The role of quantitative MRI-based prostate zonal parameters in predicting clinically significant prostate cancer

A U.S. cohort

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ABSTRACT

INTRODUCTION: We aimed to investigate the clinical utility of quantitative prostatic zonal measurements on multiparametric magnetic resonance imaging (mpMRI) for the predication of clinically significant prostate cancer (csPCa).

METHODS: A retrospective, single-institution study included 144 men who underwent mpMRI from 2015–2017. Prostate zone parameters were measured on mpMRI. Correlation and multivariable analysis evaluated the relationship between prostate zone parameters and the presence of csPCa.

RESULTS: The mean age was 66.9±7.8 years old. The median (interquartile range [IQR]) prostate volume and prostate-specific antigen (PSA) were 51.6 ml (37.1–74.5) and 6.1 ng/ml (4.5–8.2), respectively. Men with csPCa had significantly smaller total prostate volume (TPV), transitional zone volume (TZV), and transitional zone thickness (TZT), and larger transitional zone density (TZD) compared to those without PCa; however, on multivariate variable analysis, only TZD maintained significance. TZD had a comparable area under the curve to PSA density (PSAD) and PSA (0.74 vs. 0.73 vs. 0.60, respectively). In a subgroup analysis of men with PCa, PSAD and TZD were significantly higher in men with Gleason grade group (GG) ≥2 compared to those with GG <2 (p=0.002); however, this significance is not maintained on logistic regression in predicting GG.

CONCLUSIONS: Quantitative features of prostate zones on MRI may aid in identifying better predictors of csPCa. Zonal-based PSA density (TZD) may be a useful marker in identifying csPCa. Further exploration is needed to understand the clinical application of larger TZV in men with csPCa compared to those with insignificant disease.

INTRODUCTION

Prostate cancer (PCa) and benign prostatic hyperplasia (BPH) are common pathologies of the prostate in older men.[1] Therefore, in patients who presents with a history of lower urinary tract symptoms (LUTS) without evidence of infection and an elevated level of prostate-specific antigen (PSA), effective management is aimed at distinguishing between the two conditions; however, confirmatory tissue samples are often needed.[2,3] Unfortunately, post-biopsy complications, such as discomfort, transient LUTs, rectal bleeding, and infectious complications that can lead to sepsis, do arise.[4]

The prostate is separated into three unique zones: a central zone (CZ), transition zone (TZ), and a peripheral zone (PZ). The majority of PCa cases originate in the PZ of the prostate (70%), but PCa can also arise in the TZ (20%) and in the CZ (10%).[5] It is well-documented that TZ volume (TZV) correlates with age and PSA and contributes to the overall increase in gland size with minimal changes in PZ volumes (PZV). Additionally, PZV is poorly correlated with age.[6,7] Large series of radical prostatectomy specimens demonstrated that tumors from larger prostates have more favorable pathological features, including Gleason grade group (GG), smaller tumor volume, and lower risk of extraprostatic extension or seminal vesicle invasion. This suggests that a larger prostate may have a protective effect against PCa by exerting a large

KEY MESSAGES

- Our work demonstrates that transition zone parameters, such as thickness and volume, correlated with urological symptom scores and the presence of clinically significant cancer.
- Intravesical prostatic protrusion significantly predicts symptom scores.
- The use of these parameters had AUC operating curve similar to PSAD.
- We hope this work will encourage the application of prostate zone on MRI in the diagnostic workup of elevated PSA.

compressive mechanical stress on the PZ, impeding tumor growth and thinning out the PZ;[8-11] however, this inverse relationship between BPH and PCa is under continuous debate due to contradictory studies and lack of thorough exploration.[3] Further consideration of prostate zones may help to define this relationship.

Technological advances in magnetic resonance imaging (MRI) have improved the ability to localize PCa and visualize the different prostate zones.[12] The clinical application of assessing prostate zones on MRI and as a non-invasive marker for patient selection needs further exploration.[13] We aimed to investigate the clinical application of quantitative prostatic zonal measurements on MRI to predict clinically significant prostate cancer (csPCa).

