

Research Article

Utility of transperineal template-guided mapping prostate biopsy in biopsy-naïve men with PI-RADS 1-2 on multiparametric magnetic resonance imaging

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ABSTRACT

Objective: To analyze the outcomes of transperineal template-guided mapping biopsy (TTMB) in biopsy-naïve men with multiparametric magnetic resonance imaging (mpMRI) results of Prostate Imaging-Reporting and Data System (PI-RADS) 1–2.

Patients and methods: We retrospectively reviewed TTMB outcomes in biopsy naïve patients with PI-RADS 1–2 at a single center from August 2018 to May 2023. The patients' clinicopathologic data were reviewed, clinically significant prostate cancer (csPCa) detection rates were identified. We determined significant predictive factors and determined those optimal cutoff point using receiver operating characteristic (ROC) curves.

Results: 255 biopsy naïve patients with PI-RADS 1–2 underwent TTMB. 72 (28.2%) were diagnosed with prostate cancer and 30 (11.8%) were diagnosed with csPCa. ROC curves were used to identify predictive factors for diagnosing csPCa. Age (area under ROC curve [AUC]: 0.74, 95% CI: 0.65–0.83, $P < 0.001$) and prostate specific antigen density (PSAD) (AUC: 0.63, 95% CI: 0.53–0.72, $P = 0.025$) were significant predictive factors, and the optimal cutoff points determined using the Youden index were 65 years and 0.15 ng/mL/mL, respectively.

Conclusion: Of biopsy-naïve patients classified as PI-RADS 1–2, 11.8% were diagnosed with csPCa, and we identified age and PSAD as significant predictive factors. Our study will help determine the biopsy method for patients with PI-RADS 1–2 without biopsy experience.

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1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) is progressively important in the diagnosis of prostate cancer. mpMRI-supported transrectal, transperineal, and in-bore biopsies have been proven to have superior cancer detection rates than conventional transrectal ultrasound (TRUS)-guided 12-core biopsies.^{1,2} The PROMIS study reported that mpMRI outperformed conventional TRUS-guided biopsy in biopsy-naïve patients. When used as a

screening test, mpMRI can safely identify a quarter of men who can avoid unnecessary biopsies without impairing clinically significant cancer detection.³ Currently, mpMRI is recommended in several guidelines for patients with an elevated prostate specific antigen (PSA) or suspicious digital rectal exam.^{4,5} However, when comparing mpMRI findings to postoperative prostatectomy pathology findings, mpMRI misses 8–24% of clinically significant prostate cancer (csPCa).^{6–8}

Several guidelines recommend transrectal or transperineal biopsy for men with suspected prostate cancer who did not experience prostate biopsy, and targeted biopsy if mpMRI is available. However, there is no consensus on the role of TTMB.^{4,5} In The PROMIS study, the csPCa detection rate of TRUS guided prostate biopsy with TTMB as reference was only 48%.³ Several studies have shown a higher cancer detection rate with TTMB compared to TRUS guided prostate biopsy, which may be due to TTMB's superior access to prostate cancers in the anterior or apex.^{9–13} In addition, because TTMB is commonly performed under general anesthesia, a large

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number of tissues can be obtained during the prostate is immobile and the biopsy location can be viewed in three dimensions.^{14–16} In a complication perspective, TTMB has been reported to have significantly lower infection compared to TRUS guided prostate biopsy, but is more associated with urinary retention.^{17–19}

We hypothesized that the false-negative rate of mpMRI in biopsy-naïve patients could be compensated for by tumor location-independent TTMB. In this study, we aimed to evaluate the cancer detection rate of TTMB in biopsy-naïve men with mpMRI results of prostate imaging-reporting and data system (PI-RADS) 1-2. We analyzed the factors that should be considered when deciding on a biopsy in biopsy-naïve patients with PI-RADS 1-2 in real-world clinical practice.

