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FULL PAPER

Dosimetric impact of organ at risk daily variation during prostate stereotactic ablative radiotherapy

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Objective: Prostate stereotactic ablative radiotherapy (SABR) delivers large doses using a fast dose rate. This amplifies the effect geometric uncertainties have on normal tissue dose. The aim of this study was to determine whether the treatment dose–volume histogram (DVH) agrees with the planned dose to organs at risk (OAR).

Methods: 41 low–intermediate risk prostate cancer patients were treated with SABR using a linac based technique. Dose prescribed was 35 Gy in five fractions delivered on alternate days, planned using volumetric modulated arc therapy (VMAT) with 10X flattening filter free (FFF). On treatment, prostate was matched to fiducial markers on cone beam CT (CBCT). OAR were retrospectively delineated on 205 pre-treatment CBCT images. Daily CBCT contours were overlaid on the planning CT for dosimetric analysis. Verification plan used to evaluate the daily DVH for each structure. The daily doses received by OAR were recorded using the D%.

Results: The median rectum and bladder volumes at planning were 67.1 cm^3 (interquartile range 56.4–78.2) and 164.4 cm^3 (interquartile range 120.3–213.4) respectively. There was no statistically significant difference in median rectal volume at each of the five treatment scans compared to the planning scan (p = 0.99). This was also the case for median bladder volume (p = 0.79). The median dose received by rectum and bladder at each fraction was higher than planned, at the majority of dose levels. For rectum the increase ranged from 0.78–1.64Gy and for bladder 0.14–1.07Gy. The percentage of patients failing for rectum D35% < 18 Gy (p = 0.016), D10% < 28 Gy (p = 0.004), D5% < 32 Gy (p = 0.0001), D1% < 35 Gy (p = 0.0001) and bladder D1% < 35 Gy (p = 0.001) at treatment were all statistically significant.

Conclusion: In this cohort of prostate SABR patients, we estimate the OAR treatment DVH was higher than planned. This was due to rectal and bladder organ variation.

Advances in knowledge: OAR variation in prostate SABR using a FFF technique, may cause the treatment DVH to be higher than planned.

INTRODUCTION

Prostate cancer in European males has a high incidence, with nearly 450,000 cases diagnosed per year.[1] In low–intermediate risk prostate disease external beam radiotherapy is a well-established treatment either alone, or in combination with androgen deprivation therapy. Other treatment options include active surveillance, brachytherapy and surgery. Treatment choice depends on stage and associated toxicity.[2–4] Stereotactic ablative radiotherapy (SABR) delivers high doses of precise radiotherapy, over a short course.[5] The low α/β ratio of prostate cancer, compared with surrounding normal tissue supports the rationale for SABR.[6] A shorter treatment course being an attractive option for patients due to less department visits.

A meta-analysis of over 6000 low–intermediate risk prostate cancer patients treated with SABR in 5–10 Gy over 4–9 fractions, shows acceptable toxicity and patient reported quality of life.[7] Prostate SABR requires randomised controlled data to support it as standard of care, long-term effects still under review. Early reports of prostate advances in comparative evidence (PACE) study are encouraging, although recent reports from HYPO-RT-PC trial suggests ultra-hypofractionation may increase genitourinary toxicity.[8,9]

Advanced radiotherapy planning improves dose to the target volume, and minimises normal tissue dose by sculpting dose distributions. In addition, image-guided radiotherapy (IGRT) allows accurate and precise daily prostate positioning.[10,11] Current technology allows the delivery of SABR on a linear accelerator using flattening filter free (FFF) mode in around 2 min per fraction. We previously published our linac-based SABR safety and feasibility study results, showing clinically acceptable toxicity in 41 patients.[12] In a series of 90 patients the D'Agostino (2016) group in Milan, also report mild toxicity and observe minimal effect on quality of life up to 2 years using a similar FFF technique.[13]

A SABR technique improves the conformity; nonetheless there are many challenges to overcome, *e.g.* the prostate sits adjacent to organs at risk (OAR), the rectum and bladder. These organs are mobile and deform depending on patient physiology, often causing overlap of volumes. As the treatment planning system calculates the radiotherapy treatment plan based on planning CT anatomy, subsequent variations are not accounted for.