METHODS

This was a retrospective, single-institution study of biopsy-naive patients who underwent a mpMRI and transrectal ultrasound-guided (TRUS) prostate biopsy (two-core targeted biopsy per lesion and 12-core systematic biopsy) between 2015 and 2017. All patients were assessed for inclusion consecutively. Patients on BPH medications were included in the study. In patients who reported 5-alpha reductase (5-ARI) use, PSA was adjusted by multiplying the level by two. Patients with positive urine cultures, symptoms consistent with acute or chronic prostatitis, history of BPH procedures, or PCa were excluded. This study was approved by the Weill Cornell Medicine Institutional Review Board (IRB No. 1601016896A004).

Prostate volume measurements

Due to difficulty in distinguishing borders of the respective zones on MRI and to remain consistent with previously published urological literature, the "transition" zone in this paper represents the combined central and transition zones of the prostate.[14] Total prostate volume (TPV) and transition zone volume (TZV) was measured on sagittal and axial T2-weighted (T2W) MRI images using the prostate ellipsoid formula (volume=0.52 x length x width x height).[14]

The following parameters were calculated from prostate MRI images: PZV=TPV-TZV; transition zone index (TZI)=TZV/TPV; transition zone density (TZD)=PSA/TZV. The thickness of the transition zone (TZT) and peripheral zone (PZT) was measured on axial T2W MRI images as the maximal straight anterior-posterior distance between the outer and inner margins of the TZ or PZ. An example of prostate volume and the aforementioned calculation is provided in the online Appendix (Supplementary Figures 1–4; available at *cuaj.ca*).

Statistical methods

Distributions of variables were compared by the Chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables, which was not normally distributed. A non-parametric spearman correlation was performed to examined correlations between zonal measurements on MRI, as well as clinical outcomes, such as presence of PCa and csPCa. csPCa is defined as Gleason score ≥7 or GG ≥2. Fisher-Z-transformation was used to test the significance of correlations between groups. Logistic regression analysis in univariate and multivariate models (nominal for PCa and csPCa) was used to determine predictive factors for symptom scores and presence of PCa. Linear regression analysis was used to find predictors of American Urological Association symptom score (AUASS) and quality of life (QoL). Receiver operating characteristic (ROC) curves and area under ROC curve (AUC) were also computed to assess the diagnostic ability of MRI characteristics compared to prostate-specific antigen density (PSAD).

All statistical tests were two-sided, with $p<0.05$ indicating statistical significance. All statistics were performed using the statistical package JMP® (JMP Pro, Version 16 Software, Microsoft® Windows® for x 64; SAS Institute Inc., Cary, NC, U.S.A).

RESULTS

A total of 144 men were included in this study. The baseline demographic and clinical characteristics are summarized in Table 1. The median (interquartile range [IQR]) age was 67 (61–73) years old. White patients accounted for 59% of the patient cohort and African Americans accounted for 6.3%. Median body mass index (BMI) was 26.2 kg/m^2 (24.2–29.2) Median (IQR) prostate volume and PSA were 51.6 ml (37.1–74.5) and 6.1 ng/ml (4.5–8.2), respectively. PCa was detected on biopsy in 68 (47%) patients and csPCA was present in 36 (25%) patients. The majority (52%) of patients had ≥ Prostate Imaging-Reporting & Data System (PI-RADS) 4 lesions on multiparametric (mp) MRI. On mpMRI, most lesions were in the PZ (65%) and the rest were in the TZ (10%) or bordering both zones (19%).

Men with csPCa were older (p=0.001) compared to those without csPCa (Table 2). TPV, TZV, and TZT were significantly larger in those without csPCa (p=0.01); however, PZV and PZT were not significantly different between the groups. Additionally, PSA did not differ but PSAD and TZD were significantly higher in the csPCa (p<0.001). On multivariate regression, older age, higher BMI, and larger TZD were associated with the presence of csPCa (p≤0.001, p=0.003, p=0.01, respectively) (Figure 1A). PSAD was not associated with csPCa (p=0.11).

AUC for TZD (0.74) was comparable to that of PSAD (0.73) (Figure 1B). The highest Youden's index was at TZD of 0.28. At this point, the diagnosis of csPCa has a 64% sensitivity and 76% specificity compared to PSAD of 0.18 (at the highest Youden's index), which has a sensitivity of 53% and specificity of 86%. In the 107 patients who did not have csPCa on biopsy, using TZD as a predictor of csPCa, 76% (82/107) of those biopsies could have been avoided but 38% (14/37) of csPCa confirmed on biopsy would have been missed. Additionally, in the 69 patients with ≤PI-RADS 3 lesions on MRI, a TZD cutoff of 0.28 would have avoided 55/69 (80%) of biopsies.

