

Prostatic zonal parameters and lower urinary tract symptoms as quantified via magnetic resonance imaging

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ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is a common diagnosis among aging males; however, the relationship between prostate volume and lower urinary tract symptoms (LUTS) severity is imperfect. The goal of this study was to comprehensively investigate the relationship between various prostate zone-based parameters measured using magnetic resonance imaging (MRI) and LUTS.

Methods: Data were retrospectively collected for 144 patients who underwent MRI between 2015 and 2017 at a single institution. Prostate volumes were measured on sagittal and axial T2 weighted using the prostate ellipsoid formula.

Results: Only transition zone thickness (TZT) correlated with International Prostate Symptom Score (IPSS) (Pearson's $\rho=0.33$; $p=0.007$). The intraprostatic protrusion (IPP) component ($\rho=0.261$; $p=0.036$), transitional zone volume (TZV) ($\rho=0.264$; $p=0.034$), and TZT (Pearson's correlation 0.422 ; $p<0.001$) all correlated with worsening QoL scores. In total, 97.9% of men had the presence of an IPP (>0 mm) and larger IPPs were found in older men with higher postvoid residual volumes. Larger peripheral zone volume (PZV) (odds ratio [OR] 3.62, 95% confidence interval [CI] 1.07–12.30, $p<0.05$), TZV (OR 6.00, 95% CI 1.69–21.35, $p<0.05$), and TZT (OR

4.00, 95% CI 1.17–13.69, $p < 0.05$) were predictive of developing severe LUTS; however, IPP ($p = 0.122$) was not.

Conclusions: TZV, TZI, and IPP all demonstrated a role in the evaluation of LUTS with predictive capabilities. IPP is very common but not always clinically significant. Clarifying more precise zonal parameters and their relationship with LUTS may ultimately help clinicians guide the need for surgical intervention more precisely.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common diagnosis amongst aging males as approximately half of all men have histologically proven hyperplasia over the age of 50, which further increases to a prevalence of approximately 80% by the age of 80.¹ Concurrently, the likelihood of developing lower urinary tract symptoms (LUTS) increases significantly with age.² BPH with LUTS is associated with a decreased quality of life (QoL), negatively impacts mental health and may also lead to significant complications including acute urinary retention and urosepsis.^{3,4}

The relationship between prostate volume and LUTS severity is imperfect.^{5,6} The current gold standard for calculating prostate volume is using the ellipsoid formula (i.e., transverse diameter x anteroposterior diameter x length x 0.52), most commonly with images obtained by ultrasonography.⁵ This model assumes a regular ellipsoid shape, however, prostatic growth is heterogenous, and thus, this simplification may explain the lack of a clear association between prostate size and symptoms.

Delineating prostatic zonal anatomy for differential growth patterns likely better explains the association with LUTS. Given BPH arises from the transition zone, previous studies have investigated the association between transitional zone volume (TZV) and transitional zone index (TZI) on LUTS as well as responses to therapy.^{7,8} In addition, peripheral zone thickness (PZT) was demonstrated to be an independent parameter associated with LUTS in BPH.⁹ Chia, et al. were the first to describe intraprostatic protrusion (IPP) as an anatomical factor which could successfully predict bladder outlet obstruction.¹⁰ The IPP is generally defined as the distance between the bladder neck and the tip of the median lobe. Given the variety of prostatic parameters that may show clinical promise, we sought to comprehensively investigate the relationship between prostate zone-based parameters and LUTS.

METHODS

Patients

There was a total of 144 patients who underwent a multiparametric magnetic resonance imaging (MRI) between 2015 and 2017 a single center had their data retrospectively collected. These patients underwent an MRI and transrectal MRI-guided prostate biopsy for suspicion of prostate cancer. Patients using BPH medications were included in the study. Patients using a 5-alpha

reductase inhibitor had their PSA adjusted by doubling the value. Patients with a positive urine culture, symptoms of acute/chronic prostatitis, history of BPH surgical intervention or prostate cancer were excluded. Patients filled out International Prostate Symptom Score (IPSS) questionnaires within 6 months of their MRI. This study was approved by the Weill Cornell Medicine Institutional Review Board (IRB No. 1601016896A004).

