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### Authors

Banerjee, Robyn  
Park, Sang-June  
Anderson, Erik  
[et al.](#)

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# From whole gland to hemigland to ultra-focal high-dose-rate prostate brachytherapy: A dosimetric analysis

Robyn Banerjee<sup>1</sup>, Sang-June Park<sup>2</sup>, Erik Anderson<sup>2</sup>, D. Jeffrey Demanes<sup>2</sup>, Jason Wang<sup>2</sup>, Mitchell Kamrava<sup>2,\*</sup>

<sup>1</sup>Department of Oncology, University of Calgary, Calgary, Alberta T2N 4N2, Canada

<sup>2</sup>Department of Radiation Oncology, University of California Los Angeles (UCLA), Los Angeles, CA 90095, USA

## ABSTRACT

**PURPOSE:** To assess the magnitude of dosimetric reductions of a focal and ultra-focal high-dose-rate (HDR) prostate brachytherapy treatment strategy relative to standard whole gland (WG) treatment.

**METHODS AND MATERIALS:** HDR brachytherapy plans for five patients treated with WG HDR monotherapy were optimized to assess different treatment strategies. Plans were generated to treat the hemigland (HG), one-third gland (1/3G), and one-sixth gland (1/6G), as well as to assess treating the WG with a boost to one of those sub-volumes (WG + HG, WG + 1/3G, WG + 1/6G). Dosimetric parameters analyzed included Target D90%, V100%, V150%, Bladder (B), Rectal (R), Urethral (U) D0.1, 1 and 2cc, Urethral V75%, and the V50% to the contralateral HG. Two-tailed *t* tests were used for comparison of means, and *p*-values less than 0.05 were considered statistically significant.

**RESULTS:** Target objectives (D90 > 100% and V100 > 97%) were met in all cases. Significant organs at risk dose reductions were achieved for all approaches compared with WG plans. 1/6G vs WG plans resulted in the greatest reduction in dose with a mean bladder D2cc 24.7 vs 64.8%, rectal D2cc 32.8 vs 65.3%, urethral D1cc 52.1 vs 103.8%, and V75 14.5 vs 75% (*p* < 0.05 for all comparisons).

**CONCLUSION:** Significant dose reductions to organs at risk can be achieved using HDR focal brachytherapy. The magnitude of the reductions achievable with treating progressively smaller sub-volumes suggests the potential to reduce morbidity, but the clinical impact on morbidity and tumor control remain to be investigated. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

## Keywords:

Prostate cancer; HDR brachytherapy; Radiation therapy; Focal therapy

## Introduction

Focal therapy is an emerging treatment strategy for prostate cancer with two rationales being put forward to justify its development. The first is focal therapy serves as a compromise between active surveillance and whole gland (WG) therapy (1, 2). This rationale can be criticized for “overtreating” men who otherwise should be encouraged to pursue active surveillance. However, in the United States,

few men are comfortable with active surveillance and so focal approaches may actually be a reasonable compromise (3). The second rationale is that WG is not really the target for prostate cancer but rather it is the index lesion. The index lesion hypothesis suggests that the most dominant lesion in the prostate is responsible for dictating the natural history of the disease and that small insignificant satellite lesions can be followed with “active surveillance” (4).

The majority of focal therapy research at this time is exploring the efficacy and safety of various non-radiation treatment modalities including cryotherapy, high-intensity focused ultrasound, laser ablation, and photodynamic therapy (5, 6). Much less work is published on focal therapy using radiation. A consensus paper on focal low-dose-rate seed brachytherapy was published in 2012 and proposed three definitions for focal treatment: 1) An *ultra-focal*

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\* Corresponding author. UCLA Department of Radiation Oncology, 200 Medical Plaza Suite B265, Los Angeles, CA 90065. Tel.: +1 (310) 825-9775; fax: +1 (310) 794-9795.

E-mail address: mkamrava@mednet.ucla.edu (M. Kamrava).

approach treats an MRI-defined lesion plus a margin; 2) a *hemigland* approach treats half of the gland; 3) a *focused* approach treats the index lesion to full dose but the rest of the gland to a lower one (7).

