Original Article

Can lesion volume and prostate-specific antigen density play a role in detecting clinically significant prostate cancer in Prostate Imaging Reporting and Data System-3 lesions on multiparametric magnetic resonance imaging?

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ABSTRACT

Introduction: Recently, the Prostate Imaging Reporting and Data System – 3 lesions (PI-RADS 3) have been sub classified into "3a" - lesions with a volume of <0.5 mL and "3b" - lesions exceeding 0.5 mL, whereas the prostate-specific antigen density (PSAD) is an established adjunct tool for predicting clinically significant prostate cancer (csPCa). The objective of this study was to evaluate the association between the volume of PI-RADS 3 lesions and PSAD in diagnosing csPCa and to assess the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) when PSAD is combined with the lesion volume.

Methods: This retrospective single-center study reviewed the data of transperineal prostate biopsies performed under transrectal ultrasound guidance from January 2018 to December 2023. csPCa was defined as a Gleason score ≥3 + 4. Patients were divided into two groups based on the PIRADS-3 subclassification and PSAD.

Results: Out of the 108 PIRADS-3 lesions, 17 patients had csPCa. All the patients with PIRADS-3a (n = 37) had clinically insignificant tumors or benign conditions. Receiver operating characteristic curve analysis for predicting csPCa showed that the (Area under the curve) AUC values of PSAD, prostate volume, and prostate-specific antigen were 0.899, 0.746, and 0.381, respectively. 16 csPCa patients in PIRADS-3b category had PSAD ≥0.29 ng/ml^2, whereas 1 patient had PSAD <0.29 ng/ml^2. Sensitivity, specificity, PPV, and NPV of PIRADS-3b lesions were 100%, 40.66%, 23.94%, and 100%, respectively, and it became 94.12%, 74.07%, 53.33%, and 97.56%, respectively, when PSAD was added to PIRADS-3b lesions.

Conclusion: The combination of lesion volume of the PI-RADS 3 lesion and PSAD improved the PPV and specificity of detecting csPCa.

INTRODUCTION

The conclusive identification of the most prevalent cancer in men, cancer prostate (PCa), relies on the histological examination of the biopsy specimens obtained from the prostate. The increased utilization of prostate biopsy has resulted in identification of a large number of clinically insignificant prostate cancers. The European Association of Urology Guidelines recommend to use prebiopsy magnetic resonance imaging (MRI) of the prostate to detect suspicious lesions, thereby assisting in the clinical decision-making process.[1]

The Prostate Imaging-Reporting and Data System (PI-RADS) has established standardized protocols for image acquisition and reporting, offering clinical guidelines for the

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multiparametric magnetic resonance imaging (mpMRI) of the prostate.[2] However, it lacks specific recommendations for handling indeterminate PI-RADS 3 lesions, which has led to the ongoing debate regarding the necessity of prostate biopsies in such cases.

Opting for close surveillance through prostate-specific antigen (PSA) monitoring and mpMRI seems to be a viable alternative, considering that only 4%–12% of the PI-RADS 3 lesions are identified as clinically significant prostate cancer (csPCa).[3,4] Improving the specificity and potentially sparing the men with elevated PSA from undergoing the biopsy can be achieved by incorporating supplementary data such as kallikrein panels, PSA density (PSAD), and urine biomarkers (PCA-3 and TMPRSS2-ERG) alongside the MRI.[5-7]

The PI-RADS category 3 has been subdivided based on the volume of the index lesion into two subcategories: (3a) for indolent or low-risk lesions with a volume of <0.5 mL, and (3b) for substantial or high-risk lesions with a volume of 0.5 mL or more, to reduce the unnecessary biopsies and to enhance the diagnostic yield for csPCa.[8]

The objective of this study was to evaluate the association between the volume of PI-RADS 3 lesions and PSAD in diagnosing csPCa and to assess the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) when the PSAD is combined with the volume of PI-RADS 3 lesions.