Prostatic zone volumes

The transition zone volume represents both the central and transition zones of the prostate gland given the difficulty of defining these borders and which is consistent with the methods in previous literature.¹¹ Total prostate volume (TPV) and transition zone volume (TZV) were measured on sagittal and axial T2 weighted (MRI) images using the prostate ellipsoid formula (volume = transverse diameter x anteroposterior diameter x length x 0.52).

The following parameters were calculated from prostate MRI images: peripheral zone volume (PZV) = TPV - TZV; transition zone index (TZI) = TZV/TPV; transition zone density (TZD) = PSA/TZV. Thickness of the transition zone (TZT) and peripheral zone (PZT) were measured on axial T2W MRI images as the maximal straight anterior-posterior distance between the outer and inner margins of the TZ or PZ. The IPP was measured as the vertical length of intra-vesicular prostatic tissue, drawn perpendicular to a horizontal plane over the bladder neck. The presence of an IPP was defined as >0 mm. IPP was graded according to length, with ≤ 5mm, 5-10 mm, and ≥10 mm representing Grades 1, 2 and 3, respectively.

Statistical analyses

Continuous variables were presented as medians with interquartile ranges (IQR) and categorical variables were presented as proportions (%). Data was assessed for normality using the Shapiro-Wilk test. Continuous data were compared using independent Samples Kruskal-Wallis Test. Correlations were evaluated with Spearman's Rho or Pearson's correlations, as appropriate. Linear modeling was used for continuous variables. The determination of "large volumes" in Table 3 was made using 1 standard deviation greater than the mean to represent the threshold, and the variable was subsequently dichotomized. Fisher's exact test was used to determine significance for the multivariable logistic regression model. All data were analyzed using SPSS 21.0 (IBM Corp., Armonk, NY) with a p<0.05 deemed significant.

RESULTS

There were a total of 144 men included in this study. The median age was 67 years old (yo) (61.0-72.8 yo). The majority of the cohort were white (59%). The median TPV was 51.6 ml (37.1-74.5 ml) and median prostate-specific antigen (PSA) was 6.1 ng/ml (4.5-6.1 ng/ml). Overall, 97.9% (141/144) of individuals had the presence of an IPP component (>0 mm). The remainder of the cohort summary is demonstrated in Table 1.

Figure 1. depicts the relationships between TPV, IPP, PZV, TZV, PZT, TZT and LUTS, as measured by IPSS score. On linear regression analysis, the data was most fit was for TZT

($R^2=0.109$), IPP ($R^2=0.096$) and TZV ($R^2=0.085$), however only TZT significantly correlated with IPSS (Pearson's correlation 0.33; $p=0.007$). Figure 2. Demonstrates the prostatic parameters that were significantly associated with worse QoL scores; IPP (Spearman's rho 0.261; $p=0.036$), TZV (Spearman's rho 0.264; $p=0.034$) and TZT (Pearson's correlation 0.422; $p<0.001$) all significantly correlated with worsening QoL scores.

Table 2 outlines the cohort according to IPP Grade. Men with Grade 3 IPP were significantly older ($p<0.05$), had a higher PSA ($p<0.05$) and had a higher PVR ($p<0.05$) than men with Grades 1 or 2 IPP. Q_{max} trended downwards according to IPP Grade, however, the differences were not significant ($p=0.06$).

Table 3. shows the results of multivariable logistic regression for predictors of severe LUTS (IPSS ≥ 20). Larger (i.e., 1 standard deviation or greater) PZV (OR: 3.62, 95% CI 1.07-12.30, $p<0.05$), TZV (OR: 6.00, 95% CI 1.69-21.35, $p<0.05$), and TZT (OR: 4.00, 95% CI 1.17-13.69, $p<0.05$) were associated with an increased likelihood of developing severe LUTS, however not IPP ($p=0.122$).

DISCUSSION

In this study, we examined and characterized various prostatic zonal parameters with LUTS using the advantage of precise MRI-based measurements. We observed a trend towards worse LUTS as reflected by higher IPSS scores as most prostatic variables increased in size (i.e., volume, thickness, length), although the only significant correlation was with TZT (Pearson's coefficient=0.331; $p=0.007$). Additionally, increasing TZV (rho=0.264; $p=0.34$), TZT (Pearson's correlation=0.422; $p<0.001$) and IPP (rho=0.261; $p=0.036$) all significantly correlated with worse QoL scores. Lastly, large PZV (OR: 3.62, 95% CI 1.07-12.30, $p<0.05$), TZV (OR: 6.00, 95% CI 1.69-21.35, $p<0.05$), and TZT (OR: 4.00, 95% CI 1.17-13.69, $p<0.05$) all significantly predicted a higher likelihood of developing severe LUTS. Thus, less frequently reported parameters including TZT and IPP may represent ideal candidates for predicting LUTS, obstruction and need for intervention.