There are no consensus papers on focal high-dose-rate (HDR) brachytherapy and yet the versatility of being able to vary dwell positions during HDR planning make it ideal to treat various prostate sub-volumes. Our group has recently published a dosimetric comparison of WG vs hemigland HDR brachytherapy showing about a 10–25% reduction in the D2cc dose to the bladder, rectum, and urethra using a hemigland approach (5). We did not compare the dosimetric reductions that could be achieved using ultra-focal or focused approaches.

One study to date has examined HDR dosimetry using an ultra-focal approach (8). Mason et al. used a virtual catheter distribution to cover an MRI-defined target volume plus a 6 mm margin, prescribing a single 19 Gy fraction. Our study differs in terms of the catheter distribution, volume delineation, and prescription but aims to provide confirmatory evidence that focal strategies can reliably achieve target objectives with significant organs at risk (OAR) dose reductions.

This study compares treating various prostate sub-volumes with conventional WG HDR prostate monotherapy to determine the impact on target coverage and the magnitude of dose reduction to OAR achievable (Fig. 1).

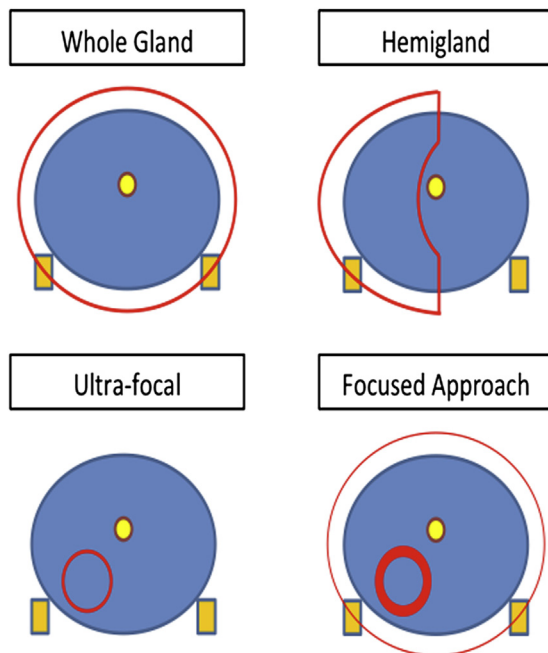


Fig. 1. Schematic representation of the treatment approaches modeled in this study. Whole gland and hemigland treatments have been previously well described. Ultra-focal therapy involves treating only a target lesion or sub-volume of the prostate (in this study 1/6 or 1/3 of the gland). A focused approach treats the whole gland to a selected dose with a boost to a sub-volume. In this study, the focused approach modeled 7.25 Gy  $\times$  4 fractions to the whole gland and 7.25 Gy  $\times$  6 fractions to the focal volume.

## Methods

CT-based HDR brachytherapy plans for five patients treated with WG HDR Ir-192 monotherapy were used to generate simulated hemigland (HG), one-third gland (1/3G), and one-sixth gland (1/6G) plans (Figs. 2 and 3). HG was defined by dividing the WG prostate contour at the urethra. The 1/6G plans were created by subdividing the right and left HG into thirds along the axial plane to generate the right and left base, mid-gland, and apex volumes. To account for lesions that might span beyond one-sixth of the prostate, volumes were constructed combining the base with mid-gland and mid-gland with apex to form the 1/3G volumes. Another set of plans was optimized to simulate a focused treatment approach delivering 7.25 Gy  $\times$  4 fractions to the WG and 7.25  $\times$  6 fractions to the boost target (WG + HG, WG + 1/3G, WG + 1/6G).

Individual plans were optimized with inverse planning simulated annealing using Oncentra Brachy Treatment Planning System, Version 4.3 (Nucletron, an Elekta company, Veenendaal, The Netherlands). Our default inverse planning simulated annealing optimization solution was used and manual graphical optimization was used to fine-tune the final plans (5). Patients were treated with 7.25 Gy  $\times$  6 fractions using a standard WG catheter distribution. The identical catheter distribution used for WG treatment was used for all plans. Dose constraints for target coverage and OARs were D90 = 100–115%; V100 = 97–100%; V150 < 35%; Rectal D0.1cc < 85%; Bladder D0.1cc = 80%; and Urethral D0.1cc% < 110%, and D1cc < 105%.

