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ORIGINAL RESEARCH

Effect of pretreatment prostate volume on urinary quality of life following intensity-modulated radiation therapy for localized prostate cancer

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Background: The aim of this study was to describe the effect of pretreatment prostate volume on urinary quality of life after intensity-modulated radiation therapy (IMRT) for clinically localized prostate cancer.

Methods: A total of 368 men treated with prostate IMRT (77.4–81 Gy) were stratified into three gland volume groups, ie, <30 g (group 1), 30–60 g (group 2), and >60 g (group 3). Post-IMRT urinary function was evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 genitourinary guidelines at one year post-IMRT, and surveyed by the International Prostate Symptom Score (IPSS) before treatment, and then at one month and one year post-IMRT.

Results: Late (one year post-IMRT) CTCAE version 4.0 genitourinary toxicity occurred in 11/368 (3.0%) men, but was not severe (grade ≥ 3); total toxicity was similar between the prostate volume groups ($P = 0.86$). Continuous prostate volume neither correlated with ($P = 0.50$) nor predicted late genitourinary toxicity (univariate odds ratio 0.99, 95% confidence interval 0.96–1.02). The total IPSS cohort, group 1 (<30 g) and 2 (30–60 g), showed a similar IPSS trend of elevation from pretreatment baseline to one month post-IMRT (each $P < 0.01$), then a reduction to baseline at one year (each $P < 0.01$). Group 3 (>60 g) had the highest pretreatment IPSS, but uniquely showed a better urinary symptom trend than the smaller volume groups, with similar IPSS from baseline to one month post-IMRT ($P = 0.88$) and improved post-treatment IPSS from baseline at one year ($P = 0.003$).

Conclusion: Pretreatment prostate volume and initial IPSS scores were not associated with increased late genitourinary toxicity after IMRT in our series. Patients with smaller prostates had an initial increase in urinary symptoms, but returned to baseline at one year. Larger prostate glands (>60 g) had comparatively worse pretreatment symptoms, but at one year showed an overall improvement in IPSS versus baseline.

Keywords: prostate, volume, radiation, intensity-modulated radiation therapy, urinary, International Prostate Symptom Score, toxicity, Common Terminology Criteria for Adverse Events

Background

Prostate cancer is the leading nondermatological cancer and the second most common cause of cancer death in US males, with an estimated 2011 incidence and mortality of 240,890 and 33,720 men, respectively.[1] External beam radiation therapy (EBRT) is one of the conventional curative treatment options for localized prostate adenocarcinoma, along with brachytherapy and radical prostatectomy. Because the overall oncological outcomes are similar between the different treatment options, there has been increasing focus on toxicity outcomes. Although high precision, tighter treatment margins, and better sparing of the bladder and rectum are advantages of intensity-modulated

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radiation therapy (IMRT), gastrointestinal and genitourinary toxicities are important treatment concerns.[2–4] Pretreatment prostate gland volume has consistently been shown to predict genitourinary toxicity after brachytherapy,[5–8] likely due to a combination of both procedural trauma and radiation effects. More recently, pretreatment prostate size has come under investigation, with potential implications for post-EBRT urinary toxicity and quality of life.

We are aware of only two studies reporting the impact of pretreatment prostate volume on EBRT-associated genitourinary toxicity and bothersome urinary symptoms. Pinkawa et al[9] compared small prostates (11–43 cm^3) and large prostates (44–151 cm^3), and found that the latter had more bothersome urinary symptoms pretreatment and on the last day of three-dimensional conformal radiation therapy; however, prostate volume did not differentially impact urinary health-related quality of life scores from 2 months after completion of radiotherapy.[9] Subsequently, Aizer et al[10] reported that patients with prostate volumes above 50 cm^3 had higher rates of acute severe genitourinary toxicity, but late genitourinary toxicity was not addressed.

In order to inform patients about the side effects of radiotherapy and expectations for recovery, we analyzed acute and late urinary toxicity in a group of consecutively enrolled men. The aim of this study was to examine and describe the effect of pretreatment prostate volume, using three size groups (<30 g, 30–60 g, and >60 g), on progression of urinary symptoms and severity of late urinary toxicity after completion of IMRT. We hope to incorporate our findings into evidence-based counseling before patients commence IMRT.

