Title

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Journal

Brachytherapy, 12(5)

ISSN

1538-4721

Authors

Kamrava, Mitchell
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et al.

Publication Date

2013-09-01

DOI

10.1016/j.brachy.2012.09.002

Peer reviewed

ELSEVIER

Brachytherapy 12 (2013) 434–441

BRACHYTHERAPY

Focal high-dose-rate brachytherapy: A dosimetric comparison of hemigland vs. conventional whole-gland treatment

Mitchell Kamrava[1,2], Melody P. Chung[1,*], Oluwatosin Kayode[1], Jason Wang[1], Leonard Marks[3], Patrick Kupelian[1], Michael Steinberg[1,2], Sang-June Park[1], D. Jeffrey Demanes[1,2]

[1]*Department of Radiation Oncology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*
[2]*Jonsson Comprehensive Cancer Center, Los Angeles, CA*
[3]*Department of Urology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

ABSTRACT

PURPOSE: To determine the utility of focal high-dose-rate brachytherapy for localized prostate cancer, we investigated the impact on target coverage and dose to organs at risk (OARs) with hemigland (HG) compared with whole-gland (WG) treatment.

METHODS AND MATERIALS: A total of 10 WG implants were used to generate 10 WG and 20 HG (left and right) treatment plans optimized with the inverse planning simulation annealing algorithm using Oncentra MasterPlan (Nucletron B.V., Veenendaal, The Netherlands). The standard distribution of 17–18 catheters designed for WG was used to generate HG plans. The same OARs namely bladder, rectum, and urethra contours and dose constraints were applied for HG and WG plans. The HG contour was a modification of the WG contour whereby the urethra divided the prostate into HGs. The prescription dose was 7.25 Gy × 6. Evaluated dose parameters were target dose D_{90}, V_{100}, and V_{150} and $D_{0.1\ cc}$, $D_{1\ cc}$, and $D_{2\ cc}$ to OARs.

RESULTS: The HG plans had a D_{90}, V_{100}, and V_{150} to the HG target of 112%, 97.6%, and 33.8%, respectively. The WG plans had a D_{90}, V_{100}, and V_{150} to the WG target of 108%, 98.8%, and 26.5%, respectively. The OAR $D_{2\ cc}$ doses were significantly lower in HG vs. WG plans: rectum (53.1% vs. 64.1%, $p < 0.0001$), bladder (55.9% vs. 67.5%, $p < 0.0001$), and urethra (69.3% vs. 95.2%, $p < 0.0001$).

CONCLUSIONS: In the present model, HG plans yielded a statistically significant decreased radiation dose to OARs and provided complete target coverage with a catheter array designed for WG coverage. The good dosimetry results obtained in this study support the feasibility of HG brachytherapy by using a subset of the WG catheter array. Catheter distribution and dosimetry refinements tailored to subtotal prostate brachytherapy should be explored to see if further improvements in dosimetry can be achieved.

Keywords: Prostate; Focal therapy; Brachytherapy

Introduction

Prostate cancer is the most common noncutaneous cancer and the second most common cause of cancer-related death in men in the United States (1). There is no agreement on what is the single best curative treatment for prostate cancer, and it is unclear whether total prostatectomy surgery or whole gland (WG) radiation therapy improve overall survival in low-risk prostate-specific antigen (PSA)–detected prostate cancer (2, 3). It is consequently significant to know which men will benefit from treatment because treatment places them at risk for long-term complications (4).

An alternative approach is active surveillance, but many of these patients eventually undergo definitive therapy. For example, 30% of 450 men in a prospective active surveillance study went on to receive definitive therapy (5).

Received 7 May 2012; received in revised form 30 August 2012; accepted 17 September 2012.

Financial Disclosures/Conflicts of Interest: There are no financials disclosures or conflicts of interest.

* Corresponding author. Department of Radiation Oncology, University of California Los Angeles, 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90095. Tel.: +1-310-825-9775; fax: +1-310-794-1984.

E-mail address: mpchung@mednet.ucla.edu (M.P. Chung).

1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2012.09.002

Focal prostate therapy is a potential compromise between definitive treatment and active surveillance. There is no standard definition of focal therapy, but in general, it refers to a tissue preservation technique that does not treat the entire prostate gland but instead focuses the treatment to either an index lesion or some defined part of the prostate (6). The concept of focal therapy is based on the premise that, in appropriately selected men, treating only part of the prostate can be as clinically effective as treating the whole prostate with less morbidity. A variety of treatment modalities have been used to deliver focal prostate cancer therapy. The literature includes reports on high-intensity–focused ultrasound (HIFU) (7, 8), cryotherapy (9–14), laser ablation (15, 16), and photodynamic therapy (17), but there are limited reports on focal high-dose-rate (HDR) or low-dose-rate (LDR) prostate brachytherapy.

HDR brachytherapy as definitive prostate cancer treatment (i.e., HDR monotherapy) is a treatment option for favorable risk group prostate cancer (18). It reliably provides controlled doses of radiation to the target within and immediately around the implanted volume by the use of a temporary robotic insertion device. This brachytherapy format allows the physician to treat all or any part of the prostate to the desired dose because the radiation source moves in predetermined steps throughout the array of implant catheters based on three-dimensional scanned images and virtual image dosimetry calculations. This study compares the target coverage and relative doses to bladder, rectum, and urethra when catheter distributions designed for WG prostate treatment are used to generate treatment plans for half the prostate, that is, hemigland (HG) vs. WG prostate dosimetry.

