



Article

# Baseline Post-Void Residual Urinary Volume Is Associated with Acute Genitourinary Toxicity After Five-Fraction Stereotactic Body Radiation Therapy for Localized Prostate Cancer

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## Abstract

**Background/Objectives:** We investigated the association between baseline post-void residual urine volume (PVR) and acute genitourinary (GU) toxicity after prostate stereotactic body radiation therapy (SBRT). **Methods:** We retrospectively analyzed 140 consecutive patients treated with 36.25 Gy in five every-other-day fractions. The primary endpoint was the maximum clinically assessed acute Grade 2 GU toxicity during treatment or within 90 days after SBRT. **Results:** Grade 2 toxicity occurred in 26/140 patients (18.6%). For PVR  $\geq$  40 mL, Grade 2 toxicity occurred in 12/34 (35.3%) versus 14/106 (13.2%) patients (unadjusted OR 3.58, 95% CI 1.46–8.82). After adjustment for age and baseline IPSS, the OR was 3.464 (95% CI 1.389–8.637;  $p = 0.0077$ ). Apparent discrimination of the adjusted model was modest (AUC 0.670 (95% CI 0.539–0.801)). **Conclusions:** Higher baseline PVR was associated with clinically assessed acute GU toxicity; the exploratory association requires prospective validation.

**Keywords:** stereotactic radiotherapy; prostate cancer; urinary toxicity

## 1. Introduction

Stereotactic body radiation therapy (SBRT) is gaining widespread acceptance as a treatment for localized prostate cancer in terms of safety and efficacy [1–5], demonstrating non-inferior outcomes when compared to conventionally fractionated radiotherapy [5] or moderately hypofractionated radiotherapy [4].

Yet, genito-urinary (GU) acute toxicity can still be a limiting factor for quality of life in a subset of patients, even requiring occasional treatment breaks for symptom control, and acute GU toxicity is a predictor for late GU toxicity in patients treated with SBRT for localized prostate cancer [6].

Therefore, defining predicting factors for GU acute toxicity for patients treated with SBRT for localized prostate cancer can help to identify subgroups of patients more likely to develop GU side effects during radiotherapy and soon after the end of treatment, ideally allowing, in a personalized medicine approach, the creation of institutional policies aiming to preserve GU treatment tolerance in subsets of patients at increased risk for toxicity.



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Furthermore, the risk of developing GU acute toxicity is likely to be multifactorial, and finding independent predictors for toxicity may permit combining them into nomograms to be implemented in clinical use for patient selection to acute toxicity prevention programs.

We investigated whether baseline PVR, a measure of bladder emptying, and the International Prostate Symptom Score (IPSS), a measure of urinary symptom burden, were associated with acute GU toxicity after five-fraction prostate SBRT. Neither measure alone establishes the presence or cause of bladder outlet obstruction.

2. Materials and Methods

We retrospectively reviewed a consecutive cohort of 140 patients with prostate cancer who were candidates for and underwent five-fraction SBRT between 2 December 2024 and 1 December 2025. No additional study-specific selection criteria were applied. Baseline PVR was measured once per patient by suprapubic ultrasound immediately after spontaneous voiding. PVR was estimated by the ultrasound device from anteroposterior and laterolateral diameters in the axial plane and the longitudinal diameter in the sagittal plane; the exact device model and calculation formula were not available in the retrospective dataset. A displayed PVR of 0 mL was retained as recorded by the ultrasound system; the instrument’s minimum detectable volume was not documented. Baseline IPSS, age, performance status, ADT prescription, and GU toxicity were abstracted from the study database. Baseline prostate volume and alpha-blocker use were not available for analysis. Patient characteristics are presented in Table 1.

Table 1. Patient characteristics.

|                            |                   |
|----------------------------|-------------------|
| Patients                   | 140               |
| Age, years, median (range) | 75 (range 60–85)  |
| KPS, median (range)        | 90 (range 80–100) |
| ADT, yes                   | 29                |
| ADT, no                    | 111               |

Patients underwent clinical assessment after each SBRT fraction and at the scheduled 3-month post-treatment visit, including clinical GU toxicity assessment and ultrasonographic PVR measurement. All 140 patients (100%) completed the 3-month follow-up visit, with GU toxicity graded according to CTCAE version 5.0. Subsequent oncological follow-up visits were scheduled every six months.