Materials and methods

Patients and study design

This study was approved by the institutional review board at the University at Buffalo School of Medicine and Biomedical Sciences. We retrospectively reviewed the electronic medical records of 368 consecutive men treated with IMRT for clinically localized prostate cancer at two radiation oncology facilities. No patients had had prior EBRT or brachytherapy. All patients had transrectal ultrasound prostate volume measurements at the time of prostate biopsy. Prostate volume was calculated by the height × width × length formula using the ultrasound computer. These volume measurements were used to stratify patients into three prostate size groups, ie, <30 g (group 1), 30–60 g (group 2), and >60 g (group 3). Volume group cutoffs were selected in 30 g increments because the upper standard deviation from the total cohort mean (41.2 ± 20.9 g) was approximately 60 g; furthermore, our largest volume group threshold of 60 g has been reported as the upper size limit for prostate brachytherapy, beyond which adverse urinary symptoms, such as prolonged retention, are increased compared with smaller prostates.[11]

Radiation treatment

Radiation was delivered using IMRT and daily imaging, with 77.4–81 Gy in 180 cGy daily fractions prescribed for the planning target volume. Three gold fiducial markers were placed into the prostate gland prior to treatment and were used for daily imaging with either orthogonal kV imaging or cone-beam computed tomography. Patients underwent a computed tomography simulation in the supine position with a comfortably full bladder and an evacuated rectum from a bowel preparation starting 12 hours previously. Most patients underwent a planning magnetic resonance imaging scan for better visualization of the prostate. The planning target volume was created by applying a 7 mm margin around the prostate in all directions except posteriorly, where only a 5 mm margin was applied. Planning optimization used common criteria to evaluate the treatment plan, as previously reported.[12] The patients were treated using Varian iX or Varian Trilogy linear accelerators (Varian Medical Systems, Palo Alto, CA). IMRT treatment delivery was via VMAT using RapidArc or a static 7 field IMRT technique. Both techniques used 6 MV photons. Neoadjuvant, concurrent, or adjuvant hormonal therapy was initiated as deemed clinically appropriate, for a recommended duration of 2 years, as per our institutional best practice standards.

Symptom progression and late toxicity

In order to quantify the effects of IMRT on urinary quality of life, post-treatment adverse urinary outcomes were evaluated by two modalities, ie, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 guidelines[13,14] and the validated International Prostate Symptom Score (IPSS) questionnaire.[15,16] Genitourinary toxicity defined per CTCAE version 4.0 was graded in all 368 men of the initial cohort at one year after completion of the IMRT treatment course. In order to trend urinary symptoms, we used the IPSS, which calculates a numeric score using seven questions, each answered on a 0–5 scale, that target the spectrum of lower urinary tract symptoms, ie, incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. IPSS values (potential score range 0–35) are symptomatically categorized as mild (0–7), moderate (8–19), or severe (20–35). We defined late

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genitourinary toxicity as those symptoms present beyond 90 days after IMRT completion and measured at one year post-IMRT. IPSS scores and CTCAE toxicity grades were obtained prospectively for all patients.

Statistics

Statistical analysis was performed using the IBM® Statistical Package for the Social Sciences® (SPSS Inc, Chicago, IL) version 19.0 software. Continuous pretreatment variables (age, prostate volume) were expressed as means and compared between the prostate volume groups by one-way analysis of variance with Bonferroni multiple comparisons testing. Categorical pretreatment variables (clinical stage, total Gleason score, alpha-adrenergic blocking therapy, hormonal therapy, prior transurethral resection of the prostate or transurethral microwave thermotherapy, IMRT prescription dose) and CTCAE genitourinary toxicities were expressed as percentages and compared between volume groups by Chi-square test. Univariate logistic regression analysis was used to assess the impact of prostate volume as a continuous variable and other pretreatment factors on prevalence of CTCAE genitourinary toxicity. Before and after volume stratification, repeated-measures one-way analysis of variance was used for comparison of absolute mean IPSS values across measured time points within each group, and the significance of IPSS differences between any two time points was assessed using the paired *t*-test. The Kruskal–Wallis test was used to compare IPSS and ΔIPSS (post-treatment minus pretreatment IPSS) medians between the volume groups, and the Mann–Whitney test was used for multiple comparisons of IPSS measures reaching significance on the Kruskal–Wallis test. The Pearson correlation was used to measure the strength of linear dependence between two variables. All reported *P* values are two-sided. Statistical significance was considered at $P < 0.05$.