2. Materials and methods

2.1. Study population

Patients who underwent TTMB at Samsung Medical Center between August 2018 and May 2023 and met the following criteria were included in this study. 1) No prior experience of prostate biopsy, 2) The results of the mpMRI performed prior to the biopsy were reported in PI-RADS 1-2, 3) a PSA elevation of 2.5 ng/ml on consecutive days at least 1 month apart (however, patients taking the previous 5 alpha-reductase inhibitor were included if $\text{PSA} \geq 1.25$ ng/ml), and 4) no evidence of urinary tract infection on urinalysis. Additionally, patients were included in the study if rectal problems made it impossible to perform TRUS prostate biopsy. Patients who met the above criteria were explained the cancer detection rates and complications of cognitive TRUS prostate biopsy and TTMB, respectively, and those who chose TTMB were included in the final study.

2.2. Biopsy protocol

All patients received bowel preparation and antibiotics prior to the procedure. Biopsy was performed in the lithotomy position under general anesthesia, and all procedures were performed aseptically by a urologist. Before the procedure, a digital rectal examination was performed and a Foley catheter was inserted.

TTMB was performed using equipment consisting of a transrectal probe covered with a water-filled balloon, sterile system drapes, disposable template grids, classic stepper, and dual-sided table mount (Fig. 1A, B).¹¹ The number of biopsy cores was based on a prostate volume of 30 cc according to the Ginsburg protocol: 24 cores if less than 30 cc, and 36-core systemic biopsy if greater than 30 cc and prostate length greater than 4 cm in sagittal view. If PI-RADS 3-5 lesions observed on mpMRI were also observed on ultrasound imaging, before performing the systematic biopsy, two cores of target biopsy were performed per lesion by adjusting the grid, followed by the systematic biopsy (Fig. 1C, D).^{20,21}

2.3. Variables included in the study

Age, PSA levels, prostate volume, prostate specific antigen density (PSAD), mpMRI results, and pathological findings were analyzed. PSAD was calculated by dividing PSA by the prostate volume measured by mpMRI. mpMRI was performed with a 3-Tesla magnetic resonance system before the prostate biopsy. mpMRI images were analyzed according to the PI-RADS version 2.0 (v2). All images were assessed by two genitourinary radiologists with 11 and 16 years of experience in prostate mpMRI using the validated PI-RADS v2. A PI-RADS v2 score ≥ 3 was considered a reliable predictor of prostate cancer in our analysis. In pathological findings, a Gleason score $\geq 3 + 4$ was classified as clinically significant prostate cancer (csPCa), and other scores were classified as clinically insignificant prostate cancer.

2.4. Statistical analysis

The primary endpoint was the cancer detection rate of TTMB in biopsy-naïve men with PI-RADS 1-2 on mpMRI. The secondary endpoint involved identifying significant predictive factors and determining the optimal cutoff point using receiver operating characteristic (ROC) curves to diagnose csPCa in PI-RADS 1-2 and assessing the corresponding risk factors. Continuous variables were presented as medians (interquartile range [IQR]). Categorical variables were presented as absolute values and percentages. ROC curves were used to identify predictive factors for diagnosing csPCa in patients, and the optimal cutoff points were determined using

