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Technical Note

CT-based online adaptive radiotherapy improves target coverage and organ at risk (OAR) avoidance in stereotactic body radiation therapy (SBRT) for prostate cancer

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ABSTRACT

Introduction: Stereotactic body radiation therapy (SBRT) is an emerging treatment modality for clinically localized prostate cancer (PCa). Online daily adaptive radiotherapy (ART) could potentially improve the therapeutic ratio of prostate SBRT by accounting for inter-fraction variation in target and OAR volumes. To our knowledge, no group has evaluated the clinical utility of a novel AI-augmented CT-based ART system for prostate SBRT. In this study we hypothesized that adaptive prostate SBRT plans would result in improved target coverage and lower dose to OARs in comparison to unadapted treatment plans.

Methods: Seven patients with favorable intermediate to oligometastatic PCa treated with 5-fx prostate adaptive SBRT were retrospectively reviewed. Patients were treated with 3625 cGy to the prostate and seminal vesicles. 6 patients additionally received 2500 cGy to the pelvic nodes, 5 patients underwent a boost to 4000 cGy to the prostate. For each fraction, a CBCT was acquired and OARs (rectum, bladder, bowel, sigmoid, femurs) were segmented/deformed using AI. CTVs were rigidly registered. Volumes were adjusted manually and PTV expansions added. Adaptive treatment plans were developed based on the contoured targets and OARs and dose to these volumes for the adapted vs. initial plans were compared for each fraction. V100 and the D0.03 cc between scheduled and adapted treatment plans were compared using a Student's *t*-test, with significance threshold of $P < 0.05$.

Results: Seven patients completed 35 Fx's of adaptive RT. Daily adaptation resulted in a statistically significant mean improvement in PTV V100 for all targets: [21.4 % ± 4.3 % for PTV 4000 ($p < 0.0001$); 8.7 % ± 1.1 % for PTV 3625 ($p < 0.0001$); and 11.5 % ± 3.1 % for PTV 2500 ($p = 0.0013$)]. Mean rectal D0.03 was significantly reduced by 38.8 cGy ± 5.95 cGy ($p < 0.0001$) per fraction (194 cGy/5 fractions) compared to the initial plans. There was a modest increase in bladder dose of 10.9 cGy ± 4.93 cGy per fraction ($p = 0.0424$) for the adaptive plans. The adaptive plans met bladder constraints for every fraction. There were no statistically significant differences between sigmoid or bowel dose for adapted vs. initial plans. No patients experienced acute CTCAE grade ≥ 3 GI/GU adverse events (median F/U 9.5 months). All statistically significant differences were maintained in the presence and absence of rectal hydrogel spacer ($p < 0.05$).

Conclusions: CT-based online adaptive SBRT resulted in statistically significant and clinically meaningful improvements in PTV coverage and D0.03 cc dose to the rectum. A trial evaluating CT adaptive whole-pelvis prostate SBRT is underway.

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Introduction

Stereotactic body radiation therapy (SBRT), also referred to as ultra-hypofractionation, is an emerging treatment modality for clinically localized prostate cancer (PCa) with reported excellent biochemical recurrence-free survival rates comparable to conventionally and moderately hypofractionated regimens [1–6]. Ultra-hypofractionation requires accurate delineation of organs at risk (OARs) to maximize target coverage and minimize treatment-related toxicity [7,8]. Online daily adaptive radiotherapy (ART) has been utilized to manage patient-specific and day-to-day variation in targets and OAR volumes, with advances in AI-enhanced auto-contouring, high-quality cone-beam computed tomography, and rapid real-time adaptive planning [9–11]. While previous studies have shown the promise of ART in treating conventionally fractionated PCa (8–9), to date no group has demonstrated the utility of CT-based ART in the context of SBRT in PCa. In this study we quantify the per fraction benefit to target coverage and OAR avoidance when using a novel AI-augmented CT-based online adaptive system versus pre-adapted scheduled treatment plans. We hypothesized that online adaptive SBRT would result in improved planning treatment volumes (PTV) PTV coverage and reduced dose to the rectum.

