advances
in radiation oncology

Scientific Article

Magnetic Resonance−Guided Prostate Stereotactic Body Radiation Therapy With Daily Online Plan Adaptation: Results of a Prospective Phase 1 Trial and Supplemental Cohort

Jonathan E. Leeman, MD,[a,*] Daniel N. Cagney, MD,[a] Raymond H. Mak, MD,[a] Mai Anh Huynh, MD, PhD,[a] Shyam K. Tanguturi, MD,[a] Lisa Singer, MD, PhD,[a,b] Paul Catalano, ScD,[a] Neil E. Martin, MD, MPH,[a] Anthony V. D'Amico, MD, PhD,[a] Kent W. Mouw, MD, PhD,[a] Paul L. Nguyen, MD,[a] Martin T. King, MD, PhD,[a] Zhaohui Han, PhD,[a] Christopher Williams, PhD,[a] and Elizabeth Huynh, PhD[a]

[a]Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [b]Department of Radiation Oncology, University of California, San Francisco, California

Abstract

Purpose: Stereotactic magnetic resonance (MR)−guided adaptive radiation therapy (SMART) for prostate cancer allows for MR-based contouring, real-time MR motion management, and daily plan adaptation. The clinical and dosimetric benefits associated with prostate SMART remain largely unknown.

Methods and Materials: A phase 1 trial of prostate SMART was conducted with primary endpoints of safety and feasibility. An additional cohort of patients similarly treated with prostate SMART were included in the analysis. SMART was delivered to 36.25 Gy in 5 fractions to the prostate ± seminal vesicles using the MRIdian linear accelerator system (ViewRay, Inc). Rates of urinary and gastrointestinal toxic effects and patient-reported outcome measures were assessed. Dosimetric analyses were conducted to evaluate the specific benefits of daily plan adaptation.

Results: The cohort included 22 patients (n = 10 phase 1, n = 12 supplemental) treated in 110 fractions. Median follow-up was 7.9 months. Acute grade 2 urinary and gastrointestinal toxic effects were observed in 22.7% and 4.5%, respectively, and 4.5% and 0%, respectively, at last follow-up. No grade 3+ events were observed. Expanded Prostate Cancer Index-26 urinary obstructive scores decreased during SMART (mean, 9.3 points; P = .03) and returned to baseline by 3 months. No other significant changes in patient-reported outcome measures were observed. One-hundred percent of fractions required plan adaptation owing to exceeding organ-at-

---

risk metrics (68%) or suboptimal target coverage (33%) resulting from anatomic changes. Minimum acceptable planning target volume, rectal, bladder, and urethra/bladder neck metrics were violated in 24%, 20%, 24%, and 33% of predicted plans, respectively; 0% of reoptimized plans violated metrics. Underlying causes for deficient dosimetry before reoptimization included changes in bladder filling, seminal vesicle position, prostate volume (median 4.7% increase by fraction 3; range, 0%-56%), and hotspots shifting into urethra/bladder neck.

Conclusions: Prostate SMART results in low risk of acute toxic effects with improvements in target and organ-at-risk dosimetry. The clinical benefits resulting from daily plan adaptation, including urethra/bladder neck protection, warrant further investigation.

Introduction

Radiation therapy is a central modality in the treatment of localized prostate cancer. Stereotactic body radiation therapy (SBRT) involves the use of a higher radiation dose delivered per fraction, a low number of total fractions, and highly conformal techniques. SBRT is increasingly being used in the management of localized prostate cancer.[1-4] However, despite the use of very precise delivery platforms, there remain significant toxic effects associated with prostate radiation resulting from irradiation of organs-at-risk (OARs) in direct contact with the prostate (ie, rectum, bladder, and urethra), which is a concern with SBRT and other radiation modalities. Furthermore, although prostate SBRT has demonstrated rates of cancer control similar to conventionally fractionated radiation, 5% to 20% of patients will develop biochemical failure after treatment.[1,5,6]

Although rates of severe toxic effects have generally been low after prostate SBRT,[1,6] some studies have found prostate SBRT to carry increased risk of urinary and gastrointestinal (GI) toxic effects. In the HYPO-RT[2] trial, which randomized patients to conventionally fractionated versus ultrahypofractionated radiation, most toxic effect endpoints were not significantly different, although physician-reported and patient-reported urinary toxic effects appeared more prominent at the end of radiation therapy and at 1-year posttreatment. Long-term data presented from Radiation Therapy Oncology Group 0938,[7] a randomized study of SBRT versus hypofractionated radiation (36.25 Gy in 5 fractions vs 51.6 Gy in 12 fractions) found the proportion of patients with patient-reported urinary symptoms (Expanded Prostate Cancer Index, EPIC urinary score decrease >2 points) to be higher in the SBRT arm at 1, 2, and 5 years. Therefore, although prostate SBRT is a more convenient treatment option, there remains room to improve the side effect profile of the treatment. As interest grows in dose escalation of prostate SBRT and intraprostatic boosting based on the recently reported Focal Lesion Ablative Microboost in Prostate Cancer (FLAME) trial,[8] the precision of SBRT delivery to higher doses is increasingly important.

Stereotactic magnetic resonance (MR)−guided adaptive radiation therapy (SMART) allows for multiple advantages in treatment delivery that may improve the integrity of prostate SBRT delivery. This technology affords 3 important advantages: (1) the ability to contour targets and OARs based on MR imaging (MRI) as opposed to computed tomography (CT); (2) the use of daily online adaptive planning; and (3) the use of real-time MR cine tracking and gating during radiation therapy delivery. A single institution trial of SMART for treatment of prostate cancer found that in 101 patients treated to a dose of 36.25 Gy in 5 fractions with a urethral-sparing technique, rates of acute grade 2 or higher urinary or GI toxic effects were favorable compared with historical controls.[9] The benefits of SMART likely lie in large part in the ability to perform daily plan adaptation to account for day-to-day anatomic changes in the pelvis. An analysis of bladder dosimetry from this trial found that the "accumulated" dose to the bladder delivered with adaptive planning more accurately predicted acute urinary toxic effects than baseline dosimetry.[10] Beyond this, the specific dosimetric gains and associated clinical benefits that can be achieved with prostate SMART have not been thoroughly studied. Herein, we report the clinical and dosimetric outcomes of a phase 1 trial of SMART and an additional similarly treated cohort of patients.

