS) version 10 by the same radiation oncologist following the male pelvis normal tissue RTOG consensus contouring guidelines [15].

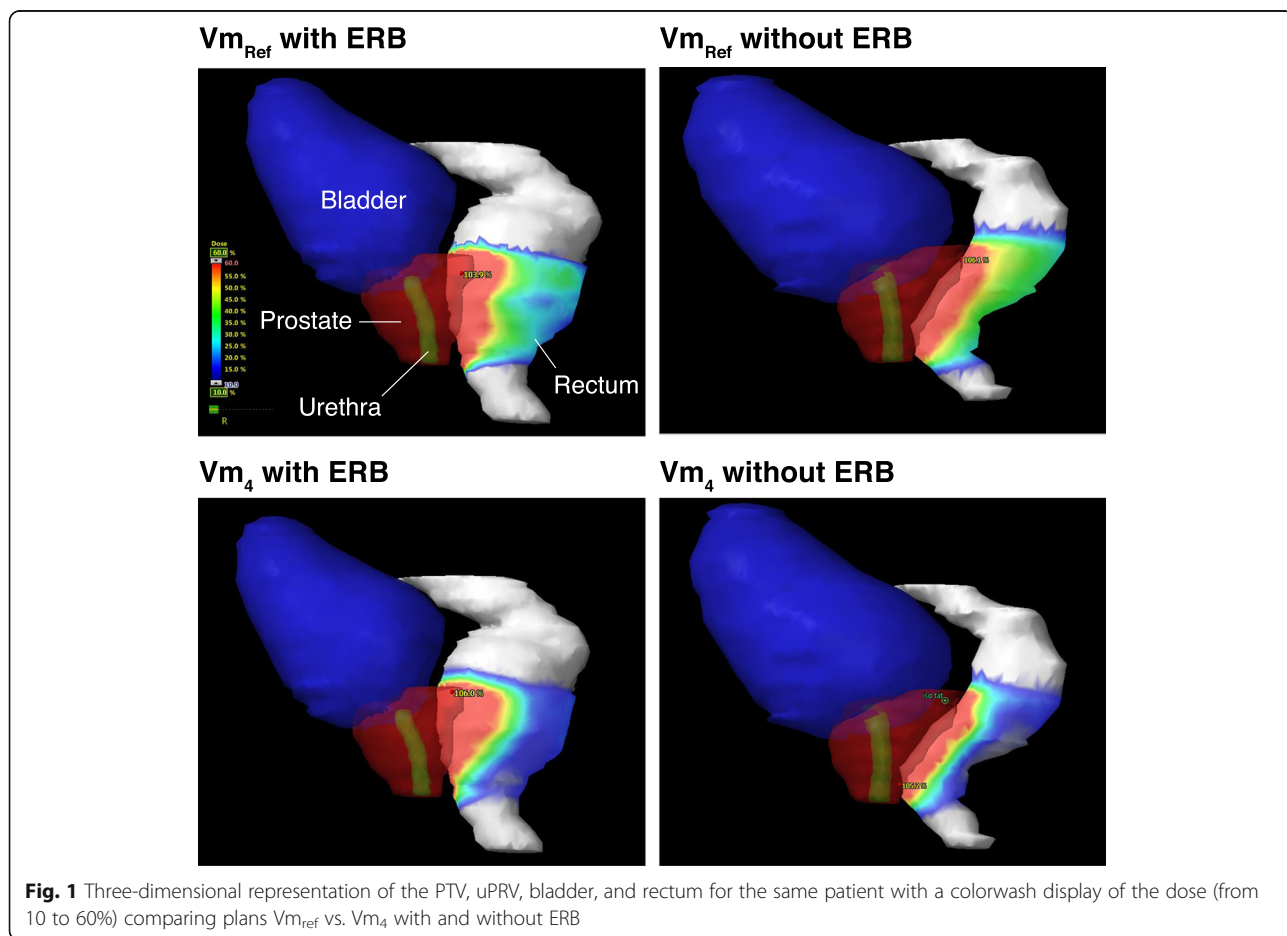
Plans were optimized with the progressive resolution optimizer (PRO v10.0.28 in Eclipse) and calculated with the analytical anisotropic algorithm (AAA v10.0.28). The treatment was delivered in two full volumetric modulated arcs (VMAT) with 6 MV beams using an accelerator equipped with a 2.5 mm leaf width HDMLC. The SBRT protocol prescribed 36.25 Gy in 5 fractions to the PTV, with a dose limit of 32.5 Gy to the uPRV, resulting in a