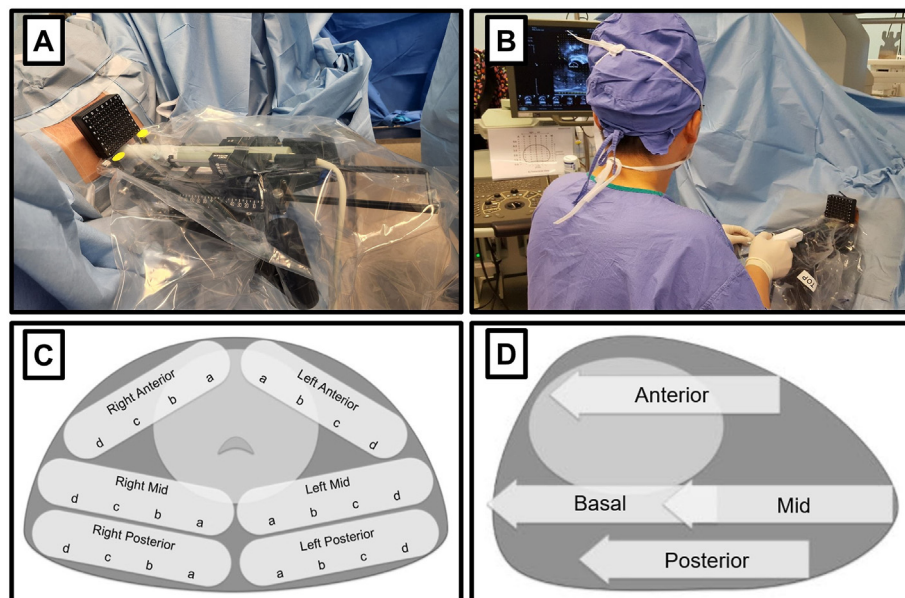


Figure 1. Transperineal template-guided mapping prostate biopsy (A) Aseptic preparation of biopsy instruments (B) Performing a systemic biopsy using grid (C) Prostate biopsy sections in axial view (D) Prostate biopsy sections in sagittal view.

the Youden index. Univariate and multivariate analyses, utilizing logistic regression, were performed to identify factors significantly associated with csPCa. Hazard ratios and 95% confidence intervals were determined. A $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the IBM SPSS Statistics, version 23.0 (IBM Co., Armonk, NY, USA).

2.5. Ethics approval

This retrospective study was approved by the Institutional Review Board of Samsung Medical Center (Institutional Review Board Number. 2024-01-003). All study protocols were performed in accordance with the principles of the Declaration of Helsinki.

3. Results

3.1. Patient demographics and characteristics

The baseline demographics and characteristics of 255 biopsy naïve men with PI-RADS 1-2 who underwent TTMB were summarized in Table 1. The median age was 61.0 years (IQR: 55.0–68.0), and the median PSA was 5.0 ng/mL (IQR: 3.6–7.1). The median prostate volume was 37.9 mL (IQR: 27.0–51.0), and the median PSAD was 0.13 ng/mL/mL (IQR: 0.10–0.19).

3.2. Biopsy outcome of TTMB

Among patients with PI-RADS 1-2, 72 (28.2%) were diagnosed with prostate cancer on TTMB. Based on prostate size, 126 (49.4%) and 129 (50.6%) patients had 24 and 36 biopsy cores, respectively. The median number of positive core was 2.0 (IQR: 1.0–5.8), and 31 (43.1%) men were diagnosed with bilateral prostate cancer. csPCa was diagnosed in 30 (11.8%), 183 (71.8%), 42 (16.5%), 3 (1.2%), 22 (8.6%), and 5 (2.0%) were categorized as benign, Gleason score 6, 7 (3 + 4), 7 (4 + 3), and 8, respectively. Of all prostate cancers, 45 (62.5%) were detected in the anterior, and 13 (43.3%) of csPCa were detected in the anterior (Table 2).

3.3. Diagnostic power risk factors for csPCa in patients with PI-RADS 1-2

ROC curves were used to identify predictive factors for diagnosing csPCa in patients in the PI-RADS 1-2 group. Age (AUC: 0.74, 95% CI: 0.65–0.83, $P < 0.001$) and PSAD (AUC: 0.63, 95% CI: 0.53–0.72, $P = 0.025$) were significant predictive factors, and the optimal cutoff points determined using the Youden index were 65

Table 1
Patient demographics and characteristics at baseline.

Variable	Biopsy naïve men with PI-RADS v2 1-2
No. of patients, n (%)	255 (100.0)
age, years	
Median (IQR)	61.0 (55.0–68.0)
Mean $\pm$ SD	60.2 $\pm$ 10.5
PSA, ng/mL	
Median (IQR)	5.0 (3.6–7.1)
Mean $\pm$ SD	5.9 $\pm$ 3.9
Prostate volume, mL	
Median (IQR)	37.9 (27.0–51.0)
Mean $\pm$ SD	41.6 $\pm$ 19.4
PSAD, mg/mL/mL	
Median (IQR)	0.13 (0.10–0.19)
Mean $\pm$ SD	0.16 $\pm$ 0.12

PI-RAD v2, Prostate Imaging Reporting and Data System, version 2; IQR, interquartile range; SD, standard deviation; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density.

Table 2
Results of transperineal template-guided mapping prostate biopsy.