Methods and Materials

Patients were treated in a prospective phase 1 trial of SMART for patients with prostate cancer. The protocol was approved by the Dana Farber Cancer Institute institutional review board. Patients were enrolled between July 2020 and March 2021. The trial was conducted as a subprotocol of a master protocol investigating SMART for multiple cancer types (NCT04115254)[11] at a single institution. The primary endpoint of the study was safety and feasibility of prostate SMART delivery. A sample size of n = 10 was chosen such that if feasibility was demonstrated in all 10 subjects (defined as enrolling subjects and delivering SMART, using MR guidance for each treatment fraction, and generating adaptive plans), the 90% lower confidence limit on the true feasibility rate would be 0.79 (close to 80%). In addition to subjects treated in this prospective protocol, a cohort of similarly treated consecutive patients who underwent prostate SMART at our

institution between November 2019 and May 2021 were included in the analysis. Analysis of this cohort was performed under a protocol approved by the Dana Farber Cancer Institute institutional review board. The phase 1 trial and additional cohort included both patients with localized prostate cancer and patients with low volume metastatic disease who were deemed appropriate for local therapy by the treating physician and genitourinary oncologist.

Stereotactic MRI-guided adaptive radiation therapy

SMART was delivered using the MRIdian linear accelerator system (ViewRay, Inc). Patients underwent CT simulation (Siemens Confidence 64 slice CT Scanner; Siemens Medical Solutions, Inc, or GE LightSpeed RT 16 CT Scanner; GE Healthcare) as well as 0.35-Tesla (T) MR simulation on MRIdian. An additional 3T MR simulation was performed with a 3T MRI Scanner (Siemens Vida; Siemens Medical Solutions) with acquisition of axial and sagittal T2 weighted images in some cases to assist with prostate delineation. When 3T MR simulation was performed, an additional sagittal T2 BLADE sequence was collected for urethral delineation. Preparation for simulation included polyethylene glycol (MiraLAX) 17 g daily for 3 days before simulation, simethicone 125 mg every 6 hours for 3 days before simulation, and saline (Fleet) enema the evening before and morning of simulation. MiraLAX and simethicone were continued throughout the course of treatment and Fleet enemas were performed before each fraction. Patients were simulated and treated with a "half-full" bladder typically achieved by drinking 4-6 oz of water 30 minutes before treatment.

The target volumes (prostate ± seminal vesicles) and OARs were contoured on the 0.35T MRI with assistance from 3T MRI (when available) and CT rigid fusion. OARs included rectum, bladder, urethra (including bladder neck), penile bulb, small bowel, large bowel, and femoral heads. The majority of patients underwent 3T MRI simulation. The urethra was delineated either on T2-weighted sequences (sagittal T2 BLADE) when available or otherwise on 0.35T simulation images. A 6- to 8-mm brush was used for urethral contouring. At the base of the prostate, at the interface with the bladder, the urethra contour was widened to include the bladder neck. For National Comprehensive Cancer Network low-risk disease, the clinical target volume (CTV) included the prostate only; for intermediate risk disease, the CTV included the prostate and proximal 1 cm of seminal vesicles; for high-risk disease, the CTV included the prostate and the entire length of seminal vesicles. For most cases with a dominant intraprostatic lesion (DIL), the DIL was contoured as the gross tumor volume using 3T MRI simulation fusion (axial T2 and apparent diffusion coefficient). This gross

tumor volume was expanded by 3 mm to a "planning target volume (PTV) high-risk" to ensure >99% coverage of the DIL. For patients with low-volume M1 disease, the prostate alone was treated unless multiparametric MRI and/or positron emission tomography revealed gross disease involving the seminal vesicles, in which case the full extent of gross disease was included. The CTV was expanded 3-mm isotropically to form the PTV.

Contours and radiation plans were generated by a radiation oncologist specializing in genitourinary malignancies and MR-guided radiation therapy. A diagnostic radiologist specializing in genitourinary radiology was also consulted in select cases. Contours were then prospectively peer reviewed by a separate radiation oncologist specializing in MR-guided radiation therapy before planning.

Radiation plans were developed by a physicist or dosimetrist specializing in MR planning on the ViewRay MRIdian platform on the 0.35T MRI to form the "original plan." All patients were treated to a dose of 36.25 Gy in 5 fractions delivered every other day over the course of 2 weeks. For the first 3 patients, 36.25 Gy in 5 fractions was prescribed to the CTV and for the subsequent 19 patients, to the PTV. Dose-limiting metrics for the OARs can be found in Table E1. The original plan and any adapted plan on treatment day were required to meet the metrics that were considered hard constraints. Metrics that were considered soft constraints represented goals for the plan, but may not have necessarily been met in the plan depending on anatomy. Static intensity modulated radiation therapy was used, with a median of 21 beams (range, 12-28) and a median of 55 segments (range, 41-65). The CT from simulation was deformed to the 0.35T MRI and used for dose calculation. Differences in air and soft-tissue between the CT and 0.35T MRI were accounted for by overriding the CT electron densities with their respective electron densities. The treatment planning system used a Monte Carlo dose calculation algorithm that accounts for magnetic field effects. Dose calculations were performed with 5 million histories and grid size of 1.5 to 2 mm.

Plans were peer reviewed and approved by a separate radiation oncologist specializing in MR-guided radiation therapy before the first fraction.