Methods and materials

Treatment planning

Separate WG and HG (left and right) treatment plans were generated for 10 different HDR prostate implants

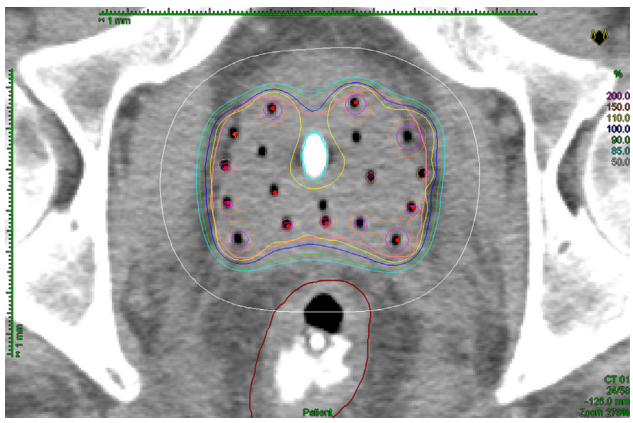

Fig. 1. Whole gland contour and isodose distributions on an axial CT scan. In the case of WG treatment plans, the contour included the entire prostate gland and proximal seminal vesicles. The target is outlined in pink, the 100% isodose line is in blue and the 50% isodose line is in white.

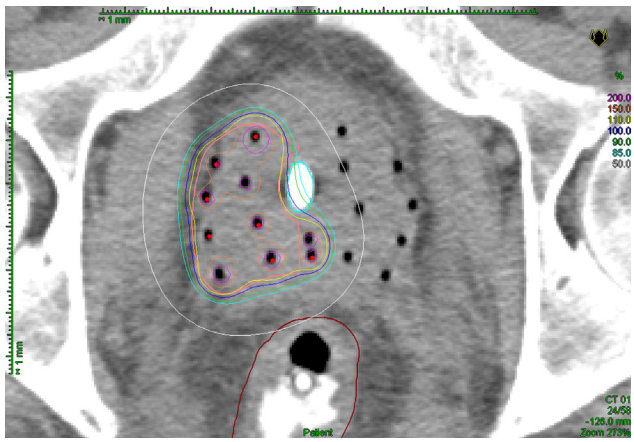

Fig. 2. Hemigland (HG) contour and isodose distributions. The same corresponding axial CT slice as in Figure 1 is presented with the HG contour. In the case of the HG, this contour was a modification of the WG contour where the urethra, as defined by the Foley catheter, served to divide the prostate gland. The HG contour was also pulled back 2 mm from the urethra contour. The target is outlined in pink, the 100% isodose line is in blue and the 50% isodose line is in white.

with the inverse planning simulation annealing (IPSA) dose optimization algorithm using the Oncentra MasterPlan (Nucletron B.V., Veenendaal, The Netherlands) treatment planning system. The distribution of catheters from the WG implants was used for the HG treatment plans. The same dose constraints for target coverage and organs at risk (OARs) were used for all plans (D_{90}, 100–115%; V_{100}, 97–100%; $V_{150} < 35\%$; rectum $D_{0.1\ cc} < 85\%$ and $D_{1.0\ cc} < 80\%$; bladder $D_{0.1\ cc} < 100\%$ and $D_{1.0\ cc} < 90\%$; and urethra $D_{0.1\ cc} < 110\%$ and $D_{1.0\ cc} < 105\%$). These dose constraints were developed through clinical experience as well as long-term followup of patients demonstrating low acute and long-term toxicity (19). The HG target was a modification of the WG target whereby the urethra was used to divide the volume into a left and right HG. The contour was also pulled back 2 mm from the urethra contour where the urethra was defined as the outer contour of the Foley catheter. The OAR contours were identical for all plans. The HG plans were not delivered to patients but were used only for dosimetric comparison. The prescription dose was 7.25 Gy × 6 fractions. The IPSA parameters to achieve the above-mentioned dosimetry constraints were maximum dose on the rectal surface 75% of the prescription with weight (50), maximum dose on the Foley

Table 1
Whole gland (WG) vs. hemigland (HG) radiation doses to organs at risk

Radiation doses	Rectum			Bladder			Urethra		
	WG	HG	*p*-value	WG	HG	*p*-value	WG	HG	*p*-value
$D_{0.1\ cc}$ (%)	76.0	71.2	0.0027	83.8	82.2	0.0925	106.5	97.7	<0.0001
$D_{1\ cc}$ (%)	68.4	59.0	<0.0001	73.4	64.0	<0.0001	103.1	82.9	<0.0001
$D_{2\ cc}$ (%)	64.1	53.1	<0.0001	67.5	55.9	<0.0001	95.2	69.3	<0.0001

$D_{xx\ cc}$ = the minimum dose in the most irradiated xx cc of the organ at risk volume reported as a percent of the prescription dose.