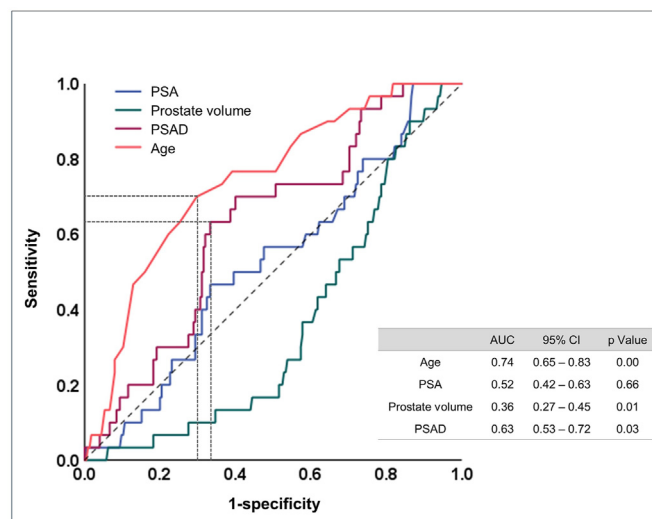
Variable	Biopsy-naïve men with PI-RADS v2 1-2
No. of patients, n (%)	255 (100.0)
No. of patients with positive TTMB, n (%)	72 (28.2)
No. of total cores, n (%)	
24 cores	126 (49.4)
36 cores	129 (50.6)
No. of positive cores ^a	
Median (IQR)	2.0 (1.0–5.8)
Mean $\pm$ SD	3.6 $\pm$ 3.5
Detection of csPCa	
Yes	30 (11.8)
No	225 (87.8)
Bilateral detection of prostate cancer, n (%) ^a	
Yes	31 (43.1)
No	41 (56.9)
Gleason score in TTMB, n (%)	
Benign	183 (71.8)
6	42 (16.5)
7 (3 + 4)	3 (1.2)
7 (4 + 3)	22 (8.6)
8	5 (2.0)
Cancer detection at anterior, n (%) ^a	
Yes	45 (62.5)
No	27 (37.5)
csPCa detection at anterior, n (%) ^b	
Yes	13 (43.3)
No	17 (56.7)

PI-RAD v2, Prostate Imaging Reporting and Data System, version 2; TTMB, transperineal template-guided mapping prostate biopsy; IQR, interquartile range; SD, standard deviation; csPCa, clinically significant prostate cancer.

^a $n = 72$.

^b $n = 30$.

years and 0.15 ng/mL/mL, respectively (Fig. 2). Of the 103 patients with PSAD >0.15 ng/mL/mL and 88 patients with age >65 , 19 (18.4%), and 21 (23.9%) were diagnosed with csPCa, respectively. Among the 32 patients with PSAD >0.15 ng/mL/mL and age >65 , 12 (37.5%) were diagnosed with csPCa (Fig. 3).²² In the multivariate analysis to find risk factors associated with csPCa in the PI-RADS 1-2, age >65 (HR: 5.2, 95% CI: 1.2–23.3, $P = 0.030$) and PSAD >0.15 ng/mL/mL (HR: 3.2, 95% CI: 1.1–9.3, $P = 0.034$) were statistically significant factors (Table 3).



ROC, receiver operating characteristic; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density

Figure 2. ROC curve in PI-RADS 1-2 patients. Discrimination for clinically significant prostate cancer.

