

## PHYSICS CONTRIBUTION

# VIRTUAL HDR<sup>SM</sup> CYBERKNIFE TREATMENT FOR LOCALIZED PROSTATIC CARCINOMA: DOSIMETRY COMPARISON WITH HDR BRACHYTHERAPY AND PRELIMINARY CLINICAL OBSERVATIONS

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**Background:** We tested our ability to approximate the dose (38 Gy), fractionation (four fractions), and distribution of high-dose-rate (HDR) brachytherapy for prostate cancer with CyberKnife (CK) stereotactic body radiotherapy (SBRT) plans. We also report early clinical observations of CK SBRT treatment.

**Methods and Materials:** Ten patients were treated with CK. For each CK SBRT plan, an HDR plan was designed using common contour sets and simulated HDR catheters. Planning target volume coverage, intraprostatic dose escalation, and urethra, rectum, and bladder exposure were compared.

**Results:** Planning target volume coverage by the prescription dose was similar for CK SBRT and HDR plans, whereas percent of volume of interest receiving 125% of prescribed radiation dose (V125) and V150 values were higher for HDR, reflecting higher doses near HDR source dwell positions. Urethra dose comparisons were lower for CK SBRT in 9 of 10 cases, suggesting that CK SBRT may more effectively limit urethra dose. Bladder maximum point doses were higher with HDR, but bladder dose falloff beyond the maximum dose region was more rapid with HDR. Maximum rectal wall doses were similar, but CK SBRT created sharper rectal dose falloff beyond the maximum dose region. Second CK SBRT plans, constructed by equating urethra radiation dose received by point of maximum exposure of volume of interest to the HDR plan, significantly increased V125 and V150. Clinically, 4-month post-CK SBRT median prostate-specific antigen levels decreased 86% from baseline. Acute toxicity was primarily urologic and returned to baseline by 2 months. Acute rectal morbidity was minimal and transient.

**Conclusions:** It is possible to construct CK SBRT plans that closely recapitulate HDR dosimetry and deliver the plans noninvasively. © 2008 Elsevier Inc.

CyberKnife, Prostate cancer, Dosimetry, High-dose-rate, Brachytherapy, Image guided, Stereotactic body radiotherapy.

## INTRODUCTION

High-dose-rate (HDR) brachytherapy is a precise and powerful hypofractionated radiation delivery mechanism, and its efficacy for prostate cancer was established (1–4). The HDR brachytherapy allows flexible radiation dose sculpting, with increased dose in the peripheral zone of the prostate so that the highest radiation dose matches the cancer-cell distribution in this region (Fig. 1) (3, 5). The dose fractionation delivered by this method also appears uniquely well suited to prostate cancer because of the purported low  $\alpha/\beta$  ratio, which indicates high sensitivity to hypofractionation (1, 6, 7). The HDR brachytherapy is widely used as monotherapy for patients with early prostate cancer (1, 8) and in combination with external beam radiotherapy in the treatment of patients with intermediate to advanced prostate cancer (2–4). The primary drawback

of HDR brachytherapy is that it is an invasive procedure requiring hospital admission, anesthesia, nursing support, and narcotic analgesia to place and manage the indwelling transperineal HDR catheters and deal with their attendant pain and risk of infection or thromboembolism.

CyberKnife (CK; Accuray Inc., Sunnyvale, CA) stereotactic body radiotherapy (SBRT) is an accurate image-guided method for delivering quantitative radiation distribution to a precisely defined three-dimensional target volume, creating very steep surrounding dose gradients. This facilitates the safe use of biologically potent, large dose-per-fraction, hypofractionated radiation dose schedules to the prostate, similar to those delivered by means of HDR brachytherapy. The CK SBRT treatment plans for the prostate showed superior bladder and rectal tissue sparing compared with intensity-modulated

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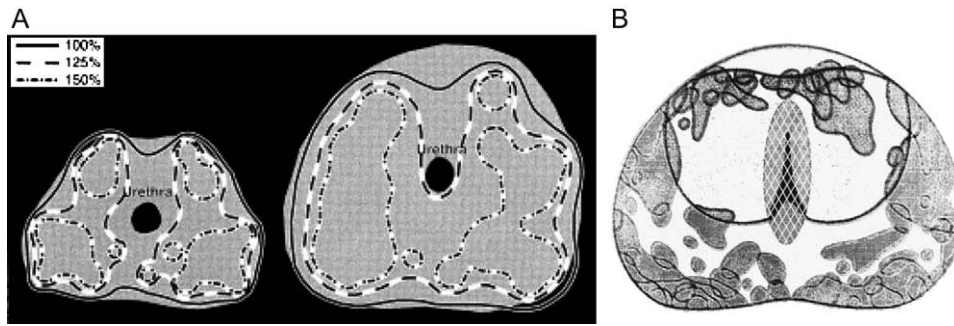


Fig. 1. High-dose-rate dose distribution vs. typical prostate peripheral zone prostate cancer distribution. (A) From Mate *et al.* (3). (B) From McNeal *et al.* (5). Panel B reprinted with permission from McNeal JE, Redwine EA, Freiha FS, *et al.* Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. *Am J Surg Pathol* 1988;12:897–906.

radiotherapy, although there is no clinical documentation of superior efficacy or reduced complications to date (6).

If CK SBRT is to be used as a method of noninvasive *virtual HDR*, it must be evaluated both technically and clinically. To this aim, we sought to create treatment parameters for CK SBRT that replicated HDR brachytherapy dosimetry. In this analysis, we examine treatment plans for 10 consecutive patients treated with CK SBRT and create simulated HDR plans to correspond to each. For each pair of plans, we compare planning target volume (PTV) coverage, intraprostatic dose escalation, and urethra, rectum, and bladder exposure. We also report early prostate-specific antigen (PSA) response and toxicity data.

