

Health-Related Quality of Life and Toxicity After Definitive High-Dose-Rate Brachytherapy Among Veterans With Prostate Cancer

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Purpose: High-dose-rate (HDR) brachytherapy (BT) is a well-tolerated and effective treatment for prostate cancer. There is limited research, however, investigating toxicity outcomes with HDRBT treatment among veterans. The objective of this study is to assess the impact on health-related quality of life (hrQOL) and physician-graded toxicities associated with HDRBT as monotherapy among veterans treated at Edward Hines, Jr. Veterans Affairs Hospital in Hines, Illinois.

Methods: Between 2016 and 2019, 74 veterans with low- or intermediate-risk prostate cancer were treated with HDRBT as monotherapy with 27 Gy in 2 fractions, delivered over 2 implants. Veteran-reported hrQOL in the genitourinary (GU), gastrointestinal (GI), and sexual domains was assessed using the International Prostate Symptoms Score (IPSS) and Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire. Mixed linear effect models were used to assess differences in the hrQOL scores at follow-up compared with baseline scores. Statistically significant differences in hrQOL scores from baseline were further assessed for clinical significance, using minimal clinically important difference (MCID) evaluations.

Results: Median follow-up was 18 months. Veterans reported declines in GU, GI, and sexual hrQOL scores immediately after treatment, with the IPSS and EPIC-26 hrQOL scores all displaying significant decrease from baseline over time. The majority of the declines in hrQOL scores met criteria for MCID. These hrQOL scores trended toward a return to baseline, with the EPIC-26 urinary obstruction score returning to baseline at the 18-month follow-up assessment and the EPIC-26 bowel score returning to baseline at the 12-month follow-up. The IPSS, urinary incontinence, and sexual scores did not return to baseline at 18 months. The grade 2 maximum physician-graded GU, GI, and sexual toxicity rates were 65%, 5%, and 53%, respectively. There was 1 incidence of grade 3 GU toxicity but no grade 3 GI or sexual toxicity.

Conclusions: HDRBT as monotherapy is a well-tolerated treatment option for veterans with low- or intermediate-risk prostate cancer, with favorable veteran-reported and physician-graded toxicities. Veterans should be educated about HDRBT as an option when counseled regarding treatment for localized prostate cancer.

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Nearly 50,000 veterans are diagnosed with cancer within the Veterans Health Administration annually with prostate cancer (PC) being the most frequently diagnosed, accounting for 29% of all cancers diagnosed.¹ The treatment of PC depends on the stage and risk group at presentation and patient preference. Men with early stage, localized PC can be managed with prostatectomy, radiation therapy, or active surveillance.²

Within the Veterans Health Administration, more patients are treated with radiation therapy than with radical prostatectomy.³ This is in contrast to the civil health system, where more patients are treated with radical prostatectomy than with radiation therapy.^{4,5} Radiation therapy for PC can be given externally with external beam radiation therapy or internally with brachytherapy (BT). BT is categorized by the rate at which the radiation dose is delivered and generally grouped as low-dose rate (LDR) or high-dose rate (HDR). LDRBT consists of permanently implanting radioactive seeds, which slowly deliver a radiation dose over an extended period. HDRBT consists of implanting catheters that allow delivery of a radio-

active source to be placed temporarily in the prostate and removed after treatment. The utilization of HDRBT has become more common as treatment has evolved to consist of fewer, larger fractions in a shorter time, making it a convenient treatment option for men with PC.⁶

The veteran population has singular medical challenges. These patients differ from the general population and are often underrepresented in medical research and published studies.⁷ There are no studies exploring the treatment-associated toxicities from HDRBT treatment for PC specifically in the veteran population. The objective of this study is to report our findings regarding the veteran-reported and physician-graded toxicities associated with HDRBT as monotherapy in veterans treated through the US Department of Veterans Affairs (VA) for PC.

