

Clinical Investigation

Urinary Outcomes for Men With High Baseline International Prostate Symptom Scores Treated With Prostate SBRT



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Abstract

Purpose: There are limited data regarding high-dose stereotactic body radiation therapy (SBRT) for prostate cancer in patients with poor baseline urinary function. The purpose of this study was to evaluate genitourinary (GU) toxicity and changes in patient-reported symptom severity scores after prostate SBRT in men with a high pretreatment International Prostate Symptom Score (IPSS).

Methods and Materials: Seven hundred fifty-three patients treated with prostate SBRT at our institution from 2012 to 2019 were identified, of whom 72 consecutive patients with baseline IPSS ≥ 15 were selected for this study. GU toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 and IPSS were prospectively documented at each follow-up visit. Univariable logistic regression was used to evaluate for potential predictors of GU toxicity.

Results: Median follow-up in survivors was 26.8 months. The rates of acute grade 2 and 3 GU toxicity were 20.8% and 1.4%, respectively. The rates of late grade 2 and 3 GU toxicity were 37.5% and 5.6%, respectively. The majority of grade 2+ toxicities resolved by last follow-up, and when toxicities were regraded per CTCAE v5.0, there were no longer any grade 3 adverse events. Total IPSS and individual symptom subscores improved over time. Compared with baseline, median total IPSS at 24 ± 6 months was significantly lower (18 vs 12; $P < .001$) and the proportion of patients with severe scores (IPSS ≥ 20) decreased from 29.2% to 13.9%. Pretreatment urinary urgency was associated with late grade 2+ GU toxicity (odds ratio, 2.10; 95% confidence interval, 1.33-3.31; $P = .001$).

Conclusions: In men with baseline IPSS ≥ 15 managed with prostate SBRT, the rate of severe GU toxicity was low and patient-reported symptoms generally improved over time. Thus, high pretreatment IPSS should not deter clinicians from offering prostate SBRT.

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Introduction

Patients with localized prostate cancer have several treatment options with similar oncological outcomes but

different side effect profiles.¹⁻³ Stereotactic body radiation therapy (SBRT) is a relatively quick, noninvasive, and cost-effective treatment approach.^{4,5} Compared with conventionally fractionated 8- to 9-week courses of

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Data sharing statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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external beam radiation, SBRT is typically completed in <2 weeks. Based on the enhanced patient convenience and excellent treatment outcomes, the use of prostate SBRT more than doubled from 2010 to 2015 and continues to rise.⁶

The most frequently reported side effects and quality of life disturbances after prostate SBRT are genitourinary (GU) in nature. Given concerns regarding the higher dose per fraction with SBRT, many trials have excluded patients with presumed predictors for GU toxicity, such as large prostate volume, prior urethral surgeries, and/or moderate-severe baseline urinary symptoms.⁷⁻¹⁰ These predictive factors, however, are extrapolated from outcomes in patients treated with other radiation modalities. For instance, in patients undergoing low-dose-rate brachytherapy implants, high pretreatment International Prostate Symptom Score (IPSS ≥ 15 -20) has been shown to be associated with increased postimplant urinary morbidity.¹¹⁻¹⁴ In the absence of data regarding GU toxicity outcomes for patients with high baseline IPSS undergoing SBRT, these patients are often assumed to be poor candidates for prostate SBRT.

Our recent study of 551 patients treated with prostate SBRT found that men with lower baseline IPSS (evaluated as a continuous variable) had significantly less late grade 2 or higher GU toxicity on multivariable analyses.¹⁵ Furthermore, patients with IPSS ≥ 15 had higher rates of late grade 2 or higher GU toxicity compared with patients with IPSS <15; however, this finding approached but did not reach statistical significance (odds ratio [OR], 1.76; $P = .055$). The purpose of the current study is to comprehensively evaluate our experience treating men with high baseline IPSS and provide a detailed report of toxicity rates and changes in GU symptoms over time.

Methods and Materials

With institutional review board approval, we reviewed the electronic medical records from all patients with prostate SBRT treated at our institution between 2012 and 2019 ($n = 753$). Patients with pretreatment IPSS ≥ 15 and at least 1 follow-up IPSS recorded were selected for further analyses ($n = 72$).

