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Simulation of an HDR “Boost” with Stereotactic Proton versus Photon Therapy in Prostate Cancer: A Dosimetric Feasibility Study

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Abstract

Purpose/Objectives: To compare the dose escalation potential of stereotactic body proton therapy (SBPT) versus stereotactic body photon therapy (SBXT) using high-dose rate prostate brachytherapy (HDR-B) dose-prescription metrics.

Patients and Methods: Twenty-five patients previously treated with radiation for prostate cancer were identified and stratified by prostate size ($\leq 50\text{cc}$; $n = 13$, $> 50\text{cc}$; $n = 12$). Initial CT simulation scans were re-planned using SBXT and SBPT modalities using a prescription dose of 19Gy in 2 fractions. Target coverage goals were designed to mimic the dose distributions of HDR-B and maximized to the upper limit constraint for the rectum and urethra. Dosimetric parameters between SBPT and SBXT were compared using the signed-rank test and again after stratification for prostate size ($\leq 50\text{cm}^3$ and $>50\text{cm}^3$) using the Wilcoxon rank test.

Results: Prostate volume receiving 100% of the dose (V100) was significantly greater for SBXT (99%) versus SBPT (96%) ($P \leq 0.01$), whereas the median V125 (82% vs. 73%, $P < 0.01$) and V200 (12% vs. 2%, $P < 0.01$) was significantly greater for SBPT compared to SBXT. Median V150 was 49% for both cohorts ($P = 0.92$). V125 and V200 were significantly correlated with prostate size. For prostates $> 50\text{cm}^3$, V200 was significantly greater with SBPT compared to SBXT (14.5% vs. 1%, $P = 0.005$), but not for prostates $\leq 50\text{cm}^3$ (9% vs 4%, $P = 0.11$). Median dose to 2cm^3 of the bladder neck was significantly lower with SBPT versus SBXT (9.6 Gy vs. 14 Gy, $P < 0.01$).

Conclusion: SBPT and SBXT can be used to simulate an HDR-B boost for locally advanced prostate cancer. SBPT demonstrated greater dose escalation potential than SBXT. These results are relevant for future trial design, particularly in patients with high risk prostate cancer who are not amenable to brachytherapy.

Keywords: prostate cancer, brachytherapy, stereotactic radiation therapy, proton therapy

Introduction

Hypofractionated radiation may improve the therapeutic ratio of prostate radiation owing to the hypothesized low α/β ratio of prostate cancer cells [1–4]. Compared to dose-escalated external beam radiation therapy (EBRT) with anti-androgen therapy, the

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combination of EBRT and a prostate brachytherapy (PB) boost with anti-androgen therapy has been shown to improve biochemical control [5–9] and may reduce the rate of distant metastases in patients with intermediate- and high-risk disease [7, 10]. Despite high-quality evidence, the clinical application of a PB boost is declining [11]. This is often attributed to resource barriers (ie, operating room time, cost of supplies, physician time), challenges with coordinating a multidisciplinary surgical procedure, and a declining number of radiation oncologists who are comfortable with performing PB. Additionally, some patients are not eligible for PB owing to unfavorable anatomy, medical comorbidities, or personal preference. The American Brachytherapy Society (ABS) also outlines some relative contraindications that include high International Prostate Symptom Score and/or large gland size (generally $>50\text{ cm}^3$) [12].

A stereotactic body photon therapy (SBXT) boost for locally advanced prostate cancer has been proposed as a more convenient, noninvasive alternative to PB. Advancements in imaging and treatment techniques including the use of magnetic resonance imaging (MRI), spacer gel to move the rectum away from the prostate [13], prostate fiducials for target localization, and intrafraction image guidance [14] have all paved the way for ultrahypofractionated SBXT. Several single-institution experiences using SBXT as a boost for intermediate- and high-risk prostate cancer have demonstrated favorable biochemical control [15–24]. However, the differences in dose distribution, compared to PB, and its radiobiological impact raise concern regarding the long-term efficacy of this approach. Prostate brachytherapy results in heterogeneous dose escalation created by dwell (or seed) positions that are intentionally placed to avoid the urethra, whereas SBXT requires a more homogenous central dose distribution to spare the urethra. The steeper dose gradient and sharp dose falloff that is achievable with PB is thought to contribute to its radioablative effects and high therapeutic ratio.

In contrast, stereotactic body proton radiation (SBPT) using intensity-modulated proton therapy (IMPT) may enable improved modulation of the dose within and around the tumor target through individually weighted, narrow beam Bragg peaks [25]. This may provide the potential advantage of greater spatial control of the dose-escalated regions and lower dose to organs at risk (OARs) than with SBXT. A study from Sweden using a hypofractionated proton boost demonstrated excellent biochemical control and prostate-cancer survival at 8 years as well as a low prevalence of both genitourinary (GU) and gastrointestinal (GI) toxicity at 5 years [26]. However, the target dose in this study was not specifically aimed to mimic the dose heterogeneity of PB and dosimetric data were not provided.

The purpose of this study is to compare the dose escalation potential between SBPT and SBXT while maintaining low doses to OARs. We hypothesize that SBPT plans will permit greater dose escalation—more similar to that of high-dose rate prostate brachytherapy (HDR-B)—than SBXT plans. A unique aspect of our study is that SBPT and SBXT dosimetry was intentionally planned to mimic HDR-B, and the effect of prostate size on dose escalation was evaluated.

Materials and Methods

Patient Selection

This study was approved by our institutional review board under a waiver of informed consent. A total of 25 patients previously treated for prostate cancer at our institution from 2016 to 2019, using IMPT ($n = 14$) or volumetric modulated arc therapy ($n = 11$), were retrospectively identified. Patients were specifically selected to represent an equally distributed range of prostate sizes within and outside of the general size criteria for brachytherapy: $\leq 50\text{ cm}^3$ ($n = 13$) and $>50\text{ cm}^3$ ($n = 12$).

