STEREOTACTIC BODY RADIOTHERAPY FOR PROSTATE CANCER

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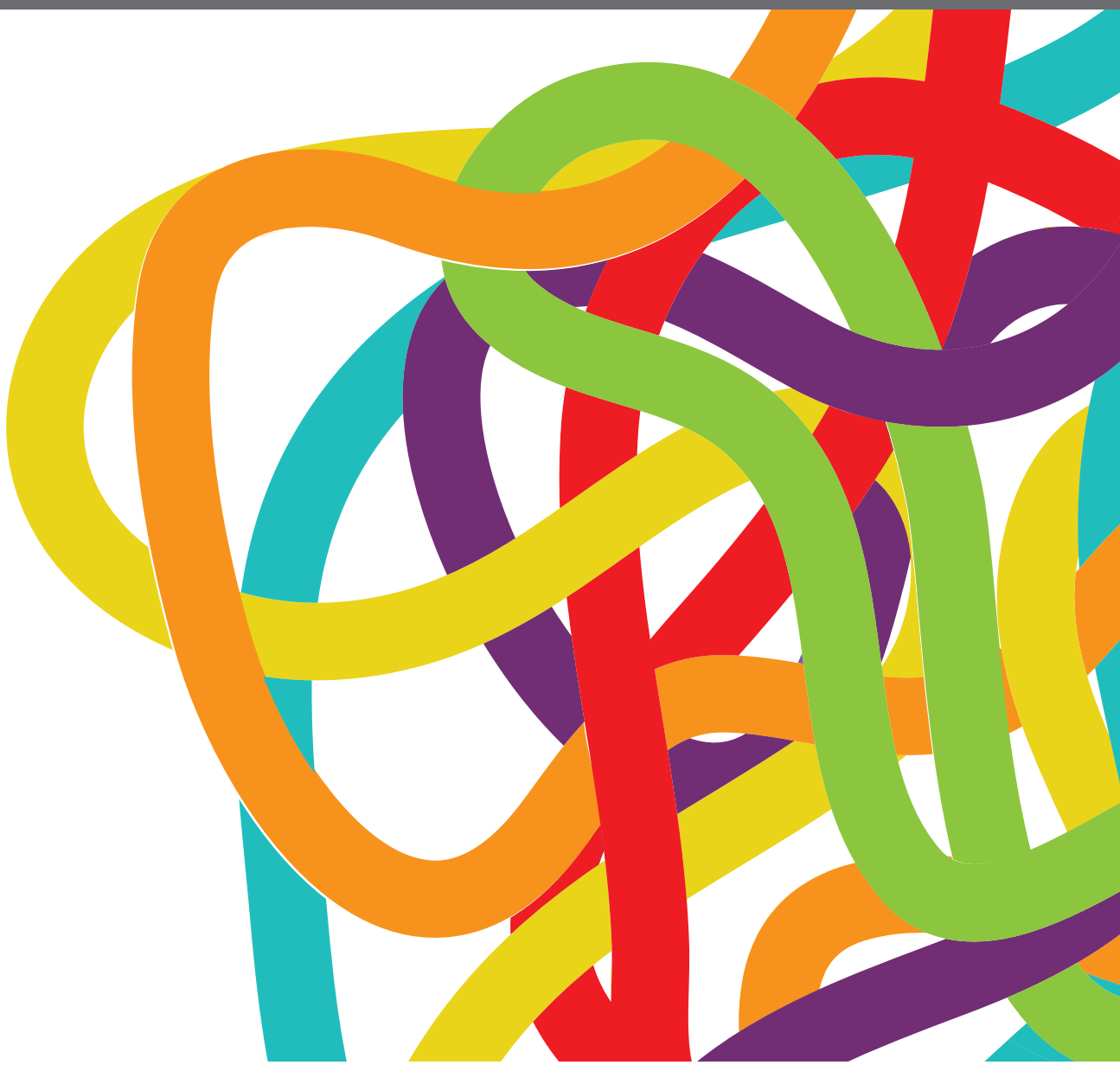

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STEREOTACTIC BODY RADIOTHERAPY FOR PROSTATE CANCER

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Table of Contents

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Editorial: Stereotactic body radiotherapy for prostate cancer

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Editorial on the Research Topic:
Stereotactic body radiotherapy for prostate cancer

Over the past few years, there has been an enormous growth in the strength of data suggesting the safety and efficacy of stereotactic body radiotherapy (SBRT) for prostate cancer. These include long-term data on ultrahypofractionated radiotherapy delivered with older techniques from the HYPO-RT-PC trial (1), early but robust data on modern SBRT from the PACE-B trial (2), and long-term follow-up data from a multi-institutional SBRT consortium (3). Further multi-institutional data (4) and several small randomized phase II trials (5, 6) have built a case for SBRT in high-risk prostate cancer and for use for metastasis-directed therapy in oligometastatic prostate cancer. Exciting clinical data also highlight the potential role for SBRT in the post-prostatectomy setting (7–10) and as a re-irradiation modality in radiorecurrent disease (11–13). Moreover, technological advances in real time image guided SBRT with MRI or PET have great potential. For example, the MIRAGE trial, the first randomized trial comparing MRI-guided with standard CT-guided SBRT seems to confirm a promising role for this innovative technique in prostate SBRT. (14) Yet, despite these advances, questions still remain. Can urinary and rectal toxicity be further mitigated? What patient factors—clinical, demographic, or otherwise—impact treatment efficacy? How can we better understand response to SBRT, both in the definitive setting and in the oligometastatic setting? And how does SBRT compare to other forms of re-irradiation?

This collection features 14 articles exploring the role of SBRT in prostate cancer across the entire spectrum of its natural history. Five manuscripts focus on practical considerations and interventions that might optimize the therapeutic ratio when delivering SBRT. Pham et al. explore the geometric distortions and variations in the urethra that might have dosimetric consequences for patients undergoing SBRT. Panizza et al. describe intrafraction motion during intact prostate SBRT as captured by electromagnetic tracking. Repka et al. review the rationale for using hydrogel spacers with prostate SBRT (Repka et al), while Kundu et al. provide a dosimetric and toxicity

analysis of patients who received SBRT and either had or did not have a spacer placed. Finally, Greco et al. describe seven year outcomes following dose-escalated SBRT wherein an endorectal balloon was used for mobilization/stabilization and a Foley catheter with implanted electromagnetic beacons was used to track and spare the urethra.

The next set of six articles explore efficacy and toxicity profiles among patients receiving SBRT for localized prostate cancer. Fuller et al. provide long-awaited 10-year outcomes from a multi-center phase II trial of high dose rate brachytherapy-like SBRT for intermediate risk prostate cancer. Three reports from the Georgetown SBRT group explore the incidence and natural history of post-SBRT hematospermia (Shah et al.), the implications of treatment interruptions (Pepin et al.), and the financial burden of SBRT (Sholklapper et al.). Correa and Loblaw provide a detailed review of the clinical evidence for SBRT in the context of high-risk disease. Finally, Liu et al. describe the ARGOS/CLIMBER protocol, in which men have pre-treatment and scheduled post-treatment multiparametric MRI and prostate specific membrane antigen positron emission tomography to establish imaging biomarkers of treatment response.

The collection is rounded out by three articles focusing on patients with recurrent disease. Cuccia et al. report on the outcomes of MRI-guided SBRT for re-irradiation of the prostate in men with radiorecurrent disease. Ryg et al. similarly explore long-term outcomes following salvage high dose-rate brachytherapy vs. salvage CT-guided SBRT. Finally, Mercier et al. report survival outcomes and failure patterns among men getting metastasis-directed SBRT for hormone sensitive or castrate resistant metastatic prostate cancer.

SBRT has demonstrated great success thus far for the definitive treatment of localized prostate cancer, but multiple important areas of investigation exist. These include: optimizing treatment by minimizing toxicity, evaluating long-term results in low and intermediate risk disease, better understanding its role in high risk disease, developing better markers of radioresponsiveness, exploring SBRT in the post-prostatectomy setting and for re-irradiation of radiorecurrent disease, and optimizing SBRT for metastasis-directed therapy. We hope that this broad collection of articles summarizes these exciting areas of active research while underscoring the efficacy and safety of SBRT for prostate cancer.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Bothersome Hematospermia Following Stereotactic Body Radiation Therapy for Prostate Cancer

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Background: Hematospermia following prostate radiation therapy is a benign and often self-limiting side effect. However, it may be bothersome to some men and their partners with a negative impact on sexual quality of life (QOL). This study sought to evaluate the incidence, duration, and resolution of hematospermia in patients following stereotactic body radiation therapy (SBRT) for prostate cancer.

Methods: 227 patients treated with SBRT from 2013 to 2019 at Georgetown University Hospital for localized prostate carcinoma with a minimum follow up of two years were included in this retrospective review of data that was prospectively collected. Patients who were greater than 70 years old and/or received hormonal therapy were excluded. Hematospermia was defined as bright red blood in the ejaculate. Time points for data collection included initial consultation, pre-treatment, 1-, 3-, 6-, 9-, 12-, 18-, 24-month. All patients were treated with the CyberKnife Radiosurgical System (Accuray). Data on hematospermia including duration, resolution and recurrence was collected. Utilization of 5-alpha reductase inhibitors was documented at each visit.

Results: 227 patients (45 low-, 177 intermediate-, and 5 high-risk according to the D'Amico classification) at a median age of 65 years (range 47-70) received SBRT for their localized prostate cancer. The 2-year cumulative incidence of hematospermia was 5.6% (14 patients). For these patients, all but one patient (93%) saw resolution of their hematospermia by two years post-SBRT. The median time for hematospermia was 9 months post-treatment. Of the 14 patients who reported hematospermia, 70% were managed with 5-alpha reductase inhibitors. Hematospermia was transient in most patients with 70% of the men reporting resolution by the next follow-up visit.

Conclusion: The incidence of bothersome hematospermia following SBRT was low. Hematospermia, as noted by other studies, often self-resolves. 5-alpha reductase inhibitors may lead to quicker resolution of bothersome hematospermia.

Keywords: prostate cancer, SBRT (stereotactic body radiation therapy), CyberKnife, hematospermia, 5-alpha reductase inhibitors

BACKGROUND

Hematospermia, defined as gross blood in the ejaculate (1), is an uncommon condition in the elderly population (< 1%) (2, 3). It is bothersome to men and their partners but is generally a benign finding that resolves on its own. Standard management is reassurance (1, 4). The most common etiology of hematospermia in the elderly population is iatrogenic including prostate biopsy (5) and prostatic fiducial placement (6). Hematospermia generally resolves in days to weeks (5). The blood is commonly bright red immediately post-procedure but can appear brown in color for months to years after the procedure as prostatic hematomas slowly resolve.

Bothersome ejaculatory symptoms following prostatic irradiation include reduced fluid volume, ejaculatory pain and hematospermia (7, 8). The etiology of post-radiation hematospermia is unclear but may involve inflammation of the seminal vesicles, vas deferens or ejaculatory ducts (**Figure 1**). It occurs months to years after treatment and generally resolves on its own without interventions but may persist in some men (7, 8). Up to 25% of patients report it following prostate EBRT and/or brachytherapy (7, 8). 5-alpha reductase inhibitors are an effective treatment for hematospermia (9) but they may cause duration-dependent decreased libido (10). This study sought to evaluate the incidence, duration, and resolution of hematospermia in patients following stereotactic body radiation therapy (SBRT) for prostate cancer.

METHODS

Patient Selection

Patients eligible for this study were those who had histologically-confirmed prostate cancer who were capable of ejaculating. Patients who were greater than 70 years old or received hormonal therapy were excluded from this study due to their known adverse effects on ejaculation (11, 12). Institutional IRB approval was obtained for retrospective review of patient medical records.

SBRT Treatment Planning and Delivery

SBRT treatment planning and delivery were conducted as previously described (13). Briefly, 4-6 gold fiducials were placed into the prostate *via* a transrectal or transperineal approach. One to two weeks after fiducial placement, CT and MR images were obtained and fused for treatment planning. The clinical target volume (CTV) included the prostate and the proximal seminal vesicles. The planning target volume (PTV) equaled the CTV expanded 3 mm posteriorly and 5 mm in all other dimensions. The prescription dose was 35-36.25 Gy to the PTV delivered in five fractions of 7-7.25 Gy over one to two weeks. In general, men initiated treatment 2-4 weeks following the treatment planning scans.

Follow-up and Statistical Analysis

Hematospermia was defined as bright red blood in the ejaculate. Brown blood in ejaculate was excluded due to its known association with post-biopsy hematomas (5, 14, 15). Patients were evaluated at initial consultation, the first day of treatment and during routine follow-up visits at one month, every 3 months for the first year and every six months for the second year. Data collected on hematospermia including duration, resolution and recurrence was collected. Time to hematospermia was recorded as the follow-up visit month at which hematospermia was first noted. Duration of hematospermia is calculated as length of time from when hematospermia was noted to subsequent visit when hematospermia was resolved. Utilization of 5-alpha reductase inhibitors was documented at baseline and at all follow-ups.

Analysis of individual characteristics was performed *via* bivariate comparison between patients experiencing hematospermia during the 2-year time and those without hematospermia. Binominal logistic regression was performed for all continuous variables and values were presented as average with standard deviation. Fisher's exact test was performed for categorical variables and values presented as number experiencing with percent of total cohort. All tests were two-tailed, and a p value <0.05 was considered significant. JMP® PRO version 15.0.0 for Macintosh was used to perform the statistical analyses (16).

RESULTS

227 patients on a prospective quality of life study (IRB#: 2009-510) with baseline ejaculatory capacity treated with prostate SBRT at Georgetown University Hospital from 2013 to 2019 were included in this analysis (**Table 1**). They were ethnically diverse with a median age of 65 years (interquartile range, 62-68 years). The median pre-treatment total serum testosterone level was 373 ng/dL (interquartile range, 287 - 483 ng/dL). When stratified by D'Amico risk group, 45 patients were low-, 179 intermediate-, and 5 high-risk (**Table 1**). For treatment, 90% of

Abbreviations: ADT, androgen deprivation therapy; CTV, clinical target volume; DVH, dose-volume histogram; GTV, gross target volume; PTV, planning target volume; QoL, quality of life; SHIM, Sexual Health Inventory for Men; EBRT, external beam radiation therapy; SBRT, stereotactic body radiation therapy; EPIC, Expanded Prostate Index Composite.

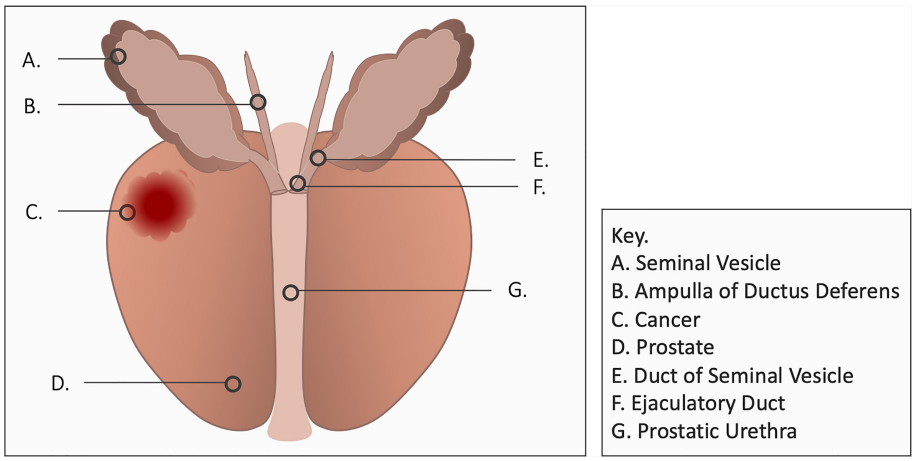


FIGURE 1 | Ejaculatory Ducts of the Prostate.

TABLE 1 | Baseline patient, disease, and treatment characteristics.

	N	(%)
Age, years		(61.6, 68.0)
Median (IQR)	65.4	(47.2, 70.8)
Mean (range)	64.2	
BMI, kg/m^2		(25.8, 31.2)
Median (IQR)	28.2	(0.9%)
<18.5	2	(17.1%)
18.5-24.9	37	(47.7%)
25-29.9	103	(31.0%)
30-39.9	67	(3.2%)
>40	7	
Race/Ethnicity		(60.2%)
White or Caucasian	136	(35.0%)
Black of AA	79	(1.3%)
Hispanic	3	(3.5%)
Other	8	
Prostate		
<40	131	(57.7%)
40-60	65	(28.6%)
>60	31	(13.7%)
α1 receptor antagonist		
Yes	197	(88.3%)
No	26	(11.7%)
PDES inhibitor		
Yes	49	(21.7%)
No	177	(78.3%)
Anticoagulant		
Yes	28	(12.3%)
No	90	(17.3%)
Missing	109	(48.0%)
Androgen deprivation therapy		
Yes	6	(2.7%)
No	216	(97.3%)
Testosterone, ng/dL		
Median (IQR)	373	(287, 483)
T-stage		
T1c-T2a	201	(88.5%)

(Continued)

TABLE 1 | Continued

	N	(%)
T2b-c	26	(11.5%)
Grade group (Gleason)		
1 (3 +3)	66	(29.3%)
2 (3 + 4)	105	(46.7%)
3 (4 + 3)	51	(22.7%)
4 (4 + 4)	3	(1.3%)
Risk group, D'Amico		
Low	45	(19.8%)
Intermediate	177	(78.0%)
High	5	(2.2%)
Pretreatment PSA, ng/mL		
Median (IQR)	7	(5.3, 10.4)
<10	167	(73.6%)
10-20	49	(21.6%)
>20	11	(4.8%)
SBRT Dose (Gy)		
35	200	(89.7%)
36.25	23	(10.3%)

patients received 36.25 Gy in five 7.25 Gy fractions. The minimum length of follow-up was 2 years and no patient initiated androgen deprivation therapy prior to SBRT or in the first two years following radiation therapy.

The prevalence of hematospermia prior to and after SBRT treatment is shown in **Table 2**. At the time of the initial SBRT treatment, no patient reported hematospermia. Levels of patient reported hematospermia increased significantly following treatment (**Table 2**), with 3% of patients reporting blood in the ejaculate at 3 and 6 months post-SBRT ($p < 0.0001$). While a low level of hematospermia was seen throughout the second years of follow-up, our 24-month prevalence of hematospermia was approaching baseline values (**Table 2**). The overall cumulative incidence of hematospermia two years post-SBRT was 5.6% (14 patients) (**Figure 2**). The mean time to developing hematospermia was 9 months post-SBRT. 70% of the patients were treated with 5-alpha reductase inhibitors. The mean duration was 3 months (range 3-12 months). **Figure 3** depicts a Swimmer's plot of hematospermia prevalence and 5-alpha reductase inhibitor utilization.

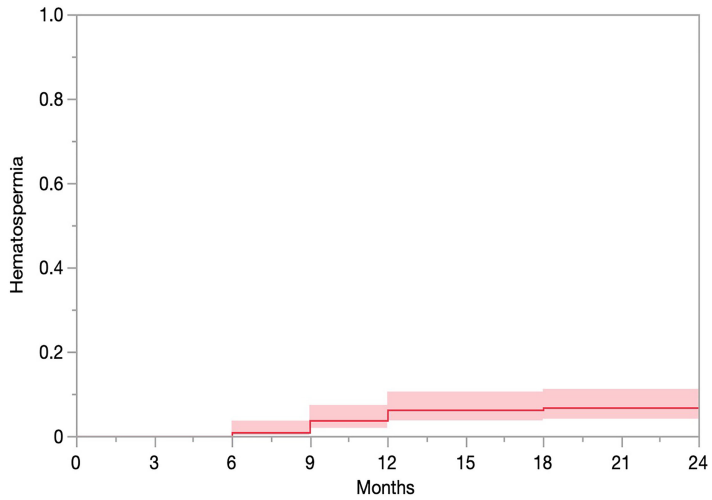
DISCUSSION

To our knowledge, this is the first study to report the hematospermia incidence following prostate SBRT. Hematospermia was uncommon at any time point and transient in most cases. The prevalence of hematospermia peaked at 6-9 months. From our clinical experience, hematospermia was rare greater than two years post-SBRT. These results appear similar to brachytherapy (7, 8). Hematospermia is a known complication of conventionally fractionated IMRT (1), however we could not identify evidence for the incidence in the current literature. Future work should compare the incidence of hematospermia following conventionally fractionated IMRT and SBRT.

Post-SBRT hematospermia is likely secondary ejaculatory duct inflammation (1, 4). Inflammation of the ejaculatory apparatus is a common cause of hematospermia (1, 4). Etiologies include epididymitis, urethritis, prostatitis and seminal vesiculitis. The timing of hematospermia following SBRT is similar to the phenomena of late urinary symptom flare (17). Late urinary symptom flare is a transient increase in

TABLE 2 | Hematospermia Incidence after SBRT.

				Men with hematospermia							
	Total	No prior hematospermia		Overall		Receiving Finasteride				Cumulative clearance of hematospermia	
	n	n	(%)	n	(%)	Yes	(%)	No	(%)	n	(%)
Treatment start	226	226	(100.0%)	0	(0.0%)	0		0		0	
1month	224	224	(100.0%)	0	(0.0%)	0		0		0	
3 months	213	213	(100.0%)	0	(0.0%)	0		0		0	
6 months	208	206	(99.0%)	2	(1.0%)	2	(100.0%)	0	(0.0%)	0	(0.0%)
9 months	202	195	(96.5%)	6	(3.0%)	2	(33.3%)	4	(66.7%)	1	(14.3%)
12 months	193	180	(93.3%)	6	(3.1%)	3	(50.0%)	3	(50.0%)	7	(53.8%)
15 months	176	168	(95.5%)	1	(0.6%)	1	(100.0%)	0	(0.0%)	7	(87.5%)
18 months	185	173	(93.5%)	2	(1.1%)	2	(100.0%)	0	(0.0%)	10	(83.3%)
21months	157	146	(93.0%)	0	(0.0%)	0		0		11	(100.0%)
24 months	159	148	(93.1%)	1	(0.6%)	0	(0.0%)	1	(100.0%)	10	(90.9%)



At Risk

Months	*0*	*3*	*6*	*9*	*12*	*18*	*24*
All	227	221	216	210	192	179	148

FIGURE 2 | Cumulative incidence of hematospermia following SBRT.

urinary symptoms seen several months following SBRT (17). It resolves on its own with time with a percentage of patients requiring a short course of anti-inflammatory medications (17). The exact etiology is unknown but likely involves post-RT inflammation of the bladder neck/prostatic urethra (18, 19).

5-alpha reductase inhibitors reduce hematospermia by reducing blood flow to the prostate (9). The Optimal Length of finasteride treatment is unknown. In general, we prescribe for three to six months then discontinued due to adverse sexual side effects. Hematospermia recurred in 1 patient but responded to a second course of 5-alpha reductase inhibitors (**Figure 3**).

Limitations

This study had several limitations. The true incidence of hematospermia is difficult to know because many elderly men are not highly sexually active. In addition, men do not commonly examine their ejaculate and if they did, they may not be able to distinguish bright red blood from brown blood. When assessing treatment toxicity, we did not specifically ask about hematospermia. In addition, it is impossible to know if hematospermia is secondary to radiation or fiducial placement. Men likely only reported hematospermia to their physician when bothersome to them and/or their partner (20, 21). Currently, there

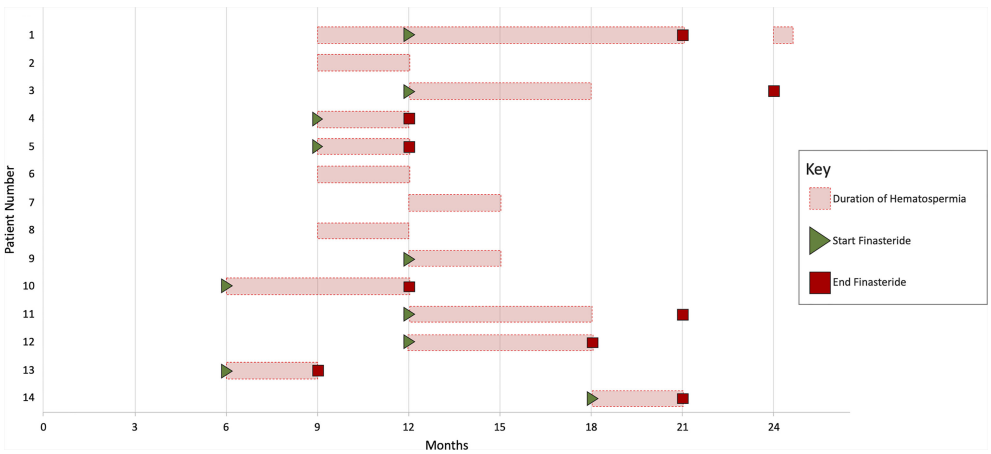


FIGURE 3 | Swimmer's plot of 14 patients who experienced hematospermia. Error bars represent the beginning and end of hematospermia in months post-SBRT. Green triangles and red boxes symbolize the start and stop of 5-alpha reductase inhibitor treatment respectively.

is no validated questionnaire to examine hematospermia (22). The cumulative incidence might have been higher if men would have been asked specifically about hematospermia at the time of follow-up and/or were able to privately document their experience *via* questionnaire (7, 23). In addition, brown blood was not recorded in our medical records do to its known association with episodic resolution of post-biopsy hematomas (24).

CONCLUSIONS

Hematospermia is a bothersome self-limiting symptom experienced by a small percentage of men following prostate SBRT. 5-alpha reductase inhibitors may lead to quicker resolution of bothersome hematospermia.

DATA AVAILABILITY STATEMENT

As per the wishes of the patients, the patient dataset is only available to those conducting research at the Georgetown University Medical Center. Requests to access the datasets should be directed to SPC9@gunet.georgetown.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Georgetown University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SaS was the lead author and participated in data collection and manuscript revision. TS and MC also contributed equally to SiS for this work and participated in data analysis, manuscript drafting, table/figure creation, and manuscript revision. AP, JC, BC, and RH aided in review and revision of the manuscript. SS is a senior author who organized the data and participated in its analysis. SC was the principal investigator who initially developed the concept of the study and the design, aided in data collected, and drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: SC serves as clinical consultants to Accuray Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Treatment Interruptions During Stereotactic Body Radiotherapy for Prostate Cancer

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Background: During the course of radiation treatment for prostate cancer, patients may have unintentional interruptions in their treatment course due to a wide variety of factors. Stereotactic body radiation therapy (SBRT) decreases the number of treatments compared to conventionally fractionated radiation; hence, it has the potential to decrease treatment delays and non-completion. This study sought to determine the incidence of treatment delay and characterize the etiology and length in a large cohort of men treated with SBRT for their prostate cancer.

Methods: One thousand three hundred and thirty-six patients treated with SBRT from 2008 to 2021 at the Georgetown University Hospital for prostate cancer were included in this retrospective study. A treatment delay was defined as a patient requiring longer than 14 days to complete 5 fractions of SBRT. Non-completion was defined as patients treated with less than 5 fractions. In the patients who experienced delays, chart review was performed to characterize the length and etiology of each delay. Multivariate analysis was performed *via* binary logistic regression modeling on PSPP.

Results: All individuals in the cohort eventually completed the planned 5-fraction regimen. Thirty-three patients experienced a treatment delay. Median length of time to complete treatment was 11 days (range 5–155 days). In patients who experienced a delay, nearly half (45.5%) experienced only a one-day delay. The most common reason for a delay was a technical issue (48.5%), including the machine maintenance, fiducial misalignment, or inadequate pretreatment bowel preparation. Other reasons included unplanned breaks due to acute side effects (21.2%), logistical issues (18.2%), non-treatment related health issues (9.1%), and inclement weather (3.0%). There were no significant sociodemographic, oncologic, or treatment variables that predicted treatment interruption on multivariate analysis.

Conclusions: The incidence of treatment interruptions in patients undergoing SBRT for their prostate cancer was low. Most treatment delays were short.

Keywords: SBRT (stereotactic body radiation therapy), prostate cancer, treatment interruption, Treatment delay, treatment noncompletion

INTRODUCTION

Prolongation of radiation treatment has the potential to increase tumor repopulation and affect tumor control rates (1–3). This is particularly true in patients with anal, cervical, lung, and head and neck cancers (3). In prostate cancer, which has a more indolent disease course, the results of treatment prolongation on outcomes have been mixed (1, 2).

Several retrospective studies have looked at treatment interruptions in prostate cancer patients treated with definitive external beam radiation therapy (EBRT). The University of Florida reported decreased rates of five-year local control in patients who had >8 weeks of treatment (4). However, their study was conducted in an era before PSA surveillance. A more contemporary study by D'Ambrosio et al., which examined patients treated between 1989 and 2004, demonstrated longer treatment durations as a risk factor for 10-year freedom from biochemical failure in low-risk patients (2). Dong et al. investigated the role of treatment interruptions in patients undergoing dose escalation to ≥74 Gy using IMRT or 3D-CRT and found no significant difference in outcomes with median follow up of 54 months (5). Although all these studies were performed using conventional radiation therapy, the results of treatment interruption are mixed perhaps due to the impact of total dose delivered and fractionation impacting oncologic outcomes.

The adoption of ultra-hypofractionated treatment regimens allows for decreased total treatment duration to one to two weeks. Recent studies comparing conventionally fractionated and ultra-fractionated radiation therapy have demonstrated the safety and efficacy of ultra-fractionation (6–8). As such, stereotactic body radiation therapy (SBRT) has been increasingly adopted in centers across the world. Despite this, many patients may still have unintentional treatment interruptions, which cause delays. The purpose of the current study is to evaluate rates of treatment delays and characterize the delays in a large institutional cohort of prostate cancer patients who underwent SBRT.

METHODS

Patient Selection

The Georgetown University Institutional Review Board approved this single institutional review (IRB# 2009-510). All individuals diagnosed with prostate cancer who received SBRT at the Medstar Georgetown University Hospital from 2008 to 2021 were eligible for inclusion. Patients treated with SBRT to prostatic fossa or distant sites were excluded.

SBRT Treatment Planning and Delivery

All men were treated with SBRT using an institutional protocol for simulation, contouring, and treatment planning (9). Patients underwent a treatment planning CT and pelvic MRI at least 1 week after placement of gold fiducial markers with or without hydrogel rectal spacers. The prescription dose was 30–37.5 Gy delivered over five fractions. The clinical target volume (CTV) included the prostate and proximal seminal vesicles. The PTV equaled the CTV expended 3 mm posteriorly and 5 mm in all other directions.

Definitions and Statistical Analysis

In eligible patients, chart review was performed to determine date from start of treatment to end of treatment. Treatment interruptions were defined as patients requiring longer than 14 days to complete 5 fractions. In the patients who experienced delays, chart review was performed to characterize the reason for treatment delay. Causes of delay were classified as technical (i.e., mechanical failure, fiducial migration), logistical (i.e., patient caring for family member, insufficient transport), acute side effects, health issues not related to radiation treatment, and inclement weather. Patients who completed under their prescribed fraction were characterized as treatment noncompletion.

Multivariate analysis was performed using binary logistic regression on PSPP. The primary dependent variable was treatment delay. Covariables were selected based on previous investigations identifying independent determinants of SBRT use (10, 11). These included sociodemographic factors, such as race and age, oncologic factors such as Gleason scoring and stage), and also treatment variables (namely, risk grouping, SBRT dose, and ADT).

RESULTS

Between 2007 and May 2021, one-thousand three hundred and thirty six patients with prostate cancer were eligible for inclusion in this study. Patient characteristics are listed in **Table 1**. The patient cohort was diverse. The median age was 70 years old (range 44–100). Approximately 59% of the cohort was white and 34.4% was African American. The cohort consisted of 20% low-risk, 68.3% intermediate-risk, 11.6% high risk, and 0.07% very high-risk individuals. Seventy-six percent of patients did not receive neoadjuvant androgen deprivation therapy. Seventy-nine percent were treated with 36.25 Gy in 5 fractions, while 20.6% underwent 35 Gy in 5 fractions.

The median time for treatment completion was 11 days. Thirty-three patients (2.5%) experienced treatment delay (**Table 2**).

TABLE 1 | Patient characteristics.

	Percent of patients (n = 1,336)
Age (Range 44–100)	
40–49	0.7% (10)
50–59	8.7% (116)
60–69	39.0% (521)
70–79	42.3% (565)
80–90	8.6% (115)
90+	0.7% (9)
Race	
African American	34.4% (459)
Caucasian	58.5% (782)
Hispanic	2.2% (29)
Other	4.9% (66)
Gleason	
4–5	0.45% (6)
6	29.6% (395)
7	62.0% (828)
8	5.8% (77)
9–10	2.2% (30)
T Stage	
T1a–T1c	68.3% (913)
T2a–T2c	30.8% (412)
T3	0.67% (9)
Tx	0.15% (2)
D'Amico Risk Group	
Low	20.0% (267)
Intermediate	68.3% (913)
High	11.6% (155)
Very High	0.07% (1)
ADT	
Yes	23.8% (318)
No	76.2% (1018)
SBRT Dose	
35	20.6% (275)
36.25	78.7% (1052)
Other	0.7% (9)

TABLE 2 | Length of Delay and Cause for Individual Patients.

Patient	Length of Delay (Days from Start of Treatment)	Cause
1	15	Technical (Machine Down)
2	15	Logistical Issue (No Ride)
3	154	Acute Side Effects (Requiring TURP)
4	16	Logistical Issue (Family Emergency)
5	14	Acute Side Effects
6	15	Technical (Poor Bowel Prep)
7	14	Acute Side Effects
8	15	Technical (Machine Down)
9	14	Technical (Machine Down)
10	14	Technical (Machine Down)
11	14	Technical (Machine Down)
12	15	Technical (Machine Down)
13	14	Technical (Machine Down)
14	23	Technical (Machine Down)
15	15	Technical (Machine Down)
16	14	Acute Side Effects
17	14	Health Issue (Arrhythmia)
18	43	Health Issue (Pyelonephritis)
19	14	Technical (Machine Down)
20	17	Technical (Machine Down)
21	15	Technical (Machine Down)
22	14	Logistical Issue (Dialysis)
23	16	Technical (Poor Bowel Prep)
24	23	Health Issue (COVID-19)
25	14	Inclement Weather
26	15	Acute Side effects
27	14	Acute Side Effects
28	14	Technical (Machine Down)
29	14	Logistical Issue (Caring for Ill Family Member)
30	28	Logistical Issue (No ride)
31	14	Acute Side Effects
32	18	Technical (Fiducial Migration)
33	24	Logistical Issue (Work Conflict)

There were no patients who experienced incompletion of treatment. The most common reason for treatment interruption was technical issues (48.5%), namely, machine downtime and fiducial migration (**Figure 1**) . Acute side effects (21.2%), logistical (18.2%), health issues not related to radiation treatment (9.1%), and inclement weather (3.0%) represented other reasons for treatment interruption. In those who experienced treatment interruption, 81.8% experienced a treatment interruption of less than or equal to one week (**Figure 2**).

Race, stage, ADT status, Gleason score, D'Amico risk grouping, and SBRT dose were not associated with significantly different odds for treatment interruption (**Supplementary Table 1**).

DISCUSSION

Our findings suggest radiation treatment interruptions and noncompletion in patients undergoing SBRT for their prostate cancer are uncommon. Our results are consistent with previously reported results which showed lower odds of treatment noncompletion in patients undergoing SBRT compared to conventionally fractionated regimens (OR 0.21) (10). The rationale for these findings are likely related to the convenience of having a smaller fraction of treatments. This is in line with the study of Han et al., which demonstrated that total treatment duration in patients undergoing proton therapy increased likelihood of treatment interruption on multivariate analysis (OR 1.05) (1).

In patients who experienced delays, many delays were unavoidable due to health concerns, patient logistical issues, or machine maintenance. This seems consistent with barriers identified in previous investigations (1). The most common cause of delay was due to technical issue. In a study investigating proton beam availability on patient treatment scheduling, it was found that machine downtime greater than 1 h may result in missed treatments (12). Because many centers have more than one linear accelerator, it is possible that treatment delays due to machine downtime may be less in patients undergoing photon-based therapy as patients can be switched between machines. In an international trial looking at linear accelerator downtime in UK, Botswana, and Nigeria facilities, downtime lasting more than 1 h was rare and occurred only 3.4% of the total faults (13). Technical delays were minimized at our center by having two robotic linear accelerators and the availability of spare parts near our center.

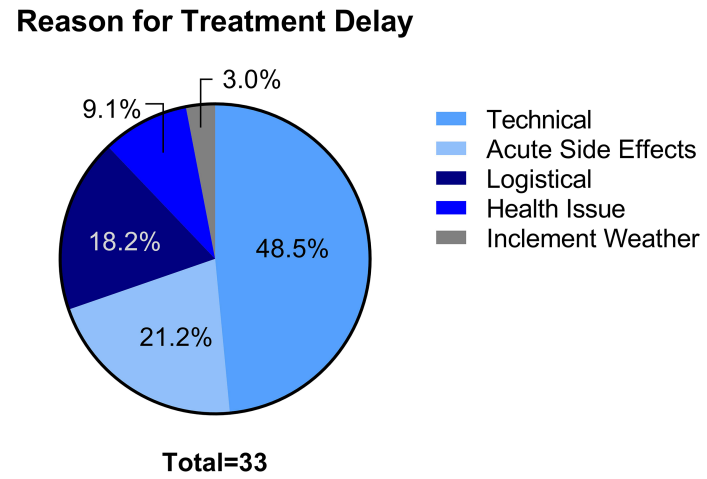

FIGURE 1 | Reason for treatment delay.

The overwhelming majority of the delays were ≤7 days in our study. In patients undergoing EBRT with RT doses of ≥74 Gy, slightly prolongation of treatment time (e.g., ≤7 days) was not associated with inferior freedom from biochemical failure (14). Extreme hypofractionated regimens may have mechanisms of cellular death more similar to brachytherapy than conventionally or moderately hypofractionated external beam radiation therapy; hence, it remains unclear if treatment delays would have significant impact on patient outcomes. Tamponi et al. demonstrated fraction size sensitivity was lower for prostate cancer compared to normal tissue late side-effects favoring the role of hypofractionated radiation in prostate cancer (15). A limited dependence on repopulation was observed in that study (15). Further investigations as to the impact of treatment delays in prostate cancer patients undergoing SBRT on freedom from biochemical failures are warranted.

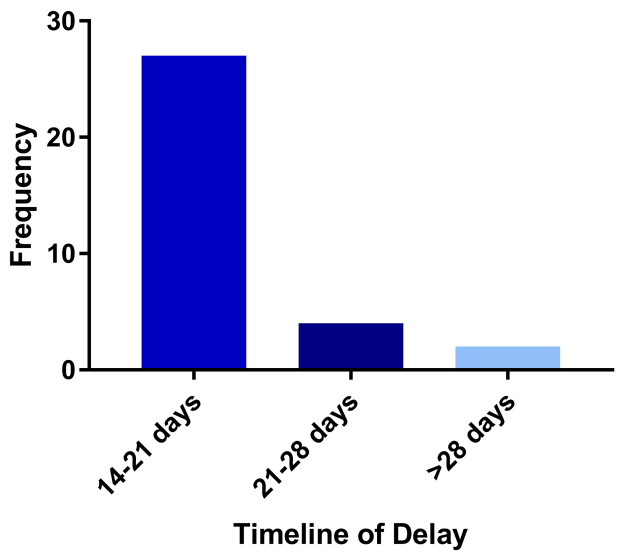

FIGURE 2 | Timeline of treatment delay.

Investigations as to optimal treatment time for SBRT are ongoing in the Patriot study with regard to biochemical failure. However, published results suggest it is safe to treat once weekly with improved quality of life scores in acute bowel and urinary scores in patients undergoing every week treatment as opposed to every other day (16).

Previous investigations have also demonstrated sociodemographic variables associated with increased rates of noncompletion and receipt of radiation therapy including younger age, black race, lower socioeconomic status, and higher risk group (10, 11). The results of our multivariate analysis failed to demonstrate age, black race, and higher risk groups as being risk factors for treatment interruption in patients undergoing SBRT for their prostate cancer.

Due to the retrospective nature of our study design, it is inherently limited. In our analysis, we have selected a number of covariates based on studies conducted from the National Cancer Database (NCDB) (10, 11). There are a number of studies documenting limitations of using the NCDB, namely, selection bias, lack of clinically relevant endpoints, and prevalence of missing data among hospital-based cancer patients (17, 18). Despite this, we believe that the results of our analysis may have been negative as nearly half of our patients who experienced delays were due to technical issues, which would be independent of sociodemographic factors.

CONCLUSION

The incidence of treatment interruptions in patients undergoing SBRT for their prostate cancer was low. Most treatment delays were short.

DATA AVAILABILITY STATEMENT

The datasets will not be made available due to patient privacy concerns. Requests to access the datasets should be directed to SPC9@gunet.georgetown.edu.

AUTHOR CONTRIBUTIONS

AP was the lead author, who participated in data collection, data analysis, manuscript drafting, table/figure creation, and manuscript revision. AZ and MD participated in data collection and data analysis while also aiding in study design. TY and MA aided in clinical data collection. DK participated in data analysis and manuscript review. BC aided in manuscript review. SS is a senior author who organized the data and participated in its analysis. NA is a senior author who aided in data analysis and manuscript review and revision. SC was the principal investigator who initially developed the concept of the study and the design, aided in data collection, and drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.796496/full#supplementary-material

Supplementary Table 1 | Rates of treatment interruption and odds ratios stratified by sociodemographic and oncologic variables.

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Rectal Radiation Dose and Clinical Outcomes in Prostate Cancer Patients Treated With Stereotactic Body Radiation Therapy With and Without Hydrogel

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Background: Patients with prostate cancer treated with stereotactic body radiation therapy (SBRT) may experience gastrointestinal (GI) toxicity. The hydrogel may mitigate this toxicity by reducing the rectal radiation dose. The purpose of this study is to compare rectal radiation dose and GI toxicity in patients receiving prostate SBRT with and without hydrogel.

Methods: Consecutive patients treated with SBRT between February 2017 and January 2020 with and without hydrogel were retrospectively identified. Baseline characteristics including prostate volume, rectal diameter, body mass index (BMI), age, pretreatment prostate-specific antigen (PSA), Gleason score, T-stage, and androgen deprivation therapy (ADT) usage were compared. Dosimetric outcomes (V40Gy, V36Gy, V32Gy, V38Gy, and V20Gy), rates of acute (≤90 days) and late (>90 days) GI toxicity, and PSA outcomes were evaluated for patients with and without hydrogel.

Results: A total of 92 patients were identified (51 hydrogel and 41 non-hydrogel). There were no significant differences in baseline characteristics. Rectal V38(cc) was significantly less in the hydrogel group (mean 0.44 vs. mean 1.41 cc, $p = 0.0002$), and the proportion of patients with V38(cc) < 2 cc was greater in the hydrogel group (92% vs. 72%, $p = 0.01$). Rectal dose was significantly lower for all institutional dose constraints in the hydrogel group ($p < 0.001$). The hydrogel group experienced significantly less acute overall GI toxicity (16% hydrogel vs. 28% non-hydrogel, $p = 0.006$), while the difference in late GI toxicity trended lower with hydrogel but was not statistically significant (4% hydrogel vs. 10% non-hydrogel, $p = 0.219$). At a median follow-up of 14.8 months, there were no biochemical recurrences in either group.

Conclusion: Hydrogel reduces rectal radiation dose in patients receiving prostate SBRT and is associated with a decreased rate of acute GI toxicity.

Keywords: hydrogel, prostate cancer, SBRT (stereotactic body radiation therapy), radiation oncology, outcomes

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is a recommended treatment for prostate cancer and is increasingly utilized (1, 2). This technique, which utilizes ultra-hypofractionated radiation regimens (≥ 5 Gy per fraction), is now standard of care and has been suggested to be non-inferior to standard fractionation radiation for biochemical and local control (3). Additionally, ultra-hypofractionated treatment courses with SBRT, which require only 5–7 visits, are significantly more convenient for patients. However, gastrointestinal (GI) toxicity remains an issue for prostate SBRT. For example, the PACE-B trial reported 53% Grade 1, 10% Grade 2, and < 1% Grade 3 Radiation Therapy Oncology Group (RTOG) GI toxicities (4). The rectum is adjacent to and often abuts the prostate and thus may receive significant incidental radiation leading to GI toxicity. Acute radiation-related rectal toxicity can occur due to inflammation, fibrosis, microvascular damage, and edema within the bowel wall and mucosa (5, 6). Late sequelae may include bleeding, urgency, and incontinence, which can be predicted by radiation volumetric dose parameters (7–10).

To limit radiation dose to the rectum, various methods have been employed to create space between the prostate and rectum, including collagen or hyaluronic acid injection, and biodegradable rectal spacer balloons (11–13). Another such method is the injection of the hydrogel into Denonvilliers' fascia between the rectum and prostate. This hydrogel is biologically inert and composed of two liquids that mix post-injection to polymerize and solidify within the patient (**Figure 1**). Hydrogel has been shown to reduce rectal dose in patients receiving standard fractionation radiation therapy (14). However, data on the safety, efficacy, and clinical outcomes of hydrogel in patients receiving SBRT are limited.

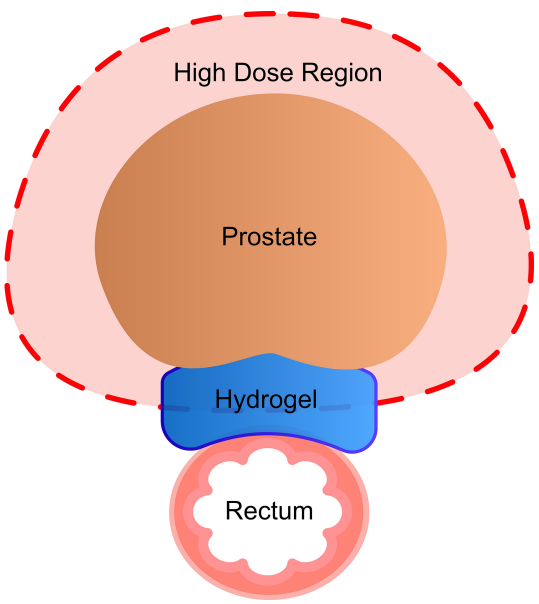

FIGURE 1 | The hydrogel pushes the rectum out of high-dose radiation field.

The purpose of this study is to compare rectal dose and associated GI toxicity with or without hydrogel in patients with prostate cancer undergoing SBRT to the prostate (Boston Scientific, Marlborough, MA, USA).

METHODS

This Institutional Review Board-approved retrospective study included patients who received SBRT for treatment of localized prostate cancer at a single academic institution between February 2017 and January 2020. All patients were aged 18 years or older and did not receive prior pelvic radiation, transurethral resection of the prostate, or any other focal treatment.

Hydrogel was offered to all patients without posterior extracapsular extension (ECE) on MRI. For patients receiving hydrogel, Denonvilliers' space was approached transperineally with a 17-gauge needle and was gently hydrodissected with 10 cm^3 of 0.9% normal saline under transrectal ultrasound guidance. Upon confirmation of Denonvilliers' space expansion and separation of Denonvilliers' fascia from the rectal wall, 10 cm^3 of hydrogel was administered into this space. All patients underwent pretreatment multiparametric MRI at diagnosis and CT simulation for SBRT treatment planning. Patients who received hydrogel also subsequently underwent MRI within 1 week of CT simulation. All patients received linear accelerator-based radiation treatment with 40 Gy in 5 fractions to the clinical target volume (CTV), which was defined as the prostate and proximal seminal vesicles. The CTV was expanded by 5 mm in all directions, except 3–4 mm posteriorly to form the planning target volume (PTV). The treatment dose was prescribed such that 95% of the PTV received the prescription dose, and the institutional dose constraints were rectum V20Gy ≤ 50%, V32Gy ≤ 20%, V36Gy ≤ 10%, and V40Gy ≤ 5%; bladder V20Gy ≤ 40% and V40Gy ≤ 10%; and small bowel V20Gy < 30 cc and D0.035cc ≤ 35 Gy.

Baseline characteristics including age, body mass index (BMI), prostate volume, rectal diameter, T-stage, Gleason Grade Group, pretreatment prostate-specific antigen (PSA), and androgen deprivation therapy (ADT) use were collected. Risk categories were defined according to the National Comprehensive Cancer Network (NCCN). Prostate volume was assessed on pretreatment MRI, and rectal diameter was measured as the largest diameter at the mid-gland level of the prostate on the CT simulation scan.

The age, BMI, prostate volume, rectal diameter, and pretreatment PSA between the hydrogel and non-hydrogel patients were compared by Student's or Welch's t-test. The Gleason scores and risk groups were compared using the Kruskal–Wallis test, while T-stage and ADT use were compared using Fisher's exact test.

Rectal dose–volume histogram (DVH) parameters corresponding to institutional dose constraints (rectum V40Gy,

V36Gy, V32Gy, and V20Gy) and V38Gy(cc), which has previously been shown to predict high-grade late hematochezia, were collected (15). Differences between the hydrogel and non-hydrogel patients in rectal dose parameters were compared using t-test for two-sample mean when variances between groups were equal and Welch's test when unequal, and the proportion of patients with V38Gy < 2 cc was compared using Fisher's exact test. The highest reported Common Terminology Criteria for Adverse Events (CTCAE) for acute (≤ 90 days) and late (> 90 days) GI toxicity scores reported during follow-up were collected and compared using Fisher's exact test. Posttreatment PSAs were collected to evaluate the incidence of biochemical recurrence per Phoenix definition (PSA nadir +2 ng/ml).

RESULTS

A total of 92 localized prostate cancer patients were identified who underwent SBRT, of whom 51 patients received hydrogel. Baseline characteristics are shown in **Table 1**, and no significant differences were observed (**Table 1**). The median overall follow-up was 14.8 months (range 3.8–41.5 months; hydrogel median 14.8 months, non-hydrogel median 16.2 months), and the median age was 72 years (range 46–85). Included in the study were 20 high-risk, 65 intermediate-risk, and 7 low-risk patients defined by NCCN criteria. A trend towards NCCN high-risk group disease in non-hydrogel patients and towards unfavorable intermediate-risk group disease in hydrogel patients was observed but was not statistically significant. A total of 3 patients (2 hydrogel patients) had T3a disease. None of these patients had posterior ECE on imaging. A total of four patients (1 hydrogel patient) had T3b disease. Androgen deprivation therapy was given to 39% and 35% of the hydrogel and non-hydrogel patients, respectively. The median time from hydrogel placement to SBRT was 10 days (range 4–25 days). At a median follow-up of 14.8 months in the hydrogel group, there were no biochemical recurrences.

Rectal dose was significantly lower for all evaluated radiation dose parameters in the hydrogel group (**Figure 2**). The greatest relative differences were seen in the high dose parameters; i.e., V40Gy was 7-fold less in the hydrogel group (0.18% vs. 1.30%). Additionally, rectal V38(cc) was significantly less in the hydrogel group (mean 0.44 vs. mean 1.41 cc, p = 0.0002), and the proportion of patients with V38(cc) < 2 cc was greater in the hydrogel group (92% vs. 72%, p = 0.01).

TABLE 1 | Baseline patient clinical characteristics.

	No hydrogel (n = 41)	Hydrogel (n = 51)	p-Value
Characteristics	**Number of patients (%)**		
Age			0.77
≤60	6 (15%)	6 (12%)	
61–70	12 (29%)	15 (29%)	
≥70	23 (56%)	30 (59%)	
	Median = 71 (range 46–85)	Median = 72 (range 52–85)	
BMI (kg/m^2)	Mean = 26.9, median = 26.4 (range 20.2–45.0)	Mean = 26.7, median = 26.4 (range 16.1–35.6)	0.77
Stage			0.70
T1–T2	37 (90%)	48 (94%)	
T3 and above	4 (10%)	3 (6%)	
Grade group			0.81
1	3 (7%)	5 (10%)	
2	17 (41%)	16 (32%)	
3	11 (27%)	22 (44%)	
4	5 (12%)	5 (10%)	
5	5 (12%)	2 (4%)	
Pretreatment PSA (ng/ml)			0.82
< 10	27 (66%)	40 (78%)	
10–20	11 (27%)	10 (20%)	
> 20	3 (7%)	1 (2%)	
	Mean = 11.4, median = 7.64, (range 2.5–77)	Mean = 12.6, median = 7.1 (range 0.9–254.4)	
ADT			0.83
Yes	16 (39%)	18 (35%)	
No	25 (61%)	31 (65%)	
	Median = 6 months, (range 3–24 months)	Median = 6 months, (range 1.5–24 months)	
NCCN risk category			0.25
Low	2 (5%)	5 (10%)	
Favorable intermediate	13 (32%)	10 (20%)	
Unfavorable intermediate	14 (34%)	28 (55%)	
High	12 (29%)	8 (16%)	
Prostate volume (cc)	Mean = 56.6, median = 52.2 (range 27.3–112.3)	Mean = 49.1, median = 45.7 (range 16.5–86.8)	0.07
Rectal diameter (cm)	Mean = 3.7, median = 3.5 (range 2.4–5.3)	Mean = 3.6, median = 3.5 (range 2.3–5.6)	0.54

BMI, body mass index; PSA, prostate-specific antigen; ADT, androgen deprivation therapy; NCCN, National Comprehensive Cancer Network.

