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## Authors

Mesko, S
Park, SJ
Kishan, AU
et al.

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# A sector-based dosimetric analysis of dose heterogeneity in high-dose-rate prostate brachytherapy

Shane Mesko[1], Sang-June Park[2], Amar U. Kishan[2], D. Jeffrey Demanes[2], Mitchell Kamrava[2,*]

[1]*UC Irvine School of Medicine, Irvine, CA*

[2]*UCLA Department of Radiation Oncology, UCLA Health System, Los Angeles, CA*

**ABSTRACT**

**PURPOSE:** High-dose-rate (HDR) prostate brachytherapy delivers a heterogeneous dose distribution throughout the prostate gland. There is however limited information regarding the spatial distribution of this dose heterogeneity. To this end, we analyzed the magnitude and location of intraprostatic dose heterogeneity in HDR prostate brachytherapy.

**METHODS AND MATERIALS:** Five consecutive prostate cancer patients treated with HDR were analyzed. Based on CT-simulation images, each prostate was divided into three sections (apex, base, and mid-gland). These were further subdivided into eight symmetrical sections to give a total of 24 sections. Dose–volume histograms were analyzed from V100–V200% for these 24 sections comparing the means of individual regions, left vs right, apex vs base vs mid-gland, lateral vs medial, and anterior vs posterior. A separate analysis on dose as a function of individual region volume was also performed.

**RESULTS:** Analyses comparing the 24 regions showed a maximum 62% difference (range, 21.9–83.9%) at V130% and 19.9% (1.9–20.8%) at V200%. Seven regions were significantly decreased and one significantly elevated from V130–V180% when compared with the mean. The means for lateral sections were 1.57-fold higher than medial sections from V110–V200% ($p < 0.0001$). The dose at the base was significantly higher than the rest of the gland from V120–V200 (V150, 35.6 ± 16.2% vs 20.9 ± 13.1%, $p < 0.0001$).

**CONCLUSIONS:** There is significant intra-prostatic dose heterogeneity in prostate HDR brachytherapy. This is most notable in the increased dose to base and lateral portions of the gland. Further studies are needed to determine the impact of heterogeneity on clinical outcomes. 

*Keywords:* High-dose-rate; Prostate; Brachytherapy

## Introduction

High-dose-rate (HDR) brachytherapy is an important treatment modality for all risk groups of prostate cancer. It provides the unique combination of hypofractionation with heterogeneous dose delivery. Stereotactic body radiation therapy (SBRT) is a non-invasive alternative to HDR that combines hypofractionation but with typically homogeneous dose delivery. Given the fact that SBRT is non-invasive and more accessible, it serves as a compelling alternative to brachytherapy, particularly if dose hypofractionation is the most important component of treatment. On the other hand, SBRT may be inferior to brachytherapy if heterogeneity is more important. Understanding the trends in the dose variation of brachytherapy is crucial in facilitating ongoing comparisons between the two modalities.

There are no prospective clinical comparisons of SBRT vs HDR to date. Most assessments at this time are dosimetric and in general demonstrate that HDR delivers an overall higher dose to the prostate for relatively lower doses to organs at risk compared with SBRT (1–6). Few dosimetry studies have actually tried to reproduce the exact distribution of HDR dose heterogeneity, which is at least partially related to the limited data available on HDR spatial dose distribution.

To truly understand the dosimetric differences between HDR brachytherapy and SBRT, a greater understanding

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* Corresponding author. 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90095. Tel.: +310-825-9775; fax: +310-794-9795.

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

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of HDR dose distribution is needed. We sought to quantify the location and magnitude of dose heterogeneity in HDR brachytherapy to help better understand the heterogeneous dose distribution of prostate HDR.