Volume Delineation

Computed tomography (CT) simulation scans were acquired by using 3-mm axial slices according to our institutional protocol. A pelvic MRI was obtained and coregistered with the CT simulation scan to aid in target delineation. The clinical tumor volume (CTV) was defined as the prostate gland only to simulate the prostate boost treatment phase, using the coregistered MRI and then modified as needed from the CT scan. A nonuniform planning tumor volume (PTV) expansion of 2 mm in all directions was used except for posteriorly in which no expansion was used to avoid overlap with the rectum [16]. Organs at risk, including the rectum, bladder, urethra, and bladder neck, were contoured. Bladder neck was delineated from a contouring method previously described [27].

Dosimetric Goals and Constraints

A common and extensively published HDR-B dose of 19 Gy in 2 fractions (9.5 Gy/fraction) [28–31] was prescribed to the PTV (SBXT) or robustly optimized CTV (SBPT). All plans were required to meet the target coverage goal for the PTV and robustly

Table 1. Treatment planning goals.

Normal tissue constraints (required)	
Rectum	$V75\% < 1 \text{ cm}^3$
Bladder	Primary: $V75\% < 1 \text{ cm}^3$ Secondary: $V75\% < 5 \text{ cm}^3$ and $V80\% < 2 \text{ cm}^3$
Urethra	$V125\% < 1 \text{ cm}^3$
CTV coverage and dose heterogeneity	
D90%	$\geq 100\%$ (goal)
V100%	$\geq 90\%$ (required) $\geq 95\%$ (goal)
V125%	$\geq 50\%$ (goal)
V150%	$\geq 25\%$, $< 50\%$ (goal)

Abbreviation: CTV, clinical tumor volume.

optimized CTV for SBXT and SBPT, respectively. To create an equal comparison between SBPT and SBXT plans, target coverage and dose heterogeneity of the CTV (prostate) was evaluated and compared. Target coverage and dose heterogeneity goals shown in **Table 1** were designed to reflect HDR-B dosimetry reported in the literature [32–34]. As per ABS guidelines, the CTV (prostate) was required to have 100% of the volume receiving 90% or greater of the prescription dose ($V100 \geq 90\%$) [12]. Other target heterogeneity goals were as follows: D90, V100, V125, and V150 had a goal of $\geq 100\%$, $\geq 95\%$, $\geq 50\%$, and $\geq 25\%$ but $< 50\%$, respectively. The conformity index (CI) was defined by the ratio of the prescription isodose volume to the prostate volume. Gradient index was defined as the ratio of the 50% isodose volume to the prescription isodose volume.

Dose constraints to OARs (**Table 1**) were based on the ABS guidelines for prostate HDR-B and a previous randomized trial [12, 30]. Organ constraints of the rectum, urethra, and bladder were $V75$ (volume receiving 75% of prescription dose) $< 1 \text{ cm}^3$, $V125 < 1 \text{ cm}^3$, and $V75 < 1 \text{ cm}^3$, respectively. The secondary bladder constraints were $V75 < 5 \text{ cm}^3$ and $V80 < 2 \text{ cm}^3$. Plans were accepted if secondary bladder constraints were met. The dose to the bladder neck was also reported for comparison purposes. For all plans, OAR constraints were prioritized over target coverage. Plan objectives were iteratively modified in order to maximize dose heterogeneity while still meeting the upper limit of OAR constraints.

Treatment Planning Techniques

Both SBXT and SBPT plans were generated by RayStation (RaySearch Laboratories, Stockholm, Sweden) treatment planning system. Plans were created by 2 physicists specialized in their assigned planning technique and blinded to the plan qualities of the alternative modality.

For SBXT, a 6X flattening filter-free beam was used on a Varian TrueBeam Edge LINAC (Varian Medical Systems, Palo Alto, CA). This machine is equipped with 2.5-mm-wide high-definition multileaf collimators, allowing it to deliver highly conformal dose distributions. Volumetric modulated arc therapy plans were generated by using 2 full arcs, with 20 and 340 collimator rotation and 2-mm dose-grid spacing [35]. A planning PTV was constructed by cropping the bladder plus 1 mm and rectum volumes from the PTV. Dose objectives for coverage were assigned to the planning PTV and it was required that 95% of the PTV receive 95% of the prescribed dose. Sharp dose drop-offs were achieved by including normal tissue dose drop-off objectives as well as maximum dose requirements specified for 2 ring annuli extending 1 to 3 mm and 3 to 10 mm from the PTV. To improve urethra sparing, a urethra plus 2-mm control structure was created with a maximum dose objective of 125%.

For SBPT, IMPT was used with a nominal spot size (σ in air) of 4 mm with available beam energy range of 70 to 245 MeV selected by the treatment planning software. Four beams were used to generate a more robust plan for stereotactic radiation delivery. The optimal beam arrangement was determined to be opposed lateral and 2 anterior oblique beams, which have been shown to be more robust to modeled RBE elevations when a spaceOAR is in place [36]. While patients in this study were treated before spaceOAR was routinely used at our institution, it is expected that spaceOAR would be used if this technique is in use clinically. Multiple field optimization was used to spare the prostatic urethra. The prostate CTV was robustly optimized by applying a beam-specific PTV [37] using a setup uncertainty of 2 mm in the X, Y, and Z direction and a 2.5% Hounsfield unit (HU) to stopping power ratio calibration uncertainty. A setup margin of 2 mm was selected to account for the reduced setup uncertainty of stereotactic radiation delivery resulting from daily cone-beam CTs aligned to fiducial markers and more consistent bladder and rectal filling (ie, utilization of Foley catheters and rectal balloons when necessary). In addition, while the current accepted standard is 3.5% HU calibration uncertainty [38], newer methods to calculate stopping power,

Table 2. Dosimetric comparison of select planning parameters for SBPT and SBXT.