The energy used was 6 MV. All plans fulfilled target coverage and organs at risk constraints according to institutional policy.

The median age was 75 years (range 60–85).

Performance status was assessed with Karnofski Performance Status (KPS), and the median KPS was 90 (range 80–100).

Acute genitourinary (GU) toxicity was assessed during SBRT and within 90 days after treatment completion. All 140 patients underwent clinical assessment during treatment and at the scheduled 3-month follow-up visit. At that visit, the treating radiation oncologist elicited new or worsening urinary symptoms occurring since SBRT completion, predominantly urinary urgency, dysuria, and increased urinary frequency (including daytime frequency and nocturia), including symptoms that had resolved, and asked about any patient-reported use of nonsteroidal anti-inflammatory drugs (NSAIDs) specifically to manage these urinary symptoms. The endpoint was the maximum acute GU toxicity grade documented during treatment or reported retrospectively for the 90-day period, rather than the grade present solely at the 3-month visit. The overall grade was recorded using a clinical operational approach informed by CTCAE v5.0: mild symptoms without anti-inflammatory

treatment were generally assigned Grade 1, whereas patient-reported NSAID use specifically for these post-treatment urinary symptoms was used as an operational criterion for Grade 2, even if the symptoms had resolved before the follow-up visit. NSAID use alone does not necessarily satisfy event-specific CTCAE v5.0 Grade 2 criteria. IPSS change and PVR were not automatically converted into toxicity grades. Individual event-specific CTCAE categories, NSAID dose/duration, and other medication changes were not captured in the analytical database.

The International Prostatic Symptoms Score (IPSS) before the start and at the end of SBRT was available in all patients.

Twenty-nine patients (20.7%) were given androgen deprivation therapy (ADT), while 111 patients (79.3%) had no hormonal manipulation.

Twenty-four (17.1%), 80 (57.2%), and 36 (25.7%) patients had low-, intermediate-, and high-risk prostate cancer, respectively.

The exploratory endpoint was maximum acute Grade 2 GU toxicity versus Grade 0–1. Binary logistic regression estimated crude associations with PVR as a continuous measure (per 1 mL),  $PVR > 0$  versus 0 mL, and  $PVR \geq 40$  versus  $<40$  mL. The 40 mL threshold was selected pragmatically a priori as a clinically interpretable low residual-volume cutoff, rather than optimized from study outcomes; no validated threshold is implied. Age and baseline IPSS were included a priori as plausible confounders; ADT was added in a sensitivity model. All models used complete cases ( $n = 140$ ; 26 Grade 2 events) with no missing values for these covariates. Odds ratios, 95% Wald confidence intervals, and two-sided Wald  $p$ -values are reported. Apparent, in-sample ROC AUCs and 95% DeLong confidence intervals describe discrimination, without optimism correction or internal/external validation.  $\Delta$ IPSS was defined as end-of-treatment IPSS minus baseline IPSS and analyzed descriptively only.

### 3. Results

Eighty-six patients developed acute GU toxicity, while 54 patients had no acute GU toxicity. Among those patients who experienced acute GU toxicity, 60 patients had G1 toxicity and 26 had G2 toxicity. All 140 patients (100%) completed the scheduled 3-month post-treatment clinical assessment, including CTCAE v5.0 GU toxicity grading. No urinary retention requiring catheterization was reported.

Median IPSS before SBRT in the whole patient population was 3 (range 0–16); it was 3 (range 0–12) in patients with no acute GU toxicity and 4 (range 0–16) in patients with G1–G2 toxicity.

Median baseline post-void PVR in the whole patient population was 0 mL (range 0–180); it was 0 mL (range 0–90) in patients with no acute GU toxicity and 10 mL (range 0–180) in patients with G1–G2 toxicity.

Median IPSS at the end of SBRT in the whole patient population was 5 (range 0–27); it was 4 (range 0–20) in patients with no acute GU toxicity and 7 (range 1–27) in patients with G1–G2 toxicity.

$\Delta$ IPSS was calculated for each patient as end-of-treatment IPSS minus baseline IPSS. Median  $\Delta$ IPSS was +2 (range –1 to +18) in the full cohort, 0 (range 0 to +14) in patients with Grade 0 toxicity, and +2 (range –1 to +18) in those with Grade 1–2 toxicity.  $\Delta$ IPSS was a concurrent symptom measure and was not included as a baseline predictor. See Table 2.