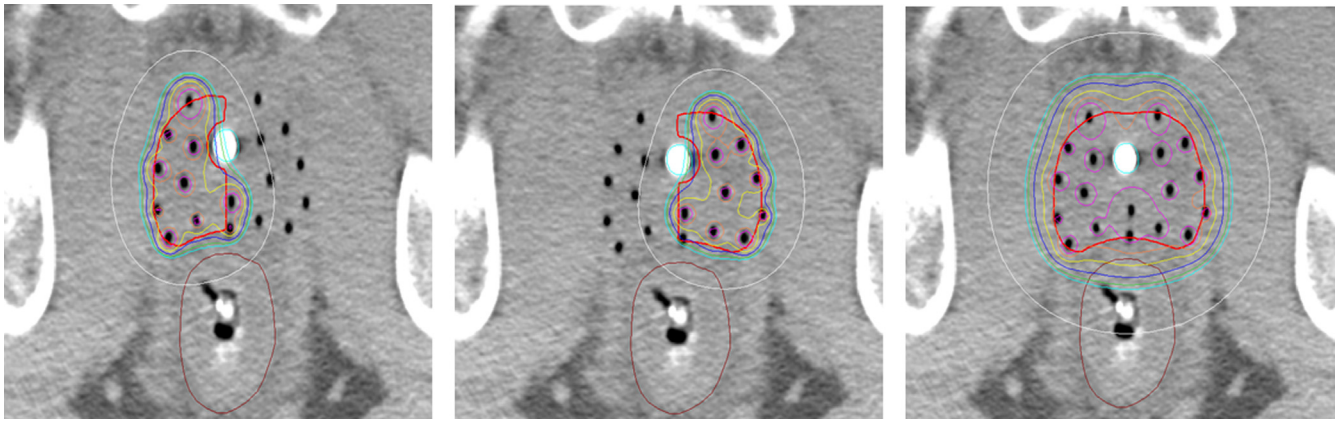

Fig. 3. Plan evaluation of combining the right and left hemigland plans. The target is outlined in red, the 100% isodose line is in blue and the 50% isodose line is in white.

balloon surface 75% of the prescription with weight (50), maximum dose on the bladder surface 85% of the prescription with weight (50), maximum dose on the urethral surface 105% of the prescription with weight (100), minimum dose of target surface 100% of the prescription with weight (200), maximum dose of the target surface 150% of the prescription with weight (30), minimum dose of the target volume 100% of the prescription with weight (200), and maximum dose in the target volume 150% of the prescription with weight (30). IPSA was used to optimize the dose distribution. Graphical optimization was then used to fine-tune the final dose distribution. A D_{90}, V_{100}, and V_{150} were calculated for both HG and WG treatments, along with the $D_{0.1\ cc}$, $D_{1\ cc}$, and $D_{2\ cc}$ to the rectum, bladder, and urethra. D_{90} is defined as the minimum dose that encompasses 90% of the contoured target (i.e., either whole prostate or half of the prostate). The V_{100} and V_{150} are defined as the percent of the target volume covered by 100% or 150% of the prescription dose, respectively. The $D_{xx\ cc}$ is defined as the minimum dose, expressed as a percent of the prescription dose, in the most irradiated tissue volume xx cc of the OARs.

Table 2
Plan evaluation of combining the right and left hemigland plans

Dosimetric variables	Right hemigland	Left hemigland	Right + left hemigland
Target (%)			
D_{90}	114.0	109.5	154.6
V_{100}	98.2	96.8	100.0
V_{150}	34.7	34.8	93.1
Bladder (%)			
$D_{0.1\ cc}$	80.0	70.8	127.6
$D_{1\ cc}$	62.7	56.7	107.7
$D_{2\ cc}$	56.2	50.9	96.8
Rectum (%)			
$D_{0.1\ cc}$	66.8	63.3	123.3
$D_{1\ cc}$	54.4	52.7	103.5
$D_{2\ cc}$	49.2	48.1	94.6
Urethra (%)			
$D_{0.1\ cc}$	96.9	90.0	169.6
$D_{1\ cc}$	80.0	75.0	157.2
$D_{2\ cc}$	63.6	61.1	127.6

To simulate whether combining the right and left hemigland plans would work as a salvage treatment option, the two plans were summed together for 1 patient, and target coverage dosimetry and doses to organs at risk were evaluated. Based on the dosimetry data, this approach would not result in an acceptable salvage option.

Statistical analysis

Any differences between the two treatments were fitted using the mixed-effect linear model to adjust for within subject correlation. We estimated the mean difference and 95% confidence intervals for selected outcome measures. The Bonferroni correction was used to adjust for bias owing to multiple comparisons. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, NC), and a significance level of p-value of 0.003 was chosen for this study to account for multiple comparisons where $p = 0.05/n$ where n is the number of selected outcomes.

Results

Compared with WG treatment, HG treatment was associated with a higher D_{90} (112% vs. 108%, $p < 0.0001$), lower V_{100} (97.6% vs. 98.8%, $p = 0.0001$), and higher V_{150} (33.8% vs. 26.5%, $p = 0.0001$). A representative axial CT slice of the radiation dose distribution and contours comparing WG vs. HG treatment are shown in Figs. 1 and 2.