Dose–volume histogram (DVH) data are derived from CT, which forecasts treatment dose, meaning effects of daily organ changes may be ignored.[14–17] For this reason, DVH being representative of the delivered plan is central to the success of an advanced planning technique.[18] Organ motion can result in setup error and geometric uncertainty, which may negatively impact target coverage and normal tissue dose.[14] There is limited evidence on the optimal planning dose constraints using a linear accelerator FFF technique, with recent consensus based on trials.[19]

In SABR, the need to reproduce and deliver the desired plan is pertinent. Any deviation could result in a geographical miss or undesirable normal tissue dose.[20] FFF delivery mode allows a faster dose delivery rate, where organ deviations and uncertainties may have more effect. Delivery of a large dose per fraction could amplify this further. As the number of fractions decrease, organ changes may impact more.[6,10,21,22] In these circumstances where the goal to enhance the therapeutic ratio with accuracy, precision, and improved conformity could be lost.[23]

We aimed to determine whether the treatment DVH agrees with the planned dose to OAR. Objectives for this study were to:

(1) Quantify variation in organ volume.
(2) Determine if on treatment rectum and bladder DVH exceeds the planned DVH.
(3) Assess if dose to rectum and bladder correlates to organ volume.

METHODS AND MATERIALS

Study design

This was a retrospective planning sub study of patients treated with prostate SABR in PRO SABR study (A pilot study to assess acute gastrointestinal and genitourinary toxicity in patients treated with FFF SABR for prostate cancer) (n = 41), ethically approved by the West of Scotland Ethics Committee on 25th April 2013 (13/WS/0091). The dose prescribed was 35 Gy in 5 fractions, delivered over alternate days using a volumetric modulated arc therapy (VMAT) 10x FFF technique (Rapidarc^{TM}, Varian Medical Systems, Palo Alto, CA) as previously described.[12]

Treatment planning

Delineation was performed on a registered MRI/CT image set. The clinical target volume (CTV) was the prostate only (or in some circumstances prostate plus seminal vesicles) as outlined by the clinical oncologist. The planning target volume (PTV) was taken as CTV with 5 mm margins added in all directions except posteriorly, where 3 mm was used to minimise rectum dose. The OAR, were the rectum (from the anus to the rectosigmoid junction), the bladder (including wall and lumen) and left and right femoral heads.

Treatment and verification

For both planning and treatment delivery, patients were instructed to use a microlax enema preparation, empty their bladder and drink 450 ml of water 30 min before scanning. Treatment was delivered on a Varian Truebeam STx linear accelerator (Varian Medical Systems, Palo Alto, CA). Immediately before each treatment following preparation and setup, participants had a pre-treatment cone-beam CT (CBCT) scan. Acquired using "Pelvis" acquisition mode, the half-fan bowtie filter, with settings of 1080mAs 125kV, 80mA. Daily CBCT images (#1–5) were registered with the planning CT (CTp) based on fiducials. Any mismatch was corrected by applying all shifts. PTV coverage and OAR position was approved online by a clinical oncologist.

CBCT contouring and plan evaluation

The CBCT image set was registered with the CTp at the online seed match treatment position. The rectum and bladder were manually contoured on CTp and each CBCT (#1–5) by one observer to ensure consistency, peer reviewed by a second observer. CBCT contours were transferred to the CTp structure set. A verification plan was created using Eclipse V10.0.39 (Varian Medical Systems, Palo Alto, CA) and calculated for 1 fraction of 700cGy on the CTp data set. Verification plans were re-calculated using anisotropic analytical algorithm (AAA 10.0.28) on a calculation grid of 1.25 mm.

Data analysis

The initial planning constraints for OAR were rectum, V18Gy < 35%, V28Gy < 10%, V32Gy < 5%, V35Gy < 1% and bladder V35Gy < 1%.

Dose received to the rectum and bladder was evaluated on the DVH at each individual fraction. To evaluate the dose received by each organ at an individual fraction, the dose to the constraint % volume of the structure was measured, and dose received at this volume recorded. The dose measured at each fraction at the specified % volume was added together to estimate the delivered DVH. This was then compared to the dose at the structure ratio (D%) of the planning DVH.

