

A Pilot Study of Intensity Modulated Radiation Therapy with Hypofractionated Stereotactic Body Radiation Therapy (SBRT) Boost in the Treatment of Intermediate- to High-Risk Prostate Cancer

www.tcr.org

Clinical data suggest that large radiation fractions are biologically superior to smaller fraction sizes in prostate cancer radiotherapy. The CyberKnife is an appealing delivery system for hypofractionated radiosurgery due to its ability to deliver highly conformal radiation and to track and adjust for prostate motion in real-time. We report our early experience using the CyberKnife to deliver a hypofractionated stereotactic body radiation therapy (SBRT) boost to patients with intermediate- to high-risk prostate cancer. Twenty-four patients were treated with hypofractionated SBRT and supplemental external radiation therapy plus or minus androgen deprivation therapy (ADT). Patients were treated with SBRT to a dose of 19.5 Gy in 3 fractions followed by intensity modulated radiation therapy (IMRT) to a dose of 50.4 Gy in 28 fractions. Quality of life data were collected with American Urological Association (AUA) symptom score and Expanded Prostate Cancer Index Composite (EPIC) questionnaires before and after treatment. PSA responses were monitored; acute urinary and rectal toxicities were assessed using Common Toxicity Criteria (CTC) v3. All 24 patients completed the planned treatment with an average follow-up of 9.3 months. For patients who did not receive ADT, the median pre-treatment PSA was 10.6 ng/ml and decreased in all patients to a median of 1.5 ng/ml by 6 months post-treatment. Acute effects associated with treatment included Grade 2 urinary and gastrointestinal toxicity but no patient experienced acute Grade 3 or greater toxicity. AUA and EPIC scores returned to baseline by six months post-treatment. Hypofractionated SBRT combined with IMRT offers radiobiological benefits of a large fraction boost for dose escalation and is a well tolerated treatment option for men with intermediate- to high-risk prostate cancer. Early results are encouraging with biochemical response and acceptable toxicity. These data provide a basis for the design of a phase II clinical trial.

Key words: Prostate Cancer; SBRT; IMRT; CyberKnife; EPIC; quality of life; Acute toxicity; Common Toxicity Criteria (CTC).

Introduction

The importance of local control in prostate cancer is clear; local failures from radiotherapy can lead to higher distant failure rates (1) and morbidity resulting from uncontrolled local disease can be significant including urinary obstruction, bleeding and pain. Achieving improved local control within the prostate

Eric K. Oermann¹
Rebecca S. Slack, M.S.²
Heather N. Hanscom¹
Sue Lei¹
Simeng Suy, Ph.D.¹
Hyeon U. Park, Ph.D.¹
Joy S. Kim¹
Benjamin A. Sherer³
Brian T. Collins, M.D.¹
Andrew N. Satinsky, M.D.¹
K. William Harter, M.D.¹
Gerald P. Batipps, M.D.³
Nicholas L. Constantinople, M.D.³
Stephen W. Dejter, M.D.³
William C. Maxted, M.D.³
James B. Regan, M.D.³
John J. Pahlira, M.D.³
Kevin G. McGeagh, M.D.³
Reena C. Jha, M.D.⁴
Nancy A. Dawson, M.D.⁵
Anatoly Dritschilo, M.D.¹
John H. Lynch, M.D.³
Sean P. Collins, M.D., Ph.D.^{1*}

¹Department of Radiation Medicine,
Georgetown University Hospital

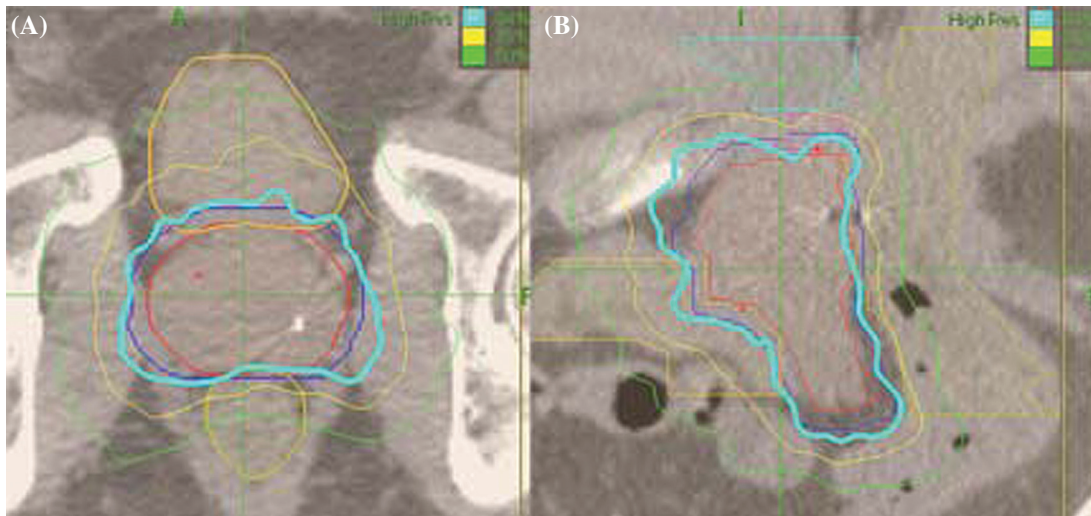
²Department of Biostatistics,
Georgetown University

