Is an Endorectal Balloon Beneficial for Rectal Sparing After Spacer Implantation in Prostate Cancer Patients Treated With Hypofractionated Intensity-modulated Proton Beam Therapy? A Dosimetric and Radiobiological Comparison Study

Dalia Ahmad Khalil

Universitätsklinikum Essen: Universitätsklinikum Essen

Jörg Wulff

University Hospital Essen: Universitätsklinikum Essen

Danny Jazmati (✉ Danny.jazmati@uk-essen.de)

University Hospital Essen: Universitätsklinikum Essen

Dirk Geismar

University Hospital Essen: Universitätsklinikum Essen

Christian Bäumer

TU Dortmund: Technische Universität Dortmund

Paul Heinz Kramer

universitätsklinikum essen

Theresa Steinmeier

Universitätsklinikum Essen: Universitätsklinikum Essen

Stefanie Schulze Schleithoff

Universitätsklinikum Essen: Universitätsklinikum Essen

Stephan Tschirdewahn

Universitätsklinikum Essen: Universitätsklinikum Essen

Boris Hadaschik

Universitätsklinikum Essen: Universitätsklinikum Essen

Beate Timmermann

Universitätsklinikum Essen: Universitätsklinikum Essen

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Abstract

Background

The aim of this study is to examine the dosimetric influence of endorectal balloons (ERB) in rectal sparing in prostate cancer patients with implanted hydrogel rectum spacers treated with dose escalated/hypofractionated intensity modulated proton beam therapy (IMPT).

Methods

Ten patients with localised prostate cancer included in the ProRegPros study and treated at our centre were investigated in this study. All patients underwent a placement of hydrogel rectum spacers before planning. Two planning CTs (with and without 120 cm³ fluid-filled ERB) were acquired for each patient. Dose prescription was set according to the used simultaneous integrated boost strategy with 72 Gray (Gy)/2.4 Gy/5 x weekly to prostate+1 cm of the seminal vesicle, and 60 Gy/2 Gy/5 x weekly to prostate+2 cm of the seminal vesicle. Planning with two lateral-opposed IMPT beams was performed in both CTs. Rectal dosimetry values including dose-volume statistics and normal tissue complication probability (NTCP) in both plans were compared (non-ERB plans vs. ERB plans).

Results

For ERB plans compared to non-ERB, the reductions were 8.51 ± 5.25 Gy (RBE) ($p= 0.000$) and 15.76 ± 11.11 Gy ($P= 0.001$) for the mean and the median rectal dose, respectively. No significant reductions in rectal volumes receiving high dose levels were found. The use of ERB resulted in significant reduction in rectal volume receiving 50 Gy (RBE), 40 Gy (RBE), 30 Gy (RBE), 20 Gy (RBE), and 10 Gy (RBE) with P values of 0.034, 0.008, 0.003, 0.001, and 0.001, respectively. For the anterior rectum, no differences between ERB and non-ERB plans were observed. For the posterior rectum, ERB reduced rectal volumes received 30 Gy (RBE), 20 Gy (RBE), and 10 Gy (RBE) with P values of 0.019, 0.003, and 0.001, respectively. No significant reductions in mean or median rectal toxicity (Late rectal bleeding ≥ 2 , necrosis/stenosis, and Late rectal toxicity ≥ 3) were observed when using the ERB according to NTCP models.

Conclusion

The ERB reduced rectal volumes exposed to intermediate/low dose levels. However, no significant reduction in rectal volumes receiving high/intermediate doses could be observed. No benefit but also no disadvantage of the ERB for late rectal toxicity was found according to available NTCP models.

