Efficacy of a rectal spacer with prostate SABR - first UK experience

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Efficacy of a Rectal Spacer with Prostate SABR – First UK Experience

Short title: Efficacy of a Rectal Spacer with Prostate SABR

Abstract

Objectives

This study assessed the use of implanted hydrogel rectal spacers for SABR-VMAT patients, investigating practicality, dosimetric impact, normal tissue complication probability (NTCP) and early toxicity.

Methods

Data from the first 6 patients treated within a prostate SABR and rectal spacer trial were examined to determine spacer insertion tolerability, resultant changes in treatment planning and dosimetry and early toxicity effects. CT scans acquired prior to spacer insertion were used to generate SABR plans which were compared to post-insertion CT plans. Plans were evaluated for target coverage, conformity, and organs at risk doses with NTCPs also determined from resultant dose fluences. Early toxicity data was also collected.

Results

All patients had successful spacer insertion under local anaesthetic with maximal grade 1 toxicity. All plans were highly conformal, with no significant differences in CTV dose coverage between pre- and post-spacer plans. Substantial improvements in rectal dose metrics were observed in post-spacer plans, e.g. rectal volume receiving 36Gy reduced by ≥42% for all patients. Median NTCP for grade 2+ rectal bleeding significantly decreased from 4.9% to 0.8% with the use of a rectal spacer ($p = 0.031$). To date, 2 episodes of acute grade 1 proctitis have been reported following treatment.

Conclusions

The spacer resulted in clinically and statistically significant reduction in rectal doses for all patients.

Advances in knowledge

This is one of the first studies to investigate the efficacy of a hydrogel spacer in prostate SABR treatments. Observed dose sparing of the rectum is predicted to result in meaningful clinical benefit.

Introduction

In light of the potentially low α/β ratio [1], stereotactic ablative radiotherapy (SABR) is increasingly being studied as a treatment option for prostate cancer, generating highly conformal dose distributions around the prostate, with steep dose gradients to spare neighbouring normal tissue [2-4]. However, despite technological advances, a major limitation to dose escalation is the increased risk of normal tissue damage, particularly to the rectum and bladder. While prostate SABR appears to be well-tolerated, there are reports of increasing rectal toxicity in SABR trials that have dose-escalated ≥40 Gy in 5 fractions [5, 6]. A number of solutions have recently been developed to address this rectal toxicity limitation, by modifying the patient's anatomy to increase the separation between the anterior rectal wall and the prostate gland [7]. Several of these spacer solutions are now commercially available and have been incorporated into a number of conventionally fractionated clinical trials which have demonstrated a reduction in acute and late rectal toxicity [7, 8].

At the Northern Ireland Cancer Centre we are currently recruiting to a randomised feasibility study, evaluating SABR treatments in high-risk localised prostate cancer with or without elective nodal irradiation (ENI), the SPORT High-Risk Trial [9]. All trial participants are implanted with a hydrogel rectal spacer system (SpaceOAR®, Augmenix, Waltham, MA, USA) prior to SABR treatment. In this report, we present our initial experience of using a hydrogel rectal spacer system with prostate SABR. We evaluate the practicality and tolerability of the hydrogel spacer and quantify its rectal dosimetry benefits for prostate SABR treatments on our initial cohort of patients, including normal tissue complication probability (NTCP) for grade 2+ rectal bleeding and acute toxicity.

Materials and methods

Ethical approval and patient selection

Ethical approval for the clinical trial was granted by the Health and Social Care Research Ethics Committee (REC) A (REC reference 15/NI/0192). The study is open to male patients ≥ 18 years old with at least one of the following criteria: histologically confirmed prostate adenocarcinoma presented with clinical stage T3a N0 M0, Gleason score 7 (4+3) or above and/or PSA > 20 and who were planned to receive 1-3 years ADT as part of their standard treatment. Six patients have currently been recruited to the SPORT trial and their data was used for analysis in this investigation.

Rectum spacer and fiducial marker implantation

All procedures were performed transperineally with patients in the dorsal lithotomy position, with local anaesthetic only, under transrectal ultrasound (TRUS) guidance. 10 mls 1% lidocaine was infiltrated into the sub-cutaneous tissues, with a further 10 mls infiltrated into the prostatic neurovascular bundles bilaterally. Six targeted intra-prostatic prostate biopsies were then taken for translational biomarker research and three intraprostatic fiducial markers (FMs) were inserted. Finally, an 18-gauge needle was inserted between the prostate and the rectum using sagittal TRUS image guidance. Normal saline was used to hydrodissect the space between the rectoprostatic fascia and anterior rectal wall, and ten millilitres of hydrogel liquid was injected into this space, where the hydrogel polymerised within seconds of injection to form a gel.