A comparison of the $D_{0.1\ cc}$, $D_{1\ cc}$, and $D_{2\ cc}$ to OAR between HG and WG plans was also performed (Table 1) The $D_{2\ cc}$ doses were significantly lower in HG vs. WG plans: rectum (53.1% vs. 64.1%, $p < 0.0001$), bladder (55.9% vs. 67.5%, $p < 0.0001$), and urethra (69.3% vs. 95.2%, $p < 0.0001$). Additional dosimetric comparisons are presented in Table 1.

By not treating the entire prostate gland, some patients may be at increased risk of subsequently failing in the contralateral HG. In anticipation of this, we investigated

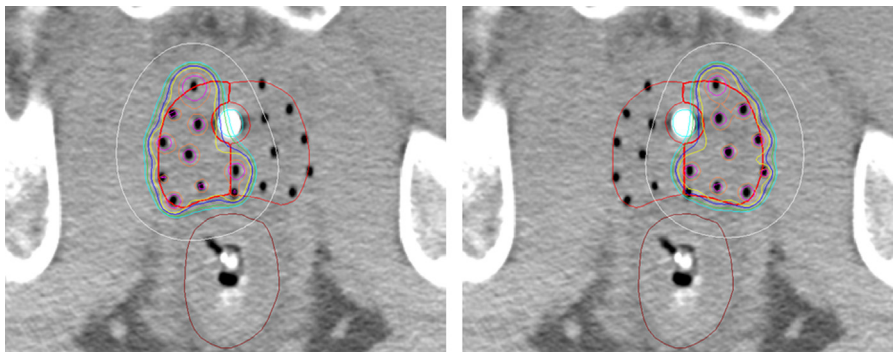

Fig. 4. Evaluation of "spill" dose from hemigland treatment to contralateral hemigland. The target is outlined in red, the 100% isodose line is in blue and the 50% isodose line is in white.

the dosimetry of possible salvage treatment options for a contralateral failure. We first assessed the results of simply combining the separate plans for each HG (i.e., right HG plan + left HG plan) for 1 patient (Fig. 3 and Table 2). As can be seen in Table 2, this did not result in acceptable dosimetry to either the target or to the OARs.

We subsequently assessed the "spill" of radiation dose to the contralateral HG in 1 patient in an effort to provide insight into a more acceptable salvage strategy. Figure 4 and Table 3 show the "spill" of radiation to the contralateral HG. These data show that the V_{50} to the right side of the prostate gland for a left HG treatment, for example, is approximately 40%. We used this information to create a contour on the right side of the prostate that matched the 50% isodose line from the original left HG treatment called right salvage target (Fig. 5). Given that the V_{50} was approximately 40%, we prescribed a dose of 450 cGy × 6 fractions to this target. The left HG plan (725 cGy × 6 fractions) was then combined with the right salvage target plan (450 cGy × 6 fractions) to create a sum plan. As can be seen in Fig. 5 and Table 4, this strategy results in acceptable dosimetry to both the target and OARs.

Table 3
Evaluation of "spill" dose from hemigland treatment to contralateral hemigland

Dosimetric variables	Dose to left side of the prostate gland for right hemigland treatment	Dose to right side of the prostate gland for left hemigland treatment
V_{100} (%)	12.5	7.1
V_{80} (%)	19.9	14.1
V_{60} (%)	33.8	27.9
V_{50} (%)	47.3	41.9
V_{20} (%)	100.0	100.0
D_{90} (%)	31.0	30.3
D_{70} (%)	38.8	37.4
D_{50} (%)	48.4	45.7
D_{30} (%)	63.9	58.2

The dosimetry of the "spill" of radiation dose from a left hemigland treatment to the contralateral right hemigland on the left and from a right hemigland treatment to the contralateral left hemigland on the right was evaluated for 1 patient.

Discussion

There is a large array of treatment modalities (i.e., HIFU, cryotherapy, radiation, laser, and photodynamic therapy) that can be used for focal therapy, but little data are available that compare these modalities or recommendations for when one modality is preferred over another. The Transatlantic Consensus Group on active surveillance and focal therapy for prostate cancer has developed guidelines for clinical practice and research for tissue-preserving strategies. This group suggests that an ablative technology must first address "whether or not it can reliably ablate cancer in the treated volume" (20). One measure of this endpoint is posttreatment positive biopsy rates. Studies using HDR brachytherapy have reported posttreatment positive prostate biopsy rates of approximately 5–10% (21, 22). Positive biopsy rates after radiation therapy, however, are not an accepted gold standard of treatment efficacy in part because of the relatively long time it takes for irradiated prostate cancer to achieve a pathophysiologic response and the risk of false positives. On the other hand, positive post-treatment biopsies are accepted as an independent predictor of outcome (23, 24). The biopsies are accepted as an independent predictor of outcome (23, 24). In any case, these low rates of positive biopsies after HDR results show that HDR reliably ablates prostate cancer and fulfills the first criterion for an ablative technology.