Our SBRT technique has been previously described.¹⁵ Briefly, patients underwent implantation of 3 intraprostatic fiducials into the base, mid-gland, and apex. Beginning in 2016, a hydrogel rectal spacer was also placed in patients without posterior extracapsular extension. Patients were then simulated with 1-mm slice thickness 3T magnetic resonance imaging (MRI) or with 2-mm slice thickness computed tomography if MRI-based planning was contraindicated. Patients were simulated and treated with a full bladder protocol (1-2 cups of water 30-45 minutes prior) and with empty rectums (enema administered 2-3 hours prior). Foley catheters were used

for simulation to improve urethral visualization and volume delineation. Patients were immobilized in the supine position with a custom thermoplastic mold (Aquaplast, Qfix; Avondale, PA).

The clinical target volume included the whole prostate gland and entire bilateral seminal vesicles. The planning target volume consisted of 5-mm circumferential and 3-mm posterior expansions from the clinical target volume. Prescription dose to the planning target volume was typically 40 Gy in 5 fractions delivered every other day; however, some patients were treated with total doses of 32.5 to 45 Gy either on a phase 1 dose escalation trial⁹ or at the treating physician's discretion. Relevant organ-at-risk planning goals consisted of the following: bladder ($D_{\max} < 105\%$, $D10\% < 90\%$, $D50\% < 50\%$), bladder trigone ($D_{\max} < 103\%$), and urethra ($D_{\max} < 105\%$, $D1cc < 100\%$).

SBRT was typically delivered using volumetric modulated arc therapy. Image guidance consisted of pretreatment orthogonal kVs to align to fiducial markers and cone beam computed tomography scans to confirm target coverage, as well as sufficient bladder filling and rectal emptying. Intrafraction motion management was used during treatment delivery.

After completing treatment, patients were generally seen in follow-up at 3 months and then every 6 months (data cutoff date: November 2019). At each follow-up visit, physician-reported toxicity was prospectively evaluated using Common Terminology Criteria for Adverse Events (CTCAE) v3.0 and patient-reported toxicity was assessed using IPSS questionnaires.^{16,17} Illegible or incomplete IPSS responses were excluded. Acute toxicity was defined as any toxicity that occurred within 3 months after SBRT, and late toxicity was defined as any toxicity that occurred thereafter. Toxicity rates were estimated with 95% confidence intervals (CIs). For patients with multiple toxicities within the same category, the highest grade was used. If a new urinary medication was started or dose increased after SBRT, a treatment-related toxicity event was recorded; however, if a urinary medication was started before SBRT, this was not considered an adverse event. Patients with grade 3 or higher toxicities per CTCAE v3.0 were also retrospectively regraded per CTCAE v5.0 to provide a more contemporary assessment of these toxicities.

Given the longitudinal nature of the IPSS data and the variability in response rate at specific timepoints, these data were evaluated with locally estimated scatterplot smoothing (LOESS) regression curves, which were overlaid on a scatterplot representing all data points. The LOESS regression represents a smoothed regression function, which allows us to demonstrate nonlinear trends. Additionally, we binned the data by 12-month intervals (± 6 months) and visualized the distribution of surveys at each interval with boxplots. Total IPSS was grouped into "mild" (0-7), "moderate" (8-19), and "severe" (20-35). Differences between timepoints were

assessed with the Wilcoxon signed rank test. Due to the number of tests (3 timepoints + 8 scores), *P* values were adjusted with the false discovery rate correction.

Univariable logistic regression was used to evaluate for potential predictors of grade ≥ 2 GU toxicity (too few patients had grade ≥ 3 toxicity). Variables included baseline IPSS (severe vs mild-moderate), IPSS subscale scores, prostate volume, androgen deprivation therapy use, use of urinary medications at baseline, and radiation dose (<40 vs ≥ 40.0 Gy).

Unless otherwise stated, unadjusted 2-sided *P* values $< .05$ were considered statistically significant. All analyses were performed with SAS 9.4 TS1M6 (The SAS Institute, Cary, NC).

Results

Patient and treatment characteristics

Seventy-two patients with IPSS ≥ 15 at initial consultation were included in this study (median baseline IPSS 18; range, 15-26). Patient characteristics and treatment details can be found in Table 1. The median follow-up time in survivors ($n = 70$) was 26.8 months (range, 1.8-97.5 months). The median age at the time of SBRT was 69 years (range, 51-89 years). Most men had National Comprehensive Cancer Network intermediate risk disease (80.6%). The median prostate volume measured by pretreatment MRI, before androgen deprivation therapy if used, was 38 cm³ (range, 9-214 cm³). Only 2 patients had a prior transurethral resection of the prostate. At initial consultation, 32 patients (44.4%) were on urinary medications (31 on alpha-blockers and 1 on an anticholinergic). The median SBRT dose was 40 Gy in 5 fractions (range, 32.5-45 Gy).