Subgroup analysis of men with PCa, PSAD, and TZD was significantly higher in men with GG ≥2 compared to those with GG <2 (p=0.002); however, this significance is not maintained on logistic regression in predicting GG.

Repeat biopsy was available for 75 patients, with a median followup of 15 months (9–33). Of the 75 patients, 30 patients were upstaged on their second biopsy. Of the 30 patients, two underwent robotic radical prostatectomies, one underwent radiotherapy, and one underwent cryotherapy.

Table 1. Demographic and clinical characteristics of all patients who underwent mpMRI and targeted biopsy

Parameters	
No. of patients	144
Age (years)	
Mean (SD)	66.9 (7.8)
Median (IQR)	67 (61–72.8)
BMI (kg/m^2)	
Mean (SD)	27.1 (4.5)
Median (IQR)	26.2 (24.2–29.2)
Race	
White	85 (59.0%)
Black	9 (6.3%)
Asian	7 (4.9%)
Latino	6 (16.0%)
Other	23 (9.7%)
Not reported	14
Prostate volume (cc)	
Mean (SD)	60.4 (33.9)
Median (IQR)	51.6 (37.1–74.5)
PSA (ng/dL)	
Mean (SD)	10.5 (37.6)
Median (IQR)	6.1 (4.5–8.2)
IPSS score, median (IQR)	9 (6–18)
IPSS categories	
Mild	27 (40.91%)
Moderate	25 (37.88%)
Severe	14 (21.21%)
Qmax (cc/sec), median (IQR)	9.6 (6.6–12.4)
PVR (cc), median (IQR)	41 (9–84)
QoL score, Median (IQR)	2 (1–3)

BMI: body mass index; GG: Gleason grade group; IPP: intraprostatic protrusion; IPSS: International Prostate Symptom Score; IQR: interquartile range; mpMRI: multiparametric magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; PSA: prostate-specific antigen; PVR: postvoid residual; Qmax: maximal urinary flow rate.

DISCUSSION

There is mixed data describing the relationships between enlarged prostates and PCa. A potential relationship becomes more apparent when examining

Table 1 (cont'd). Demographic and clinical characteristics of all patients who underwent mpMRI and targeted biopsy

Parameters (cont'd)	
MRI characteristics	
PI-RADS 2	19 (13.19%)
PI-RADS 3	50 (34.72%)
PI-RADS 4	58 (40.28%)
PI-RADS 5	17 (11.81%)
BPH severity	
Mild	38 (26.39%)
Moderate	80 (55.56%)
Severe	24 (16.67%)
Not reported	1 (0.69%)
IPP, median (IQR)	0.67 (0.40–0.95)
Biopsy pathology	
No cancer	76 (52.78%)
GG1	31 (21.53%)
GG2	29 (20.14%)
GG3	2 (1.39%)
GG4	2 (1.39%)
GG5	4 (2.78%)
α-adrenergic antagonist use	51 (35.4%)
5-α reductase inhibitor use	16 (11.1%)

BMI: body mass index; GG: Gleason grade group; IPP: intraprostatic protrusion; IPSS: International Prostate Symptom Score; IQR: interquartile range; mpMRI: multiparametric magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; PSA: prostate-specific antigen; PVR: postvoid residual; Qmax: maximal urinary flow rate.

prostate parameters at a zonal level. We examined our cohort of patients who underwent a mpMRI and prostate biopsy (target and systematic) to understand the significance of prostate zone parameters in differentiating BPH and PCa. It has been proposed that a large TZ (from BPH) is protective against PCa by exerting compressive force on the PZ, therefore thinning it out; however, this is not entirely supported by this study. Our data demonstrated that TPV, TZV, and TZT were significantly larger in those with clinically insignificant PCa compared to men with csPCa (p=0.01) but PZV and PZT were not significantly different between the groups. Additionally, on Spearman correlation, TZV and PZV were directly correlated (rho=0.56, p<0.001).