Once a technology demonstrates that it can ablate cancer, the Transatlantic Consensus Group states "it must be determined whether or not focal ablation can result in clinically meaningful results" (20). The longest followup to date in the literature for HDR monotherapy treating the whole prostate gland is published in abstract form by Mark *et al.* (25). The authors reported results on 321 patients with T1 and T2 localized prostate cancer with no Gleason score or PSA exclusions. No patients were treated with hormones. With a median followup of 102 months, the 8-year actuarial PSA disease-free survival rate was 94% for low-, 86% for intermediate-, and 65% for high-risk patients. The next longest followup on patients treated with HDR monotherapy to the whole prostate gland was recently published by

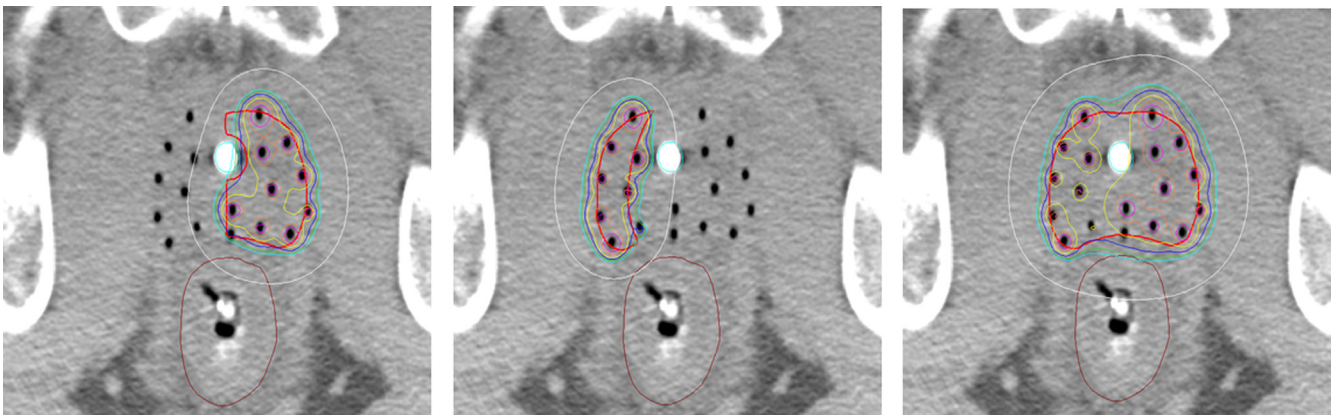

Fig. 5. Plan evaluation of combining left hemigland treatment with right salvage treatment. The target is outlined in red, the 100% isodose line is in blue and the 50% isodose line is in white.

Demanes *et al.* (19) This study shows an estimated 8-year PSA disease-free survival of 97% in a cohort of 298 patients with low- and low–intermediate-risk disease. These results demonstrate that HDR monotherapy meets the second criteria for an ablative technology as it clearly results in a high probability of long-term PSA control.

Finally, in considering a departure from standard WG therapy, it becomes important to assess what magnitude of improvement in morbidity might be achieved by treating less than the WG. With respect to HDR monotherapy toxicity, a review of the current literature demonstrates that acute (≥Grade 2) Common Terminology Criteria for Adverse Events Version 3.0 for genitourinary (GU) and gastrointestinal (GI) toxicities of 20–30% and 5–10%, respectively (26–33). Late-term Common Terminology Criteria for Adverse Events Version 3.0 assessed toxicities range from approximately 5–15% for GU side effects, 1–5% for GI side effects, and approximately 20–40% for developing erectile dysfunction (26–30, 32, 34–37). Taken together, the HDR monotherapy morbidity data suggest that focal HDR brachytherapy has the potential to reduce early and late toxicities, particularly in the GU and sexual function domains.

Table 4
Plan evaluation of combining left hemigland treatment with right salvage treatment

Dosimetric variables	Left hemigland	Right salvage	Left hemigland + right salvage
Target (%)			
D_{90}	109.5	105.7	108.3
V_{100}	96.8	96.0	97.9
V_{150}	34.8	34.5	33.7
Bladder (%)			
$D_{0.1\ cc}$	70.8	59.7	87.4
$D_{1\ cc}$	56.7	48.0	74.8
$D_{2\ cc}$	50.9	43.0	68.6
Rectum (%)			
$D_{0.1\ cc}$	63.3	47.4	83.5
$D_{1\ cc}$	52.7	37.7	71.8
$D_{2\ cc}$	48.1	33.7	66.0
Urethra (%)			
$D_{0.1\ cc}$	90.0	65.9	118.9
$D_{1\ cc}$	75.0	53.4	108.8
$D_{2\ cc}$	61.1	44.3	91.8

To simulate whether combining the left hemigland plan to a right salvage target plan (the 50% isodose line from the left hemigland treatment served as the medial edge of the right salvage target, which included the remaining right hemigland), dosages of 725 cGy × 6 fractions and 425 cGy × 6 fractions were prescribed to the left hemigland and the right salvage target, respectively. Based on the dosimetry data in the table, this approach results in an acceptable salvage treatment.

Focal brachytherapy is largely unexplored, although LDR brachytherapy has been used in an attempt to treat only the peripheral zone. Nguyen *et al.* (38) showed that the PSA failure-free survival at 5 and 8 years was 95.6% and 90.0%, respectively for low-risk patients. Not only was acceptable PSA control obtained but urinary quality of life was also improved as well (39). These results are encouraging and suggest that less than WG brachytherapy therapy can provide equivalent PSA control with potentially lower morbidity.