Table 1 Original dose-constraints for R_{wall} as used for the paired reference plans ($V_{m_{ref}}$) and the proposed additional dose-constraints based on the paired plans V_{m_4}

Volume	Original dose-constraints ($V_{m_{ref}}$)	Additional dose-constraints after optimization (V_{m_4})
R_{wall}	$V_{36.25 \text{ Gy}} < 5\%$	$V_{13.1 \text{ Gy}} \leq 30\%$
	$V_{32.6 \text{ Gy}} < 10\%$	$V_{7.2 \text{ Gy}} \leq 40\%$
	$V_{29 \text{ Gy}} < 20\%$	$D_{med} \leq 6.5 \text{ Gy}$

biologically equivalent dose in 2 Gy per fraction (EQD2) of approximately 90 Gy to the PTV ($\alpha/\beta = 1.5\text{Gy}$) and 62 Gy to the uPRV ($\alpha/\beta = 3$). The plan normalization goal aimed to achieve 98% of the PTV receiving 95% of the prescribed dose ($D_{98\%} = 34.4\text{Gy}$) with a maximum of 2% of PTV receiving no more than 107% of the prescribed dose ($D_{2\%} \leq 38.8\text{Gy}$). Similarly, the goal for the uPRV was $D_{98\%} \geq 30.9 \text{ Gy}$ (95% of 32.5Gy) and $D_{2\%} \leq 35.8 \text{ Gy}$ (107% of 32.5Gy). Dose constraints for the R_{wall} were $V_{36.25 \text{ Gy}} < 5\%$, $V_{32.6 \text{ Gy}} < 10\%$ $V_{29 \text{ Gy}} < 20\%$ (Table 1); for the B_{wall} the constraints were $V_{36.25 \text{ Gy}} < 10\%$, $V_{32.6 \text{ Gy}} < 20\%$, and $V_{18.1 \text{ Gy}} < 50\%$; while for the F_{heads} the constraint was $D_{2\%} \leq 18.1 \text{ Gy}$.

For each patient a pair of reference plans ($V_{m_{ref}}$) was created: one with ERB and one without ERB. The reference plans were optimized in order to respect the PTV and uPRV coverage objectives and the OAR dose constraints, without any additional sparing on the R_{wall} in the low or intermediate dose range. The optimization parameters were adapted separately on an individual basis for each patient/ERB combination to produce the reference plans. Then the intermediate-and-low dose sparing of the R_{wall} was forced further by adding three additional dose-volume optimization (DVO) constraints on the R_{wall} ($D_{2\%}$, $D_{10\%}$ and $D_{15\%}$) and by decreasing their value at each steps. These constraints were assigned a constant weight. Their initial values were set to start in the intermediate dose range ($D_{2\%} = 18\text{Gy}$, $D_{10\%} = 15\text{Gy}$ and $D_{15\%} = 13\text{Gy}$) down to low dose range (6, 3 and 1Gy, respectively) for the last optimization step. The additional DVO constraints were similar with and without ERB and applied for each patient. This resulted in a total of 120 plans (12 plans per patient - 6 with ERB and 6 without ERB) ranging from the reference plans ($V_{m_{ref}}$), optimized with the initial dose constraints, to extreme optimization plans (V_{m_1} to V_{m_5}), optimized with additional DVO objectives on the R_{wall} . The homogeneity



index for the PTV (HI_{PTV}) and the uPRV (HI_{uPRV}) was determined using: $(D_{2\%} - D_{98\%}) / D_{50\%}$. The Dice Similarity Coefficient (DSC) between the PTV and the volume encompassed by the 95% isodose line ($V_{95\%}$) was calculated as the ratio of their intersection and their union. $DSC = (V_{95\%} \cap PTV) / (V_{95\%} \cup PTV)$. Dosimetric parameters for the PTV, uPRV, and OAR were calculated. In addition, the median dose (D_{med}) to the R_{wall} , as well as the dose received by 10 to 60% of the R_{wall} volume, in increments of 10% ($D_{10\%}$ to $D_{60\%}$), were analyzed. The total number of monitor units (MU) was recorded.