Adaptive workflow and MRI tracking

Each patient was treated with an online adaptive treatment workflow (Fig. E1). For each fraction, the patient was setup in the treatment position determined from simulation. A 0.35T MRI of the patient was acquired and aligned to the planning image of the original plan. Contours and the electron density from the original plan were deformed to the on-treatment image. Electron densities were adjusted to account for differences in air and soft-

tissue between the deformed electron density of the original plan and the on-treatment MRI. The contours were reviewed and adjusted by the treating physician based on the current treatment day anatomy. Minimal adjustments were made to urethra contours for the purposes of adaptive planning. The dose from the original plan was calculated on the on-treatment MRI to determine the dose that would have been delivered to the patient without plan adaptation (referred to as the "predicted" plan). The treatment plan was then adapted based on the current treatment day contours by a physicist to generate the "reoptimized" plan for all treatment fractions. The treatment plan was approved by the treating physician before treatment, and the physicist evaluated online quality assurance reports (secondary dose calculation comparison with the treatment plan dose).

During treatment, the prostate was tracked in real-time with cine imaging acquired on a single sagittal plane of the 0.35T MRI. Sagittal cines were acquired with a 35 × 35 cm field of view and slice thickness of 5 to 7 mm at 4 frames/s. A boundary of 3 mm was expanded on the prostate based on the 3-dimensional 0.35T MRI, which was used to gate the radiation beam if the prostate moved outside of that 3-mm boundary. Radiation beam stoppage was triggered if 5% of more of the target was outside of the gating boundary at any time. The time taken for each step of the adaptive process and total time in the treatment room per fraction were recorded prospectively.

Dosimetric and prostate volume analysis

Dosimetry data were collected for each treatment plan (original, predicted, and reoptimized) for each patient including the following metrics: PTV V36.25, PTV V34.44, bladder V36.25, urethra V38.78, and rectum V36.25 and V38.06. Plots were generated representing each plan as a dot, showing plans that did not meet the metric (red dots) and a color scale for plans that well met the metric (green) to plans that just met the metric (blue). Plans for patients who had their prostate only treated were analyzed separately from plans that treated prostate and seminal vesicles. For all patients collectively, the median, maximum, and minimum value for each of these metrics were calculated as well as the proportion of plans that met each of the metrics. A Wilcoxon rank-sum test was used to assess the difference in metrics between the predicted and reoptimized plans, where $P < .05$ was considered statistically significant.

The change in prostate volume throughout the course of treatment was calculated from the relative difference in prostate volume at each fraction from the prostate volume at simulation. The significance of the change in prostate volume from simulation between each fraction was determined using a paired t test, where $P < .05$ was considered statistically significant.

Analysis of toxic effects

Patients were evaluated for toxic effects at least once during radiation therapy and subsequently at posttreatment at the following time points: 1 week, 4 to 8 weeks, 3 to 5 months, 6 to 8 months, 9 to 12 months, and every 6 months thereafter. Toxic effects were assessed using Common Terminology Criteria for Adverse Events version 5.0.

Patient-reported outcomes

Patients treated on the phase 1 protocol underwent assessment of patient-reported outcomes (PROMs) consisting of the EPIC-26[12] and PROMIS (Patient Reported Outcomes Measurement Information System)[13] questionnaires. PROMs data were collected at baseline before SBRT, at the end of SBRT (±1 week), and 3 months post-SBRT (±4 weeks). EPIC-26 bowel, urinary incontinence, and urinary obstructive domains were assessed at each time point; sexual and hormonal domains were not analyzed in the present study due to the heterogeneity of the patient population and the use of androgen deprivation therapies. PROMIS physical health and mental health indices were assessed at each time point. Paired t testing was used to compare changes in PROMs between baseline and end of SBRT and baseline and 3 months post-SBRT.

Results

Twenty-two patients were included in the analysis, 10 from the prospective phase 1 trial and an additional 12 from the supplemental cohort. Baseline characteristics are shown in Table 1. The median age was 70 years (range, 50-85). Thirteen patients (59%) were treated for localized prostate cancer and 9 (41%) underwent prostate SBRT in the setting of low-volume metastatic disease. The median follow-up time was 7.9 months (range, 3.3-22.0). The primary endpoints of safety and feasibility of the phase 1 cohort were met.

Dosimetry

Dosimetric evaluation of original plans (n = 22), predicted plans (n = 110 fractions), and reoptimized plans (n = 110 fractions) is shown in Table 2. Analysis of PTV coverage identified that 26 of 110 (24%) of predicted fractions did not meet the minimum coverage metric of 95% of the PTV receiving 95% of the prescription dose, which improved to 0% with daily online plan adaptation ($P < .001$). The PTV V36.25 decreased by a median of 7% from original to predicted plans. Predicted plans violated urethral maximum dose metric in 37 of 110 fractions (33%), the rectal maximum dose metrics in 22 of 110 fractions (20%), and the bladder maximum dose metrics in 26

Table 1   **Patient and treatment characteristics**

		Median	Range
Full cohort			
Age (y)		70	50-85
NCCN risk category			
Low	2 (9%)		
Intermediate	9 (41%)		
High	2 (9%)		
M1	9 (41%)		
Prostate volume (cc)		27.9	16.2-104.0
Follow-up time (mo)		5.8	0.3-18.5
Rectal spacer			
Yes	2 (9%)		
No	20 (91%)		
Localized cohort			
PSA at presentation		8.9	5.0-30.0
Gleason grade group			
1	2 (15%)		
2	5 (38%)		
3	5 (38%)		
4	0 (0%)		
5	1 (8%)		
T stage			
T1c	9 (69%)		
T2a	2 (15%)		
T2b-c	0 (0%)		
T3a	1 (8%)		
T3b	1 (8%)		
Androgen deprivation therapy			
Yes	8 (62%)		
No	5 (38%)		

Abbreviations: NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.

of 110 fractions (24%), all of which improved to 0% with plan reoptimization ($P < .001$).

Comparison of PTV, urethra, rectum, and bladder metrics is demonstrated in Figs. 1 and 2. PTV coverage on predicted plans was more substantially compromised when the prostate and seminal vesicles were treated as opposed to prostate only.

Examples of dosimetric deficiencies observed in predicted plans including PTV coverage loss due to shifting seminal vesicle position, urethral overdosing, and PTV coverage loss due to prostate swelling are shown in Fig. 3A, 3B, and 3C, respectively.