Introduction

Despite advances in radiotherapy (RT) techniques, rectal morbidity related to prostate radiation treatment cannot be entirely avoided and carries implications for quality of life (QOL). Radiation dose escalation for prostate cancer patients using modern [three-dimensional conformal radiotherapy](#) (3D-CRT) and the more

advanced Intensity modulated radiotherapy (IMRT) together with image guided radiotherapy (IGRT) has evolved over the past decade. Several randomised studies have demonstrated that dose escalation offers improved local control and biochemical control rates compared to conventional dose (1-6). However, escalating the total dose delivered to the prostate by 8- 10 Gray (Gy) relative biological effectiveness (RBE) has been shown to significantly increase the risk of rectal toxicity by about 10% (2, 7-9). Several trials relating rectum dose-volume characteristics to radiotherapy-induced rectal toxicities have been published (10-14). Based on these reports, the efforts of the radiation oncologists in the last decade have not only been directed to utilise modern radiotherapy techniques for patients with prostate cancer, but also to incorporate mechanical tools to increase the separation between prostate and rectum such as implantation of rectum-prostate spacers and/or using endorectal balloons (ERBs).

Significant reduction of intra-fractional prostate motion during radiotherapy by using ERB has been shown in a systematic review of 21 articles (15). The dosimetric effect of the ERB in reducing rectal radiation exposure during 3D-CRT, IMRT or stereotactic body radiation therapy for prostate cancer has been demonstrated by a number of studies (16-23). However, there are only few trials in the proton therapy field investigating the role of the ERB (24-28).

Because of higher sensitivity of the pencil beam scanning (PBS) technique to organ motion (29), ERB has mainly been used in our institution to stabilise the daily position and shape of the rectum and hence fixate the position of the prostate during treatment. Whether ERB retains benefit by decreasing the dose exposure to the rectum is unclear. Our goal was to explore the dosimetric impact of the ERB on rectal dose and rectal normal tissue complication probability (NTCP) values in prostate cancer patients treated with dose escalated/hypofractionated IMPT who already have implanted rectum spacers.

Methods

Since August 2015, a prospective single-centre registry evaluating proton therapy for patients with localised prostate cancer (ProRegPros) has been carried out at the West German Proton Therapy Centre Essen (WPE). Two planning computed tomography (CT) scans before and after the insertion of the ERB were obtained for 10 consecutive patients undergoing prostate cancer treatment. All ten patients had been diagnosed with T1-T4, N0, M0 and $PSA \leq 50$ ng/ml. All patients were treated with dose escalated/moderate hypofractionated IMPT with 72 Gy(RBE) in 30 fractions. All patients selected for the analysis underwent hydrogel rectal spacer insertion and fiducial marker implantation one week before planning CT acquisition.

Written informed consent was obtained from all patients for their participation in the registry. The registry was approved by the ethical committee of the University of Duisburg Essen.

CT-MRI Simulation

All patients drank 350 ml water on an empty bladder 30 minutes prior to simulation. Patients were immobilised in supine position using a thermoplastic pelvic cast. The first planning CT was acquired for each patient in 1 mm slices. After that, the thermoplastic pelvic cast was removed and the ERB catheter

was inserted in a knees-raised position and filled with 120 cm³ of fluid. Every patient was positioned and immobilized again using the laser alignment and immobilization mask markings, which had been placed during the first planning CT, and the second planning CT was acquired in 1 mm slices. T1/T2-weighted MRI were performed for all patients.

Target volumes and OARs delineation:

For each patient in every CT, prostate, seminal vesicles, clinical target volumes (CTV) and organs at risk (OARs) were contoured after CT/magnetic resonance imaging (MRI) fusion for accurate prostate delineation. Two CTVs were defined; low risk CTV1 (prostate + 5 mm peri-prostatic tissue + 2 cm of the seminal vesicles), and high risk CTV2 (prostate + 1 cm of the seminal vesicles). The margins added to the CTV to create the corresponding planning target volumes (PTVs) were 5 mm in every direction except at the seminal vesicle region, where a 7 mm margin was applied (29). Dose prescription was 60 Gy (RBE) in 2 Gy to PTV1 and 72 Gy (RBE) in 2.4 Gy to PTV2 in 30 fractions as simultaneous integrated boost (SIB). The rectum was contoured as a solid organ extending from just above the anal verge up to the sigmoid flexure. Extra contours were generated for anterior and posterior rectum.

