

# Comparison of Late Urinary Symptoms Following SBRT and SBRT with IMRT Supplementation for Prostate Cancer

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## Key Words

Prostate cancer • Radiation therapy • Urinary symptoms • Lower urinary tract symptoms • CyberKnife •

## Abstract

**Background:** Prostate cancer survivors commonly experience late-onset lower urinary tract symptoms following radiotherapy. We aimed to compare lower urinary tract symptoms in patients treated with stereotactic body radiotherapy (SBRT) to those treated with a combination of lower dose SBRT and supplemental intensity-modulated radiotherapy (SBRT + IMRT). **Methods:** Subjects with localized prostate carcinoma scheduled to receive SBRT or a combination of SBRT and IMRT were enrolled and followed for up to 2 years after treatment completion. Participants treated with SBRT received 35–36.25 Gy in 5 fractions, while those treated with SBRT + IMRT received 19.5 Gy of SBRT in 3 fractions followed by 45–50.4 Gy of IMRT in 25–28 fractions. Urinary symptoms were measured using the American Urological Association (AUA) Symptom Score. **Results:** Two hundred patients received SBRT (52% intermediate risk, 37.5% low risk according to D'Amico classification) and 145 patients received SBRT + IMRT (61.4% high risk, 35.2% intermediate risk). Both groups experienced a transient spike in urinary symptoms 1 month after treatment. More severe late urinary flare (increase in

AUA scores  $\geq 5$  points from baseline to 1 year after treatment completion and an AUA score  $\geq 15$  at 1 year after treatment) was experienced by patients who received SBRT compared to those treated with SBRT + IMRT. **Conclusion:** Participants who received SBRT and supplemental IMRT experienced less severe late urinary flare 1 year after treatment compared to those who received higher dose SBRT alone. This information can be used by clinicians to provide patients with anticipatory counseling to mitigate any psychological burden that comes with unanticipated late urinary toxicities.

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## Introduction

Prostate cancer (PCa) is the second leading cause of cancer death in men and accounts for 1 in 5 new cancer diagnoses in the United States [1]. For those men diagnosed with localized PCa, many treatment options are available including prostatectomy, radiotherapy, and in many cases of low risk disease, active surveillance [2]. Each treatment modality yields its own constellation of side effects and in the case of radiation therapy, gastro-

**Table 1.** Patient characteristics

	SBRT (n = 200)	SBRT + IMRT (n = 145)	p
Age, years	75.07 ± 7.29	73.22 ± 7.31	0.02
BMI, kg/m <sup>2</sup>	28.72 ± 7.50	28.68 ± 5.47	0.97
Race			N.A.
Asian	5 (2.5%)	3 (2.1)	
Black	77 (38.5%)	65 (44.8%)	
Hispanic	5 (2.5%)	2 (1.4%)	
White	111 (55.5%)	68 (46.9%)	
Other	2 (1%)	7 (4.8%)	
T-stage			N.A.
T1b	0 (0%)	1 (0.7%)	
T1c	150 (75%)	65 (44.8%)	
T2a	23 (11.5%)	14 (9.7%)	
T2b	18 (9%)	37 (25.5%)	
T2c	9 (4.5%)	22 (15.2%)	
T3	0 (0%)	6 (4.1%)	
Gleason score			N.A.
5	3 (1.5%)	0 (0%)	
6	88 (44%)	13 (9.0%)	
7	98 (49%)	62 (42.8%)	
8	11 (5.5%)	40 (27.6%)	
9	0 (0%)	28 (19.3%)	
10	0 (0%)	2 (1.4%)	
Risk			N.A.
Low	75 (37.5%)	5 (3.4%)	
Intermediate	104 (52%)	51 (35.2%)	
High	21 (10.5%)	89 (61.4%)	
Prostate volume, ml	42.18 ± 20.68	41.00 ± 22.76	0.62
PSA, ng/ml	7.97 ± 11.07	16.96 ± 21.42	6.5 × 10 <sup>-7</sup>

intestinal and genitourinary toxicities are not uncommon [3, 4]. Patients treated with radiation therapy often report bothersome fatigue, lower urinary tract symptoms (LUTS), bowel irritation, and sexual dysfunction [5, 6].