## Methods

This was an institutional review board-approved study of five consecutive patients treated with HDR monotherapy for prostate cancer in the Department of Radiation Oncology at the University of California Los Angeles. All five men underwent CT simulation planning and were treated with a dose of 7.25 Gy x 6 fractions. One experienced radiation oncologist performed all implants. Dose constraints for HDR monotherapy in terms of target coverage were comparable to consensus guidelines and included a CTV D90: 100–115%, CTV V100: 97–100%, CTV 150: <35%, rectal wall D0.1 cc: < 85%, bladder wall: 80% < D0.1 cc < 95%, and urethra: D0.1 cc < 110% (trans-urethral resection of the prostate [TURP] < 105%), D1 cc < 105% (7). The treatment target included the prostate and the proximal seminal vesicles. Planning was performed using inverse planning simulation annealing algorithm using Oncentra Brachy Treatment Planning System Version 4.3 (Nucletron an Elekta company, Veenendaal, Netherlands) followed by graphical optimization.

Using these planning images, each prostate was divided by equal lengths into three sections: apex, mid-gland, and base. Each of these three sections was further subdivided into eight symmetrical sections, by equal widths, to give a total of 24 sections (Fig. 1). Dose–volume histograms were then analyzed for each section from V100–V200% in delineations of 10%. For example, V100% was defined as the percentage of the given region's volume receiving 100% of the prescription dose, whereas V200% was the volume receiving double the prescription dose. Analyses were performed to determine if any prostate regions received significantly higher or lower doses by comparing the means of the 24 individual regions at each of the 10 cutoffs from V100–V200%. Similar analyses were also performed on apex vs base vs mid-gland, lateral vs medial, left vs right, and anterior vs posterior. A separate analysis on dose as a function of section volume was conducted by calculating the mean volume of all individual sections and comparing sections above vs below the mean from V100–V200%.

Single-factor analysis of variance (ANOVA) and two-sample Student's t-tests assuming unequal variances were used to evaluate the means for statistical significance, which was set at $p$-value $< 0.05$.

## Results

The mean age, trans-rectal ultrasound volume, and PSA of the five patients was 65.6 ± 3.8 years, 26.4 ± 9.0 cc, and 4.8 ± 3.1 ng/mL, respectively. Patients had either T1c or T2a disease.

The mean ± SD doses for all five patients for the V100, V150, and V200 were 98.7 ± 0.6%, 23.6 ± 4.9%, and 8.5 ± 1.4%. The mean doses for the lateral sections were significantly higher than medial ones at all dose levels from V100–V200 (Table 1). On average, the lateral regions received 1.57 times the dose compared with the medial regions from V100–V200 (Fig. 2). Analysis of base vs apex vs mid-gland showed a significant difference (ANOVA, $p < 0.001$), with the base receiving significantly higher dose than the rest of the gland from V120–V200. Fig. 3 provides a graphical illustration of the data from V100–V200% in each prostatic region. There was no significant difference in dose when comparing left vs right or anterior vs posterior from V100–V200.

The mean volume per individual section was 2.00 ± 1.04 cc. The mean volume of the base, mid-gland, and apex were significantly different at 2.57 ± 1.22 cc, 2.16 ± 0.75 cc, and 1.26 ± 0.60 cc, respectively (ANOVA, $p < 0.001$). There was no significant difference in V100–V200% for regions ≥2.00 cc vs <1.99 cc.

