

## Scientific Article

# Prostate Stereotactic Body Radiation Therapy With a Focal Simultaneous Integrated Boost: Acute Toxicity and Dosimetry Results From a Prospective Trial



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Received 22 February 2018; revised 23 July 2018; accepted 10 September 2018

## Abstract

**Purpose:** This study aimed to report the early toxicity results of a prospective clinical trial of prostate stereotactic body radiation therapy (SBRT) to the entire prostate with a simultaneous integrated boost (SIB) to magnetic resonance imaging (MRI)-defined focal lesions.

**Methods and materials:** Eligible patients included men with biopsy-proven prostate stage T1c to T2c adenocarcinoma, a Gleason score  $\leq 7$ , and prostate-specific antigen values of  $\leq 20$  ng/mL, who had at least 1 focal lesion visible on MRI and a total prostate volume no greater than 120 cm<sup>3</sup>. SBRT consisted of a dose of 36.25 Gy to the entire prostate with an SIB of 40 Gy to the MRI-defined lesions, delivered in 5 fractions. The primary purpose of the study was to confirm the feasibility of treatment planning/delivery and to estimate the rate of urinary retention requiring placement of a Foley catheter within 90 days of treatment. This study was to be considered successful if urinary retention occurred in no more than 15% of cases, with a planned enrollment of at least 25 patients.

**Results:** A total of 26 men were enrolled, and all underwent SBRT as planned. Twenty patients (77%) had intermediate-risk features, and the remainder were low risk. A treatment plan that met the protocol-defined goals for all cases was developed. Two patients (7.7%) developed acute urinary symptoms that required the temporary placement of a Foley catheter. No grade 3+ toxicity events were observed.

Meeting information: A portion of these data were presented as an abstract at the 2017 Radiosurgery Society Meeting, held in Las Vegas, NV, November 2-4, 2017.

Sources of support: This work had no specific funding.

Conflicts of interest: The authors have no conflicts of interest to disclose.

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<https://doi.org/10.1016/j.adro.2018.09.007>

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**Conclusions:** Planning and delivery of prostate SBRT with a whole prostate dose of 36.25 Gy and a focal 40 Gy SIB is feasible. Early follow-up suggests that this treatment is not associated with undue morbidity.

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## Introduction

Prostate stereotactic body radiation therapy (SBRT) is now recognized as an emerging technology that may be considered an appropriate alternative to conventional fractionation in clinics with appropriate technology and expertise. The optimal dose for prostate SBRT has yet to be fully established.<sup>1</sup> Early studies found that a dose of 33.5 Gy in 5 fractions was associated with increased biochemical failure compared with dose-escalated conventionally fractionated regimens.<sup>2</sup> Therefore, contemporary prostate SBRT studies have used higher doses.

A dose of 36.25 Gy in 5 fractions delivered to the whole prostate gland has been associated with acceptable levels of acute and late toxicity in a number of studies,<sup>3–6</sup> including a national phase 2 study,<sup>7</sup> but whether this dose is adequate to achieve long-term biochemical control is unknown, particularly among men with intermediate risk features. On the other hand, higher doses of 50 Gy in 5 fractions to the entire prostate have been associated with excellent rates of 5-year biochemical control,<sup>8</sup> at the potential expense of an increased risk of high-grade toxicity.<sup>9</sup>

Rather than escalating the SBRT dose to the entire prostate gland, another dose escalation approach is to selectively increase the dose to tumor nodules within the prostate. In most cases, prostate cancer foci can be identified with multiparametric prostate magnetic resonance imaging (MRI) protocols, and MRI-defined lesions have reasonable spatial agreement compared with whole mount prostatectomy specimens.<sup>10,11</sup> Previous studies have shown that planning a simultaneous integrated boost (SIB) to MRI-defined tumor nodules in the setting of prostate SBRT appears to be dosimetrically feasible,<sup>12,13</sup> and clinical experience using SIB techniques in the context of fractionated therapy is growing.<sup>14</sup>

To assess the clinical feasibility of whole prostate SBRT with a focal SIB, we performed this prospective pilot trial (NCT01856855). We hypothesized that treatment of the entire prostate to 36.25 Gy in 5 fractions with an SIB to 40 Gy could be delivered while still respecting accepted organ-at-risk (OAR) dosimetric constraints (such as those used by NRG Oncology) and would not result in unacceptable acute morbidity. Herein, we present the dosimetric and acute toxicity results from this clinical trial.