## METHODS AND MATERIALS

Ten consecutive patients with prostate cancer were treated with CK SBRT from July 2006 through March 2007 under our institutional review board–approved Phase II Virtual HDR<sup>sm</sup> CyberKnife prostate monotherapy protocol, open to patients with favorable prognosis (digital rectal exam stage T1–T2b, Gleason score  $\leq 6$ , and PSA level  $\leq 10$  ng/ml), and selected patients with intermediate prognosis (Gleason score of 7 or PSA level of 10.1–20 ng/ml if other favorable characteristics still present). Our series included 8 patients with favorable and 2 patients with intermediate prognosis with a me-

dian presenting PSA level of 6.9 ng/ml (range, 1.3–11.45 ng/ml). All patients received 38 Gy in four fractions, a schedule shown to be efficacious with HDR brachytherapy (8).

### Treatment planning

The PTV for all cases included the prostate as defined by our prostate magnetic resonance imaging (MRI) protocol, three-dimensionally coregistered with prostate computed tomography (CT) imaging, matching fiducial to fiducial, plus up to 2 cm of contiguous seminal vesicle and a 2-mm volume expansion in all directions, except posteriorly, where the prostate abutted the rectum. In this region, the margin expansion was reduced to zero, justified by CK system targeting accuracy (9, 10) and reports that prostate cancer does not invade posteriorly in the midline beyond Denonvilliers' fascia (11). Intermediate-risk patients had a 5-mm dorsolateral prostate-to-PTV expansion to account for their increased risk and potential distance of extracapsular extension near the neurovascular bundle (NVB) (12). Typically, the 2-mm margin expansion used in patients with favorable prognosis split the NVB as defined on T1-weighted gadolinium-enhanced MRI, whereas the 5-mm expansion used for patients with intermediate prognosis fully encompassed it (Fig. 2). This specific MRI sequence was selected to provide prostate capsular definition, apical definition, and NVB visualization while simultaneously creating a void around the implanted gold fiducial markers that enables the most accurate combination of prostate contouring and MRI-to-CT image coregistration for treatment planning.

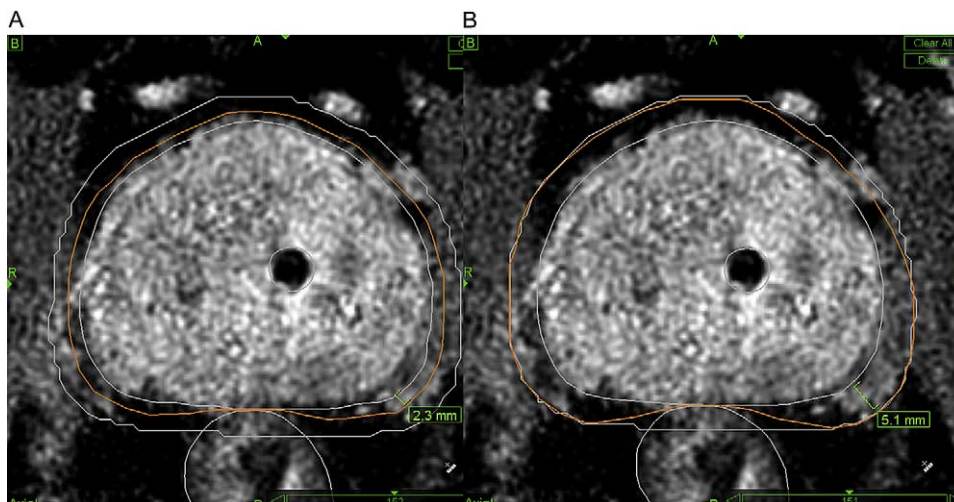


Fig. 2. (A) Favorable vs. (B) intermediate prognosis CyberKnife planning target volume treatment margin.

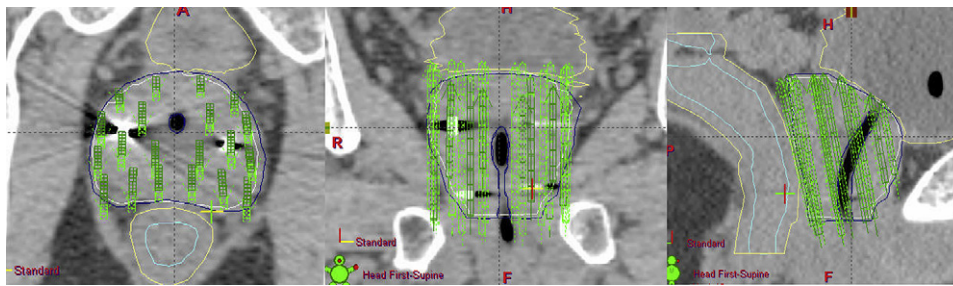


Fig. 3. Example of simulated ideal high-dose-rate catheter placement.

Although T2-weighted MRI gives detailed intraprostatic anatomic information, such as dominant intraprostatic lesion location and transition zone vs. peripheral zone delineation, the tendency of the gold fiducials to disappear within T2 hypointense signal areas has precluded making it a routine part of our CK SBRT treatment planning image fusion procedure. The urethra was identified by insertion of a Foley catheter, which also provided another reference structure to use in MRI-to-CT image coregistration.

Our CK SBRT treatment plans had a specific set of objectives and constraints, including a requirement of a minimum PTV prescription dose coverage of 95% (percent of volume of interest receiving 100% of prescribed radiation dose [V100]  $\geq$  95%) and maximum PTV dose of 200% of the prescription dose (76 Gy), with greater than 200% classified as a minor protocol deviation only. Also required were a maximum rectal wall dose of 100% of the prescription dose (38 Gy), a maximum rectal mucosa dose of 75% of the prescription dose (28.5 Gy), a maximum urethra dose of 120% of the prescription dose (45.6 Gy), and a maximum bladder dose of 120% of the prescription dose (45.6 Gy). The rectal mucosa was defined as a solid structure formed by a 3-mm contraction of the rectal wall. Normal tissue dose-limitation objectives were designed to resemble those commonly prescribed in the application of HDR brachytherapy (13).