Two consultant clinical oncologists were trained to perform the implantation procedure, both of whom were experienced in prostate brachytherapy. The first 3 cases per clinician

were supervised (i.e. all patients in this study). Antibiotic cover consisting of oral ciprofloxacin for five days was prescribed to start immediately prior to insertion. All patients were contacted on day four to assess the tolerability of the procedure.

Image acquisition and organ delineation

Prior to spacer implant, each patient had pre-spacer CT images acquired using a helical CT-simulator (512 × 512 field of view, 1 mm axial pixel resolution, 2.5mm slice width). Patients were instructed to drink 500mL of water and had a micro-enema (Micralax®) administered before CT acquisition and each treatment session. Post-spacer CT and T2-weighted MR images were acquired on the same day, one week after spacer insertion. To assist with spacer delineation, the MR images were fused with the post-spacer CT images using the Eclipse™ treatment planning system version 13.6 (Varian Medical Systems, Palo Alto, CA, USA). Structures of interest were contoured manually in Eclipse™ by one of two consultant clinical oncologists, where the treating oncologist contoured the same structures on both CT image sets to allow comparison between pre- and post-spacer plans. Pelvic nodal clinical target volumes (CTVs) were defined for patients randomised to the ENI arm, however these were not utilised in this dosimetric investigation. In this study, only the prostate and proximal 10mm of the seminal vesicles (PSV) CTV was used, reflecting the prostate only trial arm.

Treatment planning

A 5 mm margin was expanded isotropically around the CTV to generate the planning target volume (PTV). For this study, the contoured organs at risk (OARs) included the bladder, rectum, femoral heads and penile bulb. Contouring of the rectum was limited to the same number of corresponding CT slices on both image sets, to facilitate comparison between the

plans generated. All planning was performed in Eclipse using the Progressive Resolution Optimization (v.13.6), and Acuros XB dose calculation (v.13.6.23), algorithms for a Varian TrueBeam Linac. The dose calculation grid size used was 2.5mm and the heterogeneity correction and jaw tracking settings were enabled.

Plans were generated following our previously reported class solution [10], and employed a single 300° partial VMAT arc (210° - 150°), delivered using a 10 MV flattening filter free photon beam with a maximum dose-rate of 2400MU/min. For one patient (Patient 3) the class solution could not be applied due to the presence of a right hip prosthesis, therefore two 215° partial arcs (335° - 180°) were used instead. Planning objectives and constraints for targets and OARs are provided in Table I. The prescribed dose was 40Gy for the CTV and 36.25Gy for the PTV, delivered simultaneously, in 5 fractions.

Plan evaluation

The dose metrics described in Table I were used to evaluate the plans generated on the two CT images sets. In addition to these metrics, the dose conformity index ($CI = \frac{Vol_{95\%}}{PTV\ volume}$) [11] was also determined, together with the medium-dose spillage outside the PTV ($R_{50} = \frac{Vol_{50\%}}{PTV\ volume}$) [12], where $Vol_{95\%}$ and $Vol_{50\%}$ are the tissue volumes receiving at least 95% and 50% of the PTV prescription dose respectively. Also, included in Table I are definitions for minor and major variations from the dose objectives considered in this investigation. To allow for comparison between optimised plans, priority was given to achieving target structure objectives and only variations from the OAR objectives were permitted. For both datasets every effort was taken to achieve the OAR objectives without compromising dose coverage of the target structures.

TCP and NTCP

Tumour control probabilities (TCP) and normal tissue complication probabilities (NTCPs) were calculated using the Lyman–Kutcher–Burman (LKB) model [13]. Further information on these calculations, model parameters used and different endpoints are provided in Appendix A.

Statistical analysis

Statistical analysis was conducted to compare the dose volume histogram (DVH) metrics analysed for pre-spacer and post-spacer plans. This analysis was conducted in MATLAB (v. 8.2-R2013b) using the non-parametric two-sided paired-sample Wilcoxon signed rank test, the significance level was set at $p \leq 0.05$.

Results

The intra-prostatic biopsy procedure with fiducial marker and hydrogel spacer insertion was well tolerated under local anaesthetic. The total procedure time was 20-25 minutes per patient and all patients were discharged one hour after completion. Telephone follow up on day four identified two patients who experienced grade 1 rectal bleeding, two patients who had grade 1 haematuria and one patient with grade 1 urgency post-procedure. All toxicities resolved within 24-48 hours.

Dosimetric comparison of optimised plans

Figure 1 displays examples of axial and sagittal CT views, including target and OAR contours acquired before ((a), (d)) and after ((b), (e)) spacer and FM insertion. It is evident from these figures that the spacer is not easily distinguished from neighbouring soft tissue. Therefore registered MR images, acquired on the same day as the post-spacer CT, are also included in

Figure 1 panels ((c), (f)) which allow the spacer to be easily delineated. Overlaid on the CT images are the 100% (36.25Gy) and 50% (18.13Gy) isodose lines of the PTV prescription dose. The images demonstrate how the spacer has displaced the rectum away from the prostate and as a result has reduced the volume of the rectum that overlaps with the high radiation dose region.