SIB-IMPT Planning process:

Dose calculation and optimisation for IMPT plans were performed with pencil beam algorithm using the RayStation treatment planning system version 6 (RaySearch Laboratories, Stockholm, Sweden). For all patients, fixed geometry plans were generated in both CTs using two lateral-opposed IMPT beams with the same optimisation goals. A margin of 3.5% proton beam range + 2 mm was included in the PTV in the beam direction to account for field-specific range uncertainty. For more consistency, all contours were generated by the same senior radiation oncologist and the same radiation physicist created all the treatment plans.

For all dose concepts, a generic relative biological effectiveness (RBE) factor of 1.1 (relative to that of Co-60) was assumed.

DVH analysis and rectal NTCP calculation:

The dose-volume histogram (DVH) of the rectum was assessed and the following parameters were collected;

- For the whole rectum: RV (rectal volume in cc), D_{max} , D_{mean} , D_{median} , and RVxGy = percentage of rectal volume received X dose in Gy (RV72Gy, RV70Gy, RV65Gy, RV60Gy, RV55Gy, RV50Gy, RV40Gy, RV30Gy, RV20Gy, and RV10Gy).
- For the anterior rectum: D_{max} , and Ant-RVxGy = percentage of anterior rectal volume received x dose in Gy.
- For the posterior rectum: D_{max} , and Post-RVxGy = percentage of posterior rectal volume received x dose in Gy.

For the rectal NTCP calculation, the following biological models available in RayStation were employed;

- Layman Kutcher Burman (LKB) model for late rectal bleeding ≥ 2 with $D_{50} = 81.8\text{Gy}$, $\gamma = 3$, $m = 0.22$, $n = 0.29$, and $\alpha/\beta = 3$ (30) .
- Poisson-LQ model for necrosis/stenosis with $D_{50} = 80\text{ Gy}$, $\gamma = 2.2$, $S=1$, and $\alpha/\beta = 3$ (27).
- LKB model for late effects grade ≥ 3 with $D_{50} = 80\text{Gy}$, $m = 0.15$, $n = 0.06$, and $\alpha/\beta = 3.9$ (31).

We compared the rectal DVH parameters and the rectal NTCP values of the non-rectal balloon plans (non-ERB group) with those of the rectal balloon plans (ERB group). The differences in DVH and NTCP indices were calculated (Δ = mean value non-ERB plans - mean value ERB plans). Statistical analysis was performed using the IBM SPSS Statistics program V22. The Mann-Whitney-U-Test was used to compare means between the non-ERB plans and the ERB plans.

Results

DVH Analysis:

The 120 cm³ fluid-filled ERBs significantly increased the rectal volume in ERB plans compared to non-ERB plans. By analysis of the DVH of the whole rectum, we found that the ERB plans could reach lower values of $D_{\max}$, $D1$, D_{mean} , and D_{median} in comparison to non-ERB plans. However, the differences in $D_{\max}$ and $D1$ were not statistically significant. There was a minimal non-statistically significant reduction in RV72Gy in favour of non-ERB plans compared to the ERB plans. Otherwise, the ERB plans could lower the rectal volumes exposed to different radiation doses compared to the non-ERB plans, with a non-significant reduction in RV70Gy, RV65Gy, RV60Gy, and RV55Gy and a significant reduction in RV50Gy, RV40Gy, RV30Gy, RV20Gy, and RV10Gy (Table 1, Figure 1).

Regarding analysis done for the anterior rectum, we found that the ERB could reduce the $D_{\max}$, $D1$, RV72Gy, RV70Gy, RV65Gy, RV60Gy, RV55G, RV50G, RV40G, RV30Gy, RV20Gy, and RV10Gy, but no statistically significant differences could be reached (Table 2).