Statistical tests

DVH were exported from Eclipse V10.0.39 (Varian Medical Systems, Palo Alto, CA) and imported into StataCorp Stata

Table 1. Patient characteristics

Baseline characteristics (n = 41)		Median (IQR) or % (n)
Age (years)		68 (65–71)
Initial PSA (ng/ml)		10.5 (8.0–13.3)
T stage[a]	1	14.6 (6)
	2	82.9 (34)
Gleason score	6	41.5 (17)
	7	58.5 (24)
Androgen deprivation therapy	No	24.4 (10)
	Yes	75.6 (31)

IQR, interquartile range; PSA, prostate-specific antigen.
[a]T-stage not recorded for one patient

Statistical Software: v. 14.0 for analysis. Statistical significance was set at a level of 5%, and all tests used were two-sided. The Wilcoxon sign rank test of equality was used to determine if there were differences between the structure volumes at planning and treatment. McNemars test of proportions in matched pairs was used to determine if there were differences in the proportion of patients failing to meet specific constraints at treatment in comparison to planning. Spearman rank correlation coefficients were used to describe the associations between dose and organ volume.

RESULTS

All 41 patients recruited to the PRO SABR study between November 2013 to June 2016 were included for analysis. The median age was 68 years [interquartile range (IQR) 65–71]. Patient characteristics are reported in Table 1. A total of 205 pre-treatment CBCT scans were dosimetrically analysed.

Planning statistics

The median CTV and PTV volumes were 36.0 cm^3 (IQR 29.9–45.1) and 76.4 cm^3 (IQR 64.8–90.1) respectively. All plans achieved the objective that 99% of the CTV should receive at least 95% dose, and that 95% of the PTV should receive at least 95% prescribed dose.

Volume of rectum and bladder

Figure 1 shows the variation in bladder and rectum volume over the planning and five treatment fractions for patient 23. For all patients, the median rectum and bladder volumes at planning were 67.1 (IQR 56.4–78.2) and 164.4 (IQR 120.3–213.4) cm^3 respectively. Overall, there was no statistically significant difference in median rectal volume at each of the five pre-treatment scans compared to the planning scan (p = 0.99 (Table 2)). This was also the case for median bladder volume (p = 0.79). The median difference in volumes for the rectum ranged from −3 (at fraction 2) to 2.4 cm^3 (fraction 4). For the bladder volume, the difference ranged from −10.6 (fraction 3) to 17.6 cm^3 (fraction 5). In contrast, the percentage of the OAR overlapping the planning PTV increased at treatment. For the rectum, the median overlap at planning was 2.3% and this increased to 5.3% at the first treatment (p < 0.0001). Similarly, the median percentage of the bladder overlapping the planning PTV increased from 2.6% at planning to 3.9% at treatment (p < 0.0001).

Figure 2 shows the rectal and bladder volume from each pre-treatment scan plotted against the respective planning volume. The figure shows substantial regression to the mean, where there is more systematic change at the tails of the planning measurements; patients with small volumes at planning have larger volumes at treatment, and patients with large volumes at planning had lower volumes at treatment. The intrapatient correlation coefficient for rectum volume was 0.60 [95% CI 0.47–0.72) which was stronger than that found for bladder 0.45 (95% CI 0.32–0.60). The intra patient correlation coefficient indicates the degree to which volume measures are stable over fractions. Relative to the planning volume, 68% of the variation in bladder volume and 42% of variation in rectum volume was attributed to variation within patients.

Figure 1. Superimposed rectal and bladder contours from planning CT (black contour) and each fraction (white contour) for patient 23 on axial and sagittal view of original planning scan.

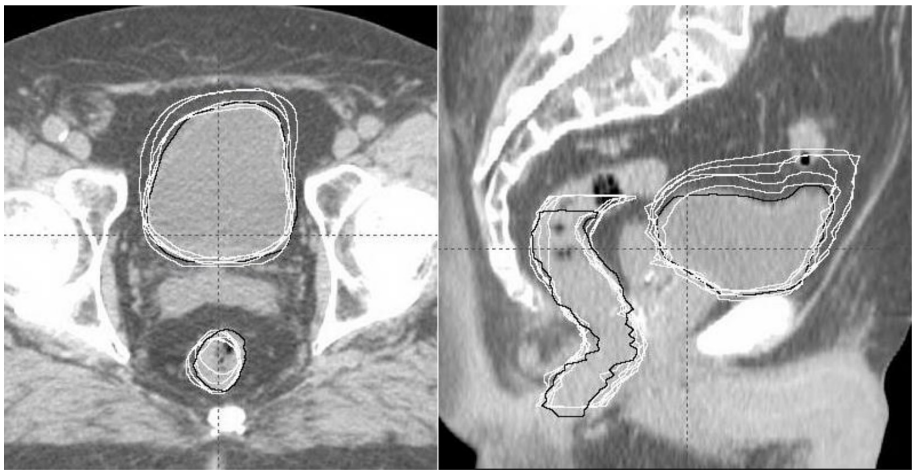


Table 2. Rectum and bladder volume at planning and each fraction with PTV overlap