Table 2. Clinical characteristics of men with and without PCa on biopsy

Parameters	No csPCa	csPCa	p
Patients, n (%)	107	37	
Age[a], years	65 (60–72)	71 (64.5–77)	**0.001**
BMI[a], kg/m^{-2}	25.8 (23.6–28.5)	26.4 (24.5–30.4)	0.06
PSA[a], ng/ml^{-1}	5.8 (4.5–8.1)	6.8 (4.8–10.7)	0.09
Race, n (%)			0.86
White	62 (63.9%)	23(69.7%)	
Black	6 (6.2%)	3 (9.1%)	
Asian	6 (6.2%)	1 (3.0%)	
Latino	5 (5.2%)	1 (3.0%)	
Other	18 (18.6%)	5 (15.2%)	
TPV[a], ml	55.2 (41–78.7)	39.8 (27.4–63)	**0.01**
TZV[a], ml	31.2 (22.9–46.4)	20.7 (13.2–38.3)	**0.01**
PZV[a], ml	22.7 (16.5–32.7)	22 (13.8–27.9)	0.33
TZI[a]	0.58 (0.50–0.67)	0.55 (0.43–0.64)	0.07
TZT[a], cm	3.21 (2.7–3.8)	2.7 (2.2–3.4)	**<0.001**
PZT[a], cm	0.84 (0.69–1.11)	0.88 (0.73–1.25)	0.22
PSAD[a], ng/ml^2	0.11 (0.08–0.15)	0.18 (0.11–0.31)	**<0.001**
TZDa, ng/ml^2	0.19 (0.12–0.28)	0.32 (0.18–0.64)	**<0.001**

[a]Continuous variables are shown as the median value and interquartile range, Wilcoxon/Kruskal-Wallis Test. OR: odds ratio; PCa: prostate cancer; PV: prostate volume; PSA: prostate-specific antigen; PSAD: PSA density; PZT: peripheral zone thickness; PZV: peripheral zone volume; TPV: total prostate volume; TZD: transitional zone density; TZI: transitional zone index; TZT: transitional zone thickness; TZV: transitional zone volume.

Compared to other prostate zones, the TZ parameters are most predictive of the presence of csPCa. TZV was trending towards significance (p=0.05). On logistic regression, TZD significantly predicted csPCa (odds ratio [OR] 19.8, 95% confidence interval [CI] 4.95–34.68); however, neither PZD nor PZT significantly predicted csPCa. Finding alternative predictors of csPCa without the consideration of prostate size is important because estimation of prostate volume relies on formulas that do not represent the irregular shape of the prostate. In fact, inter-observer calculation of the prostate volume can fluctuate up to 20%.[15] Jiang et al looked at 691 patients who underwent mpMRI prior to TRUS and found that the transverse TZ sectional area was predicative of PCa (AUC 0.81), and therefore a better predictor than PSAD (AUC 0.71).[16] Using a cross-sectional area instead of volume reduces the possibility of erroneous calculations by a multiplicative fac-

tor and may be the reason for the increase in AUC. It also worth noting that our study showed TPV was not correlated with age, which is consistent with a previous longitudinal population study that demonstrated no statistically significant correlation between age and the rate of prostate volume on MRI in a cohort of 278 men.[17]

Our data demonstrated that PSAD was not a predictor of csPCa; however TZD was and the AUC of TZD was similar to PSAD, consistent with findings from previous studies. Tanaka et al reported both TPV and PSAD levels had greater AUC values than PSA in the detection of PCa (0.71 and 0.71 vs. 0.52, respectively).[18] These AUCs are nearly identical to our study (0.71 and 0.70 vs. 0.52, respectively), further validating our methodology.

When looking at csPCa, the AUC for PSA and PSAD improved to 0.62 and 0.73, respectively. This is slightly lower than that found in a recent cohort of 900 men (AUC 0.64 PSA and AUC 0.78 PSAD).[19] In our cohort, the AUC of TZD is similar to the AUC of PSAD for csPCa (0.74 vs. 0.73, respectively). The validity of TZD in the detection of csPCa has been reported in numerous studies,[20-22] and has been shown to have a stronger correlation than PSAD for cancer de-differentiation and aggressivity.[23] PSAD has been shown to be a robust predictor for the detection of csPCa; however, our data did not demonstrate this significance.[19] The PSAD values were significantly different between the no-cancer and cancer groups. Our 53% sensitivity and 86% specificity for PSAD was much lower than that found by Yusim et al (70% sensitivity and 79% specificity).[19] Our highest Youden's index for PSAD was 0.18 ng/ml^2 compared to their 0.20 ng/ml^2. This difference could be due to inadequate sampling from our smaller sample size.