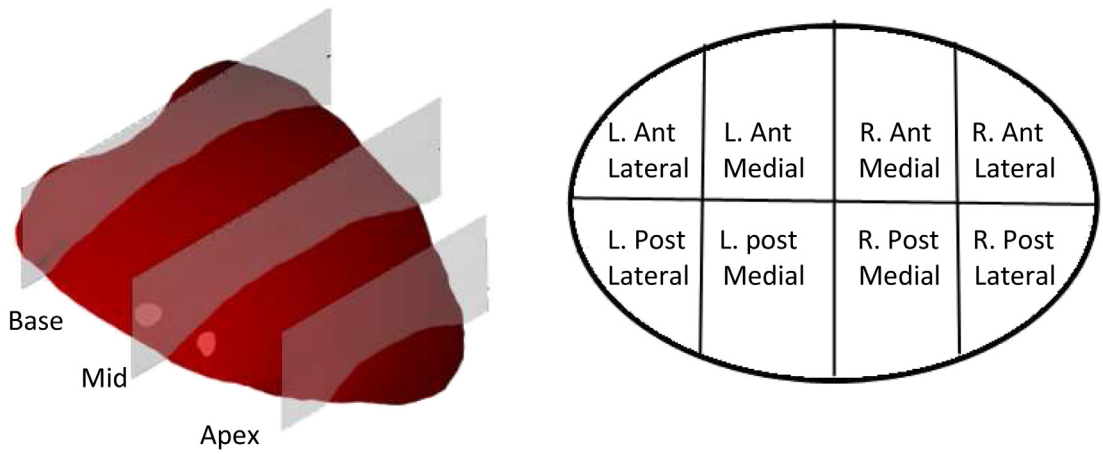


Fig. 1. Illustrates prostate division used for analyses; apex, mid-gland, and base each divided into eight 3-dimensional sections to give 24 total regions.

Table 1
Comparison of mean volume percentage from V100–V200% with *p*-values for lateral vs medial, left vs right, base vs mid vs apex, base vs all other, and anterior vs posterior

| Prostate sector | V100% | V110% | V120% | V130% | V140% | V150% | V160% | V170% | V180% | V190% | V200% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lateral | 99.8 | 95.3 | 78.7 | 58.0 | 42.9 | 32.7 | 25.8 | 20.8 | 17.1 | 14.4 | 12.4 |
| Medial | 98.9 | 84.2 | 57.0 | 38.1 | 26.3 | 19.0 | 14.7 | 11.3 | 9.1 | 7.6 | 6.5 |
| *t*-test | **0.004594** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| Left | 99.3 | 88.3 | 66.9 | 47.6 | 34.6 | 26.1 | 20.2 | 16.1 | 13.3 | 11.1 | 9.5 |
| Right | 99.4 | 91.2 | 68.8 | 48.4 | 34.6 | 25.6 | 20.2 | 15.9 | 13.0 | 10.9 | 9.3 |
| *t*-test | 0.75 | 0.20 | 0.62 | 0.83 | 0.99 | 0.89 | 0.99 | 0.90 | 0.88 | 0.87 | 0.88 |
| Base | 98.8 | 91.7 | 76.7 | 61.2 | 46.9 | 35.6 | 28.1 | 21.8 | 17.6 | 14.6 | 12.4 |
| Mid | 99.5 | 88.8 | 63.8 | 41.8 | 28.5 | 20.6 | 15.7 | 12.5 | 10.2 | 8.6 | 7.4 |
| Apex | 99.7 | 88.7 | 63.0 | 41.1 | 28.4 | 21.3 | 16.9 | 13.8 | 11.6 | 9.9 | 8.6 |
| ANOVA | 0.0510 | 0.469 | **0.004** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **0.0019** |
| Base | 98.8 | 91.7 | 76.7 | 61.2 | 46.9 | 35.6 | 28.1 | 21.8 | 17.6 | 14.6 | 12.4 |
| All other | 99.6 | 88.8 | 63.4 | 41.4 | 28.5 | 21.0 | 16.3 | 13.1 | 10.9 | 9.2 | 8.0 |
| *t*-test | 0.072008 | 0.175029 | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| Anterior | 99.1 | 89.4 | 67.4 | 47.0 | 34.0 | 25.6 | 19.9 | 16.0 | 13.2 | 11.1 | 9.6 |
| Posterior | 99.6 | 90.1 | 68.3 | 49.0 | 35.2 | 26.1 | 20.5 | 16.1 | 13.1 | 10.9 | 9.3 |
| *t*-test | 0.13 | 0.74 | 0.81 | 0.63 | 0.73 | 0.86 | 0.82 | 0.97 | 0.97 | 0.88 | 0.79 |

Significant values bolded.

The posterior right lateral base was the only section that received significantly higher dose at the V130–V180% levels when compared with the mean of each section (Section 15: V150: 53.6 ± 6.2%, $p < 0.0001$). The posterior right medial apex was the section with the lowest dose at the V130–V180% levels when compared with the mean of each section (Section 8: V150: 6.8 ± 4.6%, $p < 0.0001$). Six other regions were also significantly decreased from V130–V180% relative to other sections (Table 2).