Figure 2 displays individual DVHs for target and rectum structures for the 6 patients included in this study. When generating the optimised plans, priority was given to achieving the target volume constraints. As a result, DVHs generated for the CTVs using the two CT image sets are very similar. However, even with this approach, the pre-spacer PTV dose coverage was reduced compared to the post-spacer plans for the majority of patients, as a result of trying to achieve the rectum constraints. This is also reflected in the target dose metrics extracted from the DVHs reported in Table II (full details provided in supplementary Excel file 1). While there were no significant differences in the CTV metrics, the median pre-spacer PTV volume receiving the prescription dose was significantly reduced by 2.1 % (98.1 vs 96.0 for post-spacer and pre-spacer CTs respectively, p = 0.031).

Figure 2 also indicates that all 6 patients benefited from a large reduction in the volume of rectum exposed to high radiation doses (>18Gy), as a result of the spacer insertion. Key metrics for the OAR structures are reported in Table III, with full metrics reported in supplementary Excel file 2. Of the pre-spacer plans, only one plan (Patient 4) met all target and OAR objectives and constraints. For three patients (1, 2 and 6) it was not possible to generate treatment plans on the pre-spacer anatomy without a major variation from the V_{36Gy} < 1 cc rectum objective, i.e. V_{36Gy} > 2 cc, due to substantial overlap of the PTV and rectum volumes. In contrast, no major or minor violations of the rectum dose objectives

were observed in any of the post-spacer plans and the rectum volume receiving 36 Gy was significantly reduced (median 2.6 cc pre-spacer vs 0.3 cc post-spacer, p = 0.031). Further analysis of individual patient data (supplementary Excel file 2) revealed that all patients had a reduction in their rectal V_{36Gy} volume of more than 42% for plans generated on the post-spacer CT image sets. Table III also indicates a median reduction of 5.2 Gy in the maximum dose absorbed by 2cc of the rectum for plans generated using the spacer-modified anatomy, from 36.3 Gy in the pre-spacer plans to 31.1 Gy in the post-spacer plans. No significant difference was observed in the dose metrics recorded for the bladder, femoral heads or penile bulb when pre-spacer and post-spacer plans were compared.

EUD and NTCP Comparison

Reported in Table IV are the TCP values estimated for the prostate CTV and NTCP values for rectum and bladder toxicity endpoints. While there was no significant difference in the TCPs for the two datasets, the median NTCP for grade 2+ rectal bleeding complications [15] was significantly reduced from 4.9% in the pre-spacer dataset to 0.8% in the post-spacer dataset. NTCPs for grade 2+ rectal bleeding toxicity calculated for each patient are displayed in Figure 3. The maximum complication probability was 9.9%, calculated for the pre-spacer image set of patient 6, this was subsequently reduced to 0.0% for the plan generated using the patient's rectal spacer image set. There was no significant difference in the bladder cystitis NTCP between the two datasets.

Early Toxicity

For the 6 patients (3 prostate only, 3 ENI) acute rectal and gastrointestinal toxicity from treatment has been satisfactory to date. With five patients beyond three months' follow up and the sixth patient beyond six weeks, only 2 episodes of grade 1 proctitis have been

observed, both of which lasted less than 5 days. Clearly, longer follow-up in a larger cohort of patients is required to assess treatment related toxicity.

Discussion

In this report we have evaluated the potential dose sparing benefits from use of a hydrogel rectal spacer system in the first six patients recruited to a prostate SABR clinical trial. The spacer has been well-tolerated and allowed more patients to achieve both target volume objectives and OAR constraints, with significant improvements in rectal DVHs and corresponding NTCPs observed in the post-spacer radiotherapy plans. To date, prostate SABR has been well-tolerated by the patient cohort, although further recruitment and follow-up is required. As reported in other studies [7, 18], spacer delineation using CT images alone was difficult, therefore a multi-imaging modality approach (including MR imaging) was necessary for accurate contouring.

There is increasing evidence that biochemical control of localised prostate cancer is improved by dose-escalated radiotherapy [18]. Despite recent technological advancements, further dose-escalation is limited by the proximity of the prostate to the anterior wall of the rectum, with the rectum volume receiving ≥ 60Gy associated with a greater risk of grade 2+ rectal toxicity or bleeding in conventionally fractionated radiotherapy [15]. To reduce the dose to the rectum many clinical protocols have used an anisotropic CTV-PTV margin, limiting posterior expansion to reduce rectal radiation doses; however, a rectal spacer system provides an alternative option without having to potentially compromise target coverage.