		Volume (cm^3)		Volume overlap with PTV (%)	
Organ	Planning or treatment fraction number	Median	IQR	Median	IQR
Rectum	Planning	67.1	(56.4–78.2)	2.3	(1.0–3.4)
	1	65.7	(56.3–83.1)	5.3	(2.7–7.2)
	2	67.1	(56.3–81.2)	4.2	(1.7–7.9)
	3	66.3	(58.2–83.6)	4.1	(1.1–5.9)
	4	71.3	(58.8–78.3)	4.2	(1.6–6.1)
	5	66.6	(58.3–79.4)	5.0	(1.9–7.4)
Bladder	Planning	164.4	(120.3–213.4)	2.6	(1.6–5.9)
	1	146.8	(115.8–196.8)	3.9	(2.6–7.9)
	2	173.7	(119.6–231.2)	3.5	(1.8–6.2)
	3	162.4	(128.4–246.5)	3.1	(1.3–8.0)
	4	156.4	(114.0–247.4)	2.7	(1.6–7.2)
	5	147.9	(117.2–202.5)	3.7	(2.1–6.6)

IQR, interquartile range; PTV, planning target volume.

Dose to ratio of percentage of structure rectum and bladder

Table 3 shows the dose received by each percentage of volume on treatment and the planned dose. For both rectum and bladder, with four exceptions, the median dose received at each fraction was higher than that expected at planning. Figure 3 shows the difference in delivered dose and the planned dose. For each % of rectum the median difference between dose delivered and dose planned range from 0.78 to 1.64 Gy, for the bladder the increase was smaller and ranged from 0.14 to 1.07 Gy. The figure shows that an increase of up to 5 Gy occurred for some patients.

Dose constraints

Table 4 shows the dose constraints and the number of patients who failed at planning and at treatment. At planning, two patients [4.9%, 95% CI (0.6–15.5%)] failed to meet the constraint that the dose to 35% of the rectum (D35%) should be less than 18 Gy. At treatment, the number increased to 9 (22.0%, 95% CI (10.6–37.6%)), p = 0.016). The percentage failing each of the other constraints D10% < 28 Gy, D5% < 32 Gy and D1% < 35 Gy similarly showed a statistically significant increase at treatment compared to that expected at planning. For the dose delivered to the bladder, at planning four patients (9.8%) failed the constraint that the dose received by 1% of the bladder (D1%) should be less than 35 Gy. This increased to 18 patients (43.9%, 95% CI (28.5–60.3%)) at treatment (p = 0.001).

Table 5 presents the correlation between dose and volume when they are both expressed relative to the values expected at planning. The table shows that for 1% of the rectum the correlation was positive (p = < 0.001). This means that when the volume of 1% of the rectum was greater than that expected at planning the dose received by 1% was higher than what had been planned. For D5% and D10% there was no statistically significant association, and for D35% the correlation was negative (p =< 0.001) so that as the volume of 35% of the rectum increased relative to what had been documented at planning the dose received by 35% of the organ decreased. The correlation between relative dose and relative volume for the bladder at D1% was negative.