LUTS, in particular, significantly influence health-related quality-of-life (QoL) after completion of radiation therapy for the treatment of PCa [7]. LUTS are classified as obstructive and irritative symptoms, excluding incontinence, measured by ease and strength of urine flow, urinary frequency, dysuria, nocturia, and urgency [8]. These symptoms are observed to worsen with radiation therapy and seem rather unique to this modality of treatment [9]. Furthermore, LUTS in men treated with radiation therapy are significantly worse compared to those who receive prostatectomy alone [10]. Moreover, LUTS are also reported to persist for years after completion of radiation treatment [11, 12]. In some cases, LUTS may recur or worsen months or years following radiation therapy. This

phenomenon is classically described as late urinary flare (LUF), which is defined as a moderate (Grade ≥ 2) late genitourinary toxicity [13, 14]. While much of the literature discusses flares in relation to intensity-modulated radiation therapy (IMRT) and brachytherapy treatment modalities [15], LUF has been recently associated with stereotactic body radiation therapy (SBRT) treatment, which manifests as a symptom cluster of dysuria, urinary frequency, urinary urgency, and weak stream occurring anywhere from 6 to 18 months after treatment completion [16].

Previous studies report higher doses of radiation are associated with LUTS possibly due to inflammation of the urethra and bladder neck [17–20]. The increasing utilization of SBRT as a treatment option for localized PCa warrants investigation of its long-term side effects and its impact on urinary symptom-related QoL. In the current study, we compared late-onset LUTS as well as urinary symptom-related QoL in patients treated with SBRT alone versus those treated with reduced dose SBRT combined with conventionally fractionated IMRT.

## Materials and Methods

### Patient Selection

The current study was approved by the Institutional Review Board of MedStar Georgetown University Hospital, Washington, DC. Signed written informed consents were obtained prior to study participation. Eligibility for study inclusion was as follows: 1) histologically confirmed adenocarcinoma of the prostate; 2) clinically localized disease; 3) prostate-specific antigen (PSA) < 40 ng/ml; 4) clinical stage T1b to T3, and 5) Gleason score of ≤ 10. Exclusion criteria were as follows: 1) clinically involved lymph nodes on imaging; 2) distant metastases on bone scan; 3) prior pelvic radiotherapy and 4) prior radical prostate surgery. PCa risk stratification followed the standard D'Amico stratification algorithm [21].

### Treatment and Instruments

The CyberKnife (Accuray Inc., Sunnyvale CA, USA) was used to deliver fiducial-based image-guided SBRT. SBRT treatment planning and delivery were conducted as previously described [22, 23]. The combined CyberKnife and IMRT protocol was designed to deliver an equivalent dose in 2Gy fractions similar to that of the CyberKnife-only protocol to PCa cells. All patients were treated with IMRT immediately following CyberKnife.

Patient-reported outcomes were assessed at baseline (pre-treatment) and at follow-up visits (1, 3, 6, 9, 12, 18, and 24 months post SBRT) using the American Urological Association (AUA) symptom index [24]. The AUA symptom index is a 7-item global measurement of a subjects' urinary function, which includes frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency. The impact of LUTS on urinary symptom-related QoL was measured using the AUA bother

**Table 2.** Treatment characteristics

	ADT	No. of fractions	Radiation dose (Gy)	BED (Gy)	No. of subjects
SBRT (n = 200)	24 (12%)	5	35	198.3	24 (12%)
		5	36.2	211.5	176 (88%)
SBRT + IMRT (n = 145)	102 (70.3%)	3/25	19.5/45	203	118 (81.4%)
		3/26	19.5/46.8	205.2	2 (1.4%)
		3/28	19.5/50.4	214.9	24 (16.6%)
		5/25	22.5/45	189	1 (0.7%)

score [25]. The AUA symptom index is internally consistent (Cronbach's  $\alpha = 0.86$ ) with good test-retest reliability ( $r = 0.92$ ) [24]. AUA scores were calculated using the seven function items (1–7 mild; 8–19 moderate; 20–35 severe). LUF was defined as an increase in AUA scores by  $\geq 5$  points from baseline with a degree of severity in the moderate to severe range (AUA symptom score  $\geq 15$ ) 1 year after treatment [26].