Our dosimetric comparison between HG and WG treatment demonstrates that HG treatment can significantly reduce the dose to OARs compared with WG treatment. It is not clear what dosimetric values best predict the risk of acute and/or late-term toxicity for the bladder, the rectum, or the risk of developing erectile dysfunction after HDR monotherapy. This was recently echoed by the American Brachytherapy Society prostate HDR guidelines, which state that "given the extreme heterogeneity in dose fractionation schedules published in the literature, it is difficult to establish absolute dose guidelines for normal tissues" (40). This limitation makes it challenging to estimate whether the dose reductions we found to OARs would be clinically meaningful. Ultimately, the significance of the reduced doses can only be answered through a clinical trial. This dosimetry study is serving as the background for a Phase II prostate focal therapy study at our institution and quality-of-life outcomes will be included.

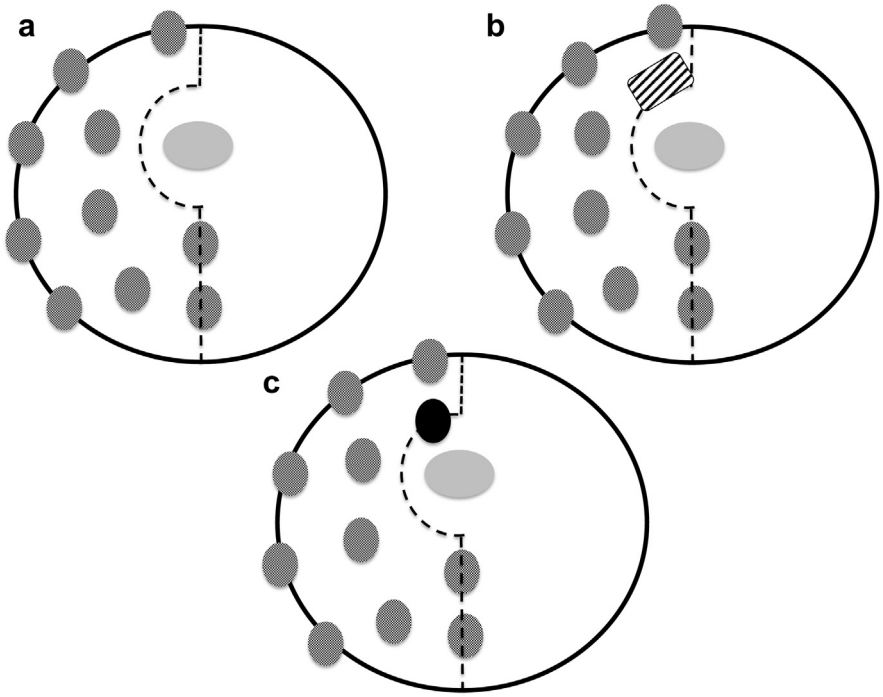

Fig. 6. Current and idealized hemigland brachytherapy catheter distribution (a) representation of the distribution of HDR brachytherapy catheters used to cover the hemigland target. This catheter arrangement uses essentially half of the catheters that are standardly used for a whole-gland implant. The gray dotted circles represent the location of the HDR brachytherapy catheters. The gray oval in the center of the prostate represents the urethra. The dotted line going through the prostate represents the medial border of the hemigland target. (b) The rectangle with the diagonal black lines represents the most common location where target coverage was noted could be improved. (c) This illustrates the location of the standard HDR brachytherapy catheter arrangement with one additional catheter (black oval) that could improve target coverage over the current standard distribution.

Despite these limitations, there are data from published studies that provide insight into the clinical impact of urethral sparing. One study used MRI-guided LDR brachytherapy to treat only the peripheral gland. The dose to any point on the urethra was lower than 200 Gy, and late urethral and/or bladder toxicity were rare (41). Monotherapy patients also had no episodes of urinary retention, hematuria, or need for postimplantation transurethral resection of the prostate.

Another study was a randomized Phase II trial using an intensity-modulated radiation therapy (IMRT) urethral sparing technique (42). Patients in the urethral sparing arm had a mean reduced dose of 36.2% and 9.6% to the proximal and distal urethra compared with standard IMRT plans. There was no improvement in health-related quality of life seen in the patients treated with the urethral sparing technique. The authors cite multiple factors including higher baseline urinary EPIC scores in their patients, confounding results based on alpha-blocker usage in the standard IMRT group, and issues related to prostate motion on urethral sparing as possible reasons why a difference in urinary outcomes was not seen.

Ultimately, we know that dose escalation results in increased acute and late-term GU toxicity. This was demonstrated in a study of more than 1500 patients treated at Memorial Sloan–Kettering Cancer Center where acute- and late-term GU symptoms were 37% and 20%, respectively in patients receiving 81 Gy with IMRT but were only 22% and 12% in patients treated to lower doses (43). The actual clinical impact on urethral toxicity of dose deescalation with focal therapy, however, is not known.

Using an HG target, we also determined that the D_{90} and V_{150} were increased in the HG vs. WG treatment plans. This finding may be related to our use of the catheter distribution for WG implants to generate the HG plans. These results suggest that there may be a better catheter distribution to cover the HG contour than simply using half of our existing WG catheter distribution. In general, we observed the most common location that had reduced coverage was around the 12-o' clock position just anterior to the urethra (Fig. 6b). We believe that the addition of another catheter in this location would improve target coverage to that of our standard WG treatment (Fig. 6c). However, an additional catheter in this location could increase the dose to the urethra and so a balance must be achieved between target coverage and minimizing dose to OARs.