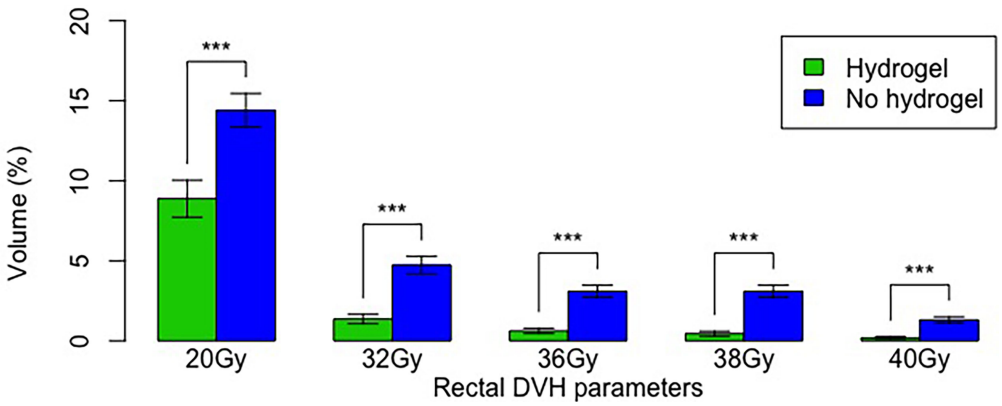

FIGURE 2 | Radiation dose parameters in the hydrogel and non-hydrogel cohorts. Error bars show standard error. "***" denotes $p < 0.001$.

TABLE 2 | Acute GI toxicity rates.

	Non-hydrogel % (n)	Hydrogel % (n)
Grade 1	24% (10)	12% (6)
Grade 2	2% (1)	4% (2)
Grade 3	2% (1)	0% (0)

GI, gastrointestinal.

The rates of acute Grade 1, 2, and 3 GI toxicities are shown in **Table 2**. Overall, the non-hydrogel group had greater acute GI toxicity ($p = 0.006$), including rectal urgency (4), constipation (2), and diarrhea (4). While most of the toxicities were Grade 1, one case of constipation was Grade 2, and one case of diarrhea was Grade 3, which later resolved. Of note, 6 minor acute Grade 1 adverse events resulting from the procedure were reported in the current cohort, and all resolved, including constipation (2), loose stools (1), and minimal or unspecified GI symptoms (3). The highest reported late GI toxicity was Grade 1 (diarrhea in all cases): 2 patients (4%) in the hydrogel group and 4 patients (10%) in the non-hydrogel group. This difference in late GI toxicity was not statistically significant ($p = 0.219$).

DISCUSSION

Hydrogel significantly reduced the relevant radiation volumetric dose parameters by creating a physical separation between the prostate and rectum and thereby displacing the rectum from the high dose radiation field. The procedure was safe and well tolerated with no short- or long-term procedural-related sequelae. Furthermore, hydrogel was associated with a significant reduction in acute GI toxicity. We did not observe a similar association for late GI toxicity; however, more events may occur with longer follow-up. The acute diarrhea reported in the hydrogel group may also be due to hydrogel, and not radiation, given that hydrogel may irritate the rectum and that patients are often prescribed a stool softener to prevent constipation.

Importantly, there were no differences in biochemical recurrence, indicating oncologic outcomes were not compromised. However, the median overall follow-up time was only 14.8 months. Furthermore, there were only three patients with ECE (none were posterior) and four patients with seminal vesicle invasion. Therefore, caution should be exercised for T3–T4 patients with posterior ECE or invasion of the rectum out of theoretical concern that gross disease may be displaced out of the intended treatment field. Therefore, pretreatment MRI is recommended to assess disease extent posteriorly.

Though data on the effects of hydrogel in patients receiving SBRT are limited, the dose reduction observed in this study is consistent with a previous study of hydrogel with dose-escalated standard fractionation radiation (14), which similarly showed the greatest relative reductions in the high dose volumetric parameters; i.e., V82Gy was also 7-fold less in the hydrogel group (0.2% vs. 1.3%). Though no difference in acute GI toxicity was reported, late Grade 1 toxicity was less frequent in the hydrogel group (16.6% vs. 41.8%). Another study of hydrogel with ultra-hypofractionation without a comparative non-hydrogel group showed similar rates of acute GI toxicity (16% Grade 1 and 4% Grade 2) and no difference in late rectal toxicity (16). Studies of MRI-guided, daily adaptive SBRT similarly show reduced rectal dose and reduced intra-fraction motion and importantly collected patient-reported outcomes that did not show decreased quality of life in patients receiving hydrogel spacers (17, 18). The acute benefit of hydrogel may be more pronounced for ultra-hypofractionation than for standard fractionation, especially given the concern for the worse acute quality of life for ultra-hypofractionation seen in the HYPO-RT-PC trial (19). Acute Bowel Quality of Life was worse at <3 months but the same at 3 months. Furthermore, the HYPO-RT-PC SBRT arm reported 9.4% acute Grade 2+ and 2.2% late 2-year Grade 2+ GI toxicity rates. The higher rate of Grade 2+ toxicity on HYPO-RT-PC compared to the current study may be due to the use of older radiation techniques. Additionally, the main rectal dose constraint used in the HYPO-RT-PC trial was V90% ≤ 15%, while our corresponding institutional constraint was

V36Gy ≤ 10%. A phase II trial of SBRT at our institution demonstrated that acute and late Grade 2 GI toxicities were 3.3% and 3.9%, respectively (20).

It is imperative that the risks and benefits of hydrogel be considered prior to its administration. Hall et al. queried the Food and Drug Administration (FDA) Manufacturer and User Facility Design Database (MAUDE) and noted 85 adverse events related to hydrogel placement, of which 69% were scored as grade ≥ 3 toxicity including descriptions of colostomy, anaphylactic events, rectal injection pulmonary emboli, and death (21). There is no doubt that these events are severe, but in relation to the total number of hydrogel cases performed (109,165 estimated), these events are rare (0.07%). Of note, adequate training and experience are critical to ensure the safety of hydrogel administration, and physicians must be credentialed to perform this procedure.

The current study has several limitations, one of which is that this is a retrospective analysis of non-randomized patients with a contemporary control used instead. Furthermore, physician preference and insurance reimbursement may have driven the decision patient decision to pursue hydrogel, and these confounders may be correlated with toxicity outcomes. Hydrogel patients were only simulated once without a separate plan to compare DVH parameters without hydrogel within the same patient. Furthermore, physician-reported toxicity may underestimate the true incidence of GI toxicities, and late GI Grade 2+ GI toxicity occurs with a mean time of 1.5 years posttreatment, which exceeds the median follow-up of the current study (22, 23).

CONCLUSION

In prostate cancer patients treated with SBRT, hydrogel is well tolerated, reduced key rectal dose parameters, and is associated with lower rates of acute GI toxicity.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: due to the nature of this research and protected health information, participants of this study did not agree for their data to be shared publicly. Requests to access these datasets should be directed to AC, ajchang@mednet.ucla.edu.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the writing and preparation of this manuscript.

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Patient-Reported Financial Burden Following Stereotactic Body Radiation Therapy for Localized Prostate Cancer

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Introduction and Objectives: In patients with localized prostate cancer, 5-fraction, stereotactic body radiation therapy (SBRT) has been found to offer comparable oncologic outcomes and potential for improved treatment compliance compared to conventional, 40-plus fraction radiation therapy (RT). Recent studies of oncologic patient experiences have highlighted both the impact of therapy-associated financial toxicity (FT) on treatment adherence and health-related quality of life (HRQOL).

Methods: A cross-sectional assessment of FT after SBRT was performed using the 12-item COST questionnaire. The total questionnaire score (range 0–44) was used to evaluate the FT grade (0–3), with a higher COST value representing lower grade. The patient zip code was used to approximate the distance from the index hospital. Univariate and multivariate analyses of the average COST score (0–4) are performed.

Results: The response rate was 57.5% (332 of 575 consented patients) with 90.7%, 8.2%, and 1.1% experiencing grade 0, 1, and 2 FT, respectively, with no grade 3. Unemployment or disability, non-white race, low income, and concurrent hormonal therapy were associated with a statistically significant worse FT (lower COST value) on univariate and multivariate analyses ($p < 0.05$). Education level and insurance status significant were evaluated on univariate analysis only. There was a non-statistically significant difference in age, marital status, time since treatment, and distance from the index hospital.

Conclusions: SBRT was associated with low FT. However, statistically significant socioeconomic disparities in FT remain despite ultra-hypofractionated treatment.

Keywords: prostate cancer, SBRT (stereotactic body radiation therapy), CyberKnife, financial toxicity, HRQoL (health-related quality of life)

INTRODUCTION

Financial toxicity (FT) is a patient-centric experience of the financial burden of disease and its management (1–3). FT has historically been analyzed objectively by looking at a patient's direct cost of disease management. Some studies report that almost half of patients undergoing cancer treatment fully deplete their life assets by 2 years post-diagnosis, with average losses approaching nearly $100,000 by year 4 (4). In the past decade, the understanding of FT has been broadened to include the subjective financial burden and indirect costs (e.g., loss of work for patient or caretaker) associated with disease (1–3).

To date, many of the studies of FT for patients with prostate cancer have relied on non-validated, subjective instruments (5, 6). The Comprehensive Score for Financial Toxicity - Functional Assessment of Chronic Illness Therapy (COST-FACIT) questionnaire (**Supplement 1**), a 12-item validated instrument for assessing financial toxicity (FT), was initially validated in patients with advanced cancer; it has recently been validated in the radiation oncology setting (7, 8). This work was recently expanded in the surgical management of prostate cancer (9).

Of all urologic malignancies, most financial toxicity research has focused on prostate cancer (1). In the past decade, emerging studies have begun identifying an association between FT for patients with prostate cancer and clinically significant factors such as health-related quality of life (HRQoL), compliance, and even survival (1, 7, 9–11). However, not all treatments are equivalent in FT, and radiation therapy (RT) is generally thought to be associated with a more severe FT than radical prostatectomy or active surveillance (5, 12).

Given the significant financial distress faced by cancer patients and the potential association between FT and other clinically significant outcomes, we must strive for highly effective treatment options that minimize FT. In patients with localized prostate cancer, 5-fraction stereotactic body radiation therapy (SBRT), moderately hypofractionated radiotherapy, and permanent seed implants offer comparable oncologic outcomes and potential for improved treatment compliance compared to conventional, 40-plus fraction radiation therapy (RT) (5, 13–17). Unfortunately, to date, there is scant data reporting FT in patients who receive prostate SBRT.

In this study, we use the COST-FACIT to evaluate the patient-reported financial toxicity after SBRT for localized prostate cancer. We aim to evaluate patient and treatment factors associated with worse financial toxicity.

MATERIALS AND METHODS

Study Cohort

Patients eligible for this cross-sectional study had histologically confirmed, localized prostate cancer and were treated at MedStar Georgetown University Hospital with five fractions SBRT. From 2012 to 2020, a total of 575 patients consented to participate in this IRB-approved (IRB 12-1175) prospective institutional quality-of-life study. Surveys were mailed to all participants or, if applicable, collected at an in-person treatment or posttreatment visit.

Outcomes

The primary outcome of this study was financial toxicity as assessed by the 12-item COST-FACIT questionnaire (version 2, www.facit.org/measures/FACIT-COST). After considering items with reverse values, the COST score was calculated as an average of the 11 scored items (range 0–4). In accordance with the FACIT-scoring guidelines, only surveys with at least 80% of the scored questions completed (at least 9 of 11) were included. A lower COST score indicated more severe financial toxicity.

COST grade (range 0–3) was determined by the total COST sum (range 0–44), which was the score calculated using the questionnaire. As described by D'Rummo et al., the COST sum was further broken down into COST sum categories of "≥26," "14–25," "1–13," and "0" representing COST grades 0, 1, 2, and 3, respectively (8). Only surveys with 100% of the scored questions completed were included. A higher COST grade indicated more severe financial toxicity.

Exposure

SBRT treatment planning and delivery were conducted as previously described (18). Briefly, gold fiducials were placed into the prostate. Fused CT and MR images were used for treatment planning. The clinical target volume (CTV) included the prostate and proximal seminal vesicles. The planning target volume (PTV) equaled the CTV expanded 3 mm posteriorly and 5 mm in all other dimensions. The prescription dose was 35–36.25 Gy to the PTV delivered in five fractions of 7–7.25 Gy over 1 to 2 weeks.

Covariates

Surveys included questions related to patient age, marital status, employment status, level of education, race and ethnicity, income level, health insurance, and hormonal therapy. Distance from the index hospital was determined using the patient-reported zip code converted to approximate latitude and longitude. The Haversine formula was used to determine the shortest distance between each set of coordinates. Time since treatment was calculated as a difference in months between survey date and treatment day 1.

Statistical Analysis

Baseline patient characteristics were summarized by the number of patients and percentage of respondents by variable. These characteristics were further delineated by COST grade, and differences among categorical survey responses were evaluated using Fisher's exact test and the one-way analysis of variance (ANOVA) method for continuous age variables. Differences in average COST score were presented by mean, difference from population mean, and range. A visual representation of the

Abbreviations: ANOVA, analysis of variance; COST-FACIT, Comprehensive Score for Financial Toxicity - Functional Assessment of Chronic Illness Therapy; CTV, clinical target volume; EBRT, external beam radiation therapy; FT, financial toxicity; HRQOL, health-related quality of life; PTV, planning target volume; RT, radiation therapy; RP, radical prostatectomy; SBRT, stereotactic body radiation therapy.

COST score was performed using a violin density plot by categorical response.

Univariate analysis and multivariate analysis were used to determine factors associated with the average COST score. For analysis, race was dichotomized as white and other, and time since SBRT was dichotomized as ≤ or >6 months. Univariate analysis of age was performed using linear regression and Wilcoxon rank-sum test or Kruskal–Wallis one-way analysis of variance for the remainder of ordinal or nominal covariates. The multivariate model was performed *via* multiple regression using the method of least squares. Backward selection was used to select variables for the multivariate model until only significant variables with $p < 0.05$ remained. All tests were two-tailed, and a p value <0.05 was considered significant. JMP® Pro, version 15.0.0 (SAS Institute Inc., Cary, NC, 1989–2021), was used to perform the statistical analyses.

RESULTS

The questionnaire response rate was 57.5%, with 332 of 575 patients completing the questionnaire and included in the analysis. Demographics and adjunct hormonal therapy are reported in **Table 1**. The median age of the cohort was 76, with a range of 54 to 92 years. A majority of the population were married (n = 257; 77.7%), retired (232; 71.4%), graduate degree-holding (207; 65.1%), white (264; 80.2%), with an income ≥$100,000 (214; 69.5%), and living within 25 miles of the hospital (247; 74.8%). Nearly the entire cohort reported having a health insurance (323; 98.2%). Of the respondents, most were more than 6 months past treatment (305; 91.9%).

The COST grade breakdown for the population was 90.7%, 8.2%, and 1.1% for grades 0, 1, and 2, respectively, with no grade 3 toxicity (**Figure 1**). Employment status ($p = 0.0045$), race ($p = 0.0481$), and health insurance status ($p = 0.0481$) significantly differed by COST grade groupings. Patient characteristics and COST grade grouping demonstrated no statistically significant differences in education level, distance from hospital, time since treatment, and hormonal therapy. Similarly, analysis of age revealed a non-statistically significant difference in age at treatment among COST grade groupings.

The average COST score for the cohort was 3.25 out of 4. In **Figure 2**, univariate analysis of covariates associated with COST score was significant for employment status (mean score: retired 3.29, working 3.21, disabled 2.05, unemployed 2.50; $p = 0.0140$), education (high-school or GED 2.92, college 3.22, graduate or professional 3.32; $p = 0.0268$), race (white or Caucasian 3.32 versus non-white 2.98; $p = 0.0001$), income (<$15,000 2.34, ≥ $150,000 3.50; $p < 0.0001$), health insurance (no health insurance 2.00 versus with health insurance 3.26; $p = 0.0146$), and hormonal therapy (current 2.80, previous 3.23, never 3.28; $p = 0.0104$). There was no difference in COST score by age, marital status, distance from the hospital, or time since treatment. Employment status ($p = 0.0002$), race ($p = 0.0122$), income ($p < 0.0001$), and hormonal therapy ($p = 0.0020$) remained significant on multiple regression.

DISCUSSION

Financial toxicity can have a significant impact on the livelihood of patients and their support system. This is especially evident given that, for patients over 50 years old, approximately 42% will completely deplete their assets within 2 years of a new cancer diagnosis (4). Further, subjective FT may have a greater negative impact on HRQoL than objective FT (10). The present study is the first to use COST-FACIT to evaluate patient-reported FT in patients with new prostate cancer diagnoses receiving RT as primary therapy.

The first publication of COST-FACIT was in 2017 and evaluated FT in patients with stage IV malignancies as part of the validation of the scoring tool (7). Since then, COST-FACIT has been used to evaluate FT in the radiation oncology setting. In a study by D'Rummo et al., 167 patients with a variety of primary malignancies and treatment courses were evaluated using this metric. Of these, 56.3% of patients experienced grade 1 FT. In our study, over 90% of patients experienced grade 0 FT (8). The reason for such low FT is likely multifactorial and may relate to the overwhelming proportion of men who were retired and report high-income levels, as well as the 5-treatment course of SBRT. Interestingly, we found no significant difference in FT for patients who were within 6 months of SBRT. In the study by D'Rummo et al., they found that patients who were within 6 months of RT were more likely to experience FT (8).

In terms of factors associated with worse FT in our patient population, unemployment or disability, non-white race, low income, and concurrent hormonal therapy were associated with a statistically significant worse FT on univariate and multivariate analyses. In the study by Stone et al., patients with localized prostate cancer who identified as either Black or Hispanic had a higher odds of financial burden when adjusted for age, insurance, education, marriage, comorbidities, and D'Amico risk group (5). However, in the present study, racial differences did not account for the greatest difference in FT. In order of decreasing severity, patients who did not have health insurance, who were disabled, or who had an income less than $14,999 annually were the three groups reporting the worst FT. A recently published abstract by Gorovets et al. reported using COST-FACIT to evaluate FT in RT. In this abstract, Gorovets et al. evaluated FT in 373 men who received SBRT, moderately hypofractionated radiotherapy, brachytherapy, or combination EBRT/brachytherapy (19). Overall, the authors report low levels of FT for each modality and SBRT had the lowest FT. Despite this, 5%–10% of patients report high levels of distress related to treatment costs. However, these patients were primarily white, married, insured, and with high annual incomes, all of which are protective factors for FT (19).

In a study by Gilligan et al. looking at objective financial burden in patients with newly diagnosed malignancies, the authors similarly found that low income is associated with a greater burden. However, they also found that patients who were retired had a higher odds of depleting their assets (4). They also suggest that improved oncologic prognosis lends itself to higher risk of asset depletion (4). Given the chronicity of most prostate

TABLE 1 | Demographics and baseline characteristics by COST toxicity grade.

	Overall		COST grade						
			Grade 0		Grade 1		Grade 2		
	N	(%)	N	(%)	N	(%)	N	(%)	*p* -value
Age at survey									0.2421
Treatment median, Y (range)	70	(47–90)							
Median, Y (range)	76	(54–92)							
<50	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	
51–64	26	(7.8%)	17	(6.7%)	4	(17.4%)	1	(33.3%)	
65–75	134	(40.4%)	109	(42.7%)	12	(52.2%)	0	(0.0%)	
>75	172	(51.8%)	129	(50.6%)	7	(30.4%)	2	(66.7%)	
Marital status									0.3433
Single	30	(9.1%)	20	(7.9%)	3	(13.0%)	1	(33.3%)	
Married	257	(77.6%)	197	(77.6%)	16	(69.6%)	2	(66.7%)	
Widowed	22	(6.6%)	19	(7.5%)	2	(8.7%)	0	(0.0%)	
Divorced	14	(4.2%)	11	(4.3%)	1	(4.3%)	0	(0.0%)	
Long-term partner	8	(2.4%)	7	(2.8%)	1	(4.3%)	0	(0.0%)	
Employment status									**0.0045**
Working	87	(26.8%)	71	(28.3%)	7	(30.4%)	1	(33.3%)	
Retired	232	(71.4%)	179	(71.3%)	14	(60.9%)	1	(33.3%)	
Disabled	3	(0.9%)	0	(0.0%)	1	(4.3%)	1	(33.3%)	
Unemployed	3	(0.9%)	1	(0.4%)	1	(4.3%)	0	(0.0%)	
Education									0.0872
No HS diploma	2	(0.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	
HS/GED	22	(6.7%)	14	(5.6%)	3	(13.0%)	1	(33.3%)	
College	97	(29.6%)	74	(29.4%)	7	(30.4%)	1	(33.3%)	
Graduate or professional	207	(63.1%)	164	(65.1%)	13	(56.5%)	1	(33.3%)	
Race									**0.0460**
White or Caucasian	264	(80.2%)	208	(81.9%)	15	(65.2%)	2	(66.7%)	
Black or AA	51	(15.5%)	34	(13.4%)	7	(30.4%)	0	(0.0%)	
Latino or Hispanic	4	(1.2%)	3	(1.2%)	1	(4.3%)	0	(0.0%)	
Asian	8	(2.4%)	7	(2.8%)	0	(0.0%)	1	(33.3%)	
Other	2	(0.6%)	2	(0.8%)	0	(0.0%)	0	(0.0%)	
Income									**<.0001**
$0–14,999	4	(1.3%)	1	(0.4%)	0	(0.0%)	1	(33.3%)	
$15,000–49,999	25	(8.1%)	15	(6.2%)	2	(8.7%)	1	(33.3%)	
$50,000–99,000	65	(21.1%)	45	(18.6%)	11	(47.8%)	0	(0.0%)	
$100,000–149,999	77	(25.0%)	62	(25.6%)	6	(26.1%)	1	(33.3%)	
$150,000 or more	137	(44.5%)	119	(49.2%)	4	(17.4%)	0	(0.0%)	
Distance from hospital									0.3180
0–25 miles	247	(74.8%)	191	(75.5%)	15	(65.2%)	3	(100.0%)	
26–50 miles	29	(8.8%)	19	(7.5%)	3	(13.0%)	0	(0.0%)	
51–100 miles	18	(5.5%)	10	(4.0%)	3	(13.0%)	0	(0.0%)	
101–300 miles	12	(3.6%)	12	(4.7%)	0	(0.0%)	0	(0.0%)	
>300 miles	24	(7.3%)	21	(8.3%)	2	(8.7%)	0	(0.0%)	
Health insurance									**0.0481**
No	6	(1.8%)	1	(0.4%)	1	(4.5%)	0	(0.0%)	
Yes	323	(98.2%)	252	(99.6%)	21	(95.5%)	3	(100.0%)	
Time since SBRT									0.2549
<6 months	27	(8.1%)	21	(8.2%)	1	(4.3%)	1	(33.3%)	
>6 months	305	(91.9%)	234	(91.8%)	22	(95.7%)	2	(66.7%)	
Hormonal therapy									0.2627
None	248	(75.6%)	195	(77.1%)	12	(54.5%)	2	(66.7%)	
Previously	61	(18.6%)	47	(18.6%)	5	(22.7%)	1	(33.3%)	
Currently	19	(5.8%)	11	(4.3%)	5	(22.7%)	0	(0.0%)	

p-value for age derived via one-way ANOVA, with the remainder calculated via Fisher's exact test.
Bolded values represent statistical significance with p-values < 0.05.

cancer diagnoses, it is too early to tell if the same is true of FT in the urologic patient population.

Previous studies have also investigated the direct and indirect objective financial burden of patients with prostate cancer. These data are generated by calculating actual costs to patients rather than a validated survey such as COST-FACIT. Jayadevappa et al. reported the direct and indirect costs across time to men with prostate cancer who were treated by radical prostatectomy (RP) or EBRT. At 3 months, the total cost to patients was $2010 *vs.* $5576 for EBRT and RP, respectively. However, this effect

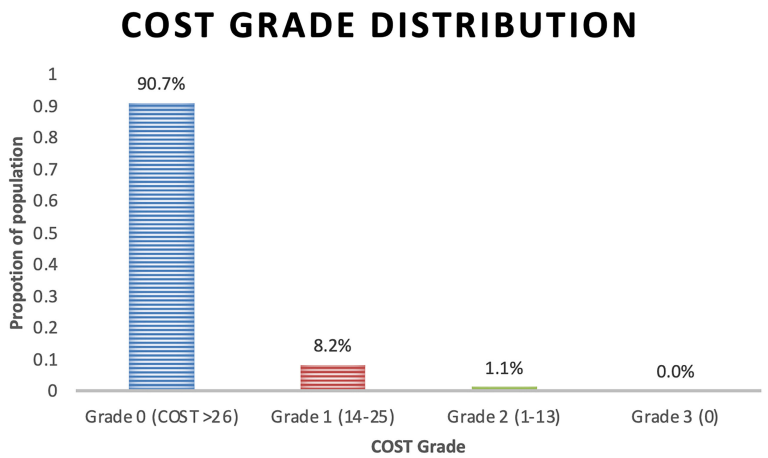

FIGURE 1 | COST Grade toxicity distribution by proportion of population.

Factors associated with COST Score

	COST Score			Graphic Representation of COST Score		Univariate	Multivariate
	Mean	Mean score Δ	(Range)	Mean score Δ	Cost Score Distribution	p-Value	p-value
Age at Survey						0.3022	
51-64	2.96	-0.28	(1.18 , 4.00)				
65-75	3.31	0.06	(1.00 , 4.00)				
>75	3.24	0.00	(0.82 , 4.00)				
Marital Status						0.6641	
Single	3.04	-0.21	(1.00 , 4.00)				
Married	3.27	0.03	(0.82 , 4.00)				
Widowed	3.26	0.01	(2.45 , 4.00)				
Divorced	3.11	-0.14	(1.60 , 4.00)				
Long Term Partner	3.25	0.00	(1.91 , 4.00)				
Employment Status						**0.0140**	**0.0002**
Working	3.21	-0.04	(0.82 , 4.00)				
Retired	3.29	0.04	(1.20 , 4.00)				
Disabled	2.05	-1.19	(1.18 , 2.70)				
Unemployed	2.50	-0.75	(2.36 , 2.64)				
Education						**0.0268**	
HS/GED	2.92	-0.33	(0.82 , 4.00)				
College	3.22	-0.03	(1.18 , 4.00)				
Graduate or professional	3.32	0.08	(1.55 , 4.00)				
Race						**0.0001**	**0.0122**
White or caucasian	3.32	0.08	(0.82 , 4.00)				
Non-White	2.98	-0.26	(1.30 , 4.00)				
Income						**<.0001**	**<.0001**
$0-14,999	2.34	-0.91	(1.18 , 3.27)				
$15,000-49,999	2.53	-0.71	(0.82 , 3.82)				
$50,000-99-000	3.09	-0.15	(1.82 , 4.00)				
$100,000-149.999	3.20	-0.04	(1.55 , 4.00)				
$150,000 or more	3.50	0.25	(1.60 , 4.00)				
Distance from Hospital						0.1376	
0-25 miles	3.25	0.01	(0.82 , 4.00)				
26-50 miles	3.13	-0.11	(1.70 , 4.00)				
51-100 miles	2.94	-0.31	(1.20 , 4.00)				
101-300 miles	3.39	0.14	(2.45 , 4.00)				
>300 miles	3.44	0.19	(1.91 , 4.00)				
Health Insurance						**0.0146**	
No	2.00	-1.25	(1.00 , 2.64)				
Yes	3.26	0.02	(0.82 , 4.00)				
Time since SBRT						0.6277	
≤6 months	3.21	-0.04	(1.55 , 4.00)				
>6 months	3.25	0.00	(0.82 , 4.00)				
Hormonal Therapy						**0.0104**	**0.002**
None	3.28	0.04	(0.82 , 4.00)				
Previously	3.23	-0.02	(1.18 , 4.00)				
Currently	2.80	-0.44	(1.70 , 3.82)				

FIGURE 2 | UVA and MVA of covariates associated with greater financial toxicity (COST Score). Mean COST Score, difference from population mean, and range in the first column; graphic representation of difference in mean COST Score and violin plot showing the distribution of individual COST Score values; vertical line represents the population mean COST Score. *p*-value of univariate analysis using linear regression for age, and Wilcoxon rank-sum or Kruskal–Wallis test for remainder of variables; multivariate analysis using multiple regression with standard least-square method.

reversed at 6 months (sum costs; EBRT: $2133, RP:$1776) and at 2 years (sum costs; EBRT: $871, RP: $458) (20). An important caveat to this study is that all men had health insurance. It is likely that the objective financial burden to under- and uninsured patients treated for prostate cancer may be greater. Additionally, practice patterns have changed with the introduction of SBRT as an alternative treatment to EBRT.

Understanding subjective FT can be as valuable as understanding objective FT and highlights one of the strengths of the present study. In a study of FT experienced by patients with urologic malignancies by Ting et al., increasing subjective FT had a greater negative impact on HRQoL than objective FT (10). The authors defined objective FT as healthcare cost-to-income ratio greater than 0.4 and subjective FT and HRQoL using the validated Personal Financial Well-being Scale and Functional Assessment of Cancer Therapy – General 7 Items Scale, respectively. While, notably, their study was based out of Malaysia, a middle-income country with a universal healthcare system, they demonstrated that universal health coverage does not eliminate the burden experienced by patients. While the present study did not capture objective FT beyond patient-reported income, the overwhelming majority of patients reported some form of healthcare coverage, therefore making it possible to delineate additional socioeconomic factors associated with greater FT.

Our study should be considered in the context of its limitations. This is a cross-sectional representation of a prospective study with a majority of respondents beyond 6 months posttreatment with SBRT. In similar studies, financial toxicity appears to be front-loaded; it is therefore possible that the distribution financial toxicity of men with prostate cancer treated by SBRT may be shifted in our cohort (5, 20). Future expansion of this cross-sectional study will capture longitudinal changes in financial toxicity as it relates to time since treatment as well as pretreatment baseline. Another limitation is the population of survey respondents, which is 80.2% white. In one of our prior publications, the 10-year demographics of our institutional prostate-cancer population, 46% of the population is white, 48% black, and 6% other (15). This sampling limitation may have also impacted the number of retired patients, graduate degree-holding, and reporting high annual incomes; however, these data were not previously evaluated in our patient population. Lastly, being the first study on FT in patients who have had SBRT for prostate cancer is both a strength and limitation, and due to the relatively small number of patients, non-parametric statistical tests were used for this analysis. Consenting additional patients and prospective financial toxicity collection should enable us to better account for many of these limitations in future analyses.

As mentioned, future financial toxicity research in patients with prostate cancer should involve longitudinal analyses. The integration of HRQoL and disease metrics will enhance the long-term analysis of FT. Several comparator studies of financial toxicity will also better elucidate the impact of treatment choice on patients with prostate cancer, specifically comparison of SBRT to active surveillance, prostatectomy, and systemic therapies.

CONCLUSION

Understanding the aspects of oncologic care that directly impact patient experience, treatment adherence, and HRQOL is of utmost importance. SBRT is associated with low overall FT. However, statistically significant socioeconomic disparities in FT remain despite ultra-hypofractionated treatment. Patients who are unemployed or have a disability, non-white, low income, or on hormonal therapy are more likely to experience significant FT after SBRT for prostate cancer.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because as per the wishes of the patients, the patient dataset is only available to those conducting research at the Georgetown University Medical Center. Requests to access the datasets should be directed to Sean Collins, SPC9@gunet.georgetown.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Georgetown University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TS, MC, AP, and SC contributed to the conception and design of the study. AZ distributed the questionnaires and organized the database. TS, MC, and SC wrote the first draft of the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.852844/full#supplementary-material

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Urethra Sparing With Target Motion Mitigation in Dose-Escalated Extreme Hypofractionated Prostate Cancer Radiotherapy: 7-Year Results From a Phase II Study

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Purpose: To explore whether the rectal distension-mediated technique, harnessing human physiology to achieve intrafractional prostate motion mitigation, enables urethra sparing by inverse dose painting, thus promoting dose escalation with extreme hypofractionated stereotactic ablative radiotherapy (SABR) in prostate cancer.

Materials and Methods: Between June 2013 and December 2018, 444 patients received 5 × 9 Gy SABR over 5 consecutive days. Rectal distension-mediated SABR was employed *via* insertion of a 150-cm^3 air-inflated endorectal balloon. A Foley catheter loaded with 3 beacon transponders was used for urethra visualization and online tracking. MRI-based planning using Volumetric Modulated Arc Therapy - Image Guided Radiotherapy (VMAT-IGRT) with inverse dose painting was employed in delivering the planning target volume (PTV) dose and in sculpting exposure of organs at risk (OARs). A 2-mm margin was used for PTV expansion, reduced to 0 mm at the interface with critical OARs. All plans fulfilled D_{mean} ≥45 Gy. Target motion ≥2 mm/5 s motions mandated treatment interruption and target realignment prior to completion of the planned dose delivery.

Results: Patient compliance to the rectal distension-mediated immobilization protocol was excellent, achieving reproducible daily prostate localization at a patient-specific retropubic niche. Online tracking recorded ≤1-mm intrafractional target deviations in 95% of treatment sessions, while target realignment in ≥2-mm deviations enabled treatment completion as scheduled in all cases. The cumulative incidence rates of late grade ≥2 genitourinary (GU) and gastrointestinal (GI) toxicities were 5.3% and 1.1%, respectively. The favorable toxicity profile was corroborated by patient-reported quality of life (QOL) outcomes. Median prostate-specific antigen (PSA) nadir by 5 years was 0.19 ng/ml. The cumulative incidence rate of biochemical failure using the Phoenix definition was 2%, 16.6%, and 27.2% for the combined low/favorable–intermediate, unfavorable intermediate, and high-risk categories, respectively. Patients with a PSA failure

underwent a ^{68}Ga-labeled prostate-specific membrane antigen (^{68}Ga-PSMA) scan showing a 20.2% cumulative incidence of intraprostatic relapses in biopsy International Society of Urological Pathology (ISUP) grade ≥3.

Conclusion: The rectal distension-mediated technique is feasible and well tolerated. Dose escalation to 45 Gy with urethra-sparing results in excellent toxicity profiles and PSA relapse rates similar to those reported by other dose-escalated regimens. The existence of intraprostatic recurrences in patients with high-risk features confirms the notion of a high α/β ratio in these phenotypes resulting in diminished effectiveness with hypofractionated dose escalation.

Keywords: SABR, SBRT, prostate cancer, dose–response, dose-painting, organ at risk (OAR), endorectal balloon

INTRODUCTION

A deeper understanding of tumor biology has progressively advanced the potentials of tumor cure in primary organ-confined human prostate cancer with radiation therapy. For instance, escalation of conventionally fractionated tumor dose has been shown to render improved local control, mitigating distant metastatic dissemination in a dose-dependent manner (1–3). However, a 15-year update of outcomes in patients treated with dose-escalated 81–86.4 Gy revealed significantly reduced freedom from biochemical prostate-specific antigen (PSA) failure [biochemical recurrence-free survival (bRFS)] (4) compared to previously published 7-year outcomes (2). The delayed manifestation of treatment failures is due to the phenotypic prostate cancer biology, expressed as slowly proliferating and late-responding tumor clonogens associated with a low linear quadratic (LQ) α/β ratio (5, 6).

In 1999, Brenner and Hall (5) suggested that prostate cancer had an α/β ratio of 1.5 Gy (95% CI 0.8–2.2 Gy), confirmed by several large-scale studies establishing ratios within the range 1–2 Gy (7–11). There is, however, emerging evidence that increasing dose per fraction in the hypofractionated mode may be associated with an increase in the α/β ratio (12, 13). Nonetheless, it is generally accepted that a low α/β ratio is a basic biological tenet of prostate cancer response to dose fractionation, with therapeutic implications (14).

These findings spurred the exploration of hypofractionated radiation treatment schedules in prostate cancer. Over the past two decades, several large prospective phase III non-inferiority trials compared classical fractionation with iso-Biologically Effective Dose (BED) schedules of moderate (≥20 fractions of 2.4–3.4 Gy) or extreme (4–7 fractions of 5–8 Gy) hypofractionation (14–18), confirming similar ≥5-year bRFS and late grade ≥2 urinary [genitourinary (GU)] and bowel [gastrointestinal (GI)] toxicities between the control and the experimental arms (15–19).

The encouraging outcomes of the non-inferiority trials have promoted a multitude of phase I–II extreme hypofractionation studies with large variations in dose per fraction. A recent meta-analysis of 2,142 patients treated with extreme hypofractionated regimens (33.5–40.0 Gy in 4–5 fractions; 88% receiving 5 fractions) rendered a 7-year bRFS of 87.2% and 82.4% in low- and intermediate-risk patients, respectively (20). Grade ≥3 late GU and GI toxicities were 2.4% and 0.4%, respectively. Similar favorable outcomes were reported by other meta-analyses (21, 22), confirming this therapeutic approach as a standard of care in low- and intermediate-risk patients (23). Recently, a PSA kinetics analysis reported greater prostate ablation and PSA decay with dose escalation up to 40 Gy (5 × 8 Gy) but not beyond allegedly due to the association with distant progression rather than intraprostatic recurrence in the event of PSA relapse at higher doses (24). Additionally, there may be a progressively diminished advantage in increasing dose/fraction as the α/β ratio may increase as a function of fraction size, resulting in a putative saturation of the dose–response in biochemical control with dose-escalated hypofractionation (13).

However, a recent dose escalation study of 257 patients treated with extreme hypofractionation (five fractions of 6.5, 7.0, 7.5, and 8.0 Gy) included a prostate biopsy assessment at 2 years post-SBRT (25). In 40 patients (15.6%), the biopsies were positive for viable tumor, decreasing in positivity rate in accordance with the four escalating treatment dose levels (37.5%, 21.4%, 19.4%, and 10.9%, respectively). Unfavorable intermediate- or high-risk disease was significantly associated with the occurrence of a positive biopsy. Importantly, only 57% of patients with positive biopsies exhibited evidence of a biochemical relapse within the first 5 years. Furthermore, the study also indicated that extreme hypofractionation with 5 × 8 Gy may be a suboptimal dose in the unfavorable category.

Dose escalation beyond 5 × 8 Gy has been addressed in a multi-institutional phase I/II trial of low- and intermediate-risk disease employing 5 fractions of 9, 9.5, or 10 Gy (26). While the 3-year bRFS was excellent at 98% (26), late GI toxicity was severe, with 6/71 (6.6%) of the patients developing grade 4 late toxicity. Insertion of a peri-rectal polyethylene glycol (PEG) hydrogel spacer systematically reduces the rectal dose and late GI damage in normofractionated prostate cancer patients (27, 28), and it was recently proven effective in a phase II study of 5 × 9 Gy (29). At a median follow-up of 48 months, there were no grade ≥3 GI toxicities, while grade 2 toxicity was initially observed in 14.3% at a median of 11.4 months, completely resolved by year 3 (29). However, the use of a hydrogel spacer does not resolve other concerns associated with prostate cancer radiotherapy, such as the high rates of urethral late grade ≥2 toxicity (30), and the treatment uncertainties associated with an unpredictable mobility of the prostate target during treatment delivery (31).

Here, we review our experience with the use of a novel approach to treat prostate cancer with extreme hypofractionated stereotactic ablative radiotherapy (SABR). We update herein our experience with the use of a unique protocol of rectal distension-mediated prostate immobilization, permitting precise negative dose painting to spare the organs at risk (OARs), with particular emphasis on the intraprostatic urethra. The current update of our initial published observations renders new information on the therapeutic response of different clinical subtypes of human prostate cancer.

MATERIALS AND METHODS

Patients

This is a progress report of an ongoing institutional review board (IRB)-approved non-randomized Phase II study of extreme hypofractionated SABR employing five daily fractions of 9 Gy in patients with organ-confined adenocarcinoma of the prostate (clinicaltrials.gov NCT02761889). All participants signed an informed consent. The present update, consisting of 444 patients (**Table 1**), a 2-fold increase over the previously reported cohort, includes patients treated between June 2013 and December 2018 with a minimum follow-up of 36 months.

Treatment Planning and Delivery

Patient setup, treatment planning, and treatment delivery were previously described in detail (32, 33). Briefly, patients were planned and treated in a supine position with leg fixation after catheterization with a 12-French gauge (4-mm diameter) Foley catheter with 3 embedded beacon transponders for intrafractional target tracking (Calypso, Varian Medical Systems, Palo Alto, CA, USA). The Foley catheter was also used to guide segmentation of the whole length of the prostatic urethra for dose reduction. Rectal distension-mediated prostate immobilization was achieved by insertion of an endorectal balloon (Rectal Pro, QLRAD Inc., FL, USA) inflated with 150 cm^3 of air. The insertion of the catheter and endorectal balloon was performed by a dedicated nurse before each session, and the patient was relieved of the endoluminal devices after the completion of the session. To avoid the risk of urinary infection, all patients received prophylactic ciprofloxacin daily during treatment and for 3 days after completion. This technique is based on understanding the physiology of prostate mobility, detailed in the *Discussion* section. A CT and a T2W 3D MR scan were acquired in treatment position.

TABLE 1 | Patient and tumor characteristics.

Characteristics	(n=444)
Age, year	
median (IQR)	70.3 (65.5-74.4)
iPSA, ng/mlL	
median (IQR)	7.1(5.6-10.4)
Gland size, cm 3	
median (IQR)	46.7 (35.1-65.1)
IUSP Grade, n (%)	
Group 1 (3+3)	70 (15.8)
Group 2 (3+4)	234 (52.7)
Group 3 (4+3)	103 (23.2)
Group 4 (4+4)	29 (6.5)
Group 5 (4+5)	8 (1.8)
T-stage, n (%)	
Tlc	28 (6.3)
T2a	106 (23.9)
T2b	124 (27.9)
T2c	182 (41.0)
NCCN Risk, n (%)	
Low	18 (4.1)
Favorable intermediate	103 (23.2)
Unfavorable intermediate	270 (60.8)
High	53 (11.9)
ADT n (%)	162 (36.4)

PSA, Prostate Specific Antigen; iPSA, initial PSA; ADT, androgen deprivation therapy; IQR, interquartile range; mo, months.

The fused image sets were used to delineate the target volume and OARs. The planning target volume (PTV) consisted of the clinical target volume (CTV) (the prostate and the proximal two-thirds of the seminal vesicles) with an anisotropic 2-mm expansion margin, reduced to 0 mm at interface with the rectal wall, the bladder, the urethra wall (defined as a 2-mm expansion around the catheter), the urogenital diaphragm (UGD), and the neurovascular bundles (NVBs). Inverse dose painting allowed effective OAR sparing, which was predicated on a reproducible high-precision positioning of the target and all OARs at every treatment session as a result of the organ motion mitigation protocol. The urethral wall was negatively dose painted to fulfill D_{1cc} <36 Gy. The other main OAR constraints were: $D_{50\%}$ <22.5 Gy and D_{1cm^3} <36 Gy for the rectal wall and $D_{50\%}$ <22.5 Gy and D_{1cm^3} <40.5 Gy for the bladder. Priority was given to OAR sparing, but for the PTV, a D_{mean} ≥45 Gy and a near-minimal dose $D_{98\%}$ >36 Gy were pursued.

Plans were optimized using penalties to control PTV dose coverage and dose constraints to OARs with the progressive resolution optimizer (PRO v10.0.28-v13.7.14 in Eclipse, Varian Medical Systems, Palo Alto, CA, USA), calculated with the analytical anisotropic algorithm (AAA v10.0.28-v13.7.14). A 10-MV Flattening Filter Free (FFF) beam energy and 4 VMAT arcs were used in all cases. Treatment was delivered on a linear accelerator with a 2.5-mm leaf-width High Definition Multi Leaf Collimator (HDMLC) (TrueBeam STx or EDGE, Varian Medical Systems, Palo Alto, CA, USA). Treatment plans were quality assured before the first treatment session using an ArcCHECK phantom (Sun Nuclear Corp., FL, USA) to confirm that they fulfilled the gamma (3%/3 mm) passing rate >90% objective according to American Association of Physicists in Medicine (AAPM) guidelines.

Onboard cone-beam computed tomography (CBCT) matching ensured reproducible patient setup and target localization. If discrepancies of ≥1 mm in translation or ≥1 degree in rotation were detected, corrections were applied *via* a 6-degrees of freedom couch (PerfectPitch 6-DoF Couch, Varian Medical Systems, Palo Alto, CA, USA). When beacon transponder signals exceeded an accepted 2-mm deviation threshold for ≥5 s, treatment was interrupted, and treatment target position was redefined by repeat CBCT. Patients received treatment daily over 5 consecutive days. **Figure 1** shows dose distributions representative of the typical plan.

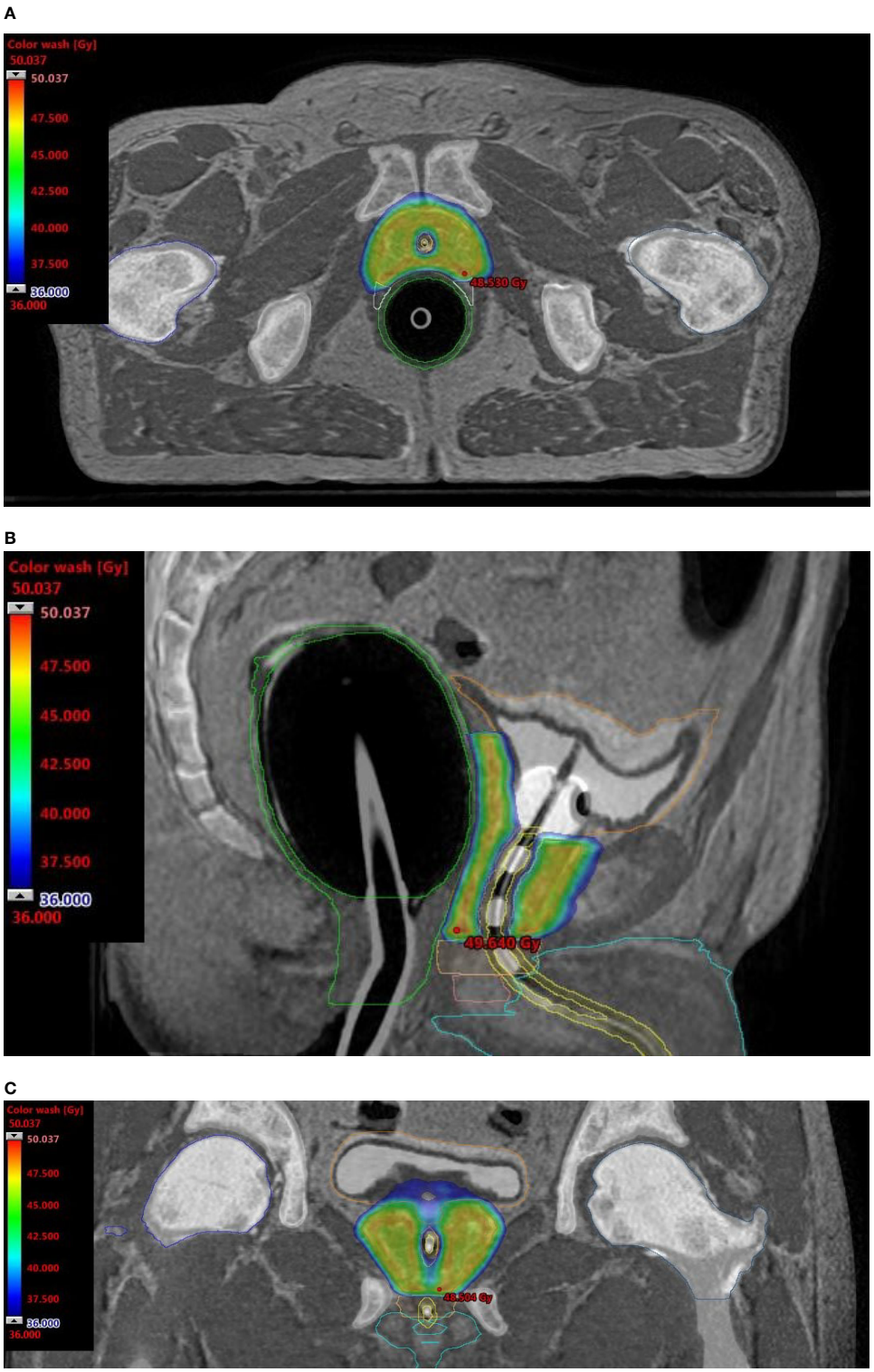

FIGURE 1 | Dosimetric plans of a patient treated with rectal distension-mediated 5 × 9 Gy extreme hypofractionated SABR. Fused CT-MR image sets show dose-sculpted distributions along the urethra, rectal wall, urogenital diaphragm, and neurovascular bundles. Color-wash dose distributions are shown on the axial **(A)**, sagittal **(B)**, and coronal **(C)** planes. An intraurethral Foley catheter loaded with 3 beacon transponders is visible on the longitudinal plane.

Characterization of Biochemically Relapsing Patients

Patients with a biochemical relapse were assessed with a ^{68}Ga-labeled prostate-specific membrane antigen (PSMA)-11 PET/CT scan to determine the existence of intraprostatic vs. extraprostatic progression. An activity of 2 MBq/kg of patient body weight of ^{68}Ga-PSMA-11 was administered using an automatic injector (INTEGO^{TM}, MEDRAD), and images were acquired at 45–60 min post-injection. The PET/CT (Gemini TF, Philips) scan was acquired with a low-dose CT (120–140 kV, 60 mA per rotation) from the skull base to the upper third of the thighs. PET data were obtained thereafter with a sequence of 6–8 bed positions, always on 3D mode for 1.5–3 min on average per bed position. In addition to visual analysis, quantitative SUV evaluation was performed within the volumetric region of interest (Extended Brilliance Workspace algorithm NM 2.0 AB-V5.4.3.40140, Philips). The Standardized Uptake Value (SUV) for the voxel with the highest activity concentration (SUV_{max}) was recorded. Institutional criteria for quantitative assessment ^{68}Ga-PSMA uptake were: SUV_{max} of lesion/SUV_{max} of normal prostate or surrounding tissues >4.0 was considered positive; 2.0–4.0, suspicious; and <2.0, negative.

In addition to ^{68}Ga-PSMA-11 PET/CT, multiparametric MRI scans of the prostate and biopsy were employed where appropriate.

Toxicity and Quality of Life Assessment

Toxicity [National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0] was assessed posttreatment at 1 month and every 3 months to 12 months (± 4 weeks), at every 6 months for years 2–5, and annually thereafter. Acute toxicity was defined as any adverse event occurring within 90 days from the beginning of treatment. International Prostate Symptom Score (IPSS), Expanded Prostate Cancer Index Composite-26 (EPIC-26), and International Index of Erectile Function Questionnaire (IIEF) questionnaires were completed at baseline and at the same time points posttreatment as above.

Statistical Methods

The primary endpoints of the study were incidence of treatment-related acute and late adverse events and PSA outcomes. Actuarial bRFS, GU and GI toxicities, and patient-reported quality of life (QOL) scores were computed from the end of treatment using the Kaplan–Meier method. For each EPIC domain, a summary score was calculated at each of the study time points. Wilcoxon signed-rank test analysis was used to assess differences in QOL scores compared to baseline, and the significance of the mean changes over time was assessed by paired mixed-effects analysis. The clinically meaningful decline in QOL [minimally important difference (MID)] was defined as one-half of the standard deviation from baseline for each domain. Univariate analysis of relevant variables was performed using the Cox proportional hazards regression method. Hazard ratio (HR) and 95% confidence intervals (CIs) were obtained, and the level of statistical significance was set at alpha = 0.05. Statistical computations were performed using the GraphPad *Prism 7.0* software (Prism Inc., Reston, VA, USA).

RESULTS

The characteristics of the 444 patients are summarized in **Table 1**. Median follow-up time was 58 months [interquartile range (IQR), 44.3–78.8]. Twelve patients succumbed to comorbidities without evidence of disease at a median follow-up time of 39.8 months, and another 29 were lost to follow-up at a median time of 34.6 months. Patients were stratified according to NCCN criteria. At the discretion of the referring physician, 162 patients received androgen deprivation therapy (ADT) for a median duration of 6 months (IQR, 3–6).

All patients were strictly planned and treated with the 150-cm^3 air-filled balloon, in full compliance with the rectal distension-mediated prostate immobilization, and the beacon transponder-loaded Foley catheter technique. Plan objectives and dosimetric results are summarized in **Table 2**. Due to the high inherent dose heterogeneity of the plan dose prescriptions, PTV doses are reported in accordance with the International Commission on Radiation Units and Measurements (ICRU) recommendations (34) as $D_{50\%}$. All plans fulfilled a $D_{50\%}$ ≥45.0 Gy and a $D_{95\%}$ ≥40.5 Gy. Patient adherence to the protocol was excellent, and all completed the planned 5 sessions over 5 consecutive days (i.e., Monday through Friday).