Assessment of prostate volume at each fraction of prostate SBRT by daily online recontouring identified significant changes during the course of treatment. The prostate volume did not change significantly between simulation and fraction 1 (median, −0.3%; range, −7.9%-17%). However, as shown in Fig. E2, prostate volume increased by a median of 3.2%, 4.7%, 4.2%, and 3.4% between fractions 2, 3, 4, and 5, respectively, compared with simulation (range, −6.1%-63.6%). The change in prostate volume from simulation to fraction 1 versus the change in prostate volume from simulation to fraction 2 was statistically significant ($P < .05$); however, the changes in prostate volume comparing simulation to fraction 2 versus simulation to fractions 3 to 5 were not statistically significant.

Analysis of predicted dosimetry according to variation in daily bladder filling did not reveal any statistically significant differences in PTV or critical OAR metrics to suggest that alterations in the bladder filling protocol would obviate the dosimetric benefits of adaptive planning (Fig. E3). Predicted urethral D_{max} and V38.78 were found to be negatively correlated with bladder volume on the day of treatment (Fig. E4), suggesting one possible mechanism underlying frequent violation of urethral metrics on predicted plans despite minimal adjustment of urethral contours. All of the urethral metric violations were remediated with plan adaptation.

Utility of intrafraction MR guidance

Real-time tracking of the prostate during treatment ensures that the treatment target is in the correct position as planned. If the prostate was not in the same position as the treatment plan within a 3-mm boundary, the patient was shifted to align the prostate to the plan. In 90% of treatment fractions (99/110), a shift was not required before or during treatment. In 8.2% of fractions (9/110) a couch shift was required before delivery of radiation, and in 1.8% of fractions (2/110) a couch shift was required after radiation delivery had begun. In these cases, 3-dimensional couch shifts were performed after re-imaging with a new MR scan. The median total in-room time of all treatment fractions was 61 minutes (range, 43-120). The median time taken for the adaptive planning workflow steps was 29 minutes (range, 12-67). Detailed information about time taken for each step of the online adaptive treatment workflow is provided in Table E2.

Toxic effects

No grade ≥3 toxic effects were observed. Five patients experienced a grade 2 urinary toxic effect (22.7%), which all occurred within the first 3 months of SBRT. At the time of last follow-up, 1 patient was experiencing a continued grade 2 urinary toxic effect (4.5%). One patient

Table 2 Dosimetric changes observed between original, predicted, and reoptimized plans

Metric		Original plan (n = 22 plans)		Predicted plan (n = 110 fractions)		Reoptimized plan (n = 110 fractions)		Wilcoxon rank sum (*P* value)
		Median (range)	Proportion that met metric	Median (range)	Proportion that met metric	Median (range)	Proportion that met metric	
PTV	V34.44 > 95%*	99.7 (95-100)	100% (22/22)	97.6 (81.3-100)	76% (84/110)	99.7 (95-100)	100% (110/110)	<.001
	V36.25 > 95%	93.9 (74.6-96.4)	23% (5/22)	86.9 (51-97.3)	2% (2/95)	93.4 (68.6-96.3)	29% (28/95)	<.001
Urethra	V38.78 < 0.03 cc*	0 (0-0)	100% (22/22)	0 (0-0.4)	66% (73/110)	0 (0-0)	100% (110/110)	<.001
Rectum	V38.06 < 0.1 cc*	0 (0-0.1)	100% (22/22)	0 (0-1.4)	84% (92/110)	0 (0-0.1)	100% (110/110)	<.001
	V36.25 < 1 cc	1 (0.3-2.2)	77% (17/22)	0.6 (0-5.6)	75% (83/110)	0.8 (0-1.9)	77% (85/110)	.09
	V36.25 < 2 cc*		95% (21/22)		90% (99/110)		100% (110/110)	
Bladder	V38.06 < 0.1 cc*	0 (0-0.1)	100% (22/22)	0 (0-1.2)	75% (83/110)	0 (0-0.1)	100% (110/110)	<.001
	V36.25 < 2 cc	2.9 (0.5-5.1)	32% (7/22)	1.9 (0-6.3)	55% (61/110)	2.6 (0.1-4.9)	37% (41/110)	<.001
	V36.25 < 5 cc*		95% (21/22)		99% (109/110)		100% (110/110)	

Abbreviation: PTV = planning target volume.