The comparison of the dosimetric parameters with and without ERB at each step of the optimization was performed using the *Friedman* non-parametric analysis of variance. *Post-hoc* tests were performed according to the *Dunn-Bonferroni* procedure, with *p-values* adjusted for multiple comparisons. Statistics were computed using SPSS version 22; *p-values* ≤ 0.05 were considered statistically significant (two-sided tests).

Results

Figure 1 displays the dose distribution in a lateral projection of a reconstructed PTV, bladder and rectum, with and without ERB, in non-optimized and optimized treatment plans ($V_{m_{ref}}$ and V_{m_4}), respectively. It illustrates that the low-to-intermediate dose to the R_{wall} (3.3–21.8 Gy, i.e. 10–60% of the prescription dose 36.25 Gy) was strongly reduced using the plan optimization strategy in a similar way with and without ERB.

Figure 2 shows the R_{wall} dose-volume histogram (DVH), with a focus on $D_{40\%}$, for plans from $V_{m_{ref}}$ to V_{m_5} with and without ERB. The optimization strategy achieves a significant decrease of low-to-intermediate dose to the R_{wall} . Step V_{m_4} halved $D_{30\%}$, $D_{40\%}$, $D_{50\%}$, and D_{med} and decreased by a third $D_{60\%}$ compared to $V_{m_{ref}}$ (Table 2).

The extreme optimization objectives on the R_{wall} worsen the target homogeneity index HI_{PTV} (*p-value* < 0.01) in a similar way with and without ERB in V_{m_5} , because of a higher $D_{2\%}$ (*p* < 0.01): 38.5 Gy vs 38.0Gy with ERB; 38.4Gy vs 37.6Gy without ERB. Both the DSC and the HI_{uPRV} remained stable (Fig. 3). No differences were observed in terms of DSC, HI_{PTV} , and HI_{uPRV} , when comparing paired plans with and without ERB.

Figure 4 shows the B_{wall} DVH, with a focus on the $V_{18.1 Gy}$, for plans from $V_{m_{ref}}$ to V_{m_5} with and without ERB. The successive optimizations on R_{wall} slightly lowered $V_{18.1 Gy}$ (*p* < 0.036) with and without ERB. A higher $D_{2\%}$ for F_{heads} is observed for plans with ERB (*p* < 0.01) (Table 2). No statistical differences in MU were observed for paired plans with and without ERB, MU increasing similarly with optimization. The fourth optimization V_{m_4} is found to be the best compromise between the R_{wall} sparing, PTV and uPRV homogeneity and dose