For the posterior rectum, the $D_{\max}$ and the $D1$ could be reduced in ERB plans in comparison to non-ERB plans, however without statistical significance. There were no statistically significant differences between the two groups regarding RV72Gy, RV70G, RV65Gy, RV60Gy, RV55Gy, or RV40Gy. Statistically significant differences were found between the two groups for rectal volumes receiving 30 Gy, 20 Gy and 10 Gy (Table 3).

NTCP results:

No statistically significant differences between the two study groups regarding the risk of NTCP for late rectal toxicities were determined. Comparisons of NTCP results for late rectal bleeding ≥ 2 , necrosis/stenosis, and late rectal toxicity ≥ 3 are presented in Table 4 (mean comparison) and in figure 2 (median and full range of variation comparison).

Discussion

Few trials using proton therapy for prostate patients have been directed to investigate the effectiveness of the ERB in rectal sparing (24), in reduction of the interfraction prostate motion (26), and in removal of rectal gas (25). Our aim was to investigate if an insertion of 120 cm³ fluid-filled ERB could spare rectum and hence reduce rectal NTCPs in patients who had undergone prior placement of hydrogel rectal spacers and were treated with dose escalated/hypofractionated IMPT to the prostate and the seminal vesicle.

In this study, the ERB increased the rectal volume by 137.35 ± 32.58 cm³. The reduction in mean radiation dose received by the whole rectum in ERB plans compared to non-ERB plans was 8.51 ± 5.25 Gy (RBE) ($P= 0.000$), and in D_{median} it was 15.76 ± 11.11 Gy (RBE) ($P= 0.001$). With regard to the maximum dose delivered to the rectum, we reported a 0.64 Gy (RBE) difference in the D_{max} , a 0.11 Gy (RBE) difference in D_1 of the rectum, and a 0.21 Gy difference in D_1 of the anterior rectum in favor of ERB plans, but with no statistical significance. For the posterior rectum, we found that the ERB could reduce the D_{max} , but with no statistical significance. In addition, the D_1 could be reduced for ERB plans by 11.11 ± 13.93 Gy (RBE) with a marginal statistical significance ($P= 0.059$). Our results are similar to those reported by Elsayed et al., who applied 3D-CRT with 59.4 Gy (RBE) + 10 Gy (RBE) high dose-rate (HDR) brachytherapy in 12 patients. The authors found that for the teletherapy applied to a PTV including prostate + 9 mm safety margins, the application of a 60 cm³ air-filled ERB could lead to a decrease in D_{max} of the anterior rectal wall and the rectum as complete organ but with no statistical significance. However, and owing to the dose distribution obtained from the 3D-CRT, the authors could demonstrate a reduction in the D_{max} of the posterior rectal wall of 18.6 Gy (RBE) (47.1 Gy for non-ERB vs. 28.5 Gy for ERB), which was found to be significant ($P= 0.01$) (32).

Regarding rectal volumes receiving different dose levels, we did not find any statistically significant differences of rectal volumes at high/intermediate dose levels. Furthermore, through a separate analysis of the anterior rectum, we found that the ERB plans could not lead to significant differences in any of the DVH parameters examined in comparison to non-ERB plans. In the case of intermediate/low dose levels, the difference in rectal volumes between non-ERB plans and ERB plans was found to be 4.58, 6.82, 9.57, 12.87, and 15.78 % for RV50Gy (RBE), RV40Gy (RBE), RV30Gy (RBE), RV20Gy (RBE), and RV10Gy (RBE), respectively, which was found to be statistically significant. By further analysis of the posterior rectum, we reported that the ERB could reduce the Post-RV30Gy (RBE) by 8.89 ± 9.92 % ($P= 0.019$), the Post-RV20Gy by 15.76 ± 12.94 % ($P=0.003$) and the Post-RV10Gy by 25.66 ± 14.21 % ($P=0.001$).

Our results are concurrent with results reported by Hille et al., who applied 72 Gy with conventional fractionation using 3D-CRT. The authors found that after inclusion of the prostate, the entire and the proximal seminal vesicles as CTV, a 60 cm³ air-filled ERB could lead to a significant decrease of the rectal wall receiving 40 Gy and 50 Gy, while no significant decrease of the rectal wall receiving 60 Gy, 65 Gy, or 70 Gy, could be found (33) .