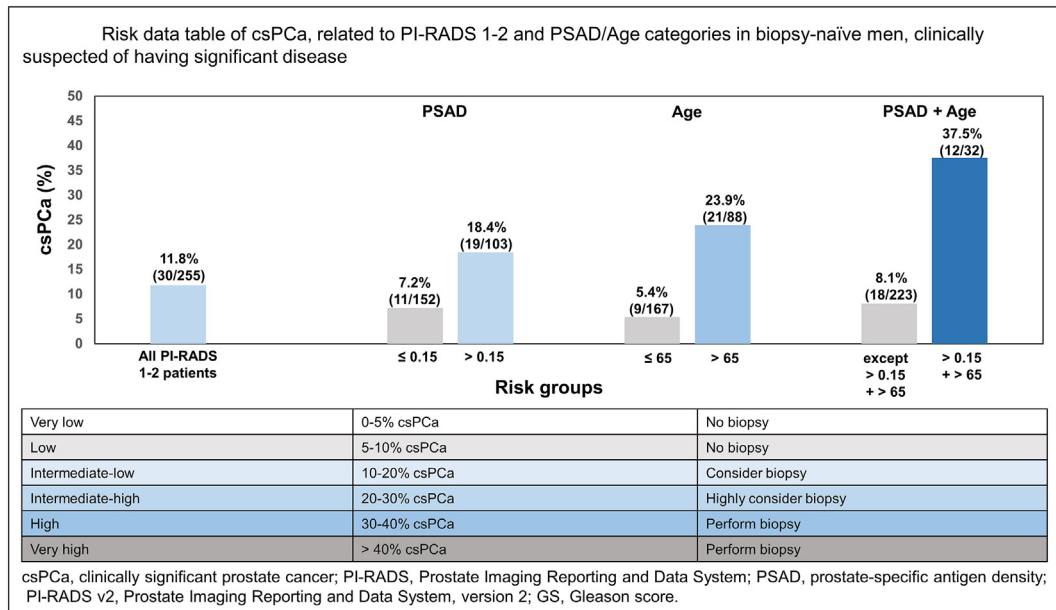


Figure 3. Risk data table of csPCa, related to PI-RADS 1-2 and PSAD/Age categories in biopsy-naïve men, clinically suspected of having significant disease.

Table 3

Multivariate logistic regression analysis of factors associated with csPCa in biopsy-naïve patients with PI-RADS 1-2.

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age				
≤ 65	—	—	—	—
> 65	3.80 (0.87–16.51)	0.075	5.23 (1.17–23.32)	0.030
PSA	1.03 (0.95–1.12)	0.485	1.02 (0.93–1.13)	0.677
Prostate volume	0.97 (0.94–0.99)	0.017	0.96 (0.92–0.99)	0.021
PSAD				
≤ 0.15	—	—	—	—
> 0.15	3.39 (1.53–7.48)	0.003	3.19 (1.09–9.33)	0.034

csPCa, clinically significant prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density.

4. Discussion

Our current study shows that in patients with suspected prostate cancer but who have not undergone a prostate biopsy if the MRI results were PI-RADS 1–2 (255 patients), the rate of csPCa on TMB was 11.8%. In patients with PI-RADS 1–2, PSAD and age were useful factors for diagnosing clinically significant prostate cancer, with cutoff values of 0.15 mg/mL/mL and 65 years, respectively, and hazard ratio was approximately three and five times, respectively. The subgroups with PSAD > 0.15 mg/mL/mL only, age > 65 only, and PSAD > 0.15 mg/mL/mL and age > 65 comprised 18.4%, 23.9%, and 37.5% of the clinically significant prostate cancer diagnoses, respectively.

The PROMIS trial, a relatively recent prospective, multicenter, paired cohort, confirmatory study, compared the diagnostic power of mpMRI and TRUS in 576 patients with no previous prostate biopsy. In a trial using a transperineal mapping biopsy as a reference test, diagnostic accuracy was analyzed by defining three definitions of csPCa. Among them, using the same definition as the current study (Any Gleason score 7 ($\geq 3 + 4$)), the negative predictive value of mpMRI was 76% (95%CI 69–82).³ Another multicenter, prospective study of mpMRI and transperineal biopsy in men with suspected prostate cancer who had no previous prostate biopsy showed

a negative predictive value of mpMRI of 80% (95%CI 75–85) using the same definition of csPCa.²³ In this study, out of 255 patients with PI-RADS 1–2, 30 (12%) were diagnosed with csPCa, with a negative predictive value of 88%. When comparing the two previous studies with the current findings, the negative predictive value of mpMRI in this study was superior. We expected this difference because the last two studies used either 1.5-T mpMRI or a combination of 1.5-T or 3.0-T mpMRI, whereas this study used only 3.0-T mpMRI. The recent accuracy study of 1.5-T versus 3.0-T mpMRI in diagnosing csPCa found a significant odds ratio of 1.59 (95%CI 1.35–1.87) for 3.0-T mpMRI compared to 1.5 T, on multivariate analysis.²⁴