Of 140 patients, 26 (18.6%) experienced physician-assessed Grade 2 GU toxicity, 60 Grade 1 toxicity, and 54 no GU toxicity. Baseline PVR was 0 mL in 79 patients and  $>0$  mL in 61. Grade 2 toxicity occurred in 9/79 (11.4%) and 17/61 (27.9%) patients, respectively (OR 3.01, 95% CI 1.23–7.33;  $p = 0.0156$ ). Using the prespecified exploratory threshold of  $\geq 40$  mL, Grade 2 events occurred in 12/34 (35.3%) versus 14/106 (13.2%) patients (OR

3.58, 95% CI 1.46–8.82;  $p = 0.0055$ ). With continuous PVR, the unadjusted OR per 1 mL increase was 1.0117 (95% CI 1.0022–1.0214;  $p = 0.0157$ ).

**Table 2.** IPSS and PVR in the patient population.

|                                                    | Total<br>Median (Range) | G0<br>Median (Range) | G1–G2<br>Median (Range) |
|----------------------------------------------------|-------------------------|----------------------|-------------------------|
| Patients                                           | 140                     | 54                   | 86                      |
| Baseline IPSS                                      | 3 (0–16)                | 3 (range 0–12)       | 4 (range 0–16)          |
| Baseline PVR, mL                                   | 0 (0–180)               | 0 (range 0–90)       | 10 (range 0–180)        |
| End-of-treatment IPSS                              | 5 (0–27)                | 4 (range 0–20)       | 7 (range 1–27)          |
| $\Delta$ IPSS<br>(end-of-treatment minus baseline) | 2 (–1 to +18)           | 0 (range 0 to +14)   | 2 (range –1 to +18)     |

The apparent AUC of the univariable PVR  $\geq 40$  mL model was 0.634 (95% CI 0.530–0.739); discrimination was limited.

Figure 1 presents the observed proportions of Grade 2 GU toxicity across baseline PVR categories. Logistic regression results are presented in Table 3.

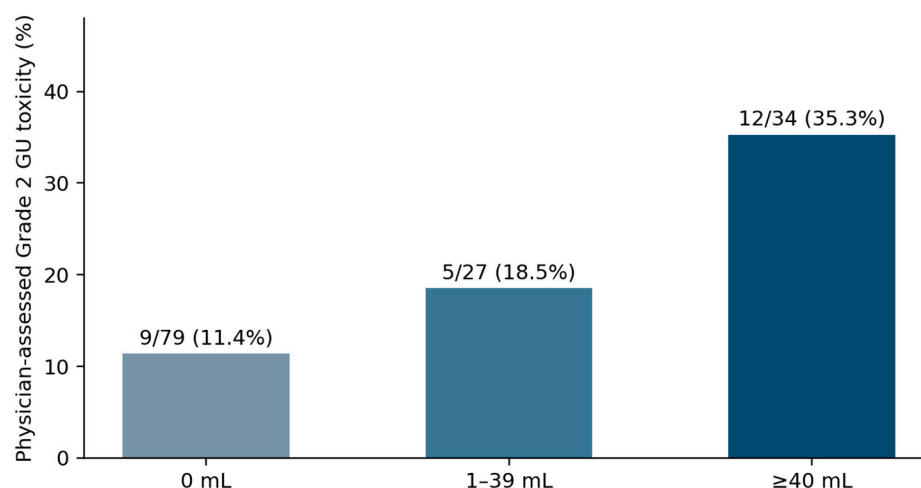


**Figure 1.** Observed proportion of physician-assessed acute Grade 2 GU toxicity by baseline PVR category. Descriptive proportions; no linear regression fitted.

**Table 3.** Logistic regression results

| Predictor                         | Endpoint              | $p$    | OR     | 95% CI        |
|-----------------------------------|-----------------------|--------|--------|---------------|
| PVR $> 0$ vs. 0 mL                | Grade 2 vs. Grade 0–1 | 0.0156 | 3.01   | 1.23–7.33     |
| PVR $\geq 40$ vs. $<40$ mL        |                       | 0.0055 | 3.58   | 1.46–8.82     |
| PVR per 1 mL                      | Grade 2 vs. Grade 0–1 | 0.0157 | 1.0117 | 1.0022–1.0214 |
| PVR $\geq 40$ ; adjusted age/IPSS |                       | 0.0077 | 3.464  | 1.389–8.637   |
| PVR per 1 mL; adjusted age/IPSS   |                       | 0.0144 | 1.012  | 1.002–1.022   |

In univariable logistic models for Grade 2 versus Grade 0–1 toxicity, no statistically significant association was detected for age, baseline IPSS, or ADT (Table 4). Nonsignificant estimates should not be interpreted as evidence of no effect.