## Discussion

Multiple studies demonstrate that HDR prostate brachytherapy enhances disease control when combined with external beam radiation therapy (8–10). Newer studies also show that HDR can be used as a monotherapy with excellent results (11–15). HDR is unique in that it provides dose escalation using a combination of hypofractionation and heterogeneous dose distribution. On one hand, hypofractionation is an important component of HDR because prostate cancer is known to have a low $\alpha/\beta$ ratio (16, 17). On the other hand, it is possible that the great clinical outcomes are related to "focal boosts" within the prostate that result from the heterogeneous dose distribution inherent with brachytherapy. It is not known which of these is most responsible for the clinical results being reported with this technique. It is important to investigate which of these factors is most important because newer external beam techniques such as SBRT are able to mimic the hypofractionation aspect of brachytherapy but have not to date been able to recapitulate the heterogeneity of HDR. In this study, we carried out a detailed analysis of the distribution of HDR dose heterogeneity to better appreciate the complexities of HDR dose distribution in prostate HDR brachytherapy.

We found that HDR plans demonstrated significant dose variation throughout the prostate. When comparing individual sections, there was nearly a four fold (minimum 21.9% vs maximum 83.9%) difference at V130% and 10 fold (minimum 1.9% vs maximum 20.8%) at V200% between sections, signifying a high degree of heterogeneity. There was also a significantly increased dose in the lateral vs medial portions of the prostate. This is expected as there are more catheters located in the peripheral prostate and the medial catheters often have less weighting to meet urethra and rectal constraints. We also found higher dose in the base compared with the mid-gland and apex. This is likely attributable to the fact that we treated the prostate plus the proximal seminal vesicles and the catheters are weighted more heavily to cover the most superior extent of the target. Our data showed no differences in left vs right or anterior vs posterior, which confirms the relative symmetry of the implant dose distribution.

In our volume analyses, a significant difference was found in the volumes of base, mid-gland, and apex regions, with the base greater than the rest of the gland. However, there was no significant difference in dose when compared with the volume of each region. This implies that although the base accounted for more of the prostate volume, this increased volume does not account for the increased doses we saw in the base vs other regions analysis. This is consistent with a prior study showing prostates with larger volumes had decreased dose percentages at V150% and V200% (18).

These results quantify the complex dose heterogeneity that exists with HDR prostate brachytherapy and the dose escalation that happens in the lateral portions of the gland, that is, the peripheral zone where most cancers develop (19–22). It is important to consider this in the context of SBRT to further the discussion of the relative effects of heterogeneity and hypofractionation. When reviewing the