Results

For the initial 368 male cohort, mean age at treatment was 68.4 ± 7.8 (range 47–87) years and overall mean prostate volume was 41.2 ± 20.9 (range 7.1–161) g. Tumor stage T1C and Gleason grade 3+3 were most common (68.5% and 59.5%, respectively). Group 1 (prostate volume < 30 g) comprised 128 men with a mean gland size of 23.1 ± 4.7 g; group 2 (prostate volume 30–60 g) comprised 185 men with a mean gland size of 42.2 ± 8.5 g; and group 3 (prostate volume > 60 g) comprised 55 men with a mean gland size of 80.0 ± 18.5 g. Table 1 shows the available pretreatment patient characteristics across the prostate volume groups; prostate size and percentage of patients on alpha-blocker therapy were significantly different (each $P < 0.01$) between the volume groups; treatment age was significantly different between group 1 and other groups ($P < 0.01$), but age at treatment between groups 2 and 3 was similar ($P > 0.1$). Other pretreatment factors were similar across the groups. Fifteen men with incomplete IPSS surveys were excluded from IPSS-based analyses; mean prostate volumes and statistical relationships of pretreatment variables were maintained from the initial patient group to the 353 male IPSS cohort.

CTCAE analysis of genitourinary toxicity

A total of 11/368 (3.0%) men developed CTCAE version 4.0 genitourinary toxicity at one year follow-up, but none above grade 2 (see Table 2). No difference in total genitourinary toxicity was noted between the three volume groups ($P = 0.86$, Chi-square test). In the nine patients who developed grade 1 toxicity, median prostate volume was 34.3 (range 10–72) g. The prostate volumes of the two patients with grade 2 toxicity were 20.2 g and 57 g. No correlation was observed between pretreatment prostate volume as a continuous variable and CTCAE genitourinary toxicity ($P = 0.50$, Pearson correlation). Using univariate logistic regression, continuous pretreatment gland volume did not predict genitourinary toxicity at one year post-IMRT (odds ratio [OR] 0.99, 95% confidence interval [CI] 0.96–1.02; $P = 0.50$).

Analysis of urinary symptom progression using IPSS

The overall median pretreatment IPSS score was 7 (range 0–32), at one month post-treatment was 10 (range 0–35), and one year post-treatment was 6 (range 0–31). After prostate volume stratification, median pretreatment IPSS increased with prostate size, ie, group 1 (<30 g) 6.0, group 2 (30–60 g) 7.0, and group 3 (>60 g) 12.0 ($P < 0.01$, see Table 3 for ranges). Median one-month IPSS was 10.0 for each prostate volume group ($P = 0.87$); median one-year IPSS was also similar across groups, ie, 5.0 for group 1 and 7.0 for groups 2 and 3 ($P = 0.053$). Overall median IPSS increased from baseline to one month ($\Delta IPSS_{1\ month}$) by 2.0 (range –22 to 21). Median $\Delta IPSS_{1\ month}$ for group 3 was –1.0 and significantly improved (negative ΔIPSS indicates urinary symptom improvement from baseline) compared with the other groups ($P = 0.001$); median $\Delta IPSS_{1\ month}$ for groups 1 and 2 was similar (4.0 and 2.0 respectively, $P = 0.11$). Overall, there was no change in median IPSS from baseline to one year ($\Delta IPSS_{1\ year} = 0.0$, range –24 to 20). There was a

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Table 1 Pretreatment patient factors

Pretreatment factor	Group I (<30)	Group II (30–60 g)	Group III (>60 g)	*P*
No pts	128	185	55	
Race (%)				
White	74.2	67.0	70.9	
Black	4.7	1.6	5.5	
Hispanic	0	2.7	0	
Not reported	21.0	28.6	23.6	
Age (yrs)	66.1 ± 8.5*	69.4 ± 7.4	70.5 ± 6.3	<0.01*
Prostate Volume (grams)	23.1 ± 4.7	42.2 ± 8.5	80.0 ± 18.5	<0.01
Clinical stage (%)				0.45
T1-T2a	93.8	94.6	98.2	
T2b-T3	6.3	5.4	1.8	
Gleason score, sum (%)				0.92
≤7	88.3	89.7	89.1	
≤8	11.7	10.3	10.9	
Alpha-blocker (%)				<0.01
Yes	14.1	17.3	40.0	
No	85.9	82.7	60.0	
Hormonal therapy (%)				0.39
Yes	9.4	14.6	12.7	
No	90.6	85.4	87.3	
Prior TURP (%)				0.31
Yes	7.0	3.2	5.5	
No	93.0	96.8	94.5	
Prior TUMT (%)				0.93
Yes	1.6	2.2	1.8	
No	98.4	97.8	98.2	
IMRT prescription dose (%)				0.25
77.4 Gy	75.0	82.7	78.2	
79.2-81 Gy	25.0	17.3	21.8	