Early investigations identified Polyethylene-glycol (PEG)-based [19] and Hyaluronic acid-based [20] hydrogels as potential prostate-rectum spacers. Commercial versions of these hydrogels, e.g. SpaceOAR® (Augmenix, Waltham, MA, USA), NASHA Spacer gel (Q-Med AB, Uppsala, Sweden) [21] and Hylaform (Genzyme Corporation, Cambridge, MA) [22], have now been incorporated into a number of clinical trials including this SABR study [9]. Human collagen has also been investigated as a potential spacer option [23], while Gez et al (2013) have evaluated the safety and efficacy of ProSpace™ (BioProtect Ltd, Kfar-Saba, Israel), a transperineal implantable biodegradable balloon system [24].

The dosimetric benefit of hydrogel rectal spacers has been reported in a number of conventionally fractionated IMRT studies [25-27]. In keeping with our results, these studies have reported >95% of spacer patients having a ≥25% reduction in rectal volume receiving high doses V_{70Gy} [26, 27]. Similar to the results reported by Pinkawa et al, we also observed a learning curve to the hydrogel spacer placement [28]. While the hydrogel placement in the first two patients exhibited a degree of asymmetry, it became increasing symmetric with each successive patient. Fischer-Valuck et al have reported that significant reduction of rectal dose can still be achieved even with asymmetric hydrogel spacer placement [29] and this was also observed in our study.

Clinical results from a recent phase III trial, that employed the SpaceOAR® hydrogel rectal spacer and recruited 222 patients, have described the acute and late toxicity benefits to a spacer system [8, 27, 30]. In agreement with the NTCPs predicted from our SABR study, long term (3 year) follow-up found that the reduction in rectal dose, as a result of using the spacer, correlated with a significant reduction in both grade 1+ (9.2% vs 2.0%) and grade 2+ (5.7% vs 0%) rectal toxicity. Given the life expectancy of these patients, these results are

both important and clinically meaningful. Quality of life (QoL), scored using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire, demonstrated statistically significant improvements in bowel QoL scores in the spacer patient group [30]. Interestingly, the authors have also reported a significant increase in the percentage of patients where the penile bulb mean dose constraint (< 23 Gy) was achieved using the rectal spacer system, which correlated with an improvement in sexual function [30].

Increased occurrences of high grade rectal toxicities have been reported in a number of recent SABR clinical trials. For instance, in a phase I / II study of prostate SABR with doses of 45-50 Gy in 5 fractions 6 out of 91 patients developed grade 3 or 4 rectal toxicity, with 5 patients requiring diverting colostomy [5]. In a separate prostate SABR study, rates of late rectal bleeding were 19.4% in 258 patients treated to 35 – 40 Gy in 5 fractions [31]. In their study, the volume of rectum receiving 38 Gy was found to be a predictor for rectal bleeding (odds ratio = 4.7 if > 2.0 cm^3). Both studies demonstrated a direct dose response for rectal toxicity with prostate SABR. The dose-sparing observed in our investigation suggests that the use of a rectal spacer may reduce the incidence of high grade rectal toxicities, although this needs tested in large prospective clinical trials.

Some groups have attempted to quantify the cost-effectiveness of rectal spacers. Vanneste et al performed a cost-benefit analysis, comparing treatment follow-up and toxicity costs with quality-adjusted life years (QALYs) [32]. They calculated a cost of €55,880 per QALY gained and, assuming the €80,000 ceiling ratio used in the Netherlands, determined a 77% probability of spacer use being cost-effective, but acknowledged that this probability could be considerably lower using the £30,000 threshold set by the UK National Institute for Health and Clinical Excellence (NICE). The group subsequently developed a set of decision

rules, based on clinical risk factors, to identify the patients expected to benefit the most from a rectal spacer [33]. Hutchinson et al evaluated the 10-year costs associated with rectal toxicity complications across different RT modalities and found that spacer use was immediately cost-effective for high dose (50 Gy) SABR [34]. This recommendation will be of particular relevance to future dose-painting trials where radiation boosts to the dominant intra-prostatic lesions (DILs) may be limited by rectum dose constraints [35, 36], with UK radiotherapy centres keenly awaiting NICE guidance for rectal spacer use in prostate radiotherapy [37].

Conclusion

Early clinical results from this UK cohort indicate that the insertion of a perirectal spacer was well tolerated by all patients. To our knowledge this is the first reported UK experience of a hydrogel rectal spacer system. Use of the spacer resulted in significant sparing of the rectum, with improvements in clinically significant rectal dose metrics and corresponding reductions in NTCPs for different rectal toxicity endpoints. This promising treatment approach merits further investigation in future prostate SABR studies.