Prostate-Specific Antigen Outcomes

A total of 37 patients developed a Phoenix-defined (nadir +2 ng/ml) PSA relapse at a median time of 36.1 months (IQR, 25.2–42.3). The 7-year cumulative incidence rate of PSA failure was 13.8% for the entire cohort. **Figure 2** shows that the cumulative incidence rates of PSA failures were 2% vs. 16.6% for the combined low and favorable intermediate-risk (FIR) groups vs. the Unfavorable Intermediate-Risk (UIR) group ($p < 0.005$; HR 0.32, 95% CI 0.14–0.71) and 27.2% for the high-risk group (unfavorable intermediate-risk vs. high-risk, $p = 0.01$, HR 0.31, 95% CI 0.12–0.77). **Figure 3** shows associations of pretreatment characteristics with bRFS probability. MRI-defined T-stage was not correlated with bRFS (87.8% vs. 84.8% for T1c-T2a vs. T2b-T2c, respectively; $p = 0.7$; HR 1.01; 95% CI, 0.55–2.20; **Figure 3A**), while pretreatment PSA (iPSA) was significantly associated with bRFS (91.4% vs. 72.5% for iPSA <10 vs. ≥10 ng/ml, respectively; $p < 0.0001$; HR 0.16; 95% CI, 0.08–0.35; **Figure 3B**). Biopsy ISUP grade group 1 vs. 2 did not significantly differ in bRFS probabilities nor did ISUP group 3 vs. 4. However, the combination of Groups 1 and 2 vs. 3 and 4 resulted in significantly different bRFS probabilities (91.5% vs. 73.5%, $p < 0.0001$; HR 0.22; 95% CI, 0.11–0.44; **Figure 3C**).

Androgen Deprivation Therapy in UIR and High-Risk Patients

The use of ADT was not one of the primary study objectives, and patients were not randomized for ADT administration, which was employed at the discretion of the referring physician. Overall, the 7-year bRFS probability for patients who received ADT was 88.1% vs. 82.0% for those who did not ($p = 0.023$; HR 0.01; 95% CI, 0.01–0.02; **Figure 4A**). Additionally, subset analysis of UIR and high-risk patients who received ADT vs.

TABLE 2 | Plan objectives and dosimetric results.

Plan dosimetry	Plan objective	Median	mean	IQR
PTV				
$D_{50\%}$ (Gy)	≥45.0	46.6	46.6	46.4-46.7
D_{mean} (Gy)	≥45.0	45.8	45.8	45.6-46.0
$D_{95\%}$ (Gy)	≥40.5	40.6	40.4	40.0-41.2
$D_{2\%}$ (Gy)	≤48.2	47.9	47.9	47.8-48.1
$D_{98\%}$ (Gy)	≥38.2	38.4	38.6	38.1-39.1
V_{45Gy} (%)	≥80	80.6	80.8	77.7-84.0
$V_{40.5Gy}$ (%)	≥95	94.6	95.1	93.9-96.2
Urethral wall				
$D_{2\%}$ (Gy)	≤40.5	38.7	38.8	38.4-39.2
$D_{1cm\ 3}$ (Gy)	≤36.0	33.7	34.4	33.8-34.9
Bladder				
$D_{2\%}$ (Gy)	≤40.5	36.8	37.5	28.2-40.6
$D_{5o\%}$ (Gy)	≤22.5	14.5	10.5	8.0-12.4
D_{1cm3} (Gy)	≤40.5	38.6	38.9	38.2-39.5
Rectal wall				
$D_{2\%}$ (Gy)	≤42.8	35.5	35.2	35.1-35.8
$D_{5\%}$ (Gy)	≤40.5	32.7	33.3	32.2-33.8
$D_{5o\%}$ (Gy)	≤22.5	9.9	14.4	7.27-17.6
D_{1cm3} (Gy)	≤36.0	35.6	35.3	35.0-35.5
UGD				
$D_{2\%}$ (Gy)	≤42.8	35.9	37.4	33.3-39.7
Penile bulb				
$D_{2\%}$ (Gy)	≤36.0	3.3	2.4	1.8-3.5
D_{1cm} (Gy)	≤22.5	2.0	1.6	1.3-2.2
NVBs				
$D_{2\%}$ (Gy)	≤45.0	39.6	41.4	39.0-44.6
$D_{5o\%}$ (Gy)	≤31.5	30.1	31.3	28.5-33.8
Femoral heads				
$D_{2\%}$ (Gy)	≤22.5	12.9	12.8	5.5-20.9

PTV, Planning Target Volume; D_{mean}. mean dose; $D_{2\%}$, $D_{5\%}$, $D_{5o\%}D_{95\%}$, $D_{98\%}$, minimum dose to n% of the structure; V_{458y}, $V_{40.58y}$, percentage of structure receiving 45Gy or 40.5Gy (100% and 90% of the prescription dose); $D1cm^3$, dose to 1 cm^3 of the structure; UGD, urogenital diaphragm; NVB, neurovascular bundles.

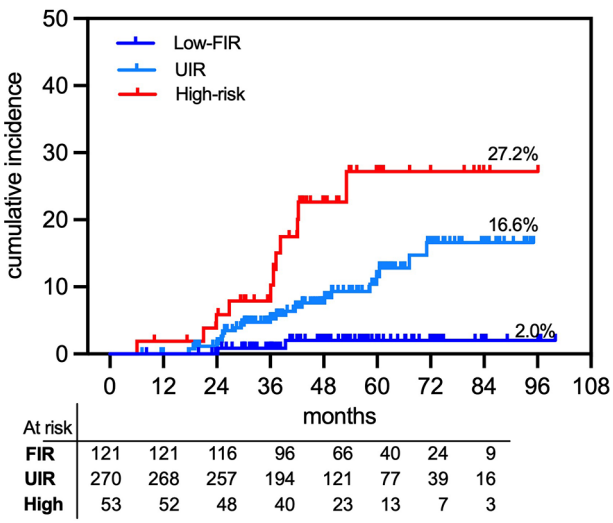

FIGURE 2 | Actuarial prostate-specific antigen (PSA) relapse in 444 organ-confined primary prostate cancer treated with rectal distension-mediated 5 × 9 Gy SABR. Patient groups are defined as combined low-risk and favorable intermediate-risk (FIR), unfavorable intermediate-risk (UIR), and high-risk (High) patients.

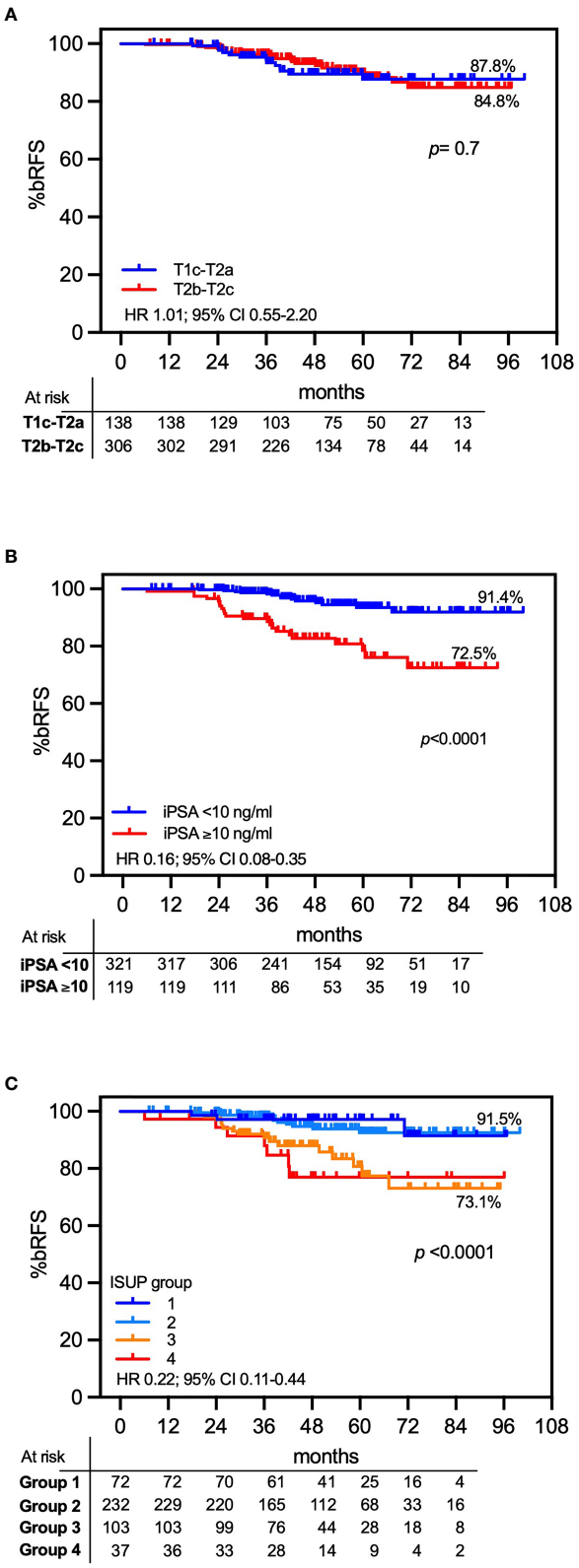

FIGURE 3 | Seven-year actuarial PSA relapse-free survival (bRFS). Actuarial bRFS is presented as a function of T stage **(A)**, initial PSA **(B)**, and biopsy ISUP grade group **(C)**.

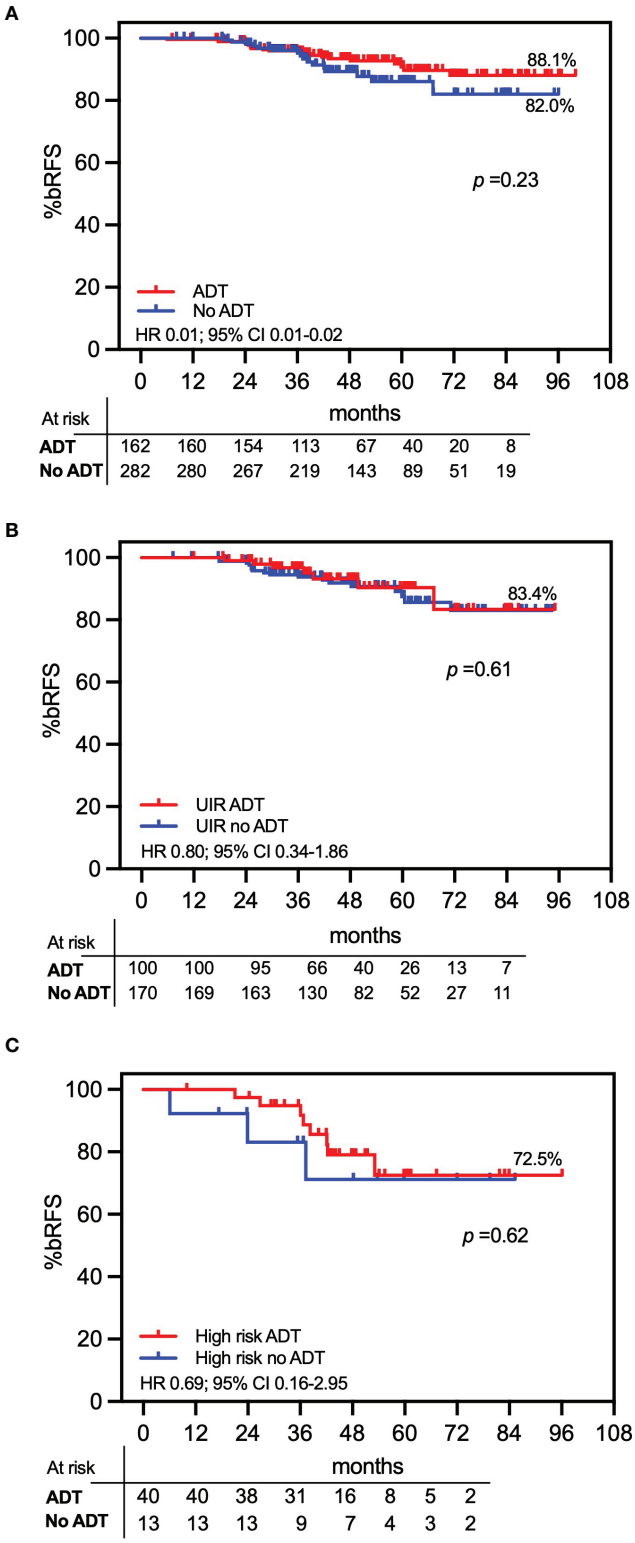

FIGURE 4 | Actuarial PSA relapse-free survival (bRFS) by androgen deprivation therapy (ADT). Patients treated with ADT are compared with patients not receiving ADT. **(A)** The total study population of 444 patients; **(B)** unfavorable intermediate-risk (UIR) patients; **(C)** high-risk patients.

those who did not showed no statistically significant differences between the two UIR subgroups (83.3% vs. 83.4%, respectively; p = 0.61; HR 0.80; 95% CI, 0.34–1.86; **Figure 4B**) and high-risk subgroups (72.5% vs. 72.3%, respectively; p = 0.62; HR 0.69; 95% CI, 0.16–2.95; **Figure 4C**).

Prostate-Specific Antigen Kinetics in No Androgen Deprivation Therapy Patients

Whereas the present study adopted tight PTV safety margins and a urethra-sparing approach, we explored established landmarks of PSA relapse predictors to ensure that the treatment protocol did not negatively affect outcomes. In the 282 patients who were not exposed to ADT, PSA gradually decreased to a median nadir of 0.19 ng/ml (IQR, 0.09–0.37), and the 3-year median PSA was 0.30 ng/ml (IQR, 0.20–0.32). Benign PSA bounces (>0.2 ng/ml over previous nadir) were observed in 36.5% (103/282) of cases and had a median magnitude of 0.57 ng/ml (IQR, 0.32–097). The median time to bounce was 12 months (IQR, 8.9–17.5), and the median duration was 3 months (IQR, 3–9). PSA bounces were significantly correlated with bRFS in this cohort (98.9% vs. 80.8% for patients with vs. without a bounce; p = 0.0008; HR 0.22; 95% CI, 0.09–0.53; **Figure 5A**). A PSA nadir (nPSA) <0.5 ng/ml was significantly correlated with an improved probability of bRFS (94.8% for nPSA <0.5 ng/ml vs. 53.7% for ≥0.5 ng/ml; $p < 0.0001$; HR 0.05; 95% CI, 0.01–0.17; **Figure 5B**). Time to nPSA (TnPSA) was significantly associated with decreased bRFS using 24 months as a cutoff point (94.3% vs. 31.6% for TnPSA <24 vs. ≥24 months, respectively; HR 0.03; 95% CI, 0.01–0.16; **Figure 5C**). Likewise, a 24-month PSA doubling time (PSADT) ≥10 months was associated with significantly decreased PSA relapse rates (90.4% vs. 53.1% for PSADT ≥10 vs. <10 months, respectively; HR 0.01; 95% CI 0.01–0.61; **Figure 5D**).

^{68}Ga-PSMA PET/CT Characterization of Prostate-Specific Antigen Relapses

To determine whether PSA relapse in ISUP groups 3 and 4 was associated with extraprostatic spread, we employed ^{68}Ga-PSMA PET/CT at the time of PSA failure. Scans were performed in 35 of the 37 patients exhibiting a PSA relapse. Median PSA at the time of relapse was 3.70 (IQR 2.39–5.20). In one patient, the ^{68}Ga-PSMA scan was inconclusive. **Figure 6** shows that for ISUP groups ≥3, the actuarial 7-year cumulative incidence rate of all ^{68}Ga-PSMA-detected intraprostatic recurrences [Local relapse (LR)] was 20.2% vs. 5.7% extraprostatic only progression. Of the 34 patients with positive ^{68}Ga-PSMA scans, 73.5% (25/34; 2 FIR, 15 UIR, and 8 high-risk) had evidence of persistent tracer uptake at the site of the pretreatment dominant lesion, 4 of whom (1 UIR and 3 high-risk) also exhibited nodal involvement. In contrast, 26.5% (9/34) of patients had evidence of extraprostatic dissemination only. The overall 7-year actuarial cumulative incidence rate of developing a ^{68}Ga-PSMA-detected intraprostatic or extraprostatic relapse was 9.9% vs. 4.6%, respectively. **Figure 7** shows an instance of a ^{68}Ga-PSMA-detected intraprostatic relapse at the same site of the initial dominant lesion for an ISUP grade 3 tumor. Biopsy ISUP grade ≥3 (i.e., Gleason primary pattern 4) was significantly associated with

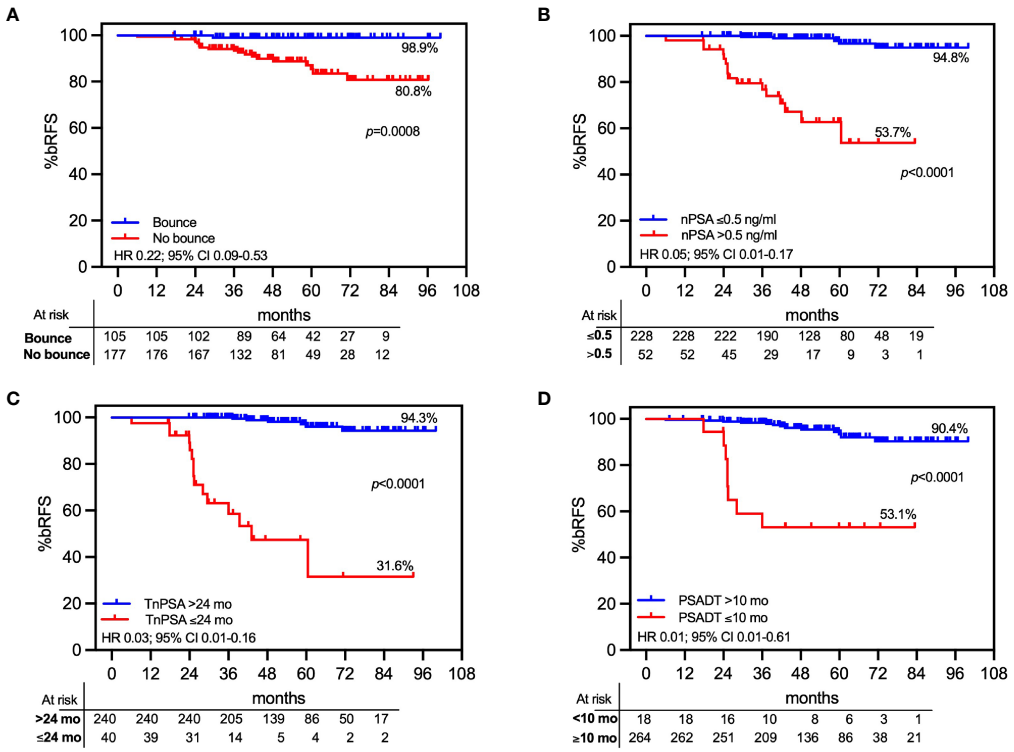

FIGURE 5 | Actuarial PSA relapse-free survival (bRFS) by landmarks of PSA relapse predictors. Only patients who did not receive androgen deprivation therapy (ADT) were included in the analyses. Patients classified by **(A)** benign PSA bounce; **(B)** nadir PSA cutoff at 0.5 mg/ml; **(C)** time to nadir PSA (TnPSA) with a cutoff time point at 24 months; **(D)** PSA doubling time with 10 months as cutoff point.

the likelihood of a ^{68}Ga-PSMA-detected intraprostatic relapse (20.2% vs. 5.6% for ISUP groups ≥3 vs. ≤2, respectively; p = 0.004; HR 0.28; 95% CI, 0.12–0.68; not shown), also differing in extraprostatic dissemination only (8.6% vs. 2.6% for ISUP groups ≥3 vs. ≤2, respectively; p = 0.0003; HR 0.11; 95% CI, 0.03–0.37; not shown).

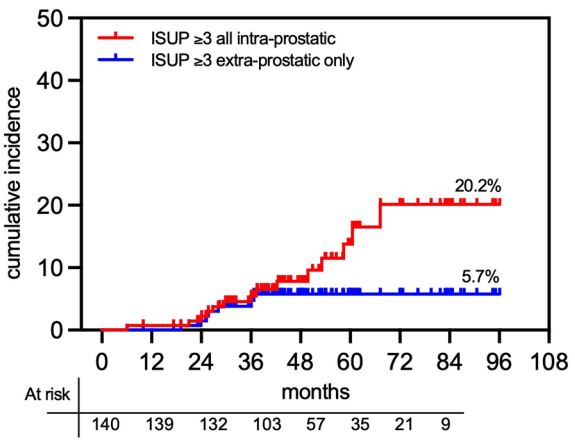

FIGURE 6 | Cumulative actuarial incidence of post-SABR prostate cancer relapse in histological ISUP ≤3 group. Relapse was detected by ^{68}PSMA PET/CT scanning detecting intraprostatic (± extraprostatic) lesions vs. extraprostatic only tumor lesions.

Adverse Events

Table 3 summarizes the incidence of acute and late adverse events. Grade 1 acute urinary (GU) symptoms peaked at 1 month posttreatment with an overall incidence of 19.8% (n = 88) largely consisting of dysuria and frequency. Acute grade 2 GU toxicity was observed in 6.8% (n = 27), including 4 cases (0.9%) of retention that needed catheterization during the first week posttherapy. There were no cases of grade 3 GU toxicity. There was no statistically significant association between baseline IPSS score ≥15 and the likelihood of developing acute grade 2 GU toxicity (Fisher's exact test p = 0.4). Acute grade 1 rectal (GI) toxicity occurred in 6.5% (n = 29) of cases and was largely represented by tenesmus. The incidence rate of acute grade 2 GI was 0.5% (n = 2), and there were no instances of acute grade 3 GI events.

Late grade 1 and grade 2 GU toxicities occurred, respectively, in 13.1% (n = 58) and 4.5% (n = 20) of patients. There was only one instance of grade 3 toxicity (0.2%) presenting at 4.3 months posttherapy as severe hematuria requiring transfusion. Median time to late GU toxicity was 12.4 months (IQR, 9.1–17.3). The actuarial cumulative incidence rates of late GU adverse events

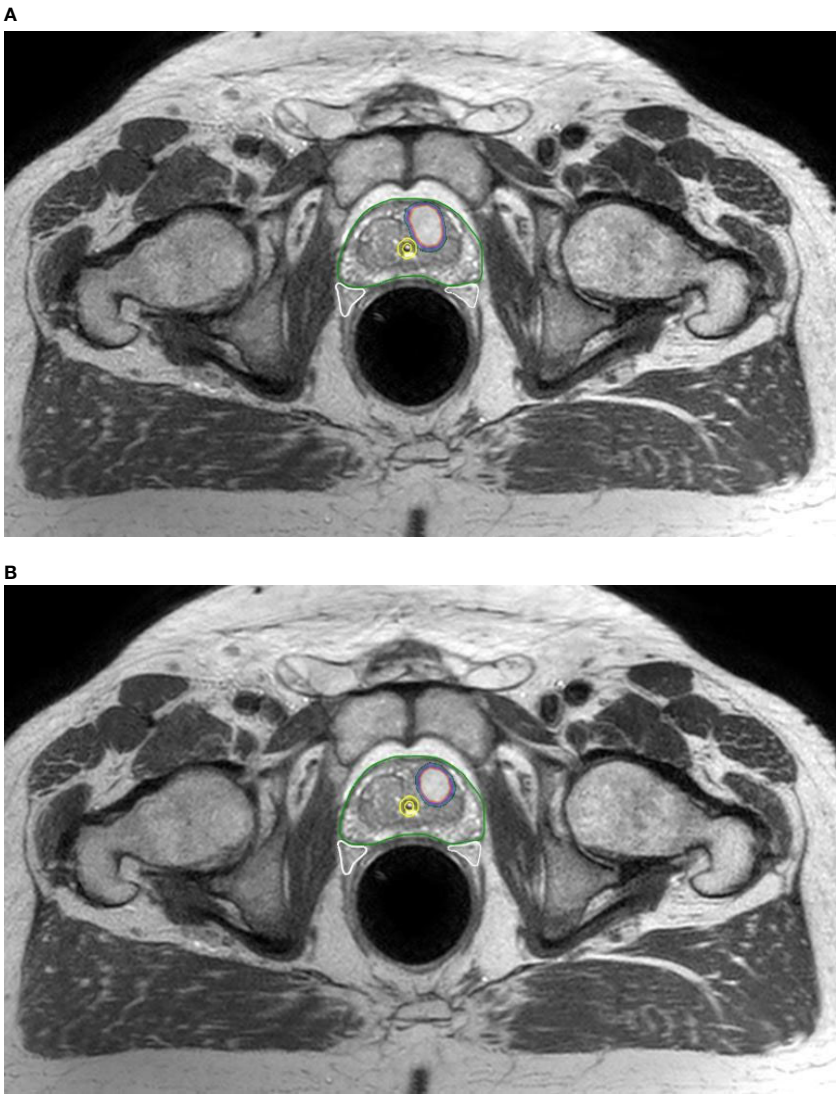

FIGURE 7 | ^{68}PSMA-detected relapse in a patient who received 5-fraction SABR. **(A)** Fused ^{68}PSMA-PET/CT and planning MRI show pretreatment location of ^{68}PSMA-detected dominant intraprostatic lesion (DIL) encompassed within the CTV and receiving the full 45 Gy prescription dose; **(B)** fused ^{68}PSMA-PET/CT acquired at the occurrence of biochemical relapse with the planning MRI scan shows persistence/recurrence of the DIL at the initial site.

TABLE 3 | Acute and late toxicities.

% (n)	Acute			Late		
	G1	G2	G3	G1	G2	G3
Any GU	19.8% (88)	6.8% (27)	0% (0)	13.1% (58)	4.5% (20)	0.2% (1)
Dysuria	11.9% (53)	4.5% (20)		5.4% (24)	1.6% (7)	
Frequency/urgency	8.1% (36)	1.1% (5)		5.2% (23)	1.3% (6)	
Nocturia	2.7% (12)			1.3% (6)	0.9% (4)	
Retention	1.1% (5)	1.8% (8)		0.7% (3)	0.2% (1)	
Incontinence	1.1% (5)	0.4% (2)		0.4% (2)	0.2% (1)	
Hematuria	0.4% (2)	0.4% (2)		3.2% (14)	0.4% (2)	0.2% (1)
Any GI	6.5% (29)	0.5% (2)	0% (0)	3.2% (14)	1.1% (5)	0% (0)
Tenesmus	3.8% (17)	0.2% (1)		0.7% (3)		
Rectal bleeding	2.2% (9)	0.2% (1)		2.0% (9)	1.1% (5)	
Diarrhea	0.9% (4)	0.2% (1)		0.7% (3)		

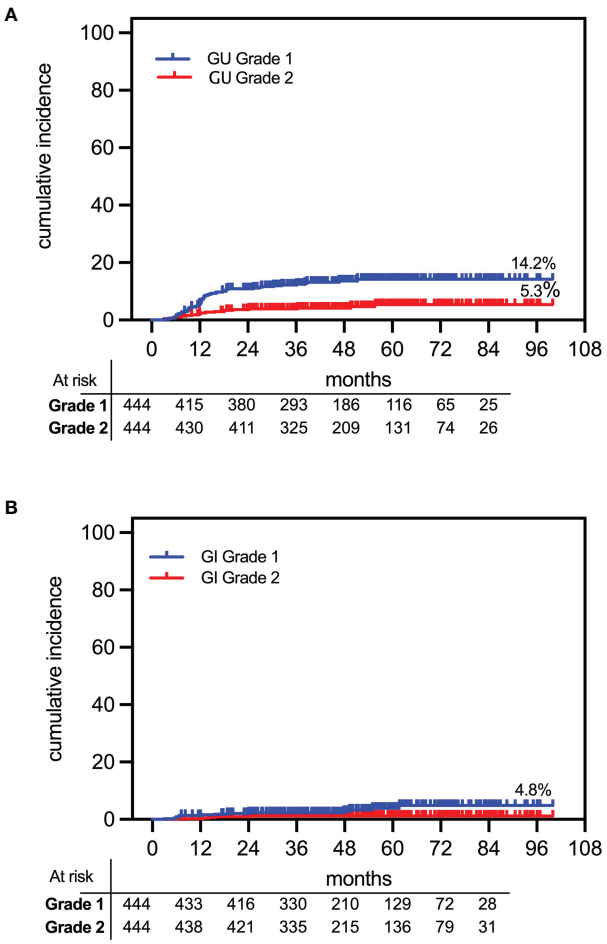

FIGURE 8 | Cumulative actuarial incidence of OAR toxicities following rectal distension-mediated 5 × 9 Gy SABR. The 7-year late grade 1 and 2 toxicities are shown for **(A)** urinary (GU) and **(B)** bowel (GI) toxicities.

were 14.2% and 5.3%, respectively, for grade 1 and grade ≥2 (**Figure 8A**). None of the patients in this cohort developed late urinary retention requiring catheterization.

Late GI toxicity occurred at a median of 14.1 months (IQR, 6.2–41.9) posttherapy, consisting of 3.2% (n = 14) grade 1 and 1.1% (n = 5) grade 2 rectal bleeding events. There were no instances of grade 3 rectal toxicity. The actuarial cumulative incidence rates of late GI adverse events were 4.8% and 1.1%, respectively, for grade 1 and grade 2 (**Figure 8B**).

Patient-Reported Quality of Life

Patient-reported QOL measures showed a transient decline in all three EPIC-26 summary score domains at 1 month after treatment, recovering at 3 months (**Figure 9**). The clinically meaningful decline in QOL was defined as one-half the standard deviation of each of the domain baseline summary scores (MID). Median changes from baseline and proportions of patients with declines above the MID for the three EPIC-26 domains at each of the study time points are summarized in **Table 4**. As far as the urinary domain is concerned, the overall magnitude of the declines over time was relatively small and the proportions of patients with urinary domain declines >MID were relatively constant over time, except for a second transient increase (34.7% of patients) at 12 months posttreatment, representing the occurrence of a temporary self-limiting pelvic flare phenomenon. Notwithstanding, in the present series, the RTOG 0938 urinary domain meaningful endpoint for the tolerability and safety of prostate SBRT (defined as declines from baseline to 1 year >2 points in ≤60% of patients) was fulfilled at 47.0%, confirming the favorable toxicity profile of the present approach also when using such a stringent endpoint metric.

The bowel domain had minimal changes over time. The RTOG 0938 bowel domain meaningful endpoint for tolerability and safety (defined as declines from baseline to 1 year >5 points in ≤55% of patients) was also met (25.9% in the present series), underlining the effectiveness of the present technique in bowel QOL preservation.

The sexual domain had the largest absolute changes between baseline and the study time points. However, the summary

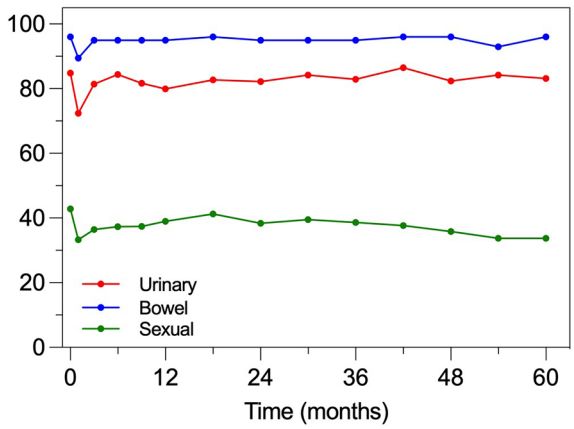

FIGURE 9 | Median EPIC-26 summary scores for the urinary, bowel, and sexual domains. EPIC-26 summary scores range between 0 and 100, with higher scores indicating better QOL.

scores were only marginally reduced compared to baseline until month 36 posttreatment, after which the magnitude of the decline and the proportions of patients with changes above MID gradually increased, suggesting that sparing of the NVBs may contribute to the sexual domain QOL preservation.

DISCUSSION

The present study provides compelling evidence for the efficacy of the rectal distension-mediated prostate cancer SABR. The ability to reproducibly immobilize the prostate within the same patient-specific anatomical niche, at the same 3D configuration, promotes the basic tenet of ablative radiotherapy, namely, high-precision tumor targeting with OAR preservation. Although post-SABR prostate biopsies were not performed in this study, an early use of ^{68}Ga-PSMA PET/CT provided an approach to detect LRs within the irradiated prostate. The low-risk/FIR patients exhibited an actuarial 7-year incidence of biochemical failure of 2%, with 2 patients failing with LR. In contrast, LRs occurred with an incidence of approximately 20% in the UIR and high-risk patients. Whereas there were no discrepancies in treatment planning or delivery in

TABLE 4 | EPIC-26 summary score changes and proportions of patients with declines above the minimally important difference.

EPIC-26	1 mo	3mo	6mo	9mo	12 mo	18 mo	24mo	30 mo	36 mo	42mo	48mo	54mo	60 mo
Urinary domain													
median =88													
SD =12.4													
Median change (IOR)	-8 (-21, 0)	0 (-6, 4)	0 (-6, 4)	0 (-9, 4)	-2 (-8, 4)	0 (-9, 4)	-2 (-7, 4)	0 (-7, 6)	0 (-8, 6)	0 (-6, 6)	0 (-7, 4)	0 (-7, 6)	-2 (-9, 4)
MID 6.2 points													
Proportion with decline >MID	54.40%	24.70%	23.10%	29.10%	34.70%	29.10%	26.40%	25.90%	26.30%	24.00%	26.00%	31.00%	33.30%
Bowel domain													
median =96													
SD =8.5													
Median change (IQR)	-3 (-11, 0)	0 (-5, 3)	0 (-5, 2)	0 (-5, 2)	0 (-6, 2)	0 (-5, 3)	0 (-5, 3)	0 (-7, 3)	0 (-5, 3)	0 (-5, 2)	0 (-3, 3)	0 (-5, 2)	0 (-6, 2)
MID 4.2 points													
Proportion with decline >MID	43.60%	27.30%	28.60%	29.00%	31.00%	28.20%	30.40%	26.50%	30.20%	25.00%	26.00%	25.00%	23.60%
Sexual domain													
median =42													
SD =26.9													
Median change (IQR)	-6(-19, -3)	-2(-15, 3)	-4(-16, 3)	0(-13, 6)	-2(-14, 6)	-2(-12, 8)	-2(-13, 8)	-2(-13, 6)	-4(-13, 8)	-7(-18, 5)	-6(-19, 6)	-6(-17, 3)	10(-23, -2)
MID 13.4 points													
Proportion with decline >MID	36.50%	29.40%	27.90%	24.20%	25.10%	22.50%	24.90%	23.10%	29.10%	34.70%	35.40%	34.60%	37.70%

these patients, this observation confirms the existence of human prostate cancer subphenotypes that exhibit resistance to the 5 × 9 Gy schedule, consistent with recent reports of an α/β ratio range of 1.3–11.1 Gy, derived from analysis of known LQ variables in subgroups of hypofractionated prostate cancer patients (12).

The Physiology of Prostate Organ Motion

The introduction of the rectal distension-mediated technique in prostate cancer SABR was derived from an understanding of prostate physiology as a mobile organ. The anatomical location of the human prostate at a resting state is in the inferior–posterior section of the pelvic diaphragm (35). It has been generally believed that the strategic location at the pelvic outlet exposes the gland to random dislocation by rectal gas or urinary bladder filling (36). In fact, cine-MRI studies showed that high-volume gas passing through the rectum induces a prostatic gland translocation of up to 12 mm, subsequently returning to its steady-state location (37), and online tracking technology disclosed unpredictable 3–10-mm prostate organ displacements during radiation treatment delivery in approximately 20% of treatment sessions (38–40), engendering uncertainties in prostate tumor targeting (41, 42).

However, anatomical studies have indicated that the human prostate cannot independently drift, as it is restricted by complex anatomical interactions with adjacent pelvic organs. At its base, the prostate is attached to the bladder neck, while at the apex, the *levator ani puborectalis* muscle tightly engulfs the gland at the level of the anorectal ring (43). Posteriorly, the prostate body and seminal vesicles blend through Denonvilliers' fascia to the *ampulla recti* (44, 45), an actively mobile structure (46, 47). Hence, prostate mobility largely represents a bystander phenomenon to the physiology of the rectum.

Stretching of the rectal wall activates efferent neuronal sensorimotor signals that coordinate the *levator ani puborectalis* muscle function in regulating anorectal junction patency (46, 47). The *levator ani puborectalis* originates at the posterior surface of the pubic ramus and runs along the right and left of the prostate/rectum complex, forming a sling around the posterior rectal wall just proximal to the anorectal junction. The muscle is permanently contracted under baseline conditions (postural reflex), forming a rectal angulation that obliterates passage of intrarectal contents (46, 47). When stretching of the rectal wall occurs, efferent neurosignals relax the *levator ani puborectalis* postural reflex (47), unfolding the loop of the rectum *via* its expansion along a superior–anterior axis, concomitantly relocating the linked prostate along the same vector.

This functional paradigm suggests an approach to immobilize the prostate for a certain period of time by introducing an endorectal air-inflated balloon during each SABR session, harnessing the physiology of the rectal/prostate mobility. A body of literature shows that 40–100 cm^3 of air-inflated endorectal balloon reduces prostate intrafractional motion, but some intrafractional motion still occurs (48–50). The suboptimal outcome of ≤100 cm^3 air-filled balloons raises the question of whether stretch receptor signals may be insufficient. In fact, human data indicate that rectal sensorimotor stretch receptors adapt with time to an isobaric rectal wall stretch, returning to baseline function at a rate that is inversely related to the isobaric volume distending the rectum (51–53). Hence, we posit that immobilization of the prostate during radiation treatment delivery requires a sustained state of near-maximal resolution of the *puborectalis* postural reflex and of the anorectal angulation, avoiding the risk of rectal stretch adaptation. Consistent with this notion, studies of escalated air volume inflation of intrarectal balloons reported that at the low air-volume range, patients consistently report mild, if any, sensation of rectal distension, while at volumes exceeding approximately 150 cm^3, patients reported an intolerable urge to evacuate (54, 55). We posited that the transition volume from tolerable to urgency/intolerable sensation might define an adequate state of near-maximal resolution of the postural reflex/anorectal angulation, which might optimize prostate immobilization during SABR treatment delivery.

Rectal Distension-Mediated Prostate Immobilization

We have tested this hypothesis in the first 189 patients of the present phase II clinical study of 5 × 9 Gy SABR (32, 41). An initial balloon-volume tolerance study was performed in the first 15 patients during simulation, demonstrating that in our air-filled endorectal balloon system, the highest tolerated air filling was 150 cm^3 (32). The rectal distension-mediated treatment protocol was employed using this volume (41), and full transponder/Linac logs from 886 treatment sessions were systematically analyzed (41). Accurate alignment of the anatomy between the planning image scan and the CBCT at the time of delivery is of paramount importance. Urethra sparing is achieved if the curvature of the intraprostatic urethra is perfectly matching, often requiring minor manual adjustments of the catheter and endorectal balloon. Of course, any small readjustment must be confirmed by a new CBCT before final registration is approved by the treating physician. Therefore, mean preparation time from online tracking inception to reference CBCT acquisition was 14.1 ± 11 min, and an average of 3.7 ± 1.7 CBCTs were required for final reference registration (41).

The overall mean session time was 19.5 ± 12 min, including 5.4 ± 5.9 min for actual treatment delivery after reference CBCT acquisition, registration, and approval (41). Treatment interruptions due to deviations requiring a realignment CBCT occurred in 6% of sessions, prolonging session time to a mean of 14.5 ± 8.4 min.

Posttreatment analysis of the log data showed that the majority of >2-mm intrafraction motions occurred in the superior-inferio (SI) (7.6%), anterior-posterior (AP) (2.8%), and left-right (LF) (3.2%) directions, indicating a relative stability along these axes (41). All detected deviations were managed either by temporary treatment interruptions until they resolved spontaneously or by target realignment following new CBCT acquisitions. Temporary deviations were rare during the first 10 min (1.4%), gradually increasing to 3.8% by 15 min, minimally prolonging the overall treatment delivery time (41). The rectal distension-mediated approach rendered recapitulation of the daily repositioning of the prostate/OAR complex into an anatomically confirmed same patient-specific retropubic niche, within a maximum standard deviation of

1.5 mm (32, 41), enabling accurate delivery of the high-heterogeneity treatment plans.

Toxicity Profile

The rectal distension-mediated prostate immobilization approach used here was well tolerated by all patients and resulted in a low cumulative incidence of acute and late grade ≥2 urinary and rectal toxicities. These favorable outcomes are to be attributed to the meticulous efforts deployed during MRI acquisition, treatment planning, and treatment delivery in ensuring maximal anatomical reproducibility. Hence, the strict implementation of stringent dose constraints for the OARs *via* negative dose painting and the tight PTV expansion margin as used in this study have rendered the low OAR toxicity rates reported herein. Additionally, the online tracking with 2-mm threshold guaranteed the applicability of such tight margins by way of correction for intrafraction motion.

While the overall 7-year cumulative incidence rate of urinary late grade ≥2 toxicity in the present study was 5.3%, studies that did not employ urethra sparing reported a significantly higher dose-dependent urinary toxicity. Helou et al. (56) reported that Radiation Therapy Oncology Group grade ≥2 late urinary toxicity sharply increases to 48% in patients receiving 40 Gy. Zhang et al. (57) showed that V42 Gy >2 cc was associated with significantly increased grade ≥2 urinary toxicity. Zelefsky et al. (58) showed that the risk of RTOG ≥2 urinary toxicity increases in a stepwise fashion in a dose escalation study (23.3%, 25.7%, 27.8%, and 31.4% for the dose levels 32.5, 35, 37.5, and 40 Gy, respectively). A recent dosimetry modeling of the risk of urinary toxicity based on the maximum urethral dose metric (MUDM; calculated in EQD_2) has shown that each increase of 1 Gy corresponds to a 1% increase in risk of grade ≥2 and 0.2% in grade 3 late urinary toxicity (30). While our experience is consistent with this model, the strict constraints employed in our study (maximal dose to the urethral wall $D_{2\%}$ ≤40.5 Gy and $D1cm^3$ ≤36 Gy) resulted in 4.7% and 0.2% CTCAE grade ≤2 and grade 3 urinary toxicities, respectively. Similar results have been reported by studies adopting urethral constraints of 34–35 Gy (late grade ≥2: 3.8%–8.3%) (59–61). Thus, our data provide compelling evidence that dose escalation in a 5-fraction SABR regimen can be safely pursued provided stringent urethra sparing and accurate target anatomical localization are deployed.

The GI toxicity profile in this study compares favorably with recently reported toxicity outcomes of dose-escalated extreme hypofractionation. For instance, Musunuru et al. (62) reported a >20% vs. 8% grade ≥2 CTCAE GI toxicity in patients treated with 40 vs. 35 Gy, respectively. In a dose escalation trial, 10% of patients treated with 50 Gy experienced grade 3–4 rectal toxicity (26). Dosimetric analysis showed a strong association between V39 Gy >35% of rectum circumference and the risk of late bowel toxicity. In addition to the anatomical reproducibility and accuracy of the technique deployed here, we believe that the maximally tolerated stretching of the rectum by the air-filled endorectal balloon reduces the exposure of most of the mucosa of the rectal wall, permitting the fulfilment of the strict $D1cm^3$ ≤36 Gy constraint. Thus, our results compare favorably with recent reports employing hydrogel spacers with dose-escalated regimens similar to ours (29, 58). Therefore, we maintain that the use of the hydrogel spacer, apart from being invasively inserted, only affords protection on the rectal mucosa and does not prevent or mitigate prostate organ motion, thereby foregoing the opportunity of accurate urethra and NVB sparing. The physician-reported toxicity profiles are corroborated by the favorable long-term patient-reported QOL outcomes. Nonetheless, the reported QOL changes following ultrahigh-dose hypofractionation reflect an existence of low-grade chronic symptoms that may be of particular interest due to the lack of severe adverse events observed with SBRT in several series (63). These observations highlight the importance of QOL evaluations in prostate cancer therapy.

Impact of Dose Escalation on Local Control

The dose prescription of the present study translates into a spectrum of high tumor ablative BED when tumors consist of LQ α/β ≤2 Gy functioning clonogens, driving the effectiveness of extreme hypofractionation. Consistent with this notion, only 2/121 (1.6%) of low-risk/FIR patients exhibited a PSA relapse, both associated with ^{68}Ga-PSMA-detected LRs, while the 7-year bRFS rate was stable at 98%. In contrast, however, the same treatment regimen employed in the UIR/high-risk category rendered a significantly higher 7-year cumulative incidence of ^{68}Ga-PSMA-detected intraprostatic relapses, as well as extraprostatic dissemination. This observation raises questions relative to the relevance of the dogmatic acceptance of a single low-range α/β phenotype in defining the LQ fractionation sensitivity in prostate cancer. In fact, Vogelius and Bentzen (13), while confirming the validity of a functional α/β ratio of 1.6 Gy, also highlighted an association between increasing dose in hypofractionation schemes and an increase of α/β values, suggesting an existence of α/β heterogeneity in prostate cancer. Datta et al. (12) confirmed the α/β heterogeneity in hypofractionation studies, ranging between 1.3 and 11.1 Gy. Our ^{68}Ga-PSMA PET/CT studies in UIR/high-risk tumors are consistent with this notion, suggesting that the continuous genomic and metabolic drivers of clonal expansion, which confer high-risk clinical features, such as ISUP grade ≥3 phenotypes, might hypothetically confer clones of high α/β in fractionation responses. Such biologic phenotypes would render hypofractionation BEDs that are significantly lower than the ablative BED $\geq_2$. Attempts to reach an ablative iso-BED_2 in 5-fraction whole-prostate SABR would require an unattainable increase in the fractional dose due to a high risk of OAR toxicity. Recent evidence, however, is emerging on the feasibility, safety, and efficacy of a simultaneous integrated boost (SIB) *via* ^{68}Ga-PSMA-directed dose painting of dominant intraprostatic lesions (DILs) (64–67). The SIB/DIL approach has been shown to be feasible in prostate cancer treated with extreme hypofractionation (68, 69), but the safety and effectiveness of SIB/DIL as described here will need to be tested in carefully designed clinical trials such as the ongoing Hypofocal-SBRT study (70).

CONCLUSION

The present clinical trial provides compelling evidence that the rectal distension-mediated technique affords a non-invasive and

safe approach to employ an ablative 5-fraction SABR regimen to treat prostate cancer, albeit maximally effective in low LQ α/β phenotypes. Approximately 20% of UIR/high-risk patients appear to develop locally relapsing, radioresistant high α/β phenotypes. There is, thus, an urgent need for new tools to discern patients who are refractory to dose-escalated 5-fraction SABR and to introduce hypofractionated-based treatment techniques to improve tumor control in this biological setting. Whether the ^{68}Ga-PSMA-directed SIB/DIL technique might comprehensively ablate clones at high LR risk as part of a 5-fraction whole-prostate SABR remains to be tested.

DATA AVAILABILITY STATEMENT

The datasets will not be made available due to patient privacy concerns. Requests to access the datasets should be directed to: carlo.greco@fundacaochampalimaud.pt.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Champalimaud Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CG was the lead author who initially developed the concept of the study, participated in data collection, data analysis, article drafting, table/figure creation, and article revision. OP, NP, VL, BN, and JK participated in clinical data collection and data analysis. JS, SV, MC DM, AS, JM, EF, and GC participated in data collection and analysis. ZF is a senior author who participated in data analysis, article drafting, review, and revision. All authors contributed to the article and approved the submitted version.

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Rationale for Utilization of Hydrogel Rectal Spacers in Dose Escalated SBRT for the Treatment of Unfavorable Risk Prostate Cancer

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In this review we outline the current evidence for the use of hydrogel rectal spacers in the treatment paradigm for prostate cancer with external beam radiation therapy. We review their development, summarize clinical evidence, risk of adverse events, best practices for placement, treatment planning considerations and finally we outline a framework and rationale for the utilization of rectal spacers when treating unfavorable risk prostate cancer with dose escalated Stereotactic Body Radiation Therapy (SBRT).

Keywords: prostate, hydrogel, rectal spacer, radiotherapy, radiation therapy, SBRT

INTRODUCTION

Prostate cancer is the most common cancer diagnosed in male patients in the United States with an estimated 248,530 cases in 2021 (1). Greater than 80% of these patients present with either localized or regional disease, and the vast majority of this subset may be eligible for curative treatment with radiotherapy. In general, biochemical disease free-survival and long-term overall survival rates are excellent in patients treated with definitive radiotherapy, even for those patients with high-risk or node-positive disease (2). However, although acute toxicity in these patients tends to be mild and self-limiting, some patients may experience late effects of radiotherapy that can be morbid and difficult to manage (3). In particular, long-term randomized quality of life (QoL) data suggest that while urinary and sexual function are at least comparable if not better than radical prostatectomy, there are higher degrees of bowel bother and rectal bleeding with definitive radiotherapy (4, 5). In rare cases, life threatening late events including fistula formation and soft tissue necrosis have been reported following dose-escalated radiotherapy (6). Multiple strategies to mitigate long-term rectal toxicity have been employed including sophisticated radiation techniques such as intensity

modulated radiotherapy (IMRT), proton beam therapy (PBT), and physical devices such as rectal balloons and implanted materials to physically separate the posterior aspect of the prostate from the anterior rectal wall (7–9). In this article, we review the development, data, and rationale for utilization of hydrogel rectal spacers in prostate SBRT dose escalation for unfavorable risk prostate cancer.

HYDROGEL RECTAL SPACER BACKGROUND AND DEVELOPMENT

Regardless of treatment site and modality, radiation dose is often only limited by the dose constraints of the surrounding organs at risk. On account of the intimate association between the posterior prostate and the anterior wall of the rectum, significant interest has arisen in developing a means of physical separation between the two organs to reduce radiation-induced rectal toxicity. The posterior prostate and seminal vesicles are separated from the rectum by a fibromuscular structure known as the rectoprostatic (Denonvilliers') fascia (10). During radical prostatectomy, the tissue plane posterior to this fascia and anterior to the muscular wall of the rectum is dissected and exploitation of this potential space has proven attractive for creating artificial geometric separation between the prostate and rectum for patient's undergoing non-operative treatments such as cryoablation (11).

Multiple different space-creating solutions have been developed over the past 10-15 years, including an implanted bio-absorbable balloon, hyaluronic acid, human collagen, and polyethylene glycol (PEG) based hydrogel (12–14). Of these various methods, the hydrogel spacer is the most widely used and has the largest wealth of supporting clinical data. In fact, extensive experience with PEG based hydrogels in humans existed prior to the development of the rectal spacer – they have been used as sealants following vascular puncture, dural repair, and pleural decortication (15–17). After placement, the hydrogel remains solid for approximately 3 months before it begins to resorb, which typically occurs by 6 months. Complete resorption in 100% of patients is seen 9 months post-placement (18).

The most widely available rectal spacer formulation, marketed as SpaceOAR™, was initially developed by a start-up company called Augmenix and received Food and Drug Administration (FDA) approval in 2015 (19). Augmenix was subsequently purchased by Boston Scientific in 2018 (20). SpaceOAR Vue™ is a newer, similar PEG hydrogel with approximately 1% iodine, allowing improved visualization on CT-based imaging and accurate spacer delineation in patients with a contraindication to MRI (21).

HYDROGEL RECTAL SPACER IN PRACTICE AND CLINICAL DATA

A single, prospective, multi-center phase III randomized trial represents the highest level of evidence in support of rectal spacer application (18, 22–24). In this study, 222 patients with clinical T1 or T2 prostate cancer were randomized to dose escalated image-guided IMRT with or without hydrogel rectal spacer placement prior to treatment. All patients received intraprostatic fiducial markers for image-guided radiotherapy (IGRT) and were treated to a total dose of 79.2 Gy in 1.8 Gy daily fractions. Pelvic lymph nodes were not included in the clinical target volume (CTV), and seminal vesicles were included at the treating physician's discretion. Statistically significant dosimetric improvements were identified in the rectal volume receiving at least 50 Gy, 60 Gy, 70 Gy, and 80 Gy. With a median follow-up of three years, patients who received a rectal spacer experienced a significantly lower incidence of grade 1 and grade 2 rectal toxicity, as well as grade 1 urinary toxicity (22). Patient reported QoL outcomes were also better in those patients with a rectal spacer, and secondary analysis suggested improvements in long-term sexual function as well – hypothetically due to lower dose to other OARs such as the penile bulb made feasible by easier attainment of rectal constraints (23).

Multiple other non-randomized studies have been performed which demonstrate the dosimetric and clinical benefits to hydrogel rectal spacer placement. Beyond improving clinical outcomes for patients treated with conventionally fractionated radiotherapy (e.g., 79.2 Gy in 44 fractions) or moderately hypofractionated treatment (e.g., 60 Gy in 20 fractions), there is considerable interest in utilizing the technology to allow for greater dose escalation, particularly in patients treated with SBRT. Although SBRT for patients with low- and intermediate-risk disease typically experience low rates of late toxicity with typical dosing (35 – 36.25 Gy in 5 fractions) (25), substantial rectal toxicity has been reported in patients treated with more aggressive regimens. For instance, in one phase II dose escalation study from the University of Texas – Southwestern, patients received escalating doses up to 50 Gy in 5 fractions, with relatively high rates of severe toxicity in this cohort (e.g. rectourethral fistula) including 5 patients who required colostomy (26, 27). Interestingly, 5 year biochemical disease control and distant metastasis free survival were 98.6% and 100%, respectively suggesting a benefit to dose escalation (28). Furthermore, the excellent long-term toxicity outcomes reported in patients treated with more typical SBRT dose regimens are achieved by maintaining strict rectal dose constraints, often at the cost of tight posterior margins and potential underdosing of the prostatic peripheral zone (29, 30) (**Figure 1**). These tight posterior margins (< 1-2 mm) may only be feasible with fastidious motion management (31).