Notes: Continuous variables were compared by one-way ANOVA with Bonferroni multiple comparisons testing and categorical variables were compared by Chi-Square test ($P < 0.05$ considered significant for all analyses). *Mean treatment age is different between groups I v. II ($P < 0.01$) and I v. III ($P < 0.01$), but similar between groups II v. III ($P > 0.1$).
Abbreviations: TURP-transurethral resection of the prostate; TUMT, transurethral microwave thermotherapy; IMRT, intensity modulated radiation therapy.

statistically significant decrease in median IPSS scores only in group 3 prostates from baseline to one year ($P = 0.003$). This represents no change in IPSS scores for small (<30 g) and medium (30–60 g) prostate sizes at one year, and represents a median IPSS improvement of –3.0 in large (>60 g) prostate sizes at one year.

The collective cohort and group 1 (<30 g) and 2 (30–60 g) showed similar mean IPSS trends across the follow-up points (see Figure 1); after IPSS elevations from pretreatment baseline to one month post-IMRT (each $P < 0.01$), a reduction to baseline values was observed at one year post-treatment (each $P < 0.01$). Pretreatment and one-year post-treatment IPSS values were similar for the ungrouped collective cohort ($P = 0.15$), and for group 1 ($P = 0.63$) and group 2 ($P = 0.49$). Group 3 (>60 g) had the highest mean pretreatment IPSS ($P < 0.01$) but did not show a one-month

Table 2 CTCAE genitourinary (GU) toxicity one year after IMRT

GU toxicity grade (CTCAE v4.0)	Group I (<30 g)	Group II (30–60 g)	Group III (>60 g)	Total cohort (N = 368)
0	124 (96.9%)	179 (96.8%)	54 (98.2%)	357 (97.0%)
1	3 (2.3%)	5 (2.7%)	1 (1.8%)	9 (2.5%)
2	1 (0.8%)	1 (0.5%)	0	2 (0.5%)
≥3	0	0	0	0
Any toxicity* (Grade > 0)	4 (3.1%)	6 (3.2%)	1 (1.8%)	11 (3.0%)

Notes: CTCAE toxicity grading: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death. Percentages = (# patients with toxicity grade)/(total # of patients in group). *Any toxicity (grade > 0) between the 3 volume groups not different by Chi-Square test ($P = 0.86$).
Abbreviations: CTCAE, common terminology criteria for adverse events; IMRT, intensity-modulated radiation therapy.

Table 3 Median IPSS and IPSS between prostate volume groups

IPSS	Group I (<30 g)	Group II (30–60 g)	Group III (>60 g)	P‡
Pretreatment	6.0	7.0	12.0	<0.01
	(range: 0–32)	(range: 0–32)	(range: 0–28)	
1 month post-tx	10.0	10.0	10.0	0.87
	(range: 0–35)	(range: 0–35)	(range: 0–32)	
1 year post-tx	5.0	7.0	7.0	0.053
	(range: 0–31)	(range: 0–25)	(range: 1–31)	
$\Delta IPSS_{1\ month}$	4.0	2.0	−1.0*	0.001*
	(range: −16 to 20)	(range: −18 to 21)	(range: −22 to 19)	
$\Delta IPSS_{1\ year}$	0.0	0.0	−3.0*	0.003*
	(range: −15 to 20)	(range: −24 to 16)	(range: −23 to 19)	

Notes: Total IPSS cohort N = 353 men. ‡Kruskal–Wallis test was used for comparison of median IPSS and ΔIPSS values across the 3 volume groups, $P < 0.05$ denotes significant difference across groups. *Mann–Whitney multiple comparisons testing: $\Delta IPSS_{1\ month}$ is different between groups III v. I ($P < 0.01$) and III v. II ($P < 0.01$), but similar between groups I v. II ($P = 0.11$); $\Delta IPSS_{1\ year}$ is different between groups III v. I ($P < 0.01$) and III v. II ($P < 0.01$), but similar between groups I v. II ($P = 0.61$).