Methods

Patient selection and treatment course

Seven patients, with favorable intermediate risk to oligometastatic PCa, eligible for 5 fraction prostate SBRT were evaluated. Patients underwent adaptive SBRT on a CT-based adaptive planning platform targeting the prostate and proximal seminal vesicles (3625 cGy/5 fractions). Six patients additionally received 2500 cGy/5 fractions simultaneously to the pelvic lymph nodes, and 5 patients underwent a simultaneous boost to the prostate to 4000 cGy/5 fractions. Patient's age, prostate size, Gleason Grade Group, presenting PSA, T-stage, N-stage, M−stage, height, weight, BMI, and presence of rectal hydrogel spacer were tabulated (Table 1).

Treatment planning and administration

Patients were treated on a Varian ETHOS adaptive radiotherapy system. All treatment planning was performed in the ETHOS (v.02.01.00) TPS. The clinical tumor volume (CTV) comprised the prostate, proximal seminal vesicles, and nodal volumes, if included. A 0.5 cm uniform volumetric expansion was applied to form a planning target volume (PTV). Organs-at-risk (OARs) were contoured at the axial slices from 3 cm below to 3 cm above the PTV.

Daily adapted plans were created based on the patient's anatomy of-the-day. The rectum, bowel and bladder were artificially segmented. The TPS automatically deformed the sigmoid and femurs according to the anatomy-of-the day. CTVs were rigidly propagated onto the patient's anatomy-of-the-day. OARs within a 3-cm contour ring were adjusted by the radiation oncologist in order to confirm accuracy. The initial simulation based treatment plan was projected on the patient anatomy-of-the-day at the same time that the re-optimized daily adapted plan was generated. The initial plan and the adapted plan were compared using dose volume histogram (DVH) objectives, and the superior plan that met all dosimetric goals was delivered.

Dosimetric analysis

For each fraction, the bladder, rectum, and bowel were auto-contoured on each daily cone-beam CT scan (CBCT) using a neural network AI algorithm. Manual edits to the OARs were made within a 3 cm contouring ring. Each clinical target volume (CTV) was rigidly registered to the CBCT, independent of the other CTVs and planning treatment volumes expansions were automatically generated. Adaptive treatment plans were developed based on the contoured targets and OAR volumes and compared to pre-adaptive scheduled treatment plans. The volume receiving 100 % of the prescription dose (V100) was evaluated for the PTVs to receive 4000 cGy (PTV_4000), 3625 cGy (PTV_3625), and 2500 cGy (PTV_2500). Similarly, the maximum point dose was assessed by calculating the maximum dose to 0.03 cc ($D_{max}0.03$) of each OAR (rectum, bladder, sigmoid, and bowel). OAR dose volume constraints are listed in supplemental Table S1.

Coverage and OAR dose analysis

The PTV_4000, PTV_3625 and PTV_2500 were compared between scheduled and adapted treatment plans of the same fraction using a paired Student's *t*-test with a significance threshold of $P < 0.05$. Similarly, differences between $D_{max}0.03$ assessed with a Student's *T*-test and $P < 0.05$ threshold.

Analysis of clinical factors associated with scheduled and adapted coverage

Correlation matrices and heatmaps were generated using the Pearson method, and the pandas and seaborn python packages, multiple linear regression analysis was performed using the stats package in R (version 4.1.1).

Results

Seven patients treated with 5-fraction online adaptive prostate SBRT using CT-based imaging to the prostate +/- the pelvic nodes at a single institution were retrospectively reviewed to evaluate coverage and OAR dosing differences between scheduled and CT-adapted prostate SBRT plans. The adapted plan was chosen over the scheduled plan for all 35 fractions on the basis of better target and/or OAR dosimetry. Patient risk groups were diverse: favorable intermediate (n = 3), unfavorable intermediate (n = 1), high (n = 2), and metastatic (n = 1). Rectal hydrogel spacer placement was present in 57 % (4/7) of patients. Prostate size ranged from 20.5 cc to 61 cc (Table 1).