Other trials applying 3D-CRT demonstrated that insertion of ERB could lower rectal volume exposed to high doses. Early in 2002, Wachter et al., using 3D-CRT with 66 Gy for prostate cancer, tested the role of a 40 cm³ air-filled ERB on the rectal dose. The authors found that for PTV prostate only plans, the proportion of the rectum volume receiving doses larger than 90% could be reduced from 24% without ERB to 20% with ERB. However, for PTV prostate+ seminal vesicle plans, it was increased from 41% without ERB to 48% with ERB, due to posterior displacement of the seminal vesicle resulting from the application of the ERB (34). Van Lin et al. conducted a planning study testing 40, 80, and 100 cm³ air-filled ERB vs. non-ERB plans, using three-dimensional conformal radiation therapy (DCRT) and IMRT plans, delivered to two different PTVs, with and without seminal vesicle. They found that in case of 3D-CRT the application of an ERB resulted in statistically significant reduction of the mean rectal wall dose, both if the amount of rectal wall volume irradiated to a dose level of 70 Gy or more and if the amount of rectal wall volume irradiated to a dose level of 50 Gy or more. However, in case of the IMRT, the authors could not report any statistically significant reduction in the rectal wall dose parameters for any of the ERBs (16). In contrast to Van Lin et al., Patel et al. conducted a planning study to detect the benefit of 60 cm³ air-filled ERB on the rectal dosimetry. They generated radiotherapy plans for 5 patients delivering 76 Gy either with 3DCRT or IMRT to target volumes with and without inclusion of the seminal vesicle and proved that inflation of the ERB in all cases and even in the context of IMRT resulted in a significant decrease in the absolute volume of rectal wall receiving greater than 60, 65, or 70 Gy (23).

The only trial investigating the role of the ERB in rectal sparing for patients treated with proton therapy was published by Vargas et al., who analyzed 20 proton plans for 15 patients who received doses of 78-82 Gy and found that the ERB decreased the volume of the rectum radiated to doses from 10 to 65 Gy ($p \leq 0.05$), while no benefit was observed for doses ≥ 70 Gy (24). In their trial, no hydrogel prostate rectum spacers were used.

Based on NTCP calculations, we found that the probability of late rectal toxicity could not be reduced by the application of the ERB. The mean NTCP for late rectal bleeding $\geq$ grade 2 was $2.6 \pm 0.97\%$ for non-ERB plans vs. $3.1 \pm 1.1\%$ for ERB plans ($P=0.15$). For necrosis/stenosis it was $5.5 \pm 1.78\%$ for non-ERB plans vs. $5.6 \pm 2.22\%$ for ERB plans ($P=0.72$); for late rectal toxicity ≥ 3 it was $13.1 \pm 1.37\%$ for non-ERB plans vs. $13.3 \pm 3.02\%$ for ERB plans ($P=0.593$). Our results are similar to those reported by Van Lin et al. who used the LKB model with Emami parameters ($n = 0.12$, $m = 0.15$, and $D50 = 80$ Gy) for late rectal NTCP calculations. In their trial, no statistically significant reduction of the NTCP could be demonstrated for the combination of IMRT with ERBs (40, 80, and 100 cm³ air-filled). However, in their analysis, the ERB could improve the results of the 3D-CRT plans, in which a statistically significant reduction in the rectal NTCP for 100 cm³ air-filled ERB plans compared to non-ERB plans (15% vs. 24%, respectively, $P<0.0001$) was found (16).