Although increased prostate size is a known risk factor for developing LUTS/BPH, many men still experience LUTS without an enlarged prostate, and vice versa; these findings are further supported by the current study given TPV was not associated or predictive of LUTS/QoL metrics.

Early investigations demonstrated parameters such as the TZV and TZI measured by ultrasound correlated strongly with LUTS⁷ and responded effectively to AB and ARIs,^{12,13} however this relationship is not consistently reported.^{11,14} PZT has been explored as an alternative parameter that can be measured more readily; the principle of PZT as a proxy for LUTS is based on the presumed circle area ratio (PCAR) theory,¹⁵ which explains that higher intraprostatic pressures exert a compressive force on the PZT and thins it. A large prospective cohort of men with BPH/LUTS assessed PZT and found that it was a significant predictor of IPSS, QoL and uroflowmetry data.⁹ The only parameter in our study that correlated significantly with IPSS, QoL and predicted severe LUTS was TZT; however, a recent retrospective study of

468 men who underwent ultrasonography reported TZT and did not find significant correlations with IPSS or QoL of scores¹¹ The conflicting reports surrounding prostatic parameters and LUTS is likely due to the heavy reliance on ultrasound guided measurements. Ultrasound is highly operator dependent and is known to have substantial intra-observer variability; in one study, the variability of measuring the TPV using ultrasound was -21% to 30% and the TZV variability ranged from -17% to 18%.¹⁶

We were also interested in further elucidating the role of the IPP in LUTS. Interestingly, we demonstrated that the vast majority of men in this cohort (97.9%) had the presence of an IPP component (>0 mm), of which, 63.9% had a Grade 2 or higher IPP. Higher Grade IPP occurred in older men and manifested with higher PVRs. The initial explanation for the underlying pathophysiology of the IPP was a “ball-valve” obstruction; during voiding, the flow of urine shifts the IPP and accentuates the obstruction. In the index study, IPP correlated strongly with bladder outlet obstruction with a positive predictive value of 94% and negative predictive value of 79%.¹⁰ Subsequent reports further corroborated the relationship between IPP and obstruction.¹⁷⁻¹⁹ For assessing bladder outlet obstruction, an IPP length of 5.5 mm was 66.7% sensitive and 80.5% specific and had an area under the curve of 0.76 (95% CI 0.66-0.86).¹⁹ Although our study corroborated that higher Grade IPP manifested with higher PVRs, we did not observe any differences between IPP Grade and Q_{max} . Furthermore, we only observed a slight worsening of QoL scores between Grades 1 and 3 IPP. Contrary to previous studies, there were no differences between all 3 Grades in IPSS, and large IPPs did not predict severe LUTS.

IPP length has been demonstrated to have impacts on management strategies. Patients with Grade 3 IPP appear to have significantly less improvements in LUTS when prescribed alpha-blockers.²⁰⁻²² Furthermore, individuals on ARIs show a higher risk of treatment failure and need for surgical intervention with the presence of an IPP.²³ Additionally, a cohort of 177 men with BPH who underwent transurethral resection of the prostate were stratified into 2 groups: “significant” IPP (≥ 5 mm) and “insignificant” IPP (<5 mm); men with a larger IPP demonstrated greater symptomatic and QoL improvement.²⁴

Prostate zonal anatomy and differential growth patterns may better predict symptoms. A strength of our study is that MRI was utilized for all measurements; MRI is superior to ultrasound in determining prostate volumes and for segmenting the prostate into the various prostatic zones.^{5,25} We were able to take advantage of a cohort of men with prior MRI results but acknowledge that routine use of MRI for BPH is not relevant in the clinical setting and is not a replacement of a detailed patient history and the use of validated symptom questionnaires.

Our study advocates for further use of zonal based parameters to help elucidate voiding symptoms. TPV is often used as an important parameter for management decisions, however, clarifying more precise zonal parameters and their relationship with LUTS may ultimately help clinicians guide the need for surgical intervention more precisely.