#### Dosimetry comparison

For each of our delivered CK SBRT plans, a corresponding simulated HDR plan with manual optimization was designed on the Varian Varisource HDR computer (Varian Medical Systems, Inc., Palo Alto, CA), using Digital Imaging and Communications in Medicine–transferred identical contour sets and 15–20 simulated “ideally placed” HDR catheters (Fig. 3). The intent was to design an identical prescription isodose volume coverage between each modality (CK SBRT vs. HDR) in the midaxial, sagittal, and coronal planes, with variation of the 100% isodose lines measuring no more than 2 mm at any point along these planes and matching the respective V100 values as closely as possible (typically with < 1%

difference between them). Simulated HDR plans also were designed to minimize the urethra and rectal wall dose by manually reducing the internal HDR dwell positions as much as possible without degrading the PTV V100 coverage result below the dosimetry comparison requirement. Dosimetry values for optimized CK SBRT and HDR plans were evaluated and compared with respect to PTV coverage (V100, V125, V150, and radiation dose received by 90% of volume of interest [D90]), urethra exposure (radiation dose received by point of maximum exposure of volume of interest [Dmax], D10, and D50), rectal wall exposure (V100, V80, Dmax, D1, D10, and D25), rectal mucosa exposure (V80, Dmax, D1, D10, and D25), and bladder exposure (Dmax and D10).

#### Second CK SBRT plan iterations

In the first 5 patients, a second CK SBRT plan iteration was designed to more exactly match the HDR urethra exposure to test the hypothesis that this modified CK SBRT dosimetry instruction would create closer matching of PTV high-dose values between CK SBRT and HDR (V125 and V150). In the second CK SBRT plan iterations, there was no specific upper boundary applied to the maximum PTV isodose value. The HDR and second CK SBRT plans were compared in a manner similar to the initial plans.

## RESULTS

#### PTV coverage

The PTV coverage comparisons are listed in Table 1. Median SBRT prescription isodose value was 56% (range, 49–67%) relative to a maximum value of 100%. Median differences in V100 values between corresponding CK SBRT and simulated HDR plans measured 0.5% (96.5% vs. 96.0%, respectively), with individual V100 values matching within  $\pm 1.0\%$  in nine of 10 cases. The sole deviation was an HDR plan with V100 coverage 2.2% less than the

Table 1. PTV statistics: Prescription dose 38 Gy/four fractions

	CyberKnife actual	High-dose-rate simulated	<i>p</i> (paired <i>t</i> test)
Isodose prescription (%)	56 (49–67)	N/A	
PTV V100* (%)	96.5 (95.6–99.2)	96.0 (93.4–99.1)	—
PTV V125 (%)	44.0 (28.4–55.5)	67.5 (53.3–75.5)	<0.001
PTV V150 (%)	8.5 (0.3–20.5)	37.8 (25.4–45.6)	<0.001
PTV D90 (Gy)	39.8 (39.3–40.9)	41.3 (39.6–43.9)	.002

Values expressed as median (range).

Abbreviations: PTV = planning target volume; Vx = percent of volume of interest receiving x% of prescribed radiation dose; D90 = radiation dose received by 90% of volume of interest; N/A = not applicable.

\* Matched parameter.