#### Statistical Analysis

A mixed model ANOVA was employed to assess changes in AUA scores over time. For this analysis, the between-subject factors were defined as AUA scores, while the within-subject factor was defined by study time points. The sphericity assumption was tested with Mauchly's test. Greenhouse-Geisser estimate of sphericity was applied to correct for degrees of freedom in the presence of violation of Mauchly's test of sphericity. AUA score differences at each time point were determined by paired *t*-test with Bonferroni corrections for multiple comparisons. Demographic data are expressed as mean  $\pm$  standard deviation. Statistical analyses were performed with SPSS statistics software version 23 (IBM SPSS, Purchase, NY, USA).

## Results

#### Patient Characteristics

A total of 200 men were treated with SBRT only, and 145 men were treated using a combination of SBRT and IMRT (table 1). The 2 cohorts were ethnically diverse, similar in age (SBRT:  $75.07 \pm 7.29$  years; SBRT + IMRT:  $73.22 \pm 7.31$  years), and similar in body mass index (SBRT:  $28.72 \pm 7.50$  kg/m<sup>2</sup>; SBRT + IMRT:  $28.68 \pm 5.47$  kg/m<sup>2</sup>). Subjects in the SBRT + IMRT group had a more significant cancer burden with the majority of subjects (61.4%) diagnosed with high risk disease [22], and an average baseline PSA level at  $16.96 \pm 21.42$  ng/ml. In contrast, subjects in the SBRT alone group had less advanced disease with the majority of subjects in the intermediate risk category (52%) [22] and an average baseline PSA level at  $7.97 \pm 11.07$  ng/ml.

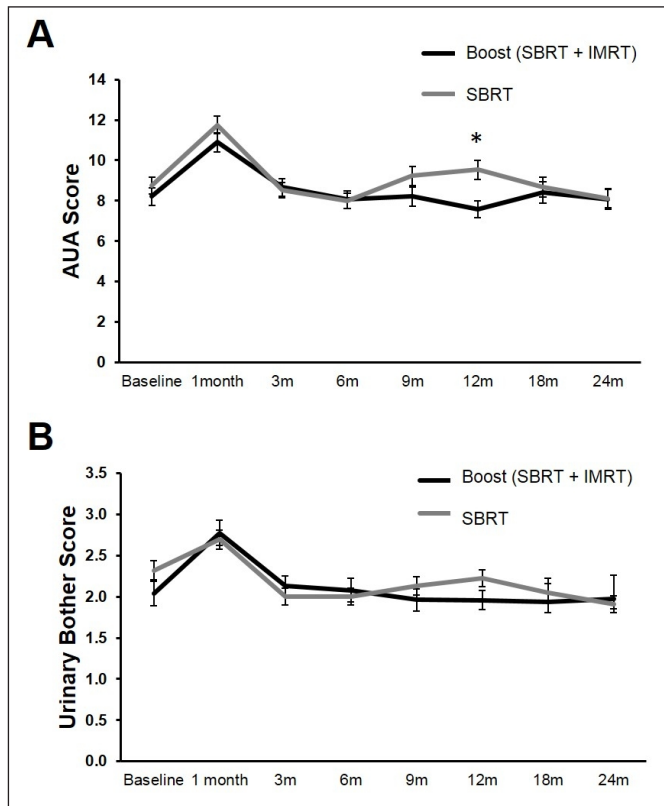
#### Treatment Characteristics

Subjects selected to be treated with SBRT received 5 fractions of a total of 35–36.35 Gy and 12% of subjects received an adjuvant androgen deprivation therapy (ADT) (table 2). The IMRT treatment plans were more homogeneous than the SBRT plans. Subjects treated with a combination of SBRT and IMRT first received 3 fractions of SBRT at 19.5 Gy followed by 25 to 28 fractions of IMRT at a total dose of 45–50.4 Gy. In addition, the majority of subjects in this treatment group also received adjuvant ADT (70.3%).

#### Urinary Symptoms

There was no significant difference in AUA scores between the two treatment groups at baseline. Urinary symptoms as measured by AUA worsened immediately following the initiation of treatment and a month after SBRT completion, but returned close to baseline levels at 3 and 6 months post SBRT (fig. 1A). One year after treatment, urinary symptoms worsened transiently in subjects treated with SBRT only compared to those treated with SBRT followed by IMRT (SBRT:  $9.53 \pm 0.47$ ; SBRT + IMRT:  $7.60 \pm 0.42$ ;  $p = 0.003$ ). The longitudinal change in AUA bother scores mirrored urinary symptoms, transiently worsening at 1 month (acute) and 1 year after treatment ( $F_{3,6, 164.1} = 5.11$ ,  $p = 0.001$ ) (fig. 1B). The difference in subjects experiencing LUF and those that did not was attributed only to treatment (SBRT versus SBRT + IMRT), but not to disease risk ( $F_{2, 344} = 0.16$ ,  $p = 0.85$ ).