³Department of Urology, Georgetown University Hospital

⁴Department of Radiology, Georgetown University Hospital

⁵Department of Medical Oncology, Georgetown University Hospital

*Corresponding Author:
Sean P. Collins, M.D., Ph.D.
Email: SPC9@georgetown.edu



(C) Critical Structure	V _x Gy	V _x Gy constraint	Allowed V _x variations	
			Minor	Major
Rectum	19.5 Gy	< 1 cc	V19.5 Gy ≥ 1 cc, but < 2 cc	V19.5 Gy > 2 cc
Bladder	19.5 Gy	< 10 cc	V19.5 Gy ≥ 10 cc, but < 20 cc	V19.5 Gy > 20 cc
Penile bulb	15 Gy	< 50%	V15 Gy ≥ 50%, but < 75%	V15 Gy > 50%
Membranous urethra	18 Gy	< 50%	V18 Gy ≥ 50%, but < 75%	V18 Gy > 75%
Sigmoid colon and other bowel	15 Gy	< 1 cc	V15 Gy ≥ 1 cc, but < 2 cc	V15 Gy > 2 cc

Figure 1: SBRT treatment planning axial (A) and sagittal (B) computed tomography images demonstrating the CTV (red), PTV1 expansion (dark blue), bladder (orange), rectum (yellow), and membranous urethra (pink). The prescription isodose lines are shown at 84% (light blue), 70% (yellow) and 50% (green). (C) Summary of SBRT dose volume constraints for the critical structures where V_x Gy denotes the volume of the structure receiving a dose of *x* Gy.

therefore carries promise of reducing the sequelae attributable to uncontrolled local disease as well as improving survival.

Radiation Oncologists' efforts to improve local control, by optimizing the therapeutic ratio, have been directed toward limiting the high dose volume to the prostate while escalating the dose within that volume. Along these lines, three-dimensional conformal radiation treatment (3DCRT) has increased local control rates with lower complication rates when compared to standard external beam techniques (2, 3). Similarly, intensity modulated radiation therapy (IMRT) has allowed dose-escalation to 81 Gy with acceptable levels of complications (4). Yet, with 8-year biochemical relapse-free rates

of 78% and 67% for intermediate- and high-risk patients, it is clear that even higher doses may be required to eradicate prostate cancer (5-7).

Recent data suggest that large radiation fraction sizes are radio-biologically favorable over smaller fraction sizes in prostate cancer radiotherapy (8). High dose rate (HDR) brachytherapy as a boost to external beam radiation therapy (EBRT) has shown promise in this regard. Several studies have reported 5-year biochemical control rates of 93-98% (9-11), 89-93% (9-11) and 69-83% (7, 9-11) for low-, intermediate-, and high-risk prostate cancer with 5-year cause-specific survival rates of 96-98% independent of risk (7, 9-12).

In an effort to further improve patient tolerance in comparison to HDR brachytherapy, we have examined the use of CyberKnife stereotactic radiosurgery as a boost to IMRT for the treatment of patients with intermediate- and high-risk clinically localized prostate cancer. The CyberKnife uses hundreds of non-isocentric beams to deliver a highly conformal radiation dose with steep dose gradients (13) which can be used to limit dose and toxicity to surrounding structures. Unlike HDR brachytherapy treatment, the CyberKnife does not require anesthesia or hospitalization. When compared to intensity modulated radiation therapy, dosimetric studies have shown that CyberKnife plans show rapid dose fall-off rates from the prostate with significantly better conformity than IMRT plans at

a relatively greater dose inhomogeneity (14). This relative inhomogeneity can be taken advantage of to allow for HDR-like dose escalation within the prostatic peripheral zone (15). The CyberKnife incorporates a dynamic tracking system consisting of an orthogonal pair of diagnostic-quality x-ray imaging devices and software that can locate fiducials implanted in or near the target. This provides updated position information in six-dimensions (3 translations combined with roll, pitch and yaw rotations) for targeting of the therapeutic beam during treatment and allows for correction of intrafraction motion (16). We report on the use of CyberKnife SBRT as a homogeneous hypofractionated boost to IMRT for the treatment of 24 prostate cancer patients.

Grade	0	1	2	3	4	5
Diarrhea	None	Increase of < 4 stools per day	Increase of 4 -6 stools per day; not interfering with ADL	Increase \geq 7 stools per day; hospitalization; interfering with ADL	Life threatening consequences	Death
Colitis	None	Asymptomatic	Abdominal pain with mucus and/or blood in stools	Abdominal pain, fever, ileus; peritoneal signs	Perforation or other complication requiring surgical intervention	Death
Proctitis	None	Rectal discomfort not requiring treatment	Medical treatment indicated, no interference with ADL	Surgical intervention indicated; interference with ADL	Life threatening consequences	Death
Rectal bleeding	None	Mild, intervention not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion or surgical intervention required	Life threatening consequences	Death
Hematuria	None	Microscopic only	Gross bleeding; medical intervention indicated	Transfusion or surgical intervention required	Life threatening consequences; open surgery indicated; necrosis	Death
Dysuria	None	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	
Urinary Incontinence	None	Occasional, pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated	Surgical intervention indicated	
Urinary Frequency/ Urgency	None	Increase up to 2x normal	Increase > 2x normal but less than hourly	More than hourly; catheter indicated		
Urinary retention	None	Dribbling	Hesitancy requiring medication	More than daily catheterization indicated; urological intervention indicated	Life-threatening consequences	Death
Fatigue	None	Mild fatigue over baseline	Moderate fatigue causing difficulty performing ADL	Severe fatigue interfering with ADL	Disabling	

Figure 2: Summary of acute toxicity scoring using the Common Toxicity Criteria version 3.0 guidelines.