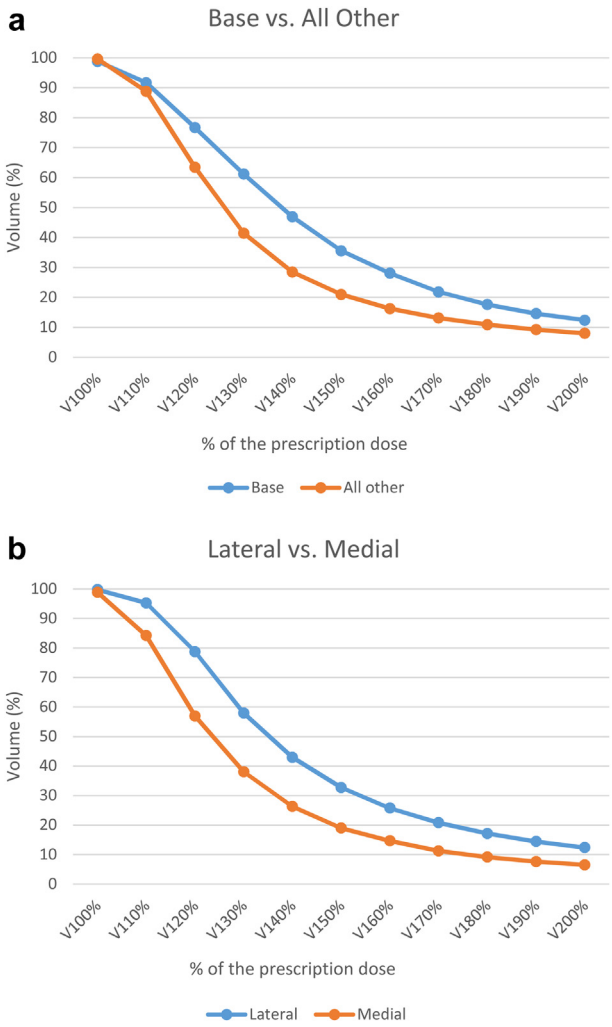


Fig. 2. (a) Graphical comparison of base vs all other regions and (b) lateral vs medial from V100–V200%. A significant difference was noted in V120–V200% when comparing the base with all other regions (apex, mid-gland) and from V100–V200% when comparing lateral vs medial portions of the gland.

literature for studies that have compared the dosimetry of HDR with SBRT, one finds that they either did not try to recreate the heterogeneity of HDR, or if they did, they tried to match the V125/V150 somewhere within the prostate without emphasizing the same distribution of an actual HDR implant (1). Other groups have tried using SBRT to the whole gland with a boost to a dominant lesion, but even small regional dose escalations have had difficulty meeting rectal constraints. Murray et al. recently assessed various methods for delivering SBRT-based dose escalation, creating 40 plans for 10 datasets (23). Such plans could be created to achieve a median dose to the dominant lesions of V125, but for five plans, the estimated rectal toxicity with conventional parameters was unacceptable. With more stringent rectal constraints, acceptable plans could be created in four of these five cases without decreasing the boost volume. Thus, it seems possible that heterogeneous

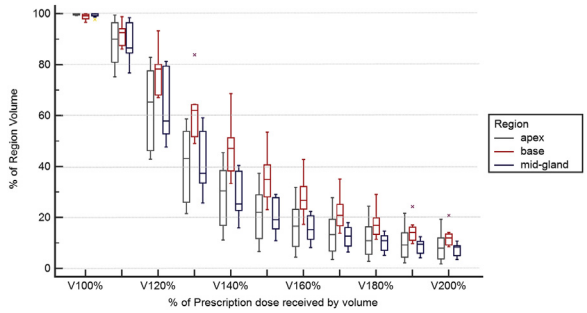


Fig. 3. Box and whisker plot of the dose median, quartiles, and range for base, mid-gland, and apex from V100–V200%. Demonstrates variation within and between each region, which the base significantly elevated from V120–V200%.

SBRT plans including simultaneous boosts to dominant lesions could be created, but great caution must be taken to limit rectal dose. This concern is underscored by the recent report of unexpectedly high grade three rectal toxicity in patients treated with 50 Gy in five fractions via SBRT (24).

Although it appears unlikely that SBRT can truly mimic the heterogeneity of HDR, it is important to consider whether this is actually a necessary prerequisite for pursuing SBRT. Although long-term studies are not yet available, SBRT demonstrates very high PSA control rates in predominantly low risk patients (25–29). Clearly, SBRT takes advantage of the principles of dose escalation and the low $\alpha/\beta$ of prostate cancer, but it is often delivered using a homogeneous dose distribution (28). Encouraging data from homogeneous delivered SBRT suggests that hypofractionation alone really is adequate with a 96% biopsy negative rate following SBRT in one series (30). Alternatively, SBRT plans can be designed to deliver heterogeneous plans. Fuller et al. conducted a study to mimic HDR brachytherapy with SBRT. They treated a cohort of patients and found similar V100% but significantly lower V150% with SBRT compared with HDR (8.5% vs 37.8%, respectively); a significant difference was seen between V125% volumes as well (1). The higher V125% and V150% in HDR was attributed to the ability to control dwell times near the urethra and reflected the proximity of the target to the radiation source in HDR. The investigators were able to virtually optimize SBRT plans to achieve similar V125% and V150% values as the HDR plans, although this increased the bladder D10. However, these plans were not delivered to patients. Jabbari et al. recently reported the results of 38 patients treated with SBRT plans, 20 of whom received SBRT alone (31). These SBRT plans were intentionally optimized to mimic the heterogeneity of HDR by prescribing to the 60–80% isodose line, leading to heterogeneity of up to 140% of the prescription dose. Clinically, both homogeneous and heterogeneous SBRT plans have good acute toxicity profiles and 3–5 year outcome data are promising; however, it is not clear which approach is ideal.