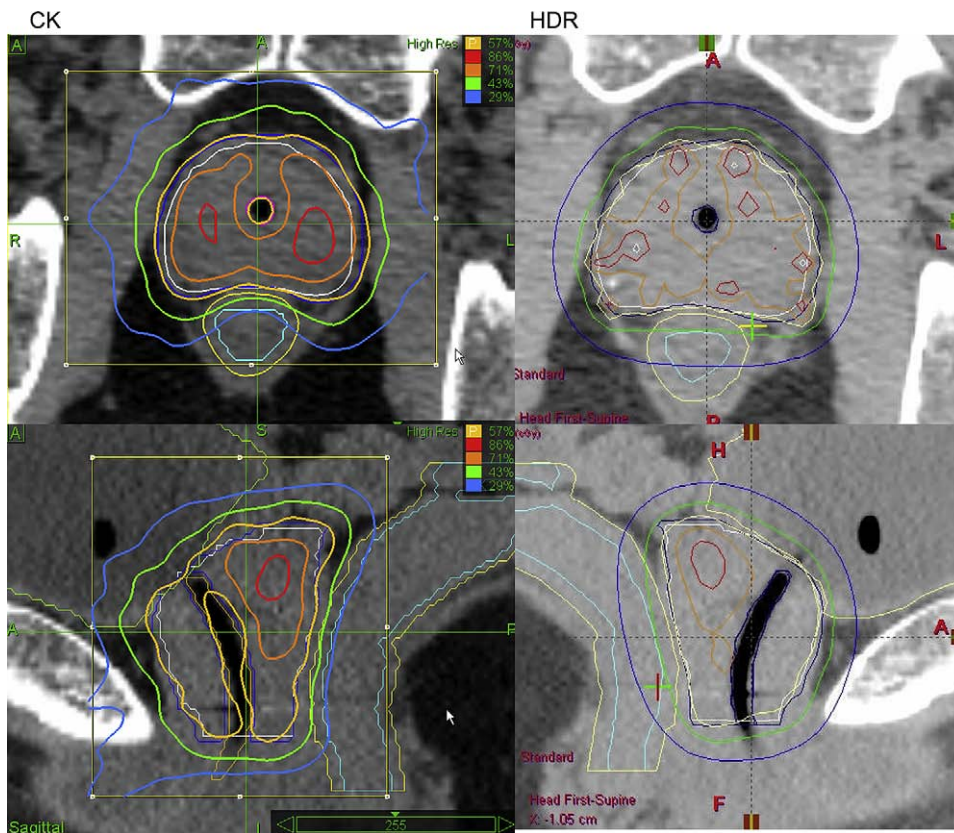


Fig. 4. Axial and sagittal comparison: CyberKnife (CK) vs. simulated high-dose-rate (HDR) dosimetry. White line = prostate contour; dark blue line = 2-mm planning target volume expansion. Isodose lines shown as follows: 150%, red; 125%, orange; 100%, yellow (very light on HDR image); 75%, green; and 50%, blue. Note similar morphologic characteristics of 100%, 125%, and 150% coverage lines, with partial exclusion of the urethra from 100% isodose volume coverage with CK (left) and lower rectal wall and mucosa 75% and 50% isodose volume with CK (left).

corresponding CK SBRT plan because of inclusion in the PTV of seminal vesicle bases in a way that was not well accessed by the simulated HDR catheters. Median PTV coverage measured by means of respective D90 values measured 39.8 Gy for SBRT vs. 41.3 Gy for simulated HDR plans ( $p = 0.002$ ). Isodose values exceeding the prescription dose within the prostate, *i.e.*, V125 and V150, were significantly higher in HDR plans (Table 1). Despite the limited number of observations ( $n = 10$ ) and small quantitative differences in D90s, the high degree of significance for dosimetric comparisons arises from having paired observations and low interpatient variance.

The interaction between dose-escalation regions (volumes receiving > 100% of prescribed dose), prescription isodose coverage boundaries (V100), and dose falloff regions (volumes receiving < 100%) is represented with isodose contours on CT-based treatment plans showing 150%, 125%, 100%, 75%, and 50% isodose (Fig. 4).

#### Urinary tract

Urethra and bladder dosimetry values are listed in Table 2. Median urethra Dmax, D10, and D50 values were less for CK SBRT relative to simulated HDR (by 5.9, 6.2, and 6.2 Gy, respectively). Only one of the simulated HDR plans created a lower urethra Dmax than its corresponding CK SBRT

plan, and in every case, the urethra D10 and D50 values were lower in the CK SBRT plans. All urethra dosimetry comparison statistics were significant (Table 2). In the bladder, simulated HDR plans had a higher median Dmax value (54 vs. 42.8 Gy, respectively), whereas CK SBRT plans had a higher median D10 value (29.3 vs. 24.1 Gy, respectively), each finding statistically significant (Table 2).

#### Rectal wall and mucosa

Table 3 lists dosimetry values for the rectal wall and rectal mucosa (mucosa defined as a 3-mm contraction of the rectal wall). Median rectal wall V80 values were similar with each modality (median, 1.3 ml; range, 0.3–4.0 ml with CK SBRT vs. median, 2.5 ml; range, 0.7–6.0 ml with HDR). Median rectal wall Dmax values were nearly identical between modalities: 37.3 Gy for SBRT vs. 37.5 Gy for HDR, whereas comparatively lower doses were seen with CK SBRT beyond the Dmax region, evidenced by increasing disparity in D1, D10, and D25 measurements. This produced progressively larger differences in favor of CK SBRT, particularly with respect to the D25 statistic, for which the median result with CK SBRT was 15.8 Gy compared with 19.4 Gy for HDR. With the exception of Dmax and V80, all rectal wall dosimetry differences were statistically significant (Table 3).

Table 2. Urethra and bladder statistics

	CyberKnife actual	High-dose-rate simulated	<i>p</i> (paired <i>t</i> -test)
Urethra Dmax (Gy)	44.3 (43.1–46.1)	50.0 (44.1–68.0)	0.01
Urethra D10 (Gy)	41 (39.8–42.5)	47.1 (41.8–52.2)	<0.001
Urethra D50 (Gy)	38.6 (37.5–40)	44.9 (41.6–46.4)	<0.001
Bladder Dmax (Gy)	42.8 (40.3–43.7)	55.5 (42.9–64.2)	<0.001
Bladder D10 (Gy)	28.2 (20.0–34.6)	23.6 (16.8–28.8)	<0.001

*Abbreviations:* Dmax = radiation dose received by point of maximum exposure of volume of interest; Dx = radiation dose received by x% of volume of interest.

Values expressed as median (range).

The median rectal mucosa V80 was negligible with either modality (0.0 vs. 0.1 ml with CK SBRT vs. HDR, respectively), whereas median Dmax values were slightly less for CK SBRT than HDR at 29.2 vs. 31.9 Gy. The same trend of increasing disparity in favor of CK SBRT with respect to the comparative rectal mucosa D1, D10, and D25 statistics was seen, with a median D25 result for SBRT vs. HDR of 14.2 vs. 19.4 Gy, respectively. With the exception of V80, all rectal mucosa dosimetry differences were statistically significant (Table 3).

*Second CK SBRT iterations.* Results of this evaluation, in which second CK SBRT plans were created in which the CK SBRT urethra Dmax matched the corresponding HDR dosimetry, are shown in Table 4 and Fig. 5. (Note that these CK plans were created for comparison purposes, they were not delivered to patients.) With urethra dosimetry equilibrated in this manner, a much closer matching of V125 and V150 parameters was observed, with 62.5% vs. 71.5% median V125 values and 31.5% vs. 40.1% median V150 values for the five comparison CK SBRT versus HDR cases, respectively. There was a minimal increase in rectal wall and mucosa dose, although CK SBRT intraprostatic dose escalation in this manner resulted in a more significantly increased median bladder D10 value, reflecting greater bladder radiation exposure to less-than-prescription isodoses with increased intraprostatic dose escalation (Table 4). Figure 6 shows four consecutive second-iteration CK plans, highlighting the case-to-case consistency of the PTV dose escalation

morphology that repeatedly creates “horseshoe-shaped” dose-escalation volumes within the lateral and posterior aspects of the prostate gland with the same basic cross-sectional configuration as an HDR brachytherapy catheter pattern.