	SBPT, median (range)	SBXT, median (range)	Median difference (SBPT–SBXT)	P value	Spearman ρ	P value
Target coverage and heterogeneity (%)						
D90 (Gy)	22 (19.1-22.7)	21.3 (19.7-22.1)	0.6	<.01	0.21	.31
V100	96 (90-99)	99 (95-100)	–3.0	<.01	–0.15	.94
V125	82 (76-84)	73 (54-80)	9.0	<.01	0.43	.03
V150	49 (44-50)	49 (14-57)	–2.0	.92	0.01	.97
V200	12 (1-20)	2 (0-11)	9.0	<.01	0.66	<.01
CI	1.8 (1.3-3.5)	1.3 (1.0-1.6)	0.7	<.01	–0.85	<.01
GI	2.4 (2.0-5.7)	4.2 (3.3-5.3)	–1.8	<.01	–0.46	.02
Bladder (cm ³)						
V75	0.7 (0-1.3)	4 (1.5-7)	–3.3	<.01	–0.73	<.01
V80	0.2 (0-0.7)	2.4 (0.8-6.3)	–2.2	<.01	–0.64	<.01
Bladder neck (Gy)						
D2cc	9.6 (4.9-17.3)	14 (6.0-20.9)	–4.6	<.01	0.43	.03

Abbreviations: SBPT, XXX; SBRT, XXX; SBXT, XXX; Vx, volume of target receiving x% of dose; CI, conformity index; GI, gradient index; D2cc, dose to 2 cm³.

including the use of dual-energy CT scans, have significantly reduced this uncertainty estimate [39]. Therefore, for the purpose of this feasibility study, we selected 2.5% HU calibration uncertainty to reflect the projected improvements in stopping power calculations. The robust optimization resulted in 12 different CTV coverage scenarios in which the worst-case scenario was required to have a minimum of 95% of the CTV receiving 95% of the prescribed dose, per our institutional protocol.

Statistical Plan

Dosimetric and CTV coverage parameters were compared between SBPT and SBXT by using the signed rank test. The same comparisons were performed for prostate size ≤ 50 cm³ and >50 cm³. For each target coverage parameter, the results were compared for prostate size ≤ 50 cm³ and >50 cm³ by using the Wilcoxon rank test. Spearman ρ was performed to measure the strength of association between prostate size and select dosimetric parameters. A P value threshold of $\leq .05$ was considered statistically significant.