Abbreviation: IPSS, international prostate symptom score.

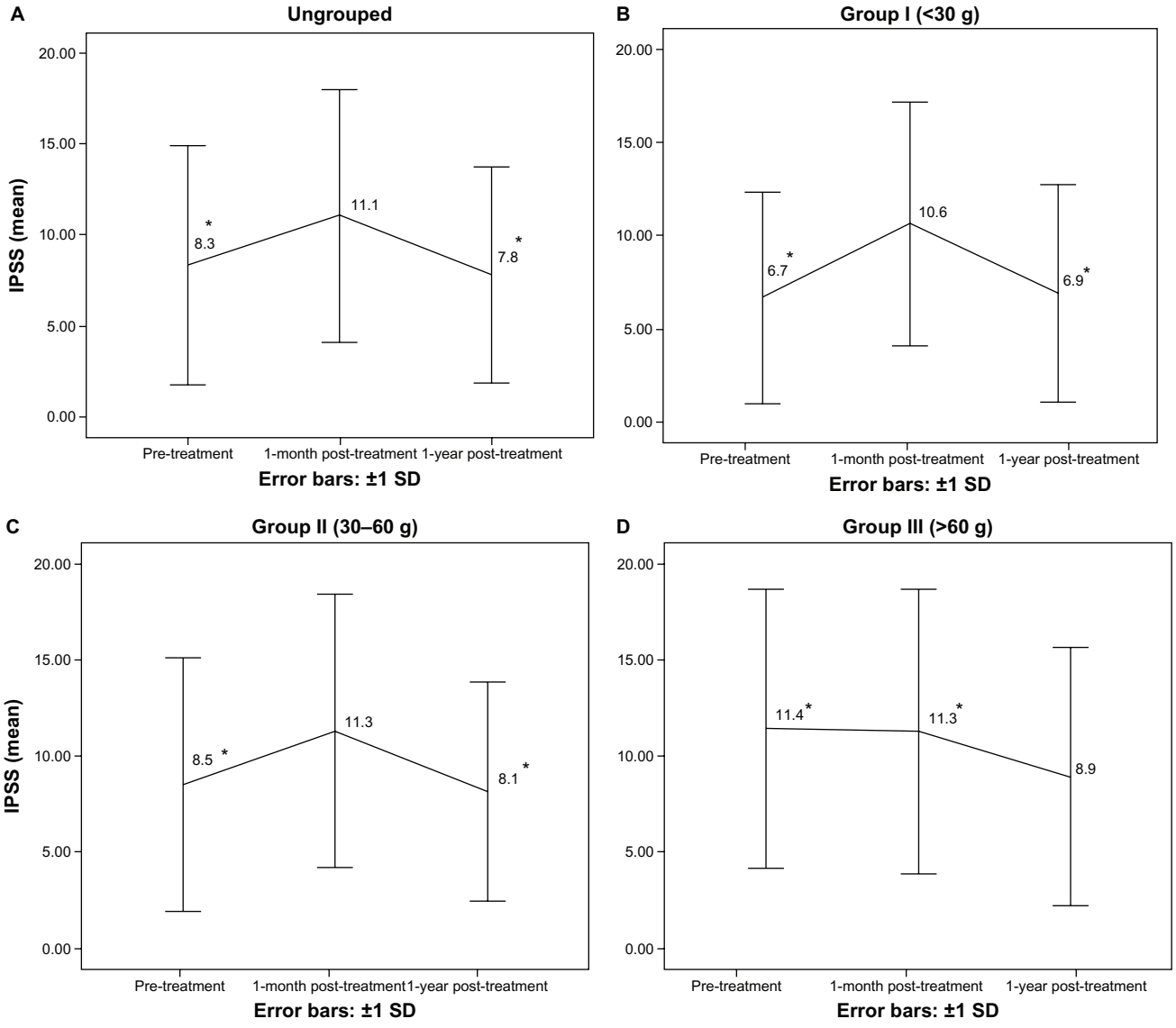

Figure 1

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post-treatment symptom spike, instead remaining stable for pretreatment and one month post-treatment IPSS ($P = 0.88$). Group 3 showed a mean IPSS reduction from one month to one year post-treatment that was similar to that in the other two volume groups ($P = 0.40$); however, the largest volume group uniquely showed a mean one-year post-treatment IPSS that improved beyond its baseline ($P = 0.003$).