## Methods and materials

### Enrollment

This trial was reviewed and approved by the institutional review board of the University of Alabama at Birmingham. Eligible patients included men age >18 years with a life expectancy exceeding 5 years, Karnofsky performance status score >60, and pathologically proven prostate adenocarcinoma with the following characteristics: clinical tumor stage T1c to T2a as assessed by digital rectal examination, prostate-specific antigen (PSA) values of <20 ng/mL, and a Gleason score of  $\leq 7$  (both Gleason 3 + 4 and 4 + 3 were allowed). MRI upstaging to T2b or T2c was allowed, but men with imaging evidence of T3 tumors were excluded. Men were excluded from the study if they had comorbid inflammatory bowel disease, use of immunosuppressive or antiplatelet/anticoagulant medications that could not be discontinued during SBRT, platelet count <70,000/ $\mu\text{L}$ , history of transurethral prostate resection, prostate volume >120  $\text{cm}^3$  measured by transrectal ultrasound (TRUS) or MRI, or tumor that was noted to involve >50% of the prostate on MRI.

### Treatment

For men with intermediate risk features (Gleason score of 7 or PSA values >10 ng/mL), androgen suppression was allowed at the discretion of the treating physician. For patients who had not previously undergone pelvic MRI, 3 Tesla pelvic MRI without rectal coil was performed. Axial T1 and T2 sequences were required, but complete multiparametric MRI was not. If MRI had been performed within the prior 6 months and was deemed clinically acceptable for treatment planning by the treating physician, then repeat MRI was not required. After MRI, 3 gold fiducial markers were implanted into the prostate gland using a standard TRUS-guided approach.

Participants were instructed to have a full bladder and empty rectum at the time of simulation. No specific bowel preparatory regimen was prescribed by the protocol; however, patients were generally instructed to use an osmotic laxative the evening before simulation to ensure a bowel movement the following morning. Computed

**Table 1** Treatment planning guidelines and achieved dosimetry

Structure	Volume	Goal	Median delivered (range)
Prostate PTV	% receiving 34.44 Gy	100%	100%
	% receiving 36.25 Gy	Not Specified	95.1% (43.3%-99.9%)
Prostate Boost PTV	Dose to 99%	Not Specified	36.3 Gy (35.0-37.0)
	% receiving 38 Gy	>95%	100% (97%-100%)
Rectum	% receiving 40 Gy	Not Specified	88% (50.2%-100%)
	Maximum dose to 1 cm <sup>3</sup>	≤38.06 Gy	35.7 Gy (34.2-36.6)
Bladder	Maximum dose to 3 cm <sup>3</sup>	<34.4 Gy	33.96 Gy (31.57-34.39)
	% receiving 36.25 Gy	<5%	0.7% (0.03%-3.91%)
	% receiving 29 Gy	<20%	11.8% (6.74%-17.91%)
	% receiving 18.125 Gy	<50%	36.98% (23.16%-49.9%)
	Maximum dose to 1 cm <sup>3</sup>	≤38.06 Gy	37.5 Gy (36.31-38.06)
Urethra	% receiving 32.625 Gy	<10%	3.86% (0.96%-8.97%)
	% receiving 18.125 Gy	<50%	14.84% (2.63%-40.29%)
Femoral heads	Maximum point dose	≤38.78 Gy	38.51 Gy (36.57-38.78)
	Maximum point dose	30 Gy	13.61 Gy (11.12-18.7)
Body	Maximum dose to 10 cm <sup>3</sup> (both sides)	20 Gy	9.9 Gy (7.95-13.97)
	Maximum point dose	Not Specified	41.91 Gy (40.26-45.81)

Abbreviation: PTV = planning target volume.

tomography (CT) simulation was performed in the supine position, and a retrograde urethrogram was performed to improve visualization of the prostate apex. Both 1 mm and 3 mm slice thicknesses were considered acceptable. CT simulation scans were fused with the MRI scans using Varian Eclipse (Varian Medical Systems, Palo Alto, CA), and treatment volumes were defined.