Results

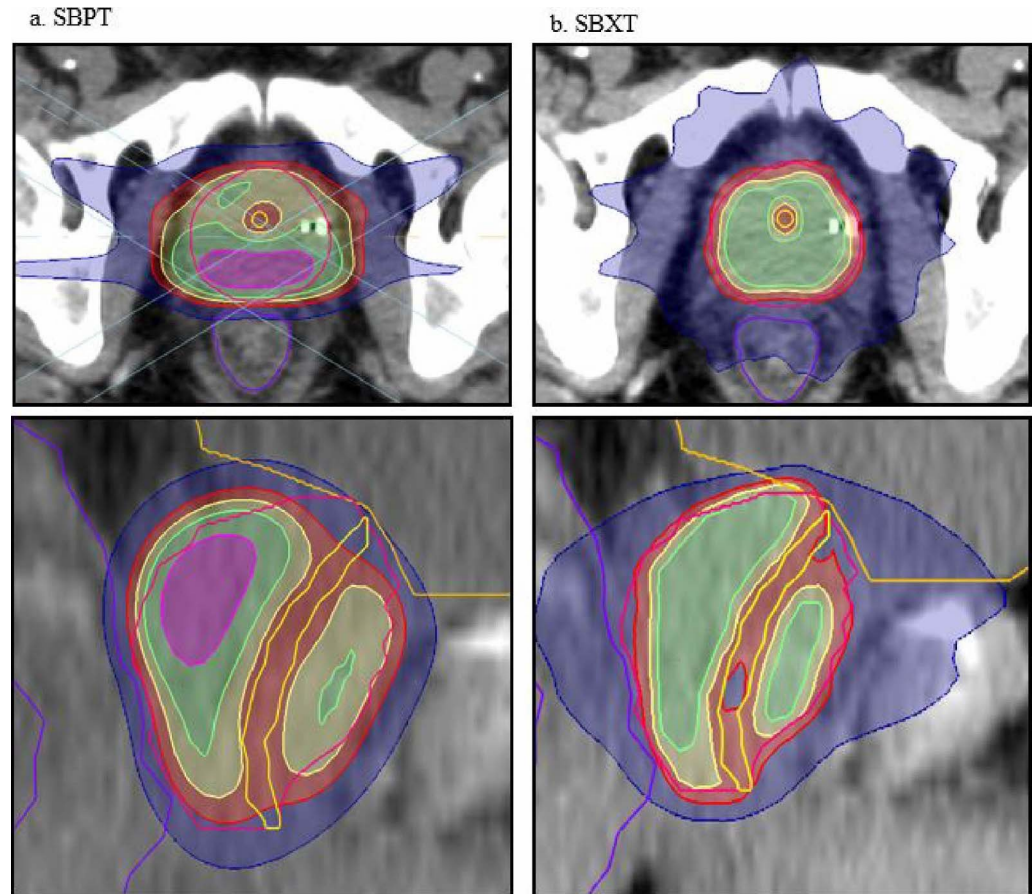
Dose to Organs at Risk

The median prostate size overall was 49 cm³. The median prostate size in the subgroup ≤ 50 cm³ (n = 13) and >50 cm³ (n = 12) was 35 cm³ (range, 15-49 cm³) and 98 cm³ (range, 52-134 cm³), respectively. All SBXT and SBPT plans met the dose constraints for the rectum and urethra, and secondary dose constraints for the bladder. A comparison of bladder and bladder neck dose between SBPT and SBXT plans is shown in **Table 2**. All SBPT plans met the primary bladder dose constraint of V75% <1 cm³ except for 4 cases in which V75 ranged from 1.1 to 1.3 cm³. In contrast, none of the SBXT plans met the primary bladder constraint with a median V75 of 4 cm³ (range, 1.5-7 cm³). The bladder V75 and V80 were significantly higher for SBXT than for SBPT with a median difference of 3.3 cm³ (P < .01) and 2.2 cm³ (P < .01), respectively. The median D2cc to the bladder neck for SBPT and SBXT was 9.6 Gy (4.9-17.3 Gy) and 14 Gy (6-20.9 Gy), respectively, with a median difference of 4.6 Gy (P < .01).

Target Coverage and Dose Heterogeneity

Representative SBPT and SBXT plans from a single patient are shown in **Figure 1**. A comparison of target coverage and dose heterogeneity parameters between SBPT and SBXT are shown in **Table 2**. All plans met the requirement of 90% of the volume receiving 100% or more of the prescription dose (V100 $\geq 90\%$) and all but 4 plans (all proton) met the target coverage goal of V100 $\geq 95\%$. The median V100 for SBPT and SBXT was 96% (90%-99%) and 99% (95%-100%), respectively, with a median difference of 3% favoring SBXT (P < .01). The median prostate D90 (dose to 90% of the prostate gland) for SBPT and SBXT was 22 Gy (19.1-22.7 Gy) and 21.3 Gy (19.7-22.1), with a median difference of 0.6 favoring SBPT (P < .01). The median

Figure 1. Comparison of dose distribution between SBPT (a) versus SBXT (b) in a patient with a prostate volume of 52 cm³ and prescribed 19 Gy in 2 fractions. Isodose lines: 200% (pink), 150% (green), 125% (yellow), 100% (red), and 50% (blue). Abbreviations: SBPT, stereotactic body proton therapy; SBXT, stereotactic body photon therapy.



V125 (82% versus 73%) and V200 (12% versus 2%) were significantly greater for SBPT than for SBXT with a median difference of 9% ($P < .01$) and 9% ($P < .01$), respectively. Both SBPT and SBXT plans met the upper limit goal for V150 of 49%.

Conformity index was 1.8 (1.3-2.5) and 1.3 (1.0-1.6) for SBPT and SBXT, respectively, with a median difference of 0.7 favoring SBXT ($P < .01$), whereas gradient index was 2.4 (2.0-5.7) and 4.2 (3.3-5.3) with a median difference of 1.8 favoring SBPT ($P < .01$).

Correlation with Prostate Size

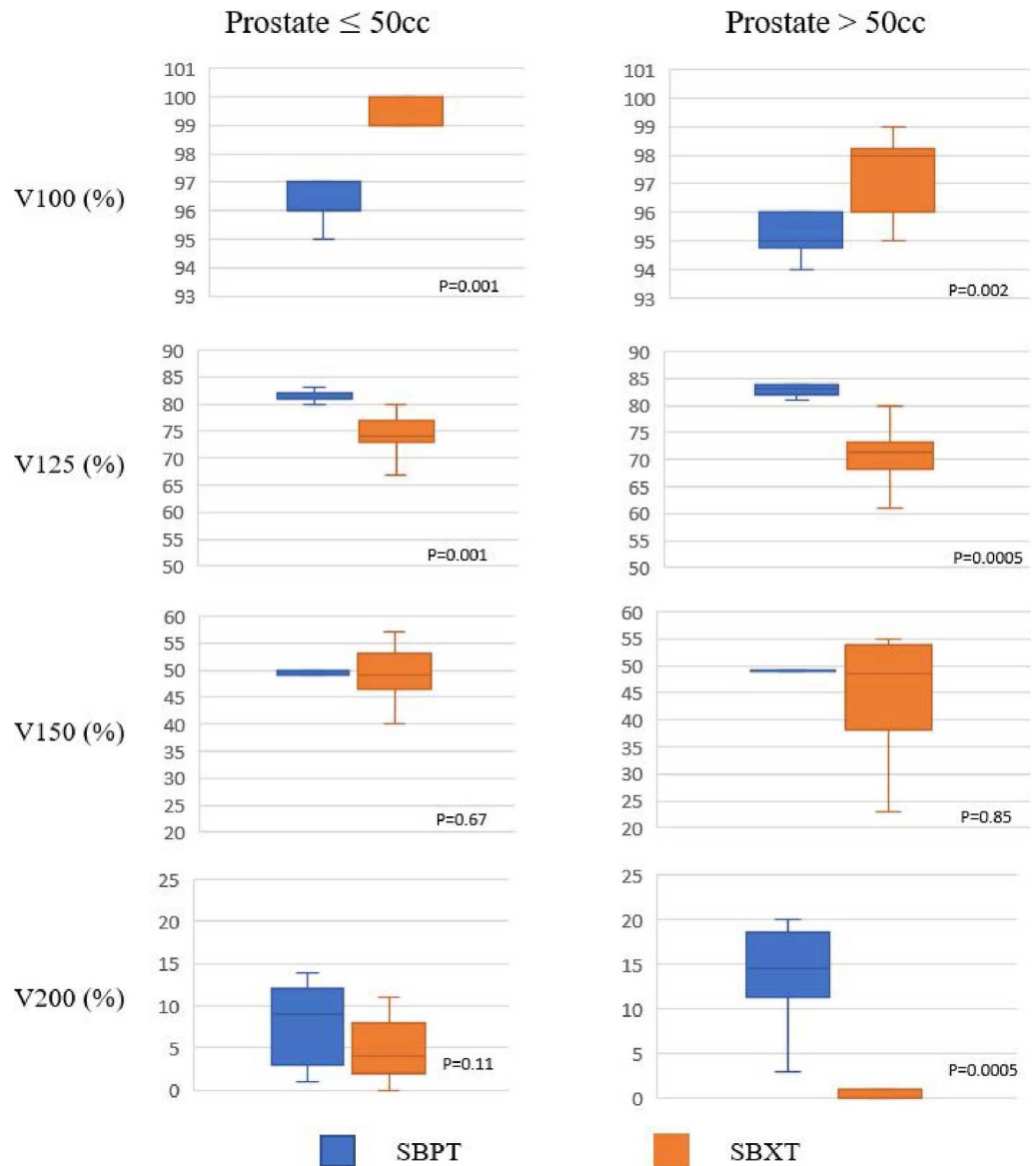
As shown in **Table 2**, a direct correlation was observed with prostate size and V125, V200, and D2cc of the bladder neck as demonstrated by a Spearman ρ correlation coefficient of 0.43 ($P = .03$), 0.66 ($P < .01$), and 0.43 ($P = .03$), respectively. An indirect correlation with prostate size was observed for CI and gradient index as demonstrated by a Spearman ρ correlation coefficient of -0.85 ($P < .01$) and -0.46 ($P = .02$), respectively.