**Table 4.** Univariable logistic models for Grade 2 versus Grade 0–1 toxicity

| Predictor                            | Endpoint              | <i>p</i> | OR    | 95% CI      |
|--------------------------------------|-----------------------|----------|-------|-------------|
| Age (per year)                       | Grade 2 vs. Grade 0–1 | 0.4179   | 1.030 | 0.959–1.107 |
| Baseline IPSS (per point)            |                       | 0.0506   | 1.116 | 1.000–1.246 |
| ADT yes vs. no                       |                       | 0.460    | 0.647 | 0.204–2.052 |
| PVR $\geq$ 40; adjusted age/IPSS/ADT |                       | 0.0062   | 3.648 | 1.445–9.208 |

After adjustment for age and baseline IPSS, PVR  $\geq$  40 mL remained associated with Grade 2 toxicity (adjusted OR 3.464 (95% CI 1.389–8.637;  $p = 0.0077$ )). The continuous PVR sensitivity model yielded an adjusted OR per mL of 1.012 (95% CI 1.002–1.022;  $p = 0.0144$ ). Apparent AUCs were 0.670 (95% CI 0.539–0.801) for the categorical PVR model and 0.662 (95% CI 0.534–0.789) for the continuous PVR model. An ADT-adjusted sensitivity model yielded an OR for PVR  $\geq$  40 mL of 3.648 (95% CI 1.445–9.208;  $p = 0.0062$ ) and an apparent AUC of 0.680 (95% CI 0.550–0.810). Complete estimates for all covariates are given in Supplementary Table S1. All models included 140 patients and 26 Grade 2 events with no missing modeled covariates.

$\Delta$ IPSS was defined as end-of-treatment IPSS minus baseline IPSS and was assessed descriptively as a concurrent symptom outcome. Because post-treatment IPSS is not a pretreatment variable, it was not used as a baseline predictor of acute GU toxicity.

Among patients with PVR = 0 mL, 9/79 (11.4%) developed Grade 2 toxicity; among those with PVR > 0 mL, 17/61 (27.9%) developed Grade 2 toxicity.

#### 4. Discussion

SBRT for localized prostate carcinoma can be safely used to give the entire dose in 5 fractions and it is a valuable tool in low, intermediate, and high-risk prostate carcinoma; further SBRT can be proposed in patients of any age since it is a well-tolerated treatment with a low frequency of gastrointestinal and genitourinary toxicity [1–5,7].

Voiding dysfunction has been investigated as a possible factor related to postoperative functional status after radical retropubic prostatectomy, and the authors concluded that the urodynamics performed, at least in selected cases, preoperatively and during follow-up could help to arrive at a precise diagnosis of the underlying dysfunction, indicate the appropriate treatment, and prevent the incidence and onset of postoperative urinary incontinence [8]. The evaluation of voiding dysfunction requires multiple steps to differentiate between outlet obstruction, bladder underactivity, and nerve dysfunction. After an initial clinical evaluation with history and physical examination and urinalysis, non-invasive investigations like post-void residual volume, uroflowmetry and renal ultrasound can be indicated. In the case of inconclusive results after non-invasive tests, invasive procedures such as cystoscopy or electromyography can help to evaluate whether structural abnormalities or neurologic origin of the urinary dysfunction are present. In men, an association was found between voiding symptoms and urgency and post-void PVR [9]. In our cohort, higher baseline PVR, a measure of bladder emptying rather than a diagnostic test for outlet obstruction, was associated with increased odds of acute GU toxicity. The observational design and modest discrimination do not establish its clinical predictive utility.

The IPSS measures lower urinary tract symptom burden and is not specific for bladder outlet obstruction. Previous studies have evaluated the tolerability of prostate SBRT in patients with high baseline IPSS [10–13]. In the present study, end-of-treatment  $\Delta$ IPSS was summarized as a concurrent symptom outcome; no association analysis of a >2-point  $\Delta$ IPSS threshold with GU toxicity is presented or claimed. No statistically significant association

between baseline IPSS and Grade 2 toxicity was detected in the present sample, although confidence intervals do not exclude a clinically relevant effect.