Methods

Patient Selection

Patients eligible for inclusion in this study had histologically confirmed adenocarcinoma of the prostate, clinical stage T1c-T3b, and a baseline AUA score of less than 20. Exclusion criteria included clinically involved lymph nodes on imaging; distant metastases on bone scan; prior pelvic radiotherapy or prior radical prostate surgery. Androgen deprivation therapy was administered at the discretion of the treating Urologist. Institutional IRB approval was obtained for the treatment protocol. All patients signed a consent form.

SBRT Treatment Planning and Delivery

All patients had at least four gold fiducials placed in the prostate prior to treatment planning: two at the apex and two at the base. To allow for fiducial stabilization, planning imaging was performed at least 7 days after fiducial placement. Patients underwent 1.5 T MR imaging followed shortly thereafter by a thin cut (1.25 mm) CT scan. Both scans were performed with an empty bladder. Patients were advised to adhere to a low-gas, low-motility diet, starting at least five days prior to all treatment planning imaging and treatment delivery. They were nothing by mouth (NPO) the

night before and an enema was administered 1-2 hours prior to imaging and treatment.

Fused CT and MR images were used for treatment planning. The clinical target volume (CTV) included the prostate, areas of radiographic extracapsular extension and the proximal seminal vesicles to the point where the left and right seminal vesicle separate (Figure 1A & B). The SBRT planning target volume (PTV1) equaled the CTV expanded 3 mm posteriorly and 5 mm in all other dimensions. The prescription dose was 19.5 Gy to the PTV1 delivered in three fractions of 6.5 Gy over 3-5 days with some patients receiving treatments on 3 consecutive days and some patients receiving treatment on alternating days. The volume of the PTV1 receiving 19.5 Gy, termed the V19.5 Gy, was to be at least 95%. Variations of the V19.5 Gy that were less than 95%, but greater than or equal to 90%, were considered minor variations; whereas major variations occurred when the V19.5 Gy was less than 90%. The prescription isodose line was limited to $\geq 75\%$ which limited the maximum prostatic urethra dose to 133% of the prescription dose. For the CTV, at least 95% of the volume was to receive 21 Gy (V21 Gy). Variations were considered minor if the V21 Gy was less than 95%, but greater than or equal to 90%; whereas variations less than 90% were considered major. The rectum, bladder, penile bulb and membranous urethra were contoured structures

Table I
Pre-treatment patient characteristics.

#	Race	PSA (ng/ml)	T Stage	Gleason Score	Prostate Volume (cc)	Risk Group	AUA	SHIM	ADT
1	AA	11.1	1c	3 + 3	49	Intermediate	12	3	No
2	C	2.5	2a	4 + 3	15	Intermediate	13	1	Yes
3	AA	4.4	1c	4 + 3	50	Intermediate	0	15	No
4	C	4.8	2a	4 + 3	34	Intermediate	3	25	No
5	AA	6.2	1c	4 + 3	31	Intermediate	10	15	No
6	AA	6.5	1c	3 + 4	36	Intermediate	8	4	No
7	C	6.6	2b	3 + 4	20	Intermediate	8	11	No
8	AA	7.9	1c	3 + 4	60	Intermediate	2	1	Yes
9	C	8.2	1c	4 + 3	45	Intermediate	5	2	Yes
10	AA	10	1c	4 + 3	33	Intermediate	9	9	No
11	AA	10	1c	3 + 4	30	Intermediate	0	4	No
12	AA	11.4	1c	3 + 4	22	Intermediate	4	20	No
13	C	14	1c	3 + 4	33	Intermediate	5	9	No
14	C	15.7	2c	3 + 4	25	High	7	1	Yes
15	C	23.1	1c	3 + 4	33	High	8	20	No
16	AA	25	1c	4 + 3	42	High	0	15	No
17	C	26	1c	4 + 3	30	High	16	1	Yes
18	AA	3.9	1c	4 + 4	37	High	9	3	Yes
19	AA	5.7	1c	3 + 5	25	High	2	23	Yes
20	C	7.7	2b	4 + 4	127	High	6	2	Yes
21	C	11.5	1c	4 + 4	45	High	12	1	Yes
22	AA	16.3	1c	4 + 4	80	High	2	1	No
23	AA	27.3	1c	4 + 4	30	High	5	15	No
24	AA	4.7	1c	4 + 5	43	High	9	16	Yes

Table II

Treatment characteristics. (A) Shown are the mean of the treatment planning parameters (percent target coverage, prescription isodose line and critical structure dose/volume results), the percent of treatment plans that met the protocol's goals and the percent that were minor and major variations from protocol. Percentage of rectum receiving 50%, 80%, 90% and 100% of the prescription dose is reported as rectum V50, V80, V90 and V100, respectively. (B) Summary of the extent of minor and major treatment variations. The treatment planning goals are in parentheses.