The median D90 for prostates ≤ 50 cm³ and > 50 cm³ was 22 Gy versus 21.6 Gy ($P = .04$) and 21.9 Gy versus 20.6 Gy ($P = .006$) for SBPT and SBXT, respectively. Target coverage parameters stratified by prostate size (≤ 50 cm³ and > 50 cm³) are shown in **Figure 2**. For prostate size ≤ 50 cm³, the median V100, V125, V150, and V200 for SBPT versus SBXT were 96% versus 99% ($P = .001$), 81% versus 74% ($P = .001$), 49% versus 49% ($P = .67$), and 9% versus 4% ($P = .11$), respectively. For prostate size > 50 cm³, the median V100, V125, V150, and V200 for SBPT versus SBXT were 95% versus 98% ($P = .002$), 83% versus 71% ($P = .0005$), 49% versus 49% ($P = .85$), and 14% versus 1% ($P = .0005$), respectively.

Discussion

In this study, we evaluated and compared the dose escalation potential of SBPT and SBXT to simulate an HDR-B boost. In comparison to SBXT, our findings demonstrate that SBPT resulted in significantly greater dose escalation as reflected by the volume of prostate gland receiving 125% and 200% of the prescription dose while maintaining acceptable low dose to OARs.

Figure 2. Target coverage parameters (V100, V125, V150, V200) between SBPT and SBXT stratified by prostate size ≤ 50 cm³ (n = 13) and prostate size >50 cm³ (n = 12). Abbreviations: SBPT, stereotactic body proton therapy; SBXT, stereotactic body photon therapy.



The difference in V200 was only significantly greater with SBPT when the prostate gland was >50 cm³. Both SBPT and SBXT plans achieved the upper limit goal of V150 $<50\%$. Despite the greater dose heterogeneity observed with SBPT, there was significantly lower dose to the bladder than with SBXT plans. Although SBPT was associated with a slightly higher CI than SBXT (1.8 versus 1.3), this occurred in the soft tissue region lateral to the prostate gland and thus was not considered to be clinically relevant.

Many institutions have reported on their experience using SBXT as a boost for intermediate- to high-risk prostate cancer, summarized in **Table 3** [15–24]. These studies vary widely in terms of boost dose, CTV definition, PTV margins, presence of a prostatic urethra avoidance structure, and use of a rectal balloon. Normal tissue constraints are also inconsistent. Despite their differences, these studies demonstrate excellent short-term biochemical control and acceptably low severe toxicity (G3-4) that are comparable to an HDR-B boost [40]. Of note most of these studies used a Cyberknife platform and only 2 institutions purposefully escalated the dose within the prostate to mimic HDR-B boost dosimetry [15, 16, 20]. Researchers at UCSF (San Francisco, CA) used a boost dose regimen of 9.5 Gy or 10.5 Gy \times 2 after conventionally fractionated EBRT [15]. HDR-B dose heterogeneity was simulated by using Cyberknife, as based on a previously published dosimetric technique [32]. They reported a prevalence of acute grade 2 GU and GI toxicity of 37% and 10%, respectively, and late GU toxicity grade 2 and grade 3 of 25% and 2%, respectively. There were no late GI toxicities higher than a grade 1 [15]. After a median follow-up of 3.5 years, they reported a 3-year biochemical control rate of 95%. Similarly, a group from Australia [20] recently reported a

dose escalation study using LINAC-based SBRT to simulate an HDR-B boost in men with high- or intermediate-risk prostate cancer. They included 36 patients treated with SBRT (10 Gy \times 2 in 9 patients, 11 Gy \times 2 in 6 patients, and 12 Gy \times 2 in 21 patients) followed by conventionally fractionated EBRT. Dose escalation was performed by using a simultaneous integrated boost technique to areas of gross disease defined by a prostate-specific membrane antigen positron emission tomography scan. After a median follow-up of 3 years, they reported a biochemical control rate of 96% and no acute or late grade 3 GU or GI toxicities [20]. While both of these clinical experiences compare favorably to randomized trials evaluating EBRT combined with a PB boost, the progression-free survival benefit associated with a PB boost is generally not evident until 3 to 4 years after treatment [5, 8]. Therefore, longer follow-up is required to determine the efficacy of an SBRT boost in comparison to PB.