Dosimetric parameters analyzed included Target D90%, V100%, V150%, Bladder (B), Rectal (R), and Urethral (U) D0.1, 1 and 2cc, Urethral (U) V75%, and the V50% to the contralateral HG (aka “spill dose”). Reported doses to the 1/3G or 1/6G represent an average of volumes from the right and left gland.

Urethral contours included the entire urethra within the prostate and three slices below (CT simulation slice thickness = 3 mm). The urethral V75% was chosen for analysis because conventional parameters based on WG treatment such as V100% or V110% do not apply to ultra-focal plans (where V100 approaches 0%).

We used various sub-volumes within the prostate rather than actual target lesions for our dosimetric analysis. This ensured generalizability of the dosimetry for a greater variety of focal targets. To confirm that the sub-volumes we selected would adequately encompass real targets, we compared sub-volumes in this study with multiparametric MRI-defined target lesions from a previous study (9).

## Statistical analysis

Statistical analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, NC). Two-tailed *t* tests were used for

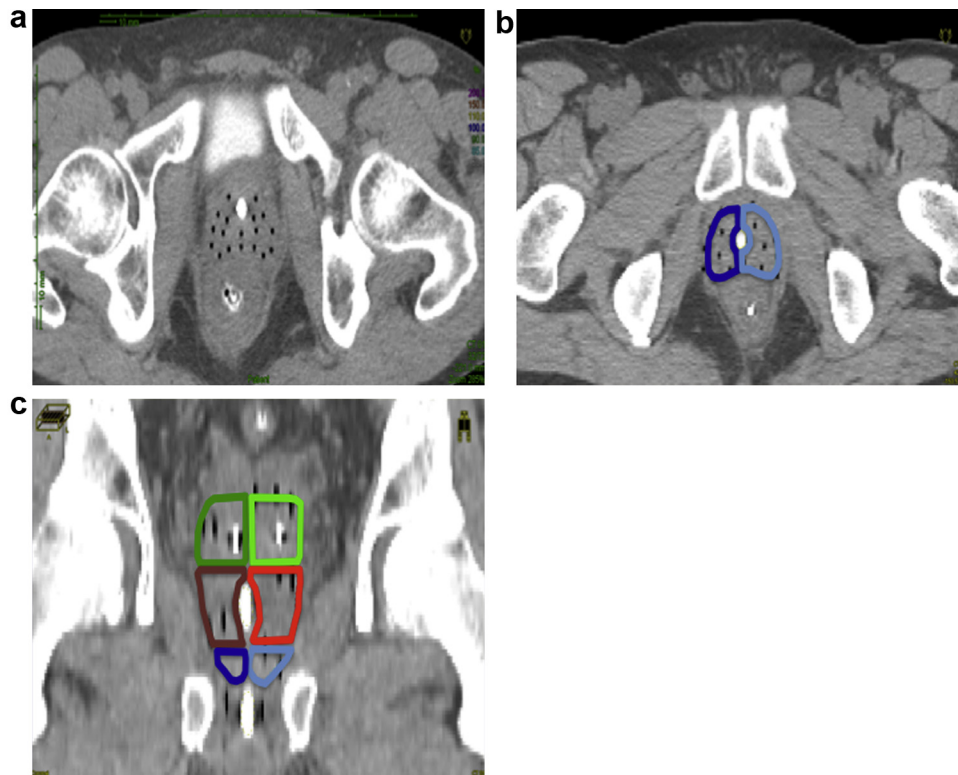


Fig. 2. (a) Axial CT slice demonstrating a standard HDR brachytherapy implant with 18 catheters were placed within the prostate and at the gland margin. (b) Hemigland volumes were defined by dividing the contoured prostate volume longitudinally at the urethra. (c) 1/6 Gland volumes were defined by subdividing the hemigland volumes into thirds along the axial plane, resulting in left and right apex, mid-gland, and base volumes.

comparison of means, and  $p$ -values less than 0.05 were considered statistically significant.