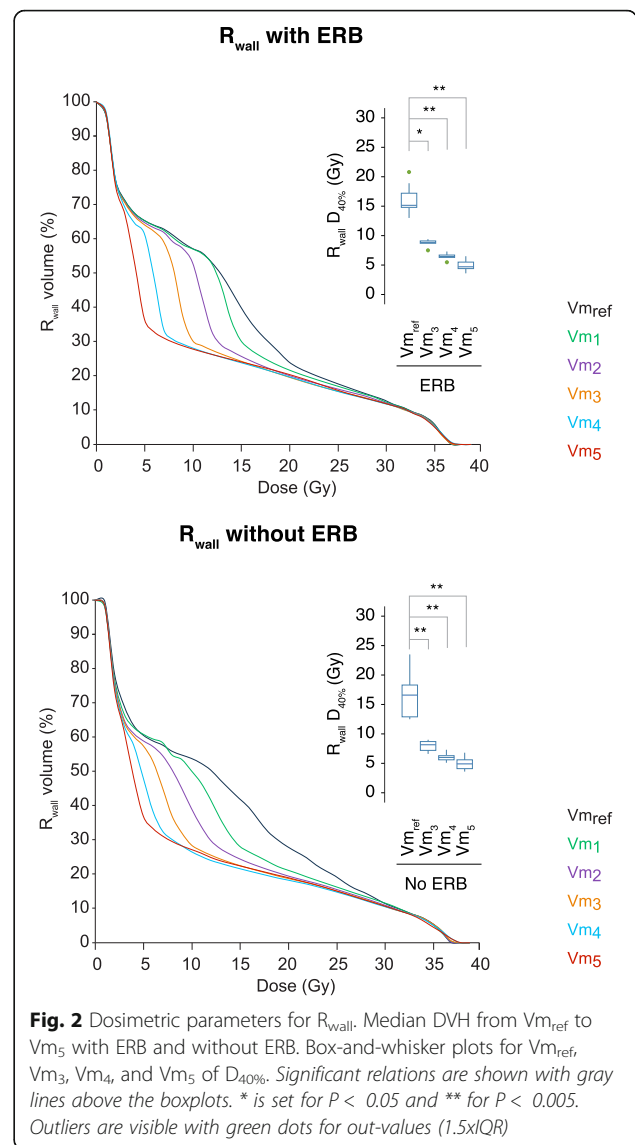


Fig. 2 Dosimetric parameters for R_{wall} . Median DVH from $V_{m_{ref}}$ to V_{m_5} with ERB and without ERB. Box-and-whisker plots for $V_{m_{ref}}$, V_{m_3} , V_{m_4} , and V_{m_5} of $D_{40\%}$. Significant relations are shown with gray lines above the boxplots. * is set for $P < 0.05$ and ** for $P < 0.005$. Outliers are visible with green dots for out-values ($1.5 \times IQR$)

coverage, and other OAR irradiation with and without ERB.

Discussion

In this study, the potential for decreasing low and intermediate doses to the R_{wall} by pushing down the dose constraints to the R_{wall} in sequential plan optimization steps was investigated with and without ERB. Starting with individually optimized plans, the R_{wall} sparing could be improved in four optimization steps (V_{m_4}) without impairing the PTV or uPRV coverage, although at the expense of more MU and slightly higher dose to the F_{heads} . The delivery of more MU and its impact on the beam-on time could be solved by using flattening filter free beams (high dose-rate) that can reduce treatment delivery time. Three additional dose-constraints to the R_{wall} (Table 1),

Table 2 Dosimetric data for PTV, uPRV and OAR with and without ERB. Comparison between the treatment plans Vm_{ref} and Vm₄

	ERB			No ERB		
	Vmref	Vm4	P-value	Vmref	Vm4	P-value
PTV						
HI (u.a.)	0.096 [0.071–0.119]	0.099 [0.082–0.121]	0.721	0.086 [0.066–0.102]	0.096 [0.076–0.105]	0.156
DSC (u.a.)	0.779 [0.714–0.898]	0.773 [0.689–0.906]	1	0.810 [0.738–0.948]	0.795 [0.698–0.89]	1
D2% (Gy)	38.0 [37–38.9]	38.1 [37.4–39]	0.433	37.6 [36.8–38.2]	38.0 [37.2–38.3]	0.276
uPRV						
HI (u.a.)	0.088 [0.051–0.13]	0.092 [0.06–0.121]	1	0.099 [0.057–0.139]	0.098 [0.063–0.199]	1
Rwall						
D10% (Gy)	32.6 [29.9–35.8]	32.4 [25.6–35.7]	0.229	31.8 [29.9–35.6]	30.9 [26.7–35.3]	0.172
D20% (Gy)	23.1 [18.2–28.8]	19.8 [10.7–27.6]	< 0.001	24.7 [19.2–29.5]	19.2 [14.4–28.5]	< 0.001
D30% (Gy)	17.9 [15–22.9]	8.5 [6.2–13.1]	< 0.001	19.6 [14.5–24.9]	8.3 [6.1–13.7]	< 0.001
D40% (Gy)	15.2 [13–20.8]	6.5 [5.5–7.3]	< 0.001	16.6 [12.5–23.5]	6.0 [5.1–7.3]	< 0.001
D50% (Gy)	12.9 [4.2–19.6]	6.0 [3.3–6.8]	< 0.001	12.8 [6.3–22.2]	5.0 [4.1–6.5]	< 0.001
D60% (Gy)	9.1 [2.5–18.2]	5.4 [2.2–6.4]	< 0.001	6.1 [2.4–19.7]	4.1 [2.2–5.8]	0.041
Dmed (Gy)	12.9 [4.1–19.5]	5.9 [3.3–6.7]	< 0.001	12.2 [6.3–22.1]	4.9 [4–6.5]	< 0.001
Bwall						
V18.1 Gy (%)	32.6 [15.6–47.5]	28.5 [13.3–45.5]	0.010	26.0 [14.9–44.8]	23.2 [13.1–41.8]	0.036
Fheads						
D2%	10.6 [9–14.1]	16.3 [13.7–17.8]	< 0.001	11 [8.3–12.6]	13.3 [10.7–16.5]	0.141
MU	2110 [1788–2478]	2897 [2515–3168]	< 0.001	2256 [1834–2897]	2763 [2419–3161]	0.002