METHODS

After obtaining the approval from the institutional review board, we carried out a retrospective analysis that encompassed all the male individuals who underwent prostate biopsy following the mpMRI at our institution between January 2018 and December 2023. Patients without a prior MRI, those with lesions classified as PI-RADS 2, 4, or 5, and individuals with a previous history of prostate biopsy or surgery were excluded from the study. All the patients were treatment naïve. Transperineal prostate biopsies were performed utilizing an automated biopsy gun and an 18-G Bard Max core needle and were guided by transrectal ultrasound (TRUS) under spinal anesthesia or sedation. csPCa was defined as Gleason score (GS) ≥3 + 4 or International Society of Urologic Pathologist ≥2, as per the PROMIS study definition.[9] This method included the acquisition of 20 systematic cores, and cognitive fusion targeted biopsy involved extracting two extra targeted samples from the suspicious regions identified on the mpMRI.

Demographic information, mpMRI data, and pathological data were collected for every patient diagnosed with a PI-RADS 3 lesion. mpMRI was performed on a 3T scanner (SIGNA™ Architect) without the use of an endorectal coil. A PI-RADS 3 lesion displayed moderate T2 hypointensity in the peripheral zone, with heterogeneous intensity, obscured margins, mild/moderate ADC hypointensity, and isointense/mildly hyperintense diffusion-weighted imaging (DWI) in the transition zone.[2] The MRI data comprised of information on the prostate volume, index lesion volume, and the location of the lesion. The index lesion was defined as the largest target lesion observed on the axial T2-weighted imaging and/or DWI, and the calculation of the lesion's volume was based on the T2-weighted and DWI data. The volume of the lesion detected by the MRI was calculated using a simplified ellipsoid volume formula, where the product of the longest perpendicular diameters (depth × width × length × 0.5) was utilized.[10] We further categorized PI-RADSv2 score 3 into two subgroups, namely PI-RADS 3a and 3b.

Biopsy data were used to categorize PI-RADS 3 lesions into two groups for analysis: Benign or clinically insignificant disease (GS = 6) and csPCa (GS ≥ 7). Gleason grading was carried out using the 2014 International Society of Urologic Pathology guidelines by a single genitourinary pathologist with over 20 years of experience.[11]

Statistical analysis

The statistical analysis was performed with IBM SPSS version 20.0 software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA: IBM Corp.). Categorical variables were expressed in the terms of frequency and percentage. Receiver operating characteristic (ROC) curve analysis was employed to identify the PSAD cutoff value for predicting cancer. To assess the statistical significance of the correlation between PSAD and csPCa, the Chi-square test was employed, and the odds ratio was calculated. Diagnostic measures such as sensitivity, specificity, predictive values, and accuracy were computed.

RESULTS

Table 1 displays the demographic and baseline characteristics of the patients with PI-RADS 3 lesions included in the analysis. ROC curve analysis for predicting csPCa showed that the AUC values of age, PSAD, PSA, and prostate volume were 0.495, 0.899, 0.746, and 0.381, respectively [Table 2]. [Figure 1] The ROC curve analysis showed a PSAD cutoff value of 0.29 ng/mL/mL for predicting csPCa. On sub-categorising the lesion volume of PI-RADS 3 lesions into categories 3a and 3b and applying a PSAD cut-off point of 0.29, four groups were established [Table 3].

None of the patients with 3a lesions had csPCa, whereas 23.94% (n = 17) patients with 3b lesions had csPCa. Consequently, the need for 37 prostate biopsies could have been avoided. In Group 3b with PSAD <0.29 ng/mL/mL, out of the 41 patients one patient had csPCa, whereas out of 30 patients with PI-RADS 3b with PSAD ≥0.29 ng/mL/mL 16 patients had csPCa.

Table 1: Demographic and baseline characteristics

Characteristics	All (*n*=108)	PI-RADS 3a (*n*=37)	PI-RADS 3b (*n*=71)	*P*
Mean age±SD (years)	63.96±6.33	64.70±6.17	63.57±6.39	0.38
Mean PSA±SD, (ng/mL)	10.43±5.24	9.4±5.36	10.95±5.10	0.143
Mean prostate volume±SD (mL)	51.2±16.22	54.3±18.36	48.9±15.39	0.108
Mean PSA density±SD, (ng/mL/mL)	0.17±0.11	0.14±0.08	0.19±0.12	0.024
Suspected DRE, *n* (%)	11 (10.18)	3 (8.1)	8 (11.27)	0.603