Both LUF and non-LUF groups experienced acute urinary symptoms immediately (within 1 month) following treatment. At 1-year post-treatment, AUA scores in subjects without LUF plateaued to a level comparable to baseline AUA scores, whereas AUA scores increased significantly in subjects with LUF. LUF was seen in 12% of subjects treated with only SBRT (LUF AUA score: 21.13



**Fig. 1.** Progression of urinary symptoms over time. **A** Both SBRT-treated and SBRT + IMRT-treated subjects experienced a transient spike in urinary symptoms 1 month after treatment, as measured by AUA symptom index. Urinary symptoms significantly changed over time, peaking transiently 1-month post-treatment in both treatment groups, while SBRT-treated subjects experienced LUF 1 year after treatment ( $F_{9,39} = 4.18$ ,  $p = 0.001$ ). Twelve months after treatment, SBRT-treated subjects exhibited worse urinary symptoms compared to subjects treated with combined SBRT and IMRT ( $p = 0.003$ ). **B** Urinary symptom-related QoL spiked 1 month after treatment for both groups and just slightly changed significantly over time ( $F_{9,37} = 2.17$ ,  $p = 0.05$ ). In addition, urinary bother did not differ significantly between SBRT-treated and SBRT + IMRT-treated subjects at each time point ( $p = 0.09$ ). Values are mean AUA scores  $\pm$  SEM. \* $p < 0.05$ .

$\pm 1.05$ ,  $F_{6,810} = 4.85$ ,  $p = 1.004 \times 10^{-10}$ ) (fig. 2A). Interestingly, supplementing SBRT with more fractionated IMRT reduced the percentage of subjects with LUF to 5.5% (LUF AUA score:  $18.25 \pm 0.75$ ,  $F_{12,444} = 4.85$ ,  $p = 2.54 \times 10^{-7}$ ) (fig. 2C). At 1 year following treatment completion, AUA bother scores were similar in subjects with LUF who were treated with SBRT alone (fig. 2B; AUA bother score:  $4.26 \pm 0.24$ ) compared to those treated with SBRT + IMRT (fig. 2D; AUA bother score:  $4.50 \pm 0.42$ ).