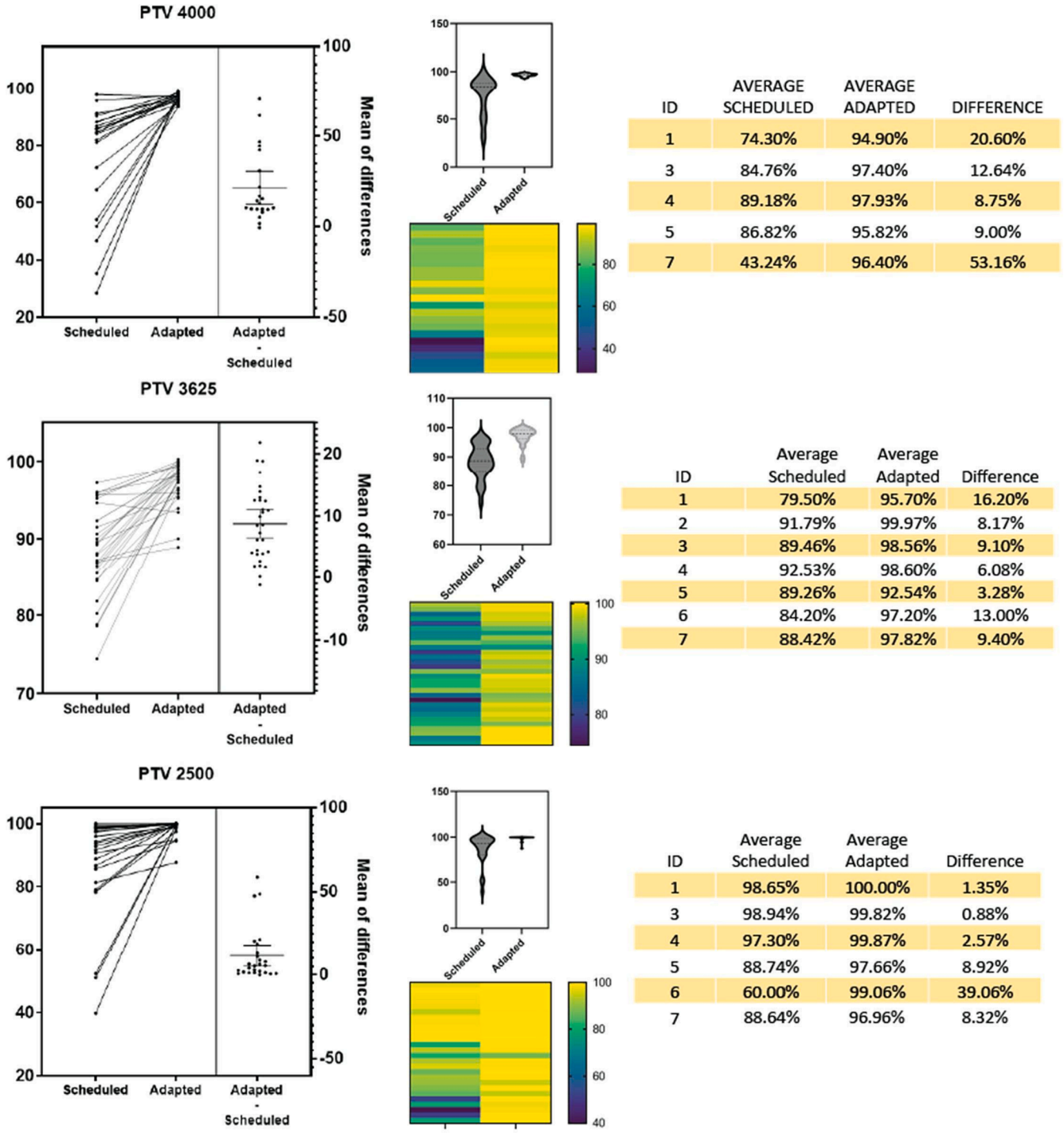
All patients received 3625 cGy in 5 fractions to the prostate and seminal vesicles. For the adapted plans, the average V100 for the PTV_3625 was 97.2 %, an 8.8 % improvement over the average V100 for the scheduled plan of 88.4 %. At the individual patient level, the 5-fraction average V100 for the adapted plan ranged from 92.5 % to 100 % vs.

Table 1
Table of patient clinical characteristics, (n = 7).