#### Clinical outcomes

*Early PSA response.* PSA response data after SBRT are shown in Fig. 7. Compared with baseline PSA levels, median 1- and 4-month decreases after protocol SBRT treatment were 74% and 86%, respectively.

*Acute toxicity and resolution.* All patients were placed on  $\alpha$ -blockade medication at the initiation of their CK SBRT treatment, and median time to  $\alpha$ -blockade withdrawal was 8 weeks, with 6 of 10 patients still using  $\alpha$ -blockers at their last follow-up appointment (maximum follow-up, 6 months after SBRT). Median and maximum International Prostate Symptom Score increases from baseline were 10 and 22 points, respectively. They typically peaked at the 2-week post-SBRT follow-up appointment and returned to within three points of the pre-SBRT baseline level by 8 weeks post-treatment in 6 of 8 patients followed up this long. No urinary obstruction was observed to date. Rectal toxicity was mild and transient, with acute Radiation Therapy Oncology Group Grade 1–2 toxicity (proctalgia and fecal urgency) appearing by the 2-week follow-up appointment in 6 of 10 patients and resolving by 4 weeks posttreatment in 5 of the 6 patients who developed it. No acute rectal bleeding was observed to date.

Table 3. Rectal wall and mucosa statistics

	CyberKnife actual	High-dose-rate simulated	<i>p</i> (paired <i>t</i> -test)
Rectal wall V80 (ml)	1.3 (0.3–4.0)	2.4 (0.6–6.0)	0.06
Rectal wall Dmax (Gy)	37.3 (34.7–38.0)	37.5 (34.6–43.3)	Not significant
Rectal wall D1 (Gy)	33.3 (29.6–34.7)	34.7 (30.5–37.2)	0.02
Rectal wall D10 (Gy)	23.2 (20.0–25.6)	25.7 (20.7–30.7)	0.002
Rectal wall D25 (Gy)	15.8 (13–18.7)	19.4 (13.7–24.5)	<0.001
Rectal mucosa V80 (ml)	0.0 (0.0–0.7)	0.1 (0.0–2.3)	Not significant
Rectal mucosa Dmax (Gy)	29.0 (25.3–33.5)	31.4 (27.4–35.0)	0.04
Rectal mucosa D1 (Gy)	25.9 Gy (22.1–30.2)	29.0 Gy (24.8–33.6)	0.001
Rectal mucosa D10	19.5 (16.3–22.7)	23.8 (18.5–28.9)	<0.001
Rectal mucosa D25 (Gy)	14.2 (11.7–17.3)	19.4 (13.6–23.8)	<0.001

*Abbreviations:* Vx = percent of volume of interest receiving x% of prescribed radiation dose; Dmax = radiation dose received by point of maximum exposure of volume of interest; Dx = radiation dose received by x% of volume of interest.

Values expressed as median (range).

Table 4. Second-iteration matched urethra CyberKnife vs. high-dose-rate: Five consecutive cases

	CyberKnife simulated	High-dose-rate simulated
Isodose prescription (%)	45 (42–49)	N/A
PTV V100 (%)	96.0 (95.3–98.1)	96.7 (95.4–99.1)
PTV V125 (%)	62.5 (57.5–72.2)	71.5 (63.3–75.5)
PTV V150 (%)	31.5 (24.7–40.9)	40.1 (27.3–45.6)
PTV D90 (Gy)	40.6 (40.0–42.2)	41.8 (40.5–43.9)
Urethra Dmax* (Gy)	51.3 (50.4–52.9)	50.9 (49.0–52.4)
Bladder Dmax (Gy)	45.8 (38.0–51.2)	53.2 (42.9–58.5)
Bladder D10 (Gy)	32.0 (18.5–46.6)	22.8 (16.9–28.5)
Rectal wall Dmax (Gy)	38.9 (36.3–39.6)	36.9 (35.0–39.1)
Rectal wall D10 (Gy)	24.2 (18.9–24.8)	25.7 (22.0–28.1)
Rectal mucosa Dmax (Gy)	30.8 (25.3–33.3)	30.8 (28.1–32.3)
Rectal mucosa D10 (Gy)	18.9 (16.4–21.0)	23.7 (21.0–26.0)

*Abbreviations:* PTV = planning target volume; V<sub>x</sub> = percent of volume of interest receiving x% of prescribed radiation dose; Dmax = radiation dose received by point of maximum exposure of volume of interest; Dx = radiation dose received by x% of volume of interest; N/A = not applicable.

Values expressed as median (range).

## DISCUSSION

It is our hypothesis that the CK may be used to deliver HDR-like dosimetry to the prostate noninvasively. Supporting this hypothesis, our dosimetry comparison between CK SBRT and simulated HDR showed close similarities between them in coverage of the prostate PTV by the prescribed radiation dose, as indicated by similar V100 characteristics (Table 1; Fig. 4). The CK SBRT also created a similar pattern of dose escalation within the prostate peripheral zone compared with HDR (Fig. 4), although the absolute peripheral zone radiation dose distribution was greater in the simulated HDR plans (Table 1), reflecting the physics inverse square law by which extreme radiation dosage is created in immediate proximity to HDR source dwell positions.

Urethra sparing was clearly more effectively accomplished by means of CK SBRT in this study, with 29 of 30 comparisons favoring the CK SBRT plans, typically by a dose difference on the order of 600 cGy (Table 2). In all except one case, attempts to match CK SBRT urethra dose sparing with simulated HDR treatment plans resulted in deviation in PTV V100 values for the HDR plans to less than the protocol requirement of 95% PTV coverage. Thus, the CK SBRT plans appeared to better maintain the protocol PTV V100 coverage requirement while also respecting the urethra dose limit when compared directly with case-matched, identically contoured, simulated HDR brachytherapy treatment plans. To our knowledge, this finding was not reported by other investigators and therefore requires additional evaluation by other investigators before definitive conclusions may be drawn.