Acute/late physician-assessed GU toxicity

The majority of acute GU toxicities were low grade, with 26.4% grade 1 and 20.8% grade 2 (Table 2). The most common grade 2 acute toxicity was related to urinary frequency/urgency (ie, increase $>2\times$ normal but less than hourly). Only a single patient (1.4%) had an acute grade 3 GU toxicity (retention resulting in prolonged catheterization).

Most of the late GU toxicities were also low grade, with 33.3% grade 1 and 37.5% grade 2. Urinary frequency/urgency was the most common late grade 2 toxicity, seen in 30.6%. The grade 2 retention rate (ie, requiring medications, not catheterization) was 19.4%. Four patients (5.6%) had late grade 3 GU toxicities. Three patients had grade 3 frequency/urgency ($>1\times$ /hour, which responded to medications). The patient who experienced the acute grade 3 urinary retention requiring prolonged catheterization was also the patient who

Table 1 Baseline patient and treatment characteristics

Characteristics	n (%)
Patients, N	72
Age at SBRT, y	
Median (range)	69 (51-89)
IPSS baseline score	
Median (range)	18 (15-26)
Pre-RT PSA (ng/mL)	
<10	54 (75)
10-20	13 (18.1)
>20	5 (6.9)
Clinical T-stage	
T1-T2a	62 (86.1)
T2b-T2c	6 (8.3)
T3-T4	4 (5.6)
Biopsy Gleason score	
6	4 (5.6)
7	60 (83.3)
8-10	8 (11.1)
NCCN risk group	
Low	4 (5.6)
Favorable-intermediate	29 (40.3)
Unfavorable-intermediate	29 (40.3)
High	9 (12.5)
Metastatic	1 (1.4)
Prostate volume	
Median (range) (n = 71)	38.0 (9.0-214.0)
Baseline urinary meds	
Yes	32 (44.4)
No	40 (55.6)
Hormone therapy	
Yes	33 (45.8)
No	39 (54.2)
Rectal spacer	
Yes	31 (43.1)
No	41 (56.9)
RT dose	
Median (range)	40.0 (32.5-45.0)
32.5 Gy	3 (4.2)
35.0 Gy	1 (1.4)
37.5 Gy	13 (18.1)
40.0 Gy	52 (72.2)
42.0 Gy	2 (2.8)
45.0 Gy	1 (1.4)

Abbreviations: IPSS = International Prostate Symptom Score; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; RT = radiation therapy; SBRT = stereotactic body radiation therapy; TURP = transurethral resection of prostate.

experienced the late grade 3 retention. When toxicities were regraded per CTCAE v5.0, no grade 3 or worse adverse events were noted.

Of the 25 patients with late grade 2+ frequency/urgency, 17 resolved (ie, improved to grade 0-1 at last follow-up) and 8 were unresolved (ie, remained grade 2+ at last follow-up). Of the 2 patients with late grade 2+ hemorrhage, both cases resolved. Of the 6 cases with late

Table 2 GU toxicity estimates by grade

Toxicity	Acute		Late	
	95% CI	Fraction	95% CI	Fraction
Any GU toxicity				
Grade 1	26.4% (16.7%-38.1%)	19/72	33.3% (22.7%-45.4%)	24/72
Grade 2	20.8% (12.2%-32.0%)	15/72	37.5% (26.4%-49.7%)	27/72
Grade 3	1.4% (0.0%-7.5%)	1/72	5.6% (1.5%-13.6%)	4/72
Cystitis				
Grade 1	6.9% (2.3%-15.5%)	5/72	1.4% (0.0%-7.5%)	1/72
Grade 2	1.4% (0.0%-7.5%)	1/72		0/72
Frequency/urgency				
Grade 1	26.4% (16.7%-38.1%)	19/72	38.9% (27.6%-51.1%)	28/72
Grade 2	15.3% (7.9%-25.7%)	11/72	30.6% (20.2%-42.5%)	22/72
Grade 3		0/72	4.2% (0.9%-11.7%)	3/72
Hemorrhage				
Grade 1	1.4% (0.0%-7.5%)	1/72	4.2% (0.9%-11.7%)	3/72
Grade 2		0/72	2.8% (0.3%-9.7%)	2/72
Incontinence				
Grade 1	6.9% (2.3%-15.5%)	5/72	20.8% (12.2%-32.0%)	15/72
Grade 2	2.8% (0.3%-9.7%)	2/72	8.3% (3.1%-17.3%)	6/72
Retention				
Grade 1	13.9% (6.9%-24.1%)	10/72	26.4% (16.7%-38.1%)	19/72
Grade 2	5.6% (1.5%-13.6%)	4/72	19.4% (11.1%-30.5%)	14/72
Grade 3	1.4% (0.0%-7.5%)	1/72	1.4% (0.0%-7.5%)	1/72