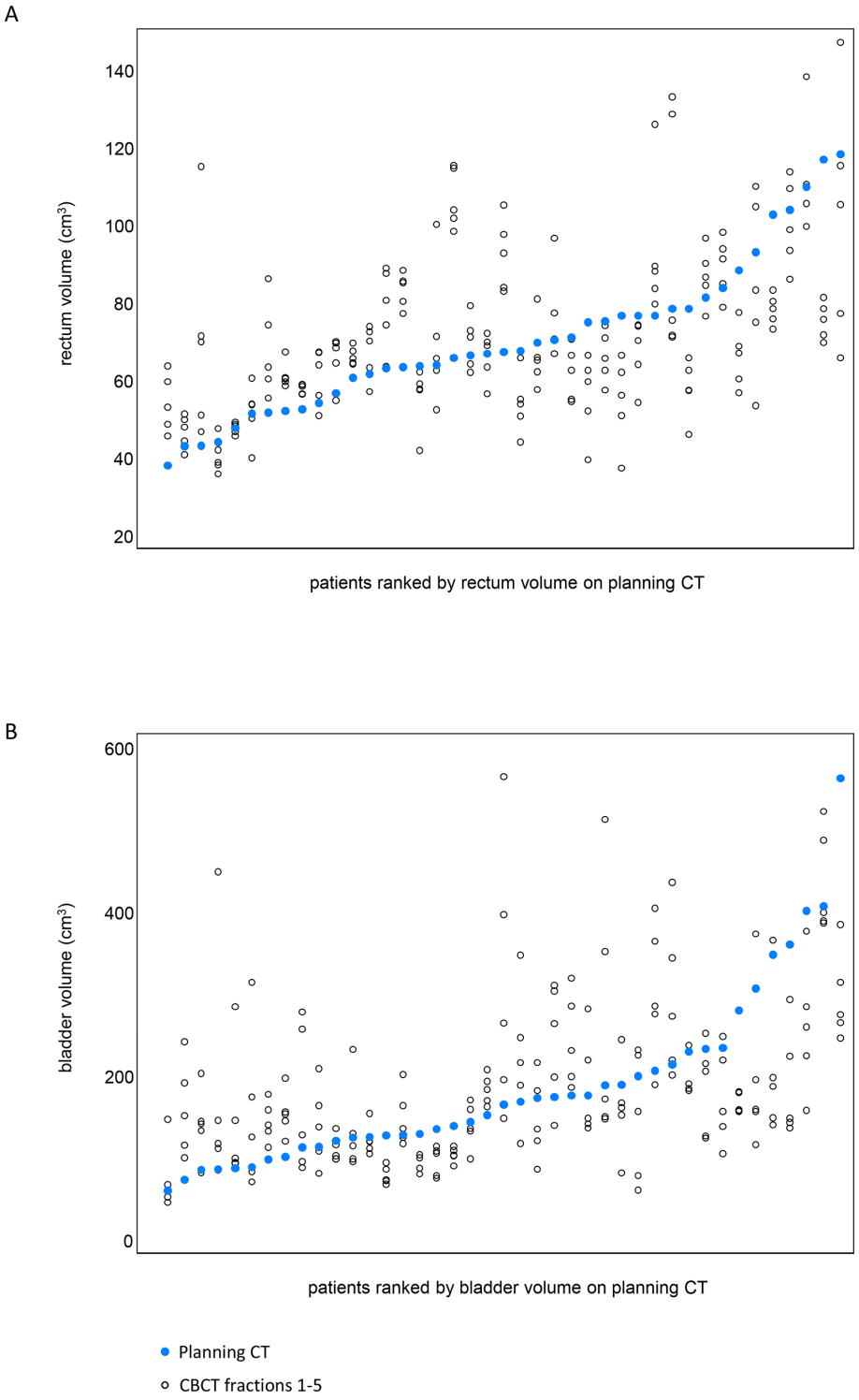
DISCUSSION

In this cohort of prostate cancer patients treated with SABR, we aimed to determine whether the treatment DVH agrees with the planned dose to OAR. Our results indicate the OAR treatment DVH was higher than planned. The volume of OAR shows inter fraction variation with significant regression to the mean, but we did not observe systematic variation during treatment. While analysis of planned DVH indicates treatment constraints would be met by most patients, on treatment DVH estimates that over 40% of patients fail these constraints. To our knowledge we are the first to report OAR variation in SABR using a linac based FFF technique.

Our findings are difficult to compare to the literature, where studies in conventional prostate radiotherapy describe varying methods to assess delivered dose with only two studies identified in the SABR setting.[15,18,24–32]

Evidence of volume changes is lacking in SABR with inter fraction rectal variation well documented in conventional radiotherapy.[17,25,26,33,34] We found no systematic change for rectal volume, although Maund et al. (2014) report rectal volume decreases on treatment. This study was without bowel preparation, only offering patients dietary advice.[33] Patients in our study were given a micro enema prior to planning and each fraction. Visual assessment led us to observe rectum filing was often to be at the superior aspect, near to the recto sigmoid junction, in agreement with previous authors.[35] Our study lacks analysis of change for any particular portion of the rectum; this could be an aspect for future work.