Detrusor overactivity consists of spontaneous, involuntary, or provoked contractions of the detrusor muscle during the bladder filling phase and it is a cause of lower urinary tract symptoms such as urgency, frequency, and urge incontinence. It can be idiopathic, neurogenic (where the causes are neurological disorders like Parkinson's disease, a previous stroke, or multiple sclerosis), or non-neurogenic (where multiple factors like constipation, urinary tract infections, and bladder outlet obstruction can be found among the determinants); it is worth noting that in a significant number of patients with prostate cancer, conditions responsible for the neurogenic or non-neurogenic types are present. Oelke and coauthors report that in patients with benign prostatic hyperplasia, the probability of detrusor overactivity rises with increasing age and bladder outlet obstruction grade [14]. Additionally, benign prostatic hyperplasia coexists in a significant number of patients with prostate carcinoma. Pepin and coauthors conclude that SBRT for clinically localized prostate cancer should not be deferred in older man solely due to concerns of increased GU morbidity [15]. No statistically significant association between age and Grade 2 GU toxicity was detected in this cohort. Frailty and age-related vulnerability may further modify the relationship between lower urinary tract symptoms and functional outcomes [16].

The association of androgen deprivation therapy (ADT) with SBRT, either short course (6 months) or long course (18–36 months), in the unfavorable intermediate and high-risk patients is still a matter of debate, and there is still a need of high quality evidence in terms of efficacy and tolerance [17,18]. The evidence regarding benefits in terms of outcome when combining ADT and SBRT derives mainly from studies where radiotherapy was conventionally fractionated or moderately hypofractionated and confirmation is needed in the setting of SBRT, given that ADT has a cardiovascular toxicity and mortality [19–21]. In our study, no statistically significant association between ADT and Grade 2 GU toxicity was detected; this finding does not establish the absence of an effect or demonstrate ADT safety.

Sorting out a subset of patients at increased risk for acute GU toxicity may allow the implementation of protocols to reduce the occurrence and severity of this side effect. In order to reduce the incidence of acute GU side effects in patients given stereotactic radiotherapy for prostate cancer, multiple steps regarding dose delivery to organs at risk, prophylactic care, and patient education are needed. The first step can be to form a multidisciplinary group where radiation oncologists, medical physics, nurses, and radiographers are involved in process of prevention of the side effects at different levels. The definition and adoption of prevention guidelines will help to standardize prevention protocols based on current evidence. Also, providing the patients with written and easily understandable material will help the patient to cope with possible side effects.

One possible approach, focusing on radiation dose reduction to organs at risk, involves planning, and patients thought to be at clinically relevant risk for acute GU toxicity could be offered a urethra-sparing technique. Urethra-sparing techniques have been reported to result in a low rate of acute and late G2 or >G2 GU toxicity [22], and two techniques are currently available, i.e., urethra-steering SBRT and urethra dose-reduction SBRT. Urethra-steering SBRT and urethra dose-reduction SBRT for prostate cancer are highly precise radiotherapy techniques that limit maximum radiation hotspots to the urethra to reduce urinary toxicity; while restricting the high-dose radiation areas away from the urethra, they deliver the prescribed dose to the remaining prostate gland, aiming to lower the risk of GU side effects without jeopardizing target volume coverage and cure probability. This requires image-guidance and the utilization of planning magnetic resonance with T2-weighted sequences to identify the urethra; additionally, advanced delivery modalities allowing steep dose gradients are mandatory. In a study where SBRT was given with a 10% dose reduction

to the urethra, the effect on urinary function and quality of life was minimal regardless of an every-other-day or once-a-week fractionation schedule [23]. In this study, a total dose of 36.25 Gy in 5 fractions was prescribed as in our patient population, while the dose to the urethra was restricted to 6.5 Gy/fraction. Hence, urethral sparing in a subset of patients at increased risk for acute GU toxicity may provide a benefit, but further investigation is needed.

Alpha-adrenergic antagonists, also known as alpha-blockers, are a type of medication that blocks the effect of alpha-adrenergic receptors in the body; by blocking these receptors, these drugs relax smooth muscles in the prostate and bladder neck, improving urine flow. Prophylactic tamsulosin was used in patients undergoing  $^{125}\text{I}$  prostate brachytherapy [24] where tamsulosin was started 4 days before prostate implantation, and it was continued for 60 days; in this study, prophylactic tamsulosin was reported to have a positive effect on urinary morbidity at week 5 after prostate implantation.