Abbreviations: CI = confidence interval; GU = genitourinary.

grade 2+ incontinence, 4 cases resolved and 2 cases were unresolved. Of the 15 cases with late grade 2+ retention, 8 resolved and 7 were unresolved by last follow-up.

The use of medications for urinary symptoms was also evaluated. There were 54 patients (75%) on alpha-blockers by the start of SBRT and 68 patients (94%) on alpha-blockers at some point during or after SBRT. There was 1 patient (1%) on an anticholinergic by the start of SBRT and 28 of 72 patients (37.5%) were prescribed anticholinergics at some point during or after SBRT. Three patients (4%) were on steroid tapers during SBRT for retention symptoms and 3 patients (4%) were on steroid tapers after SBRT for presumed noninfectious prostatitis. At 1 year, 47 patients (65.2%) were on at least 1 urinary medication. At 2 years, 39 patients (54.1%) were still on at least 1 urinary medication.

Patient-reported urinary symptoms

According to the LOESS curve, total IPSS generally improved over time (Fig 1). On average, IPSS initially decreased after SBRT, then slightly increased around 9 to 12 months, and then decreased again thereafter. Similarly, IPSS subscores either remained constant or decreased by 24 months (ie, no specific symptom clearly worsened after SBRT) (Fig 2). After initial improvement, there was a small increase in all subscores around 12 months after SBRT, similar to that seen with the total IPSS scores. The curves show that obstructive symptoms (ie, incomplete emptying, intermittency, straining, and weak stream)

typically improved by 24 months, whereas the irritative symptoms (urgency, frequency, and nocturia) remained more constant.

The boxplots show a similar overall decrease in total IPSS and symptom subscores over time (Fig 3). Total IPSS significantly decreased from a median baseline score of 18 to a median score of 15 by 12 ± 6 months ($P < .001$) and continued to decrease to a median score of 12 by 24 ± 6 months ($P < .001$).

The proportion of patients reporting mild (0-7), moderate (8-19), and severe (20-35) symptoms over time was evaluated (Table 3). At baseline, 0% had mild, 70.8% had moderate, and 29.2% had severe symptoms. At 12 ± 6 months, the proportion of patients with severe scores (IPSS ≥ 20) decreased from 29.2% to 18.1%; by 24 ± 6 months, it further decreased to 13.9%. Additionally, the proportion of patients with mild scores (IPSS ≤ 7) increased from 0% at baseline to 9.7% at 12 ± 6 months and continued to increase to 16.7% at 24 ± 6 months.

Predictors of GU toxicity

Patients with higher baseline IPSS tended to have higher odds of late grade ≥ 2 GU toxicity, but this did not reach statistical significance (OR, 1.17; 95% CI, 0.98-1.39; $P = .08$). Higher baseline straining and urgency subscores, however, were significantly associated with late toxicity (OR, 1.57; 95% CI, 1.02-2.42; $P = .040$ and OR, 2.10; 95% CI, 1.33-3.31; $P = .001$, respectively) (Table 4). Interestingly, patients receiving higher