OARs included the bladder, urethra, rectum, and femoral heads. The urethra was delineated using the fused MRI scans. The prostate clinical target volume (CTV) was defined as the entire prostate using both CT and MRI scans. The boost CTV was not explicitly defined by the protocol but was delineated in a multidisciplinary fashion by the treating radiation oncologist in conjunction with a urologic surgeon and generally consisted of a 5-mm margin around the T2 hypointense lesion corresponding to the region with biopsy-proven prostate cancer. No restrictions were placed on the location of the boost CTV within the prostate, but the volume of the boost CTV was limited to no more than 50% of the total prostate volume.

The planning target volume (PTV) expansion was 5 mm in all directions, except posteriorly where a 3-mm expansion was used. The prescription dose to the prostate PTV was 36.25 Gy, and the prescription dose to the boost PTV was 40 Gy, delivered simultaneously in 5 fractions. Treatment planning dosimetry goals are presented as Table 1. No limit on target dose heterogeneity was specified by the protocol, but effort was made to limit the maximum dose ( $D_{max}$ ) to <43.5 Gy (120% of 36.25 Gy) because of reports that increased target volume heterogeneity may be associated with greater acute morbidity.<sup>15</sup> Both sliding window intensity modulated radiation therapy and volumetric modulated arc therapy were allowed, but all treated plans consisted of 2 volumetric modulated

arcs using 10 MV photons and delivered on either a Varian TrueBeam STx or a Varian Edge linear accelerator in flattening filter free mode.

Before the delivery of each fraction, image guidance was performed using cone beam CT to confirm rectal and bladder volume and to ensure alignment with the fiducial markers. Position of the fiducial markers was again confirmed immediately before treatment with orthogonal kV radiographs, and intrafraction positioning of the target was performed with either kV orthogonal radiographs between arcs or by gantry angle—triggered kV radiographs. Fractions were delivered on nonconsecutive days with the entire treatment course to be completed within 17 calendar days.

## Endpoints and statistical methods

The primary feasibility endpoint of this study was successful plan generation and treatment of all patients who enrolled in the trial. The primary clinical endpoint of this study was the development of acute urinary retention that required the placement of a Foley catheter within 90 days from the final treatment. This study was to be considered successful if a treatment plan meeting all dosimetric criteria in Table 1 could be generated and delivered for each patient, and if urinary retention occurred in no more than 15% of cases. Accrual of ≥25 patients would result in a 1-sided binomial test having 80% power to detect that the true rate of urinary retention was no more than 30% (against the null hypothesis of 15%) at a significance level of 0.2. The remainder of the acute toxicity events that occurred within 90 days of treatment completion were graded using the Common Terminology Criteria for Adverse Events, version 4.03.

**Table 2** Demographic and disease characteristics

	Median (range) or n (%)
Race	
Caucasian	14 (53.8%)
African-American	12 (46.2%)
Gleason score	
3 + 3	7 (26.9%)
3 + 4	12 (46.2%)
4 + 3	7 (26.9%)
T-stage*	
T1c	3 (11.5%)
T2	23 (88.5%)
Baseline IPSS	
<10	19 (73.1%)
10-20	5 (19.2%)
>20	2 (7.7%)
Initial PSA (ng/mL)	6.1 (2.5-17.6)
Age (years)	63.1 (50.1-81.8)
Prostate volume (mL)	42.7 (23.6-118)
Intraprostatic lesion volume (mL)	2.1 (0.1-6.2)

Abbreviations: IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen.

\* As assessed by digital rectal examination.

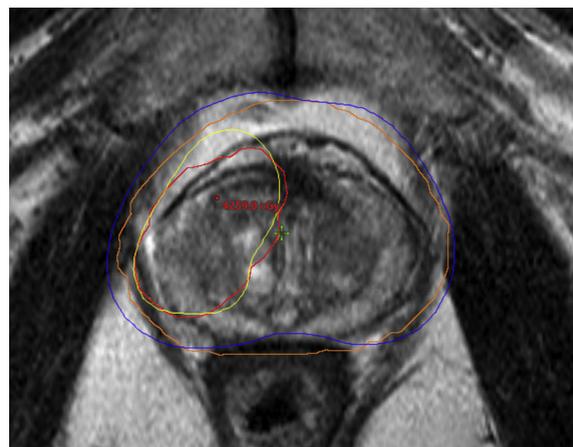
## Results

### Baseline characteristics

Between September 2013 and January 2017, a total of 26 men were enrolled in the study with a median age of 63.1 years (range, 50.1-81.8 years). All participants were followed for >90 days after their final treatment fraction. Twenty men (77%) met the criteria for the National Comprehensive Cancer Network intermediate-risk prostate cancer, and the remainder were low risk. Androgen deprivation therapy was used in 8 cases (30.8%). A comprehensive list of patient demographic and disease characteristics is presented in Table 2.