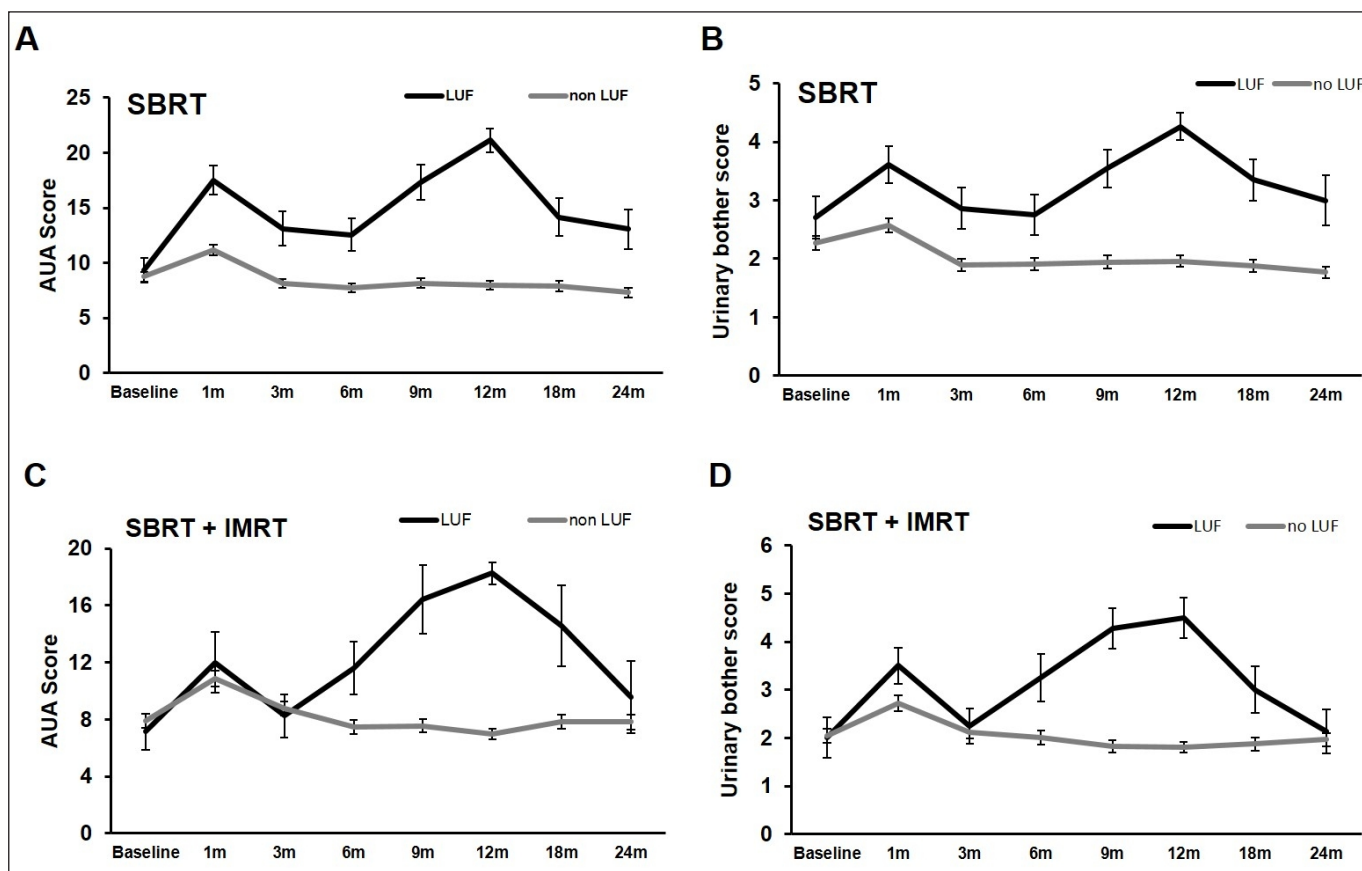
## Discussion

Although IMRT remains the standard external beam radiotherapy treatment option for clinically localized PCa [27], SBRT is a rapidly evolving and increasing utilized modality of treatment for low- to intermediate-risk PCa. SBRT offers many advantages relative to conventionally fractionated IMRT including radiobiologic gains, patient access and satisfaction, and cost-effectiveness [28, 29]. Nevertheless, any hypofractionated treatment schedule raises concerns for untoward late toxicities. In the present study, subjects treated for localized PCa using SBRT alone versus a combination of lower dose SBRT and IMRT experienced a transient spike of urinary toxicity immediately after radiation therapy that resolved over time. However, subjects treated with higher dose SBRT alone experienced worse LUF at 1-year post-treatment compared to those treated with the combined modality regimen. Although subjects with LUF in the SBRT alone group experienced more severe urinary toxicity, the percentage of subjects with LUF was comparable in both treatment groups and the absolute risk was relatively low.

In those patients with LUF who were treated with SBRT alone, there was a notable increase in both AUA score and urinary bother score that began during radiotherapy treatment and persisted throughout the follow-up period. Although the follow-up period is still short by PCa standards, this curve seems reminiscent of an early toxicity leading to a consequential late effect. In contrast, those patients with LUF who were treated with combined SBRT + IMRT demonstrated AUA and urinary bother scores nearly identical to non-LUF patients in the first 3 months of follow-up with a transient increase representing late LUF that eventually returned to those scores seen in the non-LUF cohort. Interestingly, the subjective urinary difficulty in LUF patients treated with SBRT alone appeared during the acute symptom phase and continued throughout the study. In contrast, the urinary bother scores in SBRT + IMRT LUF and non-LUF patients were similar during the acute symptom phases with a distinct flare; however, the urinary bother score in LUF patients returned to non-LUF levels by the end of the study.