The current study has limitations. Firstly, this cohort consisted of a relatively small sample size of predominantly white individuals and was derived from a single institution; thus,

our results should be interpreted in this context as it may impact the generalizability of our findings. Furthermore, all men in this cohort underwent an MRI as they were being investigated for prostate cancer. As such, they did not necessarily present with LUTS as their chief complaint which may bias the cohort; however, this bias would therefore represent a “conservative” estimate of the various prostatic zonal parameters and LUTS. Lastly, as this was an explorative study, multiple variables were simultaneously analyzed in our statistical analyses which may introduce the potential for a multiple comparisons bias in our results.

CONCLUSIONS

Our study provides a comprehensive evaluation of various prostatic parameters using precise MRI measurements. We re-demonstrate that TPV is not a useful predictive parameter for LUTS or QoL metrics. We found that parameters including TZV, TZT and IPP all demonstrated a role in the evaluation of LUTS with predictive capabilities. The presence of an IPP is very common, however, may not be clinically significant in many individuals. Clarifying more precise zonal parameters and their relationship with LUTS may ultimately help clinicians guide the need for surgical intervention more precisely.

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FIGURES AND TABLES

Figure 1. Linear regression and correlation of prostatic zonal parameters and International Prostate Symptom Score (IPSS) for (A) prostatic zonal volumes (PZV), and (B) prostatic zonal thickness/length. TPV: total prostate volume; TZV: transitional zone volume.