corresponding to the 90th percentile of the distribution of D_{30%}, D_{40%}, and D_{med} in Vm₄ plans, can be proposed to improve the R_{wall} sparing in prostate SBRT as a consequence of this study: V_{7.2Gy} < 40%, V_{13.1 Gy} < 30%, and D_{med} < 6.5 Gy. This work was carried out for an SBRT dose prescription but a similar R_{wall} sparing could be achieved in conventionally fractionated prostate treatments.

By pushing down the R_{wall} DVO constraints to the limit (i.e. until the TPS is unable to optimize without impairing the PTV coverage) we observed that treatment plans with and without ERB gave similar results in the low-to-intermediate dose range. Patel et al. showed a dose reduction to the R_{wall} from using an ERB with 3-dimensional conformal RT (3DCRT) but not with intensity modulated RT (IMRT) [16]. Van Lin et al. reported similar results with the reduction of the R_{wall} mean dose, V_{50Gy} and V_{70Gy}, with 3DCRT but not with IMRT [17]. However, Smeenk et al. found that the dose to the anorectal region was improved with an ERB, including for IMRT [18]. Two recent studies analyzed the effect of using an ERB for prostate SBRT in the range of intermediate to high doses. A linac-based study [19] found that the presence of the ERB increased the volume of the R_{wall} receiving high doses (V_{95%} and V_{99%}) whereas no statistical difference was observed at an intermediate dose level (V_{50%}). A Cyberknife-based study [20] observed that V_{50%}, V_{80%}, V_{90%} and V_{100%} were lower with an ERB.

In light of the findings of this study, it may be important for modulated delivery techniques to evaluate the dosimetric impact for the R_{wall} of the use of an ERB separately from the optimization process, which has an important influence on the dose to the OAR. Different optimization approaches may explain the conflicting results obtained in the studies above.

Avoiding the overlap of a target and an OAR in a beam projection is of critical importance for sparing healthy tissues with 3DCRT plans and direct planning software. With inverse planning techniques, convex isodoses and steep dose gradients reduce the importance of the proximity of targets and OAR for dose reduction. As reported by Kim et al., severe late rectal toxicity may be mostly correlated with the absolute volume of R_{wall} receiving high doses (>3cm³), but also with the circumference of R_{wall} receiving 39 Gy in 5 fractions (V_{39Gy} > 35%). Grade 2 acute rectal toxicity has been correlated with the circumference of R_{wall} receiving 24Gy in 5 fractions (V_{24Gy} > 50%) [7]. A recent study [8] showed that patients treated with magnetic resonance imaging (MRI)-based prostate delineation or an endorectal balloon (ERB) had favorable anorectal dose distributions (range of 5–60 Gy in 39 or 19 fractions) and favorable toxicity profiles. Van Lin et al. [21] had already observed less telangiectasia for patients with smaller volumes of R_{wall} exposed to doses >40Gy, corresponding to the group of patients with an