Improvements in target volume coverage as a result of spacer placement can be difficult to identify using standard instruments for plan evaluation in the clinical setting (32). Traditional dose-volume histogram (DVH) analysis lacks any positional data (33), and consequently it is an imprecise instrument to identify risk of recurrence when small portions of the prostate are underdosed. For example, the peripheral zone is the most common site of origin with the prostate gland for cancer development (34), and inadequate dose in small portions of this volume have been associated with increased risk of recurrence (35).

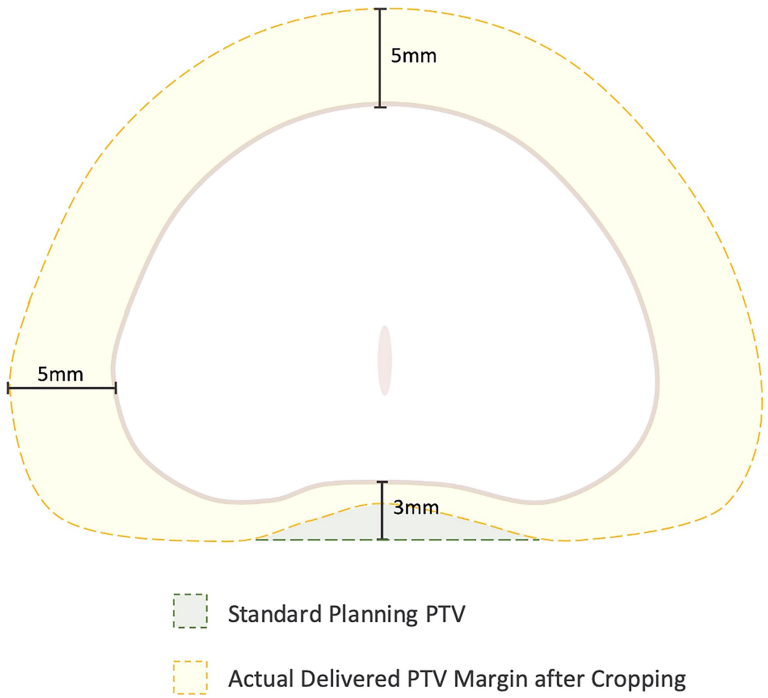

FIGURE 1 | Cropping of the Planning Target Volume (PTV) secondary to stringent rectal dose constraints. In general, the PTV is formed by expanding the prostate volume 3 mm posteriorly and 5 mm in all other dimensions. However, to achieve rectal dose constraints, the posterior margin is commonly cropped out of the rectum leading to a "true" posterior margin on such plans closer to 1-2 mm.

RATIONALE FOR UTILIZING HYDROGEL RECTAL SPACERS FOR PROSTATE SBRT

A recent randomized trial (FLAME) examined patients treated with conventional radiation (77 Gy in 2.2 Gy fractions) while using a simultaneous integrated boost (SIB) to deliver up to 95 Gy to an MRI-defined visible intraprostatic lesion (36) (**Figure 2**). There was a seven percent absolute improvement in biochemical disease-free survival (bDFS) at 5 years, without statistically significant changes in late toxicity and health-related QoL. However, standard dose constraints in this study were strictly enforced, and the mean dose delivered to the MRI-defined GTV (without PTV expansion) was lower at 91.9 Gy (37) (**Figure 3**). Given that higher GTV dose predicted increased 7-year biochemical disease-free survival (bDFS), it is reasonable to hypothesize that this benefit might have been greater with more comprehensive target coverage (**Figure 3**). In a follow-up phase II trial (hypo-FLAME), patients received SBRT (35 Gy in 5 fractions) with an SIB up to 50 Gy (38). While this approach was also well tolerated with low rates of late gastrointestinal and genitourinary toxicity, MRI-defined lesion coverage was even more difficult to achieve, with a median D99% of 40.3 Gy in this cohort. These doses may be more readily achievable with a well-placed rectal spacer (**Figure 4**).

In patients treated with SBRT, the use of a rectal spacer has demonstrated improvements in rectoprostatic separation (1.1 cm mean displacement), reduction of moderate and high rectal doses when tight PTV margins are utilized, and improvement of target volume coverage (39). Further, this displacement may lead to clinically reduced GI toxicity (40). Additionally, results from a recent prostate SBRT Phase I dose escalation study showed improved rates of pathological tumor clearance observed with higher doses (41). Preliminary data from the same group suggest that dose escalation may be even more important in unfavorable risk patients with higher tumor burdens (42). These data are supported by a recent tumor control probability (TCP) analysis that demonstrated higher doses are required to achieve a TCP of 95% in high risk patients (43). Early data from high risk patients suggest that 40 Gy in 5 fractions may improve bDFS at the cost of increased rectal toxicity when SBRT is performed without the use of a rectal spacer (44). A recent multi-institutional study of dose-escalated SBRT to 45 Gy in 5 fractions did in fact show >80% reduction in visualized rectal ulceration compared to previously observed rates in a similar patient cohort with the use of hydrogel Space OAR (45).

These studies indicate that dose escalation can produce meaningful clinical benefits for prostate cancer patients, albeit with an associated increased risk of severe long-term toxicity. While cautious planning can effectively mitigate these risks, this strategy requires sacrificing target coverage objectives and potentially abrogating or blunting the positive effects of escalation. One such approach is to deliver a moderate level of dose escalation to the entire prostate with ablative SBRT doses to

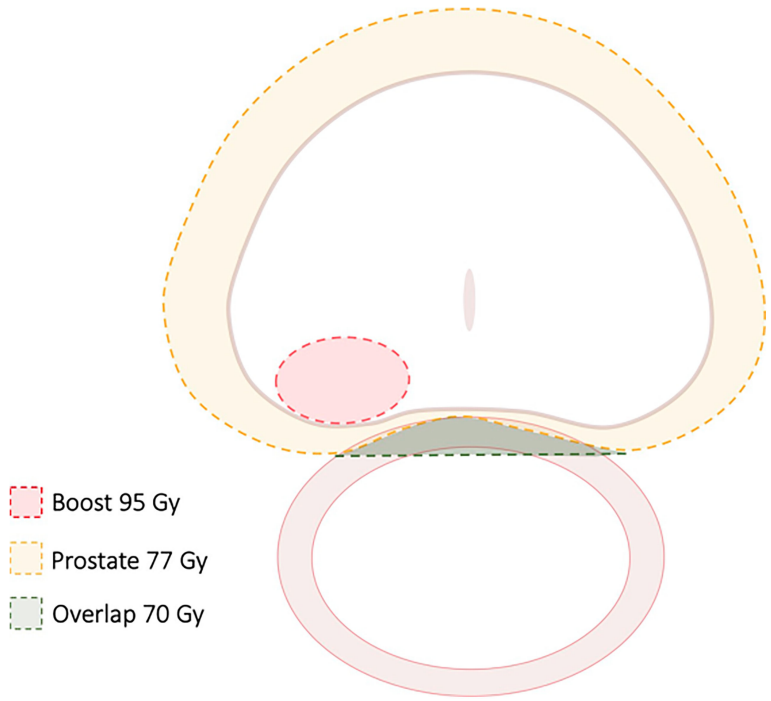

FIGURE 2 | Treatment Guidelines for FLAME study. In this randomized study of focal dose escalation, in the experimental arm patients received 77 Gy to the PTV (70 Gy where there was overlap with the rectum) and 95 Gy to the MRI-defined GTV in 35 fractions using a simultaneous integrated boost.

suspected regions of highest-grade disease. Investigators on the CK-DESPOT study deliver 40 Gy in 5 fractions to the entire prostate while delivering 45-50 Gy to PI-RADS 4-5 nodules (**Figure 4**) (46). At a median follow-up of 18 months, no grade >2 GI toxicity has been recorded. (O. Obayomi-Davies, Personal Communication, January 2022)

Moreover, even patients undergoing conventionally-dosed radiotherapy for localized prostate cancer benefit from placement of a hydrogel rectal spacer. As discussed previously, rectal spacers reduce GI toxicity and maintain bowel quality of life following standard dose IMRT, and these benefits may be markedly more pronounced in patients at increased risk for high grade toxicity including those with inflammatory bowel disease on anticoagulants, though institutional reports suggest acceptable toxicity in these populations with standard dose SBRT (47–49). Taken together, these data strongly suggest a clear use for hydrogel spacers to decrease toxicity, improve target coverage, and achieve safer, more comprehensive dose escalation.

RATIONALE FOR UTILIZING IODINATED HYDROGEL RECTAL SPACERS FOR PROSTATE SBRT

One major downside to the first generation rectal spacer is the similar radiodensities of the hydrogel and soft tissues such as the prostate and rectum. Consequently, these rectal spacers are difficult to visualize on CT scans, which can make accurate contouring challenging. For optimal delineation, a treatment planning MRI is required, but image registration and fusion is inherently inaccurate, leading to uncertainties in the gel interface with the prostate and rectum. This may lead to inaccuracies in target and OAR dose calculations. The importance of these inaccuracies is exacerbated when the prescription dose is escalated. Iodinated rectal spacers are readily visible on CT scan without altering the MRI appearance, thereby improving delineation of target volumes and OARs, which in turn helps ensure accurate dose delivery.

CONTRAINDICATIONS TO HYDROGEL RECTAL SPACER PLACEMENT

Per the manufacturer's labeling, there are no explicit contraindications to hydrogel rectal spacer placement for either the SpaceOAR or the SpaceOAR Vue hydrogels. While this may be accurate from a safety perspective, debate rages within the radiation oncology community as to whether any oncologic contraindications to treatment exist. Some practitioners advocate caution in patients with radiographic evidence of posterior extracapsular extension (ECE), while most do not consider posterior capsule abutment a contraindication (**Figure 5**). Due to these concerns, patients with more than 50% core positivity or radiographic ECE were excluded from the phase III rectal spacer trial (18). Theoretically, placing a rectal spacer in this situation might inadvertently "push" prostate cancer cells towards the

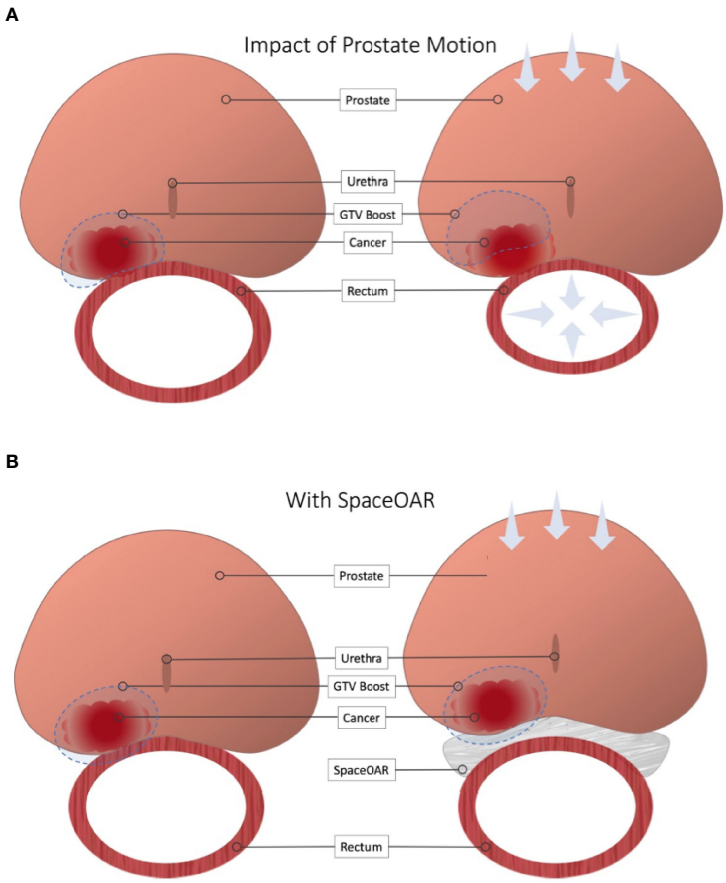

FIGURE 3 | Impact of Rectal Spacer in Focal Dose Escalation. **(A)** Close proximity to the rectal wall can necessitate compromises in order to meet OAR constraints. Furthermore, minimal or omitted boost margins mean slight changes in local anatomy can cause a geographic miss. **(B)** Placement of a rectal spacer allows for greater boost margins and safer dose escalation.

rectum and beyond the area of high-dose radiotherapy, leading to higher rates of local failure.

Another potential concern with the SpaceOAR Vue system is the presence of iodine within the hydrogel and its safety in patients with an allergy to iodinated-contrast media. Per the manufacturer's labeling "the use of this product in patients with documented iodine sensitivities or allergies has not been extensively studied. The risks and benefits of the decision to use in patients with a documented iodine allergy should be carefully considered on a case-by-case basis" (50). However, as the iodine molecules are covalently bonded to the hydrogel preventing their release into systemic circulation, the spacer should theoretically be well tolerated even in those patients with a true contrast allergy (21).

HYDROGEL RECTAL SPACER PLACEMENT PROCEDURE

Accurate placement is critical to maximize the benefits afforded by the hydrogel rectal spacer, and this is especially true when employing dose escalated regimens (51). Typically placement is performed at the same time as fiducial marker placement (or brachytherapy), adding minimal procedural time (52). The patient is positioned in the usual dorsal lithotomy position as he would be for a transperineal biopsy, fiducial placement, or brachytherapy procedure. Choice of anesthesia is at the discretion of the treating physician and anesthesiology team, but successful spacer placement has been performed under local anesthesia, light sedation, and general anesthesia. As the procedure is short and involves only a single transperineal needle, patients who undergo placement with only local anesthesia typically report minimal pain or discomfort (53). Similar to transperineal biopsy or brachytherapy, the risk of infection is much lower than transrectal procedures; while many centers employ prophylactic antibiotics others do not (54).

Once the patient is positioned, the ultrasound probe is placed within the rectum to visualize the prostate. Other procedures, such as fiducial placement or brachytherapy, should be performed prior to spacer placement as the gel can interfere with visualization of the gland on ultrasound. Placement of the needle in the correct plane and adequate hydrodissection are critical components of the procedure to ensure a high-quality spacer implant for optimal dosimetry (55). An 18G needle is placed bevel-down in the

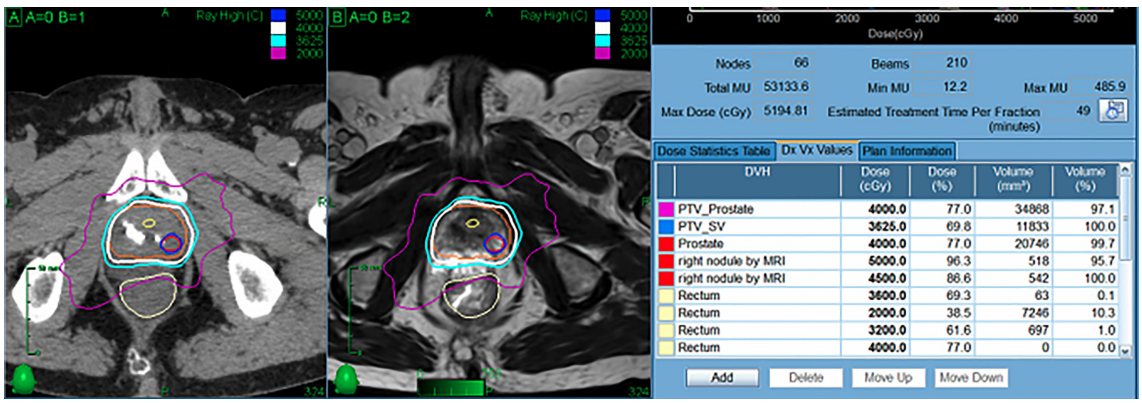

FIGURE 4 | Representative SBRT patient treated with focal dose escalation and hydrogel rectal spacer. The patient received 40 Gy in 5 fractions to the prostate with an integrated boost to 50 Gy while maintaining excellent OAR dosimetry.

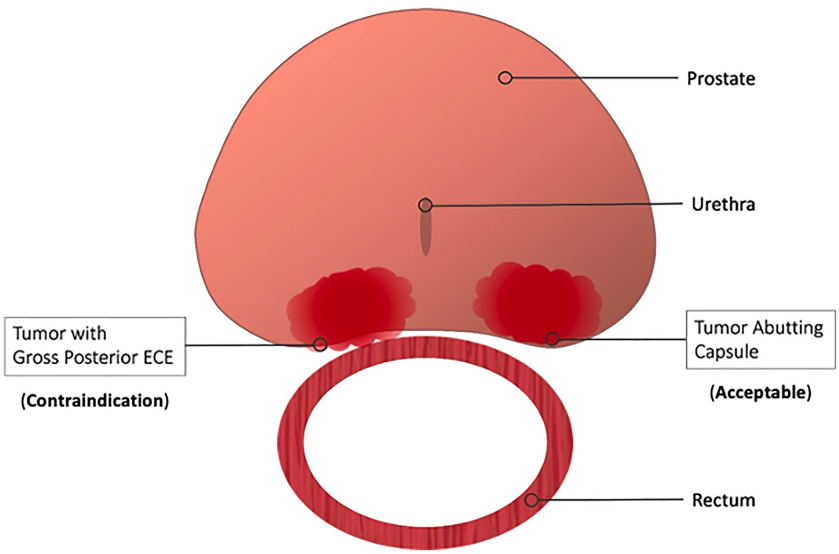

FIGURE 5 | Contraindications to Hydrogel Rectal Spacer Placement. Most practitioners consider gross or radiographic posterior ECE a contraindication to spacer placement. Contrarily, spacer placement is acceptable in those patients with capsular abutment only.

midline perineum approximately 2 cm above the TRUS probe angled slightly (~15 degrees) posteriorly. The sagittal viewing plane is used as the needle is advanced to the mid-gland in the space anterior to the rectum and posterior to the rectoprostatic fascia. The axial viewing plane should be utilized to confirm midline position of the needle, with slight needle movements to ensure the needle has not been introduced into the anterior rectal wall. A small "puff" of saline is then employed to confirm placement prior to full hydrodissection of the space with approximately 10 mL of saline. Prior to proceeding with hydrogel placement, a small amount of fluid should be aspirated to ensure the needle is not placed intravascularly.

The saline syringe is then removed, and hydrogel applicator attached to the needle. The hydrogel is then slowly injected into the hydrodissected space. For placement of the original SpaceOAR, the hydrogel is injected over 10 seconds, while the radio-opaque SpaceOAR Vue is injected over approximately 20 seconds. Once injection is started, it is critical that it be done in a continuous, smooth motion without stops to prevent polymerization and clogging within the needle. The needle is then removed, completing the procedure.

PROCEDURE-RELATED RISKS OF RECTAL SPACER PLACEMENT

In general, the procedure is well tolerated with limited risk of adverse effects. Some patients have reported self-limited

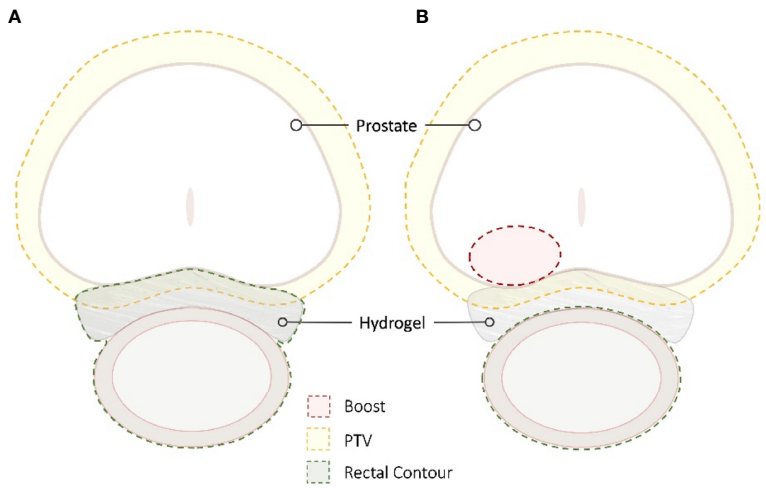

FIGURE 6 | SBRT Treatment Planning. The radiation sensitivity of the rectum in patients with inflammatory bowel disease is unknown; the goal is to decrease the rectal dose to as low as reasonably achievable (ALARA). For many patients, the hydrogel is incorporated into the rectal contour to maximize rectal spacing **(A)**. In other patients, the spacer is not incorporated to allow for dose escalation while maintaining strict rectal dose constraints **(B)**.

discomfort and rectal tenesmus following the procedure, though this appears to be relatively uncommon (18). Though cases of inadvertent injection of hydrogel into the rectal wall or bladder have been reported, the majority of these resolve with conservative management and time, which allows the hyrdrogel to slowly resorb (56, 57). Careful review of treatment planning imaging is required prior to radiotherapy to ensure appropriate spacer position.

Nonetheless, some practitioners do advocate caution before routine adoption of a hydrogel rectal spacer in all prostate cancer patients slated for radiotherapy (58). Common counter-arguments include a failure in the phase III trial to meet the primary safety endpoint (grade 1+ rectal or procedural adverse events in the first 6 months: 34·2% *vs* 31·5%, p=0.7), although secondary analyses demonstrated significant benefits in both practitioner-graded toxicities and patient-reported outcomes. Additionally, a small study of the FDA Manufacturer and User Facility Device (MAUDE) database reported severe complications in a small number of patients, 11 of whom required surgical intervention, following hydrogel rectal spacer placement (59). These complications included perineal abscess requiring drainage, rectourethral fistula, proctitis requiring colostomy, and severe urosepsis necessitating ICU level care. Two patients died following spacer placement, although in one case the cause of death was uncertain and in the other it was unrelated to the rectal spacer. Ultimately, the quality of spacer placement, benefit to the patient and potential risks are dependent on the individual provider's ability and experience, underscoring the importance of proper training and certification for providers who wish to place rectal spacers in their patients. Finally, controversy and uncertainty persist regarding the cost-effectiveness of the procedure (60).

ASSESSMENT OF SPACER PLACEMENT AND PLANNING CONSIDERATIONS

Given the limitations of trans-rectal ultrasound image quality, optimal assessment of rectal spacer placement is typically performed at the time of radiotherapy simulation. In addition to typical CT-based simulation, a dedicated treatment planning MR scan is preferred for optimal evaluation, although the advent of an iodinated, radio-opaque spacer has made treatment possible for those patients with a contraindication (21).

In the phase III spacer trial, the mean peri-rectal distance was 1.6 mm prior to placement and 12.6 mm following hydrogel application, consistent with other institutional and dosimetric studies (18). In this patient population, a secondary, *post-hoc* semi-qualitative analysis of hydrogel symmetry demonstrated that approximately 50% of patients had fully symmetrical spacer placement all levels assessed, though only 32% of patients had hydrogel present at both the base and the apex (61). Nonetheless, a 25% reduction in the rectal volume receiving at least 70 Gy (V70) with the addition of a rectal spacer was achieved in greater than 97% of patients, suggesting that the overwhelming majority of patients experience a clinical benefit even in the face of suboptimal spacer placement. Multiple other non-randomized studies have recapitulated similar results in large patient populations, and there is some evidence to suggest a learning curve effect with improvements in placement quality over time (62), consistent with similar trends observed in patients undergoing brachytherapy (63).

Concerns have arisen regarding the clinical implications of rectal wall infiltration (RWI) as identified on treatment planning MRIs. Six percent of patients on the aforementioned phase III study were noted to have RWI of the hydrogel, though more than half of these cases consisted of "small, discrete areas" of

infiltration, while only a single patient was noted to have radiographic involvement of more than 25% of the rectal wall circumference (61). Fortunately, there was no identifiable increase in toxicity in patients with RWI, and the one patient with substantial RWI experienced no procedural, acute, or late toxicity. Nonetheless, RWI should be treated with a high degree of caution given the possibility of catastrophic toxicity if it is not identified prior to definitive treatment. In one case report of a patient undergoing dose-escalated SBRT (45 Gy in 5 fractions) with a rectal spacer, RWI was not identified during treatment planning, and the patient ultimately required abdomino-perineal resection (APR), cystoprostatectomy, and ileal conduit placement secondary to complications from a large recto-urethral fistula (51). In retrospect, hydrogel was identified within the submucosa of the rectum, secondary to delamination and discontinuity of the muscularis propria. The authors of this report suggest careful evaluation of planning MRI scans for RWI and referral for endoscopic evaluation in cases of concern, with a low threshold to delay treatment until spacer resorption if any abnormalities are noted. Thankfully, while this case highlights the need for careful radiographic assessment of spacer placement, it also represents an extremely rare outlier from an otherwise safe procedure.

The optimal rectal dose constraints for patients with a rectal spacer undergoing conventionally fractionated radiotherapy, moderately hypofractionated radiotherapy, or SBRT are currently unknown. At a minimum, typical dose constraints used in non-spacer patients should be easily achievable with placement of a spacer (21), and should ideally allow for safer dose escalation (64). One frequently employed strategy to aggressively manage rectal dose is to contour the spacer itself as part of the rectal contour, although retrospective data suggest that this approach may not yield optimal treatment plans (65) (**Figure 6**).

CONCLUSIONS AND FUTURE DIRECTIONS

With the results of the recently published HYPO-RT-PC trial demonstrating excellent outcomes for prostate cancer patients treated with extreme hypofractionation as well as the disincentive to longer treatment courses predicted with implementation of the forthcoming radiation oncology payment model, utilization of SBRT is expected to increase dramatically in the coming decade (66–68). However, despite its recent adoption as an acceptable front-line treatment in the National Cancer Consensus Network (NCCN) guidelines (69), optimal dose constraints remain nebulous, especially as dose escalation becomes more widespread. Yet even with this uncertainty, placement of a hydrogel rectal spacer produces dosimetric improvements as well as clinically significant decreases in toxicity that may make it indispensable in treatment of prostate cancer patients, particularly those with high-risk disease.

Multiple forthcoming trials seek to refine dose-escalated and hypofractionated radiation schema, and the use of a hydrogel rectal spacer will be essential in many of these studies. For example, the ongoing SABRE (Effectiveness of the SpaceOAR Vue System in Subjects with Prostate Cancer being Treated with Stereotactic Body Radiotherapy) is a multi-center, prospective, randomized study which will evaluate the role of the SpaceOAR Vue in patients with intermediate risk prostate cancer (70). Patients on this study will receive dose-escalated SBRT (40 Gy in 5 fractions) with the primary outcome measure of a reduction in late GI toxicity (Grade 2+ between 3- and 24-months post-treatment).

In summary, placement of a hydrogel rectal spacer is a low-risk procedure that produces meaningful clinical benefits for patients undergoing definitive radiotherapy for localized prostate cancer. Dosimetric improvements are noted in the vast majority of cases, even when rectal spacer placement is suboptimal, though careful assessment of hydrogel placement is required for each patient. Complications associated with spacer placement; especially severe adverse events are rare. Ongoing studies will help to clarify the potential benefits in patients undergoing dose-escalated and hypofractionated regimens.

AUTHOR CONTRIBUTIONS

MR wrote the initial draft of the manuscript. MCr and OO-D created the figures. All authors participated in editing and review of the manuscript. All authors contributed to the article and approved the submitted version.

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A Prospective Study of High Dose-Rate Brachytherapy or Stereotactic Body Radiotherapy of Intra-Prostatic Recurrence: Toxicity and Long Term Clinical Outcome

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Background: Up to half of patients with localized prostate cancer experience biochemical relapse within 10 years after definitive radiotherapy. The aim of this prospective study was to investigate the toxicity, dose to the organs at risk (OARs), and efficacy of dose-intensified focal salvage radiotherapy.

Methods and Material: Thirty-three patients (median age 68.8 years) with histologically confirmed relapse after primary definitive radiotherapy were enrolled between 2012 and 2019. No patients had metastases at imaging or in bone marrow aspiration. Twenty-three patients were treated with high dose-rate brachytherapy to the recurrent tumor, defined at multiparametric MRI, with 3 fractions of 10 Gy with two weeks interval, and 10 patients by stereotactic body radiotherapy with 35 Gy to the local recurrence and 25 Gy to the whole prostate in 5 fractions. We used the RTOG-scoring system to grade genitourinary (GU) and gastrointestinal toxicity (GI) at three months (acute), and at 12, 24, and 36 months (late). Dose-volume histogram parameters to the local recurrence and the OARs were obtained and 2 Gy equivalent (EQD2) total dose was calculated using the linear-quadratic model with $\alpha/\beta = 3$ Gy. Efficacy was assessed by the progression-free interval and overall survival.

Results: Median follow-up time was 81 months (range 21–115). The cumulative moderate to severe GI and GU toxicities were 3.0% (1/33) and 15.2% (5/33). Six patients had grade 1 acute GI toxicity, none had grade 2 or 3. One patient had grade 3 acute GU toxicity, two had grade 2, and fourteen had grade 1. One patient had late GI toxicity grade 2 and eight had grade 1. Four patients had late GU toxicity grade 2 and eight had grade 1. No patients had grade 3 late toxicity. The mean total D90 to the recurrent tumor was 77.7 ± 17.0 Gy. The mean total rectum D2cc was 17.0 ± 7.9 Gy and the mean

total urethra D0.1cc was 29.1 ± 8.2 Gy. Twenty-eight patients had re-irradiation without androgen deprivation therapy (ADT). Nine of these are still relapse-free and 10 had a recurrence-free interval longer than 2 years.

Conclusion: The toxicity of salvage radiotherapy was mild to moderate. One-third of the patients achieved long-term stable disease without ADT and one-third had a recurrence-free interval longer than 2 years. Some patients progressed rapidly and probably did not benefit from re-irradiation.

Keywords: prostatic neoplasms, re-irradiation, image-guided radiotherapy, radiation dose hypofractionation, toxicity, treatment outcome

INTRODUCTION

The primary treatment options for localized prostate cancer are radiotherapy and radical prostatectomy. Biochemical relapse occurs in up to half of the patients (1–5). In contrast to the management of recurrence after prostatectomy, optimal management of recurrence after radiotherapy remains unclear due to the lack of large prospective studies in this setting (6). Even the management of a true local recurrence after definitive radiotherapy is controversial and consensus recommendation is limited (6).

Androgen deprivation therapy (ADT) is often used for radio-recurrence, but is non-curative and is associated with impaired quality of life. Local treatment could postpone the onset of ADT and thereby the development of castration-resistant disease, and potentially cure the patient (7).

Salvage prostatectomy has the longest history of use for local treatment of intra-prostatic recurrence but suffers from significant side effects. Re-irradiation has been considered to induce serious toxicity. However, more focal radiotherapies such as brachytherapy (BT) and stereotactic body radiotherapy (SBRT) are less invasive compared to prostatectomy and may circumvent the problem of overdosage to critical structures (6). This can be achieved by applying inhomogeneous dose patches that lower the dose to the whole gland and preferably re-irradiate the local recurrent tumor only. One major concern of applying salvage irradiation is that the tolerance dose to the urothelium and rectal mucosa may limit the sufficient dose delivered to the tumor. To avoid unacceptable toxicity one can use technical strategies that spare the urethra and the rectum.

A recent Delphi consensus paper investigated the expert opinion on salvage re-irradiation and reported increasing interest (8). A recent large meta-analysis reported that the genitourinary toxicity rate for re-irradiation, particularly for SBRT and high dose-rate (HDR)-BT, were significantly less than those reported after salvage prostatectomy, high-intensity focused ultrasound (HIFU), and cryotherapy (6, 9). To establish re-irradiation as a treatment option results from prospective studies with sufficient long follow-up is highly warranted (6, 7, 9–11).

Herein we report prospectively recorded acute and late gastrointestinal (GI) and genitourinary (GU) toxicity and long-term clinical outcome after re-irradiation with HDR-BT and SBRT.

MATERIALS AND METHODS

Study Population

The Regional Committee for Medical Research Ethics southeast Norway approved this prospective study of focal salvage re-irradiation (2011/954) and all patients provided written informed consent.

The main inclusion criteria were local recurrence after primary curative intended external beam radiotherapy (EBRT), defined as prostate-specific antigen (PSA) >nadir + 2 ng/ml, and no metastases neither at imaging nor in bone marrow aspiration samples. Further inclusion criteria were PSA <10 ng/ml, PSA doubling time >6 months, more than 2 years recurrence-free interval since primary radiotherapy, and ECOG 0–1 with a life expectancy >5 years.

Between 2012 and 2019, we included 33 patients previously treated with conformal RT of 70–78 Gy to the prostate and seminal vesicles (**Table 1**). At primary treatment, the patients were diagnosed with intermediate (n = 13) or high-risk disease (n = 20) according to the D'Amico risk classification system (12). At recurrence, all patients had multiparametric MRI of the pelvis and lower lumbar spine, 24 had FACBC PET/CT (trans-1-amino-3-^{18}F-fluorocyclobutanecarboxylic-acid positron emission tomography/computed tomography) and two had PSMA PET/CT (prostate-specific membrane antigen) to localize the recurrence and exclude metastatic disease. Intra-prostatic tumor recurrence was histologically verified in all but one patient.

The median age of the study population was 69.8 years (interquartile range (IQR) 6.8), and the median PSA was 4.1 ng/ml (IQR 3.8). The median time from primary radiotherapy to biochemical recurrence was 73.0 months (IQR 52.5). Twenty-eight patients were eugonadal at salvage re-irradiation while five patients received either ongoing or concomitant ADT (**Figure 1**). The first 23 patients received HDR-BT, and the last 10 patients received SBRT. A detailed overview of the study population and treatment is shown in **Table 1**.

TABLE 1 | Detailed overview of patient characteristics and treatment.

ID	Primary diagnosis				Primary treatment		Primary RT to PSA recurrence (months)	Recurrence to re-irradiation (months)	At salvage re-irradiation				Salvage re-irradiation	
	GS	T	iPSA (ng/ml)	D´Amico risk classification*	RT	ADT			Age (years)	PSA (ng/ml)	IPSS	Comorbidity	RT and dose (Gy)	ADT
1	4 + 3	T2	14.7	Intermediate	74	No	50	23	71	6.4	12	Hypertension	HDR-BT 3 × 10 Gy	No
2	3 + 4	T2	8.0	Intermediate	74	No	52	9	66	4.2	4	Other cancer	HDR-BT 3 × 10 Gy	No
3	3 + 4	T2	10	Intermediate	74	>1 yr.	77	6	68	2.8	4	None	HDR-BT 3 × 10 Gy	No
4	3 + 4	T1c	22	High	74	3 months	43	17	65	3.0	20	Arrhythmia	HDR-BT 3 × 10 Gy	No
5	4 + 5	T3b	59	High	74	>1 yr.	60	9	58	2.3	12	Diabetes	HDR-BT 3 × 10 Gy	No
6	3 + 3	T1c	42	High	74	>1 yr.	101	6	66	4.0	6	None	HDR-BT 3 × 10 Gy	No
7	4 + 3	T3b	66	High	74	>1 yr.	42	4	68	3.8	3	Cerebral insult	HDR-BT 3 × 10 Gy	No
8	2 + 3	T1c	11.3	Intermediate	74	No	152	3	67	5.5	3	Hypertension	HDR-BT 3 × 10 Gy	No
9	4 + 5	T3b	58	High	74	>1 yr.	29	1	66	3.3	0	Other cancer	HDR-BT 3 × 10 Gy	No
10	3 + 3	T2	18	Intermediate	74	No	126	4	65	4.5	NA	None	HDR-BT 3 × 10 Gy	No
11	5 + 4	T3b	39	High	74	>1 yr.	35	4	70	7.9	6	None	HDR-BT 3 × 10 Gy	Short
12	4 + 3	T3a	45	High	74	>1 yr.	73	8	68	4.5	4	None	HDR-BT 3 × 10 Gy	No
13	3 + 4	T2	13	Intermediate	74	No	114	10	64	6.5	NA	Hypertension	HDR-BT 3 × 10 Gy	No
14	3 + 3	T1c	12	Intermediate	74	6 months	143	9	70	7.2	1	Diabetes	HDR-BT 3 × 10 Gy	No
15	3 + 4	T2a	4.5	Intermediate	74	6 months	63 [3]	4	68	1.6	5	Hypertension	HDR-BT 3 × 10 Gy	No
16	3 + 4	T3a	28	High	74	>1 yr.	95	15	63	8.5	2	Hypertension	HDR-BT 3 × 10 Gy	No
17	3 + 4	T2	30	High	70	No	77	18	72	9.6	5	Arrhythmia	HDR-BT 3 × 10 Gy	No
18	4 + 4	T3b	17	High	74	>1 yr.	64	3	75	6.4	7	Diabetes	HDR-BT 3 × 10 Gy	No
19	3 + 4	T2	20	Intermediate	70	>1 yr.	41	7	70	4.2	1	Hypertension	HDR-BT 3 × 10 Gy	No
20	3 + 3	T1c	10	Intermediate	74	No	76	7	73	6.5	13	Hypertension	HDR-BT 3 × 10 Gy	No
21	3 + 4	T3a	5.4	High	74	>1 yr.	113	12	72	4.7	5	Arrhythmia	HDR-BT 3 × 10 Gy	No
22	3 + 3	T2	15.5	Intermediate	74	No	122	4	74	4.0	9	Hypertension	HDR-BT 3 × 10 Gy	3 months
23	4 + 4	T3a	9.4	High	74	>1 yr.	62	6	77	4.1	2	Hypertension	HDR-BT 3 × 10 Gy	3 months
24	4 + 4	T3a	17	High	74	>1 yr.	72	6	69	5.0	2	None	SBRT 7(5) Gy × 5	No
25	3 + 4	T2	8.0	Intermediate	78	6 months	84	8	73	3.5	20	Diabetes	SBRT 7(5) Gy × 5	No
26	3 + 5	T3a	70	High	74	>1 yr.	122	2	74	7.8	2	None	SBRT 7(5) Gy × 5	No
27	3 + 4	T3a	6.4	High	70	6 months	111	4	74	1.9	NA	Hypertension	SBRT 7(5) Gy × 5	No
28	3 + 4	T2	44	High	74	>1 yr.	65 [3]	7	78	2.5	2	Hypertension	SBRT 7(5) Gy × 5	No
29	4 + 4	T3b	7.6	High	74	>1 yr.	80	5	67	0.83 [1]	5	Other cancer	SBRT 5 Gy × 6	>1 yr.

(Continued)

TABLE 1 | Continued

ID	Primary diagnosis				Primary treatment		Primary RT to PSA recurrence (months)	Recurrence to re-irradiation (months)	At salvage re-irradiation				Salvage re-irradiation	
	GS	T	iPSA (ng/ml)	D´Amico risk classification*	RT	ADT			Age (years)	PSA (ng/ml)	IPSS	Comorbidity	RT and dose (Gy)	ADT
30	4 + 3	T3b	29	High	74	>1 yr.	85	4	75	0.31 [2]	3	None	SBRT 7(5) Gy × 5	6 months
31	4 + 3	T3a	10	High	74	>1 yr.	55	3	67	2.8	11	Arrhythmia	SBRT 7(5) Gy × 5	No
32	4 + 3	T2	8	Intermediate	74	>1 yr.	61	6	72	3.9	2	Diabetes	SBRT 5 Gy × 5 [4]	No
33	4 + 4	T3b	37	High	74	>1 yr.	52	15	76	4.6	12	None	SBRT 7(5) Gy × 5	No

*D'Amico et al. (12).
[1]Had five months of ADT before SBRT.
[2]Had two months of ADT before SBRT.
[3]Recurrence based on MRI and biopsy, not PSA. Date of recurrence is the biopsy date.
[4]Received 5 fractions without a boost to the recurrent tumor.
GS, Gleason score; T, T-stage; PSA, Prostate specific antigen; iPSA, initial PSA; ADT, androgen deprivation treatment; IPSS, The International Prostate Symptom Score; RT, radiotherapy; SBRT, stereotactic body radiotherapy; HDR-BT, high dose-rate brachytherapy; NA, not applicable.

Imaging

Multiparametric MRI prior to salvage re-irradiation included morphological T2-weighted, diffusion-weighted (DW), and dynamic contrast enhanced (DCE) sequences of the prostate. The acquisition protocol is described in detail in Tulipan et al. (13). The technical standard of the imaging protocol was in accordance with current technical requirements for prostate MRI (14). One radiologist with more than nine years of experience in prostate cancer MRI (KH) prospectively interpreted the examinations for study inclusion and biopsy guidance. The other radiologist (UR) with four years of experience retrospectively reviewed all the MRI examinations both from primary diagnosis, if available, and from the time of recurrence, with the purpose of comparing the site of the primary and recurrent tumor.

Planning and Treatment Techniques

Twenty-three patients received mainly focal HDR-BT in three fractions every second week using the microSelectron HDR 192Ir source (Nucletron B.V., Veenendaal, The Netherlands). The planning aim was 10 Gy to the gross tumor volume (GTV), which for the majority of the patients (n = 20) was defined as the recurrent tumor identified at imaging (**Figure 2**). The HDR-BT procedure has previously been described in detail in Raabe et al. (15). In short, the patients were under general anesthesia and in the lithotomy position. A Foley catheter was placed in the bladder. Guided by transrectal ultrasound (US) the needles were inserted into the gross tumor volume (GTV) through the perineum. The recurrent tumor, prostate gland, rectal wall, and the urethra (cylinder with a radius of 3 mm) were delineated by the oncologist on US images acquired both before and after needle insertion (**Figure 3**). The delineation of the recurrent tumor was guided by multiparametric MRI (**Figure 2**). Intra-operative treatment planning, namely, inverse plan optimization and consecutive graphical adjustments, was performed using Oncentra Prostate Vs.4.1.6 (Nucletron). Source positions 3 mm or closer to the urethra were not allowed to be used. Initial optimization settings and dose constraints are found in **Supplementary Tables 1–3**.

For patients 9, 11, and 23 (**Table 1**), the whole prostate gland, excluding the urethra, was defined as the GTV. For patient 23, the GTV included only the recurrent tumor on the two last fractions.

Ten patients received SBRT with 6MV flattening filter-free volumetric arc therapy (VMAT) delivered on a linear accelerator (Varian TrueBeam ™ STx, Varian Medical Systems, Palo Alto, USA). Fiducial gold markers implanted as strands along the urethra and as cubes in the prostate prior to treatment planning assisted the image-guided RT (daily cone-beam CT for target positioning and verification). The SBRT was delivered in five fractions as a simultaneous integrated boost with a planning aim of 35 Gy to the recurrent tumor and 25 Gy to the prostate gland (n = 8) or in six fractions with a planning aim of 30 Gy to the whole prostate gland (n = 1). One patient (patient 32) received only five fractions without an integrated boost to the tumor. The fractions were delivered every other day. The delineation of target volumes (recurrent tumor and/or prostate gland) and organs at risk (OARs) (urethra, bladder, rectum, anal canal, and femoral heads), and treatment planning was performed using Raystation 5 (RaySearch Laboratories, Stockholm, Sweden). An isotropic planning target volume (PTV) margin of 3 mm was used for both the recurrent tumor and the prostate. The treatment plans were optimized with a steep dose gradient to the urethra and normalized to a prescription volume that excluded the urethra with a margin of 3–5 mm. Clinical goals and dose constraints are found in **Supplementary Tables 4, 5**. Patient-specific quality assurance of the SBRT plans was performed prior to the onset of treatment using the ArcCheck® phantom (Sun Nuclear Corporation, Melbourne, USA).

Dose to 90% (D90) of the target volumes (recurrent tumor/prostate) were found from the dose volume histograms. Also, the minimum dose to the most exposed 2 and 0.1 cubic centimeter

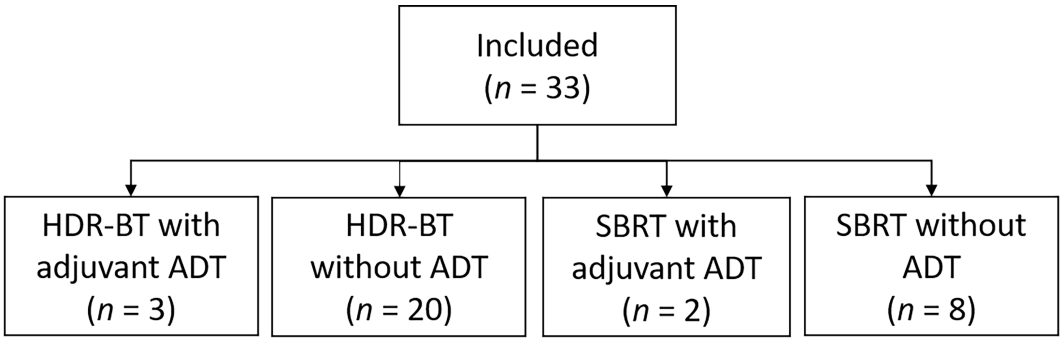

FIGURE 1 | Overview of the salvage treatment. HDR-BT, high dose-rate brachytherapy; ADT, androgen deprivation therapy; SBRT, stereotactic body radiotherapy.

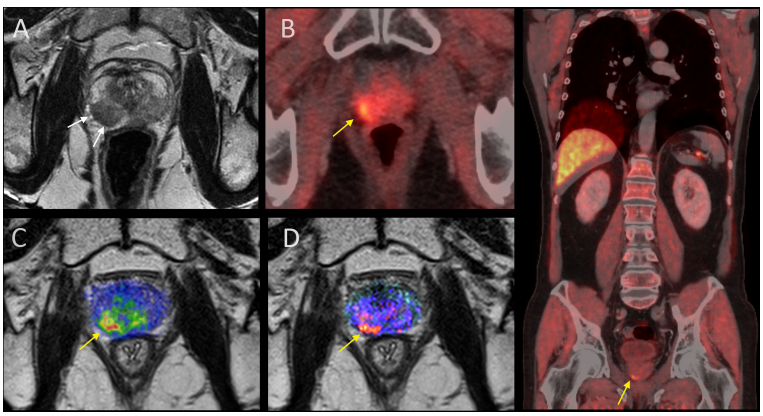

FIGURE 2 | Primary and radio-recurrent prostate cancer at imaging. **(A)** Primary tumor at T2W MRI (white arrows). **(B–D)** Recurrent tumor (yellow arrow) at FACBC PET/CT, diffusion weighting overlaid on T2W MRI, and dynamic contrast-enhanced MRI overlaid on T2W MRI. To the right: Whole-body FACBC PET/CT to prove true local recurrence only (yellow arrow).

(D2cc and D0.1cc) were recorded for the rectum and urethra, respectively. The linear-quadratic model was used to calculate 2 Gy equivalent (EQD2) total dose, assuming $\alpha/\beta = 3$ Gy for both the recurrent tumor/prostate and for the OARs.

Toxicity and Clinical Outcome

We used the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) (16) to grade gastrointestinal (GI) and genitourinary (GU) toxicity at three months (acute), and at 12, 24, and 36 months (late). RTOG-grading ceased if patients received additional treatment such as HIFU, prostatectomy, or chemotherapy.

Patients were followed every three months for the first two years, and every six months for the following years. The clinical outcome was measured as the recurrence-free interval from re-irradiation to the second recurrence, defined as PSA >2 ng/ml above nadir after salvage re-irradiation (8).

Data Analysis

Data are presented with descriptive statistics. We calculated Kaplan–Meier estimates for recurrence-free and overall survival after re-irradiation. To assess the association between dose and late toxicity, we selected the highest RTOG-scoring of the three reported late time points. We performed subgroup analyses to investigate parameters that could identify the patients who had the highest benefit from salvage re-irradiations. Data were analyzed and figures created using Prism 6 for Mac OS X version 6.0f (GraphPad Software Inc., San Diego, CA).

RESULTS

Toxicity

Figure 4 shows the course of RTOG-graded toxicity for each patient prior to, and 3, 12, 24, and 36 months after salvage re-irradiation. The cumulative moderate to severe GI and GU toxicities were 3.0% (1/33) and 15.2% (5/33). Before re-irradiation, 8 had grade 1 GI toxicity, and 7 had grade 1 GU toxicity. At 3 months, six patients had grade 1 acute GI toxicity while none had grade 2 or 3. Fourteen patients had grade 1 acute GU toxicity, two had grade 2, and one had grade 3. At later time points, eight patients had late GI toxicity grade 1, and one had

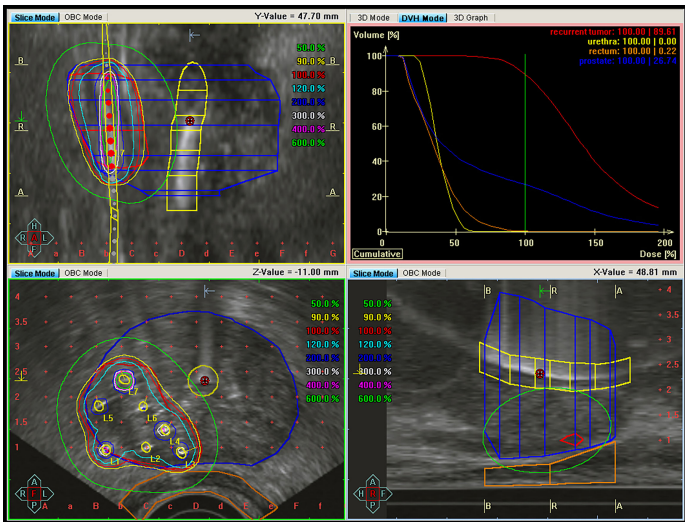

FIGURE 3 | Dose distribution for high dose-rate brachytherapy of the same patient as in **Figure 2** showing the coronal (upper left), transversal (lower left), and sagittal (lower right) plane. The recurrent tumor (red), prostate (blue), urethra (yellow), and rectum wall (brown) are delineated. Air-filled gel has been inserted in the urethra catheter to visualize the urethra in the ultrasound images. The dose-volume histograms (upper right quadrant) show the highly conformal dose distribution, sparing the rectum and urethra, achieved by brachytherapy.

grade 2. Eight had grade 1 late GU toxicity and four had grade 2. No patients had grade 3 late GI or GU toxicity.

Eight patients received additional treatment after re-irradiation. The remaining 25 patients had toxicity scored at 36 months. Compared to baseline, only two (patients 10 and 29) reported increased GI toxicity, and three (patients 5, 11, and 12) reported increased GU toxicity. Patient 18, who experienced severe toxicity, had poorly regulated diabetes.

The mean total D90 to the local recurrence was 77.7 ± 17.0 Gy. The mean total D2cc for the rectum was 17.0 Gy (SD 7.9), and the mean total D0.1cc for the urethra was 29.1 Gy (SD 8.2). Only the contribution from the re-irradiation is included in these figures. We found no association between doses to rectum and urethra from the re-irradiation, and toxicity (**Figure 5**).

Clinical Outcome

During the median follow-up after re-irradiation of 81 months (range 21–115), two patients died, one of prostate cancer and one of complications following aortic dissection (**Figure 6A**). For the entire cohort, the median biochemical progression-free survival after re-irradiation was 40 months. For the 22 patients who relapsed, the median time to secondary recurrence was 24 months (range 7–85). Data for individual patients are reported in **Figure 7**. Eleven patients, including the patient who died of complications, did not relapse, whereas 22 had a second recurrence, four within one year and six within the second year. Twelve patients had a recurrence-free interval longer than two years.

Twenty-eight patients (85%) had salvage radiotherapy without ADT. Nine of these 28 (32%) are still relapse-free, 10 (36%) had a recurrence-free interval longer than two years, and nine (32%) patients relapsed within the two years.

The clinical goal of re-irradiation is to eradicate the recurrent tumor and/or to postpone the onset of ADT. Some patients had a short recurrence-free interval after re-irradiation and probably limited clinical benefit. We sought to identify predictive parameters and hypothesized that less aggressive tumors would benefit the most. We therefore investigated whether the short time from primary radiotherapy to recurrence and low ISUP (International Society of Urological Pathology) grade groups, were markers of a long-term effect of salvage re-irradiation. No other clinical parameters were significant.

The median PFS after re-irradiation was 67 months for patients with ISUP grade groups 1–2 compared to 24 months for ISUP grade groups 3–5. Patients with ISUP grade groups 1–2 had significantly longer time from re-irradiation to recurrence and thus longer progression-free survival (**Figure 6B**, log-rank test; $p = 0.03$). However, time from primary radiotherapy to recurrence was not a significant marker of early recurrence after re-irradiation (**Figure 6C**).

Site of Recurrence

Sixteen patients had MRI both at primary diagnosis and at first recurrence. For 15 of these patients, the recurrent tumor occurred within the extent of the primary tumor (**Figure 2**). The extent of the primary tumor for the last patient could not be assessed due to artifacts from air in the rectum.