METHODS

We performed a retrospective cohort study of a prospectively maintained, institutional review board-approved database of patients treated with HDRBT for PC. Veterans were seen in consultation at Edward Hines, Jr. VA Hospital (EHJVAH) in

Hines, Illinois. This is the only VA hospital in Illinois that offers radiation therapy, so it acted as a tertiary center, receiving referrals from other, neighboring VA hospitals. If the veteran was deemed a good BT candidate and elected to proceed with HDRBT, HDR treatment was performed at a partnering academic institution equipped to provide HDRBT (Loyola University Medical Center).

We selected patients with National Cancer Center Network (NCCN) low- or intermediate-risk PC undergoing definitive HDRBT as monotherapy using 13.5 Gy x 2 fractions delivered over 2 implants that were 1 to 2 weeks apart. Patients who received androgen deprivation therapy (ADT) were excluded from this study. No patients received supplemental external beam radiation. Men with unfavorable intermediate risk PC were offered ADT and BT in accordance with NCCN guidelines. However, patients with unfavorable intermediate-risk PC who declined ADT or who were deemed poor ADT candidates due to comorbidities were treated with HDR as monotherapy and included in this study.⁸

HDR Treatment

Our HDRBT implant procedure and treatment planning details have been previously described.⁹ In brief, patients were implanted with between 17 and 22 catheters based on gland size under transrectal ultrasound guidance. After implantation, computed tomography and, when possible, magnetic resonance imaging of the prostate were obtained and registered for target delineation. The prostate was segmented, and an asymmetric planning target volume of 0 to 5 mm was created and extended to encompass the proximal seminal vesicles. The second fraction was given 1 to 2 weeks after initial treatment, based on patient, physician, and operating room availability.

Health-Related Quality of Life Assessment

Veteran-reported genitourinary (GU), gastrointestinal (GI), and sexual health-related quality of life (hrQOL) were assessed using the validated International Prostate Symptom Score (IPSS) and the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) instruments.^{10,11} Baseline veteran-reported hrQOL scores in the GU, GI, and sexual domains were obtained prior to each veteran's first HDR treatment. Veteran-reported hrQOL scores were assessed at each of the patient's follow-up appointments. Physician-graded toxicity was assessed Common Terminology Cri-

TABLE 1 Veteran Baseline Characteristics

Characteristics	Results
Median follow-up, mo	18
Median age (range), y	68 (47-78)
Median gland size (range), mL	36.2 (14.5-81)
Median PSA (range), ng/mL	7.3 (2.9-16.4)
Prostate-specific antigen, No. (%)	
< 10 ng/mL	60 (81)
10-20 ng/mL	14 (19)
Clinical T-stage, No. (%)	
T1c	57 (77)
T2a	14 (19)
T2b	2 (3%)
T2c	1 (1%)
Gleason grade group, No. (%)	
Group 1	20 (27)
Group 2	41 (55)
Group 3	13 (18)
National Comprehensive Cancer Network risk group, No. (%)	
Low	15 (20)
Favorable intermediate	40 (54)
Unfavorable intermediate	19 (26)

teria for Adverse Events (CTCAE) v 4.03 criteria.¹² Physician-graded toxicity was assessed at each follow-up visit and reported as the highest grade reported during any follow-up examination.

Follow-up appointments typically occurred at 1 month, 3 months, 6 months, 12 months, and subsequently every 6 months after the second HDR treatment. Follow-up appointments were conducted in the radiation oncology department at EHJVAH.