SD=Standard deviation, PSA=Prostate-specific antigen, PI-RADS=Prostate imaging reporting and data system, DRE= Digital Rectal examination

Table 2: Receiver operating characteristic curve analysis for predicting clinically significant prostate cancer for each factor

Variable	AUC (95% CI)	*P*
Age	0.495 (0.349–0.641)	0.95
PSA level	0.746 (0.617–0.875)	0.001
Prostate volume	0.381 (0.222–0.540)	0.121
PSAD	0.899 (0.834–0.964)	<0.001

PSA=Prostate-specific antigen, PSAD=PSA density, AUC=Area under the curve, CI=Confidence interval

Table 3: Prostate imaging-reporting and data system 3 classification as per lesion volume and prostate-specific antigen density

Variable	PI-RADS 3a (*n*=37)				PI-RADS 3b (*n*=71)			
	PSAD <0.29 (*n*=32)		PSAD ≥0.29 (*n*=5)		PSAD <0.29 (*n*=41)		PSAD ≥0.29 (*n*=30)	
	Yes	No	Yes	No	Yes	No	Yes	No
CsPCa, *n* (%)	0	32	0	5	1	40	16	14

PI-RADS=Prostate imaging-reporting and data system, PSAD=Prostate-specific antigen density, CsPCa=Clinically significant prostate cancer

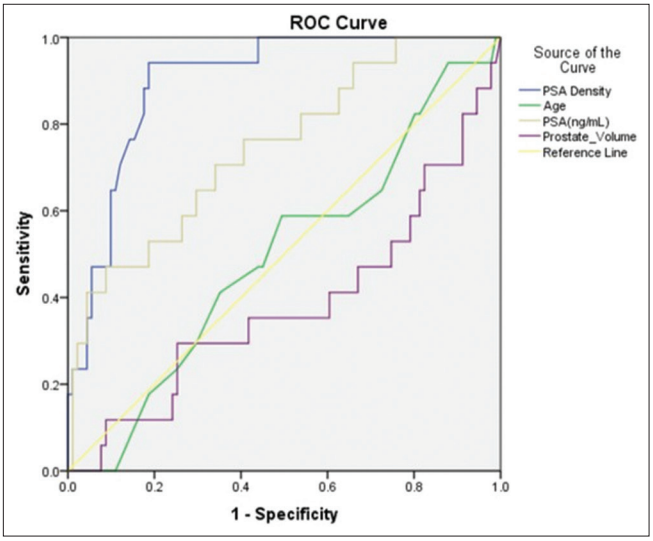

Figure 1: Receiver operating characteristic curve analysis for predicting clinically significant prostate cancer. ROC = Receiver operating characteristic

When considering PI-RADS 3b lesions alone as positive for csPCa, the sensitivity, specificity, PPV, and NPV were 100%, 40.66%, 23.94%, and 100%, respectively. When PI-RADS 3b lesions were combined with a PSAD value of ≥0.29 ng/mL/mL, the specificity and PPV increased to 74.07% and 53.33%, whereas the sensitivity and NPV were 94.12% and 97.56%, respectively.

DISCUSSION

Recent guidelines recommend the use of MRI before the prostate biopsy. The MRI-FIRST trial[12] concluded that in biopsy-naïve individuals, performing mpMRI could avoid the need for prostate biopsy if the results of the mpMRI are negative (Likert score ≤ 2) and the detection of csPCa was improved by the combining systematic and targeted biopsies. The PROMIS trial[9] showed that the primary biopsy can be avoided in 27% of the patients when the mpMRI is used as a triage test. It also showed an 18% higher detection of csPCa with mpMRI guided TRUS Biopsy pathway as compared to the TRUS-guided standard biopsy alone.

PI-RADSv2 was introduced to address the inconsistency in the score assignment, particularly in the indeterminate lesions.[2,13] At present, PI-RADSv2 designates a score of three if the lesion exhibits heterogeneous signal intensity or lacks well-defined borders with moderate hypointensity on T2-weighted imaging in the peripheral zone. In the transition zone, it is characterized by heterogeneous signal intensity with obscured margins and a focal, mildly to moderately hypointense lesion on the ADC, accompanied by isointense or mild intensity on DWI.