A					
Treatment Characteristic	Mean	Per Protocol	Minor Variations	Major Variations	
CTV	95%	70%	25%	5%	
PTV1	95%	87%	13%	0%	
Isodose Line	79%	100%	0%	0%	
Bladder (V19.5Gy)	8.1 cc	92%	8%	0%	
Penile Bulb (V15Gy)	8.0%	100%	0%	0%	
Mem. Urethra (V18Gy)	37%	87%	13%	0%	
Rectum (V19.5Gy)	0.8 cc	92%	8%	0%	
Rectum V50	47%	NA	NA	NA	
Rectum V80	13%	NA	NA	NA	
Rectum V90	6%	NA	NA	NA	
Rectum V100	1.1%	NA	NA	NA	
B					
Patient	PTV1 (>95%)	CTV (>95%)	Rectum (<1 cc)	Bladder (<10 cc)	Mem. Urethra (<50%)
2	-	-	1.3 cc	-	51%
5	-	93.0%	-	-	-
7	-	-	-	-	52%
8	94.8%	92.4%	-	-	-
9	-	-	1.5 cc	-	-
13	-	-	-	-	53%
15	-	88.2%	-	-	-
19	94.2%	93.5%	-	10.7 cc	-
20	-	94.8%	-	-	-
21	-	91.4%	-	-	-
22	94.6%	91.0%	-	-	-
23	-	-	-	10.7 cc	-

and evaluated with dose-volume histogram analysis during treatment planning using Multiplan (Accuray Inc., Sunnyvale, CA) inverse treatment planning. The neurovascular bundles and prostatic urethra were not contoured as planned due to poor visualization on the 1.5 T treatment planning MRI. The rectal contour included the lumen and rectal wall from the anal canal to the rectosigmoid flexure. The bladder and bowel contours were the larger composites of the MRI and CT volumes. Sigmoid colon and other bowel adjacent to the PTV1 were contoured if present. Our rectal dose-volume histogram (DVH) goals were <50% rectal volume receiving 50% of the prescribed dose, <20% receiving 80% of the dose, <10% receiving 90% of the dose, and <5% receiving 100% of the dose (17). Dose and volume constraints to the critical structures are summarized in Figure 1C.

Table III

Summary of CTC graded acute gastrointestinal (GI) and genitourinary (GU) toxicities.

Gastrointestinal Toxicity	Grade	Pre-Treatment		On-Treatment		1 Month		3 Month		6 Month	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Diarrhea	0	21	(88)	13	(54)	18	(75)	18	(75)	19	(79)
	1	3	(13)	10	(42)	5	(21)	6	(25)	5	(21)
	2	0	(0)	1	(4)	1	(4)	0	(0)	0	(0)
Proctitis	0	24	(100)	17	(71)	17	(71)	19	(79)	19	(79)
	1	0	(0)	7	(29)	7	(29)	5	(21)	5	(21)
	2	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Rectal Bleeding	0	23	(96)	21	(88)	22	(92)	24	(100)	24	(100)
	1	1	(4)	3	(13)	2	(8)	0	(0)	0	(0)
	2	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Highest GI	0	21	(88)	11	(46)	15	(63)	15	(63)	16	(67)
	1	3	(13)	12	(50)	8	(33)	9	(38)	8	(33)
	2	0	(0)	1	(4)	1	(4)	0	(0)	0	(0)
Genitourinary Toxicity											
Hematuria	0	24	(100)	22	(92)	24	(100)	23	(96)	23	(96)
	1	0	(0)	2	(8)	0	(0)	1	(4)	1	(4)
	2	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Dysuria	0	19	(79)	14	(58)	15	(63)	16	(67)	18	(75)
	1	4	(17)	8	(33)	6	(25)	7	(29)	5	(21)
	2	1	(4)	2	(8)	3	(13)	1	(4)	1	(4)
Incontinence	0	21	(88)	22	(92)	20	(83)	22	(92)	21	(88)
	1	1	(4)	0	(0)	2	(8)	1	(4)	2	(8)
	2	2	(8)	2	(8)	2	(8)	1	(4)	1	(4)
Urinary Frequency/Urgency	0	24	(100)	12	(50)	21	(88)	22	(92)	22	(92)
	1	0	(0)	12	(50)	3	(13)	2	(8)	2	(8)
	2	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Retention	0	11	(46)	11	(46)	8	(33)	8	(33)	14	(58)
	1	12	(50)	10	(42)	15	(63)	15	(63)	9	(38)
	2	0	(0)	3	(13)	1	(4)	1	(4)	1	(4)
Highest GU	0	9	(38)	3	(13)	5	(21)	6	(25)	11	(46)
	1	13	(54)	18	(75)	15	(63)	15	(63)	11	(46)
	2	2	(8)	3	(13)	4	(17)	3	(13)	2	(8)

IMRT

The protocol was designed to deliver a total radiation dose to the PTV1 biologically equivalent to 92.1 Gy in 2 Gy fractions assuming an α/β ratio of 1.5 Gy. To achieve this, all patients were treated with IMRT immediately following SBRT. For all IMRT treatments fiducial guidance was used for set-up. The more generous PTV2 included a margin of 1.0 cm around the CTV except at the rectal interface where a margin of 0.5 cm was added. Daily doses of 1.8 Gy were delivered to the PTV2 5 days a week to a total dose of 50.4 Gy in 28 fractions. The minimum target dose constraint to the PTV2 was 49.5 Gy and the maximum target dose constraint was 53 Gy. In addition, 100% of the PTV2 was to receive at least 95% of the prescription dose and 5% of the volume was to receive no more than 105% of the prescription dose. For the bladder and rectum,