Minimal Clinically Important Differences

To evaluate the veteran-reported hrQOL, we characterized statistically significant differences in IPSS or EPIC-26 scores over time as compared with baseline values as clinically important or not clinically important through the use of reported minimal clinically important difference (MCID) assessments.¹³⁻¹⁵ For the IPSS, we used reported data that showed a change of ≥ 3.0 points represented a clinically meaningful change in urinary function.¹⁴ For the EPIC-26 scores, we used reported data that showed a change of ≥ 6 points for urinary incontinence score, ≥ 5 points for urinary obstruction score, ≥ 4 points for bowel score, and ≥ 10 points for sexual score to represent an MCID.¹⁵

Statistical Analysis

Changes in veteran-reported hrQOL over time were compared using mixed linear effects models, with the time since the last BT

TABLE 2 Veteran Patient-Reported hrQOL Outcomes

QOL Measures		Follow-up Assessment					
		Baseline	1 mo	3 mo	6 mo	12 mo	18 mo
IPSS	No.	71	50	61	54	47	36
	Mean	7.2	15.1	10.2	10.5	9.8	9.8
	95% CI	±1.3	±2.1	±1.7	±1.9	±2.0	±1.9
	Change	---	7.9	3.0	3.3	2.6	2.6
	<i>P</i> value	---	< .001	< .001	< .001	.001	.001
EPIC Urinary Incontinence	No.	46	35	51	51	45	33
	Mean	91.1	80.2	81.3	82.3	81.8	83.7
	95% CI	±4.3	±6.1	±5.4	±5.7	±5.6	±5.1
	Change	---	-10.9	-9.7	-8.8	-9.3	-7.4
	<i>P</i> value	---	.003	.003	< .001	.002	.004
EPIC Urinary Obstruction	No.	48	34	52	51	46	34
	Mean	88.7	66.9	79.1	83.5	82.6	84.0
	95% CI	±3.5	±9.9	±5.6	±4.7	±5.0	±4.6
	Change	---	-21.8	-9.6	-5.2	-6.1	-4.7
	<i>P</i> value	---	< .001	.001	.01	.02	.31
EPIC Bowel	No.	47	35	52	52	46	36
	Mean	92.8	84.6	89.0	88.9	88.7	90.7
	95% CI	±3.3	±6.3	±4.6	±4.6	±5.7	±5.2
	Change	---	-8.2	-3.8	-3.9	-4.1	-2.1
	<i>P</i> value	---	.01	.02	.02	.19	.29
EPIC Sexual	No.	47	34	50	50	45	36
	Mean	51.3	21.7	21.9	18.6	25.7	31.2
	95% CI	±9.1	±8.3	±5.2	±4.9	±6.0	±7.0
	Change	---	-29.8	-29.6	-32.9	-25.7	-20.2
	<i>P</i> value	---	< .001	< .001	< .001	< .001	< .001

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite Short Form; hrQOL, health-related quality of life; IPSS, International Prostate Symptom Score.

implant serving as the fixed variable. Effects were deemed statistically significant if $P < .05$. If a statistically significant difference from baseline was found at any time point, additional evaluation was done to see if the numerical difference in the assessment led to an MCID as described above. IBM SPSS Statistics for Windows, version 25.0 was used for data analysis.

RESULTS

Seventy-four veterans were included in the study. The median follow-up was 18 months (range 1-43). The demographic and oncologic specifics of the treated veterans are outlined in Table 1.

There was a significant increase in IPSS ($P < .001$) with reciprocal decline in EPIC-26 urinary incontinence ($P = .008$) and EPIC-26 urinary obstruction scores ($P = .001$) from baseline over time (Table 2 and Figure 1). At the 18-month follow-up assessment, there was no longer a significant difference in the EPIC-26 urinary obstruction score from baseline (88.7 vs 84.0, $P = .31$). The increases in IPSS at the 1-, 3-, and 6-month assessments met the criteria for MCID. The decrease in EPIC-26 urinary incontinence scores at the 1-, 3-, 6-, 12-, and 18-month assessments were found to be an MCID, as were the decrease

in EPIC-26 urinary obstruction scores at the 1-, 3-, 6-, and 12-month assessments.

There was a significant decline in EPIC-26 bowel scores from baseline over time ($P = .03$). The decline in the EPIC-26 bowel hrQOL scores at the 1-, 3-, and 6-month follow-up assessment were significantly different from the baseline value. However, only the decrease seen at the 1-month assessment met criteria for MCID.