Figure 2. Scatter plot of individual patients' rectum and bladder volumes at planning and each treatment.



Bladder volume when we compare to rectal volume, shows larger inter fraction variation for all patients, agreeing with previous work in conventional regimes.[18,25,29,30,36] Our study found no statistically significant change in bladder volume from planning to treatment, as did others.[29] We found at least 20 patients on at least one occasion, had a bladder volume which was 50% greater than that at planning, and 9 patients with a bladder volume less than 50% of that at planning. Variations as large as 58% have previously been reported.[25,29]

Our analysis of bladder and rectal volumes suggests substantial regression to the mean indicating there may be an optimum planning volume which could potentially predict patients where change on treatment is most likely.

Table 3. Dose received by each percentage of volume at planning and treatment

		Percentage of organ volume							
		D1%		D5%		D10%		D35%	
Organ	Planning or treatment fraction number	Median dose (Gy)	IQR	Median dose (Gy)	IQR	Median dose (Gy)	IQR	Median dose (Gy)	IQR
Rectum	Planning	6.76	(6.68–6.88)	6.11	(5.85–6.29)	5.22	(4.92–5.43)	2.92	(2.46–3.37)
	1	7.00	(6.85–7.12)	6.52	(6.18–6.76)	5.63	(5.23–6.12)	3.20	(2.85–3.47)
	2	6.96	(6.81–7.07)	6.50	(5.90–6.78)	5.66	(4.96–6.20)	3.29	(2.72–3.56)
	3	6.98	(6.71–7.07)	6.44	(5.82–6.67)	5.61	(5.05–6.00)	3.17	(2.84–3.55)
	4	6.98	(6.77–7.08)	6.31	(5.98–6.68)	5.45	(4.91–5.97)	3.22	(2.76–3.40)
	5	6.98	(6.75–7.14)	6.40	(6.06–6.76)	5.63	(5.21–6.15)	3.32	(2.83–3.74)
Bladder	Planning	6.83	(6.68–6.89)	5.76	(5.16–6.64)	4.42	(3.72–5.76)	1.08	(0.59–2.38)
	1	7.05	(6.83–7.16)	6.45	(5.58–6.88)	4.97	(3.94–6.27)	1.65	(0.60–2.63)
	2	7.03	(6.73–7.15)	6.15	(5.10–6.78)	4.21	(3.54–5.64)	1.47	(0.50–2.35)
	3	6.97	(6.72–7.11)	5.95	(4.80–6.85)	4.20	(3.58–5.91)	1.00	(0.71–2.25)
	4	6.84	(6.70–7.12)	5.82	(5.13–6.88)	4.31	(3.52–6.24)	1.22	(0.60–2.53)
	5	6.99	(6.78–7.15)	6.26	(5.49–6.81)	4.54	(3.70–5.85)	1.60	(0.62–2.52)

IQR, interquartile range.

In the SABR setting there have been attempts to analyse delivered dose to OAR. In one analysis, real time monitored translations calculated on the CTp account for intra fraction motion, but negate daily organ variations.[32] Similarly Wahl et al. (2017) use methods that predict organ variation based on conventional radiotherapy images. The authors apply these organ changes to the SABR plan, without recognition of the daily organ variation. Our results show volume changes could be significant over the course of five fractions in an SABR plan.[24]

Our findings show large variation in delivered dose to the rectum, consistent with previously published results in SABR and conventional radiotherapy.[15,18,24,27,28,36] We found a positive association, between overall rectal volume and estimate of dose received by 1% of rectum volume; and a negative association with estimate of dose received by 35% of rectum volume. Looking at the dose received by 5 and 10% rectal volume and overall rectal volume, we found no statistically significant association.

Our analysis estimates a significant increase in delivered dose to the bladder, previous work supports this difference.[15,28,31,36–38] However, this could be attributed to the bladder only having one planning constraint set at V35Gy < 1%. Others report no significant difference between planned and delivered dose.[24,29] The correlation we observe between dose to 1% of the bladder and the volume was negative (p = 0.004). The bladder volume increase is associated with a decrease in dose which previous studies observe.[24,26,29]

Our study used dose volume analysis to estimate the delivered dose to OAR as have other researchers.[15,18,24–27,29,34,37] This methodology lacks spatial information as it provides two-dimensional data and negates three-dimensional volumetric information.