The use of a stereotactic boost using IMPT is less common. A study from Sweden [26] reported outcomes of 278 patients treated with a proton boost of 20 Gy in 5 fractions after conventional EBRT, although it is not reported whether passive scatter or IMPT was used. The plans had a homogenous dose distribution corresponding to a biologic effective dose (BED) in terms of EQD2 of 94 Gy and 87 Gy, using α/β ratio of 3 and 1.5, respectively. At 8 years, the prostate specific antigen relapse rate was 50% among patients with high-risk disease, which is notably inferior to historic controls [40]. In contrast, studies that have performed intentional dose escalation with photon SBRT were able to achieve a BED of 278 to 336 ($\alpha/\beta = 3$) and 158 to 189 ($\alpha/\beta = 1.5$) [15]. It is possible that the lower BED may have contributed to the inferior outcomes observed in this study.

While delivery of a stereotactic boost to the prostate appears to be clinically feasible and safe, dosimetric data evaluating which stereotactic modality would be more suitable to simulate an HDR-B boost are lacking. This is the first dosimetric study of its kind to compare the dose escalation potential of SBXT and SBPT and may serve as a reference point for future prospective trial design. Target dose heterogeneity goals were designed to reflect prostate HDR dosimetry reported in the literature, as shown in **Table 4**. Both SBPT and SBXT treatment plans analyzed in this study were comparable to HDR-B dosimetry [32–34]. A study performed at UCLA (Los Angeles, CA) [33] looked at 208 patients treated with HDR brachytherapy, reporting a mean V150 and V200 of 25.4% and 7.8%, respectively, while maintaining the mean dose to 1 cm³ of urethra, bladder, and rectum to 101%, 70%, and 70% of the prescription dose, respectively. Similarly, a group from Moffitt Cancer Center (Tampa, FL) [34] assessed HDR brachytherapy dosimetry in larger prostate glands (>50 cm³) and reported a mean V150 and V200 of 27% and 11%, respectively, with acceptable doses to OARs. In contrast, we were able to achieve an even higher V125 (82% versus 73%) and V200 (12% versus 2%) while maintaining the rectum (V75 < 1 cm³) and urethra (V125 < 1 cm³) constraints for both SBPT and SBXT plans, respectively.

A similar dosimetry comparison study between proton (IMPT) and photon SBRT performed at Montefiore Medical Center (Bronx, NY) demonstrated comparable doses to OARs; however, proton SBRT resulted in a higher maximum dose to the bladder and rectum after robust optimization [41]. Unlike the current study, the dose heterogeneity of the target was not reported nor was it intentionally planned to simulate HDR-B. A radiosurgery group from California [32] reported a median V125% and V150% of 67.5% and 37.8%, using SBRT planning techniques to simulate HDR-B, which is less than what we report here for both SBPT (82% and 49%) and SBRT (73% and 49%), respectively.

A unique aspect of our study is the evaluation of dose heterogeneity based on prostate size (≤ 50 cm³ and > 50 cm³). While both V125 and V200 were correlated with size, they were significantly higher with SBPT than with SBXT, regardless of size cohort. Prostate gland size (commonly defined as > 60 cm³) remains a relative contraindication to brachytherapy according to the ABS. While several studies have called this recommendation into question [34, 42–45], achieving an adequate dose distribution for larger prostate glands remains a challenge, particularly for less experienced brachytherapists. Furthermore, patients with larger prostate glands are more likely to be symptomatic often making them unsuitable candidates for PB. As a result, investigation into alternative modalities to deliver dose-escalated radiation while not compromising biochemical control and disease outcomes is important. For prostate glands > 50 cm³, a group from Moffitt Cancer Center [34] was able to achieve a median V150 and V200 of 27% and 11% respectively. Here, we demonstrated SBPT more closely simulated HDR-B in patients with larger prostates (> 50 cm³) with a median V125 and V200 of 83% and 14%, respectively, compared to 71% and 1% with SBXT, respectively. Both SBPT and SBXT met the upper limit goal of V150 < 50% at 49%.

Late severe GU toxicity remains an issue among patients treated with combination EBRT and PB, with the frequency of grade 3 urinary toxicity reported in the range of approximately 14% to 31% [8, 9, 46]. Dose to the bladder neck has been associated with urinary toxicity in patients treated with PB either alone or in combination with EBRT [27]. More specifically, 2 cm³ of the bladder neck receiving greater than 50% of the prescribed dose (D2cc > 50%) was found to significantly correlate with both early and late urinary toxicity. This is consistent with the primary role of the bladder trigone in contracting the bladder neck to allow for bladder filling [47]. We outlined the bladder neck as based on contouring guidelines previously described [27].

Table 3. Literature review of SBXT as prostate boost in intermediate- and high-risk prostate cancer.