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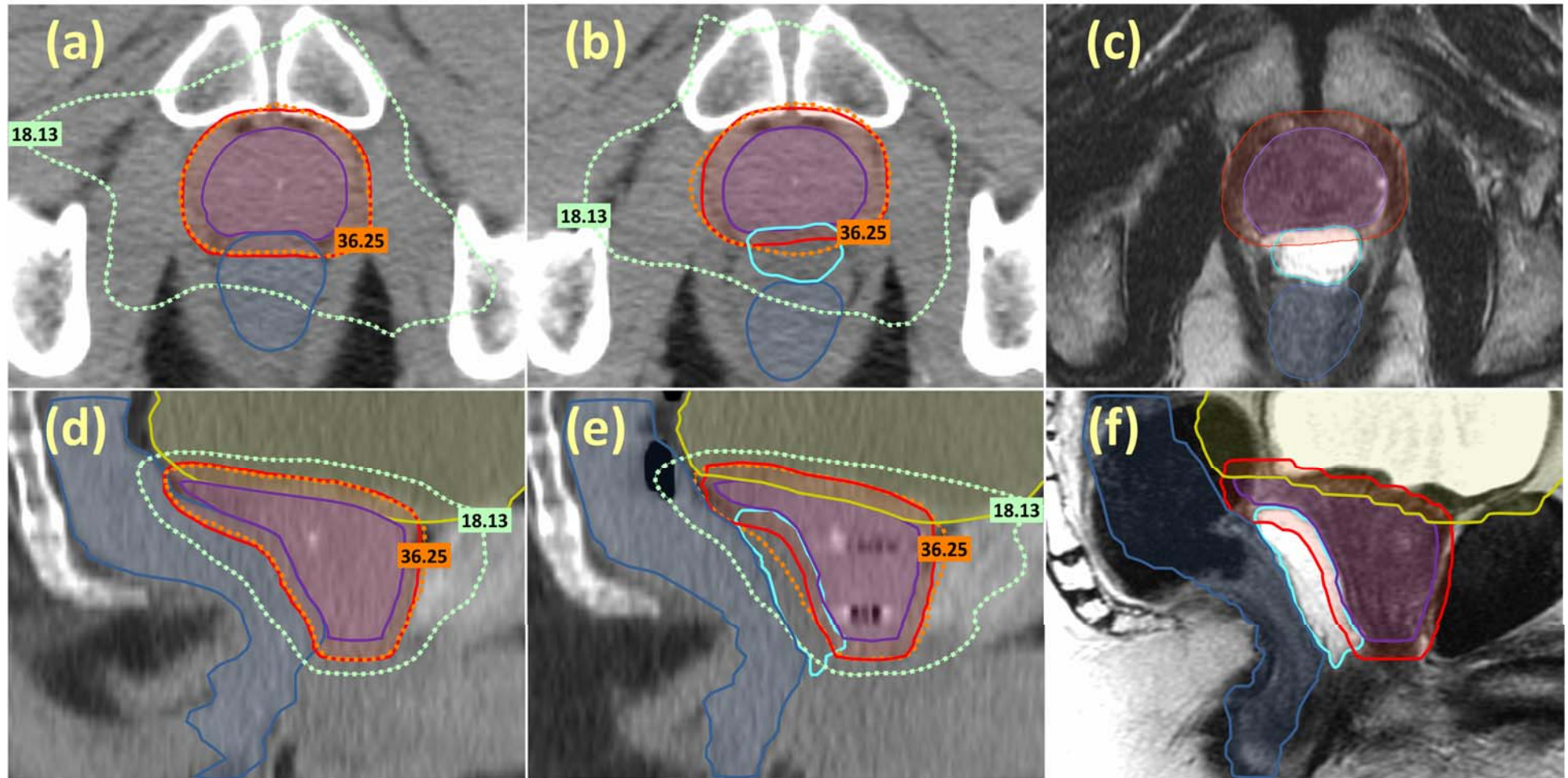
Figure 1 Axial (a – c) and sagittal (d – f) CT and MRI images acquired from patient 6 prior to and after hydrogel spacer insertion. (a) & (d) CT images acquired prior to spacer insertion. (b) & (e) CT images acquired following spacer and fiducial marker insertion. (c) & (f) Corresponding post-spacer MR images. Images include contours for the prostate and seminal vesicles CTV (purple) and PTV (red), bladder (yellow), rectum (blue) and spacer (cyan) structures