It has been proven that the rectal volumes exposed to intermediate and high doses are associated with developing late rectal toxicities. Storey et al. reported a significant correlation between the percentage of the rectum irradiated to 70 Gy or greater and the likelihood of developing late rectal complications in patients treated to 78 Gy (35). Kupelian et al. tested a short-course IMRT (70 Gy with 2.5 Gy per fraction)

and demonstrated that only the volume of rectum receiving the 70 Gy (with a cutoff of 15 cc) was a significant predictor of rectal bleeding (11). Huang et al. also observed a significant volume effect at rectal doses of 60, 70, 75.6, and 78 Gy and that the risk of developing rectal complications increased exponentially as larger volumes were irradiated (36). Zapatero et al. reported that the rectal D_{mean} and the percentage of rectum receiving >60 Gy are correlated with grade 2 or worse rectal bleeding (37). On the other hand, other investigators demonstrated the likelihood of rectal toxicity for rectal volumes receiving an intermediate dose. Tucker and colleagues found that the incidence of grade 2 or worse late rectal bleeding increases within 2 years if $\geq 80\%$ of the rectal wall is exposed to doses > 32 Gy (38). Jackson et al. reported that rectal bleeding was significantly correlated with the volumes exposed to 46 Gy in prostate cancer patients who received 70.2 and 75.6 Gy (39).

Conclusion

Our study suggests that the ERB could reduce the rectal volumes exposed to intermediate/low dose levels in prostate cancer patients with implanted rectum spacers treated with hypofractionated/dose escalated IMPT. We could not find any benefit of ERB in reducing rectal volumes receiving high/intermediate dose levels, which in turn and based on previous trials, can explain the lack of benefit of the ERB in reducing the NTCP values for late rectal toxicity in those patients. We think that the application of ERB does not add much benefit in patients treated with IMPT due to high capabilities of this technique to conform the dose to the target, which in turn reduces volumes of rectum exposed to high-dose region. Furthermore, reduction of rectum volumes receiving high dose can be achieved by spacer implantation. However, the potential effect of ERB in reducing volumetric changes of rectum filling and variabilities in rectal positioning during treatment cannot be neglected, especially for patients undergoing proton therapy due to high sensitivity of PBS dose distribution to inter- and intrafractional motion. This issue is currently under investigation at our centre and will be reported soon. Therefore, we are currently continuing to use the endorectal balloon at our centre to reduce motion

Declarations

Authors' contribution

DAK, DJ and JW wrote parts of the manuscript. BT, DG, DAK, JW designed the study. BH, CB, DG contributed significantly to the discussion on the interpretation of the results. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data and materials can be accessed via DAK, in compliance with data protection guidelines.

Consent for publication

All authors gave consent for the publication

Ethics approval and consent to participate

The registry was approved by the local ethical commission.

Conflict of Interest: All authors declare that they have no conflict of interest.

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Tables

Table 1: DVH analysis for the whole rectum comparing between the non-ERB plans and ERB plans:

	Study group	mean	SD	Range	Diff (Δ) ^d		P value
					mean	SD	
RV ^a	non-ERB	90.79	42.34	42.08-183.51	137.35	32.58	0.000
	ERB	228.14	31.65	179.79-267.54			
D _{max} ^b	non-ERB	73.62	0.77	72.6-74.8	0.64	0.85	0.103
	ERB	72.98	0.55	72.6- 74.4			
D _{mean} ^b	non-ERB	31.42	4.98	24.20-42.29	8.51	5.25	0.000
	ERB	22.91	3.0	18.79-27.53			
D _{median} ^b	non-ERB	26.34	9.66	13.06-45.25	15.76	11.11	0.001
	ERB	10.57	5.89	4.39-21.52			
D1 ^b	non-ERB	72.49	0.53	71.59-73.29	0.11	0.52	0.363
	ERB	72.38	0.16	72.21-72.78			
RV72Gy ^c	non-ERB	3.42	1.73	0.34-5.60	-0.38	2.24	0.734
	ERB	3.80	1.07	1.96-5.30			
RV70Gy ^c	non-ERB	7.90	3.4	2.12-13.29	0.58	4.42	0.597
	ERB	7.32	2.03	3.89-9.84			
RV65Gy ^c	non-ERB	13.98	4.3	5.93-21.28	1.66	5.45	0.257
	ERB	12.31	2.54	7.66-15.98			
RV60Gy ^c	non-ERB	18.74	4.85	9.63-27.32	1.10	6.99	0.345
	ERB	17.64	5.62	11.17-31.51			
RV55Gy ^c	non-ERB	23.37	6.37	13.11-37.72	4.02	8.15	0.082
	ERB	19.35	3.15	14.85-23.96			
RV50Gy ^c	non-ERB	26.87	5.59	16.49-37.51	4.58	7.37	0.034
	ERB	22.29	3.43	17.52-27.51			
RV40Gy ^c	non-ERB	34.50	6.19	23.45-46.37	6.82	8.02	0.008
	ERB	27.68	3.74	22.36-33.83			
RV30Gy ^c	non-ERB	42.67	6.60	32.64-54.68	9.57	8.23	0.003
	ERB	33.10	4.4	27.05-40.37			
RV20Gy ^c	non-ERB	52.33	7.75	42.85-65.88	12.87	8.75	0.001