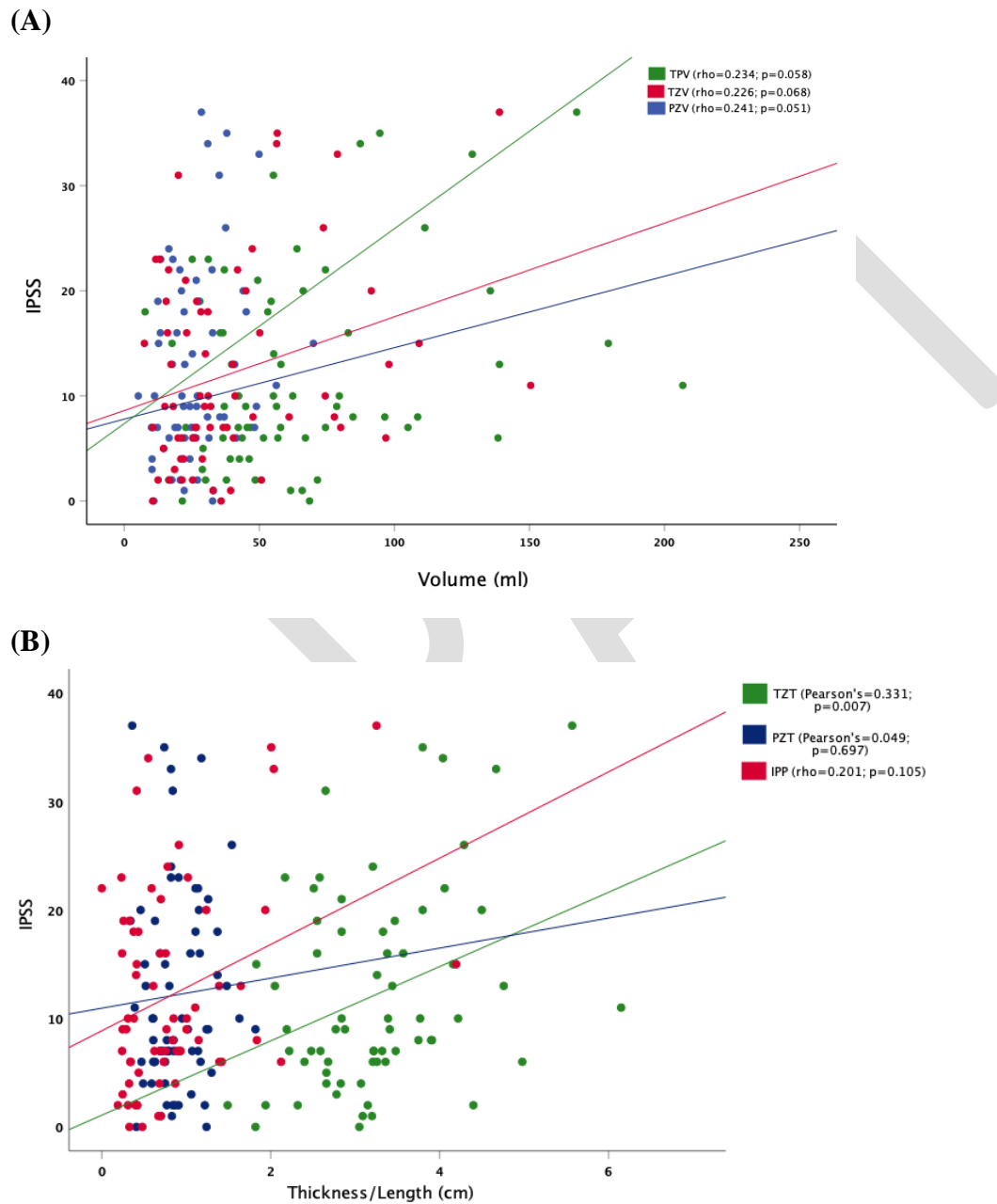


Figure 2. Linear regression and correlation of significant predictors for quality of life (QoL) scores for (A) transitional zone volume (TZV), and (B) transition zone thickness (TZT) and intraprostatic protrusion (IPP).