The PI-RADS 3 score indicates that the lesion is in the "gray zone" or is deemed "indeterminate." Although, a biopsy is recommended, monitoring of these lesions can also be a reasonable option in selected low-risk patients. van der Sar *et al*. offered patients with radiologically indeterminate MRI lesions either immediate biopsy or surveillance with regular PSA monitoring and/or mpMRI at 6–12-month intervals. 57% of the patients chose surveillance strategy, and the risk profile of the cancer identified in the initial surveillance group closely resembled that found in the immediate biopsy group.[14] In their retrospective analysis of 46 patients with PI-RADS 3 lesions, Hauth *et al*. observed that after an average follow-up of 22.6 months with mpMRI, only 4% of the lesions progressed and were reclassified as PI-RADS 4, with subsequent biopsies revealing csPCa.[15]

The incidence of prostate cancer among biopsied PI-RADS 3 lesions ranges from 6.5% to 22%, and csPCa is identified in 4.4% to 11.3% of the patients.[4] Maggi *et al*. in their meta-analysis of 25 studies found an 18.5% detection rate of

csPCa.[16] In our study, we found that 15.7% of the patients had csPCa.

Some authors consider the volume of the lesion when deciding whether to conduct a biopsy for PI-RADS 3 lesions. Scialpi *et al*. classified PI-RADS 3 lesions into two subgroups: (a) lesions at low risk with a volume <0.5 ml and (b) lesions at high risk with a volume of 0.5 ml or greater.[8] In their retrospective analysis of 155 patients, they found a 2.8% detection rate of csPCa in 3a lesions and 27.5% in 3b category lesions.[17] In our study, none of the 3a category patients had csPCa; in the 3b category, 17 patients had csPCa. Martorana *et al*. also reported a 0% detection rate of csPCa when the lesion volume <0.5ml, whereas 14.8% had csPCa when the lesion volume was >0.5ml.[18]

Various approaches involve incorporating additional information, such as PSA and molecular markers, with the mpMRI findings to predict the risk of csPCa. These strategies can assist in advising men on the necessity of undergoing a biopsy.

In their study, Venderink *et al*.[19] reported that in 42% of the patients with PI-RADS 3 lesions, who were evaluated with PSAD to predict the presence of csPCa, biopsy would have been avoided if a cutoff of PSAD ≥0.15 ng/mL/mL for the biopsy was added. When the PSAD cutoff value was lowered to 0.12 ng/mL/mL, 26% of the patients would have avoided the biopsy without missing any csPCa. Washino *et al*.[7] found that by integrating PI-RADS score and PSAD values, a PSAD cutoff of ≥0.30 ng/mL/mL in PI-RADS 3 lesions was linked with an 86% detection rate of csPCa. In contrast, patients with a PSAD cutoff <0.15 ng/mL/mL showed no detection of csPCa. Schoots and Padhani.[20] developed a risk-adapted data table of csPCa using a combination of PI-RADS score and PSAD. They identified a 4% risk of csPCa for PI-RADS 3 score and PSAD <0.1 ng/mL/mL, suggesting that biopsies could potentially be avoided. On the other hand, high-risk cases with PSAD >0.2 ng/mL/mL had a 29% risk, indicating the need for both systematic and targeted biopsies. In our study, we found that a PSAD cutoff 0.29 ng/ml/ml alone had the highest sensitivity and specificity of 94.12% and 79.12% in detecting csPCa. Furthermore, considering PI-RADS 3b lesion as positive for csPCa, the sensitivity, specificity, PPV, and NPV were 100%, 40.66%, 23.94%, and 100%, respectively. Specificity and PPV increased to 74.07% and 53.33% when PI-RADS 3b lesions were combined with a PSAD value of ≥0.29 ng/ml/ml. Therefore, the measurement of the volume of a PI-RADS 3 lesion and combining it with PSAD could represent a better predictive tool for diagnosing the csPCa and unnecessary biopsies can be avoided.

There are limitations to our study. It was a retrospective analysis conducted at a single center with a limited sample size (n = 108). The use of mpMRI reporting with PI-RADSv2.1 could have been preferable to reduce interobserver variability among radiologists.

CONCLUSION

The combination of the volume of the PI-RADS 3 lesion with PSAD enhances the PPV and specificity of detecting csPCa. These observations should be validated through extensive prospective studies.

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