DISCUSSION

This prospective study reports toxicity and long-term clinical outcome after salvage re-irradiation of localized intra-prostatic recurrence. The study cohort consisted of 33 patients who

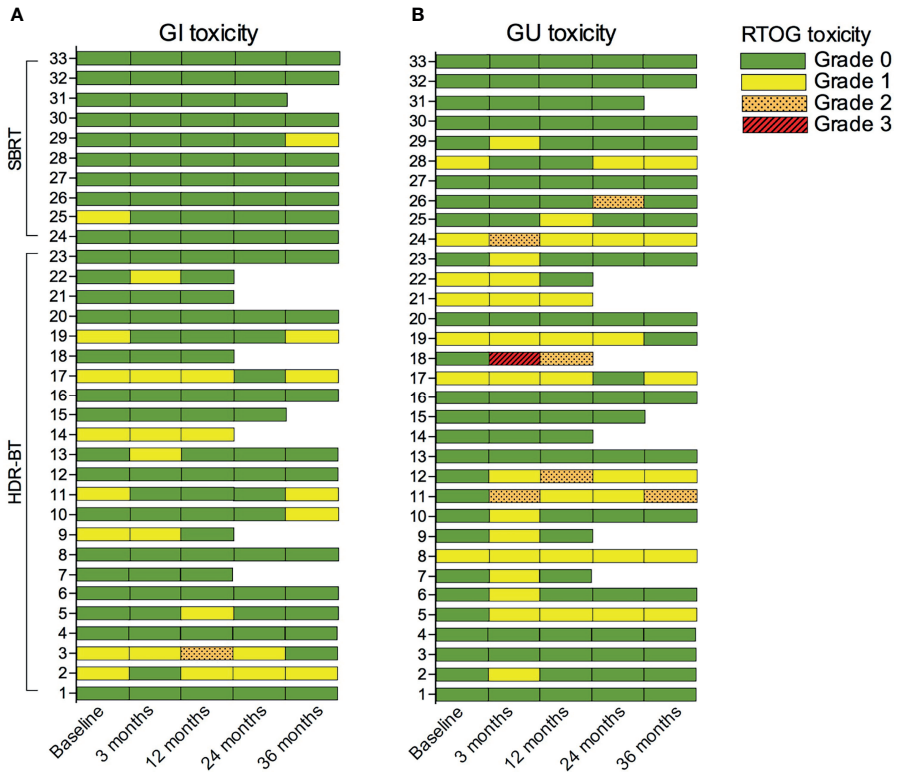

FIGURE 4 | RTOG-graded gastrointestinal (GI) **(A)** and genitourinary (GU) **(B)** toxicity before (baseline) and following salvage re-irradiation. RTOG grading ceased if patients received additional local treatment such as HIFU, prostatectomy, or chemotherapy. HDR-BT, High dose-rate brachytherapy; SBRT, Stereotactic body radiotherapy.

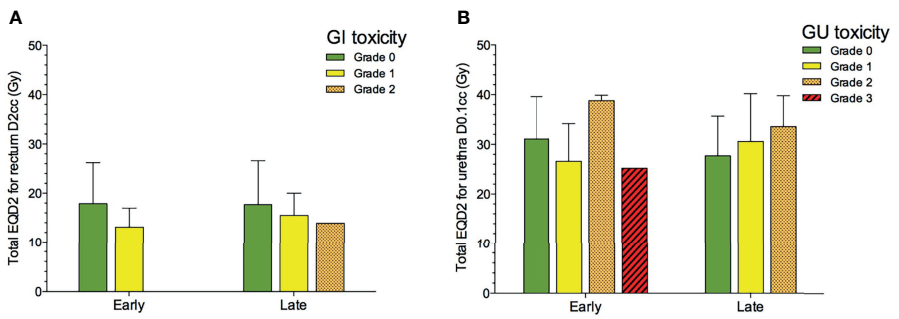

FIGURE 5 | Total EQD2 for rectum D2cc **(A)** and urethra D0.1cc **(B)** from the re-irradiation and RTOG-graded gastrointestinal (GI) and genitourinary (GU) toxicity after salvage re-irradiation (n = 33). Bars represent mean values, and whiskers SD.

initially were treated with primary EBRT (70–78 Gy). All had a true local recurrence verified by biopsy and no metastases at imaging or in bone marrow samples. For most patients (28/33) salvage re-irradiation was delivered without androgen deprivation therapy. Overall, the GU and GI toxicity was mild to moderate. One-third of the patients had a biochemical relapse within the first two years, one third relapsed later than two years, and one-third of the patients are still relapse-free.

There are several studies that have reported results from salvage re-irradiation (6, 7, 10, 11, 17). However, there is a large heterogeneity among the reported studies: different primary treatment (prostatectomy, cryotherapy, HIFU, low dose-rate (LDR) brachytherapy, EBRT, and combinations), limited follow-up time, peri-salvage use and inconsistent reporting of ADT, and retrospective study design. The limited GU/GI toxicity in our patients is in line with the reasonable toxicity reported in the prospective phase II RTOG-0526 trial (17) and two recent large systematic reviews and meta-analyses (6, 7).

In the RTOG-0526 applying salvage LDR-BT 14% had grade 3 GU toxicity compared to 3% in our study. Because only one

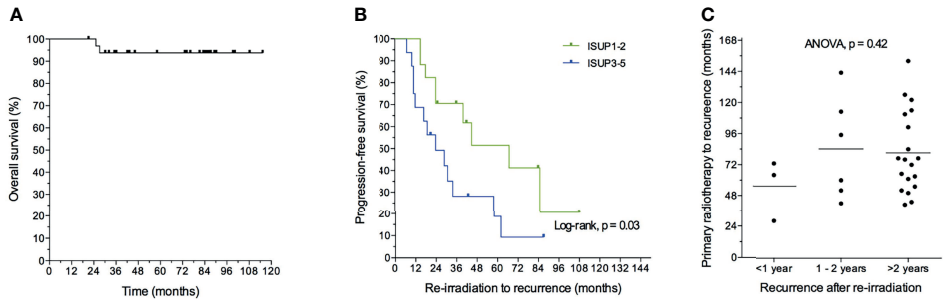

FIGURE 6 | Kaplan–Meier estimate of overall survival **(A)** and progression-free survival **(B)** after re-irradiation without androgen deprivation treatment (n = 28). Time to first recurrence for patients recurring within one, two, or more than two years after re-irradiation **(C)**.

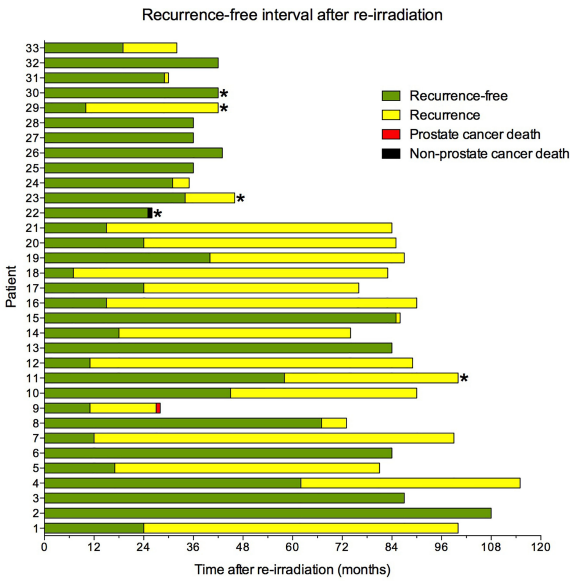

FIGURE 7 | Recurrence-free interval after re-irradiation. *Patients who received androgen deprivation treatment at salvage re-irradiation.

patient in our study had grade 3 GU toxicity, the data is too sparse to assess if this was associated with primary and salvage treatments. The patients in the RTOG-0526 study received 78 Gy/39 fractions or 81 Gy/45 fractions, a slightly higher dose than in our cohort. Nearly all patients in the RTOG-0526 study had whole-gland salvage LDR brachytherapy, whereas we used focal HDR-BT/SBRT and delivered a boosted dose to the recurrent tumor with pre-specified low tolerance dose to the urethra (**Supplementary Tables 3**, **5**).

The 2-year biochemical recurrence-free survival was 68% (19 of 28 patients). In the review from Valle et al. 2-year recurrence-free survival was 62% for SBRT and 77% for HDR-BT, however, about 40% of these patients received peri-salvage ADT (6). Corkum et al. (7) reported the random effect of biochemical recurrence-free survival (BRFS) to be 60% with a significant heterogeneity (50–70%). Crook et al. have recently published their long-term clinical outcome of the RTOG-0526 trial and found a 5-year disease-free survival of 61%. Their results seem in line with ours, but they had longer follow-up time, excluded high-risk patients, and permitted up to six months of peri-salvage ADT. The majority of our patients had high-risk disease.

In the setting of radio-recurrence, salvage prostatectomy and ADT are the guideline-recommended standard options. A longstanding principle in radiation oncology is that after EBRT, re-irradiation will exceed normal tissue tolerances leading to potentially serious toxicity (7–9). A recent ESTRO ACROP consensus paper agrees that re-irradiation is a feasible therapeutic option for selected patients (8). The meta-analyses from Valle et al. reported significantly less GU toxicity rates for SBRT and BT than after prostatectomy, HIFU, and cryotherapy (6, 9). In the current study, we demonstrate that re-irradiation, without rectal spacer devices, is feasible and tolerable provided stringent dose constraints to the urethra and rectum (**Supplementary Tables 3**, **5**). In the future, the assessment of germline variants that predict clinical radio-sensitivity could be implemented to improve patient selection and further reduce toxicity (18).

The therapeutic goal of re-irradiation is the eradication of the recurrence or substantial delay of onset of ADT and subsequent development of castration-resistant disease. One-third of the patients in our study had an early second biochemical relapse within two years, indicating that not all patients will benefit from re-irradiation. The only marker of poor clinical outcome was the high ISUP grade group of the primary tumor. Two-thirds of the patients saw clinical benefits, more than 2-years BFS, probably because the patients were carefully selected by strict inclusion criteria and thorough imaging to localize the site and extent of the recurrence and exclude metastatic disease. The ESTRO APCO Delphi consensus also agrees on and highlights the need for strict inclusion criteria and state-of-the-art imaging (8).

All recurrences occurred within the extent of the primary tumor for the 15 patients in which we had MRI with sufficient image quality at primary diagnosis. Jalloh et al. (19) also found that nearly all recurrences were within the extent of the primary index tumor. These findings indicate that the radiotherapy of

primary prostate cancer could be improved by dose escalation (20). Modern dose painting techniques may deliver increased dose selectively to the radio-persisting intra-prostatic lesion without increasing the dose to the OARs (21).

The major limitations of our study are the limited sample size and the lack of a control group. The minor limitations are that not all patients had the same treatment, some had HDR-BT, some had SBRT, and five patients received peri-salvage ADT. The major strengths are the prospective design, clearly defined inclusion criteria, modern ultra-hypofractionated image-guided radiotherapy, a long follow-up time, and state-of-the-art imaging. Furthermore, most of the patients (28/33) did not have ADT. As such, our prospective study does not provide a high level of evidence but adds to the body of knowledge.

CONCLUSION

Re-irradiation of intra-prostatic recurrence with HDR-BT and SBRT is feasible and resulted in mild to moderate GU or GI toxicity. Two-thirds of the patients experienced more than 2-years BFS, one-third are still recurrence-free without ADT. Some patients progressed rapidly and may not have benefitted from salvage radiotherapy. Careful selection of patients is needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Regional Committee for Medical Research Ethics South East Norway. The patients/participants provided their written informed consent to participate in this study.

AUTHORS CONTRIBUTIONS

Conceptualization, TS, KH, AK, and WL. Methodology, UR, TS, LN, TH, LD, HG, KH, and WL. Formal analysis, TS. Investigation, UR, TS, LN, TH, LD, HG, JH, KH, and WL. Resources, WL. Writing—Original Draft, UR, TS, KH, and WL. Writing—Review & Editing, UR, TS, LN, TH, LD, HG, JH, AK, KH, and WL. Visualization, TS and KH. Supervision, TS, KH, and WL. Funding Acquisition, WL. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.861127/full#supplementary-material

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Intrafraction Prostate Motion Management During Dose-Escalated Linac-Based Stereotactic Body Radiation Therapy

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Background: Extreme hypofractionation requires tight planning margins, high dose gradients, and strict adherence to planning criteria in terms of patient positioning and organ motion mitigation. This study reports the first clinical experience worldwide using a novel electromagnetic (EM) tracking device for intrafraction prostate motion management during dose-escalated linac-based stereotactic body radiation therapy (SBRT).

Methods: Thirteen patients with organ-confined prostate cancer underwent dose-escalated SBRT using flattening filter-free (FFF) volumetric modulated arc therapy (VMAT). The EM tracking device consisted of an integrated Foley catheter with a transmitter. Patients were simulated and treated with a filled bladder and an empty rectum. Setup accuracy was achieved by ConeBeam-CT (CBCT) matching, and motion was tracked during all the procedure. Treatment was interrupted when the signals exceeded a 2 mm threshold in any of the three spatial directions and, unless the offset was transient, target position was re-defined by repeating CBCT. Moreover, the displacements that would have occurred without any intrafraction organ motion management (i.e. no interruptions and repositionings) were simulated.

Results: In 31 out of 56 monitored fractions (55%), no intervention was required to correct the target position. In 25 (45%) a correction was mandated, but only in 10 (18%), the beam delivery was interrupted. Total treatment time lasted on average 10.2 minutes, 6.7 minutes for setup, and 3.5 minutes for beam delivery. Without any intrafraction motion management, the overall mean treatment time and the mean delivery time would have been 6.9 minutes and 3.2 minutes, respectively. The prostate would have been found outside the tolerance in 8% of the total session time, in 4% of the time during the setup, and in 14% during the beam-on phase. Predominant motion pattern was posterior and its probability increased with time, with a mean motion ≤ 2 mm occurring within 10 minutes.

Conclusions: EM real-time tracking was successfully implemented for intrafraction motion management during dose-escalated prostate SBRT. Results showed that most of the observed displacements were < 2 mm in any direction; however, there were a non-insignificant number of fractions with motion exceeding the predefined threshold, which would have otherwise gone undetected without intrafraction motion management.

Keywords: prostate cancer, Steretactic Body Radiation Therapy (SBRT), extreme hypofractionation, Image-guided Radiation Therapy (IGRT), intrafraction motion mitigation, real-time electromagnetic tracking

BACKGROUND

Clinical results from retrospective studies allowed to formulate the hypothesis that the linear quadratic α/β ratio of prostate cancer is generally lower than in the majority of other human tumors (estimated to ~ 1.5 Gy) (1–3). Based on this strong radiobiologic rationale, various trials (4–7) showed that prostate cancer could benefit from hypofractionated regimens of Radiation Therapy (RT). Along with huge advances in radiation technology that have permitted improved precision in radiation delivery and increased protection of the organs at risk (OARs), extreme hypofractionation using Stereotactic Body Radiation Therapy (SBRT) has also been explored with optimal results in terms of biochemical control and side effects (8), becoming the standard of care treatment option of low-intermediate risk prostate cancer (9). The findings from two large systematic reviews (10, 11) and of the one phase III study, HYPO-RT-PC (12), established the most compelling evidence in favor of extreme hypofractionation, while the efficacy data for the PACE-B trial (13) are still pending.

Due to the inherent dose per fraction escalation and the low number of fractions used, SBRT necessitates high dose gradients to be employed with tighter margins than conventional treatment. Therefore, errors in actual dose delivery precision and accuracy can lead to inadequate target coverage and/or overdose of surrounding OARs. The major drawback remains the significant and unpredictable intrafraction prostate motion, mainly due to rectal and bladder filling (14–18). Without continuous monitoring and intervention, in approximately 10% of patients, intrafractional motion would lead to target missing (19). The Calypso System (Varian Medical Systems, Palo Alto, CA), which uses 3 radiofrequency beacons implanted in the prostate to localize and monitor its motion in real-time (20–22), is an example of different methods for imaging, tracking, and correcting for prostate displacements during treatment delivery. Despite its proven accuracy, the Calypso system is an invasive technique for the patient, and the severe artifacts on Magnetic Resonance Imaging (MRI) caused by the beacons could impact treatment planning and radiological follow-up assessments.

A novel electromagnetic (EM) transmitter-based device without surgical intervention to localize and monitor the prostate and the urethra was implemented in the first clinical use worldwide. This study reports the results of tracking in real-time the organ motion during dose-escalated linac-based SBRT for organ-confined unfavorable prostate tumors.

METHODS

Patient Setup and Treatment Planning

Patient population and treatment planning protocol have been described previously (23). Briefly, patients were immobilized in the supine position with arms over their chest using the FeetFix system (CIVCO Medical Solutions, Iowa, US) attached to the couch for ankle fixation. The bladder was filled with 100 cc of saline solution *via* a 16 French Foley catheter during the simulation and a rectal micro-enema was administered. Same bladder and bowel preparation was repeated for each fraction to assess anatomical reproducibility and limit prostate mobility. No rectal immobilization or rectal spacer devices were adopted. To properly delineate the target volume and the OARs, a non-contrast enhancement computed tomography (CT) and a T2-weighted 3D MRI scans were acquired and fused. The planning target volume (PTV) consisted of the prostate gland and the seminal vesicles with a 2 mm isotropic expansion. A margin of 2 mm was applied around the catheter to calculate a planning organ at risk volume (PRV) for the urethra and to enable significant dose-sparing at this level, by allowing a negative dose-painting in order to reduce the risk of treatment-related urinary toxicity.

The treatment schedule consisted of 40 Gy in 5 fractions or 38 Gy in 4 fractions delivered consecutively over one week. With an α/β ratio of 1.5 Gy, the corresponding Biologically Effective Dose (BED) was 253 Gy and 279 Gy, respectively. Treatment was planned with volumetric modulated arc therapy (VMAT) using typically two 10 MV flattening filter-free (FFF) arcs on a VersaHD linear accelerator (Elekta AB, Stockholm, Sweden). Plans were optimized using penalties and priorities to have the 95% isodose covering at least 95% of the PTV and to fulfill the dose-volume constraints to OARs, such as bladder, PRV of urethra rectum, rectum wall, and penile bulb, and were calculated with the Monte Carlo algorithm (1 mm grid spacing and 1% statistical uncertainty for calculation) of Monaco Treatment Planning System (Elekta AB, Stockholm, Sweden).

Abbreviations: RT, Radiation Therapy; OARs, Organs at Risk; SBRT, Stereotactic Body Radiation Therapy; MRI, Magnetic Resonance Imaging; EM, Electromagnetic; CT, Computed Tomography; PTV, Planning Target Volume; PRV, Planning Organ at Risk Volume; BED, Biologically Effective Dose; VMAT, Volumetric Modulated Arc Therapy; FFF, Flattening Filter-Free; SD, Standard Deviation; CBCT, Cone Beam Computed Tomography; IGRT, Image Guided Radiation Therapy; CK, CyberKnife.

Intrafraction Motion Tracking and Intervention

The intrafraction organ motion evaluation was performed by RayPilot System (24, 25) (Micropos Medical AB, Gothenburg, Sweden), a novel real-time EM tracking device. The system consists of a wired transmitter, that is integrated into a dedicated lumen of the RayPilot HypoCath, a Foley catheter inserted into the patient, and the RayPilot Receiver, a platform that is placed on the existing carbon fiber couch under the patient. The transmitter, consisting of a choke coil (diameter 3 mm, length 11 mm) and a cable, is connected to the receiver plate during each fraction to activate the device. An antenna array captures the signal sent by the transmitter, and the position of the transmitter is located. The system was calibrated to the treatment room isocenter and allowed for treatment localization as well as motion tracking. The position is given along the three-dimensional axes (lateral, longitudinal, and vertical) at a sampling frequency of 30 Hz. Rotations around the vertical axis (yaw) and the lateral axis (pitch) are also detected by the system. Treatment couch bending due to patient weight was measured and considered in the system.

Accurate patient setup was achieved by a ConeBeam-CT (CBCT) soft tissue matching prior to treatment (**Figure 1**). Motion tracking was enabled immediately after the start of the CBCT acquisition by setting the initial position detected by the system equal to zero. A shift in the transmitter position was used as a surrogate for the prostate motion. Due to the demand for a very accurate delivery in such treatments, the beam delivery was promptly interrupted every time a shift of the transmitter exceeded more than 2 mm from its planned position in any of the three spatial directions. In case of prolonged drift outside this tolerance (15 seconds), a new CBCT was acquired and matched and the couch position corrected for taking into account the prostate motion before resuming the beam. Anytime a CBCT acquisition was mandated, a new RayPilot position was set in the system to get a new starting point with respect to which displacements were calculated and shown. Because the prostate may also move between the initial target positioning procedure and the beam-on time, this real-time tracking system allowed to detect and correct any possible target displacement observed in the setup phase according to the aforementioned rules. With conventional Image Guided Radiation Therapy (IGRT), this shift would have gone unnoticed and not accounted for.

Data Processing and Analysis

Real-time measurement of the transmitter displacement was recorded for each treatment fraction. After the treatment, the log files including the transmitter positions and beam-on indications were exported with an update rate of 15 Hz in XML format. Intrafraction motion was calculated by computing prostate shifts for the translational and rotational axes relative to the initial zero position. A C++ program was developed for the analysis of the data files produced by the tracking system software; ROOT data analysis framework libraries were exploited for the graphical representation of target translational and rotational deviations. The main objective of the program elaboration was to automate as much as possible the analysis procedure, minimizing the required user actions. Treatment sessions were analyzed with and without beam gating and motion correction interventions. Real prostate motion data (i.e. with no interruptions and repositioning included) were obtained by removing all changes due to the reset of the transmitter position with the acquisition of a new CBCT. Moreover, the trajectories that would have occurred without any organ motion management and beam gating were simulated by adjusting setup and delivery duration. A fixed duration of 3.5 minutes was used to include the time for the CBCT acquisition and the registration to the reference planning CT. For the delivery, the real delivery time of the specific treatment plan without interruptions was used.

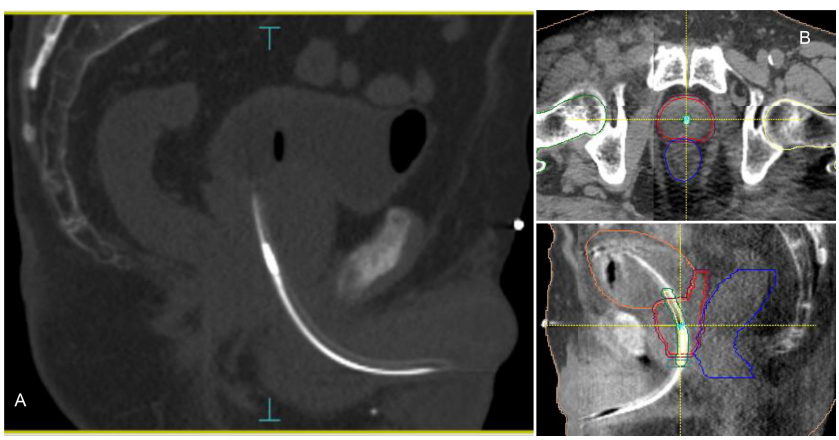

FIGURE 1 | RayPilot HypoCath. The transmitter choke is visible inside the urinary catheter within the prostatic urethra **(A)**. Planning CT to daily CBCT matching: proper rectum and bladder filling verification, in addition to transmitter and urethra localizations; in case of deformation or deviation of the urethral path, the catheter was placed inside the urethra PRV along with the entire extension of the prostate **(B)**.

RESULTS

The localization uncertainty of the RayPilot System, measured in a precision test procedure, was 0.34 ± 0.18 mm [radial mean ± standard deviation (SD)]. The procedure consisted of calculating the radial error in 4 displacements from the calibration center point (i.e. 2 longitudinal and 2 vertical and lateral diagonal positions on each side of the center point, respectively), assessed in both laboratory and clinical environment.

Overall, 56 treatment fractions were delivered and analyzed, and 84 CBCT to planning CT matchings were performed. In 31 sessions, corresponding to 55% of the total, the signal remained within the predefined tolerance for the whole treatment time and no intervention was required to correct the target position as a result of an excessive prostate movement. Only in 3 of those cases (5%), the target moved out of the 2 mm threshold, but it promptly returned within the safety threshold. In the other 25 sessions (45%) the prostate exceeded the tolerance after the initial CBCT verification. In 10 cases (18%) a non-re-entering prostate shift occurred during the treatment delivery, requiring a beam interruption and a new CBCT.

Considering all fractions, the median duration from the start of the EM tracking procedure to the end of the delivery was 8 minutes, with an average time of 10.2 ± 4.2 minutes (range 5.5 - 22.7), 6.7 ± 3.8 minutes (range 2.7 - 17.8) for patient setup and 3.5 ± 0.9 minutes (range 2.5 - 7.3) for beam delivery (beam-on time + interruptions). Noteworthy since the intervention procedure in halting the beam was manual, there was a lag between the alert and beam-off estimated in approximately 1 second, a small amount of the 150- to 250-second beam-on time. Without any intrafraction motion management, the overall mean treatment time and the mean delivery time would have been 6.9 minutes (range 5.5 - 9.9) and 3.2 minutes (range 2.5 - 4.2), respectively. The evaluation of the transmitter trajectories of the gated treatments has been described previously (22). Without any intrafraction motion management, (i.e. without beam gating and patient position corrections) the prostate would have been found outside the 2 mm tolerance in 8% of the total session time, namely in 4% during the setup time and in 14% during the beam delivery, respectively. **Table 1** illustrates the percentage of time that the prostate spent outside the 2 mm threshold in each of the three spatial directions during the setup, delivery, and total treatment either without or with the intrafractional organ motion management. The difference in time percentages between the two scenarios is also reported.

Real prostate motion data analyzed from all the patients are presented in **Table 2**. Mean displacements in lateral, longitudinal, and vertical directions were < 1 mm, indicating that the overall motion occurred randomly. The vertical axis showed the higher mean value in the posterior direction and also the mean standard deviation was wider than in the other two directions. Mean absolute values of real prostate motion were found within our PTV margins, but the mean absolute maximum was not in two of the three axes. The prostate predominant displacements occurred in the inferior and posterior directions. It is also apparent from **Figure 2** that the distribution of the real prostate translational shift along the three directions was asymmetrical. A systematic drift in the mean prostate position to the right, inferiorly, and posteriorly was noticed. To confirm these data, real prostate motion was plotted as a function of treatment time, considering t = 0 at the beginning of the initial CBCT (**Figure 3**).

The analysis of the probability of real prostate motion as a function of time is shown in **Figure 4**. The probability of motion > 2 mm in the lateral, longitudinal, and vertical direction after 5 minutes was 3.6% (2/56), 8.9% (5/56), and 14.3% (8/56), respectively. Overall, half of the fractions were accomplished within 8 minutes. In that time, the same probability was 11.1% (3/27), 37.0% (10/27), and 40.7% (11/27) for the three directions. The probabilities of motion > 3 mm in lateral, longitudinal, and vertical direction after 5 and 8 minutes were 1.8% (1/56), 3.6% (2/56), 3.6% (2/56), and 7.4% (2/27), 14.8% (4/27), 33.3% (9/27), respectively. There were no fractions that had a prostate deviation > 5 mm in any direction after 5 minutes, while only 1 fraction out of 27 (3.7%) moved out of 5 mm posteriorly after 8 minutes.

TABLE 2 | Mean, standard deviation (SD), mean absolute, and mean max absolute of the real prostate translational data from all the 56 fractions with no interruptions and patient position corrections.

Direction	Mean (mm)	SD (mm)	Mean absolute (mm)	Mean max absolute (mm)
Lateral	-0.36	0.95	0.65	1.78
Longitudinal	-0.21	1.69	1.17	3.17
Vertical	-0.92	1.95	1.42	3.83

The negative sign represents a displacement in right, inferior, and posterior directions, respectively. Max deviation represents the absolute maximum displacement for time point in the 3 spatial directions.

TABLE 1 | Percentage of the setup time, delivery time, and total treatment time spent by the prostate outside the 2 mm threshold by spatial direction (LAT, lateral; LNG, longitudinal; VRT, vertical) without the intrafractional organ motion management and with the real-time management.

Time spent outside the 2 mm threshold	Setup			Delivery			Treatment		
	LAT	LNG	VRT	LAT	LNG	VRT	LAT	LNG	VRT
Without intrafraction motion management	0%	2%	3%	5%	9%	14%	2%	5%	8%
With intrafraction motion management	3%	5%	8%	1%	2%	4%	2%	4%	7%
Difference	-3%	-3%	-5%	4%	7%	10%	0%	1%	1%

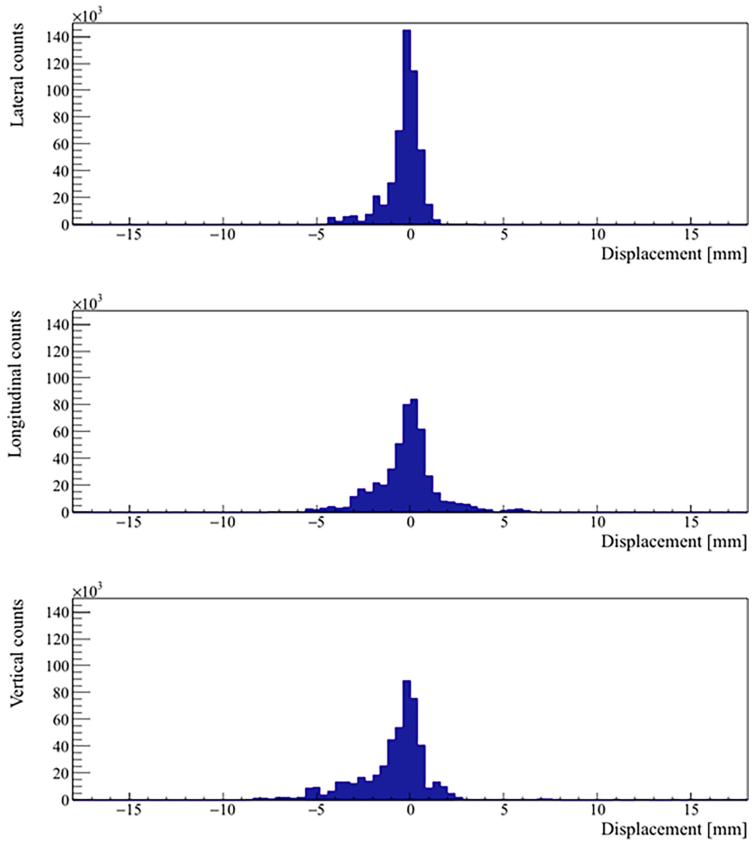

FIGURE 2 | Distribution of the real prostate translational motion with no interruptions and patient position corrections. The positive axis represents a displacement in left, superior, and anterior directions, respectively.

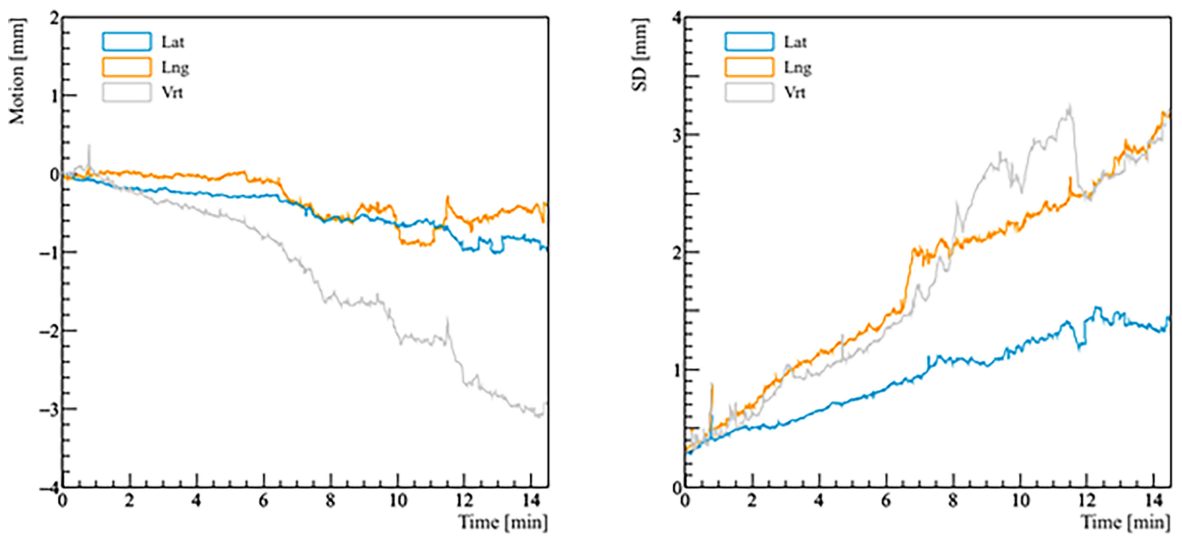

FIGURE 3 | Real prostate motion with no interruptions and patient position corrections as a function of time (t = 0 at the beginning of the initial CBCT). The left panel shows the mean variations from the initial position of the prostate, the right panel shows the standard deviation (SD) of the mean motion.

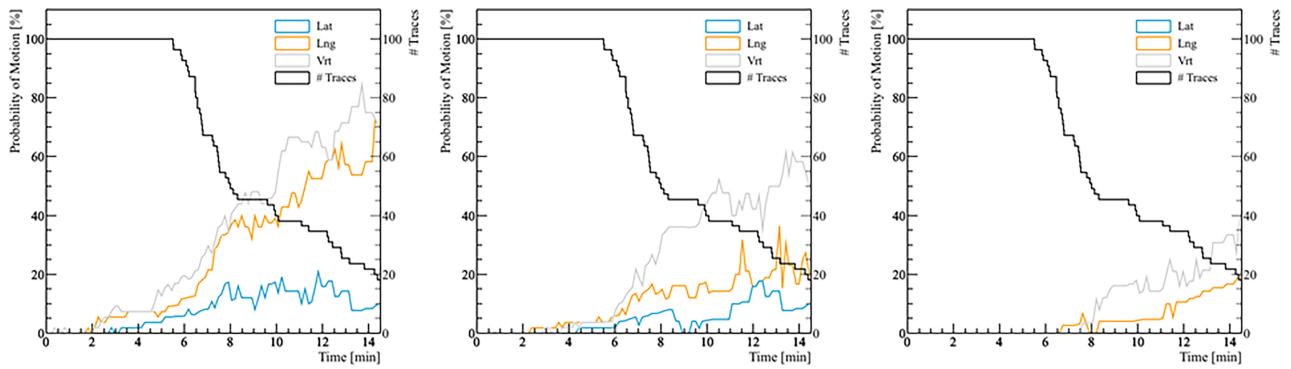

FIGURE 4 | The probability of real prostate motion with no interruptions and patient position corrections as a function of time. The left panel shows the probability of motion > 2 mm, the middle panel for motion > 3 mm, and the right panel for motion > 5 mm. The black line represents the number of traces analyzed with respect to treatment time.

TABLE 3 | Mean, standard deviation, and range of the real prostate rotational variations with no interruptions and patient position corrections.

Axis	Mean angle	SD	Min angle	Max angle
Pitch	-0.2°	2.6°	-15.2°	11.0°
Yaw	0.0°	0.8°	-2.8°	3.6°

The mean, standard deviation, minimum, and maximum of the rotation angles determined from all the patients are shown in **Table 3**. In the pitch axis, a systematic rotation, which is absent in the yaw axis, was observed. Meanwhile, the range and standard deviation of rotation angles were larger in the pitch axis. The distribution of prostate rotation angles in the two axes, graphically represented in **Figure 5**, showed an asymmetric distribution to the negative axes and extreme rotations beyond 10 degrees in some instances.

DISCUSSION

IGRT has been demonstrated to improve treatment accuracy and reduce side effects associated with prostate irradiation (26–28). In this study, intrafraction motion management was not the only strategy employed to assure the SBRT efficacy and an acceptable toxicity profile. Further refinements to aim at this purpose included strict bowel preparation, bladder filling, MR-based treatment planning with negative dose-painting around the urethra, and fast treatment delivery time with FFF VMAT beams. Although most patients experienced minimal motion during treatment, some fractions required beam interruptions to correct for prostate displacement. Indeed the 45% of treated fractions would have resulted in undetected displacements of more than 2 mm without intrafraction motion management. In the context of extreme hypofractionation, even a single fraction

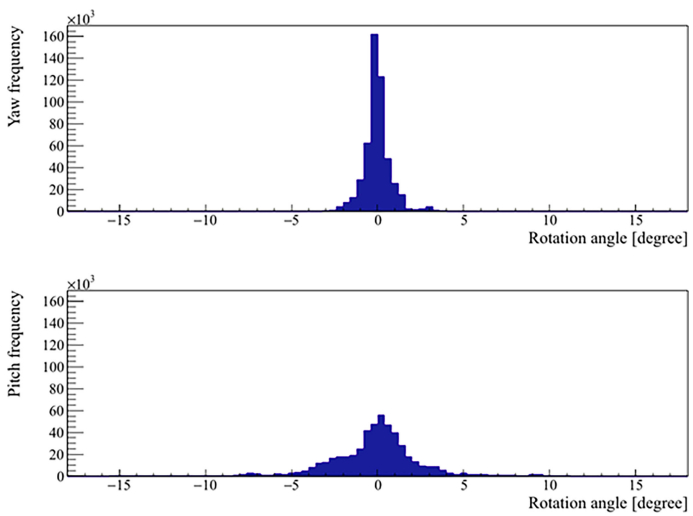

FIGURE 5 | Distribution of the real prostate rotational variations with no interruptions and patient position corrections.

with unexpected organ motion can lead to potentially detrimental dosimetric and clinical consequences. The excellent early toxicity rates, compliance, and biochemical outcomes seen in the present series (23) suggest that treatment was delivered accurately and precisely.

Pretreatment orthogonal radiographs, CBCT, and/or ultrasound are commonly employed methods to accomplish interfraction motion management. These approaches are useful for verifying initial patient setup but are difficult to use in assessing intrafraction organ motion during treatment delivery. To continuously track the prostate during treatment, several commercially available techniques, including surface monitoring, kV and MV X-ray imaging-based methods, marker implantation, and real-time segmentation in kV and MV images, EM transponders or transmitters, ultrasound acquisitions, and MRI techniques, are now routinely used in practice (29). Several of them are expensive, requiring additional equipment unavailable on a standard LINAC. The most consistent example is the CyberKnife (CK) robotic radiosurgery system. The CK technique requires an invasive procedure by the positioning of fiducials within the prostate parenchyma. A complex X-ray imaging system that captures high-resolution images onto paired orthogonal amorphous silicon flat-panel detectors ensures target tracking (30). Our findings indicated that, even when the treatment was interrupted for prostate motion correction, the majority of fractions were delivered in less than 10 minutes. This is remarkable for an ultrahypofractionated treatment, especially in light of the significant amount of time of CK treatments, ranging from 20 to 90 minutes (31–33). Longer treatments may increase the risk of errors and patient discomfort, affecting the intrafraction motion and potentially reducing the clinical benefits associated with the use of a cutting-edge technology (34, 35).

Our measured intrafractional data on prostate real motion are similar to previously published observations (19, 36–40). The predominant motion was anteriorly-posteriorly, which is consistent with the current literature, although a not null value was detected also in the mean lateral displacement. From the analysis of the prostate motion as a function of treatment time, we showed that the probability of motion increased with time, with a mean real motion ≤ 2 mm within 10 minutes. Remarkably, Legge et al. (18) have noted translations as small as 0.01 ± 0.23 mm, 0.21 ± 0.12 mm, and 0.11 ± 0.64 mm in lateral, longitudinal, and vertical direction, respectively, with the incorporation of a rectal retractor device and real-time kV infraction monitoring. It should be noted that the calculated prostate real motion reflects a scenario in which intrafractional displacements are not corrected in real-time. With the integration of real-time intrafractional motion monitoring, the use of tighter than conventional margins (5 mm, 3 mm posteriorly) is conceivable with adequate target coverage. According to our findings, it could be argued that the vast majority of the patients would not have required intrafractional adjustment if the PTV margins were set up to 5 mm. However, with wider margins, it would not have been possible to escalate the dose while respecting the dose-volume constraints for the rectum and the bladder due to the increasing overlap between target volumes and organs at risk.

Additionally, we observed a minor asymmetry in the distribution of prostate rotations, particularly in the pitch axis. Pitch can be thought of as a tilt in the longitudinal plane and thus is the most strongly affected by any alterations in rectal volume. Our observed rotations were smaller than those observed by Wolf et al. (41). This may be due to our strict adherence to the empty bowel protocol prior to both planning and treatment, minimizing the rectal filling from the proximal direction. It has previously been reported that in plans optimized for motion robustness, clinical target volume D95 is insensitive to yaw and roll of up to 10°, but it's more sensitive to pitch, which leads to poorer dosimetric results already at around 5° (42).

RayPilot System is a non-ionizing non-interfering real-time positioning system that has the advantage of being removed upon treatment completion, enabling MRI follow-up without any artifact, and does not require any permanent treatment room installations, thus providing a theoretical improvement over available options (20, 21). Furthermore, the introduction of the RayPilot HypoCath resulted in a less invasive and more stable device than the transperineal implanted wired transmitter (43, 44). However, since the absolute localization accuracy of the system may not be high enough for interfraction localization of the prostate, mostly due to the uncertain positional reproducibility of the catheter balloon with respect to the bladder wall, we recommend to combine real-time prostate motion monitoring by RayPilot with an independent IGRT system, and namely a volumetric one, to account for the optimal rectal and bladder filling.

CONCLUSION

EM real-time tracking was successfully implemented for intrafraction motion management during dose-escalated prostate SBRT. Findings showed that most of the observed displacements were < 2 mm in any direction; however, there were a non-insignificant number of fractions with a motion exceeding the predefined threshold, which would have otherwise gone undetected without intrafraction motion management.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DP was the lead author, who participated in data collection, data analysis, manuscript drafting, table/figure creation, and manuscript revision while also aiding in study design. VF and RL contributed equally to this work and participated in data analysis, manuscript drafting, table/figure creation, and manuscript revision. MD organized and performed the analysis of the dataset. ST, PC, and VP participated in data collection and data analysis. EP is a senior author who aided in data analysis and manuscript revision. SA was the principal investigator who developed the concept of the study and the design, aided in data collection, and drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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1.5T MR-Guided Daily Adaptive Stereotactic Body Radiotherapy for Prostate Re-Irradiation: A Preliminary Report of Toxicity and Clinical Outcomes

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Background: Prostate re-irradiation is an attractive treatment option in the case of local relapse after previous radiotherapy, either in the definitive or in the post-operative setting. In this scenario, the introduction of MR-linacs may represent a helpful tool to improve the accuracy and precision of the treatment.

Methods: This study reports the preliminary data of a cohort of 22 patients treated with 1.5T MR-Linacs for prostate or prostate bed re-irradiation. Toxicity was prospectively assessed and collected according to CTCAE v5.0. Survival endpoints were measured using Kaplan-Meier method.

Results: From October 2019 to October 2021, 22 patients received 1.5T MR-guided stereotactic body radiotherapy for prostate or prostate-bed re-irradiation. In 12 cases SBRT was delivered to the prostate, in 10 to the prostate bed. The median time to re-RT was 72 months (range, 12-1460). SBRT was delivered concurrently with ADT in 4 cases. Acute toxicity was: for GU G1 in 11/22 and G2 in 4/22; for GI G1 in 7/22, G2 in 4/22. With a median follow-up of 8 months (3-21), late G1 and G2 GU events were respectively 11/22 and 4/22. Regarding GI toxicity, G1 were 6/22, while G2 3/22. No acute/late G≥3 GI/GU events occurred. All patients are alive. The median PSA-nadir was 0.49 ng/ml (0.08-5.26 ng/ml), for 1-year BRFS and DPFS rates of 85.9%. Twenty patients remained free from ADT with 1-year ADT-free survival rates of 91.3%.

Conclusions: Our experience supports the use of MR-linacs for prostate or prostate bed re-irradiation as a feasible and safe treatment option with minimal toxicity and encouraging results in terms of clinical outcomes.

Keywords: MR-guided, stereotactic ablative body radiation, prostate, re-irradiation, MR-linac

INTRODUCTION

Prostate cancer is the most frequent tumor diagnosed in male population (1). The incidence of local relapses after primary external beam radiotherapy either in the definitive or post-operative setting may occur in a proportion of patients up to the 40% of cases (2).

Historically, these patients were managed with androgen deprivation therapy (ADT), as a sort of palliative treatment with a not negligible detrimental impact on quality of life (QoL) (3, 4). In recent years, there is an increasing attention towards local re-treatments in the case of previous radiotherapy (5).

Specifically in the case of cryotherapy and highly intensity-focused ultrasound (HIFU), encouraging data are reported from very small series, as these treatment approaches remain niches (6, 7).

As initially brachytherapy was the preferred option, due to the need to deliver higher doses to small volumes with the aim to spare the nearby healthy structures, more recently, stereotactic body radiotherapy (SBRT) represents an attractive non-invasive alternative in order to safely propose prostate or prostate bed re-irradiation (7, 8).

Preliminary experiences report encouraging results in terms of toxicity assessment and initial clinical outcomes (9); noteworthy, this approach is further supported by the availability of reliable imaging exams that have significantly improved the detection of the real disease burden even for lower PSA values, such as PSMA-positron emission tomography (PET) or magnetic resonance-imaging (MRI) (10).

In this scenario, the recent introduction of hybrid MRI-linear accelerators represents another helpful device for this specific setting, due to the favorable combination of a superior pelvic anatomy visualization with the possibility to daily adapt the plan based on the real-time shape and size of both target and organs-at-risk (OARs) (11).

This technology is of great interest in a setting as the re-irradiation, in which a refined identification of both target and nearby healthy structures becomes crucial in order to reduce the risk of major side effects. More specifically, available literature experiences have reported a superior outcome of SBRT both in terms of biochemical control and toxicity incidence, when compared to conventional fractionation studies (12).

In our Department we have started our clinical activity with 1.5T MR-Linac in October 2019. In the present study, approved by the local Ethical Committee on April 2019 (MRI/LINAC n°23,748), we report the preliminary results in terms of safety and efficacy for prostate and prostate bed stereotactic re-irradiation.

MATERIALS AND METHODS

This study depicts the preliminary results of the first 22 patients who received 1.5T MR-guided stereotactic re-irradiation for prostate cancer after previous definitive or post-operative radiotherapy. In all cases, patients had only local relapse with no evidence of regional or distant relapses.

All patients were treated with 1.5T MR-Linac Unity (Elekta, Stockholm, Sweden).

Inclusion criteria for the purpose of this study were: radiological evidence of local recurrence after PSA rising (PSA value: nadir + 2 ng/ml for definitive RT, or an increase above 0.2 ng/ml for post-operative RT) detected by means of MRI, Ga-PSMA or Choline-PET performed depending on PSA levels, a minimum interval of 12 months from the previous radiotherapy course, International Prostate Symptom Score (IPSS) <10, Karnosky Performance Status (KPS) ≤70, and specific written informed consent. A re-biopsy was not considered as mandatory. Patients' characteristics are summarized in **Table 1**.

Radiotherapy Procedures

For the simulation process, patients were educated to have a comfortably full bladder (to drink 500cc of water 15-20 minutes before the scan) and to have an empty rectum (to use a fleet enema 2 hours before the scan). The same protocol was applied prior to each fraction. For all patients, a 3mm slice thickness pelvis-CT was acquired in supine position for dose calculation purposes. Afterwards, a T2-weighted gradient-echo was acquired in the same position using the KneeSTEP and FeetSTEP MR-compatible devices (Elekta, Stockholm, Sweden). As a part of the positioning process, the coil is positioned anteriorly and fixed to the table (13).

Regarding clinical target volume (CTV) delineation, the clinical target volume consisted of the entire prostate gland or of the PET-positive area within the prostate bed in the post-operative setting.

The planning target volume (PTV) was generated by applying to the CTV a 3-5 mm margin in all directions. The following structures were delineated as organs at risk (OARs): rectum, bladder and prostatic urethra, penile bulb and femurs.

Our planning objectives were to have a dose distribution normalized to guarantee a minimum 95% of the PTV coverage by at least the 95% of the prescribed dose, with less than 2% of the PTV to receive the 107% of the prescribed dose. Intensity modulated radiotherapy (IMRT) offline plan optimization was performed applying 16 static fields in step-and-shoot modality. The same approach was used for daily online 'adapt-to-shape' (ATS) workflow. For the OARs, the following constraints were

TABLE 1 | Patient characteristics.

Characteristic	N
Median age	66 years (51-85)
Risk Group	
Low risk	3
Intermediate risk	7
High risk	12
Median time interval between RT courses	72 months (12-1460)
Median PSA pre-reSBRT	1.7 ng/ml (0.34 - 8.58 ng/ml)
Site of recurrence	
Prostate bed	10/22
Prostate	12/22
Re-SBRT dose	30 Gy/5 fractions
Concurrent ADT	4/22

applied for baseline treatment planning and for all the daily-adapted sessions: V10<40%, V18<20% for rectum; V10<25%, V18<15% for bladder; Dmax<30Gy for urethra; V24<10% for femurs; V24<50% for penile bulb (14).

The daily-adaptive workflow for Elekta Unity is based on two alternative strategies: the 'adapt-to-position' (ATP) and ATS methods. The ATP workflow mainly consists of a daily update of the isocenter position, and it does not require daily re-contouring. For ATS, a full re-contouring of both target and OARs is performed on the daily MRI, and afterwards a full re-planning is performed based on the anatomy of the day.

A detailed description of the daily procedure for prostate SBRT has already been reported in a previous study (15).

Briefly, prior to each fraction a T2-weighted MRI (pre-MRI) is acquired and rigidly fused with the baseline planning MRI. The original set of structures is projected onto the daily pre-MRI and edited as necessary by the physician. Then, the plan is fully re-calculated and optimized. Afterwards, a second verification MRI is acquired to check on any deformation of bladder and rectum. In the case of not negligible deformations, the patient is invited to repeat the entire procedure, otherwise the treatment is delivered using a cine MRI in coronal and sagittal planes to assess organ motion during the delivery phase.

Toxicity and Quality of Life Assessment

Acute and late toxicity data were prospectively collected and assessed using the Common Terminology Criteria for Adverse Events (CTCAE v5,0), assuming as acute any adverse event occurring within 90 days from the end of treatment, and as late any adverse event occurring after 90 days from the end of treatment. For all patients, after the end of SBRT, the first follow up was scheduled after 60 days, and then every three months for the first year.

Statistical Analysis

Descriptive statistics were collected for baseline patients' characteristics.

Toxicity assessment was the primary endpoint of the study, while secondary endpoints were: biochemical relapse-free survival (BRFS), distant progression-free survival (DPFS) and overall survival (OS). Survival estimates were performed with the Kaplan-Meier method Statistical analysis was performed using Medcalc v20.023 (MedCalc Software Ltd – Ostend, Belgium).

RESULTS

Patients' Characteristics

From October 2019 to October 2021 a total of 22 patients received 1.5T MR-guided stereotactic body radiotherapy for prostate or prostate-bed re-irradiation. In 12 cases SBRT was delivered to the prostate after primary curative EBRT in 10 patients (including one case who received curative SBRT as first treatment) and brachytherapy in 2 patients. The remaining 10 patients received MR-guided SBRT to the prostate bed after previous post-operative conventional radiotherapy (respectively 4 adjuvant and 6 salvage RT). The median interval between the two courses of RT was 72 months (range, 12-1460), with local relapse detected by means of Choline-PET in 5 patients, PSMA-PET in 15 patients and MRI scan in 4 patients. Median pre-SBRT PSA value was 1.7 ng/ml (range, 0.34-8.58 ng/ml). SBRT treatment was delivered concurrently with ADT in 4 cases, with all patients who were already ongoing with systemic treatment. Median CTV and PTV were respectively 11.65 cc (range, 0.8-30.3 cc) and 23.3 cc (range, 4.8-64.2 cc), with no statistically significant variations of PTV volume between the sessions. All patients received a total dose of 30 Gy in 5 sessions delivered on alternate days in 19 patients and on consecutive days in 3 patients.

Toxicity

All patients completed the scheduled treatment with no interruptions. Acute toxicity rates were as follows: for genitourinary (GU) adverse events, we recorded G1 in 50% (n=11), and G2 in 18% (n=4); urinary tract pain and urinary obstruction were the most frequent side effects; for gastrointestinal (GI) adverse events, G1 toxicity was observed in 31.8% (n=7) of cases, while G2 events occurred in 18% (n=4) of patients.

With a median follow-up of 8 months (range, 3-21), for late toxicity, we have recorded G1 and G2 GU events respectively in 50% (n=11) and 18% (n=4) of cases. For GI toxicity, G1 events were reported in 27% (n=6) of cases, while G2 in 13.6% (n=3) of patients. No acute or late G3 or higher GI/GU events occurred. (**Tables 2**–**4**).

Clinical Outcomes

All patients are currently alive, with no death occurred until the last follow-up. The median PSA-nadir value after MR-guided SBRT was 0.49 ng/ml (range, 0.08-5.26 ng/ml) (**Figure 1**). For all patients, biochemical failure was associated with a radiological disease progression, with 1-year BRFS and DPFS rates of 85.9%. Three patients developed a biochemical and radiological failure, with two of them candidate to ADT due to the evidence of polymetastatic spread. The remaining one received a further SBRT treatment to the lymph-nodal site of oligoprogression.

TABLE 2 | Acute (A) and late (B) toxicity patterns for the entire population.