There was a significant decline in EPIC-26 sexual scores from baseline over time ($P < .001$). The decline in EPIC-26 sexual score noted at each follow-up compared with baseline was statistically significant. Each of these declines met criteria for an MCID.

The rate of grade 2 GU, GI, and sexual physician-graded toxicity was 65%, 5%, and 53%, respectively (Figure 2). There was a single incident of grade 3 GU toxicity, which was a urethral stricture. There were no reported grade 3 GI or sexual toxicities, nor were there grade 4 or 5 toxicities. There were 5 total incidents of acute urinary retention for a 6.8% rate overall.

DISCUSSION

We performed a retrospective study of veterans with low- or intermediate-risk PC undergoing

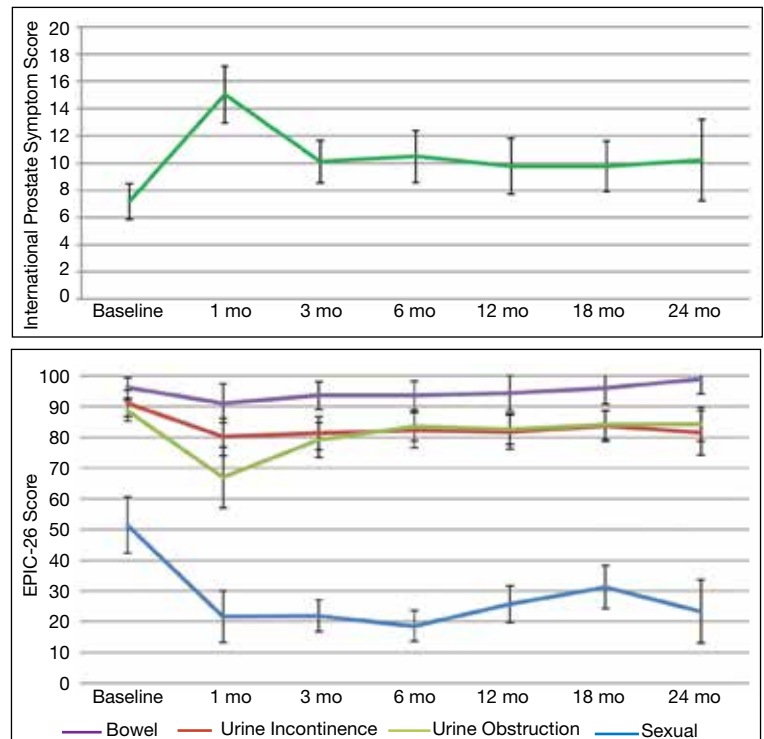
definitive HDR prostate BT as monotherapy. We found that veterans experienced immediate declines in GU, GI, and sexual hrQOL after treatment. However, each trended toward a return to baseline over time, with the EPIC-26 urinary obstruction and the EPIC-26 bowel scores showing no difference from the baseline value within 18 months and 12 months, respectively. The physician-reported toxicities were low, with only 1 incidence of grade 3 GU toxicity, no grade 3 GI or sexual toxicities, and no grade 4 or 5 toxicity. This suggests that HDRBT is a well-tolerated and safe, definitive treatment for veterans with localized PC.

In a series similar to ours, Gaudet and colleagues reported on their single institutional results of treating 30 low- or intermediate-risk PC patients with HDRBT as monotherapy.¹⁶ Patients included in their study were civilians from the general population, treated in a similar fashion to the veterans treated in our study. Each patient received 27 Gy in 2 fractions given over 2 implants. The authors collected patient-reported hrQOL results using the IPSS and EPIC questionnaires and found that 57% of patients treated experienced moderate-to-severe urinary symptoms at the 1-month assessment after implantation, with a rapid recovery toward baseline over time. In contrast, GI symptoms did not change from baseline, while sexual symptoms worsened after implantation and failed to return to baseline.