A higher bladder Dmax was obtained with simulated HDR plans, reflecting the proximity of HDR point source dwell positions relative to the bladder, whereas the higher bladder D10 level seen in the CK SBRT plans likely reflects the effect of streaming CK radiation beams through larger bladder volumes (Table 2). The clinical significance of these observed bladder dosimetry differences is unknown.

Nearly identical rectal wall Dmax values were obtained with CK SBRT and HDR plans, with a slightly lower median rectal mucosa Dmax value observed in CK SBRT plans. With increasing distance from the point of maximum rectal dose exposure (Dmax), progressively larger differences in rectal wall and mucosa radiation dose sparing in favor of CK SBRT were observed, indicating sharper dose falloff beyond the rectal Dmax point with CK SBRT relative to HDR (Table 3; Fig. 4). Because reported HDR rectal morbidity rates tend to be very low (1, 14, 15), it is unclear whether this more rapid rectal radiation dose falloff with CK SBRT will bring an added clinical benefit, although it suggests

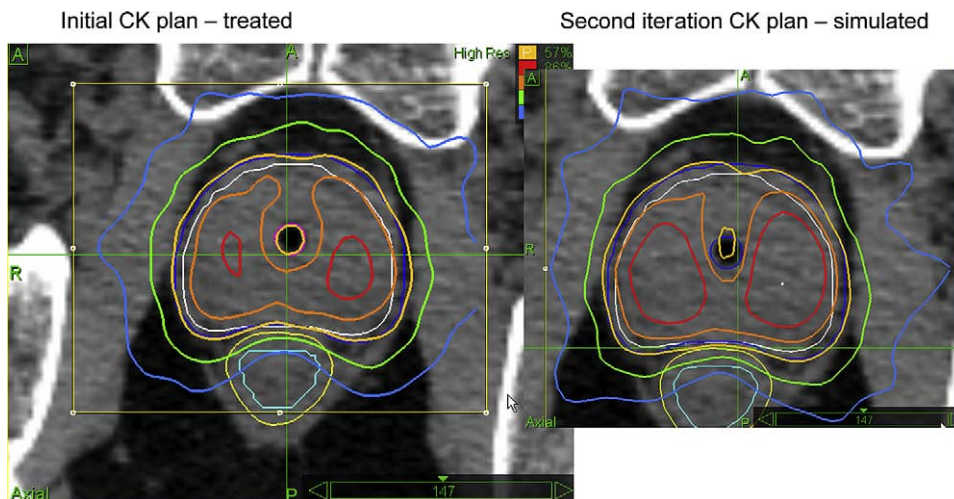


Fig. 5. Second-iteration CyberKnife plan (right panel; first plan is on left) with equilibrated CK high-dose-rate urethra radiation dose received by point of maximum exposure of volume of interest (Dmax). In particular, note enlargement of the 125% and 150% isodose coverage volumes within the peripheral zone in the second-iteration CK plan (right panel; orange and red lines, respectively), with minimal change in prescription dose coverage volume (yellow line) or rectal dose exposure illustrated by respective 75% (green) and 50% isodose (blue) lines.