For the ungrouped collective cohort, pretreatment IPSS correlated positively (r = 0.28) with pretreatment prostate volume ($P < 0.01$, Pearson correlation); after volume stratification, this correlation was more pronounced (r = 0.44) only in the largest volume group ($P < 0.01$). Group 3 also showed a positive correlation (r = 0.36) between one-year post-treatment IPSS and pretreatment volume ($P = 0.01$). Absolute one-month and one-year post-treatment IPSS values were similar between the volume groups ($P = 0.87$ and $P = 0.053$, respectively). Total CTCAE genitourinary toxicity in this cohort was 10/353 (2.8%). Pretreatment IPSS did not correlate with CTCAE genitourinary toxicity at one year post-treatment ($P = 0.50$), and did not predict for toxicity on univariate logistic regression (OR 1.05, 95% CI 0.96–1.1, $P = 0.30$). One-year post-IMRT IPSS in the patients with CTCAE genitourinary toxicity was significantly higher than in the men without genitourinary toxicity (12.0 ± 6.1 versus 7.7 ± 5.9, $P = 0.03$).

Analysis of remaining pretreatment variables

The remaining pretreatment variables (ie, age and categorical factors, as shown in Table 1) were evaluated for interaction with CTCAE genitourinary toxicity and IPSS trends. In the initial cohort, pretreatment alpha-blocker therapy predicted for increased CTCAE genitourinary toxicity on univariate logistic regression (OR 3.6, 95% CI 1.1–12.2; $P = 0.04$); 72 of 368 (19.6%) men received pretreatment alpha-blockers, including five of the 11 (45.5%) men who developed CTCAE genitourinary toxicity. Patients who received pretreatment alpha-blocker therapy had a larger mean pretreatment prostate volume than those who did not (50.9 ± 27.5 g versus 39.1 ± 18.5 g, $P < 0.01$). In the ungrouped collective IPSS cohort, pretreatment alpha-blocker therapy showed a significant association with measured IPSS values ($P < 0.01$ for between-measurement effects, repeated-measures one-way analysis of variance). Table 4 shows that 67 of 353 (19.0%) patients on alpha-blockers started with a higher mean pretreatment IPSS, but experienced an attenuated rise in $\Delta IPSS_{1\ month}$ ($P = 0.02$) and improved $\Delta IPSS_{1\ year}$ ($P = 0.02$) compared with the men not on alpha-blockers. Use of an alpha-blocker did not show a confounding interaction with our prostate volume-stratified IPSS findings ($P = 0.06$ for between-measurement interaction effects, repeated measures one-way analysis of variance). Observed IPSS trends, including IPSS improvement in group 3 (>60 g), remained statistically significant after exclusion from IPSS cohort analysis of men on alpha-blockers. Because the volume group and alpha-blocker interaction approached significance ($P = 0.06$), a within-group analysis of alpha-blocker effects on IPSS was performed. Numbers of patients on pretreatment alpha-blockers after volume grouping were as follows: group 1 (<30 g) 15/121 (12.4%); group 2 (30–60 g) 31/178 (17.4%); and group 3 (>60 g) 21/54 (38.9%, $P < 0.01$ on Chi-square test). Only group 2 patients on alpha-blockers showed an improved mean $\Delta IPSS_{1\ year}$ versus their counterparts not on alpha-blockers (–3.9 ± 9.4 versus 0.39 ± 5.9; $P = 0.02$, unpaired *t*-test). Other pretreatment variables did not predict for CTCAE genitourinary toxicity on univariate analysis (each $P > 0.1$) and did not show a significant association with IPSS findings (each $P > 0.1$).

Table 4 Total cohort mean IPSS by pretreatment alpha-blocker

IPSS	Pretreatment alpha-blocker		*P*
	Yes (N=67)	No (N=286)	
Pretreatment	12.2 ± 8.0	7.4 ± 5.9	<0.01
1 month post-tx	12.7 ± 7.5	10.7 ± 6.8	0.04
1 year post-tx	9.5 ± 7.4	7.4 ± 5.5	0.03
$\Delta IPSS_{1\ month}$	0.49 ± 9.0	3.3 ± 6.8	0.02
$\Delta IPSS_{1\ year}$	–2.6 ± 9.0	0.01 ± 5.6	0.02

Notes: Unpaired t-test was used for comparison of mean IPSS values between alpha-blocker treatment groups; $P < 0.05$ considered significant.
Abbreviation: IPSS, international prostate symptom score.