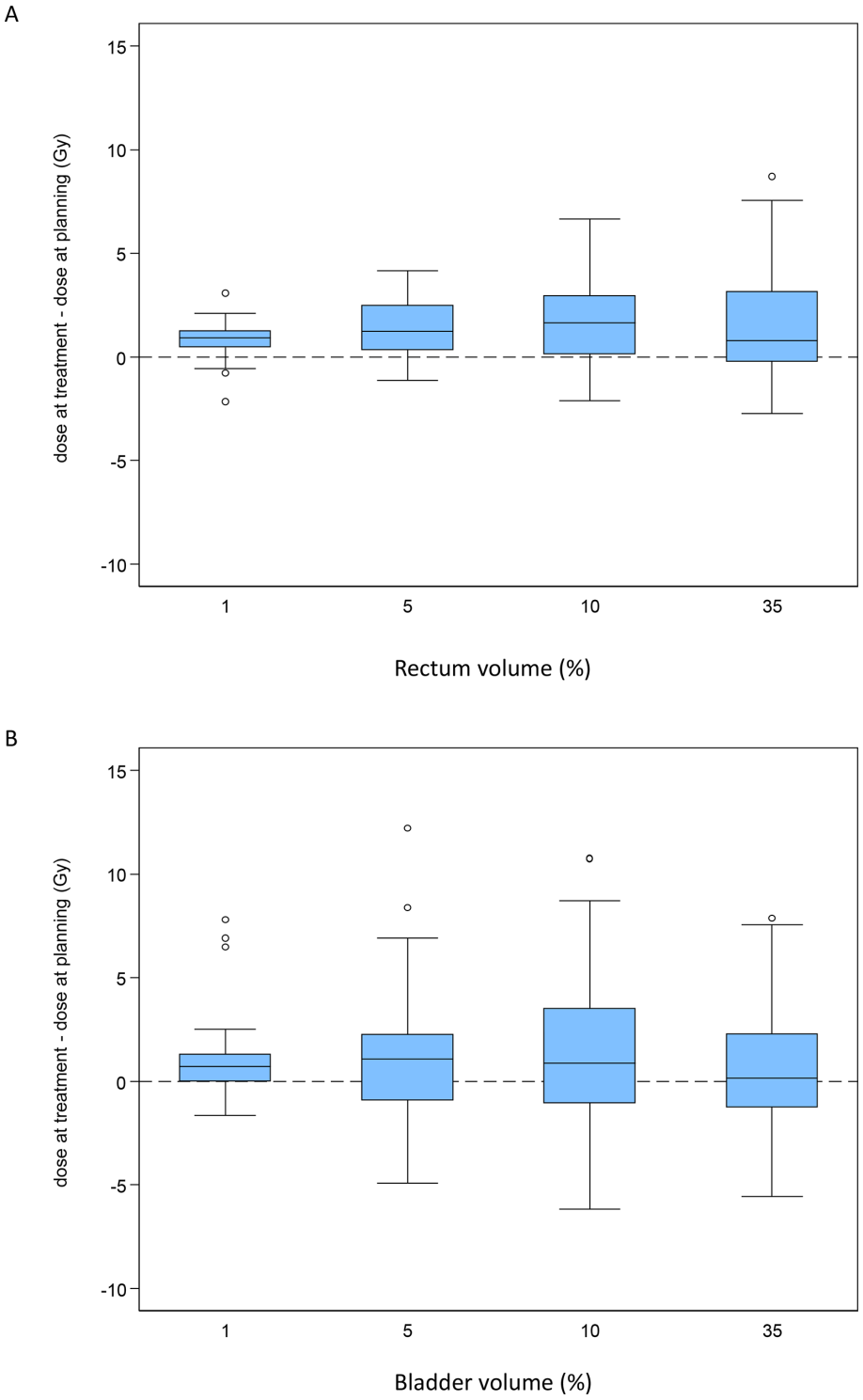
A variety of approaches have been undertaken to add spatial information. The summation of DVH's in a vector based method which minimises effects of overlying dose distributions, deformable image registration (DIR), and using commercially available programs to develop dose accumulation on a voxel by voxel basis.[31,36,39–42] Others adopt multivariate analysis in the form of models to predict dose.[30]