A	Genitourinary	G1	G2	
	Urinary Tract Pain Urinary	7	2	
	Urgency	3		
	Urethral Stenosis	1	2	
A	**Gastrointestinal**	**G1**	**G2**	
	Diarrhea			
	Rectal Tenesmus	5	4	
	Rectal Proctitis	2		
B	**Genitourinary**	**G1**	**G2**	**G3**
	Urinary Tract Pain Urinary	7	2	
	Urgency		2	
	Urethral Stenosis	4		
B	**Gastrointestinal**	**G1**	**G2**	**G3**
	Diarrhea	4		
	Rectal Tenesmus	2	3	
	Rectal Bleeding			

TABLE 3 | Acute toxicity patterns for prostate and prostate bed re-irradiation.

Prostate	Genitourinary	G1	G2	G3
	Urinary Tract Pain Urinary	4	1	
	Urgency	3		
	Urethral Stenosis	1	2	
Prostate	**Gastrointestinal**	**G1**	**G2**	**G3**
	Diarrhea			
	Rectal Tenesmus	3	3	
	Rectal Proctitis	1		
Prostate bed	**Genitourinary**	**G1**	**G2**	**G3**
	Urinary Tract Pain	3	1	
	Urinary Urgency			
	Urethral Stenosis			
Prostate bed	**Gastrointestinal**	**G1**	**G2**	**G3**
	Diarrhea			
	Rectal Tenesmus	2	1	
	Rectal Proctitis	1		

TABLE 4 | Late toxicity patterns for prostate and prostate bed re-irradiation.

Prostate	Genitourinary	G1	G2	G3
	Urinary Tract Pain	4	2	
	Urethral Stenosis		2	
	Urinary Urgency	1		
Prostate	**Gastrointestinal**	**G1**	**G2**	**G3**
	Diarrhea	3		
	Rectal Tenesmus	1	3	
	Rectal Bleeding			
Prostate bed	**Genitourinary**	**G1**	**G2?**	**G3**
	Urinary Tract Pain	3	2	
	Urethral Stenosis			
	Urinary Urgency	3		
Prostate	**Gastrointestinal**	**G1**	**G2**	**G3**
	Diarrhea	1		
	Rectal Tenesmus	1		
	Rectal Bleeding			

Twenty patients remained free from ADT until the last follow-up with 1-year ADT free survival rates of 91.3%. (**Figures 2**, **3**).

DISCUSSION

In the present experience we have reported the preliminary outcomes of a cohort of 22 patients who received stereotactic re-irradiation for prostate or prostate bed local relapses treated by means of 1.5T MR-guided daily-adapted RT. Due to the relative novelty of this technology, there is a lack of literature data reporting the outcomes of patients treated with hybrid MR-linacs.

Recently, Michalet et al. (16) published preliminary data regarding the first 20 patients with isolated prostate or prostate bed recurrence after previous radiotherapy, who received stereotactic re-irradiation by means of 0.35T MR-Linac. In this study, preliminary toxicity assessment was promising with no evidence of G3 toxicity, although follow-up was quite limited and several fractionation regimens were applied.

Compared to the abovementioned experience, in our series there is a substantial homogeneity in dose prescription with all the patients receiving 30 Gy in 5 fractions, as it represents the most frequently adopted schedule reported in the literature (17). In agreement with the other MR-guided SBRT study, no G3 acute or late event was recorded, supporting the promising toxicity profile of this treatment, and highlighting the potentially favorable impact of this technology in refining the accuracy and precision for SBRT re-irradiation.

The safety profile of prostate re-irradiation was also found in a previous experience of our Department concerning 24 patients treated with conventional linacs (18); however, the use of daily-adapted radiotherapy with real-time replanning may result in

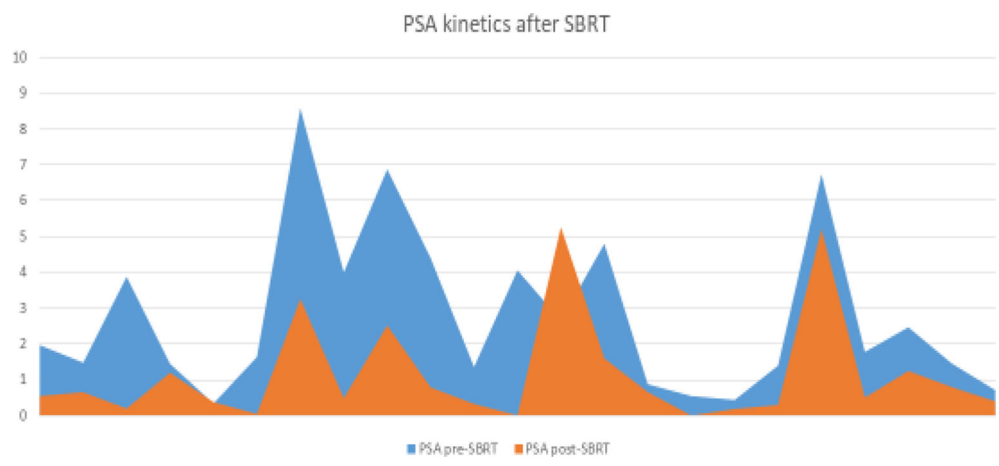

FIGURE 1 | PSA kinetics after SBRT.

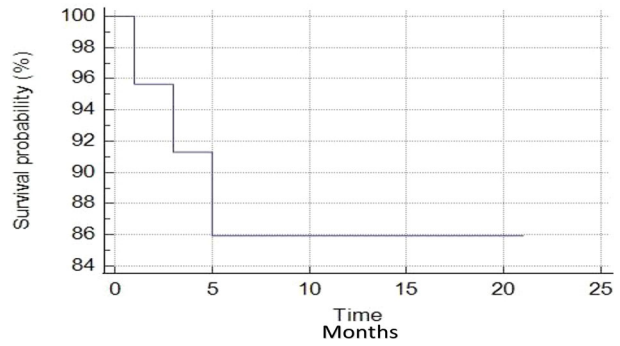

FIGURE 2 | Biochemical relapse-free survival curve.

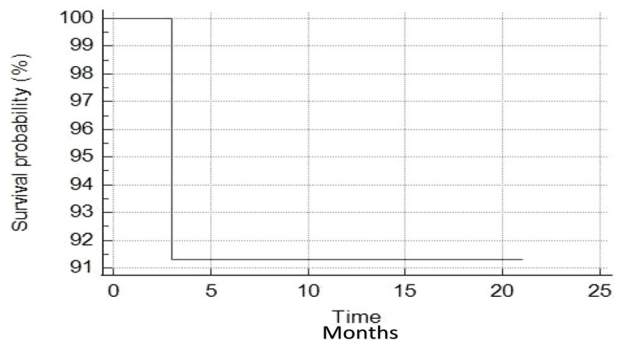

FIGURE 3 | Androgen deprivation therapy-free survival curve.

superior organs-at-risk sparing and improved target coverage. This was also reported in a previous study of comparison between MR-guided SBRT and conventional linac-based SBRT for curative prostate cancer treatment, resulting in a lower rate of constraint violations in the cohort of patients treated with 1.5T MR-Linac (19).

The favorable toxicity pattern of the present study is in agreement with the available literature evidence: when compared to other treatment modalities such as radical prostatectomy, as reported in the MASTER meta-analysis, HDR- and LDR-brachytherapy along with SBRT have been described as the techniques collecting a lower incidence of severe GI and GU adverse events (5).

In our series, no re-biopsy was performed for a histological confirmation of recurrence. As also stated in the ESTRO-ACROP consensus, this issue remains a matter of debate as some Authors support the reliability of modern metabolic and morphologic imaging as a trustworthy surrogate of pathological confirmation (6).

Also the optimal total dose remains a matter of debate, with some Authors hypothesizing a potential radiosensitizer effect of ADT; therefore, we decided to apply the most commonly adopted fractionation regimen according to other literature experiences and institutional previous studies (20). Nonetheless, given the constantly growing attention towards this treatment option and the encouraging results recorded to date, future phase I-II trials may provide stronger evidence to identify the optimal dose to achieve a longer ADT-free interval.

Concerning the target volume delineation in the case of prostate re-irradiation, we decided to treat the entire gland in light of the multifocal nature of prostate cancer, although some experiences favorably report the role of focal re-irradiation as a means to achieve improved toxicity outcomes (21).

As far as clinical outcomes, keeping in mind the limited follow-up, our data are in agreement with previously published experiences, supporting the role of re-irradiation as an effective alternative to the premature start of ADT, with only 2 patients that received ADT after the SBRT treatment.

The present study has some limitations: first, the small sample size of the cohort affects the power of the evidence, secondly, the follow-up is relatively short. Nonetheless, this experience represents the largest series of patients treated with MR-guided daily adapted stereotactic re-irradiation for prostate cancer.

CONCLUSIONS

Our experience supports the use of MR-linacs for prostate or prostate bed re-irradiation as a feasible and safe treatment option with minimal toxicity and encouraging results in terms of clinical outcomes. More mature data are warranted in order to further confirm the preliminary data of this study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

Conception of the study: FC, MR, FA. Drafting of the manuscript: FC, MR, VF, RM. Data collection: LN, FR, NGL, GT. Data analysis: DG, SN, GS, ADS, Manuscript editing: RR, FA.

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Imaging Biomarkers in Prostate Stereotactic Body Radiotherapy: A Review and Clinical Trial Protocol

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Advances in imaging have changed prostate radiotherapy through improved biochemical control from focal boost and improved detection of recurrence. These advances are reviewed in the context of prostate stereotactic body radiation therapy (SBRT) and the ARGOS/CLIMBER trial protocol. ARGOS/CLIMBER will evaluate 1) the safety and feasibility of SBRT with focal boost guided by multiparametric MRI (mpMRI) and ^{18}F-PSMA-1007 PET and 2) imaging and laboratory biomarkers for response to SBRT. To date, response to prostate SBRT is most commonly evaluated using the Phoenix Criteria for biochemical failure. The drawbacks of this approach include lack of lesion identification, a high false-positive rate, and delay in identifying treatment failure. Patients in ARGOS/CLIMBER will receive dynamic ^{18}F-PSMA-1007 PET and mpMRI prior to SBRT for treatment planning and at 6 and 24 months after SBRT to assess response. Imaging findings will be correlated with prostate-specific antigen (PSA) and biopsy results, with the goal of early, non-invasive, and accurate identification of treatment failure.

Keywords: SBRT, prostate cancer, PSMA PET, MRI, stereotactic, ultrahypofractionated

INTRODUCTION AND BACKGROUND

External beam radiation therapy (EBRT) is a primary treatment modality for men with intermediate and high-risk prostate cancer. Conventional treatments are typically with fractions of 1.8–2.0 Gray (Gy)/day over a treatment duration of up to 8 weeks (70–80 Gy in 35–40 fractions). Biochemical failure (BF), as defined by the Phoenix Criteria (prostate-specific antigen [PSA] rise by 2 ng/ml or

more above nadir PSA) (1), occurs in up to 35% of treated patients treated with standard EBRT by 10 years (2). Recent advances in image guidance and dose delivery have enabled new forms of EBRT, including stereotactic body radiation therapy (SBRT) (3) and focal intra-prostatic boost (4–6).

After radiation therapy, local recurrence occurs primarily at the sites of macroscopic dominant intraprostatic lesions (DILs) (7, 8). Comprehensive planning studies suggest that focal EBRT boost to DILs is dosimetrically feasible for a wide range of dose fractionations without exceeding normal tissue tolerances (9, 10). Most studies have used multiparametric MRI (mpMRI) to identify DILs in focal prostate radiation therapy (**Table 1**). The randomized controlled clinical trial FLAME showed that focal boost to DILs using standard fractionations improves the 5-year biochemical progression-free survival (bPFS) with acceptable toxicity (5, 12). DELINEATE, a single-center prospective phase II multicohort study, also confirmed the feasibility of DIL boost with standard and moderate fractionations with rectal and genitourinary (GU) toxicity comparable to contemporary series without intraprostatic boost (11). The safety and feasibility of DIL boost in extreme hypofractionation (five fractions) were validated in the Phase II 5STAR and Hypo-Flame trials (4, 6). These trials showed that toxicity for DIL boost with extreme hypofractionation compares to toxicity without boost and was lower than toxicity in the FLAME trial. Even with focal boost, however, intra-prostatic failure may be seen as a site of failure (13). Early detection of local recurrence after radiotherapy enables deployment of potentially curative salvage therapies (14, 15).

Multiple studies have evaluated the boost of DILs using mpMRI for target delineation. However, mpMRI can miss some intraprostatic lesions or significantly underestimate lesion size (16). Prostate-specific membrane antigen (PSMA)-targeted positron emission tomography (PET) complements mpMRI and improves the detection and characterization of intraprostatic cancer and nodal disease in the primary setting (17–20). As such, it may improve oncologic outcomes through more accurate delineation of focal boost volumes (17, 18, 21). Additionally, PSMA PET provides better distant staging and can identify extra-prostatic extension, especially among men with higher risk disease (22). ^{68}Ga-PSMA-11 is the most widely studied and ^{18}F-DCFPyL is the next most commonly studied PSMA radioligand (23, 24). The advantages of fluorinated compounds like ^{18}F-DCFPyL compared to gallium-based compounds like ^{68}Ga-PSMA-11 include improved spatial resolution and a longer half-life, which allows for centralized production and transportation to remote facilities (25). ^{18}F-PSMA-1007 is a third PSMA radioligand with a growing body of evidence. The primary advantage of ^{18}F-PSMA-1007 compared to ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL is its reduced urinary clearance, which allows for improved assessment of the pelvic region, making it especially suitable for the evaluation of DILs in the base of the prostate (26). A potential disadvantage of ^{18}F-PSMA-1007 is a higher number of false-positive bone marrow lesions noted in some series (26).

In recent years, the clinical use of ^{18}F-labeled PSMA-targeted compounds has significantly increased. ^{18}F-DCFPyL and ^{18}F-PSMA-1007 are the most clinically established ^{18}F-labeled radiotracers for PSMA-targeted PET imaging (25). For instance, ^{18}F-DCFPyL demonstrated high sensitivity for the detection of clinically significant intraprostatic tumors and biochemically recurrent prostate cancer, in addition to a high potential to measure total tumor burden for treatment planning (27, 28). We have demonstrated through a prospective trial of the preoperative imaging that ^{18}F-DCFPyL-PET/MRI could identify DILs as verified by whole-mount pathology images (29). The performance of delineation of DILs for focal treatment could be optimized by using a 67% threshold of the maximum intra-

TABLE 1 | Selected prospective evidence for focal intra-prostatic boost.

Trial	Trial type	Groups	Number of patients in analysis	Dose/ fractionation to prostate	Dose/ fractionation to pelvic nodes	Boost volume definition	Dose/ fractionation to boost volume	Primary endpoint result
FLAME (5)	Multicenter RCT	Prostate RT ± GTV boost	571 total	77 Gy/35	n/a	GTV on mpMRI	Up to 95 Gy/ 35	Improved 5-year biochemical DFS in boost arm (92% vs. 85%)
DELINEATE (11)	Prospective single-center multi-cohort trial	Cohorts A (standard fractionation) and B (moderately hypofractionated)	105 total	Cohort A: 74 Gy/37 Cohort B: 60 Gy/20	n/a	GTV on mpMRI plus 2-mm expansion, excluding the urethra	Cohort A: up to 82 Gy/37 Cohort B: up to 67 Gy/20	Grade 2+ late rectal toxicity at 1 year was 4% for Cohort A and 8% for Cohort B
Hypo-FLAME (4)	Prospective multicenter single-arm trial	Single cohort	100	35 Gy/5 delivered weekly over 29 days	n/a	GTV on mpMRI	Up to 50 Gy/ 5	Acute grade 2+ GI toxicity 5%, acute grade 2+ GU toxicity 34%
5STAR (6)	Prospective single-center single arm trial	Single cohort	30	35 Gy/5 delivered weekly over 29 days	25 Gy/5	GTV on mpMRI	Up to 50 Gy/ 5	Acute grade 2+ GI toxicity 5%, acute grade 2+ GU toxicity 20%

RCT, randomized controlled trial; GTV, gross tumor volume; mpMRI, multiparametric MRI; DFS, disease-free survival; GU, genitourinary; n/a, not applicable.

prostatic standard uptake value (SUV) with an 8-mm margin to maximize coverage of histologically defined lesions (30).

The alternate PSMA-targeting agent, ^{18}F-PSMA-1007, offers additional advantages related to the delineation of intraprostatic lesions. While ^{18}F-DCFPyL is excreted by renal clearance into the urinary bladder, ^{18}F-PSMA-1007 is excreted by the hepatobiliary system and therefore causes no or minimal bladder activity. A comparison of ^{18}F-PSMA-1007 PET/CT with radical prostatectomy histology and mpMRI (n = 10) showed a slightly better performance than mpMRI with fewer false negatives and fewer false positives (31). A clinical comparison of [^{18}F]DCFPyL and ^{18}F-PSMA-1007 (n = 12) found excellent image quality and identical clinical findings. Both radiotracers were equivalent for imaging of local and metastatic prostate cancer. However, the non-urinary excretion of ^{18}F-PSMA-1007 offers advantages regarding the delineation of local recurrences and lymph node metastases (32). Prive et al. evaluated ^{18}F-PSMA-1007 and mpMRI and compared their histopathology for the primary staging of prostate cancer in 53 patients diagnosed with intermediate and high-risk prostate cancer. PSMA improved the detection of seminal vesicle invasion, while MRI offered a better resolution in evaluating extracapsular extension (33). The study suggested that dual imaging may improve the staging of prostate cancer. A 20% SUVmax threshold using ^{18}F-PSMA-1007 was recently demonstrated to offer the best combination of sensitivity and specificity in delineating DILs, and volumes so defined accounted for approximately 21% of the total prostate volume on average (18).

Another application for advanced imaging in SBRT prostate treatment is in response assessment. To date, evaluation of success following SBRT is most commonly by biochemical means, and successful SBRT is associated with low PSA nadirs comparable to those noted with brachytherapy (34). Biochemical control is a suboptimal method to assess recurrence in patients due to a lack of spatial information, potential false positives, and delayed identification of failure based on rising PSA. First, the lack of lesion identification using PSA-based criteria alone prevents successful local or metastasis-directed salvage without the use of imaging. Given the potential toxicity of local salvage, identification of isolated local recurrence is critical (14). Secondly, the Phoenix Criteria has a false-positive rate in patients who receive SBRT. In a multi-institutional pooled analysis of over 2,000 patients who received prostate SBRT, the Phoenix Criteria was associated with a false-positive rate of 30% (35). Finally, the Phoenix Criteria occurs late. Patients who have local failure may not reach the Phoenix Criteria for years and may lose the opportunity for successful local salvage. A retrospective study showed that up to 38% of patients who received SBRT to doses of 32.5 Gy or higher in 5 fractions had a positive prostate biopsy 2 years after SBRT (36). However, just 12.5% of these patients had reached the Phoenix Criteria at the time of biopsy. Even in patients with a PSA of less than 1 ng/ml prior to biopsy, up to 25% of patients had a positive biopsy (36). Most patients with a positive 2-year biopsy would reach BF at 5 years (57% vs. 7% as compared to those with a negative biopsy), even after 35% of patients with a positive 2-year biopsy received salvage therapies. In another retrospective study, 63 patients, mostly with high-risk prostate cancer (40/63, 64%), received PSMA-targeted PET/CT for rising PSA that did not meet the Phoenix Criteria after primary conventional or moderately hypofractionated EBRT (37). Median rise above nadir PSA prior to PET was 1.2 ng/ml, and median PSA was 1.3 ng/ml. Recurrence was detected in 84% of patients (53/63). While 21/63 patients (33%) had local recurrence only, 14/63 (22%) had nodal recurrence without distant metastases, and 18/63 (18%) had distant metastases. Given the efficacy and toxicity of curative-intent local salvage treatments, improved and early identification of isolated local recurrence is needed (14, 15).

Identification of local recurrence after EBRT has been explored with timed biopsy or mpMRI after radiotherapy (38). Prostate biopsy at 2 years posttreatment has been associated with clinical endpoints such as subsequent BF and distant metastases (36, 39). However, drawbacks of biopsy include unreliable results at earlier timepoints and potential morbidity (39). "Metabolic clearance" as defined by serial MRI with spectroscopy has been associated with durable biochemical control in retrospective series of men treated with conventional external beam radiotherapy (40–43). Recently, standardized mpMRI reporting for the locally recurrent disease has been proposed but has not yet been validated in larger prospective series (44). Additionally, there is a lack of prospective studies validating posttreatment mpMRI as a predictive biomarker in larger populations and men treated with SBRT.

PSMA-targeted PET/CT in addition to mpMRI improves detection of local recurrence after EBRT (45). However, while criteria for the response have been broadly defined (46), the significance of PSMA response and correlation with clinical endpoints are not known (47). As such, longitudinal monitoring of PSMA PET/CT changes post-radiotherapy, including changes in SUVmax and other PSMA PET based metrics, should be investigated as potential non-invasive biomarkers of treatment response after SBRT to the prostate. Integration of earlier PET-based response assessment, compared to triggered restaging at the time of BF, may provide an opportunity for earlier targeted salvage, but a lack of prospective longitudinal series of men so monitored is a gap in the current evidence base (23). Indeed, reports of false-positive PET scans in previously treated patients underscore the importance of systematically characterizing the normal patterns of PSMA PET/CT changes after SBRT and their correlation with clinical endpoints (48, 49).

Beyond identifying local recurrence, determining the presence and extent of extra-prostatic recurrence has historically been challenging to determine due to the poor sensitivity of CT and bone scans. PET-based imaging potentially addresses this gap (23). A number of PET tracers have been developed for the detection of recurrent prostate cancer, including ^{18}F-NaF, ^{18}F-FACBC (fluciclovine), ^{18}F-choline, and ^{11}C-choline (50). More recently, PSMA-targeted PET has demonstrated improved detection rates as compared to previous modalities and is recommended for restaging recurrent

disease (23, 24, 50, 51). Specifically, for patients with BF after primary radiotherapy, a prospective trial showed that compared to conventional imaging, PSMA-targeted PET/CT detected extra-prostatic recurrence in twice as many patients (39% vs. 19%) (52, 53). Furthermore, in a network meta-analysis of intra-individual imaging studies of different radiotracers, PSMA-based tracers in general, and ^{18}F-PSMA-1007 specifically, were found to have superior detection rates at any site as compared to other traces, including ^{18}F-FACBC, ^{18}F-choline, and ^{11}C-choline (54). However, the strength of these findings was tempered by the relatively small number of ^{18}F-1007 patients evaluated directly. While PSMA-targeted PET/CT has increased detection rates in recurrent prostate cancer, a drawback is the risk of false-positive findings. In a prospective trial that evaluated the positive predictive value of PSMA-targeted PET/CT in patients with recurrent prostate cancer, the per-region false-positive rate based on a clinical endpoint was 8% (55).

We plan to evaluate the safety of SBRT with PSMA PET/MRI-guided focal boost in a prospective early phase trial, "PSMA MRI Guided prOstate SBRT(ARGOS)." As noted, while the advanced imaging techniques described show promise for the characterization of primary or recurrent prostate cancer, no study has prospectively and longitudinally evaluated them after primary radiotherapy to characterize expected changes in response to treatment and to non-invasively identify early treatment failure. All patients in ARGOS will enter the translational component of the study Comprehensive, Longitudinal Evaluation of Imaging Biomarkers Post Radiotherapy (CLIMBER). We will use advanced imaging analysis techniques to evaluate longitudinal changes in a comprehensive battery of anatomic and functional prostate imaging panels using ^{18}F-PSMA 1007 and mpMRI acquired prior to and after SBRT. ^{18}F-PSMA-1007 is chosen given its favorable pharmacokinetics profile with primarily gastrointestinal elimination, reducing tracer accumulation in the bladder and allowing better visualization of prostate and pelvic lymph nodes. The knowledge obtained from ARGOS/CLIMBER will improve the understanding of imaging changes post-prostate SBRT and will have increasing clinical importance with increasing use of these techniques. The ARGOS/CLIMBER protocol as outlined below is due to open in early 2022, with a plan for accrual of 50 men over 3 years and with follow-up of up to 5 years for clinical endpoints.

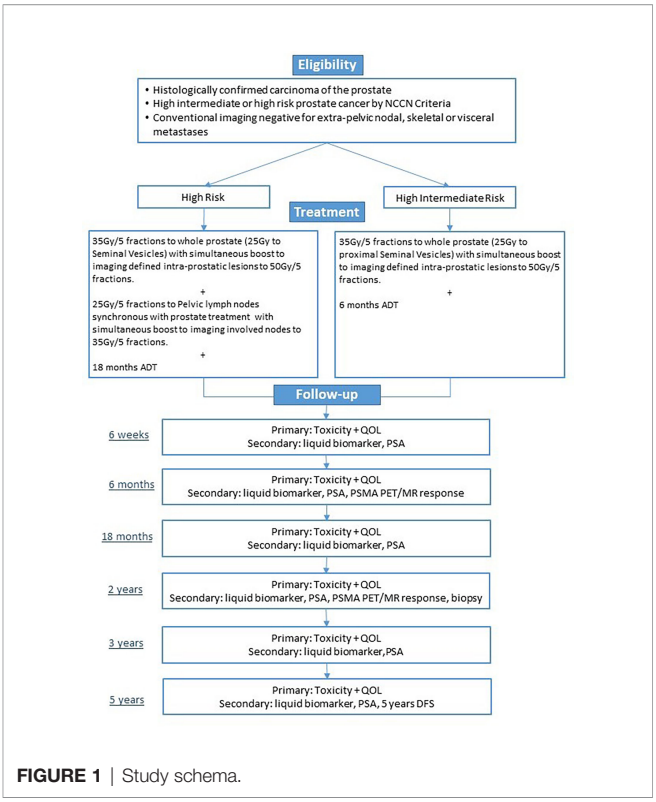

FIGURE 1 | Study schema.

ARGOS/CLIMBER

Study Design

This study is (NCT05269550) a prospective single-arm trial enrolling men with National Comprehensive Cancer Network (NCCN) unfavorable intermediate-fiducial risk, high-risk, or very-high-risk prostate cancer. The study schema is provided in **Figure 1**. All men will have PSMA-targeted PET (using the PSMA-targeting ligand ^{18}F-PSMA-1007) and mpMRI including T2-weighted (T2W), diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC), and dynamic contrast-enhanced (DCE) sequences. Delineation of intra-prostatic foci of cancer (using 20% SUVmax and suspicious mpMRI appearance) and any involved regional lymph nodes (based on MI-ES score of 2 or greater or suspicious mpMRI appearance suspicious for cancer) will be performed (16, 18). Tumor delineation will be performed by fusing the PSMA PET and mpMRI with planning CT simulation images. Fiducial marker implantation for treatment guidance will be mandatory, but the use of other organs at risk protection strategies (i.e., SpaceOAR and GU-Lok) will be allowed but not mandatory. Patients will be treated with image-guided SBRT using the fiducial markers for inter- and intra-fraction motion management. The prostate will receive 35 Gy/5 fractions, and the proximal or entire seminal vesicle will receive 25 Gy/5 fractions (**Table 2**). Dose escalation to imaging-defined targets will be accomplished through a simultaneous boost technique (targeted maximum dose of 50 Gy/5 fractions to imaging-defined prostatic lesion and 35 Gy/5 fractions to imaging-defined involved nodes; see **Figure 2**). Maintaining dose to organs at risk will take precedence over boost dose targets (**Table 3**). Patients with high-risk disease or calculated nodal involvement risk of more than 15% will receive 25 Gy/5 fractions delivered to the regional lymph nodes synchronously with the prostate treatment.

The primary endpoints of the trial will be 6-week and 6-month gastrointestinal (GI) and GU toxicity using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). While other prospective trials have confirmed the safety of an mpMRI-defined intra-prostatic boost with external beam radiotherapy (4, 6), the proposed boost volume in ARGOS/CLIMBER will be based on mpMRI and PSMA PET-targeted

TABLE 2 | Target structures nomenclature and descriptions.

Name*	Description
High intermediate risk	
CTV_35Gy	Entire prostate including the GTVp_boost volumes
PTV_35Gy	CTV_35Gy + 3–4 mm
GTVp_boost	Intraprostatic GTV delineated as the union of mpMRI-defined PiRADS 4–5 intra-prostatic lesions with the PET-defined intra-prostatic lesions using threshold of 20% SUVmax (see text above). Where the seminal vesicle(s) are involved by PET or MRI, the involved portion will be included in the GTVp_boost volume(s)
PTVp_boost	GTVp_boost + 3–4 mm
CTV_ProxSV_25Gy	Proximal 1.0 cm of the seminal vesicles. The 1 cm of the seminal vesicles is measured superiorly from its origin at the prostate (not from the superior aspect of the prostate)
PTV_ProxSV_25Gy	CTV_ProxSV_25Gy + 4 mm
High or Very High Risk	
CTV_35Gy	Entire prostate including the GTVp_boost volumes
PTV_35Gy	CTV_35Gy + 3–4 mm
GTVp_boost	Intraprostatic GTV delineated as the union of mpMRI-defined PiRADS 4–5 intra-prostatic lesions with the PET-defined intra-prostatic lesions using threshold of 20% SUVmax (see text above). Where the seminal vesicle(s) are involved by PET or MRI, the involved portion will be included in the GTVp_boost volume(s)
PTVp_boost	GTVp_boost + 3–4 mm
CTV_ SV_25Gy	Entire seminal vesicle volume
PTV_SV_25Gy	CTV_SV_25Gy + 6 mm
CTVn_25Gy	Pelvic lymph nodes. To be contoured according to the NRG guidelines [51] to encompass a 0.7-cm radial expansion around the external iliac, internal iliac vessels, and obturator and presacral spaces
PTVn_25Gy	CTVn_25Gy + 6 mm
GTVn_boost	Positive pelvic lymph nodes delineated on PET/MRI as MI-ES 2 or higher
PTVn_boost	GTVn_boost + 6 mm

**GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; mpMRI, multiparametric MRI.*

PET (17), and thus there is a need to demonstrate the safety of such a multi-modality defined boost volume. Secondary endpoints include Quality of life measured by the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaires and 5-year disease-free survival (DFS) as a composite of BF, patient death, or development of clinical metastases or institution of salvage ADT.

All grade 3 or higher toxicity will be reported to the principal investigator. An independent data and safety monitoring board (IDSMB) will perform a formal interim analysis for safety and toxicity when half of the patients have been accrued or after 1 year, whichever comes first. The study will be discontinued if the projected rate of grade 3 or higher urinary or bowel toxicity exceeds 30%. IDSMB will meet at least annually to review trial data.

Unique to the ARGOS/CLIMBER protocol is the integration of longitudinal imaging with PSMA-directed PET and mpMRI pretreatment and posttreatment. Serial PSMA PET/MR images will be collected at baseline, 6 months, and 2 years to characterize the imaging response of prostate cancer to treatment and potentially identify imaging biomarkers (including pharmacokinetics, radiomics, and quantitative PET and

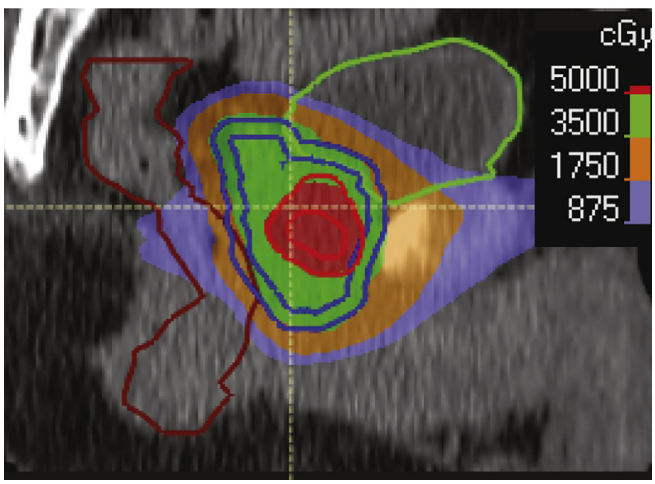

FIGURE 2 | Example of focal dose escalation.

TABLE 3 | Dose constraints.

Structures and dose constraints (acceptable deviations)			
Rectum	V20Gy ≤ 50% (optimal) V28Gy ≤ 15% (20%) V32Gy ≤ 10% (15%) V35Gy ≤ 2 cc (4 cc) V38Gy ≤ 1 cc Dmax ≤ 40.6 Gy	**Bladder**	V20Gy ≤ 50% (optimal) V28Gy ≤ 15% (20%) V32Gy ≤ 10% (15%) V38Gy ≤ 6 cc V39.5Gy ≤ 2 cc
Rectum_PRV	Dmax ≤ 45 Gy	**Bladder_PRV**	Dmax ≤ 46 Gy (optimal)
Urethra_PRV	Dmax ≤ 52 Gy D10% ≤ 47.2 Gy D50% ≤ 42 Gy (optimal)	**Penile Bulb**	V20Gy ≤ 40% (90%) V35Gy ≤ 4%
Bowel_Small	V25Gy ≤ 20 cc (40cc) V30Gy ≤ 2 cc Dmax ≤ 3 5Gy	**Bowel_Large**	V25Gy ≤ 20 cc (40 cc) Dmax ≤ 38 Gy
Femur_R and Femur_L	V28Gy ≤ 5%		

mpMRI metrics) that predict for 5-year DFS (**Table 4**). Additionally, baseline collection of diagnostic tissue biopsy samples and serial collection of blood and urine over multiple time points (baseline, 6 months, 1 year, and 2 years post-SBRT) will be performed for correlative biologic biomarker analyses with imaging changes, DFS, and toxicity posttreatment. Analysis of prostate biopsy at baseline and 2 years will allow for correlation of histopathology with PSMA PET/MR images. We will investigate whether a negative posttreatment PSMA PET/MRI is correlated with a negative 2-year posttreatment biopsy and long-term disease control (36, 39). We also plan to examine novel clinical prognostic biomarkers (i.e., absolute percentage of Gleason Pattern 4 on biopsy and 4-year PSA response rate) and their correlation with imaging findings and 5-year DFS.

PET Imaging Acquisition

Integrated PSMA PET/MRI is preferred with the goal of achieving co-registered PSMA PET and MR images with high spatial fidelity for planning and assessing response to treatment. PSMA PET/CT plus mpMRI are also allowed within the protocol if there is an unavailability of a PET/MRI scanner. We have previously demonstrated the value of early dynamic PET imaging in the identification of intra-prostatic lesions and will incorporate both dynamic and delayed PET imaging (56).

The evening before each PSMA PET examination, patients will be asked to take 30 ml of milk of magnesia, an over-the-counter laxative, which will be provided. Patients should be NPO overnight prior to the exam (~12 h). The bladder should be comfortably full and the rectum as empty as possible prior to image acquisition.

For dynamic PET imaging, the participants will be injected with 3–4 MBq/kg (up to a maximum 400 MBq) of ^{18}F-PSMA-1007. Dynamic PET acquisitions will start immediately prior to ^{18}F-PSMA 1007 injection and will be acquired simultaneously with the cross-sectional pelvic MR images (for PET/MRI) or CT images (for PET/CT). Dynamic PET acquisition will cover the whole prostate up to the iliac crest. An image-derived arterial time–activity curve required for kinetic analysis of dynamic PET data will be acquired from an internal iliac artery to generate parametric maps. Starting at the injection of ^{18}F-PSMA-1007 as a bolus into an antecubital vein, the dynamic PET scan will be acquired over 22 min with seven framing intervals: 10, 20, 40, 60,

TABLE 4 | Schedule of events.

Event	Weeks (week 0 is start of RT)										Q6mo (30–60mo)
	–3	–2	0	1 EOT	3	8 (6 weeks post-RT)	6 months post-RT	12 months post-RT	18 months post-RT	24 months post-RT	
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11–15
Start alpha antagonists, simethicone	x										
Fiducial marker insertion		x									
Simulation and planning		x									
Treatment (5 fractions q2d, 10–12 days)			x	x							
CTCAE v5.0	x		x	x	x	x	x	x	x	x	x
EPIC-26 questionnaires	x		x	x		x	x	x	x	x	x
PSA and testosterone	x					x	x	x	x	x	
PSMA PET/MRI		x					x			x	
Liquid biomarker collection		x				x	x	x		x	
Transperineal biopsy		x								x	

CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

and 180 s. Early time standardized uptake (SUV_{early}) in g/ml will be measured as the average of the last four dynamic PET volumes (10–22 min post-injection). The acquired dynamic volumes will be analyzed to generate parametric maps of the whole prostate, including influx rate constant (K_1), efflux rate constant (k_2), binding rate constant (k_3), dissociation rate constant (k_4), net uptake rate constant from plasma (K_i), and distribution volume (DV) maps by deconvolving the arterial time–activity curve from tissue time–activity curve using a flow-modified two-tissue compartment (F2TC) model. After dynamic pelvic PET, participants will be allowed to get up and take a break/empty their bladder prior to the acquisition of late uptake PSMA-1007 PET images (60–120 min post-injection). For PET/CT, the PET images will be acquired with corresponding axial CT images obtained (for anatomic correlation and attenuation correction).

For PET/MRI, a whole-body MRI scout scan (to plan the study) and B0 homogenization using gradient enhancement (HUGE) acquisition (to correct for truncation of arms) will be acquired first. In both acquisitions, the table moves continuously for approximately 1 min as it scans the subject from head to thigh. Whole-body PET/MRI is acquired in multiple bed positions. For men of average height, 5 overlapping table positions will be used, with taller subjects requiring an additional table position. At each table position, a 5-min PET acquisition will be acquired along with simultaneous MRI consisting of MRI-based attenuation correction, coronal T2-weighted fast spin-echo with Short-TI Inversion Recovery (STIR) sequence during flat breathing, and axial Half-Fourier Acquisition Single-shot Turbo spin-Echo (HASTE) single-shot T2-weighted sequence. For thoracic and abdominal table positions, the HASTE MRI will be captured over 4 breath-holds of 14 s. If unable to do so, these can be done with flat breathing only.

Pelvic Multiparametric MRI Acquisition

For men imaged with PET/MRI, the pelvic mpMRI will be acquired after whole-body PET/MRI on the PET/MRI scanner. For men imaged with PET/CT, mpMRI will be acquired as a separate study on a 3T magnetic resonance scanner. The bladder should be comfortably full and the rectum as empty as possible prior to the mpMRI scanning. For mpMRI scout scans, sagittal 2D T2-weighted, coronal 2D T2-weighted MRI, axial 3D T2-weighted, and 2D axial diffusion-weighted EPI will be acquired. Prior to a 3D DCE T1-weighted MRI, a radiologist or designate will administer an intravenous injection of GADOVIST® 1.0 (Gadobutrol) with the MEDRAD Injection System (0.1 mmol/kg). Following DCE-MRI, whole-body late gadolinium-enhanced MRI will be acquired with T1-weighted volumetric interpolated breath-hold examination (VIBE) with fat saturation and breath-hold in thoracic and abdominal table positions.

Primary Endpoint and Sample Size

This will be a single-phase pilot study of 50 patients with a primary endpoint of GI and GU toxicity as measured by CTCAE v5.0.

Unacceptable toxicity will be defined as acute (6 weeks) or intermediate (6 months) grade >3 GI or GU toxicity. The proposed treatment will be deemed too toxic if >30% of patients have unacceptable toxicity. This study tests the hypothesis that acute toxicity is <30% (alpha = 0.05, power = 81%, one-sided, H0: p = .30, HA: p <.30), with an assumed true proportion in this study of 15%. These calculations were done based on a Z test (normal approximation). We will test this assumption with the exact test approach if we do not meet our target accrual of 50 men or the proportion of Grade 3 toxicity is significantly less than 15% (conditions where normal approximation is not met).

Given that the proPSMA study demonstrated that 16% of men with high-risk prostate cancer had extra-prostatic disease beyond regional nodal metastases at initial staging and the fact our population will be a mix of high-intermediate and high-risk men, we will plan to enroll a total of 55 men (22). Those men with extra-prostatic spread beyond regional pelvic lymph nodes on their pretreatment PSMA PET imaging will be treated off protocol at the attending physician's discretion.

Secondary Endpoints

Quality of Life

Descriptive statistics and diagrams will be used to characterize changes in Quality of Life metrics as measured by the EPIC-26. A linear mixed model with random intercept by an individual to account for the correlation present within individuals will be used to compare pretreatment vs. posttreatment quality of life measures at multiple timepoints with the goal of tracking minimally important differences in these parameters (57).

Disease-Free Survival

Five-year DFS will be determined as a composite of biochemical control, patient death or development of clinical metastases, or institution of salvage ADT. DFS will be estimated with a Kaplan–Meier (KM) curve, with the 5-year estimate extracted from the KM curve.

Translational Imaging Endpoints

Changes in SUV metrics (SUVmax, SUVmean) within PSMA PET regions of interest (ROI) will be compared between the pre-RT PSMA PET and the 6-month post-RT PSMA PET. ROIs to be examined will include the dominant intra-prostatic lesions (DILs), the prostate as a whole, and, in the cases of men with PET-detected nodal disease, involved node ROIs. Descriptive statistics and diagrams (i.e., waterfall plots) will be used to characterize changes in SUV metrics. A linear mixed model with random intercept by an individual to account for the correlation present within individuals will be used to compare pretreatment vs. posttreatment SUV values at multiple timepoints. Overall response rates will be calculated in accordance with recent consensus guidelines (46).

Intra-prostatic mpMRI (T2W, DWI, and DCE-MRI) acquired pre-RT and 6 and 24 months post-RT will be reported by expert readers based on PI-RADS 2.1 and the complementary Prostate Imaging for Recurrence Reporting (PI-RR) system to identify intra-prostatic ROIs (44). Quantitative MRI metrics will be extracted, including ADC and pharmacokinetics parameters derived from dynamic PET and DCE-MRI. Radiomics approaches will be used to characterize the evolution of higher-level feature changes in PET and mpMRI over the course of treatment.

We will correlate changes in PET and mpMRI metrics at 6 and 24 months with 5-year DFS using linear regression models. We will also perform supervised machine learning to train support vector machines and random forest classifiers to predict response based on the pretreatment images. We will also perform a delta-radiomics analysis to predict response based on the radiomics trajectory computed from the first two time points. We will measure the performance of the classifiers using a cross-validation design, with metrics including the area under the receiver operating characteristic (ROC) curve and the error rate, false-positive rate, and false-negative rate computed at a point on the ROC curve that best balance the false-positive and false-negative rates. We will develop radiomics-based classifiers to predict 5-year DFS.

Baseline (pretreatment) and 24-month (posttreatment) tissue samples will be acquired for histopathologic correlations with PET/MR images. Specifically, baseline biopsy will provide histologic correlation for the PSMA- and mpMRI-identified dominant intra-prostatic lesions. Additionally, 24-month biopsies have been shown to correlate with long-term failure-free survival (36, 39), and rates of cancer clearance after stereotactic techniques have been shown to increase with increasing doses of radiation (58). Understanding histologic correlations and clearance of cancer from the boosted and non-boosted prostate areas will be of interest and will allow for correlation with PET/MR images to validate PET+MRI as non-invasive surrogates for identifying intra-prostatic cancer foci.

DISCUSSION/CONCLUSION

Advanced prostate imaging with mpMRI and novel PET agents has the potential to improve prostate cancer management across the disease spectrum (23). In the primary management of prostate cancer, improved imaging guidance has allowed for radiotherapy advances for prostate cancer, including prostate SBRT and focal boost (3–6, 11). Ongoing trials are evaluating SBRT with focal boost guided by mpMRI and PSMA-PET (NCT04243941, NCT04402151, and NCT04599699) (21, 59). The ARGOS/CLIMBER trial will explore the safety of SBRT with focal boost guided by mpMRI and ^{18}F-PSMA-1007 PET.

In addition, advanced imaging has improved the ability to characterize patterns of disease recurrence and identify men with isolated local recurrence who may be suitable for local salvage or oligometastatic recurrence who may be eligible for metastasis-directed therapy (14, 45, 52, 60). To date, response to prostate SBRT is mostly commonly evaluated using biochemical response with the Phoenix Criteria for BF. The drawbacks of this approach include lack of lesion identification, a high false-positive rate, and delay in identifying treatment failure. An important knowledge gap is the expected evolution of imaging changes post-SBRT and whether patterns in these changes can serve as early biomarkers of disease recurrence. Patients in ARGOS/CLIMBER will receive dynamic ^{18}F-PSMA-1007 PET and mpMRI prior to SBRT and at 6 and 24 months after SBRT. Imaging findings will be correlated with PSA and biopsy results, with the goal of early, non-invasive, and accurate identification of treatment failure.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ontario Cancer Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the project design and manuscript drafting. All authors approved the publication of the content and agree to be accountable for all aspects of the work.

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Survival Outcomes and Pattern of Relapse After SABR for Oligometastatic Prostate Cancer

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Introduction: The addition of stereotactic ablative radiotherapy (SABR) to standard of care for patients with oligometastatic prostate cancer has the potential of improving survival and delaying further metastases. The primary aim of this analysis is to report survival outcomes and pattern of recurrence of patients with hormone-sensitive (HSPC) and castrate-resistant (CRPC) oligometastatic prostate cancer treated with SABR.

Methods: This is a single-center retrospective study of patients with oligometastatic prostate cancer treated in Iridium Network between 2014 and 2018. All patients with oligometastatic (≤3 active lesions) HSPC and CRPC treated with SABR were included. Data were collected using electronic records. Patterns of first progression following SABR were reported. Kaplan-Meier methods were used to determine survival outcomes.

Results: Eighty-seven men received SABR to 115 metastases. Nineteen patients were castrate-resistant and 68 hormone-sensitive at the time of SABR. Median follow-up was 41.6 months. In 25% of patients, no decline from baseline PSA was recorded. Median bPFS was 11.7 months (95% CI 7.6 - 18.3) for HSPC as well as CRPC (95% CI 6.4 - 24.0) (p=0.27). Median DMFS was 21.8 (95% CI 16.9 - 43.2) versus 17.6 months (95% CI 6.7 - 26.2) for HSPC versus CRPC, respectively (p=0.018). Median OS was 72.6 months (95% CI 72.6 – not reached) for HSPC and not reached for CRPC (95% CI 35.4 months – not reached) (p=0.026). For the subgroup of oligorecurrent HSPC, short-term androgen-deprivation therapy was associated with improved bPFS (median 6.0 vs. 18.3 months, HR 0.31, p<0.001) and DMFS (median 15.8 vs 29.6 months, HR 0.5, p=0.06). Information on pattern of relapse was retrieved for 79 patients: 45% (36/79) of these patients were long-term disease-free (>18 months), 28% (22/79) of patients wmere oligoprogressive (≤3 new lesions) and 27% (21/79) developed a polymetastatic relapse.

Conclusion: In this cohort, oligometastatic HSPC showed potential benefit from SABR with a median DMFS of 21.8 months. Well-selected patients with oligometastatic CRPC may also benefit from SABR. For patients with metachronous and repeat oligorecurrent HSPC, combining SABR with short-term androgen-deprivation therapy was associated with improved bPFS and DMFS. Overall, 36/87 (41%) of patients were still free from clinical relapse at 18 months.

Keywords: oligometastasis, stereotactic ablative radiotherapy, stereotactic body radiotherapy, radiosurgery, prostate cancer, prostatic neoplasms, neoplasm recurrence, neoplasm metastasis

INTRODUCTION

Oligometastatic disease (OMD) is defined as an intermediate stage of cancer spread between locoregional and widespread metastatic disease and can include a wide spectrum of disease biologies and clinical behaviors (1). OMD is increasingly diagnosed in prostate cancer (PCa) owing on the one hand to improved detection with advanced imaging like prostate-specific membrane antigen (PSMA) PET-CT and on the other hand to the success of systemic therapies in prolonging cancer survival. Even so, the biological features of OMD are poorly defined. Until biomarkers are identified to distinguish OMDs with truly limited metastatic capacity from those with fast-progressing behavior, it is a reasonable strategy to select patients based on clinical assumptions. The European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) have proposed a classification in nine OMD subtypes, reflecting the different clinical states and underlying biological processes of OMD (2).

There is increasing evidence to suggest that patients with prostate OMD could benefit from more aggressive local treatment of the metastases, so-called metastasis-directed treatment, to obtain deep remission or possibly cure while preserving functional status (3, 4). In this regard, stereotactic ablative radiotherapy (SABR) offers a safe and effective treatment option.

Considering the lack of a standardized definition of oligometastatic disease, patient selection for SABR needs to be clarified. Therefore, the primary aim of this analysis was to report survival outcomes of a heterogeneous group of patients from a real-world setting with hormone-sensitive (HSPC) and castrate-resistant (CRPC) oligometastatic prostate cancer treated with SABR and analyze pattern of relapse.

MATERIALS AND METHODS

Study Population

The current analysis is based on a single-center retrospective database of patients with oligometastatic PCa treated in Iridium Network between December 2014 and December 2018. All patients with oligometastatic (≤3 active lesions) HSPC and CRPC treated with SABR were included. Metastatic lesions could be diagnosed on conventional (bone scintigraphy or CT) or innovative (whole body magnetic resonance imaging; choline or PSMA PET-CT) imaging techniques. The analysis was approved by the Ethics committee of GZA Hospitals on 30 March 2021.

Treatment

Technical aspects of SABR delivery for spinal, bone and lymph node metastases in our center have been previously described in detail (5, 6). Briefly, patients were simulated with CT scan in a comfortable, stable, and reproducible supine position. Gross tumor volume (GTV) was delineated on CT using all relevant co-registered diagnostic imaging. For spinal lesions, a clinical target volume (CTV) was delineated following the international consensus guideline (7). For other locations, CTV was equal to GTV and an isotropic margin of 3-5 mm, depending on disease site and dimensions, was added to CTV to obtain the planning target volume (PTV). Patients were treated with volumetric modulated arc therapy technique. Patient's position was evaluated daily with cone-beam CT imaging before each treatment session. Optical surface monitoring was applied during patient set-up and treatment delivery.

A risk-adapted approach was used for dose-prescription, with targets located near organs at risk receiving a more fractionated treatment. Single, 3- and 5 fraction schedules were applied. Dose per fraction ranged from 5.0 to 20.0 Gy. The use of a short-course (i.e., 6 months) of androgen-deprivation therapy, given concurrently with SABR, was always suggested but was never mandatory. For CRPC patients, the current systemic treatment was generally continued during and after SABR, until further progression.

Endpoint Assessment

Follow-up was typically scheduled every 3 months for the first 2 years following SABR and every 6 months from then on. Clinical examination and PSA values were obtained for every visit, while diagnostic imaging was planned according to physician choice.

Data were collected using electronic records. Best PSA response, biochemical progression-free survival (bPFS), distant metastasis-free survival (DMFS), overall survival (OS), local control of treated metastases (LC), as well as recurrence pattern were analyzed as endpoints. Survival endpoints were calculated from start of SABR to last follow-up or the occurrence of an event. For patients who had undergone radical prostatectomy, biochemical failure was defined as a PSA rise to 0.2 ng/mL from nadir after SABR or, if PSA did not nadir below

0.2 ng/mL, the first rise in PSA after reaching nadir. For patients treated with radiotherapy to the primary prostate, the Phoenix definition of biochemical progression was upheld, i.e., PSA nadir +2 ng/mL. Initiation of systemic therapy, local recurrence or distant recurrence prior to reaching numerical definition of PSA failure was considered as biochemical failure in both instances. Distant metastasis was defined as a new, metastatic lesion outside the SABR target volumes. Survival was defined as death from any cause. Local control was defined as the absence of radiological tumor growth within the irradiated region. Regarding recurrence pattern, there were 3 categories: long-term (>18 months) disease free, oligoprogressor (≤ 3 new lesions) and polymetastatic progressor (>3 new lesions).

Statistical Analysis

Median follow-up was calculated using the reverse Kaplan-Meier method. Kaplan-Meier survivor function and log rank test were used to calculate time-to-event outcomes. Univariate analysis was performed to evaluate the association between clinical factors and survival with the log-rank test, and Cox proportional hazards regression was used to estimate hazard ratios (HR).

RESULTS

Patient and Treatment Characteristics

We identified 87 patients receiving SABR to a total of 115 metastases. Patient, tumor and treatment characteristics are depicted in **Table 1**. The median PSA level at the time of SABR was 2.8 ng/mL; 19 patients (22%) were castrate-resistant and 68 (78%) hormone-sensitive at that time. Most patients (60/87, 69%) presented with a single metastasis, only three (3%) patients were treated for 3 lesions. Two patients with 2 metastases were treated with SABR for their spinal lesion and a moderate hypofractionated regimen for their non-spinal bone lesion. Of the 87 patients, 13 (15%) had pelvic lymph nodes, 7 (8%) had presence of M1 nodes, 63 (72%) had bone-only disease and 4 had both lymph node and bone metastases. Following the ESTRO/EORTC consensus recommendation of OMD (2), patients were classified as follows: 6/87 (7%) with synchronous OMD and 66/87 (76%) with metachronous OMD of which 52/87 (60%) metachronous oligorecurrence and 14/87 (16%) metachronous oligoprogression; 10/87 (11%) repeat OMD of which 8/87 (9%) repeat oligorecurrence and 2% repeat oligoprogression. There were 5 (6%) patients with polymetastatic disease having oligoprogression (4/87, 5%) or oligopersistence (1%).