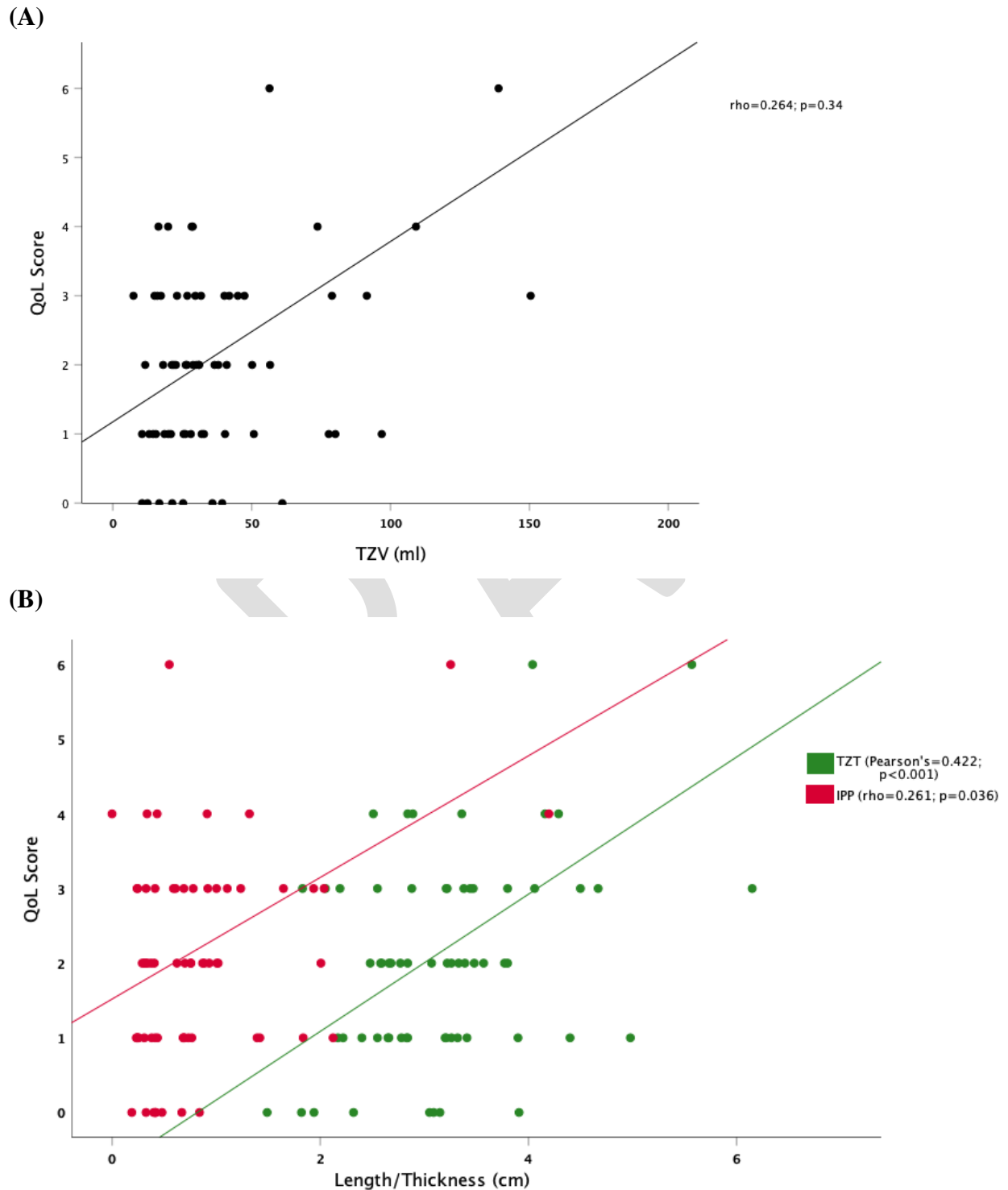


Table 1. Baseline demographic and clinical data	
Overview	
Cohort size (n)	144
Age (years)	67 (61–72.75)
White	59% (85)
Non-White	41% (59)
Alpha-blocker	35.4% (51)
5-alpha-reductase inhibitor	11.1% (16)
Comorbidity	
Body mass index (kg/m ²)	26.21 (24.05–29.25)
Coronary artery disease	10.4% (15)
Diabetes mellitus	10.4% (15)
Hypertension	47.2% (68)
Prostatic parameters and questionnaire scores	
PSA (ng/ml)	6.09 (4.54–6.09)
Total prostate volume (ml)	51.6 (37.14–74.52)
Presence of IPP (>0 mm)	97.9% (141)
Q _{max} (ml/sec)	9.6 (6.6–12.4)
Postvoid residual (ml)	41 (9–84)
IPSS	9 (6–18.25)
AUA QoL score	2 (1–3)

Data presented as median and interquartile range in parenthesis or a proportion of individuals for dichotomous data. AUA: American Urological Association; IPP: intraprostatic protrusion; IPSS: International Prostate Symptom Score; PSA: prostate-specific antigen; Q_{max}: maximum urinary flow rate; QoL: quality of life

Table 2. Cohort characteristics stratified by IPP grading			
	Grade 1 (≤5 mm)	Grade 2 (5–10 mm)	Grade 3 (≥10 mm)
Patients	36.1% (52)	41.0% (59)	22.9% (33)
Age (years)	66 (60–72) ^c	65 (60–71) ^b	71 (65–76.5) ^{b,c}
PSA (ng/ml)	5.42 (4.12–7.85) ^c	5.8 (4.8–8.2)	7 (5.39–11.15) ^c
Postvoid residual (m)	20 (0.5–62.5) ^c	40 (20–80) ^b	92 (15–249) ^{b,c}
Q _{max} (ml/sec)	11 (8.7–14)	9 (6.6–12.4)	6.8 (4.6–10.3)
IPSS	9 (2–18)	7.5 (6.75–17.25)	13 (8–21.5)
QoL score	1 (1–3) ^c	2 (1–3)	3 (1.5–3.5) ^c

Independent samples Kruskal-Wallis test. ^aSignificant difference between Grade 1 and Grade 2.

^bSignificant difference between Grade 2 and Grade 3. ^cSignificant difference between Grade 1 and Grade 3. IPSS: International Prostate Symptom Score; PSA: prostate-specific antigen; Q_{max}: maximum urinary flow rate; QoL: quality of life.

	Severe LUTS	
	OR (95% CI)	p*
TPV	2.71 (0.81–9.14)	0.095
IPP	2.47 (0.74–8.25)	0.122
PZV	3.62 (1.07–12.30)	0.037
PZT	1.54 (0.46–5.16)	0.342
TZV	6.00 (1.69–21.35)	0.005
TZT	4.00 (1.17–13.69)	0.027

N.B. Threshold for “large” was ≥ 1 SD and severe LUTS represented an IPSS ≥ 20 .

*Fisher’s exact test. CI: confidence interval; IPP: intraprostatic protrusion; LUTS: lower urinary tract symptoms; OR: odds ratio; PZT: peripheral zone thickness; PZV: peripheral zone volume; TPV: total prostate volume; TZT: transition zone thickness; TZV: transition zone thickness.

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