	N	Median FU, mo	Boost modality	Simulated		Treatment technique	Normal tissue constraints for boost	Biochemical control	Toxicity ^a
				HDR dosimetry	Dose				
Katz et al (2010) [18]	73	33	CK	No	Dose escalation trial 6 Gy × 3 (n = 28) 6.5 Gy × 3 (n = 28) 7 Gy × 3 (n = 17)	<ul style="list-style-type: none"> MRI fusion 4 fiducials with motion tracking GTV = prostate PTV = 5 mm, except 3 mm posteriorly pUrethra not contoured Bowel prep before each tx 	NS	3 y – 89.5% (IR), 78% (HR)	(RTOG scale) <i>Acute:</i> GU: 7% (G2) GI: 7% (G2) <i>Late:</i> GU: 4.1% (G2), 1.4% (G3) GI: 8.2% (G2)
Oermann et al (2010) [17]	24	9.3	CK	No	6.5 Gy × 3	<ul style="list-style-type: none"> MRI fusion 4 fiducials CTV = prostate + pSV PTV = 5 mm, except 3 mm posteriorly pUrethra not contoured Bladder empty Low gas and motility diet NPO night before, enema 1-2 h prior 	<i>Rectum:</i> V19.5Gy < 1 cm ³ <i>Bladder:</i> V19.5Gy < 10 cm ³ <i>Penile bulb:</i> V15Gy < 50% <i>pUrethra:</i> Dmax < 133% <i>mUrethra:</i> V18Gy < 50% <i>Sigmoid:</i> V15Gy < 1 cm ³	NS	<i>Acute:</i> GU: 17% (G2) GI: 4% (G2) <i>Late:</i> GU: 8% (G2) GI: none ≥G2 (QoL PROs also reported)
Miralbell et al (2010) [19]	50	63	IMRT	No	Dose escalation trial 2 × 5 Gy (n = 5) 2 × 6 Gy (n = 8) 2 × 7 Gy (n = 8) 2 × 8 Gy (n = 29)	<ul style="list-style-type: none"> External skin markers Rectal balloon CTV = customized for each patient pUrethra contoured (urinary catheter at sim) 	NS	5 y – 98%	(RTOG scale) <i>Acute:</i> GU: 46% (G2) GI: 8% (G2) <i>Late:</i> GU: 12% (G2) GI: 10% (G2), 10% (G3)
Jabbari et al (2012) [16]	38	18.3	CK	Yes	9.5 Gy × 2 (boost; n = 18) 9.5 Gy × 4 (mono tx; n = 20)	<ul style="list-style-type: none"> MRI fusion 3 fiducials with motion tracking CTV = prostate + SV (portion of) No PTV margin (n = 15) PTV = 2 mm, except 0 mm posteriorly pUrethra contoured 	<i>Rectal wall:</i> Dmax ≤ 100% <i>Rectal mucosa:</i> Dmax ≤ 75% <i>Urethra:</i> Dmax ≤ 120% <i>Bladder:</i> Dmax ≤ 120%	NS	<i>Acute:</i> GU: 42% (G2) GI: 11% (G2) <i>Late:</i> GU: 8% (G2), 5% (G3) GI: 3% (G2)
Anwar et al (2016) [15]	48	42.7	CK	Yes	9.5 or 10.5 Gy × 2	Same as Jabbari et al [16]	Same as Jabbari et al [16]	3 y – 95% 4 y – 90% 5 y – 90%	<i>Acute:</i> GU: 37% (G2) GI: 10% (G2) <i>Late:</i> GU: 25% (G2), 2% (G3) GI: none ≥G2
Mercado et al (2016) [21], Paydar et al (2017) [22]	108	51	CK	No	6.5 Gy × 3	<ul style="list-style-type: none"> MRI fusion 4 fiducials CTV = prostate + pSV PTV = 5 mm, except 3 mm posteriorly pUrethra not contoured Bladder empty Bowel regimen NPO night before 	<i>Rectum:</i> V19.5Gy < 1 cm ³ <i>Bladder:</i> V19.5Gy < 5 cm ³ <i>Penile bulb:</i> V15Gy < 50% <i>pUrethra:</i> Dmax < 133% <i>mUrethra:</i> V18Gy < 50% <i>Sigmoid:</i> V15Gy < 1 cm ³	3 y – 100% (IR), 89.8% (HR)	<i>Acute:</i> GU: 18% (G2), 1% (G3) GI: 7% (G2) <i>Late:</i> GU: 34% (G2), 6% (G3) GI: 12% (≥G2) (QoL PROs also reported)

Table 3. Continued.

	N	Median FU, mo	Boost modality	Simulated HDR dosimetry	Dose	Treatment technique	Normal tissue constraints for boost	Biochemical control	Toxicity ^a
Eade et al (2019) [20]	36	24	SBXT	Yes	Dose escalation trial 2 × 10 Gy (n = 9) 2 × 11 Gy (n = 6) 2 × 12 Gy (n = 21)	<ul style="list-style-type: none"> MRI and PMSA PET fusion Calypso beacons/fiducial markers or triggered imaging with TrueBeam software Hydrogel offered but not mandated CTV = prostate + pSV PTV = 5 mm, except 3 mm posteriorly pUrethra contoured (indwelling urinary catheter at sim) 	NS	3 y – 93%	<i>Acute:</i> GU: 19% (G2) Note: 2 patients required temporary catheterization <i>Late:</i> GU: 19% (G2) GI: none ≥G2
Alayed et al (2019) [23]	30	72	SBXT	No	Dose escalation trial 1 × 10 Gy (n = 10) 1 × 12.5 Gy (n = 10) 1 × 15 Gy (n = 10) *Used hypofractionated (2.5 Gy/fx) to the pelvic LNs)	<ul style="list-style-type: none"> MRI fusion 3 fiducials CTV = prostate PTV = 3 mm Intrarectal balloon and Foley catheter with full bladder 	NS	NS	<i>Acute:</i> GU: 30% (G2) GI: none ≥G2 <i>Late:</i> GU: 43% (G2), 3% (G3) GI: 26% (G2), 3% (G4) (QoL PROs also reported)
Pasquier et al (2020) [24]	76	62	CK (79%), SBXT (21%)	No	3 × 6 Gy	<ul style="list-style-type: none"> MRI fusion Fiducials with motion tracking (CK) CTV = prostate PTV = 5 mm Bowel regimen Full bladder 	NS	5 y – 87%	<i>Acute:</i> GU: 23% (≥G2) GI: 13% (≥G2) <i>Late:</i> GU: 1% (≥G2) GI: 9% (≥G2)

Abbreviations: SBXT, stereotactic body photon therapy; FU, follow-up; HDR, high-dose rate; CK, Cyberknife; MRI, magnetic resonance imaging; GTV, gross tumor volume; PTV, planning tumor volume; pUrethra, prostatic urethra; tx, treatment; NS, not specified; IR, intermediate risk; HR, high risk; RTOG, Radiation Therapy Oncology Group; GU, genitourinary; GI, gastrointestinal; CTV, clinical tumor volume; pSV, proximal seminal vesicle; NPO, nothing by mouth; mUrethra, membranous urethra; QoL, quality of life; PROs, patient-reported outcomes; IMRT, intensity-modulated radiation therapy; SV, seminal vesicle; PMSA, prostate-specific membrane antigen; PET, positron emission tomography; LNs, lymph nodes; CTCAE, Common Terminology Criteria for Adverse Events.