Discussion

Our study describes the impact of pretreatment prostate volume on progression of urinary symptoms and severity of late (one year post-treatment) urinary toxicity after IMRT monotherapy. The total National Cancer Institute CTCAE version 4.0 genitourinary toxicity in our series was exceptionally low (3.0%), with no severe (grade ≥ 3) toxicity observed. Similarly low severe late genitourinary toxicity rates after IMRT have been described previously. Eade et al reported a 0.5% risk of late grade 3 genitourinary toxicity after IMRT, using 3-year Kaplan–Meier estimates of a modified Radiation Therapy Oncology Group toxicity scale, and the risk of late grade ≥ 2 genitourinary toxicity was 3.5%.[17] Mohammed et al reported an incidence of 4.1% for late Common Toxicity Criteria version 3.0 genitourinary toxicity grade ≥ 3 at 1.1 years after IMRT.[18] Appropriate time points for late toxicity

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outcomes in IMRT are still being resolved, and follow-up in our patient series beyond one year post-radiotherapy may bear witness to developing genitourinary toxicity.

No association between pretreatment prostate volume and genitourinary toxicity at one year post-IMRT was found in our patient series, with pretreatment prostate size neither correlating with (P = 0.63) nor predicting for (univariate OR 0.99, CI 0.96–1.02, $P > 0.1$) late CTCAE genitourinary toxicity. Pretreatment urinary symptom scores have been suggested to predict for post-treatment urinary toxicity.[6,19] In our IPSS cohort, pretreatment IPSS did not correlate with (P = 0.50) or predict for late CTCAE genitourinary toxicity (OR 1.05, 95% CI 0.96–1.1, P = 0.30); however, one year post-treatment, IPSS was expectedly higher in men with late CTCAE genitourinary toxicity (12.0 ± 6.1 versus 7.7 ± 5.9 in men without toxicity, P = 0.03).

We found that IPSS scores were worse at one month for smaller (≤60 g) prostate sizes but stable for larger prostates. At one year, patients with smaller-sized prostates had IPSS scores which had returned to baseline, while those with larger prostate sizes had improved from their baseline IPSS scores. Similar results were reported by Pinkawa et al,[9] who observed that their large (44–151 g) prostate group had lower/worse pretreatment urinary health-related quality of life bother scores compared with their small (11–43 g) volume group. Both prostate volume groups developed significantly more bothersome urinary symptoms only on the last day of three-dimensional conformal radiation therapy, with comparatively worse symptoms in the large prostate group. Both groups had returned to their pretreatment bother levels at 2 months post-radiotherapy, but at 16 months, only the large prostate volume group experienced a significant three-point improvement from pretreatment urinary function.

Furthermore, Malik et al[19] have previously analyzed IPSS data combined from whole-pelvic radiotherapy and IMRT. Men with moderate to poor pretreatment urinary function, defined in the study as IPSS ≥ 15, showed a 5-week post-EBRT IPSS drop of −2 points from a median pretreatment baseline IPSS of 18 ($P < 0.01$); at 40 months post-EBRT, there was an IPSS drop of −7 points from baseline ($P < 0.01$). Pretreatment IPSS in our study correlated directly with continuous prostate volume for the entire cohort (r = 0.28, $P < 0.01$) and more strongly within the largest volume group (r = 0.44, $P < 0.01$); accordingly, the post-treatment IPSS trends for the worst pretreatment urinary symptom group in the Malik et al study paralleled the IPSS findings in our largest (>60 g) volume group. Also, in the study by Malik et al, reductions from pretreatment IPSS occurred regardless of androgen deprivation therapy. This androgen deprivation therapy-independent post-radiotherapy IPSS improvement was affirmed in our study.