In a previous study we did on 601 biopsy-naïve patients, two (4%) of 50 men who were PI-RADS 1-2 had csPCa on TRUS-Bx. This study, conducted at the same institution as the current study, used the same equipment as the current study except for the biopsy method, and the baseline characteristics of the patients were similar. Comparing the two studies, the current study detected 11.8% of csPCa, while the previous study detected about three times fewer.²⁵ In the PROMIS trial, TRUS guided prostate biopsy had a sensitivity of 48% (95%CI 43–54) when transperineal mapping biopsy was used as a reference test. This means that about half of the csPCa found on transperineal mapping biopsy was missed on TRUS biopsy.³ Two recently published systematic reviews found that MRI-guided transperineal biopsy was associated with a statistically significant higher csPCa detection rate than MRI-guided transrectal biopsy (relative risk 1.28 95%CI 1.03–1.60, $P = 0.03$). They also found a difference in the detection rate of csPCa based on tumor location, as the two biopsies approached the tumor differently. In particular, MRI-guided transperineal biopsy was more than two times superior to the MRI-guided transrectal biopsy in detecting csPCa (relative risk 2.46 95% CI 1.22–4.98, $P = 0.01$).^{26,27} In the current study, of the 30 patients diagnosed with csPCa, 13 (43%) had cancer detected in the anterior prostate. These results support the argument that the transperineal approach has an advantage in detecting csPCa compared to the transrectal approach compared to our previous transrectal biopsy results and other previous studies.

Several factors have been studied as predictors for prostate biopsy, and PSAD is an independent predictor of csPCa.²⁸ A recent review examined the detection rate of csPCa by risk stratification

using PI-RADS and PSAD. In biopsy-naïve patients, an MRI-detected targeted biopsy was performed, and csPca detection rates were analyzed by dividing PSAD into <0.10 , 0.10 – 0.20 , and >0.20 ng/mL/mL. csPca was diagnosed in 24% of patients with PI-RADS 1–2 and a PSAD >0.20 ng/mL/mL.²² These results suggest that a prostate biopsy should be strongly considered in patients with a high PSAD, even if they are PI-RADS 1–2. In another study combining MRI and PSAD to predict biopsy results in prostate biopsy-naïve patients, independent predictors of csPca by multivariate analysis were the PSAD and the PI-RADS score. In risk stratification using PSAD and PI-RADS, the csPca detection rates of a PSAD of 0.15 – 0.29 and ≥ 0.3 ng/mL/mL among patients with PI-RADS 1–2 were 20 and 30%, respectively. In the present study, the csPca detection rate was 18.4% in PI-RADS 1–2 patients with a PSAD >0.15 ng/mL/mL and 37.5% in patients aged >65 and a PSAD >0.15 ng/mL/mL. These findings suggest that PI-RADS 1–2 patients should be strongly considered for prostate biopsy after risk stratification.

To our knowledge, the current study is the largest study of TTMB in PI-RADS 1–2 biopsy-naïve patients. As the TTMB under general anesthesia in PI-RADS 1–2 biopsy-naïve patients are rarely performed in clinical practice, these results are meaningful for the decision of whether to perform a biopsy in MRI-negative patients with suspected prostate cancer. The study also performed 3.0 T MRI on all patients, which allowed for superior image interpretation compared to previous studies that used a combination of 1.5 and 3.0 T MRI. Several limitations existed in this study. The analysis was retrospective, and patient selection bias may be present. In addition, the TTMB in this study was performed with 24 or 36 cores, a different method from that used in other studies, making comparison of biopsy outcomes challenging. This study used a Gleason Score $\geq 3 + 4$ to define csPca, but other studies have used different definitions of csPca, so comparisons should be made with caution.

5. Conclusions

In biopsy naïve men with mpMRI results of PI-RADS 1–2, approximately thrice as many csPca were detected with TTMB than those with TRUS biopsy. In addition, csPca is detected in approximately 20% of patients >65 years age or with a PSAD >0.15 ng/mL/mL, and TTMB should be considered in these cases. These findings may be helpful when counseling biopsy-naïve patients on the need for a prostate biopsy when the MRI result is PI-RADS 1–2.

Conflicts of interest

There is no conflicts of interest for the publication of this article.

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