* Indicates "hard" metrics that were required to be met per protocol. The remaining metrics were considered "soft" and were not always met depending on the individual plan and daily anatomy. Priority listings of "soft" metrics are shown in Table E1.
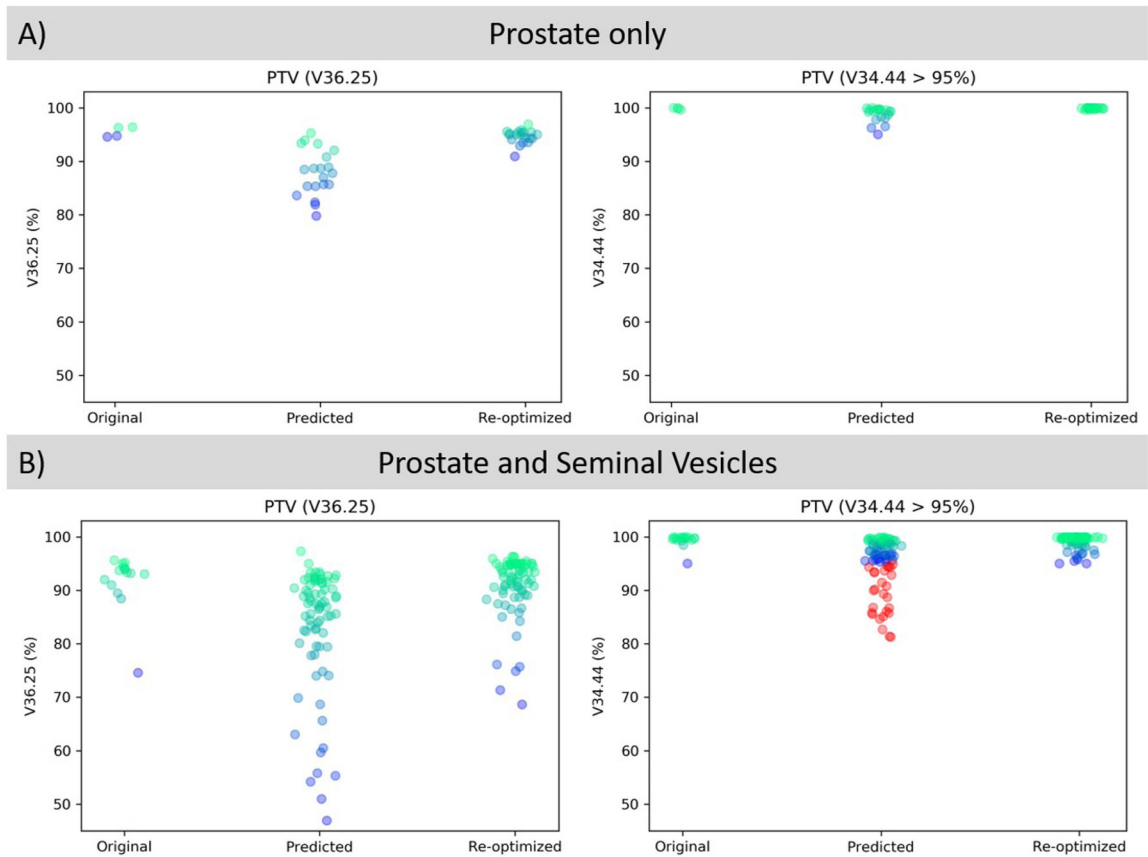
Fig. 1 Planning target volume (PTV) coverage metrics during the course of magnetic resonance−guided prostate stereotactic body radiation therapy with daily plan adaptation. PTV coverage metrics (V36.25 and V34.44) are shown for each adapted fraction for cases that included treatment of the prostate only **(A)** or prostate and seminal vesicles **(B)**. Predicted coverage was typically decreased on the predicted plan compared with the original plan and restored on reoptimized plans that were delivered.
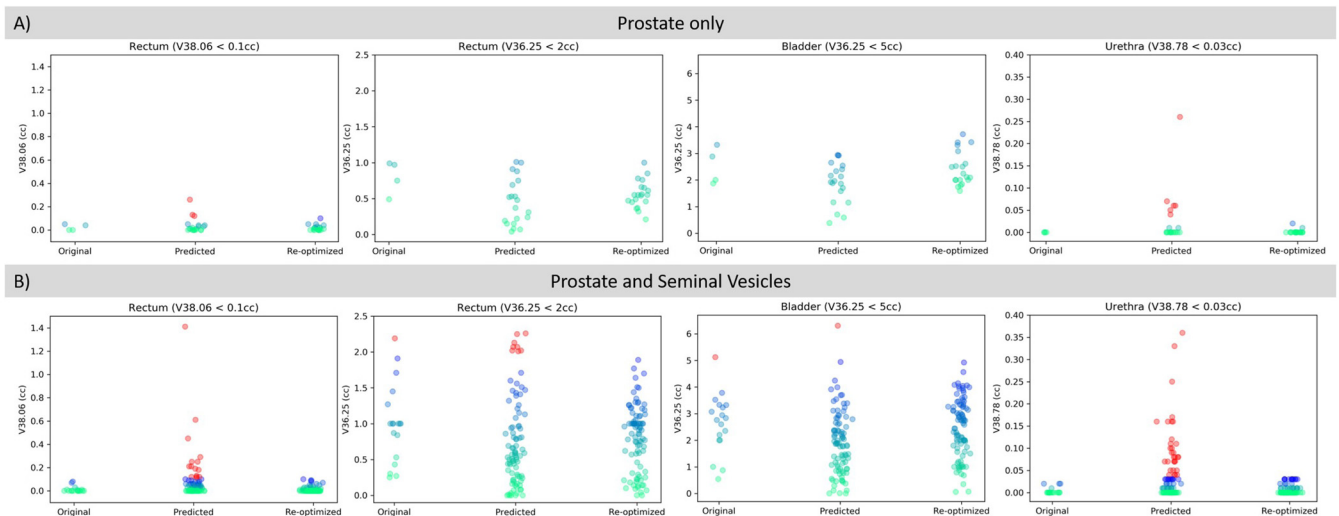

Fig. 2 Rectum, bladder, and urethra metrics during the course of magnetic resonance−guided prostate stereotactic body radiation therapy with daily plan adaptation. Rectum V38.06 and V36.25, bladder V36.25, and urethra V38.78 are shown for each adapted fraction for cases that included treatment of the prostate only **(A)** or prostate and seminal vesicles **(B)**.
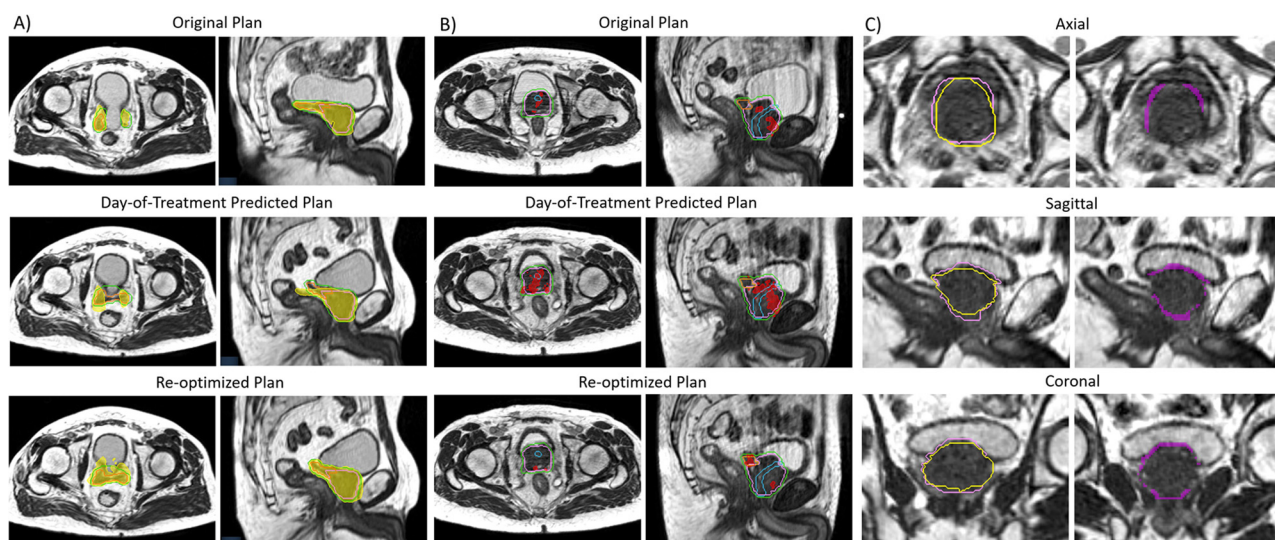
Fig. 3 Examples of magnetic resonance imaging−guided plan adaptation. A predicted plan resulting in undercoverage of the seminal vesicles and overdose of rectum is shown in (**A**). Reoptimization restored coverage of the seminal vesicles and rectal sparing. A predicted plan showing overdose of the urethra is shown in (**B**). Reoptimization restored urethral protection. Prostate = pink, seminal vesicles = orange, urethra = blue, 3-mm planning target volume expansion = green, 100% isodose line = yellow color wash, 107% isodose line = red color wash. An example of prostate volume change is shown in (**C**). Simulation contours are shown in yellow and fraction 3 contours in pink, and subtraction is shown in purple. In this case, the prostate volume increased by 18% and the maximum differences in superior/inferior, lateral, and anterior/posterior dimensions of prostate contours were 4, 5.8, and 4.1 mm, respectively.