## Results

### Determination of appropriate sub-volume to treat

Table 1 demonstrates the tumor volume characteristics for a previously studied group of patients with multi-parametric MRI-defined lesions. The average diameter of target lesions in low- and intermediate-risk patients was 1.4 and 1.5 cm, corresponding to treatment volumes of 1.4 and 1.8 cm<sup>3</sup>. Recent work comparing imaging-defined lesions to pathologic specimens demonstrates that a 5 mm margin on imaging-defined lesions covers 95% of the tumor volume that is missed on the imaging-defined capsular border alone (10). Adding a 5 mm margin to the MRI-defined lesions results in mean treatment volumes of 3.5 and 4.3 cm<sup>3</sup> for low- and intermediate-risk groups. In our study, the mean 1/6G volume was 8.4 cm<sup>3</sup> (range, 3.7–19.2 cm<sup>3</sup>), suggesting that a 1/6G volume would encompass most low- and intermediate-risk targets plus a margin.

### Hemigland and ultra-focal strategies

CT-based prostate volumes ranged from 40.5 to 80.4 cm<sup>3</sup>. Target coverage dosimetry is reported in

Table 2. Compared with WG, HG and 1/6G plans had similar D90% and V100% coverage. Higher V150% volumes were seen in the 1/6G plans but remained below 50% in all cases. Among the 1/6G plans, the highest V150% was seen in the base alone plans.

Doses to OAR are displayed in Table 3. Compared with WG, HG D2.0cc doses to the bladder and rectum were

OAR Doses for WG vs. HG, 1/3G and 1/6G

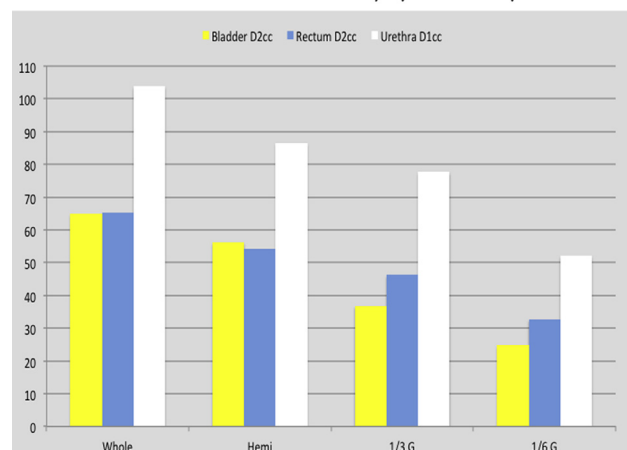


Fig. 3. Organ at risk (OAR) doses (as % of prescription dose) as a function of different treatment volumes.

Table 1  
Estimated tumor volume characteristics for patients

Risk group (n)	TD (mean ± SD) (cm)	Estimated mean volume (cm <sup>3</sup> )	Range (cm <sup>3</sup> )	Range (including 5 mm margin) (cm <sup>3</sup> )
Stratified by risk group				
Low (n = 14)	1.38 ± 0.64	1.37	0.21–4.30	1.00–8.37
Intermediate (n = 20)	1.52 ± 0.70	1.82	0.29–5.66	1.20–10.53
High (n = 12)	1.83 ± 0.67	3.18	0.81–8.14	2.39–14.13
Stratified by intraprostatic location				
Base (n = 7)	1.56 ± 0.71	1.98	0.32–6.08	1.29–11.12
Mid-gland (n = 27)	1.51 ± 0.60	1.79	0.40–4.87	1.47–9.30
Apex (n = 21)	1.63 ± 0.76	2.26	0.34–7.17	1.34–12.63

TD = maximum tumor diameter; SD = standard deviation.

Estimated mean volume =  $(4/3) \cdot \pi \cdot (TD/2)^3$ ; volume range =  $(4/3) \cdot \pi \cdot [(TD-SD)/2]^3 - (4/3) \cdot \pi \cdot [(TD + SD)/2]^3$ ; volume range (including 5 mm margin) =  $(4/3) \cdot \pi \cdot [(TD-SD+0.5)/2]^3 - (4/3) \cdot \pi \cdot [(TD + SD + 0.5)/2]^3$ . Adapted from Anderson et al. 2014.

significantly lower (bladder 65% vs 56%,  $p = 0.02$ , rectum 65% vs 54%,  $p < 0.01$ ). Treating 1/6G volumes resulted in substantially lower doses to OAR when compared with WG plans. The bladder D2cc was an average of 43% lower for the 1/3G plans and 62% lower for the 1/6G plans. Treatment of the unilateral apex alone resulted in a bladder D2cc of 6%.