and dashed lines corresponding to the 100% and 50% isodoses of the PTV prescription dose.
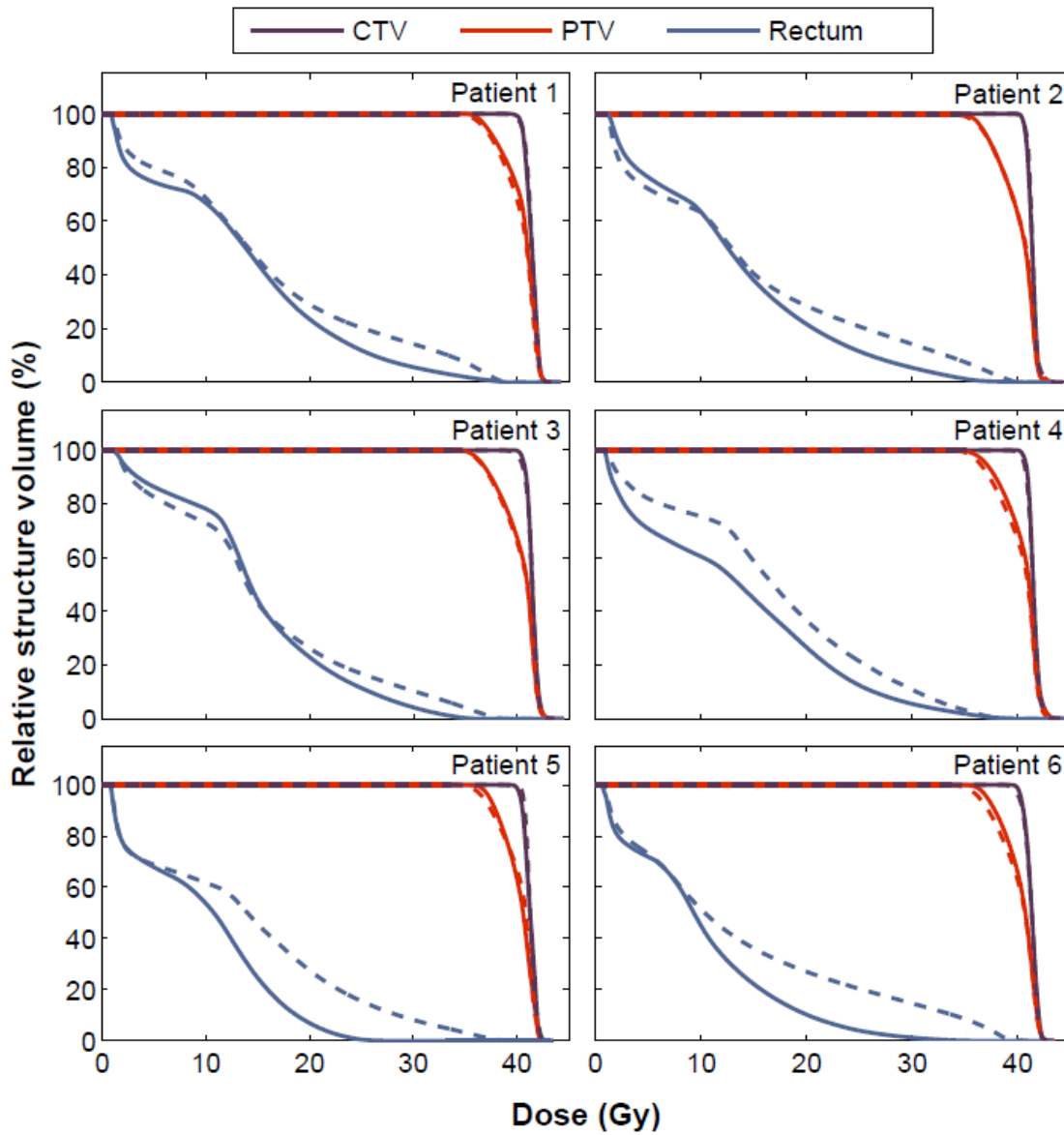
Figure 2 Dose volume histograms for target structures and rectum for individual patients, for optimised plans generated using the post-spacer (solid lines) or pre-spacer (dashed lines) CT images.
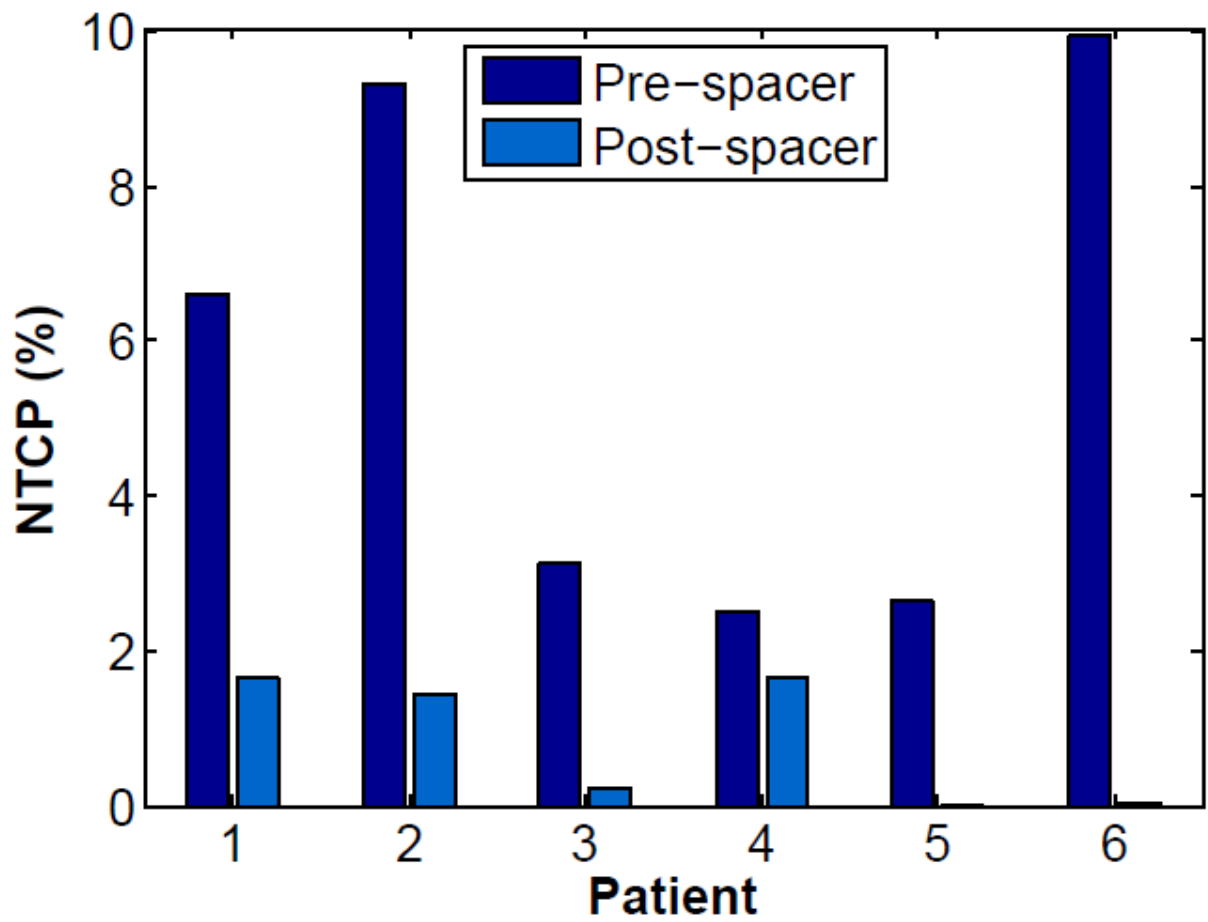
Figure 3 Change in grade 2+ rectal bleeding NTCP, calculated using QUANTEC LKB model parameters [15], for individual patients as a result of using a hydrogel rectal spacer.