We acknowledge further studies with larger cohorts are needed to find the optimal cutoff point for TDZ; however, this does not underscore that TZD is a useful predictive tool that can be applied clinically. In our multivariable regression, TZD but not PSAD predicted csPCa. Similar studies have demonstrated that TZD may have stronger predictive power to discriminate PCa from BPH.[18,23] Our study highlights more specific prostatic parameters that may help guide clinical decision-making following imaging.

Limitations

Our study has certain limitations. Our cohort consists of mild to moderate-sized prostates and is predominantly Caucasian. Additionally, our sample size is small and may not be sufficient to truly assess the significance of TZD in aiding cancer detection when considering predicted lesions scored by PI-RADS. Due to the nature of a retrospective study, it was difficult to assess baseline patient characteristics, including medical history, duration of medication usage, and social history at the time of the MRI and biopsy. In our cohort, with relatively large median prostate volumes, alpha-blocker usage was only 30%, which seems lower. The cohort for symptom-specific analysis was smaller due to the limitation in the availability of clinical data and variability in administering symptoms scores. Additionally, as with any retrospective study, the risk of selection bias in assessing the prostate zone measurements was present. To address this, measurements were averaged from three independent readers under the guidance of

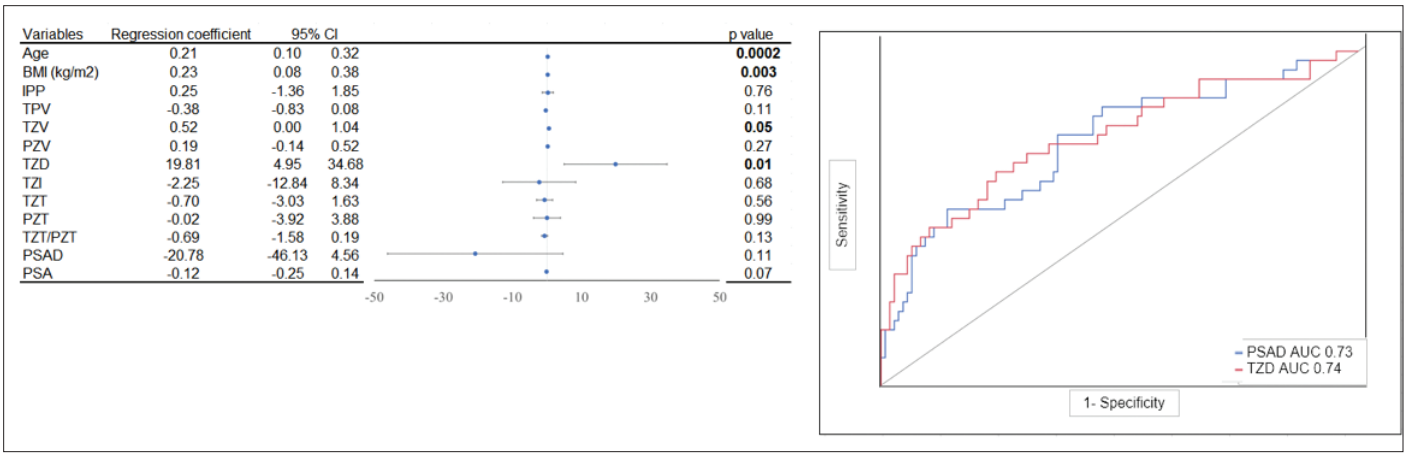

Figure 1. Prostatic parameters to predict clinically significant prostate cancer; (A) multivariate regression model, (B) receiver operating characteristic for transition zone density (red) and prostate-specific antigen (PSA) density (blue). AUC: area under the curve; BMI: body mass index; CI: confidence interval; IPP: intravescical prostatic protrusion; PSAD: prostate-specific antigen density; PZT: peripheral zone thickness; PZV: peripheral zone volume; TPV: total prostate volume; TZD: transitional zone density; TZI: transitional zone index; TZT: transitional zone thickness; TZV: transitional zone volume.

a senior radiologist. Lastly, the entire study was conducted with subjects from one institution; however, targeted biopsy was performed by three urologists with distinct practices that represent the variability of experience in the community.

CONCLUSIONS

Quantitative features of prostate zones on MRI may aid in identifying better predictors of csPCa. Zonal-based PSA density (TZD) may be a useful marker in identifying csPCa. As the use of mpMRI increases in the realm of PCa, further studies are required to understand the potential clinical applications of larger TZV for men with csPCa.

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This paper has been peer-reviewed.

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