The rectal D2cc was reduced by 29% for the 1/3G plans and 50% for the 1/6G plans. Treatments of the base alone resulted in the greatest rectal sparing, with an average D2cc of 25% ( $p < 0.01$  for all values compared with either WG or HG).

The urethral D1cc was reduced from 104% for WG to 87% for the HG plans ( $p < 0.01$ ) and further reduced to 51%, 60%, and 45% for the apex, mid, and base volumes, respectively ( $p \leq 0.01$  compared with WG or HG). Urethral V75 was 78% for WG compared with 57% for HG ( $p = 0.02$ ), and 36% and 14.5% for 1/3G and 1/6G ( $p < 0.001$ ).

We previously outlined the concept of “spill” dose expressed as the V50% of the contralateral HG (5). The spill dose provides insight into the feasibility of salvage therapy in the event of recurrent disease in the contralateral gland. 1/6G treatments resulted in contralateral V50% of 12% compared with 47% for the HG plans ( $p < 0.001$ ).

Table 2  
Target dose coverage (%)

Target	D90%	V100%	V150%
WG	109.3	98.7	23.5
HG	112.7	97.8	32.9
1/3 G	112.6	97.4	34.2
1/6 G	114.7	97.3	44.9
Whole + 1/3 G	112.5	98.6	34.1
Whole + 1/6 G	111.1	98.7	28.3

WG = whole gland; HG = hemigland; 1/3 G = one-third gland sub-volume; 1/6 G = one-sixth gland sub-volume; whole + 1/3 G = focused boost treating whole gland to 7.25 Gy × 4 and 1/3 G to 7.25 Gy × 6; whole + 1/6 G = focused boost treating whole gland to 7.25 Gy × 4 and 1/6 G to 7.25 Gy × 6.

### Focused “boost” strategy

The focused strategy models 7.25 Gy × 4 to the WG plus an additional 7.25 × 2 to the target. As with the HG 1/6G strategies, target D90 and V100 were not significantly different (Table 2).

Bladder D2cc was reduced by 11.2% and 14.8% for the WG + 1/3G and WG + 1/6G plans ( $p \leq 0.001$ ) (Table 3). Rectal D2cc was 12% and 20% lower for the WG + 1/3G and WG + 1/6G plans ( $p < 0.001$ ). Urethral doses were lower compared with WG, with urethral D1cc reduced by an average of 9% and 19% in the WG + 1/3G and WG + 1/6G plans ( $p \leq 0.001$ ) (Fig. 4).

### Discussion

In this study, we investigated the dosimetric outcomes of various focal treatment strategies for prostate cancer using HDR brachytherapy. Our objective was to quantify the magnitude of dose reduction to OAR when treating the WG vs various progressively smaller focal volumes. While it stands to reason that treating smaller volumes will reduce dose to OARs, if the magnitude of these reductions is minimal, then a clinical benefit is unlikely to be observed. Such an analysis is therefore needed to learn how to strike a balance between providing equal tumor control with a reasonable expectation that the sub-volume treated will reduce acute and long-term morbidity.

It is important to acknowledge that current outcomes with WG HDR monotherapy are excellent and modifying the current approach stands to compromise these results. Oncologic outcomes for HDR monotherapy for low- and intermediate-risk patients demonstrate PSA control rates in the >90% range (11). The most common short-term morbidity is urethritis, which is temporary in the majority of men with only about 10% having some type of persistent severe urinary change (11). Late-term rectal toxicity is in the range of a few percent. The most common long-term toxicity is erectile dysfunction (ED) and its incidence varies among studies and ranges between 20 and 50% (12, 13).