	ERB	39.46	5.09	32.58-47.58			
RV10Gy ^c	non-ERB	64.57	8.55	54.38-81.85	15.78	8.91	0.001
	ERB	48.77	6.13	40.99-57.68			

^a Rectal volume in cm³; ^b Dose in Gy; ^c RVXGy =Percentage of rectal volume received x dose;

^d Δ difference between the non-ERB plans and the ERB plans (mean value non-ERB plans - mean value ERB plans)

Table 2: DVH analysis for the anterior rectum comparing between the non-ERB plans and ERB plans:

	Study group	mean	SD	Range	Diff (Δ) ^c		P value
					mean	SD	
Ant-D _{max} ^a	non-ERB	73.62	0.77	72.6-74.8	0.64	0.85	0.103
	ERB	72.98	0.545	72.6- 74.4			
Ant-D1 ^a	non-ERB	72.77	0.72	71.31-73.73	0.21	0.69	0.326
	ERB	72.56	0.23	72.30-73.01			
Ant-RV72Gy ^b	non-ERB	5.99	3.17	0.66-12.32	-1.14	3.71	0.290
	ERB	7.13	2.1	3.78-10.29			
Ant-RV70Gy ^b	non-ERB	14.44	5.36	4.98-21.80	-0.95	6.49	0.705
	ERB	15.39	3.98	8.28-20.98			
Ant-RV65Gy ^b	non-ERB	22.84	5.75	11.39-31.05	-1.22	8.41	0.940
	ERB	24.05	5.7	14.79-31.02			
Ant-RV60Gy ^b	non-ERB	31.74	7.51	18.49-41.66	0.93	9.11	0.545
	ERB	30.81	6.61	21.55-39.18			
Ant-RV55Gy ^b	non-ERB	38.66	8.32	25.13-48.53	1.19	10.52	0.734
	ERB	37.47	7.16	28.65-48.53			
Ant-RV50Gy ^b	non-ERB	47.34	7.41	31.36-56.39	3.88	11.14	0.226
	ERB	43.46	7.29	34.42-54.28			
Ant-RV40Gy ^b	non-ERB	59.11	7.64	42.45-68.87	6.6	11.88	0.174
	ERB	52.51	8.60	42.48-65.22			
Ant-RV30Gy ^b	non-ERB	69.25	7.9	52.49-78.39	7.65	12.21	0.059
	ERB	61.60	9.05	50.20-76.17			
Ant-RV20Gy ^b	non-ERB	78.84	9.65	61.83-89.52	8.31	12.81	0.059
	ERB	70.53	9.03	58.28-84.13			
Ant-RV10Gy ^b	non-ERB	85.2	9.44	71.7-96.11	4.17	11.75	0.174
	ERB	81.03	7.9	68.21-91.01			

^a Dose in Gy; ^b RVXGy =Percentage of ant-rectal volume received X dose; ^c Δ difference between the non-ERB plans and the ERB plans (mean value non-ERB plans - mean value ERB plans)