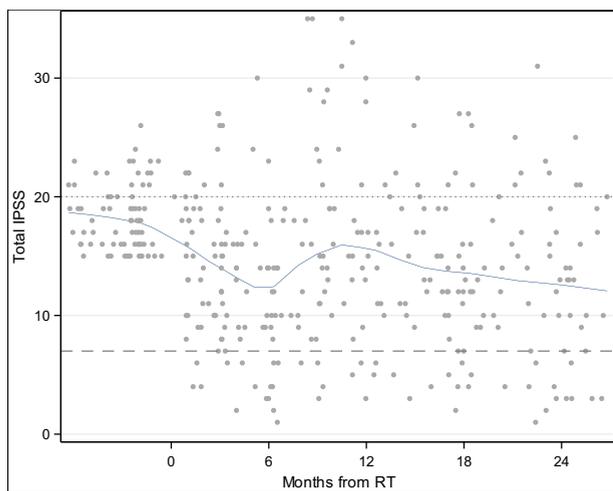


Figure 1 This figure represents all available total International Prostate Symptom Scores (IPSS) represented by dots in a scatter plot overlaid with a locally estimated scatterplot smoothing (LOESS) regression curve represented by a thick solid line. The LOESS curve calculates a local weighted polynomial regression with an automatic smoothing parameter and this represents a trend in total IPSS over time for all patients. T = 0 represents the first stereotactic body radiation therapy fraction, therefore dots to the left of T = 0 are pretreatment IPSS responses and dots to the right of T = 0 were recorded after treatment. The dashed line at IPSS = 7 distinguishes “mild” from “moderate” severity scores and the dotted line at IPSS = 20 distinguishes “moderate” from “severe” scores.

prescription doses (≥ 40 Gy vs < 40 Gy) had significantly lower odds of acute toxicity (OR, 0.19; 95% CI, 0.06-0.64; $P = .008$) but no significant difference in late toxicity (OR, 0.73; $P = .52$). No other significant associations were found between the baseline characteristics evaluated and the rates of GU toxicity. As previously noted, the use of a rectal spacer was significantly associated with less GU toxicity in the prior report of a larger cohort of patients with any IPSS, but in this analysis this did not reach statistical significance for acute or late GU toxicity (OR, 0.52; $P = .28$ and OR, 0.73; $P = .52$).

Discussion

Our results demonstrate that patients with baseline urinary dysfunction (IPSS ≥ 15) treated with prostate SBRT had a low rate of severe GU toxicity, and symptoms generally improved over time. By 12 months, IPSS scores were significantly lower than baseline and continued to decline. Furthermore, by 24 months the proportion of patients with severe pretreatment GU symptoms (IPSS > 20) decreased from approximately 30% to $< 15\%$.

Despite poor baseline urinary symptoms, the rate of grade 3 GU toxicity was only 5.6% when prospectively assessed per CTCAE v3.0 and 0% when regraded per CTCAE v5.0. Although median follow-up was just over 2