Age	Size (g)	Risk Category	Gleason Grade Group	iPSA	T Stage	N Stage	M Stage	Rectal Hydrogel?	Height (inches)	Weight	BMI
65	61	Favorable Intermediate	2	5.1	T1c	0	0	No	69	215	31.7
55	20.45	Favorable Intermediate	3	6.6	T1c	0	0	Yes	75	187	23.3
59	38.7	Unfavorable Intermediate	2	17.9	T1c	0	0	Yes	71	197	27.4
81	59.5	Favorable Intermediate	2	6.4	T1c	0	0	Yes	70	173	24.8
71	42	High	5	11.2	T4	0	0	No	70	206	29.5
62	36.2	Metastatic	5	19	T1c	1	1	Yes	70	198	28.4
73	60.8	High	5	7.1	T2a	0	0	No	71	200	27.8

79.5 % to 92.5 % for the scheduled plan (Fig. 1). For the adapted plans, the average V100 for the PTV_4000 was 96.7 % compared to 75.2 % for the scheduled plan, an improvement of 21.5 %. At the individual patient level, the 5-fraction average V100 for the adapted plan for PTV_4000 ranged from 94.9 to 97.9 % vs. 43.2 % – 89.2 % for the scheduled plan. For the adapted plans, the average V100 for the PTV_2500 was 98.7 % vs. 87.2 % for the average V100 for the scheduled plans, an improvement of 11.5 %. At the individual patient level, the 5-fraction average V100 for the adapted plan for PTV_2500 was 96.9 % – 100 % vs. 60.0 – 98.9 % for the scheduled plans (Fig. 1). All of the V100 PTV differences between adapted and scheduled plans were statistically significant. No clinical factors, including presence of rectal hydrogel spacer were significantly associated with changes in PTV coverage as assessed by multivariable linear regression (not shown); however, BMI was inversely correlated with both adapted and scheduled PTV_3625, and positively correlated with the difference between scheduled PTV_3625 and adapted PTV_3625 (supplemental Fig. S1).

With regards to organs at risk, mean rectal D0.03 cc was significantly reduced by 38.8 cGy ± 5.95 cGy ($p < 0.0001$) per fraction (194 cGy/5 fractions) with the adapted vs. the scheduled plans (Fig. 2). Bladder dose



ID	AVERAGE SCHEDULED	AVERAGE ADAPTED	DIFFERENCE
1	74.30%	94.90%	20.60%
3	84.76%	97.40%	12.64%
4	89.18%	97.93%	8.75%
5	86.82%	95.82%	9.00%
7	43.24%	96.40%	53.16%

ID	Average Scheduled	Average Adapted	Difference
1	79.50%	95.70%	16.20%
2	91.79%	99.97%	8.17%
3	89.46%	98.56%	9.10%
4	92.53%	98.60%	6.08%
5	89.26%	92.54%	3.28%
6	84.20%	97.20%	13.00%
7	88.42%	97.82%	9.40%

ID	Average Scheduled	Average Adapted	Difference
1	98.65%	100.00%	1.35%
3	98.94%	99.82%	0.88%
4	97.30%	99.87%	2.57%
5	88.74%	97.66%	8.92%
6	60.00%	99.06%	39.06%
7	88.64%	96.96%	8.32%

Fig. 1. Coverage of PTV comparing scheduled and adapted plans (V100). **(A)** Paired differences between scheduled and adapted plans. **(B, top)** Violin plots of V100 distribution between scheduled and adapted plans. **(B, bottom)** Heatmap of changes in V100 coverage between scheduled and adapted fractions. **(C)** Individual patient 5 fraction averages between scheduled and adapted V100.

Structure	Scheduled	Adapted	p-value
Rectum	805.2	766.4	<0.0001
Bladder	822.4	833.3	0.0424
Sigmoid	536	543.1	0.0603
Bowel	536.8	540.4	0.3355