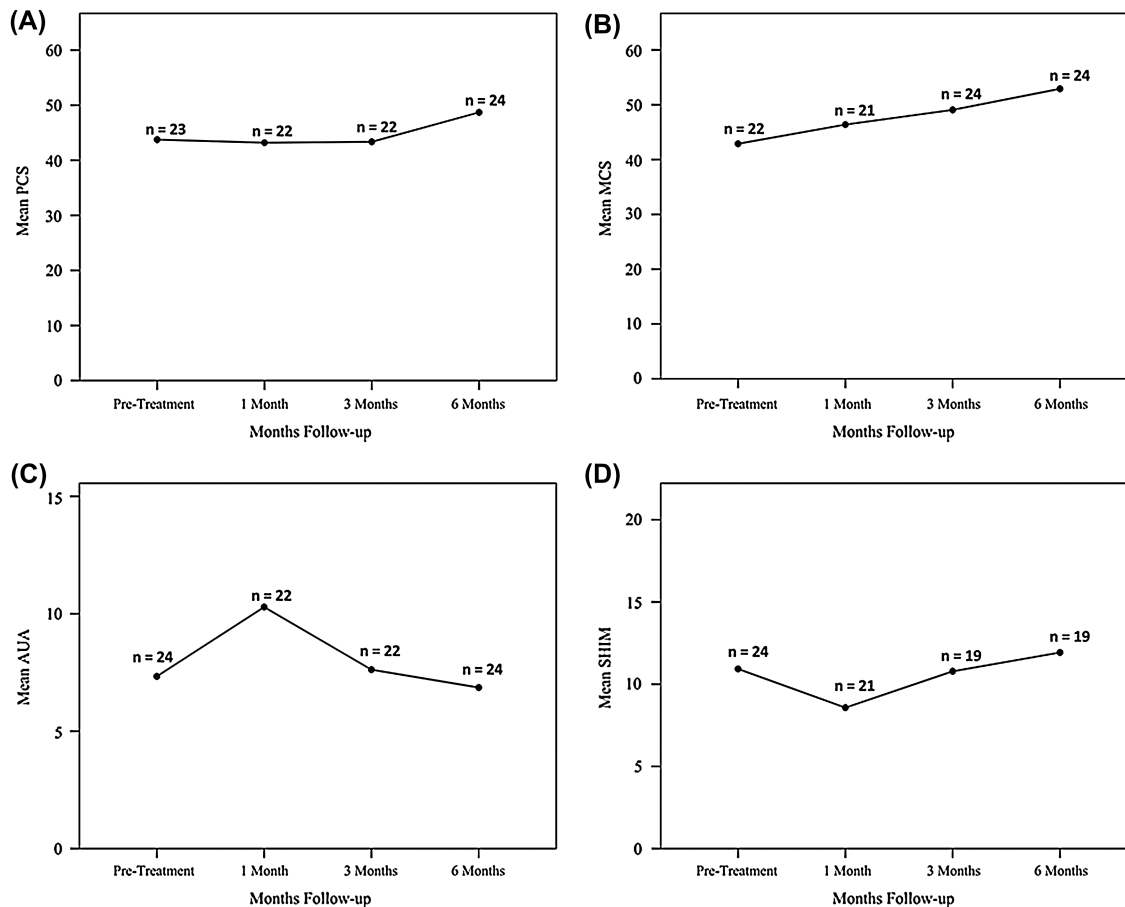


Figure 3: Summary of patient quality of life: (A) SF-12 physical component (PC) score, (B) SF-12 mental component (MC) score, (C) AUA score and (D) SHIM score. The graphs show unadjusted changes in mean toxicity and QOL scores over time. SF-12 scores range from 0-100 with higher values representing improved health status. AUA scores range from 0-35 with higher values representing worsening urinary symptoms. SHIM scores range from 0-25 with lower values representing worsening sexual function. Numbers above each time point indicate the number of observations contributing to the mean.

the maximum dose constraint limit was 50 Gy, the full-volume dose constraint limit was 30 Gy and no part of either volume received more than 55.5 Gy. Dose to the femoral heads was limited to 45 Gy.

Follow-up

Acute toxicity was defined as those events that presented and resolved within the first 6 months following completion of treatment. Toxicity was assessed pre-treatment, during treatment and at 1, 3 and 6 months using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 3.0 (Figure 2) and the American Urological Association (AUA) symptom score (also known as International Prostate Symptom Score) (18). Quality of life (QoL) was assessed pre-treatment and at follow-up visits using the Short Form-12 Health Survey (SF-12), the Expanded Prostate Cancer Index Composite (EPIC) questionnaire (19) and the Sexual Health Inventory for Men (SHIM) questionnaire (20).

Statistical Methods

A pilot protocol was written to test whether patients could have CyberKnife plans developed and delivered with no major treatment planning variations, with early stopping if there was 1 major variation in the first 10 patients. Toxicity and treatment planning variations have been tabulated. Differences in ongoing quality of life scores were compared to baseline using paired t-tests. Mean scores at baseline, 1, 3, and 6 months were presented graphically.

Results

From April 2008 to April 2009, 24 prostate cancer patients were accrued for the IRB approved protocol. The median patient age was 68.5 years (range, 47-80 years). Similar numbers of Caucasians (C) and African Americans (AA) were enrolled reflecting the distribution of our normal patient population. Thirteen patients were intermediate-risk and eleven were high-risk using the D'Amico Risk