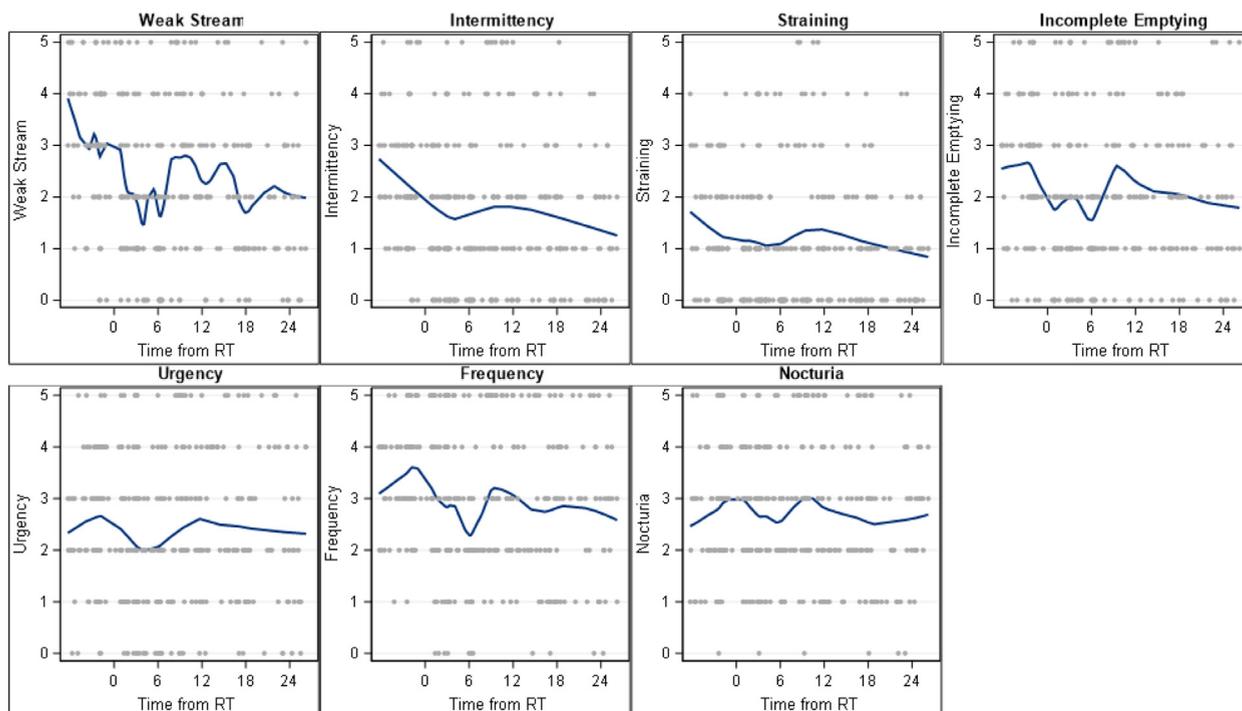


Figure 2 These figures represent scatter plots of each of the International Prostate Symptom Score subscales overlaid with locally estimated scatterplot smoothing regression curves (see Fig 1 legend for details).

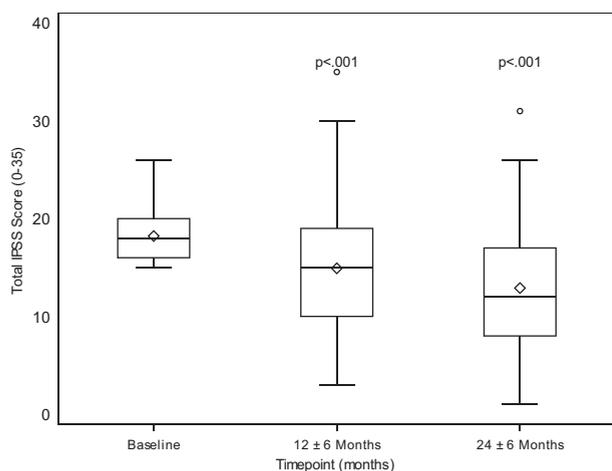


Figure 3 Boxplots for total International Prostate Symptom Scores at baseline (ie, initial consultation), 12 ± 6 months, and 24 ± 6 months. The boxes extend to 25th and 75th percentiles with the lines in the center representing the median and diamonds representing means. The whiskers extend to the minimum and maximum values up to 1.5x the interquartile range. Points outside the whiskers represent outliers.

years, these rates appear similar to other large prostate SBRT studies that excluded patients with severe urinary dysfunction.^{18,19} Aghdam et al²⁰ recently reported the results of 53 patients with IPSS ≥ 15 treated with prostate SBRT and found a 7.5% 3-year rate of grade 3 GU toxicity per CTCAE v4.0. Consistent with our results, they also reported a significant improvement in IPSS over time. These findings are different from those of studies of unselected patients (ie, with any IPSS) that showed acute worsening of GU symptoms followed by a return to baseline with longer follow-up.^{21,22} The improvement in IPSS demonstrated in our study and in the study by Aghdam et al is likely related to the selection of patients with high baseline IPSS who then receive effective medical management. It is worth noting, however, that at 2 years the mean IPSS in our study was 12 and most patients still reported moderate symptoms. Therefore, although improvements in IPSS were observed, many of these patients were still more symptomatic than the average patient with prostate cancer treated with radiation.

As expected, we demonstrated a relatively high rate of grade 2 GU toxicity in this patient population (20.8%

acute and 37.5% late) compared with historical outcomes, where grade 2 toxicity is often reported at $<20\%$.^{7,23-27} The predominant grade 2+ toxicity in the current study consisted of urinary urgency and frequency that resulted in medical intervention (ie, medications prescribed). Interestingly, higher baseline urgency score was a significant predictor of late grade 2+ toxicity. Thus, irritative symptoms after SBRT might not necessarily be related to the development of new urinary problems but instead might at least in part represent a recurrence of pretreatment symptoms. Notably, we found that although overall GU symptoms improved over time, this appeared to mostly be driven by a reduction in obstructive complaints by 2 years.