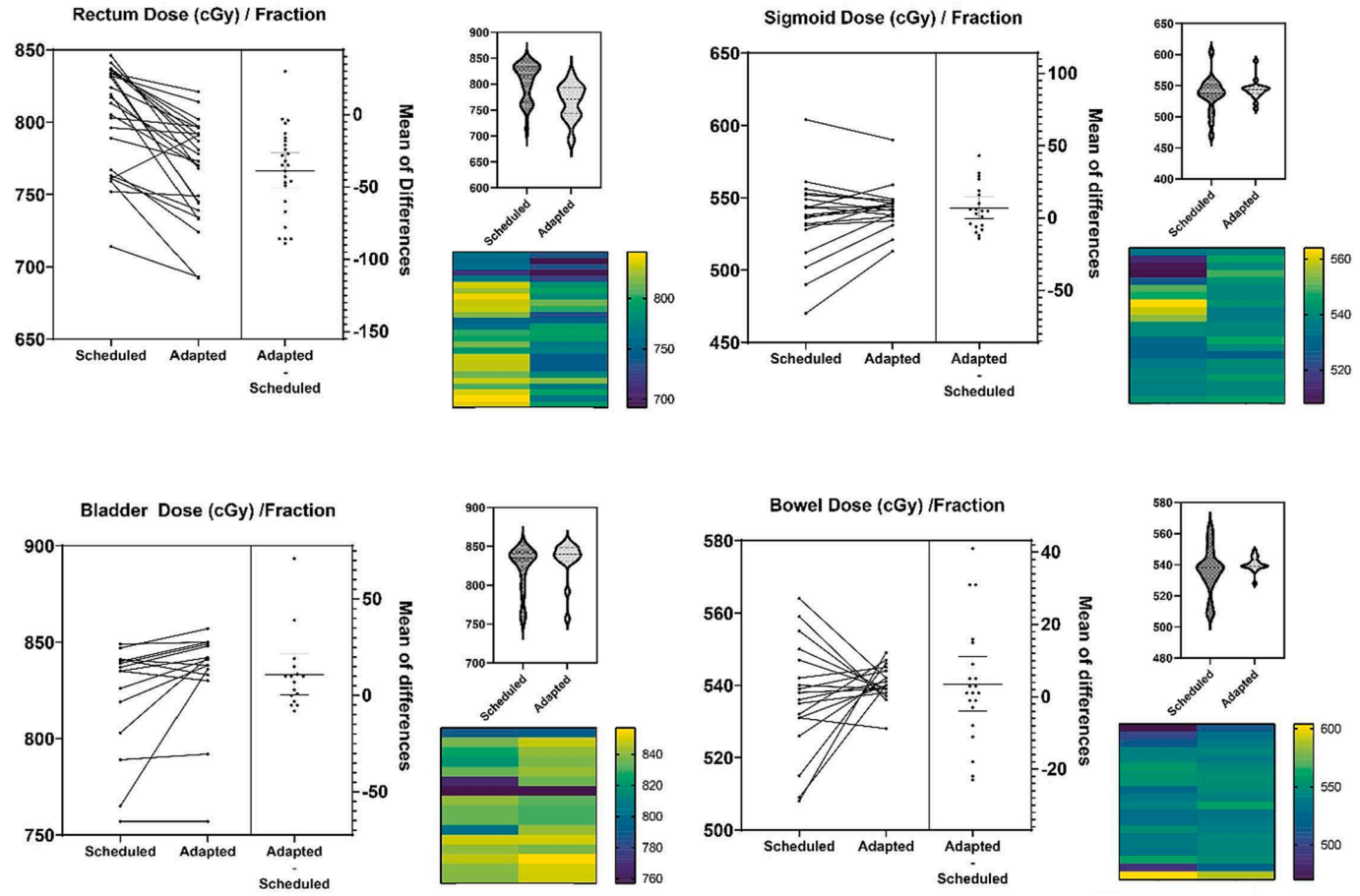


Fig. 2. OAR dosimetry between scheduled vs adapted plans. **(A)** Differences between average per fraction dose between scheduled and adapted plans for given OARs. **(B)** Paired individual fraction $D_{max}0.03$ differences between scheduled and adapted plans, violin plots of $D_{max}0.03$ distribution between scheduled and adapted plans. Heatmap of changes in $D_{max}0.03$ between scheduled and adapted fractions.

was increased with the adapted plans, 10.9 cGy ± 4.93 cGy per fraction (55 cGy/5 fractions) ($p < 0.0424$). Though bladder dose was increased with the adaptive plans, bladder dose constraints were met for all of the adaptive treatment plans. There were no statistically significant differences between sigmoid or bowel dose comparing the adapted vs. the scheduled plans (Fig. 2). No patients experienced acute CTCAE grade ≥ 3 GI/GU adverse events with a median follow up of 9.5 months.