Of the 68 patients (78%) who were hormone-sensitive, there were 31 patients (36%) who refused hormonal therapy concurrent with SABR. Of the other 37 HSPC patients, 19 patients were on androgen-deprivation therapy (ADT) for ≤6 months, five were on anti-androgen monotherapy, and 13 remained on ADT for at least 2 years. Eighty-nine of the 115 metastases (77%) were detected by PSMA or choline PET-CT, and 4 patients (3%) were staged with whole-body MRI. The remaining 22 lesions (19%) were detected on conventional CT and bone scintigraphy.

Most lesions (68/115, 59%) were treated with a 3-fraction schedule with a median dose of 10 Gy per fraction (range 6-10). Other commonly used fractionation schedules were a single fraction of 20 Gy (used for 23/115 lesions, 20%) and 5 fractions with a median dose of 7 Gy per fraction (range 5-7). Median biological effective dose (BED), calculated assuming an α/β-ratio of 1.5 Gy for prostate carcinoma using the linear quadratic model, was 230 Gy (8).

PSA Response

Figure 1 depicts the maximum change in PSA from baseline. In 26% of patients (23/87), no decline from baseline PSA was recorded. Of the patients without a PSA decline, four had castration-resistant disease (5%). Regarding oligorecurrent mHSPC patients, PSA declined in 27/29 (93%) patients receiving SABR + hormone therapy in comparison with only in 14/31 (45%) patients receiving SABR only.

Survival Outcomes

Median follow up time was 41. 6 months (IQR 35.7 - 50.8). Median bPFS was 11.7 months (95% CI 7.6 - 18.3) for HSPC with a 3-year rate of 25% (95% CI 16 - 39) compared to 11.7 months (95% CI 6.4 - 24.0) and 6% (95% CI 1 - 43) for CRPC, respectively (p=0.27). Median DMFS was 21.8 months (95% CI 16.9 - 43.2) with a 3-year rate of 38% (95% CI 28 - 53) in the HSPC cohort, compared to 17.6 months (95% CI 6.7 - 26.2) and 6% (95% CI 1 - 43) for CRPC, respectively (p=0.018). A median OS of 72.6 months (95% CI 72.6 – not reached) and 3-year rate of 89% (95% CI 81 - 97) was observed in the HSPC group; median OS was not reached (95% CI 35.4 months – not reached) and 3-year OS rate was 68% (95% CI 49 - 93) in the CRPC group (p=0.026). Kaplan-Meier survival curves for bPFS, DMFS and OS are shown in **Figure 2**.

For the subgroup of metachronous and repeat oligorecurrent metastatic HSPC (mHSPC), the impact of the addition of ≤6 months ADT to SABR on bPFS and DMFS was evaluated. On univariate analysis, short-term ADT was associated with improved bPFS (median 6.0 vs. 18.3 months, HR 0.31, p<0.001) and DMFS (median 15.8 vs 29.6 months, HR 0.5, p=0.06; **Figure 2**).

Pattern of Relapse

Information on pattern of first progression after SABR could be retrieved for 79 patients. Patients were categorized within 3 categories: long-term (>18 months) disease free, oligoprogressor (≤ 3 new lesions) and polymetastatic progressor (>3 new lesions): 45% (36/79) of the evaluable patients did not develop a new recurrence within 18 months, 28% (22/79) of patients were oligoprogressive (≤3 new lesions) at first recurrence and 27% (21/79) developed a polymetastatic relapse (**Table 2**). Overall, 36/87 (41%) of patients were still free from clinical relapse at 18 months.

Local relapse in the treated metastasis was detected in 7 bony lesions (5 originating from HSPC, 2 from CRPC), having received a median BED of 198 Gy (IQR 152 – 230). If local

TABLE 1 | Patient, tumor and treatment characteristics.

Variable		n	%
Age (yr.)	Median [IQR]	69	[63 - 77]
Time from primary treatment (yr.)	Median [IQR]	4.5	[2.6 - 7.5]
ISUP Grade	1	17	20%
	2	18	21%
	3	17	20%
	4	20	23%
	5	13	15%
	NA	2	2%
Primary treatment modality	Surgery	52	60%
	Radiotherapy	28	32%
	Other[a]	7	8%
PSA at SABR (ng/mL)	Median [IQR]	2.8	[0.9 - 6.2]
ESTRO-EORTC classification	*De novo* synchronous OMD	6	7%
	Metachronous oligorecurrence	52	60%
	Metachronous oligoprogression[b]	14	16%
	Repeat oligorecurrence	8	9%
	Repeat oligoprogression	2	2%
	Induced OMD	5	6%
Androgen deprivation status	Hormone-sensitive	68	78%
	Castrate-resistant	19	22%
Concurrent hormonal therapy			
HSPC	ADT ≤ 6 months	19	22%
	ADT ≥ 2 year	13	15%
	Anti-androgen monotherapy	5	6%
	None	31	36%
CRPC	ADT	13	15%
	ADT + ARTA	6	7%
Number of lesions	1	60	69%
	2[c]	24	28%
	3	3	3%
Type of lesion	Lymph node (N1)	13	15%
	Lymph node (M1a)	7	8%
	Bone[d] (M1b)	67	77%
Imaging (n=115)	Conventional	22	19%
	PSMA or choline PET-CT	89	77%
	whole body MRI	4	3%
Nr of fractions (n=115)	1	23	20%
	3	68	59%
	5	24	21%
Biologically Effective Dose (Gy)	Median [IQR]	230	[189 - 230]

[a]*hormonal therapy, chemotherapy, High Intensity Focused Ultrasound.*

[b]*2 patients were progressive under treatment with anti-androgen monotherapy; the others received androgen-deprivation therapy (ADT).*

[c]*two patients with 2 metastases were treated with SABR for their spinal lesion and a moderate hypofractionated regimen for their non-spine bone lesion.*

[d]*4 patients had bone as well as lymph node metastases.*

ADT, androgen-deprivation therapy; ARTA, androgen receptor-targeted agents; CRPC, castrate-resistant prostate cancer; HSPC, hormone-sensitive prostate cancer; ISUP, International Society of Urological Pathology; OMD, oligometastatic disease; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SABR, stereotactic ablative radiotherapy.

relapse occurred, it was detected after a median time of 38 months (IQR 22 – 57). LC rates at 1 year and 3 years were 100% and 96%, respectively.

DISCUSSION

In this article, we describe a single-institution experience treating PCa OMD with SABR at a median follow-up of 41.6 months. Our cohort consisted of 87 patients, a mixture of metachronous as well as synchronous OMD, HSPC as well as CRPC, oligorecurrent as well as oligoprogressive mPCa. In total, 41% of patients remained free from new metastases for a period of >18 months, and 25% of patients developed limited new metastases potentially amenable for repeat MDT within the first 18 months following SABR.

As a subgroup analysis, PSA response, bPFS and DMFS in (metachronous as well as repeat) oligorecurrent HSPC was evaluated. Two phase II RCT's compared SABR to surveillance in the setting of metachronous oligorecurrent HSPC detected on choline PET-CT (3) or conventional CT and bone scintigraphy (4, 10), showing an advantage for MDT in terms of ADT-free survival and PFS. Despite 77% of our patients having PSMA PET-selected OMD, a more sensitive selection method than conventional CT, bone scintigraphy or choline PET-CT (11), our data do not compare as favorable as those reported in the aforementioned trials. It is remarkable that in our analysis, a PSA decline was measured in only 45% of

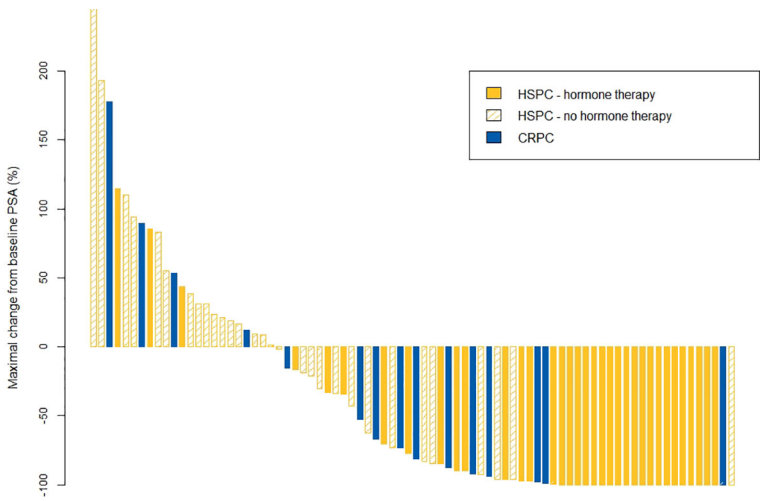

FIGURE 1 | Waterfall plot for maximal changes in PSA value. CRPC, castrate-resistant prostate cancer; HSPC, hormone-sensitive prostate cancer; PSA, prostate-specific antigen.

patients receiving SABR without additional systemic treatment, as opposed to 75% in STOMP; median bPFS was 6 months in our cohort as opposed to >24 months in ORIOLE. These observations are probably related to several reasons, such as different bPFS definitions or the inclusion of 8 repeat oligorecurrent HSPC's in our cohort.

However, it seems that still some cases were labelled as OMD if in fact it was only the tip of the iceberg for a subclinical polymetastatic disease. Therefore, we evaluated the impact of adding short-term ADT to SABR, to see if it is possible to eliminate potential micrometastases that are not (yet) visible and enhance the therapeutic effect. In our cohort, the addition of ADT for oligorecurrent HSPC was associated with improved bPFS (median 6.0 vs. 18.3 months, HR 0.31, p<0.001) and DMFS (median 15.8 vs 29.6 months, HR 0.5, p=0.06). While this analysis is exploratory and only hypothesis-generating, several phase II-III trials are currently testing the combination of SABR with either short course ADT (12–14) or androgen receptor pathway inhibitors (15). The main goal of this approach remains to postpone the start of lifelong ADT. Adding temporary hormonal treatment has already demonstrated improved LC, OS and MFS in primary treatment of high risk PCa (10).

New biomarkers may be critically important to help determining the natural history of the disease and to select the patients who could actually benefit from MDT. As of now, treatment decisions for OMD are based on clinical parameters such as number of metastases, time to recurrence and PSA doubling time. In a study by Deek et al., the presence of high-risk mutations was an independent prognostic factor allowing identification of patients who need more aggressive approaches beyond metastases-directed therapy (16). This suggests that tumor mutational profiles can provide a biological definition of OMD and complement currently used numerical definitions. Strategies for improved candidate selection have already been incorporated in prospective trials to provide a deeper understanding of the predictive role of biomarkers (12–14).

Looking at the oligo-CRPC patients of our analysis, DMFS and OS were significantly shorter compared to the HSPC patients, owing to the more advanced disease stage. Despite the more aggressive setting, median DMFS was still 17.6 months. During this time interval, it was not necessary to switch to a next line of systemic therapy. Moreover, in-field control was excellent, confirming the radiosensitivity of CRPC and the high efficacy of SABR on local metastatic control. While retrospective analyses testing the addition of SABR report encouraging results with DMFS ranging between 11 – 12 months (17–19), prospective data on the use of SABR in oligometastatic CRPC remain scarce, and several questions remain to be answered. For example, should we rather add SABR to the mainline systemic treatment to postpone next systemic treatment, or radically treat the visible metastases using SABR in combination with a switch to a next type of systemic treatment to target macroscopic as well as microscopic treatment-resistant disease? Regarding outcomes, is PFS a meaningful endpoint, or should we enroll larger patient groups and maintain long follow-up periods to evaluate OS endpoints? These questions warrant further exploration in prospective trials using standardized treatments to validate the potential benefit and to define the group of CRPC patients expected to profit from SABR. Ongoing prospective trials, such as the single-arm phase II TRAP trial (20) and the Medcare trial (21), are investigating the role of SABR for oligometastatic CRPC. Since immune-checkpoint inhibitor monotherapy has shown only modest benefits in the mCRPC setting, the ICE-PAC trial aimed at improving outcomes by combining the PD-L1 checkpoint inhibitor avelumab with SABR in patients with both low- as well as high-volume mCRPC after prior androgen-receptor pathway inhibitor therapy (22). A median radiographic PFS of 8.4

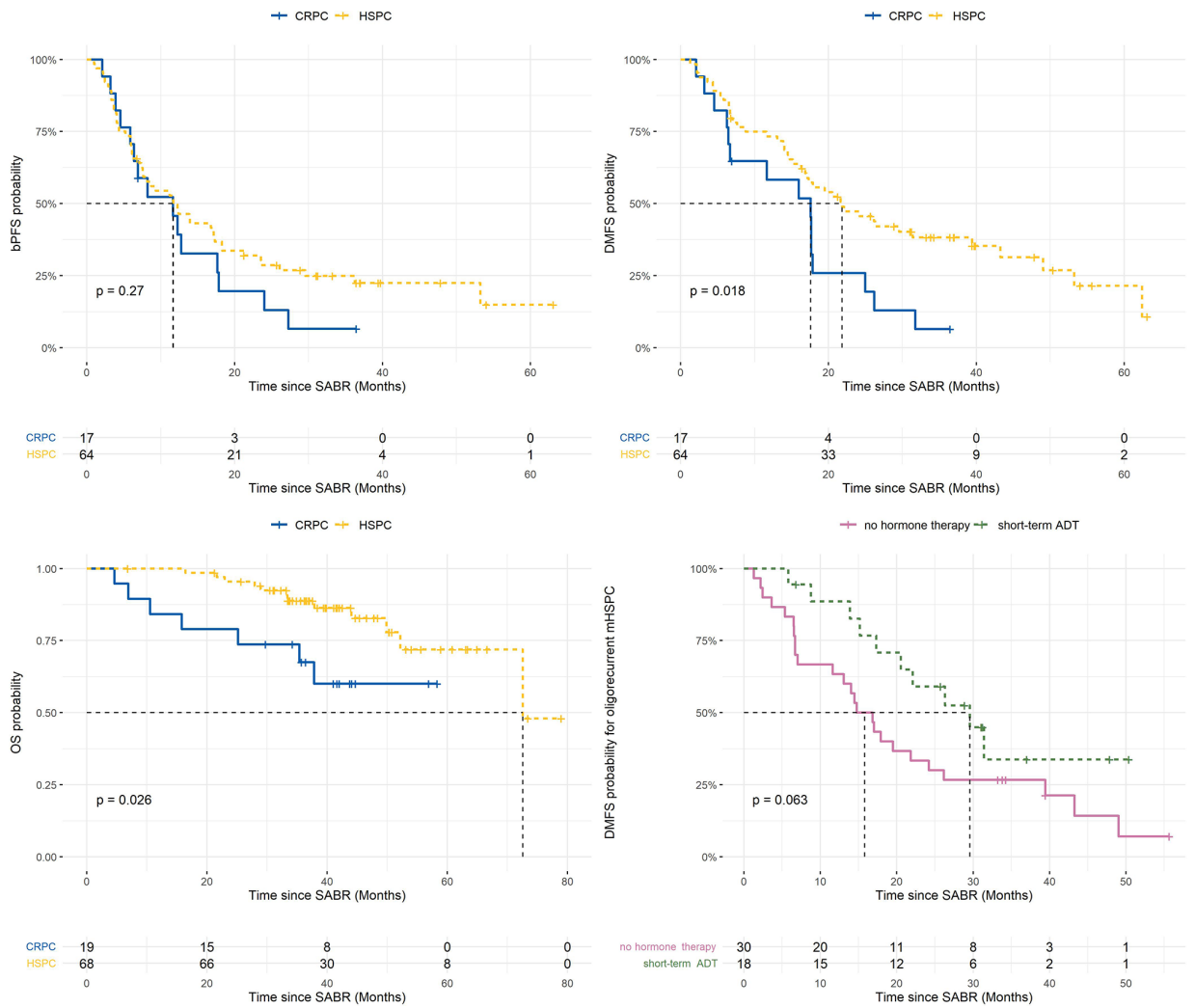

FIGURE 2 | Kaplan-Meier plots of survival outcomes (9). ADT, androgen deprivation therapy; BPFS, biochemical progression-free survival; CRPC, castrate-resistant prostate cancer; DMFS, distant metastasis-free survival; HSPC, hormone-sensitive prostate cancer; OS, overall survival; SABR, stereotactic ablative radiotherapy. Risk tables are presented under the survival curves.

months was observed in this heavily pretreated patient group, of which the majority had >10 metastases.

The present study was limited by its retrospective nature, by the relatively small patient group and by the rather heterogeneous patient, imaging and tumor characteristics. The current cohort reflects a real-world representation of the imaging evolution in recurrent prostate cancer. Initially, conventional imaging was supplemented with whole body MRI before the advent of choline PET-CT and PSMA PET-CT improved the detection of oligometastatic disease. The results might have been even better when patients received the most sensitive imaging at restaging, as was also shown in ORIOLE where PFS and DMFS was improved when all PSMA-PET positive lesions were treated with SABR (4).

TABLE 2 | Pattern of first progression after SABR.

	n	%
Long-term disease free (> 18 months)	36	41%
Oligoprogressive	22	25%
Polymetastatic relapse	21	24%
NA (lost to follow-up)	8	9%

SABR, stereotactic ablative radiotherapy.

CONCLUSION

In this cohort, patients with hormone-sensitive oligometastatic disease showed potential benefit from SABR with a median distant metastasis-free survival of 22 months. Well-selected patients with oligometastatic CRPC may also benefit from SABR. For patients with metachronous and repeat oligorecurrent HSPC,

combining SABR with short-term androgen-deprivation therapy was associated with improved bPFS and DMFS. Overall, 36/87 (41%) of patients were still free from clinical relapse at 18 months.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author, CM, carole.mercier@gza.be. The data are not publicly available due to their containing information that could compromise the privacy of patients.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Commissie Medische Ethiek GZA Ziekenhuizen, Oosterveldlaan 22, 2610 Wilrijk. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: CM, PD, and PO. Acquisition of data: CM and PD. Analysis and interpretation of data: CM, PD, and PO. Drafting of the manuscript: CM, MC, BT, TD, KF, HV, PO, and PD. Critical revision of the manuscript for important intellectual content: CM, MC, BT, TD, KF, HV, PO, and PD. Statistical analysis: CM, PD, and PO. Supervision: CM, PD, and PO. All authors contributed to the article and approved the submitted version.

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REVIEW
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Stereotactic Body Radiotherapy: Hitting Harder, Faster, and Smarter in High-Risk Prostate Cancer

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Stereotactic body radiotherapy (SBRT) is a technologically sophisticated form of radiotherapy that holds significant potential to effectively treat high-risk prostate cancer (HRPC). Prostate SBRT has been the subject of intense investigation in the context of low- and intermediate-risk disease, but less so for HRPC. However, emerging data are demonstrating its potential to safely and efficiently delivery curative doses of radiotherapy, both to the prostate and elective lymph nodes. SBRT theoretically hits harder through radiobiological dose escalation facilitated by ultra-hypofractionation (UHRT), faster with only five treatment fractions, and smarter by using targeted, focal dose escalation to maximally ablate the dominant intraprostatic lesion (while maximally protecting normal tissues). To achieve this, advanced imaging modalities like magnetic resonance imaging and prostate specific membrane antigen positron emmission tomography (PSMA-PET) are leveraged in combination with cutting-edge radiotherapy planning and delivery technology. In this focused narrative review, we discuss key evidence and upcoming clinical trials evaluating SBRT for HRPC with a focus on dose escalation, elective nodal irradiation, and focal boost.

Keywords: high-risk prostate cancer, elective nodal irradiation (ENI), PSMA-PET, dose escalation, stereotactic body radiotherapy (SBRT)

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INTRODUCTION

The National Comprehensive Cancer Network (NCCN) defines high-risk prostate cancer (HRPC) by any of the following high-risk features: ≥T3a, grade group ≥ 4, or PSA > 20. Very high-risk disease is a subset with any of the following: T3b-c, >4 cores of grade group 4 or 5, primary Gleason pattern 5, or any two high-risk features. Primary surgery can be utilized for HRPC but is associated with high rates of recurrence. In a study of 2,643 consecutive patients who underwent radical prostatectomy (RP) at a high-volume, tertiary care center, those with high-risk disease had a 5-year recurrence-free estimate of only 34.3% (1). Similarly, a European retrospective analysis of 4,041 men with high- and very high-risk disease who underwent RP demonstrated 8-year biochemical recurrence-free survival of 43.1% and 25.4% for the high- and very high-risk subsets, respectively (2).

Both radiotherapy and surgery are standard of care options for HRPC as per the NCCN (2022 update, version 3.0). These guidelines also permit the use of stereotactic body radiotherapy (SBRT) for high- or very high-risk disease, stating that "SBRT combined with ADT can be considered if

delivering longer courses of EBRT would present a medical or social hardship." Evidence continues to emerge in support of SBRT as a safe, tolerable, and effective option in HRPC. Herein, we review the literature supporting prostate SBRT for HRPC focusing on dose escalation and elective nodal irradiation (ENI) strategies, the impact of molecular imaging, and upcoming clinical trials.

DOSE ESCALATION FOR HIGH-RISK PROSTATE CANCER

The value of dose escalation in HRPC is well established. Using brachytherapy (BT) boost, the landmark ASCENDE-RT trial set an important benchmark of long-term biochemical control achievable through whole-gland dose escalation (3). This randomized trial compared EBRT plus low-dose rate prostate BT (LDR-BT) boost versus dose-escalated (DE) EBRT, revealing significant improvement with BT boost: biochemical recurrence-free survival at 5 and 9 years were 86% and 83% versus 75% and 62%, respectively, and men receiving DE-EBRT were twice as likely to experience biochemical failure. However, these superior biochemical outcomes came at the cost of substantially increased toxicity in the BT arm: 5-year cumulative incidence of grade 3 genitourinary (GU) events were 18.4% versus 5.2% (4). High-dose rate (HDR) BT has also demonstrated superiority over conventionally fractionated radiotherapy (CFRT) for HRPC and is generally associated with less GU toxicity than LDR (5). Early randomized evidence from Sathya and colleagues demonstrated superior outcomes of HDR BT boost over CFRT, albeit to a relatively low dose of 66 Gy in 33 fractions by current standards (6, 7). Taken together, the biochemical outcome data following BT boost are a clear demonstration that HRPC requires escalation of dose beyond what is possible or practical with CFRT.

Ultra-Hypofractionation and SBRT: Leveraging Radiobiology for Dose Escalation

Rather than dose escalating through ever-increasing fractions of CFRT, contemporary radiotherapy is instead moving toward fewer fractions and higher dose per fraction. Moderate hypofractionation (2.4–3.4 Gy per fraction)—and to a greater extent, UHRT (>5 Gy per fraction) (8)—aim to leverage the low α/β of prostate cancer to maximize biologically effective dose. The analysis by Vogelius and Bentzen using only randomised data (13 randomized controlled trials (RCTs), including hypofractionated and UHRT) has estimated the α/β for prostate cancers at 1.6 Gy (95% confidence interval (CI): 1.3–2.0) (9). Such models come with the caveat is that the linear quadratic model may not be accurate for larger fractional doses (over 6 Gy per day). Moreover, although this radiobiological rationale is intriguing and hypothesis-generating, empirical evidence is awaited to truly demonstrate the biological effectiveness of UHRT.

At present, the largest available randomized evidence for UHRT comes from HYPO-RT-PC, a non-inferiority RCT that randomized 1,200 prostate cancer patients to UHRT (42.7 Gy in 7 fractions) versus CFRT (78 Gy in 39 fractions)—including 126 high-risk patients. No androgen deprivation therapy was used. HYPO-RT-PC met its primary endpoint and demonstrated non-inferiority of UHRT, with 5-year failure-free survival (FFS) in both groups of 84% (95% CI: 80–87%) (10). Although equally effective, UHRT was associated with increased physician-reported GU toxicity (Radiation Therapy Oncology Group (RTOG) grade 2 or worse) at 1 year ($p = 0.0037$) (10). Patient-reported outcomes and quality-of-life (QoL) analysis correspondingly showed more GU/gastrointestinal (GI) symptoms acutely and more GU bother at 1 year in the UHRT arm. This greater toxicity might have been mitigated if true stereotactic technique was used. In HYPO-RT-PC, 80% of patients were treated with 7-mm planning target volume (PTV) margins and three-dimensional conformal radiotherapy. It is likely that contemporary planning and delivery techniques could achieve lower doses to organs at risk (OARs), which is known to correlate with toxicity and/or QoL (11).

SBRT can be considered a technologically advanced form of UHRT, leveraging technology for high-precision radiotherapy planning and delivery [e.g., image-guided radiotherapy (IGRT), modulated arc therapy (VMAT), robotic radiotherapy (CyberKnife), and magnetic resonance imaging (MRI)–guided or MRI-adaptive delivery]. In doing so, SBRT escalates dose while sparing OARs, thus maximizing the therapeutic ratio. True SBRT is being evaluated in the international PACE-B study, a non-inferiority RCT comparing SBRT to CFRT or moderately hypofractionated RT in 874 men. SBRT required implanted fiducials with 4- to 5-mm (3–5 mm posteriorly) PTV expansions. Prescription dose is specified as 36.25 Gy in 5 fractions to the PTV with a secondary dose target of 40 Gy to the CTV. IGRT delivery is mandatory (CyberKnife or conventional linear accelerator), and MRI-aided planning (fiducial-matched) is preferred. Although high-risk patients were not included in this trial, it is still relevant to consider the impact of rigorous SBRT technique on toxicity: PACE-B demonstrated that acute GU and GI toxicity rates were no different between SBRT and CFRT (12), in apparent contrast to HYPO-RT-PC. It should be acknowledged that the UHRT arm of HYPO-RT-PC used a higher PTV dose, which may also have contributed to higher toxicity. However, the rigorous standards for true SBRT technique in PACE-B, which were not mandated in HYPO-RT-PC, may also explain the isotoxicity of SBRT demonstrated in this trial.

Why was UHRT not superior to CFRT with respect to FFS in HYPO-RT-PC? After all, the equivalent doses in 2 Gy per fraction (EQD2) using an α/β of 1.6 Gy are 91.3 Gy versus 78 Gy for the UHRT versus CFRT arms, respectively. It is also interesting to note that HYPO-RT-PC was originally designed as a superiority trial (its sample size was increased from 800 to 1,200 at interim analysis to accommodate a revised, non-inferiority design). Explanations for isoeffectiveness may include statistical considerations, but a dosimetric explanation

is also possible: because radiotherapy was "prescribed as mean PTV dose," portions of the PTV received less/more than prescription dose by definition. Further dosimetric details were not specified (e.g., PTV/CTV coverage requirements, heterogeneity, and hotspots); therefore, it is conceivable that actual delivered dose to the CTV was lower than expected (which is known to correlate with biochemical recurrence-free survival in a dose–response relationship) (13). Conversely, it is also possible that in the absence of androgen deprivation therapy (ADT), there is a ceiling of effectiveness for local EBRT—even when dose-escalated *via* UHRT. However, without clarity on the proportion of local versus distant failure events, this is not certain. Ultimately, as we discuss below, further study of SBRT in the high-risk setting is needed, comparing against BT as the standard of care for dose escalation and with appropriate use of ADT.SBRT in HRPC: Emerging Evidence

Studies of SBRT including patients with HRPC have been reviewed exhaustively elsewhere (14), including a recent systematic review (15). However, the existing data are limited by several factors: predominantly retrospective studies, a wide range of SBRT techniques and dose/fractionation schedules utilized, short follow-up sometimes confounded by use of androgen deprivation therapy, and, chiefly, a relatively small proportion of study patients with high-risk disease who have been included.

An early pooled analysis from a multi-institutional consortium of prospective, phase II trials of prostate SBRT (King et al., 2013) included 125 patients with HRPC and demonstrated an encouraging a 5-year biochemical recurrence-free survival estimate of 81.2% (16). More recently, the SHARP consortium reported individual-patient data from patients with HRPC treated with SBRT (17). Their analysis included 344 patients (72% received ADT and 19% received ENI) who were followed for a median of 49.5 months. The estimated 4-year biochemical recurrence-free survival and distant metastasis-free survival rates were 81.7% and 89.1%, respectively. Interestingly, on multivariable analysis, lower dose (7 versus 8 Gy per fraction) was significantly associated with increased risk of biochemical failure (HR: 2.15; 95% CI: 1.07–4.32).

Here, we will focus on the few prospective studies that have investigated SBRT specifically for unfavorable or HRPC. Our discussion of these trials will encapsulate both lessons learned from early experiences and contemporary approaches in ongoing trials.

Early SBRT Trials for HRPC: Millimeters Matter

Since 2001, Sunnybrook Hospital's Odette Cancer Centre has explored increasingly hypo-fractionated, accelerated radiotherapy for prostate cancer through a series of iterative clinical trials, including for HRPC (11). In 2011, Sunnybrook launched one of the first prospective trials of prostate SBRT specifically for HRPC, enrolling 30 patients, 37% of whom had grade group 5 disease (18). Fiducial markers and daily IGRT were mandated, as was 12–18 months of ADT. Treatment volumes included the whole prostate (CTV2) plus proximal 1.5 cm of seminal vesicles (SV) or entire SV if T3b (CTV1). CTVs were expanded by 5 mm to create two separate PTVs. Radiotherapy dose was 40 and 30 Gy in 5 fractions to prostate and prostate + SVs, respectively. This SBRT regimen achieved a biochemical control rate of 85% and was generally well tolerated, with 0% and 3% late grade 3 GU and GI toxicity reported (11). However, the cumulative incidence of late hematochezia was notable at 42%. This was significantly higher than prior SBRT trials at Sunnybrook for low- and intermediate-risk disease that had treated prostate only (not including SVs). These trials utilized 35 Gy in 5 fractions (4-mm PTV margins) or 40 Gy in 5 fractions (5-mm PTV margin), yielding hematochezia rates of 4.9% and 27.2%, respectively (19). Combining these trial data, analysis of clinical and dosimetric predictors of hematochezia revealed that the volume of rectum receiving 38 Gy (V38) was a strong predictor of hematochezia. Furthermore, on multivariable analysis, V38 > 2cc, use of anticoagulants, and hemorrhoids emerged as the strongest predictive factors (19).

These important, empirical lessons regarding the safe delivery of prostate SBRT led to Sunnybrook's next-generation SBRT protocol for HRPC: the SATURN trial (NCT01953055) (20). SATURN accrued 30 patients from 2013 to 2014 who were treated with 12–18 months of ADT and 5 fractions to the pelvis and entire SVs (CTV1) with a SIB to prostate alone (CTV2). PTV expansions of 6 and 3 mm generated PTV1 and PTV2, which were prescribed 25 and 40 Gy in 5 fractions, respectively. SATURN aimed to avoid the toxicity seen in prior studies by sharpening the penumbra and dose fall-off from the CTV. The prostate CTV received 99% of the 40-Gy prescription, whereas PTV1 and PTV2 received 23.75 Gy (95% of prescription) and 33.25 Gy, respectively. At a median of 72 months, there were zero biochemical failure events and no grade ≥ 3 GI or GU toxicities reported (21). Although the prevalence of grade 2 GU toxicity was 52% (persisting at last follow-up), it is important to note that 30% of patients had pre-existing grade 2 GU symptoms at baseline. Grade 2 GI toxicity prevalence was 24%, with 3% of patients reporting grade 2 GI symptoms at baseline (20).

Another early Canadian trial of SBRT was FASTR (NCT01439542) (22). This pilot study only enrolled patients with HRPC at the London Health Sciences Centre (London, Canada). Investigators targeted pelvic lymph nodes (CTV1) and prostate plus proximal 1 cm of SVs (CTV2). PTV expansions were 5 mm, and no fiducials or ancillary devices (e.g., rectal balloon) were used. PTV1 and PTV2 were prescribed 25 and 40 Gy (SIB) to 95% of their volume in 5 weekly fractions, respectively. IGRT with pre-fraction cone-beam CT (CBCT) was utilized. Unfortunately, FASTR was terminated early after the first 16 patients were accrued, owing to higher-than-expected rectal toxicity. Grade ≥ 3 GI events were seen in 25% (four patients), including 1 grade 4 event (bowel toxicity requiring partial colectomy). Analysis of dose–volume histogram parameters revealed that higher dose volumes to the rectum (i.e., volume receiving 20–40 Gy, or V20–V40) were most strongly associated with clinically significant bleeding. The FASTR investigators concluded that a larger high-dose CTV (including proximal SVs) and the 5-mm PTV margin likely

account for the higher rectal toxicity observed (23). In essence, the prioritization of target coverage over OARs, among other factors, seemed to have contributed to the high rates of toxicity.

A subsequent trial, FASTR2, was launched from the same institution. This trial enrolled 30 patients with HRPC and very HRPC who were otherwise unable to complete a protracted course of CFRT due to frailty or geographic considerations. Unlike the original FASTR trial, in FASTR2, the posterior PTV margin was reduced to 4 mm, the dose was reduced to 35 Gy in 5 fractions, and tighter OAR constraints were used for rectum and bladder. This was better tolerated than the original FASTR trial, with no grade ≥3 toxicities and no rectal bleeding reported (24).

It is apparent from these pioneering SBRT trials in HRPC that small differences of a few millimeters in planning can make large differences when it comes to late rectal toxicity. Essential for safe delivery is IGRT with use of fiducials to tighten margins, as well as inverse radiotherapy planning (e.g., VMAT) to sharpen penumbra, achieve rapid dose fall-off, and respect normal tissue dose limits.

SBRT With MRI-Enabled Focal Boost: Smarter Dose Escalation

Early SBRT dose-escalation studies have empirically established the limitations of dose to the whole gland. In low- and intermediate-risk disease, doses of 45–50 Gy in 5 fractions were associated with high toxicity, including grade IV cystitis and rectal complications requiring colostomy (25–27). Building upon these data and the pioneering HRPC SBRT studies discussed above, the next generation of SBRT trials seeks to achieve precision dose escalation of the dominant intraprostatic lesion (DIL), hitting HRPC harder in a smarter, more targeted fashion by leveraging advanced imaging technology.

The value of focal boost has now been established by the phase III FLAME RCT (28), which randomized 571 men with unfavorable disease (85% HRPC) to 77 Gy in 35 fractions (EQD2 of 81.8 Gy) to the whole prostate with or without focal simultaneous integrated boost (SIB) to 95 Gy (EQD2 115.8 Gy), targeting the MRI-defined DIL and reduced as needed to respect normal tissue constraints. At a median 72 months follow-up, the 5-year biochemical DFS was 92% with focal boost, significantly better than without (85%). Toxicity and QoL were favorable in both arms, and differences were small a not statistically significant. Likewise, a patterns of failure analysis of the FLAME trial demonstrated focal boost decreased both local and regional or distant metastatic failure (29). Although there was also a clear inverse relationship between achieved dose to the GTV and probability of biochemical failure, there appears to be saturation as the curve starts to plateau beyond 85–90 Gy (96–106 EQD2, α/β of 1.2) (28).

SBRT with integrated focal DIL boost is also being explored. One of the earlier studies evaluating this technique in HRPC was launched in 2017 at Sunnybrook and will soon read out its 5-year outcomes. The 5STAR trial (30) enrolled 30 patients with unfavorable disease (63% HRPC). All patients received prostate SBRT with focal DIL boost (35 Gy to prostate and up to 50 Gy to the DIL) plus ENI (25 Gy) in 5 weekly fractions. A fused MRI was used to delineate the DIL. A prostate PTV expansion of 2 mm (2.5 mm superior-inferiorly) was achieved with the use of fiducial markers and an endorectal immobilization device called GU-Lok (31). Nodal and prostate PTVs received 23.75 and 33.25 Gy, respectively. A CT urethrogram was done at time of CT simulation, and urethral Dmax was limited to <52 Gy. Daily CBCT was utilized for IGRT. The median DIL D90% delivered was 48.3 Gy (range: 45.2–51.9). No grade 3 events were observed. Cumulative grade 2 acute (<6 months) or late (6–24 months) GU toxicities were 67% and 46.7%, respectively, and GI toxicities were 16.7% and 13.3%, respectively. At approximately 5 years of follow-up, only a single patient (3.3%) has experienced biochemical failure in the form an out-of-field, non-regional nodal recurrence detected on PSMA-PET (abstract submitted to ASTRO 2022).

Other studies have also evaluated SBRT with focal boost in HRPC. The hypo-FLAME trial was launched to test DIL boost up to 50 Gy in the context of prostate SBRT (35 Gy in 5 fractions to the whole prostate). One-hundred men (75% HRPC) were enrolled and received a median D_{mean} of 44.6 Gy to the DIL. No acute grade ≥ 3 toxicity observed at a median follow-up of 18 months. Biochemical outcomes have not been reported at this early time point (32). The UK's SPARC trial has also reported early data, specifically an interim safety analysis of eight patients with HRPC that received CyberKnife prostate SBRT (36.25 Gy to prostate) with up to 47.5 Gy boost to the DIL. Acute and late grade ≥2 toxicity was modest, the latter being 12.5% and 0% in the GU and GI domains, respectively. There were no biochemical failures in these eight patients after a median of 56 months follow-up (33).

Hannan and colleagues (34) recently reported a phase I trial of dose escalation to the DIL *beyond* 50 Gy. Fifty-five men with HRPC received pelvic and prostate SBRT with the prostate PTV prescribed 47.5 Gy and the DIL to 55 Gy in sequential cohorts. The pelvis received 22.5–25 Gy. Fused diagnostic mpMRI was used to delineate the DIL. Fiducial markers, hydrogel spacer, prophylactic alpha-blockers, and pre-fraction dexamethasone (4 mg) were utilized. A 2-year ADT course is planned. At a median follow-up of 18 months, grade 2 GI and GU toxicity was modest. One patient (lowest dose cohort) suffered a late grade 3 urinary retention requiring transurethral resection of prostate (TURP). A single biochemical failure was reported at 18 months, with subsequent development of widely metastatic disease in that patient. Although the technical achievement of focal dose escalation to this extreme is commendable, it is unclear whether the risk of increased toxicity is justified from an oncological perspective. The recently published FLAME trial patterns-of-failure analysis suggests that there are diminishing returns to dose escalation to the DIL in excess of 100 Gy EQD2 (α/β of 1.2), both in terms of local failure and regional/distant metastatic failure (29).

Molecular imaging with PSMA-PET imaging may also play an important role in focal DIL boost, in addition to its added diagnostic value (35) and superior accuracy for staging HRPC (36). Alfano and colleagues utilized PSMA-PET/MRI images co-registered with prostatectomy whole-mount histologic sections

to determine a standard uptake value (SUV) threshold-based margin to aid in the accurate delineation of DILs for focal boost (37). Thus, it may be beneficial to fuse and integrate PSMA-PET imaging data into the contouring and planning workflow for DIL boost, and further study of this approach is warranted. Another challenge is so called "mpRMI invisibility" of some clinically significant lesions (38) and the known multi-focality of many prostate cancers (39). To address these challenges, the SPIRIT study is combining mpMRI, PSMA-PET, and whole-mount histology with genomic and methylomic analysis of malignant intraprostatic lesions (40). This has revealed a novel correlation between certain mpMRI higher-order radiomic features and genomic copy-number alteration, the latter of which is a surrogate for genomic instability and aggressive disease. In an expanded cohort, the next phase of this study aims to identify additional PSMA-PET/MRI radio-biologic correlations. In turn, these radiomic features could serve as "imaging biomarkers" to improve identification and delineation of the most aggressive lesions to facilitate focal boost.Elective Nodal Irradiation

The use of pelvic elective nodal radiotherapy (ENI) in HRPC remains controversial, chiefly due to a lack of overall or progression-free survival benefit in RCTs of ENI versus prostate-alone radiotherapy. This may be explained by several factors, and a nuanced discussion on this topic is beyond the scope of this focused review; moreover, it has been expertly reviewed recently (41). Definitive evidence is anticipated from RTOG 0924, which is assessing ADT and high-dose external beam radiotherapy to the prostate with or without the addition of whole-pelvis RT (NCT01368588). However, early results are expected to read out only after 2030. In the HRPC setting, trials evaluating increasingly hypofractionated ENI (combined with prostate boost) have demonstrated safety and favorable oncological outcomes, supporting the value of ENI in well-selected patients.

Moderate Hypofractionation for ENI

In the high-risk setting, moderately hypofractionated prostate and pelvic EBRT has shown favorable outcomes. Once again, Sunnybrook was among the first to explore this approach through a study launched in 2004. This prospective, single-arm trial enrolled 230 patients with HRPC (prostate SIB to 68 Gy with 45 Gy in 25 fractions to the whole pelvis). The 5-year biochemical failure, distant metastasis, and overall survival rates were 15%, 6.6%, and 92.9%, respectively. Cumulative incidence rates of late grade ≥ 3 GI and GU toxicity were low at 2.5% and 7.5%, respectively. At 10 years, acceptable rates of biochemical failure, distant metastasis, and overall survival were maintained at 33.4%, 16.5%, and 76.3%, respectively (42).

More recently, the landmark trial POP-RT RCT randomized 224 men with HR and very HRPC to prostate only (68 Gy in 25 fractions) versus whole-pelvis RT (68 Gy prostate SIB with 50 Gy in 25 fractions to the pelvis, including common iliac nodes). At 68 months of median follow-up, biochemical FFS (bFFS) was remarkably high at 95% for whole-pelvis RT and significantly better than for prostate-only RT (81.2%). Disease-free survival and distant metastasis-free survival were also significantly higher for whole-pelvis RT, without a significant overall survival benefit (43). Of note, cumulative late GU toxicity (Gr. ≥ 2 RTOG) was significantly higher for whole-pelvis RT (20.0% *vs*. 8.9%), but neither late GI toxicity nor acute GU/GI toxicity differed between arms. The high rates of bFFS in POP-RT are likely attributable to several factors, including a higher ENI dose (50 Gy in POP-RT) and inclusion of common iliac nodes in the pelvic treatment volume. In addition, contributory was careful patient selection with inclusion of patients with HRPC at very high risk of nodal disease (median 38% by Roach formula) combined with the use of PSMA-PET staging in 80% to exclude occult nodal disease.

There is a great deal of enthusiasm around PSMA in HR PCa. The recent proPSMA trial supports the superiority of PSMA over conventional imaging with CT and bone scan for staging of HRPC (36). As PSMA-PET is increasingly adopted into routine practice, including for staging of HRPC, it will likely induce a so-called "Will Rogers" phenomenon (44), whereby outcomes for HRPC will appear to improve due to exclusion of early N+ and oligo-M1 disease identified by PSMA-PET (otherwise occult on conventional imaging). Average outcomes for the N+/oligo-M1 population will also improve as a consequence, because patients with occult (but PET-detectable) regional or distant disease will now be counted amongst those harboring conventionally detected, higher-volume nodal or metastatic disease. PSMA-PET also holds great potential to aid in the definition ENI treatment volumes. PSMA-PET studies have shown that elective volumes should be extended to cover to include the common iliac nodes up to the aortic bifurcation, thus providing justification for current NRG consensus contouring guidelines (45).

Prostate and Pelvis SBRT: Ultra-Hypofractionated ENI With Simultaneous Integrated Prostate Boost

Using contemporary techniques for radiotherapy planning and delivery, anultra-hypofractionated course of ENI is possible. This approach is faster, more cost-effective, and more convenient for patients (18). It has been evaluated in the context of both prostate BT boost and SBRT boost. A recent pooled analysis evaluating four prospective clinical trials testing this "pelvic SBRT" approach in both contexts demonstrated its safety and tolerability in patients with unfavorable-intermediate risk (UIR) and HRPC (46). In 165 patients, worst grade 2 GU and GI toxicity rates were 48% and 7.5%, respectively. There were no grade 4 events and 2.7% of patients experienced grade 3 GU toxicity (0% GI). At a median follow-up of 38 months, late GU and GI toxicity rates (cumulative incidence of worst toxicity) were 41.1% and 10.5%, respectively. Grade 3 GY toxicity was 1.5%. Moreover, the strategy was associated with favorable rates of biochemical recurrence-free survival: 98% at 3 years, and no patient had pelvic failures. Pelvic SBRT following BT boost is currently being evaluated in ongoing RCTs including the HOPE (NCT04197141) (47) and SHARP (NCT04861415) trials based at London Health Sciences Centre and Sunnybrook Hospital, respectively. These trials are randomizing patients to UHRT ENI (25 Gy in 5 fractions) versus CFRT (37.5–46 Gy in 15–25 fractions) after single-fraction 15-Gy HDR BT boost.

An alternate approach that circumvents a BT procedure is the use of SBRT prostate boost plus ENI (CFRT or UHRT). One way to do this is with CFRT ENI and sequential prostate SBRT boost wherein 45–50.4 Gy is delivered in 1.8- to 2-Gy daily fractions to the pelvis followed by 19–21 Gy in 2–3 fractions to the prostate. Studies using this approach have been recently reviewed (14), and it is the subject of an ongoing RCT called PBS (Prostate Boost irradiation with SBRT) randomizing 100 men to CFRT versus SBRT boost (NCT03380806).

Alternately, and arguably more efficient and cost-effective, is the use of UHRT ENI with a prostate SIB. This is essentially simultaneous "SBRT to prostate and pelvis" and is a novel strategy that has also been explored in HRPC. The SATURN trial from Sunnybrook (discussed above) was one of the first to evaluate this paradigm (20), treating 30 patients with HRPC with 25 Gy in 5 fractions to the pelvis and 40 Gy in 5 fraction to the prostate (SIB). When individual patient data from SATURN were compared with a parallel trial of prostate-only SBRT, it was found that the addition of ENI did not significantly increase toxicity (11). Interestingly, there was also a trend toward superior biochemical control with the additional of ENI. Although intriguing, this *post hoc* comparison between two small prospective trials is hypothesis-generating at best but, nonetheless, paves the way for future prospective comparisons. The multi-center 5STAR-PC trial (n = 75) builds upon the initial 5STAR study (n = 30) discussed above, permitting the use of a focal DIL boost up to 50 Gy in the context of pelvic SBRT. 5STAR-PC has completed accrual and has reported favorable early (median 25 month) toxicity and QoL data. Encouragingly, there have been no biochemical failures reported thus far (46).

Murthy and colleagues have also evaluated pelvic SBRT (48). Using a prospective registry, 68 patients with HR (30%), very HR (16%), and N+ (54%) patients were treated with SBRT to the prostate and entire SVs (35–37.5 Gy), pelvis (25 Gy), and gross nodes (35–37.5 Gy) in 5 fractions. PTV expansion was 5 mm for elective and gross nodes, whereas prostate and SVs were expanded 3 mm posteriorly. Patients were also treated with neoadjuvant, concurrent, and adjuvant ADT (median 15 months total). SBRT was well tolerated with no acute grade 3 events. Grade 2 GU and GI toxicity rates were 12% and 3%, respectively. Although median follow-up was only 18 months, late toxicity rates was also favorable, with two patients experiencing grade 3 GU toxicity. Grade 2 GU and GI event rates were also very low at 4.5% and 4%, respectively. Encouragingly, 94% of patients were biochemically controlled and none of the N+ patients recurred, albeit with very limited follow-up.

FUTURE DIRECTIONS

The encouraging data reviewed above establish a strong rationale to evaluate prostate and pelvic SBRT in a randomized setting. The phase III ASCENDE-SBRT trial is launching soon to do so (**Figure 1**). This multi-center RCT will enroll 710 patients with UIR or HRPC and randomize to ENI plus BT versus SBRT boost. The BT arm will receive CFRT (46 Gy in 23 fractions) following HDR (15 Gy) or LDR (115 Gy I-125) BT boost. The SBRT arm will treat with 25 and 40 Gy in 5 fractions to the pelvis and prostate, respectively. Patients in both arms will receive ADT (4–6 months for UIR and 18–36 months for HR). The primary outcome is 5-year PFS (includes biochemical failure, local salvage, metastasis, or death) and is powered for non-inferiority. Secondary endpoints include toxicity, 4-year PSA response rate, metastasis free survival (MFS), cause specific survival (CSS), overall survival (OS), QoL, and cost effectiveness. The hypothesis of ADCENDE-SBRT is that SBRT

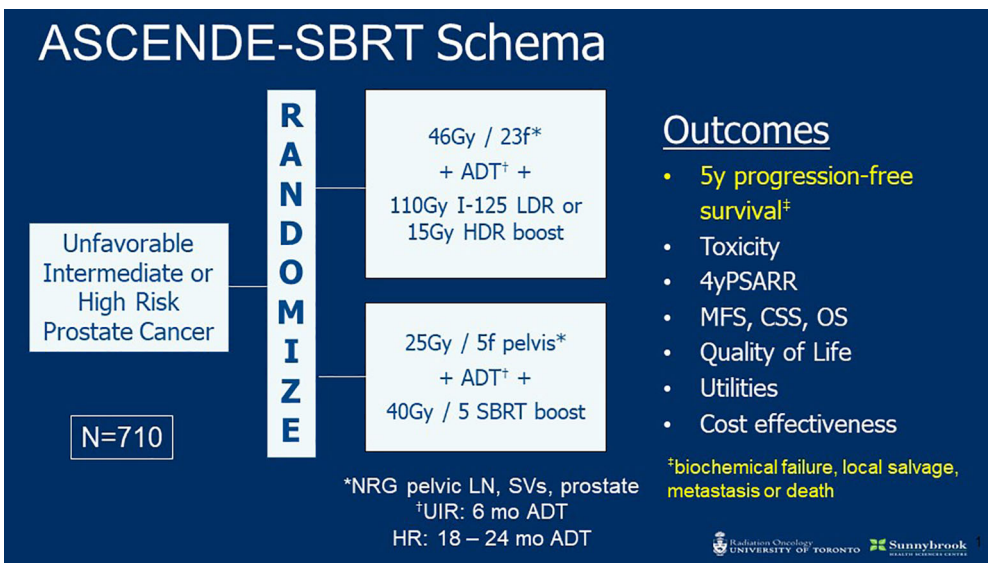

FIGURE 1 | ASCENDE-SBRT Trial Schema.

prostate boost with simultaneous ENI will achieve similar outcomes to BT boost followed by ENI.

Other important trials are evaluating SBRT in HRPC. The PRIME trial (NCT03561961) is a phase III RCT comparing the efficacy of moderate hypofractionation (50 Gy to pelvis and 66–68 Gy to prostate in 25 fractions) with SBRT (25 Gy to pelvis, 35–36.5 Gy to prostate, and 30–35 Gy to gross nodes all in 5 fractions) in HRPC and N+ prostate cancer. The primary outcome is bFFS at 5 years, and it is powered for non-inferiority with a target accrual of 464 men. Another trial that will evaluate SBRT in HRPC—specifically pelvic SBRT—is PACE-NODES. Akin to POP-RT, which compared moderately hypofractionated RT to prostate only versus whole pelvis, this RCT will compare prostate-only versus prostate and pelvis SBRT, evaluating acute and late toxicity as well as bFFS in men with localized HRPC.

The increasing importance of PSMA-PET in the management of prostate cancer raises interesting questions regarding regional nodal disease. For instance, how should small PSMA-avid lymph nodes that do not meet size criteria by conventional imaging be managed? In the context of pelvic RT (including SBRT), what is the optimal nodal boost dose that adequately balances efficacy with potential toxicity? It will thus be important to conduct further study of PSMA-PET imaging as this technology integrates into the management pathway of HRPC. The ARGOS/CLIMBER trial, which is opening jointly through London Health Sciences Centre and Sunnybrook Hospital, is directly addressing this. It is discussed in a separate article by Liu and colleagues in this issue of *Frontiers Oncology*.

Future trials will also need to account for the rapidly evolving landscape of systemic therapy for advanced prostate cancer, and how this impacts the management of HR disease. The recently published STAMPEDE-platform RCT of abiraterone acetate (and prednisone) with or without enzalutamide for non-metastatic HRPC demonstrated significant oncological benefit with addition the former drug to ADT (49). It is interesting that protocol radiotherapy for this trial is described as "treatment of the prostate and SVs to 74 Gy in 37 fractions or equivalent hypofractionation" (i.e., does not appear to include elective nodes). Thus, in the context of systemic therapy intensification for HRPC, the role of ENI as well as whole-gland dose escalation (with BT or SBRT) and/or focal dose escalation with micro-boost would require further investigation.

CONCLUSION

Contemporary radiotherapy has achieved excellent outcomes for patients with HRPC, as evidenced by the results of several prospective trials, including phase III studies such as FLAME and POP-RT discussed above. Such promising data have led some to wonder whether high-technology radiotherapy will emerge as the favored treatment option over surgery for HRPC (50). SBRT holds great potential to achieve favorable outcomes in HRPC. It encapsulates technologically driven UHRT for radiobiological dose escalation and can deliver simultaneous ENI and MRI-directed focal boost. SBRT has the potential to hit harder, faster, and smarter and all for less cost and greater convenience for patients. This paradigm is now being tested at the phase III level, with international RCTs like the ASCENDE-SBRT study launching soon.

AUTHOR CONTRIBUTIONS

RJMC and AL: writing and revising. All authors contributed to the article and approved the submitted version.

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Urethral Interfractional Geometric and Dosimetric Variations of Prostate Cancer Patients: A Study Using an Onboard MRI

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Purpose: For a cohort of prostate cancer patients treated on an MR-guided radiotherapy (MRgRT) system, we retrospectively analyzed urethral interfractional geometric and dosimetric variations based on onboard MRIs acquired at different timepoints and evaluated onboard prostatic urethra visualization for urethra-focused online adaptive RT.