Table 2
Whole gland and individual section means for five patients from V100–V200%

| Section | | | | | V100% | V110% | V120% | V130% | V140% | V150% | V160% | V170% | V180% | V190% | V200% |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| All | Whole | Whole | Whole | Whole | 98.7 | 82.6 | 61.9 | 44.2 | 31.8 | 23.6 | 18.2 | 14.5 | 11.8 | 9.9 | 8.5 |
| 1 | Apex | ANT | LT | Lat | 99.9 | 96.3 | 71.3 | 46.4 | 33.3 | 24.7 | 19.2 | 15.8 | 13.7 | 12.1 | 10.7 |
| **2** | **Apex** | **ANT** | **LT** | **Med** | 99.3 | 75.3 | 44.6 | ***25.4*** | ***16.0*** | ***11.0*** | ***8.0*** | ***6.2*** | ***5.0*** | 4.1 | 3.4 |
| 3 | Apex | ANT | RT | Lat | 100.0 | 99.4 | 83.0 | 54.9 | 38.2 | 29.0 | 23.5 | 19.8 | 17.1 | 15.0 | 13.3 |
| **4** | **Apex** | **ANT** | **RT** | **Med** | 99.6 | 84.3 | 47.9 | ***27.1*** | ***17.7*** | ***12.8*** | ***9.8*** | ***7.6*** | ***6.1*** | 4.9 | 4.1 |
| 5 | Apex | POST | LT | Lat | 99.8 | 95.8 | 77.4 | 59.0 | 45.3 | 37.5 | 32.0 | 27.8 | 24.5 | 21.6 | 19.2 |
| 6 | Apex | POST | LT | Med | 99.9 | 82.5 | 59.3 | 40.5 | 27.5 | 19.8 | 14.5 | 10.6 | 8.1 | 6.3 | 5.1 |
| 7 | Apex | POST | RT | Lat | 100.0 | 96.9 | 77.9 | 53.2 | 38.4 | 29.3 | 23.2 | 18.9 | 15.6 | 12.9 | 10.7 |
| **8** | **Apex** | **POST** | **RT** | **Med** | 99.3 | 79.4 | 42.9 | ***21.9*** | ***11.1*** | ***6.8*** | ***4.7*** | ***3.5*** | ***2.7*** | 2.2 | 1.9 |
| 9 | BASE | ANT | LT | Lat | 99.5 | 94.8 | 79.2 | 64.1 | 51.3 | 41.2 | 33.1 | 26.3 | 21.0 | 17.1 | 14.2 |
| 10 | BASE | ANT | LT | Med | 96.6 | 86.1 | 67.2 | 52.5 | 40.6 | 30.8 | 23.6 | 18.7 | 15.3 | 12.9 | 11.1 |
| 11 | BASE | ANT | RT | Lat | 98.8 | 93.4 | 80.7 | 64.4 | 51.3 | 40.3 | 31.3 | 24.0 | 18.8 | 15.3 | 12.8 |
| 12 | BASE | ANT | RT | Med | 98.8 | 88.4 | 68.2 | 49.1 | 33.5 | 23.1 | 17.3 | 13.9 | 11.5 | 9.8 | 8.6 |
| 13 | BASE | POST | LT | Lat | 99.8 | 91.7 | 79.4 | 64.3 | 48.9 | 36.9 | 28.9 | 22.9 | 18.5 | 15.2 | 12.8 |
| 14 | BASE | POST | LT | Med | 99.4 | 93.5 | 77.4 | 60.0 | 45.2 | 33.1 | 24.5 | 18.8 | 14.7 | 11.9 | 9.9 |
| **15** | **BASE** | **POST** | **RT** | **Lat** | 100.0 | 98.9 | 93.4 | *83.9* | *68.6* | *53.6* | *42.8* | *35.1* | *29.0* | 24.3 | 20.8 |
| 16 | BASE | POST | RT | Med | 97.4 | 86.6 | 68.1 | 51.1 | 36.0 | 25.5 | 23.1 | 15.0 | 12.1 | 10.0 | 8.5 |
| 17 | MID | ANT | LT | Lat | 100.0 | 96.6 | 79.0 | 51.0 | 36.2 | 27.1 | 20.5 | 16.0 | 13.0 | 10.9 | 9.3 |
| 18 | MID | ANT | LT | Med | 97.7 | 76.7 | 52.2 | 36.4 | 26.1 | 19.5 | 15.5 | 12.9 | 10.9 | 9.5 | 8.3 |
| 19 | MID | ANT | RT | Lat | 100.0 | 96.5 | 81.4 | 59.2 | 40.1 | 29.0 | 22.4 | 18.0 | 14.7 | 12.5 | 10.8 |
| **20** | **MID** | **ANT** | **RT** | **Med** | 98.7 | 84.6 | 54.0 | ***34.1*** | ***24.2*** | ***18.7*** | ***15.0*** | ***12.5*** | ***10.8*** | 9.5 | 8.4 |
| **21** | **MID** | **POST** | **LT** | **Lat** | 99.5 | 84.6 | 62.0 | ***38.4*** | ***23.6*** | ***15.5*** | ***11.2*** | ***8.8*** | ***7.1*** | 5.9 | 5.0 |
| **22** | **MID** | **POST** | **LT** | **Med** | 99.8 | 85.9 | 53.8 | ***33.0*** | ***21.9*** | ***15.7*** | ***11.7*** | ***9.0*** | ***7.3*** | 6.1 | 5.1 |
| 23 | MID | POST | RT | Lat | 100.0 | 98.4 | 80.2 | 56.7 | 40.2 | 28.6 | 20.8 | 16.0 | 12.7 | 10.2 | 8.6 |
| **24** | **MID** | **POST** | **RT** | **Med** | 100.0 | 87.2 | 47.8 | ***25.7*** | ***15.9*** | ***11.0*** | ***8.2*** | ***6.4*** | ***5.1*** | 4.2 | 3.6 |