Our results mirror this experience, with similar rates of patient-reported hrQOL scores and physician-graded toxicities. Patients reported similar rates of decline in GU, GI, and sexual hrQOL after treatment. The patient-reported GU and GI hrQOL scores worsened immediately after treatment, with a return toward baseline over time. However, the patient-reported sexual hrQOL dropped after treatment and had a subtle trend toward a return to baseline. Our data show higher rates of maximum physician-graded GU toxicity rates of 23%, 65%, and 1% grade 1, 2, and 3, respectively. This is likely due in part to our prophylactic use of tamsulosin. Patients who continued tamsulosin after the implant out of preference were technically grade 2 based on CTCAE v5.0 criteria. GI and sexual toxicity were substantially lower with rates of 15% and 5% grade 1 and grade 2 bowel toxicity with no grade 3 events, and 15% and 52% grade 1 and grade 2 sexual toxicity, respectively.

Contreras and colleagues also reported on treating civilian patients with HDRBT as

FIGURE 1 Veteran-Reported Health-Related Quality of Life Scores and 95% CI



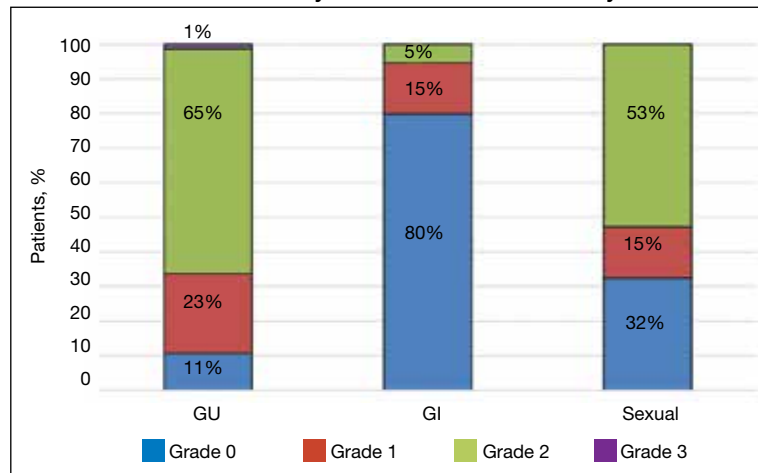
Abbreviations: EPIC, Expanded Prostate Cancer Index Composite Short Form; hrQOL, health-related quality of life.

monotherapy for PC.¹⁷ They, too, found similar results as in our veteran study, with a rapid decline in GU, GI, and sexual hrQOL scores immediately after treatment. They also found a gradual return to baseline in the GU hrQOL scores. Contrary to our results, they reported a return to baseline in sexual hrQOL scores, while their patients did not report a return to baseline in the GI hrQOL scores.

Limitations

To the authors' knowledge, there are no other studies exploring HDR prostate BT toxicity in a veteran-specific population, and our study is novel in addressing this question. One limitation of the study is the relatively short median follow-up time of 18 months. With this limitation, our data were not yet sufficiently mature to perform biochemical control or overall survival analyses. The next step in our study is to calculate these clinical endpoints from our data after longer follow-up.

An additional limitation to our study is the single institutional nature of the design. While veterans from neighboring VA hospitals were

FIGURE 2 Maximum Physician-Graded Toxicity

Abbreviations: GI, gastrointestinal; GU, genitourinary.

included in the study by way of referral and treatment at our center, the only VA hospital in the state to provide radiation therapy, our patient population remains limited. Further multi-institutional and prospective data are needed to validate our findings.

CONCLUSIONS

HDR prostate BT as monotherapy is feasible with a favorable veteran-reported hrQOL and physician-graded toxicity profile. Veterans should be educated about this treatment modality when considering the optimal treatment for their localized prostate cancer.

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