Most methodologies have recognised issues. In a deforming organ, some suggest fraction dose cannot be added, offering DIR as a solution.[36] Studies have used DIR to add spatial information to DVH analysis.[36,38,42] However, DIR may be unreliable in the pelvis due to the nature of organ changes, with arguments that deforming dose to assess accumulation should not be used clinically.[43–46] Deformable dose accumulation techniques produce one resultant dose distribution, which may be a limitation.[42] Interestingly, in a study using DVH analysis and DIR, Andersen et al. conclude that adding DVHs is a good indicator of bladder delivered dose.[38] They assessed and compare using a DIR method which did little to further evaluate delivered dose.

Commercially available DIR algorithms have improved recently, with each algorithm handling clinical case specific scenarios differently. Quality assurance of each algorithm is essential for safe clinical interpretation to aid an adaptive workflow.[47] Challenges, specifically in the pelvic region where tissues that are "sliding tissues," *e.g.* bladder and rectum can cause suboptimal registrations.[48,49]

A limitation of our study is that CBCT images were acquired pre-treatment and our data lack intrafraction motion, previous work discusses this.[18] The findings we report here could therefore be greater, as they assume a perfect fiducial marker match

Figure 3. The difference in cumulative and planned dose to rectum and bladder at specified volumes.



throughout treatment. In the SABR setting this a concern where margins are tighter and dose gradients steeper than conventional techniques.

In a planning study, MacDougall et al suggest intrafraction motion can be mitigated with a strict rectal and bladder protocol.[50] However, we observed large volume variations in this patient population, even with a robust patient preparation protocol. This implies intrafraction motion could be more of an issue in SABR than this paper details. Our findings lead us to question how effective our local bowel and bladder preparation is, although it is unclear how we could improve this, with lack of consensus in the literature.[35]

Table 4. Dose (Gy) to ratio (D%) of rectum and bladder structures at planning and treatment

	Planning			Treatment			
Dose to ratio of structure	Patients failing constraint	%	95% CI	Patients failing constraint	%	95% CI	
Rectum							
D35% < 18 Gy	2	4.9	(0.6–15.5)	9	22.0	(10.6–37.6)	$p = 0.016$
D10% < 28 Gy	7	17.1	(7.1–32.1)	19	46.3	(30.7–62.6)	$p = 0.004$
D5% < 32 Gy	4	9.8	(2.7–23.1)	19	46.3	(30.7–62.6)	$p = 0.0001$
D1% < 35 Gy	2	4.9	(0.6–15.5)	17	41.5	(26.3–57.9)	$p = 0.0001$
Bladder							
D1% < 35 Gy	4	9.8	(2.7–23.1)	18	43.9	(28.5–60.3)	$p = 0.0001$

CI, confidence interval.
p-values based on McNemars test of proportions in matched pairs.

Online plan adaption is a solution to mitigate daily prostate deformation and organ changes. Future developments of the MR linac are exciting, enabling real-time planning in a timely manner, accounting for intra- and interfraction errors.[51] Potentially hypofractionated regimes could benefit most from these new adaptive strategies, given the capability of delivering daily optimised plans, ensuring normal tissue dose is minimised.

A strength of our study is that this is a homogenous group of patients, who were part of a clinical trial planning protocol and dose constraints. Our results, based on daily imaging information, give full treatment course information.

Table 5. Association between relative dose and relative volume

	Spearman rank correlation	*p*-value
Rectum volume (%)		
1	0.364	$p < 0.0001$
5	0.088	$p = 0.21$
10	−0.087	$p = 0.22$
35	−0.460	$p < 0.0001$
Bladder volume (%)		
1	−0.245	$p = 0.0004$

Correlation shows if there is association between relative dose (relative to planning) and relative volume (relative to planning volume).

CONCLUSION

In this cohort of prostate cancer patients, treated with linac-based SABR, we estimate the OAR treatment DVH was higher than anticipated at planning. Our findings estimate the delivered dose to rectum and bladder to be higher at the majority of dose levels. We have demonstrated safety and feasibility in this group of patients, however the interfraction organ variations we observe here may be a cause for concern.[12] To our knowledge, this is the first study to report interfraction organ variation in a series of prostate SABR patients using daily CBCT images and DVH analysis. Further work in the SABR setting is required to investigate delivered dose to normal tissue.

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