Region 15 in italics had significantly higher doses from V130–V180%, whereas the seven regions in bold and italics were significantly lower when compared with mean from V130–V180%. All other regions were non-significant.

When looking at the HDR monotherapy data, some insight can be gleaned regarding the importance of dose vs heterogeneity (32, 33). Rogers et al. recently reported on a series of 284 intermediate risk patients treated with 6.5 Gy x 6 fractions and reported 5 year biochemical disease-free survival of 94% (34). Higher T stage and greater than 75% biopsy cores predicted for worse biochemical outcomes with HDR monotherapy. This demonstrates that despite hypofractionation and the heterogeneity of HDR that additional dose is still needed in high volume cases (33, 35). Ultimately, data from multiparametric MRI performed before treatment where target lesions can be identified and volumes determined are needed for correlation with outcomes using homogeneous vs heterogeneous dose distributions.

There are some limitations to this analysis. The first is that HDR monotherapy is typically given in two separate implants. The distribution of dose is not identical between implants and so the exact final distribution of dose is not entirely captured by only looking at the dosimetry of one implant. Given the difficulties with summing the dose from separate implants, we chose only to focus on the dosimetry of one implant. We felt this was reasonable, given our previous analysis demonstrating no significant difference in D90, V90, V100, V150, and V200 when comparing first and second implant dosimetry values over a wide range of target volumes (18). Another limitation is that the distribution of dose described in this article is unique to the catheter distribution that we use at our institution. It is important to consider differences among operators; however, we were unable to perform this analysis as the same physician performed all implants in this series. Finally, our heterogeneity data provide an insightful, albeit limited, comparison of the theoretical differences between SBRT and HDR dose distribution. A true comparison with data directly looking at the outcomes of SBRT and HDR would augment this discussion.

## Conclusions

Our study provides a detailed analysis of the distribution of dose heterogeneity in HDR brachytherapy plans. HDR results in a 1.57 fold increase in dose in the lateral vs medial portions of the prostate allowing for dose escalation to where there is most likely to be cancer. Whether this unique dose heterogeneity is required to achieve the excellent results of HDR or whether the dose escalation afforded by hypofractionation alone is sufficient merits further investigation.

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