Possible mechanisms that may be contributing to urinary symptom improvement after EBRT have been suggested previously, and include patient subjectivity, radiation-mediated prostate gland cytoreduction, and alpha-blocking therapy.[19] Patients with large prostates and pre-existing severe urinary bother may be biased against the acute urinary morbidity from radiation and likely have well-ingrained lifestyle modifications that may prevent perception of added urinary insult from IMRT. The generally less common group of patients with a large prostate volume and minimal pretreatment urinary bother[20] may experience post-IMRT urinary symptom profiles comparable with those of patients with smaller prostates. Acute urinary symptoms (dysuria, urgency, frequency) are transient and usually subside.[21] In the largest prostate group, this recovery translated to symptom improvement beyond baseline because of IPSS stability at one month post-IMRT unique to this group. IPSS improvement after one month, by essentially the same magnitude in all size groups, may reflect recovery from uniform IMRT dosing across prostate volumes. The shrinking effect of radiotherapy on the prostate is a known clinical finding, secondary to cellular water loss and fibrosis.[22,23] Recent studies show that IMRT induces volume decreases prominently in the peripheral zone (−20.3%, $P < 0.001$) and central gland (−8.4%, $P < 0.005$), with the main shrinking effect seeming to occur during IMRT.[24,25] Applying these findings to our study, our group with the largest prostate volume may be experiencing more available cytoreduction during radiotherapy that is offsetting the IMRT-induced acute-phase edema or inflammatory reaction, allowing this group to remain acutely symptomatically stable from baseline. In contrast, smaller prostate groups may not experience adequate volume shrinkage to counteract the acute urinary morbidity from radiation.

Analysis of the remaining pretreatment factors in our study showed that patients on alpha-blockers generally had larger pretreatment prostate volumes (50.9 ± 27.5 g versus 39.1 ± 18.5 g, $P < 0.01$). On univariate analysis, presence of alpha-blocker therapy predicted for increased CTCAE genitourinary toxicity (OR 3.6, 95% CI 1.1–12.2; P = 0.04); therefore, men with pretreatment urinary symptoms severe enough to need alpha-blocker therapy should be advised of the higher potential risk of genitourinary toxicity at one year post-IMRT. Use of alpha-blockers did not show a confounding interaction with the IPSS findings grouped according to prostate volume, and our observed trends in IPSS improvement remained statistically significant even

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after exclusion of men on alpha-blockers from the IPSS cohort analysis. Although the collective group of patients on alpha-blocker therapy showed a comparatively smaller elevation in $\Delta IPSS_{1\ month}$ and improved $\Delta IPSS_{1\ year}$ (see Table 4), further volume-grouped analysis revealed that only group 2 (30–60 g) patients using alpha-blocking therapy had such a similarly favorable IPSS trend relative to their counterparts not using alpha-blockers.

These data are important for several reasons. First of all, they represent a large number of patients in a community setting treated with IMRT and use both physician-scored as well as patient-scored toxicity metrics. Therefore, our findings are very relevant for community physicians in discussion of treatment-related genitourinary toxicity in terms of what patients can potentially expect from radiotherapy for prostate cancer. We feel it is important that worse pretreatment IPSS did not predict for late CTCAE genitourinary toxicity and that pretreatment prostate size was also not associated with late genitourinary toxicity. Similarly, we found that IPSS scores returned to baseline at one year for small (<30 g) and medium (30–60 g) prostates and improved versus baseline for large (>60 g) prostates. This is valuable in counseling patients as to when they should expect genitourinary function to return to normal and is important in that patients with large prostates are not likely to have an increase in genitourinary toxicity at one month or to have an improvement in IPSS score at one year. These data are useful in helping patients decide on treatment options, especially given that brachytherapy is known to increase late toxicity in patients with large prostates.

One of the weaknesses of the study is its retrospective nature, although this weakness was in part tempered by prospective collection of IPSS. A shortcoming in our IPSS collection was not doing so during radiotherapy, which may have provided a useful datum point in trending progression of urinary symptoms. Also, we were unable to control for alpha-blocker usage. Our use of patient-subjective IPSS warranted addressing the potential influence of pretreatment alpha-blocker therapy, given that alpha-blocker therapy does not affect prostate volume and is a routine consideration during radiotherapy,[26–28] but investigating alpha-blocker effects was not a primary aim in this study. Therefore, an inherent analytic weakness is our lack of differentiation between types of pretreatment alpha-blocking medication, ie, prophylactic, symptomatic, or chronic.

Conclusion

Pretreatment prostate volume was not associated with increased late genitourinary toxicity after IMRT in our series. The observed urinary morbidity in our patients with smaller prostates (<60 g) was early and self-limiting; in comparison, larger glands (>60 g) had worse baseline urinary symptoms, but showed a distinctly more favorable symptom trend from pretreatment to one year post-treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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