Discussion

In this study we show that daily adaptation resulted in a statistically significant mean improvement in PTV V100 for all targets. Further, we found that the adaptive plan reduced rectal D0.03 cc by 38.8 cGy ± 5.95 cGy ($p < 0.0001$) per fraction, which represents a nearly 2 Gy reduction in rectal D0.03 cc over a full course of SBRT treatment. While there was a modest increase in bladder dose of 10.9 cGy ± 4.93 cGy per fraction ($p = 0.0424$) for the adaptive plans, the adaptive plans still met all bladder constraints. While reviewing this point, the authors found that often in order to improve coverage to the PTV, the bladder received a higher dose of radiation therapy while still meeting constraints. The adaptive plans were not associated with statistically significant improvements in sigmoid or bowel dose. Preliminary data on acute grade ≥ 3 GI/GU adverse events is promising with this approach, with no grade 3 events reported to-date. Additionally of note, the authors observed the sporadic presence of low PTV coverage in scheduled plans which further highlights the utility of online adaptation, especially in the presence of hypofractionated/SBRT treatment plans.

This study is consistent with and extends beyond the existing literature. Multiple studies have previously shown the feasibility and efficacy of MR- guided online adaptive stereotactic body radiation therapy, including studies demonstrating low toxicity rates, as well as improvements in target and organ-at-risk dosimetry [11–13]. This study applies a similar methodology to CT-based adaptive with AI-auto-segmentation and rapid adaptive planning.

To our knowledge, this is the first study to apply online adaptive planning to pelvic nodal prostate SBRT. This study shows the potential value of online adaptive SBRT for combined pelvic node and prostate with physicians able to simultaneously align each structure. Not only did the adapted plan improve coverage to the high-dose prostate PTVs, but it also significantly improved coverage to the pelvic nodal targets, which

offers an opportunity to shrink nodal PTV margins, limiting dose to uninvolved bowel and bladder. With the publication of the POP-RT trial showing an improvement in biochemical control and a reduction in distant metastases with the use of elective nodal RT for high-risk patients, elective nodal RT is likely to be utilized more in the future[14]. This study adds to the very limited literature suggesting that pelvic nodal prostate SBRT is reasonably safe and well-tolerated [15].

This study is also noteworthy for providing useful data to quantify actual dose delivery on a per-fraction basis for prostate SBRT. Prior to an online workflow, it was difficult to quantify actual dose delivery on a per-fraction basis to the target and OARs. This study provides data to suggest that actual PTV coverage based on the sum of each individual fraction using the scheduled plan is lower than expected. Similarly, dose to the rectum can be higher than expected.

This study also provides valuable preliminary data on the impact of rectal hydrogel spacer for patients treated with online adaptive prostate SBRT. Improvements in PTV and rectal dosimetry for the adapted vs. scheduled plans were seen for both rectal hydrogel spacer and and non-hydrogel patients. Therefore, the presence of hydrogel does not appear to negate the benefit of online adaptive therapy.

Limitations of the study include the small sample size and the lack of prolonged follow-up. It is unclear if the improvements in target coverage and dose to the OARs reported here would translate into meaningful clinical endpoints. A clinical trial using this approach is currently underway at our institution to evaluate these questions.

Disclosures

All authors report no relevant disclosures.

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Data sharing

All data, generated and analyzed during this study are included in this published article (and supplementary information files).

Statistics

Performed by Michael Waters MD PhD.

CRediT authorship contribution statement

Michael Waters: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Alex Price:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Eric Laugeman:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Lauren Henke:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Geoff Hugo:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Hayley Stowe:** Formal analysis, Writing – original draft, Writing – review & editing. **Neal Andruska:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Randall Brenneman:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Yao Hao:** Conceptualization, Methodology, Writing – review & editing. **Olga Green:** Conceptualization, Methodology, Writing – review & editing. **Clifford Robinson:** Conceptualization, Methodology, Writing – review & editing. **Hiram Gay:** Methodology, Writing – review & editing. **Jeff Michalski:** Conceptualization, Methodology, Writing – review & editing. **Brian C. Baumann:** Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100693.

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