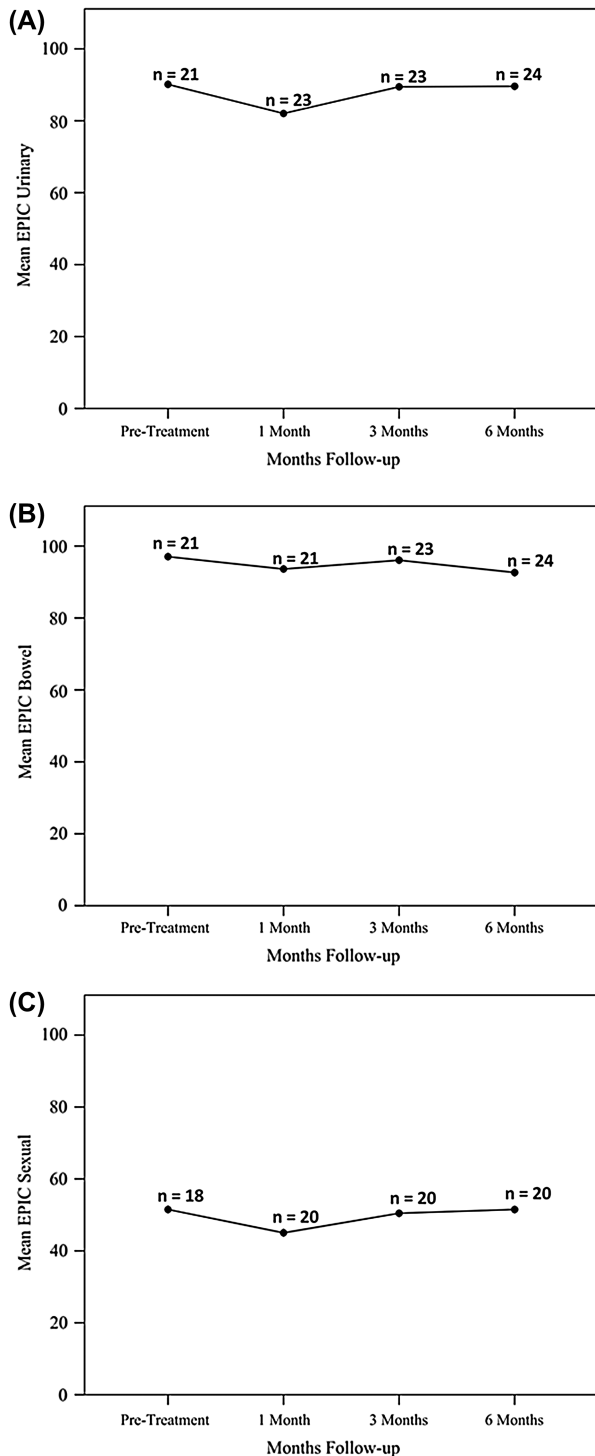


Figure 4: EPIC quality of life for (A) urinary, (B) bowel, and (C) sexual function. The graphs show unadjusted changes in mean QOL scores over time for each domain. EPIC scores range from 0-100 with higher values representing a more favorable health-related QOL. Numbers above each time point indicate the number of observations contributing to the mean.

Classification (21). Baseline median PSA was 9.1 ng/ml (range, 2.5-27.3 ng/ml). Forty-two percent of patients received androgen deprivation therapy (ADT). For patients who did

not receive ADT, the median pre-treatment PSA was 10.6 ng/ml. Table I provides detailed patient characteristics.

Table IIA provides a summary of the treatment characteristics. Minor protocol variations occurred in 50% of the patients, but these were small deviations from the planned treatment and likely of little clinical significance (Table IIB). One major variation from the treatment protocol occurred. In this case, the dose to the CTV was limited to maintain the rectal dose within protocol limits. Our rectal DVH goals were obtained in most patients.

At an average follow-up of 9.3 months (range: 6.6-16.9 months), the initial PSA response has been favorable. The median 6 month post-treatment PSA was 1.5 ng/ml for patients who did not receive ADT. Toxicity has been minimal with no Grade 3 or higher gastrointestinal (GI) or gastrourinary (GU) toxicities (Table III). Grade 2 toxicities included urinary symptoms requiring alpha blockers and bowel frequency/spasms requiring antidiarrheals.

Figures III and IV present a summary of the changes in quality of life indicators over time. By six months post-treatment, the patients' perceptions of their physical health (Figure 3A) and mental health (Figure 3B) had improved. In the case of mental health, this improvement was significant ($p = 0.03$; Table IV). At one month post-treatment the mean AUA toxicity scores had increased to a value of 10.7 from a baseline of 7.4 ($p = 0.01$; Figure 3C, Table IV). By 6-months post-treatment the mean AUA toxicity score had returned to baseline. Similarly, at one month post-treatment the mean SHIM scores had decreased to a value of 8.6 from a baseline of 10.9 (Figure 3D). Mean SHIM quality of life returned to baseline by 6 months (Table IV). As with the AUA and SHIM scores, the EPIC urinary and EPIC sexual scores decreased at one month and returned to baseline by 6 months (Figures IVA and IVC, Table IV). The mean EPIC bowel score decreased slightly at one month and six months (Figure IVB). However, the decrease at six months was not significant (Table IV).

Discussion

This study aimed at assessing the feasibility and safety of performing IMRT with CyberKnife SBRT boost for intermediate- to high-risk clinically localized prostate cancer. Hypofractionated SBRT boost was chosen for this study due to the potential benefits of hypofractionation (8) including radiobiologic dose escalation. In addition, SBRT does not require anesthesia and/or hospitalization expanding its potential utilization in the elderly prostate cancer patient population.

Acute Grade 2 GU toxicities and GI toxicities were observed in 13% and 4% of patients, respectively. There were no toxicities

Table IV
Overview of patient quality of life (QoL).