### Target characterization and dosimetry

A treatment plan could be developed that met all protocol-defined goals for all cases (Fig 1). The median CT-defined prostate volume across all patients was 44.3 cm<sup>3</sup> (range, 26.7-133.7 cm<sup>3</sup>). One patient who had a CT-defined prostate volume of >120 cm<sup>3</sup> was allowed to enroll in the study because his whole prostate volume was 110 cm<sup>3</sup>, as measured on TRUS volumetric assessment. At least 1 focal T2 hypointense lesion was identified in all cases, with 2 lesions identified in 6 cases (23.1%) and 3 lesions in 1 case (3.8%). Although not mandated by the protocol, all lesions were correlated with positive biopsy results, either via the original biopsy or additional MRI-guided fusion biopsy. The median prostate PTV V36.25Gy[%] was 95.1% (range, 43.3%-99.9%), and the



**Figure 1** Axial slice of example plan. Boost planning target volume delineated in red, and prostate planning target volume delineated in orange. The 40-Gy isodose line is in yellow, and the 36.25-Gy isodose line in orange. (A color version of this figure is available at <https://doi.org/10.1016/j.adro.2018.09.007>.)

V32.63Gy[%] (ie, 95% prescription isodose volume) was 100% in all cases.

The one case with a prostate PTV V36.25Gy[%] of 43.3% was a significant outlier, and the next lowest prostate PTV V36.25Gy[%] was 82.1%. The median boost PTV V40Gy[%] was 88% (range, 50.2%-100%), and V38Gy[%] was >97% in all cases. The median D<sub>max</sub> was 41.8 Gy (range, 40.3-45.87 Gy), and D<sub>max</sub> exceeded 43.5 Gy in 4 cases. Additional descriptions of target and OAR dosimetry are included in Table 1.

### Acute toxicity

A complete description of acute toxicity events is presented in Table 3. Two patients (7.7%) developed acute urinary symptoms requiring short-term placement of a Foley catheter. In the first case, urinary retention developed after the third fraction of treatment, and the catheter could be removed within 2 weeks of the completion of SBRT. In the second case, urinary retention developed 2 weeks after the final treatment, and the

**Table 3** Acute toxicity events

Genitourinary toxicity	Grade 1	Grade 2
Dysuria	3 (11.5%)	4 (15.4%)
Frequency	4 (15.4%)	6 (23.1%)
Hesitancy	5 (19.2%)	2 (7.7%)
Hematuria	0	1 (3.8%)
Gastrointestinal toxicity		
Diarrhea	3 (11.5%)	1 (3.8%)
Hematochezia	3 (11.5%)	0
Pain	1 (3.8%)	0
Urgency	1 (3.8%)	1 (3.8%)

catheter could be removed after being in place for less than 1 week. Neither patient has required the placement of a Foley catheter again, and they are now 9 and 5 months, respectively, from their final fraction of treatment. More details on each case resulting in acute urinary retention is provided in the [Supplement](#) (available online at <https://doi.org/10.1016/j.adro.2018.09.007>). Urinary hesitancy prompting initiation of tamsulosin was observed in 8 participants (30.7%).

## Discussion

This study was motivated by the hypothesis that SBRT dose escalation in men with intermediate-risk prostate cancer may improve biochemical control, combined with concerns that treating the entire prostate beyond 36.25 Gy would increase toxicity. Focal escalation of the radiation dose may achieve an oncologic benefit similar to that of whole prostate dose escalation, but with potentially less toxicity. Therefore, SBRT is an attractive alternative to whole prostate dose escalation. The advent of multiparametric MRI with high field strength magnets and specialized coils to improve signal-to-noise ratio has allowed for identification of focal lesions within the prostate, and pathologic correlate studies indicate that areas of higher-grade histology tend to be limited to the vicinity of the imaging abnormality.<sup>10</sup> Restricting additional dose escalation to these areas, particularly when combined with MRI targeted biopsy (which has been shown to optimize detection of clinically significant prostate cancer foci<sup>16,17</sup>), may improve the therapeutic ratio of treatment. Other institutions have reported experiences incorporating a focal boost to dominant tumor into fractionated therapy,<sup>14,18,19</sup> but feasibility data on using a focal boost in the setting of SBRT are sparse.