Most data show that obstructive voiding symptoms tend to increase immediately after treatment but then resolve in the weeks to months after radiation, likely secondary to transient edema/inflammation.²⁸⁻³³ Acute urinary retention could be an even greater concern with SBRT given the high dose per fraction; however, in our cohort, only a single patient required a catheter (1.4% rate) despite moderate to severe baseline obstructive symptoms in most patients. It is worth noting that our institutional practice, although not standardized, is often to prescribe alpha-blockers before SBRT, especially to those with high pretreatment IPSS and obstructive symptoms, to improve baseline symptomology and potentially mitigate treatment-related side effects. Some institutions also give prophylactic corticosteroids in an attempt to prevent acute swelling and urinary retention.³⁴ It is possible that our generous use of alpha-blockers contributed to the low rate of retention but also contributed to our relatively high rate of grade 2 toxicity.³⁵ A group from Georgetown University, who often use prophylactic alpha-blockers, evaluated obstructive symptoms after SBRT.²⁸ In this study, 269 patients with any baseline IPSS (median 8) were treated with 35 to 36.25 Gy in 5 fractions every other day. The rate of urinary retention resulting in catheterization was 1.5%, which is essentially the same as that reported in our study. The Georgetown group found a peak in obstructive symptoms at 1 month after SBRT followed by a return to baseline in over 90% at 3 months. Only 7.1% of patients had “moderate to big” problems with obstructive symptoms at 2 years. In a separate publication, this group also showed that men with baseline IPSS ≥ 15 had a significant and clinically meaningful improvement in Expanded Prostate Cancer Index Composite-26 obstructive/irritative domain scores after SBRT.²⁰ Furthermore, this group evaluated men with moderate to severe baseline irritative urinary symptoms and showed a statistically and clinically meaningful improvement in symptom scores at 3 years compared with baseline.³⁶ These results, as well as other studies examining quality of life after SBRT, suggest that despite the occurrence of grade 2 GU toxicities, most patients, even those with baseline urinary complaints, eventually either return to baseline or improve by 2 to 3 years after SBRT.³⁷⁻³⁹

Table 3 Patient-reported symptom severity

IPSS severity	Baseline	12 mo*	24 mo*
Mild (0-7)	0 (0)	7 (9.7)	12 (16.7)
Moderate (8-19)	51 (70.8)	43 (59.7)	27 (37.5)
Severe (20-35)	21 (29.2)	13 (18.1)	10 (13.9)
Unknown	0 (0)	9 (12.5)	23 (31.9)

Abbreviation: IPSS = International Prostate Symptom Score.

* ± 6 months

Table 4 Univariable analysis for predictors of acute and late grade 2+ GU toxicity

Factor	Acute grade 2+ GU toxicity				Late grade 2+ GU toxicity			
	N(#E)	OR	95% CI	P value	N(#E)	OR	95% CI	P value
IPSS*	72 (16)	1.03	0.84-1.25	.80	72 (31)	1.17	0.98-1.39	.08
Frequency*	72 (16)	1.15	0.65-2.04	.63	72 (31)	0.78	0.48-1.26	.31
Incomplete emptying*	72 (16)	0.87	0.58-1.30	.49	72 (31)	0.71	0.49-1.01	.060
Intermittency*	72 (16)	0.80	0.49-1.30	.37	72 (31)	0.84	0.57-1.26	.41
Nocturia*	72 (16)	1.22	0.77-1.93	.40	72 (31)	1.08	0.73-1.59	.71
Straining*	72 (16)	0.87	0.53-1.44	.60	72 (31)	1.57	1.02-2.42	.040*
Urgency*	72 (16)	1.56	0.96-2.52	.07	72 (31)	2.10	1.33-3.31	.001*
Baseline weak stream	72 (16)	0.92	0.60-1.42	.71	72 (31)	1.42	0.96-2.11	.08
Prostate volume	71 (15)	1.01	1.00-1.03	.12	71 (31)	1.00	0.98-1.01	.58
Androgen deprivation								
Yes	33 (10)	2.39	0.76-7.50	.14	33 (17)	1.90	0.74-4.88	.18
No	39 (6)	REF			39 (14)	REF		
Urinary medications†								
Yes	32 (5)	0.49	0.15-1.59	.23	32 (15)	1.32	0.52-3.39	.56
No	40 (11)	REF			40 (16)	REF		
Radiation dose (Gy)								
≥40	55 (8)	0.19	0.06-0.64	.008*	55 (22)	0.59	0.20-1.77	.35
<40	17 (8)	REF			17 (9)	REF		
Rectal spacer								
Yes	31 (5)	0.52	0.16-1.71	.28	31 (12)	0.73	0.28-1.89	.52
No	41 (11)	REF			41 (19)	REF		

Abbreviations: CI = confidence interval; GU = genitourinary; IPSS = International Prostate Symptom Score; OR = odds ratio.