experienced a transient grade 2 GI toxic effect (proctitis, 4.5%), and at the time of last follow-up no patients were experiencing grade ≥2 GI toxic effects. Of patients with a baseline prostate volume >40 cc, 5 of 7 (71%) experienced an acute grade 2 toxic effect (urinary or GI). Of patients with a baseline prostate volume <40 cc, 1 of 15 experienced a grade 2 toxic effect (6.7%).

Patient-reported outcomes

Ninety percent of patients treated on the phase 1 protocol had complete PROM data. Changes in PROMs between baseline, end of SBRT, and 3-months post-SBRT are shown in Fig. 4. EPIC-26 bowel and urinary incontinence scores did not change significantly from baseline to end of SBRT to 3-months post-SBRT. EPIC-26 urinary obstructive scores decreased by a mean of 9.4 points (out of 100) between baseline and end of SBRT (P = .03). Urinary obstructive scores subsequently improved by 3 months and were not significantly different from baseline. No difference in PROMIS physical or mental domain scores were observed at any time point.

Discussion

In this analysis of 22 patients who underwent SMART for prostate cancer, rates of acute toxic effects were low and confirmed by PROMs. We identified significant

dosimetric gains achieved through the use of online adaptive planning. Specifically, predicted dosimetry before plan adaptation identified deficiencies in both target coverage as well as OAR metrics. Twenty-four percent of predicted plans did not meet the minimum PTV coverage threshold, 20% of predicted fractions would have overdosed the rectum, 24% would have overdosed the bladder, and 33% would have overdosed the urethra/bladder neck. Importantly, online plan adaptation was able to correct deficiencies in OAR and coverage metrics to more closely restore the original intended dosimetry.

In the present study, we found that "predicted" target coverage (PTV V36.25) typically decreased by an average of 7% due to anatomic changes between fractions, which was corrected with adaptive planning. The significance of decreased coverage that was observed without the use of adaptive planning remains unknown, but the use of daily online plan adaptation may result in improved disease control by preserving the integrity of the delivered treatment without increasing rates of toxic effects, as opposed to the strategy of whole gland dose escalation, which has been shown to improve biochemical control and post-treatment positive biopsy rates but at the cost of increased urinary and GI toxic effects.[6,14,15] The observed deficiencies in coverage were most prominent in cases where the seminal vesicles were treated in addition to the prostate. For patients undergoing prostate SBRT with inclusion of the partial or whole seminal vesicles (commonly for intermediate- or high-risk prostate cancer), the use of adaptive planning may be of higher value. We also observed that
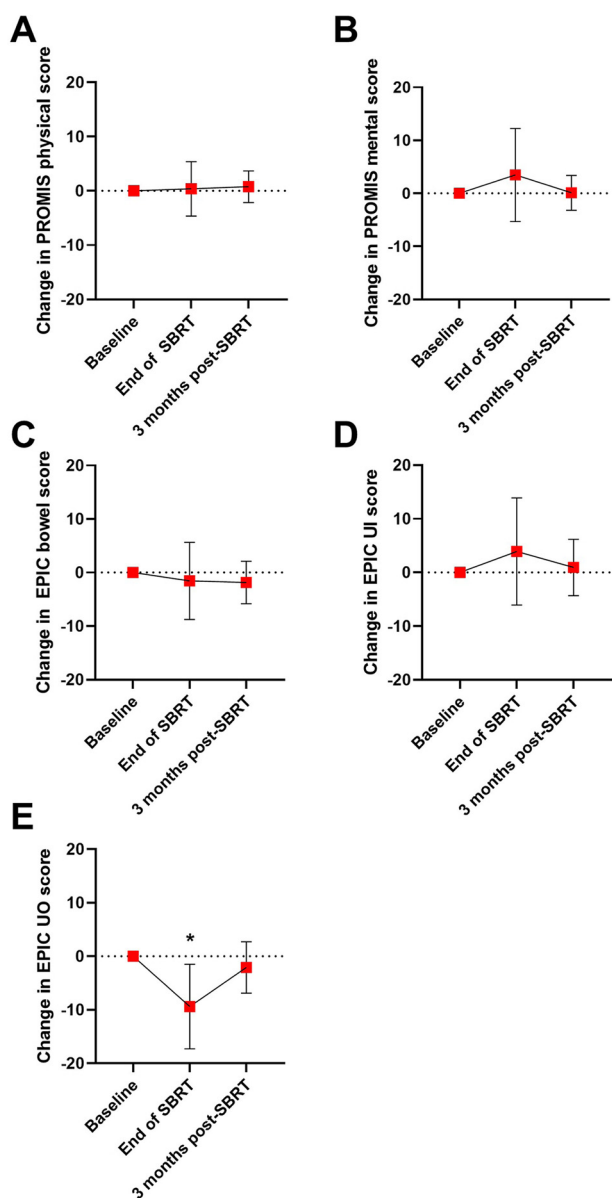
Fig. 4 Patient-reported outcome measures during magnetic resonance–guided adaptive prostate stereotactic body radiation therapy (SBRT). Change in score of **(A)** PROMIS (Patient Reported Outcomes Measurement Information System) physical domain, **(B)** PROMIS mental domain, **(C)** EPIC (Expanded Prostate Cancer Index) bowel domain, **(D)** EPIC urinary incontinence domain, and **(E)** EPIC urinary obstruction domain is shown comparing baseline, end of SBRT, and 3-month time points. EPIC urinary obstruction score decreased significantly at the end of RT by a mean of 9.4 points ($P = .03$). No other statistically significant changes were observed.