Lastly, until we fully understand appropriate patient selection for focal therapy, this treatment could increase the risk of failure over WG therapy. In this dosimetry study, we show that simply adding left and right HG plans is not acceptable. This is because there is a significant

amount of ''spill'' over to the contralateral HG. Whether this ''spill'' is a good or a bad thing is not really clear. It may be good from the standpoint that the contralateral HG does receive radiation dose, and so undetected disease will get some treatment but it can also be a bad thing because it creates challenges for safe salvage options.

After evaluating the magnitude of ''spill'' from a HG treatment, we were able to come up with a salvage plan that has acceptable target and OAR coverage. A limitation of this approach is that it assumes that the recurrence is not central but rather in the periphery. This may or may not actually be the case in reality. Retreatment for a central lesion could be difficult and other salvage options such as observation, surgery, hormones, HIFU, or cryotherapy may need to be considered. Another limitation of this analysis is that we did not attempt to account for temporal or fractionation biologic effects.

Conclusions

The HG plans result in a significant decreased dose to OARs and provides complete target coverage with a catheter array designed for WG coverage. The good dosimetry results obtained in this study support the feasibility of HG brachytherapy by using subset of the WG catheter array. Catheter distribution and dosimetry refinements tailored to subtotal prostate brachytherapy should be explored to see if further improvements in dosimetry can be achieved.

References

[1] Cancer Prevention and Control: Cancer among men. 2011. Available at: www.cdc.gov/cancer/dcpc/data/men.htm. Accessed March 21, 2012.

[2] Wilt TJ, Brawer MK, Barry MJ, *et al*. The Prostate cancer Intervention Versus Observation Trial:VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): Design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. *Contemp Clin Trials* 2009;30:81–87.

[3] Bill-Axelson A, Holmberg L, Ruutu M, *et al*. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011; 364:1708–1717.

[4] Sanda MG, Dunn RL, Michalski J, *et al*. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250–1261.

[5] Klotz L, Zhang L, Lam A, *et al*. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010;28:126–131.

[6] Langley S, Ahmed HU, Al-Qaisieh B, *et al*. Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer. *BJU Int* 2012;109:7–16.

[7] Ahmed HU, Freeman A, Kirkham A, *et al*. Focal therapy for localized prostate cancer: A phase I/II trial. *J Urol* 2011;185:1246–1254.

[8] Muto S, Yoshii T, Saito K, *et al*. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. *Jpn J Clin Oncol* 2008;38:192–199.

[9] Lambert EH, Bolte K, Masson P, *et al*. Focal cryosurgery: Encouraging health outcomes for unifocal prostate cancer. *Urology* 2007; 69:1117–1120.

[10] Onik G, Vaughan D, Lotenfoe R, *et al*. The ''male lumpectomy'': Focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. *Urol Oncol* 2008;26:500–505.

[11] Ellis DS, Manny TB Jr, Rewcastle JC. Focal cryosurgery followed by penile rehabilitation as primary treatment for localized prostate cancer: Initial results. *Urology* 2007;70(Suppl. 6):9–15.

[12] Truesdale MD, Cheetham PJ, Hruby GW, *et al*. An evaluation of patient selection criteria on predicting progression-free survival after primary focal unilateral nerve-sparing cryoablation for prostate cancer: Recommendations for follow up. *Cancer J* 2010;16: 544–549.

[13] Onik G, Narayan P, Vaughan D, *et al*. Focal ''nerve-sparing'' cryosurgery for treatment of primary prostate cancer: A new approach to preserving potency. *Urology* 2002;60:109–114.

[14] Bahn DK, Silverman P, Lee F Sr, *et al*. Focal prostate cryoablation: Initial results show cancer control and potency preservation. *J Endourol* 2006;20:688–692.

[15] Lindner U, Weersink RA, Haider MA, *et al*. Image guided photothermal focal therapy for localized prostate cancer: Phase I trial. *J Urol* 2009;182:1371–1377.

[16] Lindner U, Lawrentschuk N, Weersink RA, *et al*. Focal laser ablation for prostate cancer followed by radical prostatectomy: Validation of focal therapy and imaging accuracy. *Eur Urol* 2010;57: 1111–1114.

[17] Colin P, Estevez JP, Betrouni N, *et al*. Therapie photodynamique et cancer de la prostate. (Photodynamic therapy and prostate cancer). *Prog Urol* 2011;21:85–92.

[18] Rogers CL, Alder SC, Rogers RL, *et al*. High dose brachytherapy as monotherapy for intermediate risk prostate cancer. *J Urol* 2012;187: 109–116.

[19] Demanes DJ, Martinez AA, Ghilezan M, *et al*. High-dose-rate monotherapy: Safe and effective brachytherapy for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;81:1286–1292.

[20] Ahmed HU, Akin O, Coleman JA, *et al*. Transatlantic Consensus Group on active surveillance and focal therapy for prostate cancer. *BJU Int* 2012;109:1636–1647.