* P-value <.05.

† At initial consultation

Outside of the low-dose-rate brachytherapy literature, our results are concordant with other studies that evaluated postradiation therapy urinary dysfunction in patients with poor baseline function. Malik et al,⁴⁰ for instance, found that men with baseline IPSS ≥15 treated with conventionally fractionated external beam radiation to a median dose of 75.6 Gy had more grade 2 GU toxicity compared with patients with baseline IPSS <15, but grade 3 toxicity was only 3% in both groups. Also, similar to our results, IPSS improved with time in the patients with baseline IPSS ≥15. Morgan et al⁴¹ evaluated high-dose-rate brachytherapy in patients with pretreatment IPSS ≥15. They also showed an improvement in patient-reported urinary symptoms by 24 months posttreatment compared with baseline. These results taken together suggest that patients with poor baseline urinary function undergoing radiation seem to tolerate treatment both in the acute and long-term setting.

There appears to be no clear subgroup of patients with relative contraindications to SBRT based on concerns regarding severe GU toxicity (ie, grade 3 or higher). Our prior study of 551 unselected patients¹⁵ and the current study both suggest that higher baseline IPSS is likely associated with higher rates of grade 2 toxicity, but in the current study, these findings did not reach statistical significance. This was likely due to the relatively small number of patients included and lack of variability in

baseline scores. Prostate size as a predictor of GU toxicity has been evaluated by multiple groups. In the current study and our previous reported experience, we found no significant association with prostate volume and incidence of grade 2 or higher GU toxicity.¹⁵ Janowski et al⁴² similarly reported a rate of late grade 3 GU toxicity of only 3.5% in patients with prostates >50 cm³ undergoing SBRT. Katz and Kang²⁵ did report higher rates of both grades 2 and 3 GU toxicity in patients with prostate volume >60 cm³ compared with patients with prostate volume ≤60 cm³; however, these differences did not reach statistical significance, the absolute differences were small, and the rate of grade 3 toxicity in the patients with large prostates was only 3.1%. Similarly, patients with prior transurethral resection of the prostate also appear to tolerate SBRT without a significant increase in severe toxicity.⁴³ It is also worth noting that medical comorbidities, such as uncontrolled diabetes, chronic prostatitis, neurologic conditions, and autoimmune disorders, as well as the use of certain medications (ie, diuretics and anti-coagulants) could have affected the rate of urinary toxicity in this patient population, but this was not specifically assessed in this study.^{44,45} Additionally, GU toxicity is likely related to factors beyond patient selection, such as treatment planning and delivery techniques, dose to critical structures (ie, bladder, bladder trigone, urethra), and even fractionation scheme (ie, daily vs every other day

treatments), which were not evaluated in the current analysis. It is worth noting that we found a paradoxical relationship with dose and acute toxicity that may be explained by many of the patients who received <40 Gy and were treated on our dose escalation study, which enrolled patients from 2009 to 2012.⁹ Thus, it is possible that changes in our treatment planning and delivery techniques over time affected our results.

Although we prospectively collected CTCAE v3.0 toxicity data and IPSS scores, several limitations exist, including the relatively small cohort size, missing data, relatively short follow-up, and the retrospective nature of the analysis. Additionally, there could be unaccounted for side effects between follow-ups. Lastly, we did not prospectively compare outcomes with other treatment modalities, so we cannot conclude that these high baseline IPSS patients would have had better or worse quality of life or toxicity with SBRT versus an alternative radiation technique, such as moderate or conventionally fractionated radiation; however, studies like this are planned.

Conclusions

The low rate of severe GU toxicity and decline in average IPSS observed over time suggest that SBRT is an appropriate option for patients with baseline IPSS scores ≥ 15 . Although these patients had a relatively high incidence of grade 2 GU toxicity and frequently required urinary medications, their symptoms generally improved. Based on these findings, our group does not believe high pretreatment IPSS should be a contraindication to SBRT.

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