Table 3  
OAR doses (%)

	Bladder			Rectum			Urethra				Contra hemi	
	D0.1cc	D1.0cc	D2.0cc	D0.1cc	D1.0cc	D2.0cc	D0.1cc	D1.0cc	D2.0cc	V75	V50	
WG	82.3	70.6	64.8	77.6	70.1	65.3	107.9	103.8	88.7	78.0		
HG	81.8	64.2	56.2	74.5	60.7	54.2	101.5	86.5	67.5	57.1	47.3	
1/3 G	54.5	41.9	36.9	66.5	52.9	46.3	98.1	77.6	44.0	36.0	29.4	
1/6 G	37.3	28.4	24.7	54.6	39.5	32.8	88.5	52.1	19.4	14.5	12.2	
Apex	7.5	6.4	5.9	68.0	46.8	38.0	89.0	50.7	21.2	12.6	7.8	
Mid	30.8	23.6	20.8	56.3	41.8	35.2	97.0	60.2	25.4	20.4	14.9	
Base	73.6	55.1	47.5	39.6	30.0	25.1	79.4	45.3	11.7	10.5	14.1	
WG + 1/3 G	69.7	58.7	53.7	72.1	62.6	57.6	103.3	94.2	73.5	67.0		
WG + 1/6 G	64.8	54.8	50.0	66.3	56.9	52.4	98.7	84.1	66.3	51.8		

WG = whole gland; HG = hemigland; Contra hemi = contralateral hemigland.

Focal HDR treatments can be expected to improve on short-term urethritis and late-term sexual dysfunction.

Ultimately, this analysis aimed to quantify in dosimetric terms what might be gained by treating volumes less than a hemigland to help estimate what may be gained clinically by pursuing such an approach.

#### Urinary toxicity

The most common acute side effect of HDR prostate brachytherapy is worsening urinary symptoms (14, 15). Most studies suggest that these side effects are associated with urethritis as opposed to prostatitis or cystitis (11). Consistent reproducible dose–volume parameters associated with urinary toxicity for HDR prostate brachytherapy have not been established. Morton et al. showed a correlation between the maximal dose to 10% of the urethra (D10) and decreasing urinary health-related quality of life using the Expanded Prostate Cancer Index Composite at 1 year post-single fraction HDR boost followed by external beam to 37.5 Gy in 15 fractions (14). A clinically

significant detriment in Expanded Prostate Cancer Index Composite urinary scores was observed for patients with a mean urethral D10 of 121% compared with 119%. Akimoto et al. observed higher acute urinary toxicity (Radiation Therapy Oncology Group [RTOG] grading) associated with urethral D10 and D20 in patients treated with hypofractionated EBRT and two 9 Gy HDR brachytherapy fractions (15). Urethral V120 has been associated with increased late-grade 3 toxicity in HDR monotherapy patients (16). Dosimetric analysis from Radiation Therapy Oncology Group 0321 also demonstrated a correlation with urethral dose and worsening Common Terminology Criteria for Adverse Events (CTCAE) v3 genitourinary toxicity (17). These studies were performed using HDR brachytherapy as a boost. In the monotherapy setting, overall high-grade acute and late urinary toxicity is generally <15%, but no data correlating toxicity with dosimetric parameters have been published. Limitations of our current understanding can also be seen in the variation in urethral constraints put forth by HDR monotherapy experts in the recent ABS guidelines (11).

Clinical data are mixed in terms of reduced treatment volumes translating into improved urinary morbidity. Initial data from partial gland brachytherapy using low-dose rate seeds showed a borderline impact on urinary toxicity when treating a mean volume of 34% in 21 patients (18). Additional data are needed to understand the relationship between dose to sub-volumes of the prostate treated and its impact on urinary morbidity. Current literature is also hampered by the majority of studies reporting physician assessed toxicities, which are known to underestimate true toxicity relative to patient-reported outcomes (19).

In our analysis, the reduction in dose to the urethra using an HG approach was relatively modest compared with the 1/3G or 1/6G targets. While existing OAR constraints are weakly validated to correlate with toxicities, the substantial reductions in urethral dose seen in the 1/3G or 1/6G targets could translate into meaningful clinical differences in outcomes.