QoL Measure	Pre-Treatment	1 Month	3 Month	6 Month
SF-12 PCS	43.8 (0–61.6)	43.2 (0–61.5)	43.4 (0–59.5)	48.7 (22.9–62.9)
SF-12 MCS	42.9 (0–64.3)	46.4 (0–63.7)	49.1 (0–61.7)	52.9 (34.4–62.6)
AUA	7.4 (0–24)	10.7 (0–22)	7.7 (0–16)	7.1 (0–25)
SHIM	10.9 (1–25)	8.6 (1–25)	10.8 (1–25)	11.9 (1–25)
EPIC Urinary	90.1 (71.3–100)	82.0 (52.8–100)	89.4 (71.3–100)	89.6 (71.3–100)
EPIC Bowel	97.1 (83.3–100)	93.6 (62.5–100)	96.1 (75–100)	92.6 (37.5–100)
EPIC Sexual	51.5 (12.5–91.7)	45.0 (0–91.7)	50.5 (4.2–91.7)	51.5 (9.7–91.7)

The table shows unadjusted changes in mean toxicity and QOL scores over time. SF-12 scores range from 0-100 with higher values representing improved health status. AUA scores range from 0-35 with higher values representing worsening urinary symptoms. SHIM scores range from 0-25 with lower values representing worsening sexual function. EPIC scores range from 0-100 with higher values representing a more favorable health-related QOL. **Bold numbers** designate time points at which scores differed significantly from pre-treatment ($p < 0.05$).

greater than Grade 2. In comparison, published brachytherapy boost publications have reported acute Grade 2 and 3 GU toxicity rates ranging from 5.5-22.5% and 1.8-3.9%, respectively; reported Grade 2 GI toxicities for HDR boost have ranged from 3.9-7% (16-19). Table V provides an overview of observed acute toxicities for prostate boost publications reporting with the CTC criteria. Our results appear comparable to others.

Preliminary quality of life also appears favorable with AUA, SHIM and EPIC scores returning to baseline by six months after treatment. A study of prostate cancer patient quality of

life using EPIC examined patients treated with external beam radiation therapy (EBRT) alone, EBRT plus low dose rate (LDR) brachytherapy and LDR brachytherapy alone (22). At six months, EPIC scores had not returned to baseline.

Summary

Hypofractionated SBRT combined with IMRT is a promising new treatment option for men with intermediate- and high-risk prostate cancer. Acute toxicity in this pilot study was minimal and the treatment appears well

Table V
Summary of brachytherapy boost publications reporting CTC acute toxicity.

GU Toxicity	Grade	Hurwitz et al. (23) EBRT + LDR	Valero et al. (24) EBRT + HDR	Martin et al. (25) 3DCRT + HDR	Sato et al. (26) HDR + EBRT	Current Study IMRT + CyberKnife
Hematuria	2	–	0%	–	–	0%
	3	–	0%	–	–	0%
Dysuria	2	5%	2.2%	–	–	4%
	3	3%	0%	–	–	0%
Incontinence	2	5%	0%	–	–	0%
	3	0%	0%	–	–	0%
Urinary Frequency	2	16%	6%	–	–	0%
Urgency	3	2%	0%	3.9%	–	0%
Retention	2	7%	0.7%	–	–	13%
	3	0%	3.0%	–	–	0%
Overall	2	–	–	22.5%	5.5%	13%
	3	–	3.0%	3.9%	1.8%	0%
GI Toxicity						
Diarrhea	2	–	2.2%	–	–	4%
	3	–	0.7%	–	–	0%
Proctitis	2	7%	4.5%	–	–	0%
	3	0%	0%	–	–	0%
Rectal Bleeding	2	–	0%	–	–	0%
	3	–	0%	–	–	0%
Overall	2	–	–	7.8%	3.8%	4%
	3	–	0.7%	0%	0%	0%

A ‘–’ indicates the value was not reported in that publication.

tolerated with little impact on quality of life. Early results suggest encouraging biochemical response with low toxicity. These data provide a basis for the design of a phase II clinical trial.

Conflicts of Interest: None.

Acknowledgements

We acknowledge Robert Meier, M.D, Solomon B. Makgoeng, Kathryn Taylor, Ph.D. and Arnold L. Potosky, Ph.D. for helpful discussions. We gratefully acknowledge the editorial assistance of Pam Commike, Ph.D., Accuray Incorporated. The views expressed here are entirely the authors'; Accuray did not provide assistance with data collection, compilation, or interpretation.