the volume of the prostate does not remain static during the course of SBRT, with a median increase of 4.7% in volume that typically occurs by the third fraction and is preserved through the remainder of fractions. This also has implications for how coverage of the prostate may

suffer without the use of adaptive planning, particularly when narrow PTV margins are used.

Two of 22 (9%) patients within the study cohort were treated with a rectal spacer. Rates of GI toxic effects were low: no patients experienced grade ≥3 toxic effects, and a single patient (4.5%) experienced transient grade 2 proctitis in the week after SBRT, which quickly resolved with the use of hydrocortisone. Of note, this patient had a 104 cc prostate, the largest in the study. Though the current study describes a relatively small cohort with limited follow-up, rates of acute grade 2 GI toxic effects appear low without the use of a rectal spacer, which may be a result of the relatively strict rectal metrics used and/or the benefits of adaptive planning and MRI guidance. A similar low risk of acute GI toxic effects (5%) was observed in a phase 2 study of MR-guided adaptive prostate SBRT using a similar approach.[9] We also note that a recent study of patients treated with non-adaptive MR-guided prostate SBRT has also shown promising early results of toxic effects.[16] Ultimately, a direct comparison of adaptive versus non-adaptive SBRT would be important for evaluating possible benefits of daily adaptive planning. As technology platforms for daily adaptive planning become more efficient and techniques for online adaptation become more streamlined and accessible, it will be critical to evaluate differences in outcomes between adaptive and non-adaptive prostate SBRT as well as MR-guided versus CT-guided prostate SBRT. An ongoing randomized trial evaluating MR-guided versus CT-guided SBRT without a requirement for adaptive planning is ongoing.[17]

Urinary toxic effects resulting from prostate radiation therapy are multifactorial processes that are related to patient factors such as prostate volume and baseline urinary function as well as treatment-related factors such as radiation dose and, specifically, dose to the urinary bladder and intraprostatic urethra.[18] In the present study, a strict constraint of V38.78 < 0.03 cc for the intraprostatic urethra was employed (107% of prescription dose). Minimal adjustments were made to the urethral contour at the time of treatment. This is due to the observation that with MR-based alignment, the position of the urethra within the prostate did not appear to vary significantly from day to day. Despite this, interestingly, the urethral metric would have been violated in one-third of fractions without online plan adaptation based on predicted dosimetry. Furthermore, maximum doses within the PTV outside of the urethra were generally constrained, with only a slightly higher allowance of 110% of the prescription dose (V39.87 < 0.03 cc). As many SBRT protocols allow higher hot-spots within the PTV, there is potential for delivered doses to the intraprostatic urethra to be substantial when daily online adaptive planning is not used. As investigation of boost doses to intraprostatic lesions is gaining interest, similarly the risk of overdosing the urethra or bladder neck may be high without the use of adaptive planning. Prospective studies of "urethral-sparing"

prostate SBRT with reduction of dose to the urethra below the prescription dose have reported promisingly low rates of urinary toxic effects.[9,19-21] And a recent combined analysis of 23 prospective trials demonstrated that urinary complications from prostate SBRT are closely linked to urethral dose.[23] Approaches for improving urethral dosimetry in this setting through the use of online adaptive planning therefore warrant further investigation. Analysis of a phase 2 study of patients who were treated similarly with MR-guided adaptive prostate SBRT found that "accumulated" bladder dosimetry superiorly predicted changes in urinary function compared with baseline original dosimetry.[10]

It should be noted that our protocol involves treatment with a "half-full" bladder as opposed to a strict full bladder as is commonly employed for prostate radiation therapy. Achieving a consistently full bladder was a challenge that we noted early on in our experience of prostate SMART, given the on-table time required currently for online adaptive planning. Instead, the approach of a "half full" bladder was adopted to achieve reproducibility and with the observation that the bladder will fill during the course of the adaptive planning workflow. Importantly, we observed that the anatomy of the prostate and interfaces with the bladder and rectum were preserved throughout the course of the treatment fraction using this technique. Conversely, in cases where the bladder became very full during the course of the adaptive workflow, for example in instances where the patient was on the table for an extended period of time due to a machine issue, we frequently observed that the prostate position and shape became less stable and was displaced posteriorly. In addition, in some cases, a very full bladder can push the seminal vesicles against the rectum, making for suboptimal anatomy for treatment of the seminal vesicles. Therefore, it is our opinion that the benefits and necessity of a strictly full bladder are less clear in the setting of prostate SBRT with narrow treatment margins and image guided treatment[22] and particularly when adaptive planning is employed to account for daily anatomic variation. Furthermore, our analysis of predicted dosimetry did not demonstrate any significant relationship between bladder fullness and predicted dosimetry (Fig. E3), suggesting that even a highly consistent bladder filling protocol, if this could be practically achieved, would not obviate the need for adaptive planning. In fact, there appeared to be a nonsignificant trend toward detrimental predicted bladder dosimetry with a fuller bladder, suggesting that "overfilling" of the bladder may carry risks, particularly without the use of daily adaptive planning to account for such changes.