^aCTCAE unless otherwise specified.

Table 4. Literature review of HDR brachytherapy dose heterogeneity.

	V100	V125	V150	V200
HDR-B				
White et al [33] ^a	99.5 (93.7-100)	NS	25.4 (15.5-42.2)	7.8 (4.7-13.2)
Yang et al [34] ^a	94 (87-98)	NS	27 (20-36)	11 (7-22)
SBXT				
Eade et al [20]	95%	30%	<5%	NS
Fuller et al [32] ^b	96 (93.4-99.1)	67.5 (53.3-75.5)	37.9 (25.4-45.6)	NS
Current study				
SBPT ^b	96 (90-99)	82 (76-84)	49 (44-50)	11 (1-15)
SBXT ^b	99 (95-100)	73 (54-80)	49 (14-57)	2 (0-11)

Abbreviations: HDR-B, high-dose rate prostate brachytherapy; NS, not specified; SBPT, stereotactic body proton therapy; SBXT, stereotactic body photon therapy.

^aValues represent mean.

^bValues represent median.

To remain within the scope of our current practice, no specific constraint was applied to the bladder neck; however, we found that 12 SBPT plans (48%) had a D2cc <50%, whereas only 1 SBXT plan satisfied this parameter ($P = .03$). This is a hypothesis-generating finding and warrants further exploration in a more rigorous setting in which this structure is included in planning optimization.

There are several limitations to this study. In PB, the radioactive sources are directly inserted into the prostate gland, resulting in a heterogeneous distribution of hot spots surrounding dwell positions. In contrast, the dose escalation in SBPT and SBXT is achieved through spot weighting and multileaf collimator modulation, respectively, resulting in a more uniform dose distribution. Whether the dose distribution of stereotactic radiation would have the same radiobiological effect as the heterogeneous dose escalation of PB is unknown. A major limitation in comparing the dose escalation potential between these 2 modalities is the variation in how target coverage is evaluated. For proton therapy, our institutional practice is to evaluate CTV robustness by setup and HU calibration uncertainty [37], whereas for photon therapy the PTV and CTV coverage are evaluated separately. For the purpose of this dosimetric feasibility study, we evaluated dose heterogeneity of the CTV (prostate) only while also ensuring there was adequate coverage of the PTV (SBXT) and robustly optimized CTV (SBPT). One could argue that the dose heterogeneity of the PTV should be evaluated to account for setup uncertainty; however, this would have resulted in a larger target volume than with SBPT and thus limited the interpretation of the results. The PTV margin (2 mm except 0 mm posteriorly) was modeled off a technique previously reported by Jabbari et al [16], despite the fact that no intrafraction motion “tracking” was anticipated for either modality in this comparison. Other studies that did not use intrafraction motion tracking used a PTV margin of 3 to 5 mm [17, 21–23]. For the purpose of maximizing the dose escalation potential of each modality and minimizing dose to normal tissue, we chose to use a smaller PTV margin. In a clinical setting, careful consideration of the image-guidance capabilities of a treatment machine is necessary when determining the PTV margin. Regarding the setup variation estimate used in CTV-robust optimization for proton therapy, we used 2 mm as opposed to the standard 3 mm; the coincidence between radiation and imaging isocenter for both machines is within 1 mm and spot placement accuracy is expected to be less than 1.4 mm. Taking that into account, we chose to use 2 mm for setup uncertainty under the assumption that with SBRT delivery, setup uncertainties are reduced through the use of fiducial markers, daily cone-beam CT, and more consistent bladder and rectal filling via Foley catheter and rectal balloon, respectively. The precision and accuracy required with treatment delivery is another limitation of this treatment strategy. Daily variations in bladder/bowel filling can alter the position of the prostate gland. Immobilization strategies including the use of an endorectal balloon and intraurethral Foley catheters have demonstrated success when treating with SBRT [48, 49]. Rectal spacer gel has also resulted in decreased rectal dose and toxicity [13], allowing for safer delivery of hypofractionated radiation. Proton therapy may be more susceptible to interfractional variation owing to the greater impact of tissue density and depth on dose deposition, particularly in the longitudinal direction [50]. Interestingly, however, a prospective study comparing the effects of interfractional variation between protons versus photons for conventionally fractionated prostate radiation found no difference in target coverage or dose to OARs when using fiducial markers with daily image guidance [51].

Here, we have shown the dose heterogeneity of SBPT and SBXT dosimetry is similar to HDR-B boost for prostate cancer. For certain parameters, SBPT demonstrated a significantly greater dose escalation potential than SBXT, with this difference becoming more magnified with increasing prostate size. Despite this, dose to the bladder was less with SBPT than with SBXT, although the absolute difference was small. Our findings suggest that SBPT should be favored in future prospective trials seeking to optimize results of prostate radiation therapy in patients ineligible for brachytherapy.

ADDITIONAL INFORMATION AND DECLARATIONS

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

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