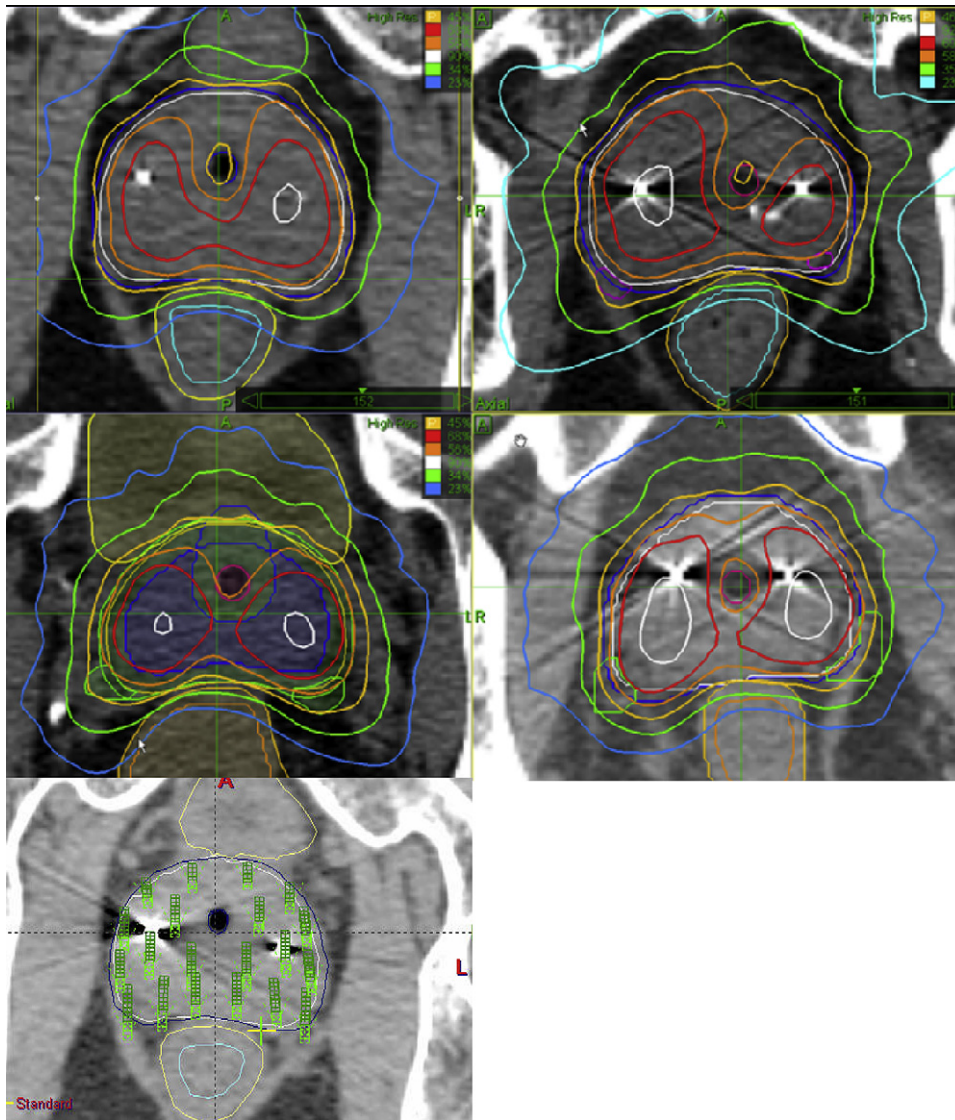


Fig. 6. Four consecutive second-iteration CyberKnife plans show a consistent pattern of dose escalation within the prostate. Isodose lines shown as follows: 200%, white; 150%, red; 125%, orange; 100%, yellow; 75%, green; and 50%, blue. A typical cross-sectional high-dose-rate (HDR) catheter pattern is also included to illustrate the spatial similarity of CyberKnife dose escalation regions with HDR catheter locations.

that the low rectal injury rates observed with HDR should be equaled or even lower with CK SBRT. In this context, it was reported that a greater incidence of Grade 2 or higher rectal bleeding with HDR brachytherapy was obtained when a larger volume of the rectum received low- to moderate-dose radiation (10–50% of prescribed); this is the rectal exposure range at which we observed the largest differential rectal sparing with CK SBRT relative to HDR (16). Again, it should be emphasized that until our intermodality dosimetry findings are evaluated by other investigators, any conclusions regarding the relative rectal-sparing capability of CK SBRT vs. HDR brachytherapy are preliminary.

It should be noted that both CK and HDR radiation dose sculpting platforms are extremely user programmable, which complicates the direct comparison of these radiation delivery modalities. It is possible that some untested combination of HDR brachytherapy catheter configuration and source dwell

position instructions would create a more favorable HDR brachytherapy result, although our relative CK SBRT vs. HDR dosimetry observation trends seemed consistent across the range of prostate volumes and catheter configurations analyzed in our study. Likewise, it also is possible that more effective CK SBRT treatment planning and radiation beam collimator selection could create a more favorable CK SBRT dosimetry result. Despite these caveats, the present study clearly shows that treatment plans that closely approximate those used in HDR brachytherapy for patients with prostate cancer may be constructed and delivered using the CK system.

#### *Further intraprostatic CK SBRT dose escalation*

Our early observation of dosimetry trends that favored HDR for the volume of PTV exceeding the prescription dose by 25% or more and CK SBRT for urethra sparing

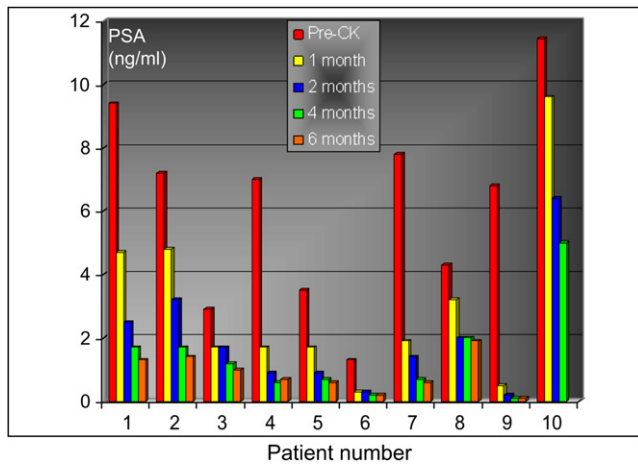


Fig. 7. Post-CyberKnife (CK) prostate-specific antigen (PSA) response in protocol patients.

prompted us to run second CK SBRT plan iterations in the first 5 patients. For this exercise, the CK planning computer was instructed to match the urethra Dmax of the corresponding HDR plan while relaxing the CK PTV Dmax limitation and maintaining all other dose limitations to see whether this approach would allow CK SBRT plans to more closely resemble HDR V125 and V150 values. This is exactly what we found; second-iteration CK SBRT V125 and V150 measurements much more closely approached the median simulated HDR V125 and V150 values, more effectively matching HDR PTV dose escalation volumes (Table 4; Fig. 5). Bladder Dmax and all rectal dosimetry parameters changed very little in the second-iteration CK SBRT plans compared with the *de novo* SBRT plans, although there was a more significant and variable increase in the bladder D10 dosimetry statistic, indicating that more stringent attention to bladder sparing may be required if extreme intraprostatic dose escalation is attempted with CK.

In summary, our second-iteration CK SBRT plans show that intraprostatic dose escalation approaching parity with HDR appears possible, although with attendant partial or complete loss of the superior urethra sparing observed in the initial CK SBRT plans. Because urethral strictures were reported with HDR brachytherapy (1), a reasonable strategy might be to escalate intraprostatic dose as much as possible with CK SBRT while still respecting the urethra dose limits of the CK protocol. This is the approach we continue to use in our ongoing Virtual HDR<sup>sm</sup> CyberKnife clinical trial, which shows increasing PTV V125 and V150 trend lines over sequential patients.