We have also observed that urethral metrics were frequently violated despite minimal adjustment of urethral contours. Possible explanations for this include change in patient size or how adipose tissue falls each day; changes in rectal shape or gas, which may shift the prostate and

result in more or less beams traversing through bone; or changes in bladder filling, which may influence the dose distribution, as demonstrated in Fig. E4.

Our study comes with some important limitations. Most notably, these include the limited sample size of the study and relatively short follow-up time. Additionally, there was some heterogeneity of treatment specifically with regard to the use of androgen deprivation therapy and the use of rectal spacers, and the cohort was comprised of a mixture of patients with low- volume metastatic disease and patients undergoing curative intent treatment for localized disease.

Conclusion

Prostate SMART results in low risk of acute toxic effects with improvements in target and OAR dosimetry. The clinical benefits resulting from daily plan adaptation, including urethra/bladder neck protection, warrant further investigation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2022.100934.

References

1. Kishan AU, Dang A, Katz AJ, et al. Long-term outcomes of stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer. *JAMA Netw Open*. 2019;2: e188006.
2. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet Lond Engl*. 2019;394:385–395.
3. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): Acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20:1531–1543.
4. Mahase SS, D'Angelo D, Kang J, Hu JC, Barbieri CE, Nagar H. Trends in the use of stereotactic body radiotherapy for treatment of prostate cancer in the United States. *JAMA Netw Open*. 2020;3: e1920471.
5. van Dams R, Jiang NY, Fuller DB, et al. Stereotactic Body Radiotherapy for High-Risk Localized Carcinoma of the Prostate (SHARP) consortium: Analysis of 344 prospectively treated patients. *Int J Radiat Oncol Biol Phys*. 2021;110:731–737.
6. Jackson WC, Silva J, Hartman HE, et al. Stereotactic body radiation therapy for localized prostate cancer: A systematic review and meta-analysis of over 6,000 patients treated on prospective studies. *Int J Radiat Oncol Biol Phys*. 2019;104:778–789.
7. Lukka H, Deshmukh S, Bruner DW, et al. Patient reported outcomes in NRG Oncology/RTOG 0938, a randomized phase II study evaluating 2 ultrahypofractionated regimens (UHR) for prostate cancer (CaP). *Int J Radiat Oncol Biol Phys*. 2020;108:S119–S120.
8. Draulans C, van der Heide UA, Haustermans K, et al. Primary endpoint analysis of the multicentre phase II hypo-FLAME trial for intermediate and high risk prostate cancer. *Radiother Oncol*. 2020;147:92–98.

9. Bruynzeel AME, Tetar SU, Oei SS, et al. A prospective single-arm phase 2 study of stereotactic magnetic resonance guided adaptive radiation therapy for prostate cancer: Early toxicity results. *Int J Radiat Oncol Biol Phys*. 2019;105:1086−1094.

10. Bohoudi O, Bruynzeel AME, Tetar S, Slotman BJ, Palacios MA, Lagerwaard FJ. Dose accumulation for personalized stereotactic MR-guided adaptive radiation therapy in prostate cancer. *Radiother Oncol*. 2021;157:197−202.

11. Bitterman DS, Cagney DN, Singer LL, Nguyen PL, Catalano PJ, Mak RH. Master protocol trial design for efficient and rational evaluation of novel therapeutic oncology devices. *J Natl Cancer Inst*. 2020;112:229−237.

12. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology*. 2010;76:1245−1250.

13. Cella D, Yount S, Rothrock N, et al. The patient-reported outcomes measurement information system (PROMIS): Progress of an NIH roadmap cooperative group during its first two years. *Med Care*. 2007;45(5 Suppl 1):S3−S11.

14. Zelefsky MJ, Kollmeier M, McBride S, et al. Five-year outcomes of a phase 1 dose-escalation study using stereotactic body radiosurgery for patients with low-risk and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2019;104:42−49.

15. Hannan R, Tumati V, Xie XJ, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer-Results from a multi-institutional clinical trial. *Eur J Cancer Oxf Engl*. 2016;59:142−151.

16. Sandoval ML, Youssef I, Latifi K, et al. Non-adaptive MR-guided radiotherapy for prostate SBRT: Less time, equal results. *J Clin Med*. 2021;10:3396.

17. Ma TM, Lamb JM, Casado M, et al. Magnetic resonance imaging-guided stereotactic body radiotherapy for prostate cancer (MIRAGE): A phase III randomized trial. *BMC Cancer*. 2021;21:538.

18. Wang K, Mavroidis P, Royce TJ, et al. Prostate stereotactic body radiation therapy: An overview of toxicity and dose response. *Int J Radiat Oncol Biol Phys*. 2021;110:237−248.

19. Zilli T, Jorcano S, Bral S, et al. Once-a-week or every-other-day urethra-sparing prostate cancer stereotactic body radiotherapy, a randomized phase II trial: 18 months follow-up results. *Cancer Med*. 2020;9:3097−3106.

20. Alongi F, Mazzola R, Fiorentino A, et al. Phase II study of accelerated Linac-based SBRT in five consecutive fractions for localized prostate cancer. *Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al*. 2019;195:113−120.

21. D'Agostino GR, Mancosu P, Di Brina L, et al. Stereotactic body radiation therapy for intermediate-risk prostate cancer with VMAT and real-time electromagnetic tracking: A phase II study. *Am J Clin Oncol*. 2020;43:628−635.

22. Byun DJ, Gorovets DJ, Jacobs LM, et al. Strict bladder filling and rectal emptying during prostate SBRT: Does it make a dosimetric or clinical difference? *Radiat Oncol Lond Engl*. 2020;15:239.

23. Leeman JE, Cagney DN, Mak R, et al. MR-guided prostate SBRT with daily online plan adaptation: Results of a prospective phase I trial and supplemental cohort. Adv Radiat Oncol *in press* Mar 2022.