Table I Planning objectives and constraints for targets and OARs

Target	Objective	Dose Variation	
		Minor	**Major**
PTV / CTV	$V_{Prescription} \geq 95\%$	$90\% \leq V_{Prescription} < 95\%$	$V_{Prescription} < 90\%$
PTV	$D_{98\%} \geq 34.4$ Gy		
	$D_{max} < 48$ Gy		
	$D_{2\%} \leq 42.8$ Gy		
OAR	**Dose constraints**		
Rectum	$V_{18.1Gy} < 50\%$		
	$V_{29Gy} < 20\%$		
	$V_{36Gy} < 1cc$	$1cc \leq V_{36Gy} < 2cc$	$V_{36Gy} \geq 2cc$
Bladder	$V_{18.1Gy} < 40\%$		
	$V_{37Gy} < 10cc$	$10cc \leq V_{37Gy} < 20cc$	$V_{37Gy} \geq 20cc$
Penile bulb	$V_{29.5Gy} < 50\%$		
Femoral head	$V_{14.5Gy} < 5\%$		

Table II Summary of key plan evaluation and target structure DVH metrics for patient cohort, median (min – max).

Metric	Objective	Target Volume	Pre-spacer plans	Post-spacer plans
$V_{Prescription}$ (%)	>95%	CTV	98.8 (96.3 - 99.7)	99.5 (98.6 - 100.0)
			96.0 (95.4 - 97.1)	98.1* (96.5 - 99.4)
$D_{98\%}$ (Gy)	PTV > 34.4 Gy		35.6 (35.4 - 35.9)	36.2* (35.8 - 36.7)
$D_{2\%}$ (Gy)	PTV <42.8 Gy	PTV	42.3 (42.2 - 42.4)	42.3 (42.0 - 42.7)
MU			2272 (2248 - 2475)	2240 (2143 - 2423)
CI	<1.2		1.0 (1.0 - 1.1)	1.0 (1.0 - 1.1)

*p ≤ 0.05 considered statistical significant

Table III Key DVH metrics of patient cohort for rectum and bladder OARs, median (min – max).