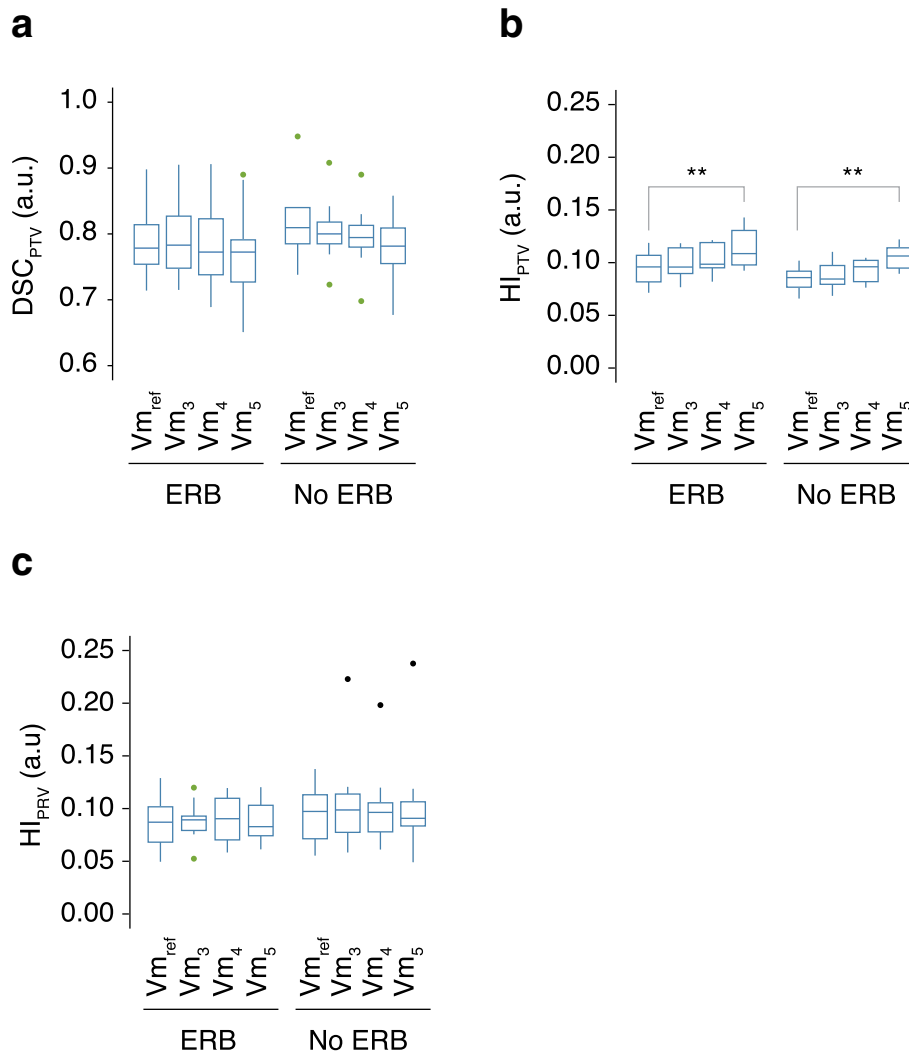


Fig. 3 Box-and-whisker plots of (A) DSC_{PTV} , (B) HI_{PTV} and (C) HI_{UPRV} with ERB and without ERB for Vm_{ref} , Vm_3 , Vm_4 , and Vm_5 . Outliers are visible with green dots for out-values ($1.5 \times IQR$) and black dots for extreme out-values ($3 \times IQR$). Significant relations are shown with gray lines above the boxplots. * is set for $P < 0.05$ and ** for $P < 0.005$

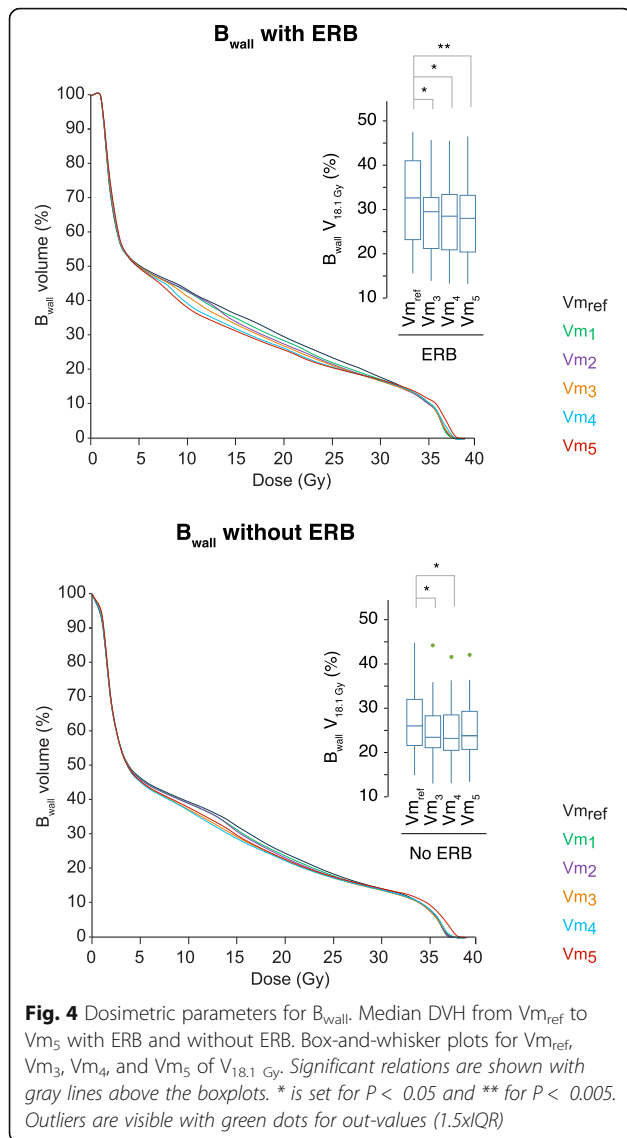
ERB in their 3DCRT study. Based on these observations, it seems prudent to lower the intermediate doses to the R_{wall} by pushing down the DVO constraints on the R_{wall} regardless of the use or not of an ERB. To further decrease the highest doses received by the R_{wall} , while maintaining optimal target coverage, only the use of reabsorbable gel-spacers implanted between the anterior R_{wall} and the posterior aspect of the prostate gland before SBRT may help [12, 22, 23].