The treatment plans were successful in satisfying the protocol-defined goals in all cases; thus, the primary feasibility endpoint was met. Prostate PTV coverage was excellent, with 95% of the 36.25 Gy prescription covering the entire prostate PTV in all cases, and the 100% volume covering more than 90% in 20 cases (77%). Boost PTV coverage was good at the 95% level, being greater than 97% in all cases, but the 100% isodose coverage was <90% in 14 cases to respect OAR constraints. Interestingly, all plans used in this study met all OAR constraints included in the NRG/RTOG0938 study,<sup>7</sup> and only 4 cases would have been considered a minor violation of the  $D_{max}$  <43.5 Gy heterogeneity constraint allowed for CyberKnife treatment (despite our use of a 40 Gy SIB).

The creation of the primary clinical endpoint of this study must be understood in the context of when the trial was designed. Reports suggesting that urinary retention is an uncommon occurrence after SBRT<sup>20</sup> were not readily available; instead, contemporary low-dose-rate brachytherapy experience was used as a reference. If a 15% or

higher rate of urinary retention was observed with SBRT in this trial, then this technique would be considered to have significantly worse urinary morbidity than low-dose-rate brachytherapy, and further trials would not be justified. The ultimate rate of acute urinary retention requiring temporary placement of a Foley catheter fell below the prespecified acceptable threshold of 15%; thus, this study met its primary toxicity endpoint.

The frequency and severity of the remaining acute grade 2 toxicity were similar to our previous experience with moderate hypofractionation,<sup>21</sup> but self-limited (grade 1) rectal bleeding did occur more commonly than would be expected from fractionated treatment regimens. We did not observe the acute or subacute hematuria that has been reported in some CyberKnife (Accuray Incorporated, Sunnyvale, CA) series.<sup>22,23</sup> Although no formal comparison can be drawn between this study and other studies, the toxicity resulting from treatment on this study appears similar to what has been reported in studies of 36.25 Gy prostate SBRT without an SIB.<sup>3,7,24,25</sup>

The primary limitations of this study are those common to small, single-institution clinical trials, including a relatively small sample size and the potential for enrollment bias. Other potential criticisms of the study design that we recognize are that no enrollment restriction was placed concerning pretreatment urinary morbidity score and that repeat MRI after neoadjuvant androgen suppression was not mandated. The predetermined threshold for 15% or less urinary retention as a clinical acceptability criterion appears high in retrospect, but as stated, fewer data were available to draw upon at the time this study was designed.

## Conclusions

The results of this study met the predefined criteria for planning feasibility and treatment tolerance, and we are continuing to assess biochemical, late-toxicity, and patient-reported quality of life outcomes data as they mature. This study was originally conceived in 2012 to inform the design of a larger clinical trial with this SBRT technique. We recognize that significant progress in prostate SBRT has been made since that time. The results from larger single-arm studies and registries now support the safety of 40 Gy in 5 fractions to the entire prostate.<sup>20,26,27</sup> A hydrogel spacer, which is used to separate the prostate and rectum, has been developed and validated for men undergoing fractionated radiation therapy<sup>28</sup> and is now being incorporated into ongoing SBRT trials.

In light of these new developments, the follow-up clinical trial that we originally envisioned may no longer be needed; however, the results of this pilot trial may still be useful for future studies. First, this study supports that a focal SIB to intraprostatic tumor nodules can be feasibly planned and that a focal SIB to 40 Gy can be incorporated

into prostate SBRT without dramatically worsening the acute toxicity profile. If the long-term outcomes of ongoing studies investigating whole prostate dose escalation beyond 36.25 Gy in 5 fractions suggest greater than expected toxicity, the dose regimen used in this pilot study may provide an option for dose escalation while continuing to respect widely accepted OAR constraints, even though it is not a radical departure from more common SBRT approaches.

## Supplementary data

Supplementary material for this article can be found at <https://doi.org/10.1016/j.adro.2018.09.007>.

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