Methods: Twenty-six prostate cancer patients were prospectively scanned on a 0.35-T MRgRT system using an optimized T2-weighted HASTE sequence at simulation and final fraction. Two radiation oncologists (RO1 and RO2) contoured the urethras on all HASTE images. The simulation and final fraction HASTE images were rigidly registered, and urethral interobserver and interfractional geometric variation was evaluated using the 95th percentile Hausdorff distance (HD95), mean distance to agreement (MDA), center-of-mass shift (COMS), and DICE coefficient. For dosimetric analysis, simulation and final fraction HASTE images were registered to the 3D bSSFP planning MRI and 3D bSSFP final setup MRI, respectively. Both ROs' urethra contours were transferred from HASTE images for initial treatment plan optimization and final fraction dose estimation separately. Stereotactic body radiotherapy (SBRT) plans, 40 Gy in 5 fractions, were optimized to meet clinical constraints, including urethral V42Gy ≤0.03 cc, on the planning MRI. The initial plan was then forward calculated on the final setup MRI to estimate urethral dose on the final fraction and evaluate urethral dosimetric impact due to anatomy change.

Results: The average interobserver HD95, MDA, COMS, and DICE were 2.85 ± 1.34 mm, 1.02 ± 0.36 mm, 3.16 ± 1.61 mm, and 0.58 ± 0.15, respectively. The average interfractional HD95, MDA, COMS, and DICE were 3.26 ± 1.54 mm, 1.29 ± 0.54 mm, 3.34 ± 2.01 mm, and 0.49 ± 0.18, respectively. All patient simulation MRgRT plans met all clinical constraints. For RO1 and RO2, 23/26 (88%) and 21/26 (81%) patients' final fraction estimated urethral dose did not meet the planned constraint. The average urethral V42Gy change was 0.48 ± 0.58 cc.

Conclusion: Urethral interfractional motion and anatomic change can result in daily treatment violating urethral constraints. Onboard MRI with good visualization of the prostatic urethra can be a valuable tool to help better protect the urethra through patient setup or online adaptive RT.

Keywords: MR-guided radiation therapy (MRgRT), prostate cancer, dosimetry, toxicity, urethra

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is now a widely accepted standard-of-care option for localized prostate cancer (1). Despite an overall highly favorable safety profile, SBRT late (13.3%) grade ≥2 genitourinary (GU) toxicity rates remain a significant challenge (2–5). Past efforts for reducing late GU toxicities have been focused on bladder sparing (6). However, urethral injury is also a significant contributor to GU toxicity (7, 8). The urethra can be constrained below the prescription dose (urethra sparing) or above (hotspot limitation). Prospective SBRT trials have reported allowable urethra doses ranging between 34.7 and 52.5 Gy in 5 fractions (9, 10). Leeman et al. analyzed patients enrolled in trials for SBRT and showed that an increase in the maximum urethral dose metric (MUDM) correlated to an increase in acute (≤3 months) and late (>3 months) grade ≥2 GU toxicity rates (8). While urethral sparing approaches are appealing from the standpoint of limiting toxicity, postradiation patterns of failure studies have suggested that periurethral recurrences are common, and therefore, hotspot limitation may be a better goal for minimizing toxicity while maintaining efficacy (11).

In addition to urethral dose constraints, urethra delineation uncertainty and intrafractional/interfractional motion can also contribute to GU toxicity. Delineating the urethra on computed tomography (CT) images is non-trivial due to the lack of contrast between the urethra and prostate (12). Foley catheters have been used to delineate the urethra on planning CTs; however, the catheter can also displace and deform the urethra, resulting in urethra misposition (13, 14). Alternatively, magnetic resonance images (MRIs) can be acquired and registered to planning CTs for urethra delineation (15). Diagnostic 3T T2-weighted MRI has shown good urethra visualization and low interobserver urethra contouring variation (16, 17). However, contouring uncertainty from cross-modality registration adds uncertainties (18). Moreover, the shape and location of the urethra may change between diagnostic MRI and planning CT acquisitions, which are often acquired on different days with different patient positions. As for urethra intrafractional/interfractional motion, little has been studied and its impact on urethral dose is unknown due to limited urethra visualization tools.

Recently, advancements in MR-guided radiation therapy (MRgRT) and the development of MR linear accelerators (MR-LINAC), equipped with onboard MRI, have allowed the application of MRI for prostate treatment planning, adaptation, and monitoring. MRI provides high soft-tissue contrast for accurate tumor and critical structure delineation (19). MR-Linac's onboard MRIs allow for fiducial-free daily patient setup and interfractional MR-guided online adaptive radiation therapy (MRgART), where initial treatment plans can be recalculated or reoptimized based on the patient's daily anatomy (20). Real-time cine MR can also be acquired during treatment delivery to monitor intrafraction motion and gate treatment (21). Consistent and frequent radiation-free MR imaging, throughout patient treatment, enables the use of smaller planning margins and improved critical structure sparing (5). Furthermore, the MRgRT workflow minimizes cross-modality and cross-system registration errors as the MRIs are acquired on the same system with the patient in the treatment position.

Currently, it is standard practice to acquire a 3D balanced steady-state free precession (bSSFP) MRI for MRgRT treatment planning and daily patient setup using the ViewRay MRIdian MR-Linac (ViewRay Inc., Oakwood Village, OH, USA). Clinical bSSFP is intrinsically fast and has a high signal-to-noise ratio (SNR). However, it is T2/T1-weighted and provides lower urethral contrast than T2-weighted scans (22). As a result, at our institution, a T2-weighted MRI sequence is optimized and performed at the end of patient MR simulation for urethra delineation (22). Due to time constraints, T2-weighted MRIs are not acquired for daily patient setup and are acquired with a smaller FOV covering only the prostate gland. Herein, we analyze interobserver variability as well as geometric and dosimetric changes in the urethra between the simulation scan and the final fraction of SBRT in a cohort of prospectively treated patients to determine the clinical significance of onboard urethra visualization for urethra-focused MRgART.

METHODS AND MATERIALS

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the University of California, Los Angeles, IRB #17-001064, on December 6, 2017. Twenty-six prostate cancer patients undergoing MRgRT SBRT between June 2020 and June 2021 were prospectively included. Prior to patient simulation and each treatment fraction, patients were instructed to follow the institutional bladder filling and rectum emptying protocol. For CT simulation, patients were immobilized with a vacuum bag and a pelvic CT was acquired on a 16-slice CT scanner (Sensation Open, Siemens Medical Solutions, Erlangen, Germany). For MR simulation and before each treatment fraction, a clinical bSSFP MRI was acquired on a 0.35-T MR-Linac system (ViewRay MRIdian, ViewRay Inc., Cleveland, OH, USA) using the same immobilization device.

Additionally, a urethra-specific T2-weighted 3D half-Fourier acquisition single-shot turbo spin-echo (3D HASTE) was acquired at simulation (HASTE 1) and at the end of the final treatment fraction (HASTE 2). Urethra imaging was only acquired at two timepoints due to clinical time constraint. 3D HASTE sequence parameters are as follows: repetition time (TR) = 1,800 ms, echo time (TE) = 246 ms, voxel size 1.5 mm isotropic, FOV = 227 × 400 mm^2, number of slices = 40, number of averages = 6, and acquisition time = 8:06 min. A more detailed explanation of 3D HASTE sequence optimization can be found in Pham et al. (22).

The simulation clinical bSSFP MRI serves as the primary treatment planning image (planning MRI). An attending physician contoured the prostate gland as the clinical target volume (CTV) and all critical structures on the planning MRI in MIM Software (Cleveland, OH, USA). Due to high MRI prostate visualization and MRgRT daily/real-time image guidance, the planning target volume (PTV) was constructed by isotropically expanding the CTV by 2 mm. Two radiation oncologists (RO1 and RO2) independently contoured the prostatic urethras on both HASTE 1 and HASTE 2 for all patients. Prostatic urethra contours were cropped to be within the PTV. HASTE 1 and 2 were rigidly registered in MIM Software using box-based assisted alignment on the prostate. Afterward, a medical physicist checked the registration and manual translational/rotational adjustments were made if necessary. Urethral interobserver and interfractional geometric variation was evaluated using the 95th percentile Hausdorff distance (HD95), mean distance agreement (MDA), center-of-mass shift (COMS), and DICE coefficient. A DICE coefficient score of >0.70 reflects a good spatial and volumetric agreement between observers or no geometrical change between imaging fractions (17). Additionally, HASTE 1 and 2 bladder volumes were estimated, and the association between bladder volume change and urethral motion was assessed using regression analysis. Due to HASTE images' limited FOV, complete bladder volume could not be measured, and as a result, a surrogate area index (Area = A × B) was used, in which the long axis (A) and the perpendicular short axis (B) of the bladder in the central sagittal plane were measured.

Furthermore, each RO qualitatively scored the urethra visibility of each image on a 4-point scale: 1 = no conspicuity; 2 = some conspicuity, the urethra can be identified, but not very clear; 3 = good conspicuity, the urethra can be identified clearly; and 4 = excellent conspicuity. RO1 and RO2's urethra visibility scores were compared using the Wilcoxon signed-rank test with a significance level of 0.05.

For dosimetric analysis, HASTE 1 and HASTE 2 were rigidly registered to their respective clinical bSSFP MRI. Both RO's urethra contours were transferred separately from HASTE images for treatment planning and dose estimation. For each RO, an MRgRT treatment plan was generated on the planning MRI using clinical contours and their respective HASTE 1 urethra contours. MRgRT plans were prescribed to deliver 40 Gy to 95% of PTV [5 fractions (Fx); 8 Gy/Fx]. Each plan was optimized to meet clinical constraints (**Table 1**), including a urethral hotspot limiting constraint (V42Gy ≤ 0.03 cc). Urethral hotspot limitation constraint was prioritized over urethral sparing to maintain treatment efficacy and reduce the risk of disease recurrence. The dose was calculated on the planning MRI with deformably registered electron density information from simulation CT using the MRgRT treatment planning system. Afterward, the final fraction urethral dose was estimated by performing a forward calculation of the initial plan onto the final fraction patient setup bSSFP MRI. Urethral constraint, mean dose, D0.03cc, V42Gy, and PTV mean dose change between simulation and final fraction were evaluated. Simulation and final fraction dose parameters were compared using paired t-test with a significance level of 0.05.

RESULTS

The average time between simulation and final fraction imaging was 21.4 ± 4.6 days. RO1's and RO2's average qualitative urethra visibility scores were 1.8 ± 0.7 and 3.2 ± 0.7, respectively. RO2 scored urethra visibility significantly greater than RO1 ($p < 0.05$). The average HD95, MDA, COMS, and DICE between RO1 and RO2's urethra contours were 2.85 ± 1.34 mm, 1.02 ± 0.36 mm, 3.16 ± 1.61 mm, and 0.58 ± 0.15.

Figures 1–**4** show four prostate patients' (*Patients* A–D) HASTE 1 and 2 with RO1 and RO2 contours. Patients A–D showed ok–good interobserver contour agreement (DICE > 0.60). Patients A and B showed minimal urethral interfractional change (DICE > 0.62), while patients C and D showed significant urethral interfractional change (DICE < 0.54). The combined RO average HD95, MDA, COMS, and DICE between simulation and final fraction urethra contours for all patients were 3.26 ± 1.54 mm, 1.29 ± 0.54 mm, 3.34 ± 2.01 mm, and 0.49 ± 0.18, respectively. No correlation between urethral motion and the bladder volume surrogate was observed ($R^2 < 0.1$).

All patient simulation MRgRT plans met all clinical constraints, including urethral hotspot constraints. The combined RO average simulation urethral mean dose, D0.03cc, V42Gy, and PTV mean dose were 40.69 ± 0.37 Gy, 41.83 ± 0.21 Gy, 0.02 ± 0.01 cc, and 41.29 ± 0.22 Gy, respectively. However, for RO1 and RO2, 23/26 (88%) and 21/26 (81%) patients' final fraction estimated urethral dose did not meet V42Gy ≤0.03 cc. The combined RO average final

TABLE 1 | Clinical constraints for prostate patients.

Constraint	
PTV V40Gy	≥95%
PTV V42Gy	<30%
Rectum V20Gy	<50%
Rectum V36Gy	<10%
Rectum V40Gy	<5%
Bowel V20Gy	<30 cc
Urethra V42Gy	≤0.03 cc
Bladder V20Gy	<40%
Bladder V39Gy	<4 cc
Bladder V40Gy	<10%

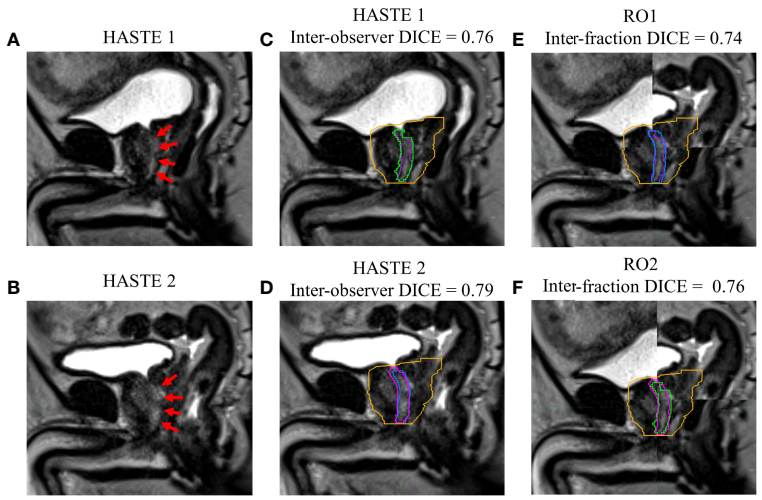

FIGURE 1 | Patient A's **(A)** simulation (HASTE 1) and **(B)** final fraction (HASTE 2) urethra images (red arrows pointing to the urethra). **(C)** Interobserver urethra contour agreement between RO1 (purple) and RO2 (green) for HASTE 1. **(D)** Interobserver urethra contour agreement between RO1 (blue) and RO2 (pink) for HASTE 2. Planning target volume (PTV) is contoured in orange. Interfractional urethra changes for **(E)** RO1 and **(F)** RO2 on fused (checkerboard layout) HASTE 1 and 2 images.

fraction urethral mean dose, D0.03cc, V42Gy, and PTV mean dose were 41.10 ± 0.68 Gy, 42.62 ± 0.72 Gy, 0.50 ± 0.58 cc, and 40.84 ± 0.65 Gy, respectively. The final fraction urethral dose parameters were significantly greater than the simulation ($p < 0.05$), whereas the PTV dose parameters were significantly less ($p < 0.05$). The combined RO average urethral mean dose, D0.03cc, V42Gy, and PTV mean dose change were 0.41 ± 0.60 Gy, 0.79 ± 0.74 Gy, 0.48 ± 0.58 cc, and −0.45 ± 0.71, respectively. Overall, dose parameters and urethral constraint change were consistent for both ROs.

Figures 5, **6** show both ROs' patients' A–D calculated (simulation) and estimated (final fraction) dose and urethra V42Gy. Patient A demonstrated minimal geometric urethral change and, as a result, little urethral dose change. Alternatively, Patient B showed minimal geometric urethral change but significant urethral dose changes due to other anatomical changes such as differential bladder filling. Patient C exhibited significant geometric urethral change, resulting in the urethra moving into hotspot regions. Patient D showed significant geometric urethral change but little dose change,

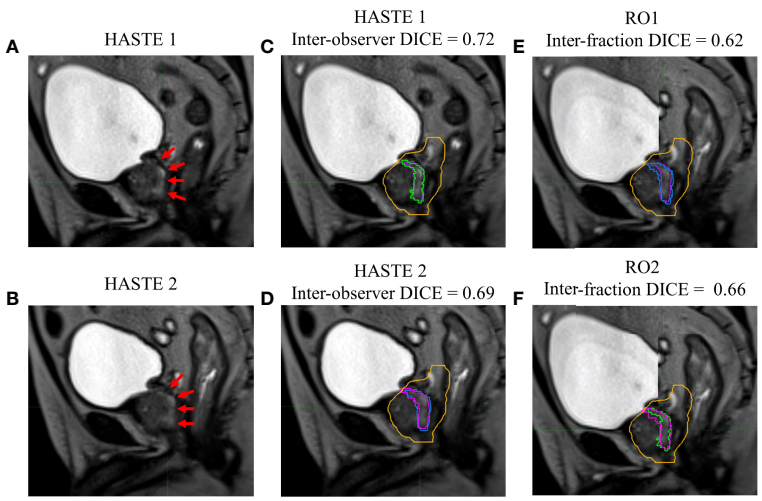

FIGURE 2 | Patient B's **(A)** simulation (HASTE 1) and **(B)** final fraction (HASTE 2) urethra images (red arrows pointing to the urethra). **(C)** Interobserver urethra contour agreement between RO1 (purple) and RO2 (green) for HASTE 1. **(D)** Interobserver urethra contour agreement between RO1 (blue) and RO2 (pink) for HASTE 2. Planning target volume (PTV) is contoured in orange. Interfractional urethra changes for **(E)** RO1 and **(F)** RO2 on fused (checkerboard layout) HASTE 1 and 2 images.

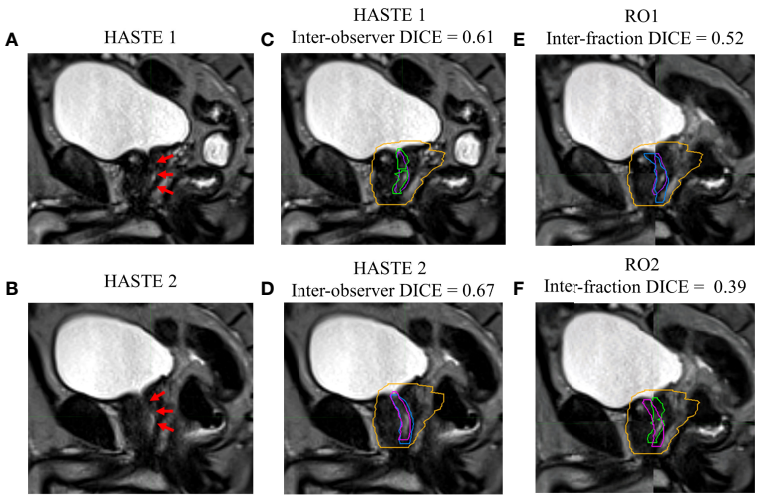

FIGURE 3 | Patient C's **(A)** simulation (HASTE 1) and **(B)** final fraction (HASTE 2) urethra images (red arrows pointing to the urethra). **(C)** Interobserver urethra contour agreement between RO1 (purple) and RO2 (green) for HASTE 1. **(D)** Interobserver urethra contour agreement between RO1 (blue) and RO2 (pink) for HASTE 2. Planning target volume (PTV) is contoured in orange. Interfractional urethra changes for **(E)** RO1 and **(F)** RO2 on fused (checkerboard layout) HASTE 1 and 2 images.

demonstrating the importance of hotspot location and robustness of each MRgRT IMRT plan.

DISCUSSION

This study evaluated prostate cancer patients' interfractional urethral geometric and dosimetric changes. Significant geometric and spatial urethral changes between simulation and the final fraction were noticed, indicating the potential need for daily urethral imaging to achieve better urethra protection by limiting urethral hotspots in MRgRT treatment planning and delivery. Our study reveals that the efficacy of urethral hotspot-limiting constraints depends on interfractional urethral geometric and anatomic changes as more than 80% of patients had a failing final fraction urethra V42Gy constraint. In other words, interfractional urethral geometric changes can result in a significant volume of the urethra moving into planned hotspot regions as shown in **Figures 5**, **6**. Additionally, interfractional anatomical changes such as the bladder filling variation and

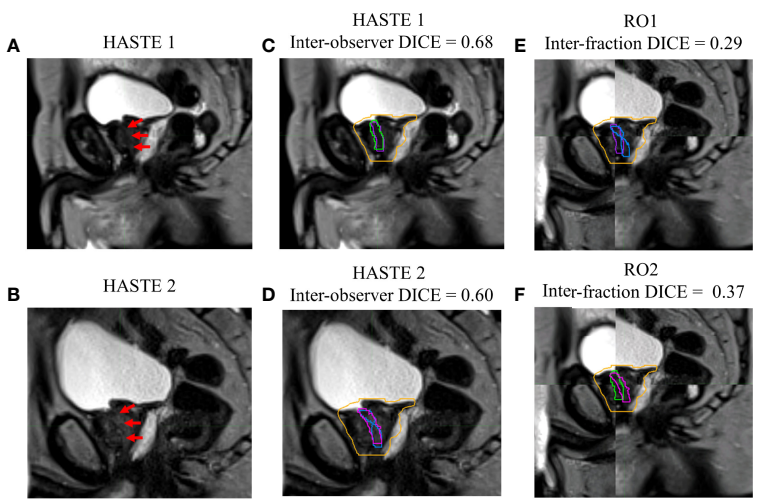

FIGURE 4 | Patient D's **(A)** simulation (HASTE 1) and **(B)** final fraction (HASTE 2) urethra images (red arrows pointing to the urethra). **(C)** Interobserver urethra contour agreement between RO1 (purple) and RO2 (green) for HASTE 1. **(D)** Interobserver urethra contour agreement between RO1 (blue) and RO2 (pink) for HASTE 2. Planning target volume (PTV) is contoured in orange. Interfractional urethra changes for **(E)** RO1 and **(F)** RO2 on fused (checkerboard layout) HASTE 1 and 2 images.

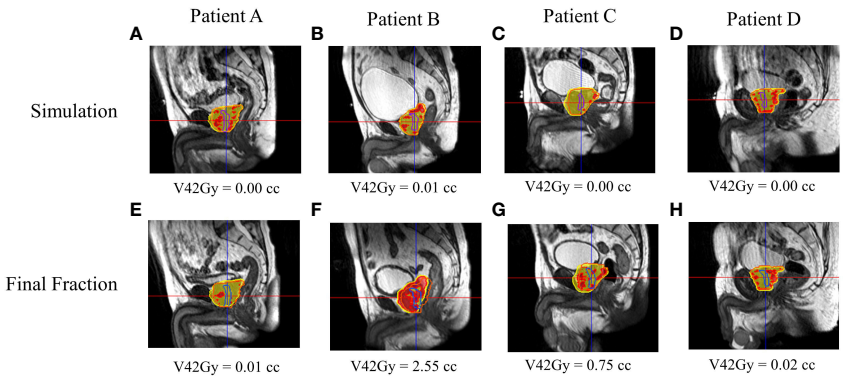

FIGURE 5 | RO1's calculated and estimated dose and urethral V42Gy for patient A–D's simulation **(A–D)** and final fraction **(E–H)** bSSFP. RO1 simulation/final HASTE urethra contour—purple/blue. Orange contour—PTV. Red—105% (42 Gy) isodose region, yellow—95% (38 Gy) isodose region.

prostate swelling can significantly alter the planned dose distribution and result in a higher urethral dose (23). Currently, there is no well-established dosimetric constraint for the urethra. Prostate cancer patients were prescribed a 5Fx × 8-Gy SBRT schedule to the PTV, which is a higher dose than the more common, lower dose 5Fx × 7.25Gy schedule. In principle, a lower prescription dose may have a lower likelihood of GU toxicity; however, urethral hotspots remain a concern for the 5Fx × 7.25Gy schedule as the CTV, containing the urethra, is still prescribed to receive 40 Gy (3). The MRgART workflow with onboard urethral imaging may be valuable to account for the daily urethral change as shown in this study, and if necessary, treatment reoptimization may be utilized to replan and reduce daily urethral hotspots and, as a result, GU toxicity.

This study had several limitations. First, there is a lack of urethra ground truth to reference, and as a result, interfractional urethral geometric and dosimetric changes are reported as relative changes. Currently, there is no gold-standard ground truth for urethra localization at the time of treatment. Nonetheless, the much improved soft-tissue contrast with the urethral-specific MRI makes us more confident in urethra localization. Second, urethra qualitative visibility with our current MRI sequence varied considerably between patients and between observers. Interpatient urethral visibility variance may be due to varying amounts of residual urine in the prostatic urethra, surrounding fat and motion/ghosting artifacts, as well as nearby prostatic hyperplasia compressing the prostatic urethra (16). Interobserver urethral visibility variance can also be due to different observer experiences. Further MRI sequence and imaging protocol optimization is necessary to achieve more robust urethral visualization. Third, the reported urethral MRI sequence took 7–8 min, which may be impractical for the already time-intensive MRgART workflow. The long urethral scan time can increase the chance of unwanted patient motion and anatomical changes. Therefore, future work will explore MR sequence acceleration strategies. Lastly, due to long urethral imaging times and clinical time constraints, urethra images were only acquired at simulation and at the final fraction, which limits the accuracy of the reported urethral interfractional geometric and dosimetric changes or variations. Despite this, a total of 26 prostate cancer patients were recruited, and the reported results of the entire cohort can be used to estimate urethral interfractional variations.

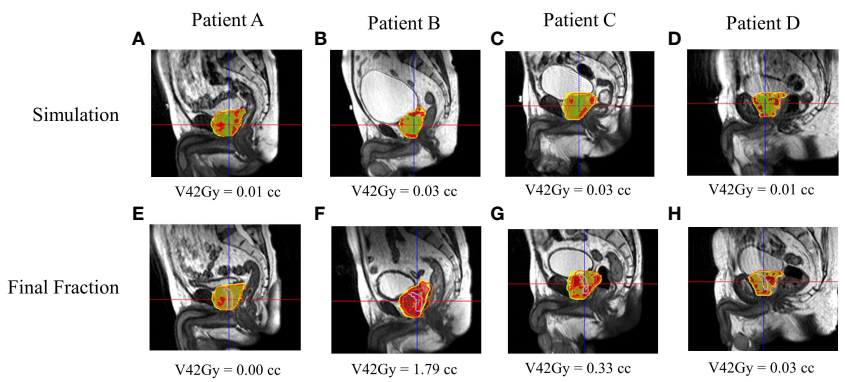

FIGURE 6 | RO2's calculated and estimated dose and urethral V42Gy for patient A–D's simulation **(A–D)** and final fraction **(E–H)** bSSFP. RO2 simulation/final HASTE urethra contour—purple/blue. Orange contour—PTV. Red—105% (42 Gy) isodose region, yellow—95% (38 Gy) isodose region.

CONCLUSION

Interfractional urethral geometric or anatomical changes can result in clinically significant urethral dose change for prostate cancer patients treated with urethral hotspot-limiting MRgRT plans, potentially contributing to an increased urethral dose. The MRgART workflow with onboard urethral imaging may be used to reduce daily urethral hotspots and, as a result, GU toxicity.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the dataset will not be made available due to patient privacy concerns. Requests to access the datasets should be directed to jonathanpham@mednet.ucla.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of University of California, Los Angeles, IRB #17-001064. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JP was the lead author and contributed in data collection, data analysis, manuscript drafting, table/figure creation, and manuscript revision. RS and SY contributed in data collection and manuscript review. TY contributed in data analysis and manuscript review. YG, MC, PH, KS, DL, MS, and AK aided in manuscript review. YY was the senior author who developed the concept of the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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High Dose "HDR-Like" Prostate SBRT: PSA 10-Year Results From a Mature, Multi-Institutional Clinical Trial

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Purpose/Objective(s): Although ample intermediate-term prostate stereotactic body radiotherapy (SBRT) outcomes have been reported, 10-year results remain relatively sparse.

Materials/Methods: Eighteen institutions enrolled 259 low- and intermediate-risk patients. Median follow-up is 5.5 years, with 66 patients followed ≥ 10 years. This SBRT regimen specifically emulated an existing HDR brachytherapy dose schedule and isodose morphology, prescribed to 38 Gy/4 fractions, delivered daily by robotic SBRT, mandating > 150% dose escalation in the peripheral zone. Androgen deprivation therapy was not allowed, and a hydrogel spacer was not available at that time.

Results: Median pre-SBRT PSA 5.12 ng/mL decreased to 0.1 ng/mL by 3.5 years, with further decrease to a nadir of < 0.1 ng/mL by 7 years, maintained through 10 years. Ten-year freedom from biochemical recurrence measured 100% for low-risk, 84.3% for favorable intermediate risk (FIR), and 68.4% for unfavorable intermediate (UIR) cases. Multivariable analysis revealed that the UIR group bifurcated into two distinct prognostic subgroups. Those so classified by having Gleason score 4 + 3 and/or clinical stage T2 (versus T1b/T1c) had a significantly poorer 10 year freedom from biochemical recurrence rate, 54.8% if either or both factors were present, while UIR patients without these specific factors had a 94.4% 10-year freedom from biochemical recurrence rate. The cumulative incidence of grade 2 GU toxicity modestly increased over time – 16.3% at 5 years increased to 19.2% at 10 years– while the incidence of grade 3+ GU and GI toxicity remained low and stable to 10 years - 2.6% and 0%, respectively. The grade 2 GI toxicity incidence also remained low and stable to 10 years – 4.1% with no further events after year 5.

Conclusion: This HDR-like SBRT regimen prescribing 38 Gy/4 fractions but delivering much higher intraprostatic doses on a daily basis is safe and effective. This treatment achieves a median PSA nadir of <0.1 ng/mL and provides high long-term disease control rates without ADT except for a subgroup of unfavorable intermediate-risk patients.

Keywords: prostate cancer, SBRT, PSA nadir, HDR, relapse free rate, CyberKnife

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INTRODUCTION

Stereotactic body radiotherapy (SBRT) is by now a well-recognized treatment option for patients with clinically localized prostate cancer. The recognition of a low alpha-beta ratio (1), suggesting prostate cancer to be relatively more responsive to higher doses per fraction, as well as improved treatment delivery precision that limits collateral organ at risk dose exposure, is the basis for the use of hypofractionated radiotherapy for this disease, culminating in the adoption of ≤ 5 fraction regimens, delivered by SBRT methodology.

Preceding contemporary SBRT and also in parallel, a different method of extremely hypofractionated radiotherapy has used high dose rate (HDR) brachytherapy to deliver the entire course in a similar number of fractions, with excellent disease control and acceptable toxicity (2). The power and convenience of HDR brachytherapy come at the expense of requiring an invasive procedure, a requisite period of hospitalization to accomplish, and is hindered by a small set of physicians skilled at this technique nationwide.

SBRT can be designed to deliver dose fractionation and isodose morphology substantially identical to that of HDR brachytherapy, with the obvious advantages of being noninvasive and potentially more widely available (3). In spite of the potential advantages of prostate SBRT, one of the factors limiting its further use is a continued relative scarceness of long-term data – a necessary essential to document both efficacy and safety relative to other radiotherapy modalities that have a longer history.

Herein, we present the mature results of a multi-institutional clinical trial of "HDR-like" SBRT, reporting the late PSA kinetics, disease-free survival, and toxicity of this regimen to 10 years. A well-established radiation dosing schedule of 38 Gy in four fractions has demonstrated excellent efficacy with high-dose-rate (HDR) brachytherapy, and is recognized by the American Brachytherapy Society as a standard treatment option (4). The current prospective multi-center Phase II trial was designed to emulate this regimen with SBRT; both the dose fractionation and the internal prostatic isodose morphology, described in greater detail in our original study of this technique (3), while eliminating the invasiveness and inconvenience of brachytherapy.

MATERIAL (PATIENTS) AND METHODS

Patients and Treatment

Eligible patients included those with low- and intermediate-risk prostate cancer using the D'Amico classification (5). All pathology was centrally reviewed (Bostwick Labs). Patients were treated from December 2007 through February 2012 at 18 institutions, the majority of which are community-based practices (**Appendix Table 1**). This clinical trial was registered with clinicaltrials.gov (NCT00643617) with all participating institutions receiving IRB-approval.

Patients received 38 Gy in four daily fractions of 9.5 Gy per fraction, using a fiducial-guided robotic SBRT technique (CyberKnife®; Accuray, Sunnyvale, CA, USA). Androgen deprivation therapy was not allowed in this trial. CT-based simulation was done with Foley catheter for urethra delineation; prostate MRI with image co-registration to the CT was encouraged but not required. The clinical target volume (CTV) included the prostate for all patients; intermediate-risk patients also included 1 cm of proximal seminal vesicles. PTV margin was a 2-mm volume expansion in all directions from the prostate, except posteriorly where the prostate abutted the rectum, which was manually adjusted on the computer to a 0-mm margin. For Gleason 7 cancer patients, the ipsilateral side(s) of the involved prostate had a 5-mm PTV expansion to cover potential extracapsular extension more thoroughly. Treatment planning coverage and normal tissue constraints are detailed in **Appendix Table 2**. The trial required plans with >1% of the PTV receiving at least 150% of the prescription dose (≥57 Gy), to emulate HDR brachytherapy dosimetry (**Figure 1**). It should be noted that this trial did not mandate a prostate size cut-off (the largest prostate volume was 155 cc). Of note, this entire trial happened before the availability of hydrogel spacers.

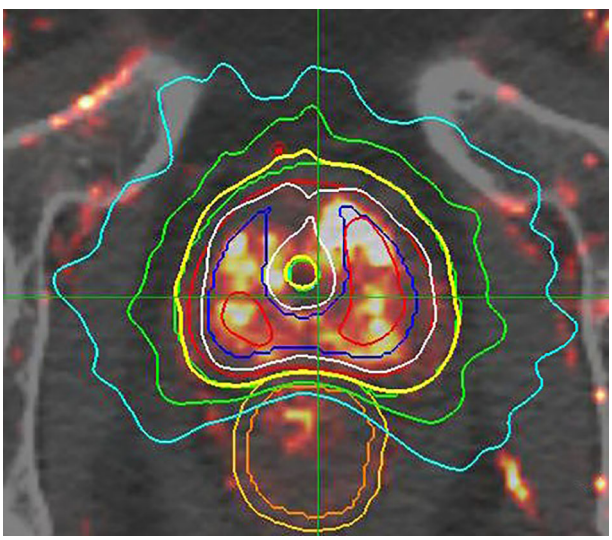

FIGURE 1 | Sample HDR-like treatment plan, with contours and isodose display: This image set consists of a DCE enhanced MRI, superimposed over a standard planning CT image. The prostate GTV is contoured in red. The asymmetrically expanded PTV is contoured in green, revealing a 2 mm GTV to PTV expansion on the right (lesser involved side); a 5 mm GTV to PTV expansion on the left side (heavier involvement and with Gleason 7 disease); with manual "shaving" of GTV to PTV expansion down to zero mm adjacent to the rectum. This plan was constructed before the advent of SpaceOAR. This case is prescribed to 3800cGy/4 fractions, displayed by the yellow isodose line, with extreme conformality around the underlying green PTV contour. Additional isodose information: 125% = white, 150% = red, 75% = green, and 50% = aqua. NOTE that the yellow prescription isodose line touches, but does not breach, the outer rectal wall, and also has a central dip to relatively spare the urethra, while the 75% green isodose line touches but does not breach the rectal mucosa, defined as a 3 mm contraction from the outer rectal wall. This design morphology concentrates the greatest dose in the peripheral zone of the most heavily involved left lobe, with wider coverage margins adjacent to that region.

Outcomes Assessed

Patients were evaluated 3, 6, and 12 months out, semiannually during years 2 through 5 and annually after that to year 10. Biochemical recurrence was defined using the Phoenix definition (nadir plus 2 ng/mL) (6). We report freedom from biochemical recurrence and clinical recurrence, stratified by risk groups. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical Methods

The Kaplan-Meier method was used to estimate toxicity over time and freedom from recurrence. The log-rank test was used to compare risk groups. Univariate and multivariable Cox proportional hazard models were used to evaluate factors associated with freedom from biochemical recurrence. All statistical analysis was performed using SAS version 9.4 (Cary, NC), and two-sided p-values of <0.05 were considered statistically significant.

RESULTS

Overall, 259 patients were enrolled, with median age being 68.7 years (**Table 1**); 43% (112) were low-risk and 57% were intermediate-risk (101/147 favorable; 46/147 unfavorable). The median follow-up is 5.5 years, with 66/259 (25%) followed ≥ 10 years.

PSA Response and Freedom From Recurrence

From an initial median PSA level of 5.12 ng/mL, the median PSA continued to decrease to 0.1 ng/mL by 42 months, and then to < 0.1 ng/mL at year 7, maintained through year 10 (**Figure 2**). The 10-year freedom from biochemical recurrence (FFBR) measured

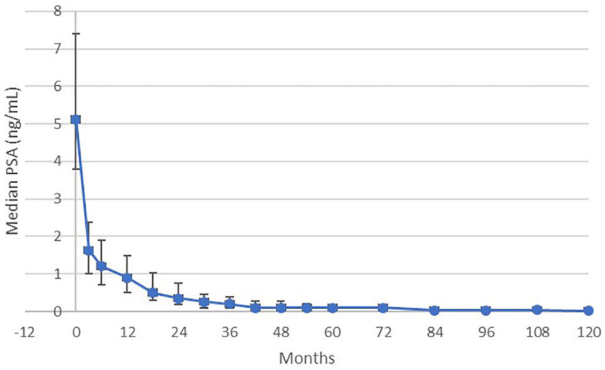

FIGURE 2 | Median PSA level (with +/- one standard deviation bar) for patients on trial.

100% for low-risk, 84.3% for favorable intermediate-risk, and 68.4% for unfavorable intermediate-risk (p=0.0001 – univariate analysis; **Figure 3**).

For the minority of patients with clinical relapse, the pattern is primarily distant, representing 78% of the total. 10-year local relapse-free survival measured 99%, while 10-year distant relapse-free survival measured 95.5%. All clinical failures occurred in the intermediate-risk cohort, with the majority of distant failures occurring in the unfavorable intermediate-risk group. There was one prostate cancer-specific death within the first 10 years of follow-up, translating to 99.5% 10-year disease-specific survival.

On multivariable analysis, Gleason score 4 + 3 = 7 (p=0.0477) and the presence of palpable as opposed to impalpable disease (stage T2a/T2b versus stage T1c) (p = 0.0359) were significantly associated with FFBR (**Table 1**).

Patients with Gleason score 4+3=7 and/or stage T2a/T2b disease had a 54.8% 10-year FFBF, versus 92.8% for all other

TABLE 1 | Multivariable analysis for freedom from biochemical recurrence.

	Univariate		Multivariable	
	Hazard Ratio	**P-value**	**Hazard Ratio**	**P-value**
Age	1.084 (per year)	0.0326	1.059	0.1982
iPSA (REF: 0-4.0 ng/mL)		0.1915		0.0958
4.01-10 ng/mL	2.062		1.426	
10.01-20 ng/mL	5.272		9.359	
Risk Group (REF: Low/fav int)		0.0007		0.3804
Unfavorable Intermediate	4.969		1.810	
Gleason (REF: 3 + 3)		0.0008		0.0477
3+4	3.656		2.699	
4+3	10.804		8.827	
T-Stage (REF: T1c)	2.939	0.0231	3.143	0.0359
T2a/T2b				
# (+) Biopsy Cores	1.064 (per core)	0.5607	1.028 (per core)	0.8249

Low-risk group has no events.
T2b only has three subjects so was combined with T2a.

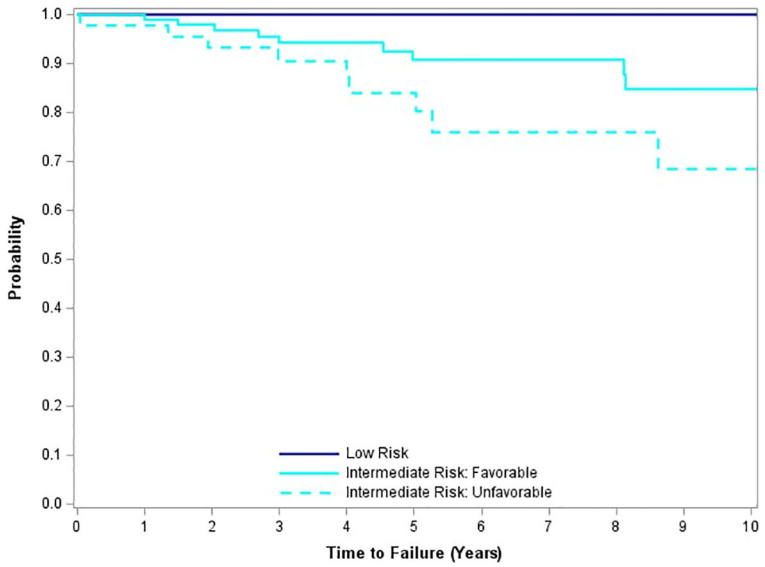

FIGURE 3 | Freedom from biochemical recurrence by risk group.

patients in the trial. For the subgroup of UIR patients without a Gleason score of 4 + 3 or palpable disease, the 10-year freedom from biochemical recurrence rate was 94.4%. Although risk group classification was highly significant on univariate analysis (p=0.0001; worsened outcome with increased risk group), this finding disappeared on multivariable analysis. **Figure 4** illustrates the large curve separation of Gleason 4 + 3 = 7 and/or palpation stage T2 cases, versus all remaining study cases.

Toxicity

Acute genitourinary (GU) toxicity (≤ 90 days) measured 35.1% for grade 2 and 1.1% for grade 3; including one patient (0.4%) with catheter dependent urinary retention and two (0.8%) with severe frequency/dysuria. Acute gastrointestinal (GI) toxicity measured 6.9% grade 2 with no grade 3 or higher acute GI events. Regarding chronic toxicity (> 3 months), the cumulative incidence of grade 2 or higher GU toxicity measured 16.3% by

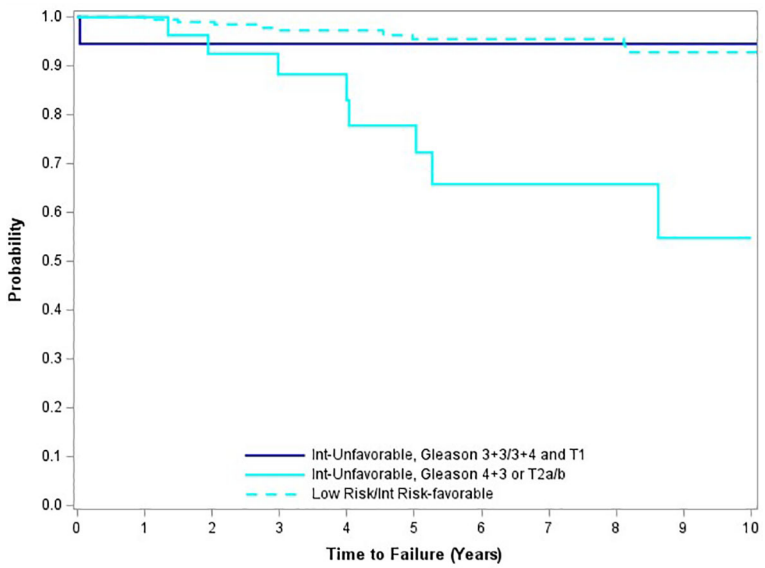

FIGURE 4 | Freedom from biochemical recurrence for subgroups of unfavorable intermediate-risk patients.

year 5, modestly increased to 19.2% by year 10. The cumulative incidence of grade 3 and higher GU toxicity was 2.6% at 5- and 10-years. The cumulative incidence of grade 2 GI toxicity was 4.1% at 5 and 10 years, with 1.1% so classified due to rectal bleeding. We observed no grade 3 or higher long-term GI toxicity in this study.

DISCUSSION

Prostate cancer radiotherapy continues to evolve, progressed from "standard" or "conventional" fractionation (8-9.5 weeks) to moderate hypofractionation (4-5.5 weeks), to an increasing prevalence of SBRT (1-2 weeks). Initially, commonly published SBRT regimens often applied 35-36.25 Gy in five fractions over 1 to 2 weeks (7–9). As there were minimal efficacy and safety data for SBRT for any fractionation at protocol inception, our dosing schedule was derived from a well-established "safe and effective" HDR brachytherapy regimen (2). Using HDR-like heterogeneous planning and a higher total dose (38 Gy in four fractions), as reported in this study, represents a more intensive treatment regimen than other prostate SBRT regimens. Philosophically, we sought to recapitulate this HDR brachytherapy dose fractionation and isodose morphology regimen as exactly as possible, using robotic SBRT as the delivery mechanism (3).

Assuming an alpha/beta ratio of prostate cancer to be 2.0, this regimen delivered an equivalent dose at 2 Gy per fraction (EQD2) of 109 Gy to the margin of the PTV, with a substantially higher dose throughout the substance of the extra-urethral prostate due to "HDR-like" isodose morphology. This equates to an (Equivalent Uniform Dose) EUD to the entire PTV of approximately 48 Gy/4 fractions (125% of the prescription isodose level), which translates to an "average" intraprostatic EQD2 of 181 Gy. This compares to an EQD2 of 83 Gy at the periphery and approximately 111 Gy "average" intraprostatic EQD2 for the common 36.25 Gy/5-fraction SBRT regimen (assumes the dose prescribed to the 83% isodose line). Compared to standard fractionation IMRT, prescribed to 80 Gy/40 fractions, both SBRT regimens are hotter, as this IMRT regimen creates an EQD2 of 80 Gy at the margin of the PTV and an "average" intraprostatic EQD2 of approximately 86 Gy (assumes the dose prescribed to the 95% isodose line, with less intraprostatic dose heterogeneity). It is worth noting that our SBRT prescription regimen is similar in concept to "micro-boosting" that is now more commonly studied in IMRT and SBRT trials. Our HDR-like SBRT regimen in essence boosted bilateral extra-urethral prostate to much higher doses than the prescription dose, and in this manuscript, we demonstrate the long-term efficacy and safety of this technique.

We show that this treatment achieves a median nadir of < 0.1 ng/mL at 7 years, continuously maintained thereafter through 10 years. This level of "surgical" PSA result is not commonly seen with prostate IMRT without ADT. Clinically, the 10-year local relapse-free survival rate measures 99%, with no additional local relapses seen after year three. Additionally, the 100% 10-year rate of freedom from any form of relapse, including biochemical relapse, in low-risk patients, is a result that has not been previously reported, to the knowledge of the authors. These attributes appear to validate the high radiobiologic potency implied by the above-described EQD2 discussion.

Although all published SBRT regimens create a low PSA nadir, the more conservatively dosed regimens (33.5 – 37.5 Gy/5 fractions) do not reach a full ablation level, with reported nadirs from 0.2 – 0.48 ng/mL (10–12). One institution published two separate post-SBRT PSA kinetic response papers, using a dose of 35-37.5 ng/mL, demonstrating that the median PSA level decreased from 0.3 ng/mL at 3 years to 0.2 ng/mL at 5.6 years of median follow-up, though only 40% of the patients in the longer-term study achieved an "ablation" PSA nadir level (11, 12). Once again, this suggests that the more conservatively dosed regimens are potent, but not routinely ablative. The more conservatively dosed prostate SBRT regimens create a PSA nadir that resembles that of dose escalated IMRT (6, 10).

Of note, a radiologically ablative regimen does not necessarily translate to cured prostate cancer either, as reported in a pooled multi-institutional SBRT dose response analysis (13). This report indicated that although 38 Gy/4 fractions produced the steepest PSA decline slope and lowest absolute PSA nadir versus all other evaluated prostate SBRT regimens, this attribute did not translate to an improved biochemical relapse-free rate versus the slightly less radiobiologically aggressive 40 Gy/5 fraction regimen. In our series, this appears particularly so for the subset of patients with unfavorable intermediate-risk disease, so classified due to Gleason score 4 + 3 = 7 and/or palpable (T2a/T2b) disease, who have a relapse rate in excess of 40% in spite of the locally ablative nature of their primary treatment.

Clinically, unfavorable intermediate-risk patients, and particularly those with the specific findings of Gleason 4 + 3 or palpation stage T2 (as opposed to T1) disease, have a higher propensity to distant relapse. As such, these patients should be more thoroughly staged prior to treatment, ideally now including a contemporary "prostate specific" PET/CT scan, which may be more sensitive to the detection of small metastatic foci that may evade conventional imaging evaluation. Additional treatment intensification measures should also be considered for these patients, potentially including the addition of prophylactic pelvic lymph node radiotherapy, the addition of androgen deprivation therapy, or both.

Interestingly, unfavorable intermediate-risk patients without the specific negative attributes described in the paragraph above had a much more favorable outcome, similar to the remainder of the patients in this series, a bifurcation in the UIR risk group that has not been previously reported to the knowledge of these authors. Possibly, this difference suggests that UIR patients with Gleason score 4 + 3 and/or palpable disease have a significantly higher metastatic potential or existing micro-metastatic disease at diagnosis, while the remainder of the UIR group could tend to have higher volume local disease of lesser metastatic potential, thus well treated by locally ablative sole modality SBRT.

In parallel, we now observe a similar UIR outcome dichotomy predicted by advanced tumor genomic profiling, specifically, the CCR score, with a result below 2.114 similarly predicting a much more favorable 10-year UIR radiotherapy efficacy result, regardless of whether or not ADT is added to the regimen

(14). In the future, it would be interesting to see if our own dichotomous UIR outcome based on traditional factors has identified substantially the same prognostic bifurcation, now detected by contemporary genomic profiling.

Due to potential toxicity of a high EQD2 at the PTV margin, this trial was designed with small CTV to PTV margins (2-5 mm, with any 5 mm expansion limited to high extracapsular extension risk sub-regions). Posteriorly, there was further "shaving" to a zero mm margin, to spare the rectum. This did not lead to an excess incidence of missing extra-prostatic disease, as no posterior marginal relapses were observed. However, the result of this specific approach may not be generalizable to all SBRT methods; there remains a lack of data on the efficacy of lower dose prostate SBRT using non-CyberKnife treatment machines, with a CTV to PTV margin expansion this small.

The higher biologically effective dose delivered with "HDR-like" SBRT could also result in increased toxicity (bowel, bladder, and/or urethra). A prior study using SEER-Medicare claims data suggested high toxicity rates after SBRT, highlighting this concern (15). Although we did observe a modest further increase in the cumulative incidence grade 2 GU toxicity between year 5 (16.3%) and year 10 (19.2%), there was no further increase in grade 2 GI toxicity after year 5 (4.1%). This modest increase in urinary symptoms over time could be due to treatment, but could also be due to aging of enrolled patients progressing from a median 68.7 years at enrollment to 78.7 years of age, by 10 years later. The cumulative grade 2 GU and GI toxicity rates we report are slightly lower versus a recently published modern, aggressive conventional fractionation radiotherapy series, the "FLAME" series, which reported cumulative grade 2+ GU and GI toxicity rates of 27.1% and 10.2% in their dose-escalated arm, respectively (16). Likewise, our delayed grade 2 GU and GI toxicity incidence is virtually identical to the 10-year incidence with a well-established and more mature 81 Gy/45 fraction IMRT regimen, reported by Zelefsky, et al. – 20% and 5%, respectively, in their series versus 19.2% and 4.1% in our current report (17).

Finally and reassuringly, the low rate of grade 3 or higher GU and GI toxicity has no further progression after year 5 in our series. It is notable that we demonstrate these results delivering SBRT daily (not every other day as commonly used in other SBRT regimens). Once again, our 10-year cumulative grade 3 toxicity incidence remains competitive with modern conventional prostate IMRT - 2.6% for grade 3+ GU and 0% for grade 3+ GI toxicity through year 10 in our own series - virtually identical versus the 3% GU and 1% GI incidence reported in the Zelefsky IMRT series described above (17). Thus, we have confirmed no delayed severe toxicity surprises with this regimen.

The toxicity profile of this SBRT regimen also compares favorably with brachytherapy. Post-brachytherapy catheter dependent urinary retention has been reported following both permanent source and HDR prostate brachytherapy, with an incidence of 9% or greater (18, 19). The presently described SBRT trial had a <1% incidence of catheter dependent urinary retention. Avoidance of needle trauma, a possible contributor to acute post-brachytherapy urinary retention, might explain the low rate of retention observed in this trial.

As the 10-year local control rate in this series is 99%, perhaps there is also some room to de-escalate the total dose. In fact, subsequent to the inception of this protocol, we launched a lower dose "HDR like" prostate SBRT dose regimen – 34 Gy/5 fractions, using proportionately identical isodose morphology but scaled to the lower total dose. This regimen has very similar freedom from biochemical recurrence rates to 5 years, with a minimally higher PSA nadir value (0.1 ng/mL versus < 0.1 ng/mL). There is less confirmation of long-term efficacy with this lower dose regimen, due to its later inception, with a resulting smaller percentage of patients at risk for 10 or more years (20).

In our own practice, the practical application of the subtle differential PSA nadir and follow-up discrepancy between regimens is a tendency to apply the higher dose regimen to patients with a greater than 20-year life expectancy and/or with higher volume local disease. We more commonly use the lower dose regimen for those who have lower-volume lesions, lesser potential longevity, and/or a higher toxicity risk (e.g., large prostate, high IPSS score, prior TURP); also for those who are extremely concerned regarding potentially different quality of life implications of the different regimens.

CONCLUSION

In summary, an HDR-like SBRT regimen prescribing 38 Gy/4 fractions but delivering much higher intraprostatic doses on a daily basis is safe and effective. This treatment achieves a median PSA nadir of <0.1 ng/mL and provides high long-term disease control rates without ADT except for a subgroup of unfavorable intermediate-risk patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Scripps IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the data collection, the manuscript was primarily prepared by DF and RC, statistical analysis was performed by TC. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.935310/full#supplementary-material

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