The etiology of variations in LUF between these 2 groups is not entirely clear. Given the biologically effective dose (BED) was higher in the SBRT + IMRT group (table 2), it appears radiobiologic differences in dose delivery is not the whole story. However, this may be an indication that classical BED calculations may breakdown at these extreme hypofractionation levels. A more compelling rationale for these differences in LUF is





**Fig. 2.** Comparison of those patients with and without LUTS 1-year post-treatment. **(A)** SBRT: 12% (24 out of 200) of subjects experienced LUF and urinary symptoms changed significantly over time ( $F_{6, 810} = 4.85$ ,  $p = 1.004 \times 10^{-10}$ ). **(B)** Urinary bother scores in the SBRT group exhibited the same longitudinal trend as urinary symptom scores ( $F_{5, 648} = 3.61$ ,  $p = 0.004$ ), as measured by the AUA questionnaire. **(C)** SBRT + IMRT: 5.5% (8 out of 145) of subjects experienced LUF and urinary symptoms changed significantly over time ( $F_{12, 444} = 4.85$ ,  $p = 2.54 \times 10^{-7}$ ). **(D)** Urinary bother in subjects treated with SBRT + IMRT reflected urinary symptoms ( $F_{9, 349} = 5.54$ ,  $p = 0.00001$ ).

variation in dose distribution between these 2 groups. Indeed, SBRT has historically erred on the side of extreme conformality often at the expense of dose heterogeneity within the target. However, the location of the prostatic urethra at the center of the gland makes treatment of PCa with SBRT unique in the family of other cancers treated with SBRT/SRS, such as non-small cell lung cancer and brain metastases, where a normal structure does not lie at the center of the target. As a result, it is possible that differences in dose uniformity within the target between the SBRT alone and SBRT + IMRT groups lead to variations in hotspot placement within the urethra and adjacent bladder neck. At our institution, we have enacted a clinical policy to limit the dose to the prostatic urethra to  $< 40$  Gy in order to reduce this observed LUF. After

enacting this policy, we have seen a significant reduction in incidence of LUF. Future research should explore the specific dosimetric parameters which explain the differences in LUF observed in these 2 groups. Previous work demonstrated an association of delayed radiation-induced cystourethritis and the development of urinary symptoms 1 year after hypofractionated radiotherapy [30], which is consistent with our current finding that hypofractionated radiotherapy results in more severe urinary toxicity compared to conventionally fractionated radiotherapy. The role of inflammation in the pathogenic process of late urinary toxicities is further supported by the observation that these symptoms respond well to oral corticosteroids (dexamethasone 4 mg/day for 1 week followed by 2 mg for 1 week) [16]. Future studies should explore the cor-

relation between target volume dose distribution and late urinary symptoms [31].

One caveat of our study is that the majority of subjects treated with SBRT and IMRT also received ADT. In addition, most of the subjects in this group were high-risk patients. In order to rule out the potential contribution of hormones, we compared subjects who received ADT with those who did not, and did not detect any difference in their urinary toxicities ( $p > 0.05$ ). In addition, subjects in different disease risk categories did not differ in AUA scores. This suggests that the difference in late urinary toxicities 1-year post-treatment is most likely attributable to the difference in radiation treatment modalities.

For some patients, the advantage of a hypofractionated treatment outweighs the transient urinary toxicity that may occur 1 year following SBRT [27, 32, 33]. The late onset urinary toxicities following SBRT treatment will become a more important issue as SBRT gains popularity as a primary treatment option for localized PCa. Previous studies have shown that educating patients on treatment-related side effects can decrease the psychological burden and increase satisfaction with the chosen treatment [34]. Findings in our current study will help clinicians remain informed and provide patients with anticipatory counseling to mitigate any psychological burden that comes with unanticipated late urinary toxicities.

## Conclusion

Prostate SBRT is a rapidly emerging treatment modality for patients with localized PCa, however it is important to explore variations in late toxicity profile for any hypofractionated treatment regimen. Here we report an increased frequency and severity of LUF in patients treated with higher dose SBRT alone versus those with lower dose SBRT combined with supplemental IMRT. These variations in late LUF may be a consequence of variations in dose distribution within the prostate gland itself.

## Clinical Practice Points

Late-onset urinary symptoms are common in PCa patients following radiotherapy and negatively impact patients' QoL. Supplementing SBRT with IMRT decreases incidence and severity of late onset urinary symptoms compared to SBRT alone. This information can be used by clinicians to provide patients with anticipatory counseling to mitigate any psychological burden that comes with unanticipated late urinary toxicities.

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