Table 3: DVH analysis for the posterior rectum comparing between the non-ERB plans and ERB plans:

	Study group	mean	SD	Range	Diff (Δ) ^c		Pvalue
					mean	SD	
D _{max} ^a	non-ERB	60.24	9.16	47.60 -72.60	3.83	12.41	0.406
	ERB	56.41	10.54	42.80-70.60			
D1 ^a	non-ERB	37.36	11.82	23.66-57.94	11.11	13.93	0.059
	ERB	72.56	0.23	72.3 -73.01			
Post-RV72Gy ^b	non-ERB	0.11	0.35	0- 1.14	0.11	0.36	0.317
	ERB	0	0	0			
Post-RV70Gy ^b	non-ERB	0.51	1.6	0 - 5.06	0.51	1.6	0.503
	ERB	0	0	0 - 0.02			
Post-RV65Gy ^b	non-ERB	1.08	3.31	0- 10.49	1.06	3.29	0.829
	ERB	0.03	0.07	0 - 0.22			
Post-RV60Gy ^b	non-ERB	1.67	4.5	0 - 14.4	1.56	4.44	0.518
	ERB	0.11	0.23	0 - 0.71			
Post-RV55Gy ^b	non-ERB	2.38	5.47	0 - 17.67	2.14	5.39	0.435
	ERB	0.24	0.46	0 - 1.45			
Post-RV50Gy ^b	non-ERB	3.01	6.39	0 - 20.57	2.55	6.25	0.286
	ERB	0.451	0.70	0 - 2.25			
Post-RV40Gy ^b	non-ERB	4.98	8.05	0.2 - 27.09	3.83	7.79	0.069
	ERB	1.148	1.309	0.06 - 4.03			
Post-RV30Gy ^b	non-ERB	11.59	10.90	0.88 - 36.46	8.86	9.92	0.019
	ERB	2.7	2.26	0.33 - 6.68			
Post-RV20Gy ^b	non-ERB	21.92	14.84	3.83 - 49.00	15.76	12.94	0.003
	ERB	6.165	3.711	1.59 - 10.87			
Post-RV10Gy ^b	non-ERB	39.54	17.17	14.87 -71.37	25.66	14.21	0.001
	ERB	13.88	6.695	3.97 - 22.05			

^a Dose in Gy; ^b RVXGy =Percentage of post-rectal volume receiving X dose; ^c Δ difference between the non-ERB plans and the ERB plans (mean value non-ERB plans - mean value ERB plans)

Table 4: NTCP results for the whole rectum comparing between the non-ERB plans and ERB plans:

NTCP ^a	Study group	mean	SD	Range	Diff (Δ) ^b		<i>P</i> value
					mean	SD	
Late rectal bleeding ≥ 2	non-ERB	2.6	0.97	2-5	-0.5	1.18	0.150
	ERB	3.1	1.1	1-5			
Necrosis/stenosis	non-ERB	5.5	1.78	1-7	-0.1	2.02	0.728
	ERB	5.6	2.22	1-8			
Late rectal toxicity ≥ 3	non-ERB	13.1	1.37	11-15	-0.2	3.82	0.593
	ERB	13.3	3.02	7-17			

^a NTCP results in %; ^b Δ difference between the non-ERB plans and the ERB plans (mean value non-ERB plans - mean value ERB plans)

Figures

Figure 1

Example of IMPT dose distribution for cT2N0M0 Prostate cancer patient. (A) non-ERB plan. (B) ERB plan.

Figure 2

Box plot illustrates the difference (Δ) in percentage of rectal volume received x dose between the non-ERB plans and ERB plans (mean value non-ERB plans- mean value ERB plans)

Figure 3

Box plot comparing median and full range of variation of the rectal NTCP rates for late rectal bleeding ≥ 2 , necrosis/stenosis, and late toxicity ≥ 3 for non-ERB plans vs. ERB plans.