[21] Bachand F, Martin AG, Beaulieu L, *et al*. An eight-year experience of HDR brachytherapy boost for localized prostate cancer: Biopsy and PSA outcome. *Int J Radiat Oncol Biol Phys* 2009;73:679–684.

[22] Morton G, Loblaw A, Cheung P, *et al*. Is single fraction 15 Gy the preferred high dose-rate brachytherapy boost dose for prostate cancer? *Radiother Oncol* 2011;100:463–467.

[23] Crook J, Malone S, Perry G, *et al*. Postradiotherapy prostate biopsies: What do they really mean? Results for 498 patients. *Int J Radiat Oncol Biol Phys* 2000;48:355–367.

[24] Crook JM, Malone S, Perry G, *et al*. Twenty-four-month postradiation prostate biopsies are strongly predictive of 7-year disease-free survival: Results from a Canadian randomized trial. *Cancer* 2009; 115:673–679.

[25] Mark RJ, White D, Akins R. Interstitial high-dose-rate (HDR) brachytherapy as monotherapy for early stage prostate cancer: Median 8 year results in 321 patients. *Int J Radiat Oncol Biol Phys* 2011;81:S14.

[26] Ghadjar P, Keller T, Rentsch CA, *et al*. Toxicity and early treatment outcomes in low- and intermediate-risk prostate cancer managed by high-dose-rate brachytherapy as a monotherapy. *Brachytherapy* 2009;8:45–51.

[27] Grills IS, Martinez AA, Hollander M, *et al*. High-dose-rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. *J Urol* 2004;171: 1098–1104.

[28] Hoskin P, Rojas A, Lowe G, *et al*. High-dose-rate brachytherapy alone for localized prostate cancer in patients at moderate or high risk of biochemical recurrence. *Int J Radiat Oncol Biol Phys* 2012;82: 1376–1384.

[29] Barkati M, Williams SG, Foroudi F, *et al*. High-dose-rate brachytherapy as a monotherapy for favorable-risk prostate cancer: A phase II trial. *Int J Radiat Oncol Biol Phys* 2012;82:1889–1896.

[30] Martinez AA, Demanes J, Vargas C, *et al*. High-dose-rate prostate brachytherapy: An excellent accelerated-hypofractionated treatment for favorable prostate cancer. *Am J Clin Oncol* 2010;33:481–488.

[31] Martin T, Baltas D, Kurek R, *et al*. 3-D conformal HDR brachytherapy as monotherapy for localized prostate cancer. A pilot study. *Strahlenther Onkol* 2004;180:225–232.

[32] Yoshioka Y, Konishi K, Oh RJ, *et al*. High-dose-rate brachytherapy without external beam irradiation for locally advanced prostate cancer. *Radiother Oncol* 2006;80:62–68.

[33] Ghilezan M, Martinez A, Gustafson G, *et al*. High-dose-rate brachytherapy as monotherapy delivered in two fractions within one day for favorable/intermediate-risk prostate cancer: Preliminary toxicity data. *Int J Radiat Oncol Biol Phys* 2012;83:927–932.

[34] Demanes DJ, Gilhezan M, Schour L, *et al*. High-dose-rate brachytherapy (HDR-BT) as monotherapy for favorable prostate cancer: Excellent 5-year control rates and low toxicity. *Int J Radiat Oncol Biol Phys* 2007;69:S83.

[35] Ghilezan M, Vargas C, Gustafson G, *et al*. HDR vs. LDR (Pd103 permanent implants) brachytherapy as monotherapy for prostate cancer: Timing to onset and predictors of erectile dysfunction. *Int J Radiat Oncol Biol Phys* 2004;60:S442.

[36] Mark RJ, Akins RS, Anderson PJ. Interstitial high-dose-rate (HDR) brachytherapy as monotherapy for early stage prostate cancer: A report of 206 cases. *Int J Radiat Oncol Biol Phys* 2007;69:S329.

[37] Yamada Y, Bhatia S, Zaider M, *et al*. Favorable clinical outcomes of three-dimensional computer-optimized high-dose-rate prostate brachytherapy in the management of localized prostate cancer. *Brachytherapy* 2006;5:157–164.

[38] Nguyen PL, Chen MH, Zhang Y, *et al*. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. *J Urol* 2012 Oct;188(4):1151–1156.

[39] Seo PH, D'Amico AV, Clark JA, *et al*. Assessing a prostate cancer brachytherapy technique using early patient-reported symptoms: A potential early indicator for technology assessment? *Clin Prostate Cancer* 2004;3:38–42.

[40] Yamada Y, Rogers L, Demanes DJ, *et al*. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. *Brachytherapy* 2012;11:20–32.

[41] Albert M, Tempany CM, Schultz D, *et al*. Late genitourinary and gastrointestinal toxicity after magnetic resonance image-guided prostate brachytherapy with or without neoadjuvant external beam radiation therapy. *Cancer* 2003;98:949–954.

[42] Vainshtein JM, Abu-Isa E, Olson KB, *et al*. Randomized phase II trial of urethral sparing intensity modulated radiation therapy in low-risk prostate cancer: Implications for focal therapy. *Radiat Oncol* 2012;7:82.

[43] Zelefsky MJ, Levin EJ, Hunt M, *et al*. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:1124–1129.