OAR	Metric	Constraint	Pre-spacer plans	Post-spacer plans
Rectum	D_{Mean} (Gy)		15.0 (13.8 - 16.9)	13.4* (9.9 - 14.9)
	D_{2cc} (Gy)		36.3 (34.1 - 37.8)	31.1* (21.5 - 33.6)
	$V_{18.1Gy}$ (%)	<50 %	33.0 (30.0 - 44.2)	28.0* (11.9 - 33.4)
	V_{29Gy} (%)	<20%	14.1 (9.4 - 15.7)	5.9* (0.0 - 6.6)
	V_{36Gy} (cc)	<1cc	2.6 (1.0 - 4.1)	0.3* (0.0 - 1.0)
	V_{38Gy} (cc)		0.5 (0.2 – 1.7)	0.1 (0.0 - 0.3)
Bladder	D_{Mean} (Gy)		8.5 (5.8 - 11.1)	9.2 (5.8 - 15.3)
	D_{2cc} (Gy)		39.9 (38.7 - 41.1)	39.6 (38.1 - 41.6)
	$V_{18.1Gy}$ (%)	<40%	20.6 (11.0 - 25.4)	21.7 (11.9 - 38.5)
	V_{37Gy} (cc)	<10cc	6.9 (4.4 - 13.9)	7.0 (3.4 - 12.5)

*p ≤ 0.05 considered statistical significant

Table IV TCP / NTCP analysis performed on the CTV, bladder and rectum structures, median (min – max).

Structure	TCP / NTCP	Pre-spacer plans	Post-spacer plans
CTV	Tumour Control [14]	98.8 (98.6 - 98.8)	98.7 (98.6 - 98.9)
Rectum	Bleeding 2+ [15]	4.9 (2.5 - 9.9)	0.8* (0.0 - 1.7)
	Incontinence [16]	3.4 (3.0 - 3.9)	2.8* (1.9 - 3.0)
	Severe frequency [17]	0.9 (0.5 - 1.0)	0.3* (0.0 - 0.3)
Bladder	Cystitis / loss of volume [18]	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)

*p ≤ 0.05 considered statistical significant

Appendix A: EUD, TCP and NTCP Calculation

The equivalent uniform dose (EUD) reduces a non-uniform dose distribution to a single dose, which in a uniformly irradiated tissue would result in the same level of cell kill / tumour control probability (TCP), or normal tissue complication probability (NTCP), as with the non-uniform dose:

$$EUD = \left(\sum_i v_i D_i^a \right)^{\frac{1}{a}}$$ A.1

The sum is calculated over all bins (v_i, D_i) of the differential DVH, and a parameter is associated with the strength of the volume effect. When a is a large positive number the EUD is approaches the maximum dose, whereas for a = 1 it gives the mean dose; as it decreases to a large negative number the EUD approaches the minimum dose [1].

TCP/NTCP was then calculated using the Lyman–Kutcher–Burman (LKB) model [2]:

$$TCP/NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} exp\left(\frac{x^2}{2}\right) dx$$ A.2

where $t = \frac{EUD - TD_{50}}{m \cdot TD_{50}}$ and TD_{50} is the dose that will result in 50% probability of tumour control or normal tissue complication in a uniformly irradiated tissue and m is inversely proportional to the slope of the steepest point on the TCP or NTCP vs. dose response curve (thus larger values of m represent more shallow dose-complication slopes). The model parameters used to calculate TCP for the CTV structure [3], and NTCP for different toxicity endpoints to the rectum [4, 5] and bladder [6] structures are reported in Table S.I.

Table A.I Model parameters used for TCP and NTCP calculations.

Type	Organ	a	TD_{50}	m	Endpoint
Tumour	CTV(psv)	-10	67.5*	0.24	Tumour control [13]
OAR	Rectum	11.11	80	0.13	Grade 2+ bleeding ¥ [14]
		1	105	0.43	Incontinence* [15]
		2.56	84	0.24	Severe frequency¤ [15]
OAR	Bladder	2	80	0.11	Cystitis \ contracture \ volume loss [16]

TD_{50}: The dose required for 50% probability of tumour control or 50% probability of normal tissue complication. ¥QUANTEC model based on 3D CRT data. §Model based on IMRT treatment doses. *Model parameters for anus (defined as the most caudal 3cm of the rectum). Incontinence is defined as the loss of mucous, stool or blood necessitating the use of pads at least twice per week. ¤Stool frequency of six or greater times per day.

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Supplementary Excel file 1.

Reports individual plan evaluation and DVH metrics for target structures for each of the six patients investigated.

Supplementary Excel file 2.

Reports individual organ at risk DVH metrics for each of the six patients investigated.