References

- Fuks, Z., Leibel, S. A., Wallner, K. E., Begg, C. B., Fair, W. R., Anderson, L. L., Hilaris, B. S., Whitmore, W. F. The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation. *Int J Radiat Oncol Biol Phys* 21, 537-547 (1991).
- Dearnaley, D. P., Khoo, V. S., Norman, A. R., Meyer, L., Nahum, A., Tait, D., Yarnold, J., Horwich, A. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 353, 267-272 (1999).
- Beard, C. J., Kaplan, I. D., Coleman, C. N. The challenge for conformal therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 26, 705-707 (1993).
- Zelevsky, M. J., Chan, H., Hunt, M., Yamada, Y., Shippy, A. M., Amols, H. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol* 176, 1415-1419 (2006).
- Kuban, D. A., Levy, L. B., Cheung, M. R., Lee, A. K., Choi, S., Frank, S., Pollack, A. Long-term Failure Patterns and Survival in a Randomized Dose-Escalation Trial for Prostate Cancer. *Who Dies of Disease? Int J Radiat Oncol Biol Phys*, In Press.
- Stone, N. N., Potters, L., Davis, B. J., Ciezki, J. P., Zelevsky, M. J., Roach, M., Shinohara, K., Fearn, P. A., Kattan, M. W., Stock, R. G. Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with Gleason score 7-10 prostate cancer treated with permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 73, 341-346 (2009).
- Martinez, A. A., Gustafson, G., Gonzalez, J., Armour, E., Mitchell, C., Edmundson, G., Spencer, W., Stromberg, J., Huang, R., Vicini, F. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer. *Int J Radiat Oncol Biol Phys* 53, 316-327 (2002).
- Fowler, J. F. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. *Acta Oncol* 44, 265-276 (2005).
- Phan, T. P., Syed, A. M., Puthawala, A., Sharma, A., Khan, F. High dose rate brachytherapy as a boost for the treatment of localized prostate cancer. *J Urol* 177, 123-127; discussion 127 (2007).
- Demanis, D. J., Rodriguez, R. R., Schour, L., Brandt, D., Altieri, G. High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. *Int J Radiat Oncol Biol Phys* 61, 1306-1316 (2005).
- Galalae, R. M., Martinez, A., Mate, T., Mitchell, C., Edmundson, G., Nuernberg, N., Eulau, S., Gustafson, G., Gribble, M., Kovacs, G. Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 58, 1048-1055 (2004).
- Hiratsuka, J., Jo, Y., Yoshida, K., Nagase, N., Fujisawa, M., Imajo, Y. Clinical results of combined treatment conformal high-dose-rate iridium-192 brachytherapy and external beam radiotherapy using staging lymphadenectomy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 59, 684-690 (2004).
- Webb, S. Conformal intensity-modulated radiotherapy (IMRT) delivered by robotic linac--testing IMRT to the limit? *Phys Med Biol* 44, 1639-1654 (1999).
- Hossain, S., Xia, P., Huang, K., Descovich, M., Chuang, C., Gottschalk, A. R., Roach, M., III, Ma, L. Dose Gradient Near Target-Normal Structure Interface for Nonisocentric CyberKnife and Iso-centric Intensity-Modulated Body Radiotherapy for Prostate Cancer. *Int J Radiat Oncol Biol Phys*, In Press.
- Fuller, D. B., Naitoh, J., Lee, C., Hardy, S., Jin, H. Virtual HDR CyberKnife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. *Int J Radiat Oncol Biol Phys* 70, 1588-1597 (2008).
- Xie, Y., Djajaputra, D., King, C. R., Hossain, S., Ma, L., Xing, L. Intrafractional motion of the prostate during hypofractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 72, 236-246 (2008).
- King, C. R., Brooks, J. D., Gill, H., Pawlicki, T., Cotrutz, C., Presti, J. C., Jr. Stereotactic Body Radiotherapy for Localized Prostate Cancer: Interim Results of a Prospective Phase II Clinical Trial. *Int J Radiat Oncol Biol Phys* 73, 1043-1048 (2009).
- Barry, M. J., Fowler, F. J., Jr., O'Leary, M. P., Bruskewitz, R. C., Holtgrewe, H. L., Mebust, W. K., Cockett, A. T. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 148, 1549-1557; discussion 1564 (1992).
- Wei, J.T., Dunn, R. L., Litwin, M. S., Sandler, H. M., Sanda, M. G. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 56, 899-905 (2000).
- Rosen, R. C., Cappelleri, J. C., Gendrano, N, III. The International Index of Erectile Function (IIEF): a state-of-the-science review. *Int J Impot Res* 14, 226-244 (2002).
- D'Amico, A. V., Whittington, R., Malkowicz, S. B., Schultz, D., Blank, K., Broderick, G. A., Tomaszewski, J. E., Renshaw, A. A., Kaplan, I., Beard, C. J., Wein, A. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *Jama* 280, 969-974 (1998).
- Sanda, M. G., Dunn, R. L., Michalski, J., Sandler, H. M., Northouse, L., Hembroff, L., Lin, X., Greenfield, T. K., Litwin, M. S., Saigal, C. S., Mahadevan, A., Klein, E., Kibel, A., Pisters, L. L., Kuban, D., Kaplan, I., Wood, D., Ciezki, J., Shah, N., Wei, J. T. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 358, 1250-1261 (2008).
- Hurwitz, M. D., Halabi, S., Ou, S. S., McGinnis, L. S., Keuttel, M. R., Dibiase, S. J., Small, E. J. Combination external beam radiation and brachytherapy boost with androgen suppression for treatment of intermediate-risk prostate cancer: an initial report of CALGB 99809. *Int J Radiat Oncol Biol Phys* 72, 814-819 (2008).
- Valero, J., Cambeiro, M., Galan, C., Teixeira, M., Romero, P., Zudaire, J., Moreno, M., Ciervide, R., Aristu, J. J., Martinez-Monge R. Phase II Trial of Radiation Dose Escalation with Conformal External Beam Radiotherapy and High-Dose-Rate Brachytherapy

- Combined with Long-Term Androgen Suppression in Unfavorable Prostate Cancer: Feasibility Report. *Int J Radiat Oncol Biol Phys* 76, 386-392 (2009).
25. Martin, T., Roddiger, S., Kurek, R., Dannenberg, T., Eckart, O., Kolotas, C., Heyd, R., Rogge, B., Baltas, D., Tunn, U., Zamboglou, N. 3D conformal HDR brachytherapy and external beam irradiation combined with temporary androgen deprivation in the treatment of localized prostate cancer. *Radiother Oncol* 71, 35-41 (2004).
26. Sato, M., Mori, T., Shirai, S., Kishi, K., Inagaki, T., Hara, I. High-dose-rate brachytherapy of a single implant with two fractions combined with external beam radiotherapy for hormone-naive prostate cancer. *Int J Radiat Oncol Biol Phys* 72, 1002-1009 (2008).

Received: May 1, 2010; Revised: June 10, 2010;

Accepted: July 26, 2010