Although our CT and MRI planning sequences are not specifically designed to delineate the peripheral zone, inspection of the 125% (orange) and 150% (red) isodose lines shown in Figs. 4–6 compared with the pathologic illustration provided in Fig. 1 suggests a significant degree of coincidence between CK dose escalation zones and the anatomic peripheral zone of the prostate. A more direct approach would be to perform specific peripheral zone and dominant intraprostatic lesion

dosimetry comparisons between the modalities from T2-weighted MRI imaging sequences should such images become available for inspection in future patients.

#### *Radiobiologic relevance of intraprostatic dose escalation*

Whether the radiation dose delivery platform is CK SBRT or HDR, the prescription dose of 38 Gy in four fractions is the dose calculated to deliver a biologically lethal blow to the cancer; therefore, it is unclear to what extent further dose escalation beyond this level within the prostate may be necessary or beneficial. However, the exact  $\alpha/\beta$  ratio of prostate cancer upon which hypofractionation schedules are calculated remains uncertain, as discussed in the recent report of Williams *et al.* (7). If we use the HDR literature to justify CK treatment, an argument may be made that CK practitioners are well advised to mimic HDR intraprostatic dose distribution as closely as possible to maximize the possibility of reproducing the favorable HDR clinical result. Intraprostatic dose escalation beyond the prescribed dose level, as naturally occurs with any form of brachytherapy, provides backup cancer-cell-killing power in the event that cancer-cell populations with higher  $\alpha/\beta$  ratios exist within heterogeneous populations of prostate cancers and patients with prostate cancer. It also should be noted that Lotan *et al.* (17) obtained the most reliable tumor ablation in prostate cancers in a nude mouse model with a dose of 45 Gy in three fractions, a more aggressive dosing schedule than described in our study or reported in the HDR literature, again making a case for intraprostatic dose escalation.

#### *Treatment delivery and dosimetry accuracy*

Even infinite computerized dose-sculpting capability is clinically meaningless unless the targeting accuracy of the delivery system is sufficient to ensure precise delivery of the treatment plan. Unlike typical image-guided radiotherapy systems, which detect and correct the target volume position only once at the beginning of each treatment, the CK robotic delivery system uses a unique stereoscopic X-ray-based tracking system that updates and corrects robotic linear accelerator position with regard to both translational and rotational target volume movements up to 100 or more times per treatment, resulting in submillimeter targeting accuracy for brain and spine applications (9, 10).

Because the fiducial-based CK tracking procedure for prostate treatment is comparable, the delivery accuracy for prostate cancer theoretically should be identical to that described for brain and spine applications, but with the important caveat that prostate motion is potentially more complex to accurately track and correct for than relatively more fixed brain and spinal targets. Movement caused by bowel peristalsis and bladder filling can cause a rapidly shifting, rotating, and even deforming prostate target volume (18). Until the quantitative effects of these added prostate motion and potential deformation complexities are understood in greater detail, this remains a valid point of criticism for investigators who discuss CK system targeting accuracy in the treatment of prostate cancer.

HDR brachytherapy accuracy is also subject to potential error and distortion because of such factors as variable and potentially significant HDR source transit dose contribution that is neglected by HDR planning computers (19), prostate volume fluctuation caused by needle trauma (20), and longitudinal HDR catheter translocation during the course of the patient's hospitalization (21), with the latter likely representing the largest source of potential HDR brachytherapy targeting error.

Regarding the resemblance of the computer-generated treatment plan to the actual delivered treatment, both CK and HDR brachytherapy have potential dosimetry deviations. Because the sources of dosimetry errors and targeting inaccuracy are different between these modalities, their relative magnitudes are speculative, and as such, it is unknown which modality most consistently delivers its treatment plan more accurately.

#### Clinical discussion

Our Virtual HDR<sup>sm</sup> CyberKnife clinical series is small, with maximum follow-up limited to 12 months; however, some preliminary clinical observations may be reported. Our continuously decreasing median 4-month post-CK PSA value of 0.95 ng/ml suggests a similar response slope to that described by the Stanford group, who reported a median 18-month post-CK PSA value of 0.22 ng/ml (22). On a larger scale of comparison, our observed median 4-month post-CK PSA decrease of 86% appears comparable to the short-term PSA response magnitude reported with other radiation-based approaches, including standard external beam radiotherapy (23) and <sup>103</sup>Pd seed brachytherapy (24), with much longer term follow-up required to assess durability of the response.

Early post-HDR brachytherapy PSA responses, similar to the present data, have not been reported to our knowledge. As our series matures, relative PSA-based disease-free survival rates will be compared.

Acute toxicity of Virtual HDR<sup>sm</sup> CK monotherapy was self-limited and manageable, primarily consisting of several months of  $\alpha$ -blocker-dependent irritative/obstructive uropathy, as well as fatigue, and a less than 100% incidence of typically Grade I proctalgia/rectal urgency that usually resolved by 3–4 weeks after CK treatment. Although our early post-CK toxicity data appear very encouraging, definitive toxicity assessment requires significantly longer follow-up because serious radiation-related complications may not manifest until 1 to 2 years posttreatment. Our series is too small and follow-up is too short to make a meaningful statement about the incidence of post-CK erectile dysfunction, although this domain will be assessed in detail as the fully accrued study matures. For long-term toxicity evaluation, the Virtual HDR<sup>sm</sup> CK monotherapy protocol includes the long-form Expanded Prostate Cancer Index Composite assessment, which measures urinary, gastrointestinal, sexual, and hormonal-mediated sequelae of therapy (25).

#### Summary

We conclude that CK robotic radiosurgery is a noninvasive method to deliver radiation dose distributions that very closely resemble those delivered by using HDR brachytherapy. Early clinical results are encouraging. Our Virtual HDR<sup>sm</sup> CyberKnife monotherapy clinical series to test the short- and long-term morbidity and PSA-based disease-free survival equivalence to HDR brachytherapy and other methods of radiation delivery continues.

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