Combining urethra-sparing techniques and alpha-adrenergic antagonists has been investigated as a possible strategy to mitigate acute GU toxicity. In a study considering 102 patients with clinically localized prostate cancer treated with robotic SBRT to a total dose of 35–36.25 Gy in 5 fractions, acute urinary morbidity with the combination of prophylactic alpha-adrenergic antagonists and urethral dose reduction was investigated [25]; in this patient population, no patient experienced acute urinary retention requiring catheterization, and SBRT was well tolerated as far as acute urinary function is concerned.

Several limitations warrant consideration. This retrospective single-center study included only 26 Grade 2 events, limiting precision and model complexity. Prostate volume, alpha-blocker exposure, prior bladder outlet surgery, and urinary dosimetry were unavailable for adjustment, leaving potential residual confounding. Although all 140 patients attended the 3-month assessment, events developing and resolving between visits depended on patient recall and may have been missed, potentially underestimating transient acute toxicity; exact onset and duration could not be reconstructed reliably. The overall GU grade, rather than individual event-specific CTCAE categories, was available, and NSAID use specifically for post-treatment urinary urgency, dysuria, or increased frequency was based on patient report without detailed medication records. Importantly, NSAID use was an operational criterion for Grade 2, not necessarily equivalent to formal event-specific CTCAE v5.0 grading, creating potential outcome misclassification. Baseline PVR was obtained once; ultrasound device identification, exact volume formula, and measurement precision were not documented. In particular, recorded 0 mL versus >0 mL may be sensitive to instrument resolution and measurement error. The pragmatically selected 40 mL threshold has not been validated. Apparent discrimination was modest (adjusted categorical PVR model AUC 0.670 (95% CI 0.539–0.801)), and no internal or external validation was performed. The findings are associative and do not establish causality or justify PVR-guided prophylaxis.

## 5. Conclusions

Acute GU toxicity can significantly affect the quality of life of patients undergoing SBRT for prostate cancer, although SBRT for prostate cancer is generally well tolerated. To reduce the risk of developing acute GU toxicity, it is necessary to highlight predisposing factors for urinary morbidity.

In this retrospective study, higher baseline PVR was associated with physician-assessed acute Grade 2 GU toxicity after prostate SBRT. PVR is readily assessed by ultrasound, but its incremental clinical predictive value remains uncertain.

The possible role of baseline PVR in identifying patients for closer symptom monitoring or tailored preventive strategies merits prospective investigation. This analysis does

not demonstrate that prophylactic alpha-blockers or urethra-sparing treatment improve outcomes in patients selected by PVR.

Results should be interpreted cautiously because of residual confounding, limited discrimination, and the absence of model validation. Prospective multicenter studies incorporating prostate volume, baseline urinary medication, standardized CTCAE grading, and longitudinal symptom assessment are needed before PVR thresholds can be recommended for clinical risk stratification.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jpm16110548/s1>, Table S1: Complete multivariable logistic regression models.

**Author Contributions:** Conceptualization, E.R.; methodology, E.R. and C.F.; validation, E.R., C.F. and A.M.; formal analysis, C.F. and E.R.; investigation, A.M. and E.R.; resources, A.M. and E.R.; data curation, E.R. and C.F.; writing—original draft preparation, E.R.; writing—review and editing, E.R., C.F. and A.M.; visualization, F.C., M.C. (Margherita Crespi), A.S., M.C. (Mariateresa Cefaratti) and V.B.; supervision, A.M. All authors have read and agreed to the published version of the manuscript.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Data are unavailable due to privacy restrictions

**Conflicts of Interest:** The authors declare no conflicts of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

|       |                                                |
|-------|------------------------------------------------|
| SBRT  | Stereotactic Body Radiation Therapy            |
| GU    | Genito-Urinary                                 |
| PVR   | Post-Void Residual Urine Volume                |
| IPSS  | International Prostatic Symptoms Score         |
| Gy    | Gray                                           |
| G     | Grade                                          |
| ADT   | Androgen Deprivation Therapy                   |
| KPS   | Karnofski Performance Status                   |
| VMAT  | Volumetric Modulated Arc Therapy               |
| CTCAE | Common Terminology Criteria for Adverse Events |

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