The number of patients selected for this dosimetric study, although small, was consistent with the previous studies for 3DCRT, IMRT and SBRT. Because the patients had repeated CT scans with and without ERB, a rigorous controlled comparison could be made. This is an important advantage compared to previous studies because an inflated ERB can modify the shape of the adjacent organs. The

optimization strategy of reducing the dose to an organ, such as the R_{wall} , in a stepwise manner while keeping the other constraints constant is comparable to a Pareto optimal front technique [24]. The preparation, by a single planner, of many plans per patient, is time-consuming and can potentially introduce planning bias [25]. Our methodology can be used as an alternative for centers that are not equipped with Pareto-surface based multicriteria optimization (MCO) planning software [26]. The interest of this kind of software is that it is fast and can contribute to removing manual planning bias.

Conclusions

In conclusion, further optimization of the dose to the R_{wall} , beyond the usual recommendations for SBRT of prostate cancer, was feasible without compromising dose



homogeneity to the target (i.e., the PTV and the uPRV) with and without an ERB. Nonetheless, a larger amount of MU were required for the fully optimized plans. The main outcome of this work was to establish that one optimal technique for reducing the low- to- intermediate dose to the R_{wall} was a step wise optimization approach. Despite the inherent limitations of our study, we were unable to demonstrate that the use of an ERB allows additional low-to-intermediate dose reduction to R_{wall} .

Abbreviations

3DCRT: 3-dimensional conformal RT; B_{wall} : bladder wall; CT_{sim} : computed tomography simulation scan; D_{med} : median dose; DSC: Dice similarity coefficient; DVH: dose-volume histogram; DVO: dose-volume optimization; $D_{xx\%}$: dose received by xx% of a volume; EQD2: equivalent dose in 2 Gy per fraction; ERB: endorectal balloon; F_{heads} : femoral heads; HI_{PTV} : homogeneity index for PTV; HI_{uPRV} : homogeneity index for uPRV; IMRT: intensity modulated RT; MCO: multicriteria optimization; MRI: magnetic resonance imaging; MU: monitor units; OAR: organ at risk; PTV: planning treatment

volume; R_{wall} : rectal wall; SBRT: stereotactic body radiotherapy; TPS: treatment planning system; uPRV: urethral planning risk volume; V_{m_1} to V_{m_5} : optimized plans in 5 sequential steps; VMAT: volumetric modulated arcs; $V_{m_{ref}}$: reference plans; $V_{xx\%}$: volume encompassed by the xx% isodose line

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Availability of data and materials

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Authors' contributions

AD, MR, TZ and RM designed the study and wrote the manuscript. MR created the dosimetric plans and collected the data. AD and TZ performed the statistical modeling and analyzed the data. LT, WV, MB, NL, JL, JP, ZO and LE helped with writing the manuscript. RM supervised the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This is a dosimetric sub-study from a prospective multicentric randomized phase-II trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01764646) Identifier NCT01764646). The trial obtained the ethics approval from Geneva University Hospital Protocole 11–196 (NAC 11–089).

Consent for publication

We obtained written informed consent to publish from patients.

Competing interests

The authors declare that they have no competing interests.

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