OAR Doses: Boost Approach

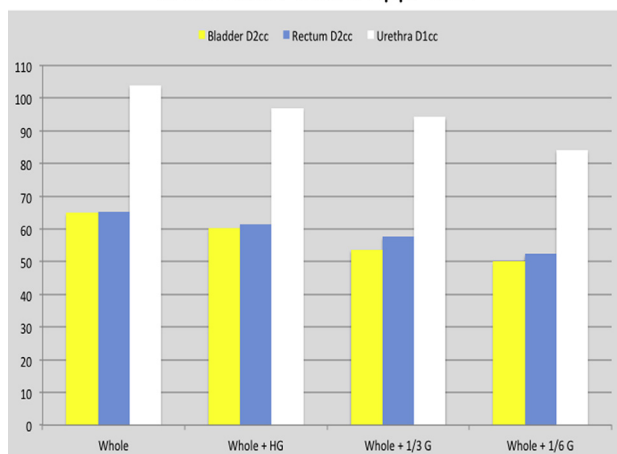


Fig. 4. Organ at risk (OAR) doses (as % of prescription dose) as a function of different treatment volumes using a boost approach.

### Rectal toxicity

Our analysis focused on the D2cc rectal volume as this has been validated in the gynecologic literature for LENT/SOMA G2-4 toxicity (20). Focal therapy may be least likely to improve rectal toxicity, given the already low reported rates associated with HDR prostate monotherapy. The largest reported series of HDR monotherapy observed a 1.6% rate of late grade 3 + rectal toxicity (21). Patient-reported outcomes demonstrate higher rates of rectal toxicity and impact on quality of life and the reductions in dose of >30% seen with 1/3 and 1/6G targets in this study may result in real improvements in patient-reported outcomes.

### Sexual toxicity

The most commonly encountered long-term adverse effect of all prostate radiation treatments is ED with reported rates of complete ED between 14 and 61% post-external beam treatment or brachytherapy (22). Although a clear etiology of ED after radiation treatment remains elusive, reasonable hypotheses center on total radiation dose to the neurovascular bundles, penile structures including the penile bulb and corpus cavernosa and their vascular supply, and yet to be implicated structures. New or worsening ED after radiation treatment occurs regardless of treatment modality and remains a concern even with prophylactic or post-treatment medical therapy (23). We found it difficult to model whether any of the less than WG approaches might improve rates of developing ED as we did not have a structure that we could contour. What is emerging from the data of focal treatments is that treating less than the whole gland does not necessarily result in reduced ED rates (24). In one study reporting changes in International Index of Erectile Function Questionnaire (IEFF) scores at 1 year after various focal approaches, all patients had reductions in their scores. The etiology of ED is complicated and is associated with multiple factors including age and various comorbidities. As this is the main toxicity after WG HDR brachytherapy, further research is especially needed to determine dosimetric factors associated with greater risk of ED. Until this information is available and can help us understand what reductions in dose to what structure may improve outcomes, thoughtful prospective assessment of ED when pursuing focal therapy approaches is necessary.

### Study limitations

Interpreting the potential impact of the dose reductions seen is challenging. Our hypothesis is that substantial dose reductions to OARs including the bladder, urethra, and rectum would ultimately decrease both acute and chronic toxicity. This hypothesis stems from multiple large scale studies that show dose escalation is significantly correlated with the development of late grade 2 or higher

genitourinary/gastrointestinal toxicities (25, 26). We are unaware of clear dosimetric correlations with acute and later morbidities after HDR monotherapy, which makes it difficult to know what dosimetric variables to assess and how to interpret the potential significance of dosimetric reductions.

Another limitation is the small sample of cases used for this dosimetric analysis. Yet the range in gland size (40–88 cm<sup>3</sup> measured by CT) represents most prostate brachytherapy patients. Individual variations in gland size and anatomy are inevitable, but these results are considered generalizable in terms of providing a reference for the dose reductions achievable with ultra-focal treatments.

This analysis did not assess dose structures potentially associated with ED including the neurovascular bundles and other vasculature. Future analysis should incorporate additional imaging modalities that can assess these structures and correlate dose to clinical outcomes. It will be interesting to correlate these data to clinical outcomes for patients that receive focal and ultra-focal treatment strategies going forward, as we assess the absolute impact of OAR dose reduction on long-term toxicity.

### Conclusions

This study demonstrates the magnitude of reduction in radiation dose to normal tissue achievable using HDR brachytherapy to treat progressively smaller volumes for prostate cancer. The significant dose reductions achieved by treating 1/6G (reduction in key dose metrics >50% compared with WG) may correlate to meaningful decreases in toxicity. Prospective clinical studies are needed to test if this strategy can result in reduced morbidity while still being able to maintain excellent disease control.

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