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Usefulness of Prostate-Specific Antigen Density as an Indicator for Recommending Prebiopsy Magnetic Resonance Imaging to Prevent Missed Prostate Cancer Diagnoses

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Purpose: To identify the indication for recommending prebiopsy magnetic resonance imaging (MRI) to prevent prostate cancer missed diagnoses in cases without prebiopsy MRI.

Materials and Methods: Between January 2017 and September 2020, 585 patients suspected with prostate cancer underwent prostate biopsy after MRI. For patients with visible lesions, MRI-targeted biopsy using an image-based fusion program was performed in addition to the 12-core systematic biopsy. Patients for whom MRI was performed in other institutions (n=4) and patients who underwent target biopsy alone (n=7) were excluded.

Results: Of 574 patients (median prostate-specific antigen [PSA] level, 6.88 ng/mL; mean age, 68.2 years), 342 (59.6%) were diagnosed with prostate cancer (visible lesions=312/449 [69.5%]; nonvisible lesions=30/123 [24.0%]). The detection rates of visible lesions stratified using the Prostate Imaging Reporting and Data System score (3 vs. 4 vs. 5) were 30.9% (54 of 175), 61.2% (150 of 245), and 90.1% (127 of 141), respectively. Multivariate analysis showed that PSA density was a significant factor for presence of visible lesions, prostate cancer, and significant prostate cancer diagnosis. Among patients with positive lesions, 27 (8.2%) were diagnosed with prostate cancer concomitant with negative systematic biopsy results. A PSA density of 0.15 ng/mL/cm^3 was identified as the significant cutoff value for predicting positive target biopsy in groups with negative systematic biopsy. Sixty of the negative target lesions (26.1%) were diagnosed using systematic biopsy.

Conclusions: To maximize cancer detection rates, both targeted and systematic biopsies should be implemented. PSA density was identified as a useful factor for recommending prebiopsy MRI to patients suspected with prostate cancer.

Key Words: Magnetic resonance imaging, Prostate cancer, Prostate-specific antigen

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INTRODUCTION

Magnetic resonance imaging (MRI) before biopsy is recommended for patients suspected with prostate cancer, according to the National Comprehensive Cancer Network guideline.[1] There are several known reasons for the efficacy of MRI in improving cancer detection rates. Specifically, for cancers missed at the initial prostate biopsy because of their location in the anterior region of the prostate, MRI improves the prostate cancer diagnostic accuracy as well as enhances the sampling of clinically significant prostate cancer (csPCa).[2-4]

Numerous studies related to MRI-targeted biopsy have focused on cancer detection rates and clinical variables. A recent multicenter paired validating confirmatory study reported that MRI is useful for avoiding 27% of primary biopsies and reducing 5% of insignificant prostate cancer diagnoses.[5] To avoid unnecessary prostate biopsy, several studies presented MRI findings and prostate-specific antigen (PSA) density as criteria for decision-making.[6]

Nevertheless, the indication for performing expensive MRI for patients suspected with prostate cancer needs to be identified.[7] To further increase the cost-effectiveness of MRI, an indication for preventing missed prostate cancer diagnoses in cases without prebiopsy MRI is required. Therefore, this study aimed to investigate the factors useful for detecting the presence of visible lesions, predicting cancer diagnosis, and predicting csPCa. Accordingly, we identified the indication for recommending MRI to prevent missed diagnoses in cases of prostate biopsy without MRI.

MATERIALS AND METHODS

1. Ethics Statement

Institutional Review Board approval was obtained for this study to collect data on all patients suspected with prostate cancer at Yonsei University College of Medicine (approval number: 3-2017-0324). The requirement of written informed consent was waived owing to the retrospective nature of the study.

2. Study Population and Data Collection

We reviewed the data of 585 patients suspected with prostate cancer who underwent prostate biopsy after MRI between January 2017 and September 2020. Among them, patients for whom MRI was performed in other institutions (n=4) and patients who underwent target biopsy alone because of using antiplatelet agents or old age (≥85 years) (n=7) were excluded from the analysis; thus, 574 patients were included in the final analysis. Clinical variables relevant to the study included age, serum PSA level, prostate volume, clinical stage, biopsy Gleason score, and MRI findings.

3. MRI Protocol

The imaging investigation was performed using a 3.0 Tesla MRI system (Intera Achieva 3.0 T, Phillips Medical System, Best, Netherlands) equipped with a phased array coil (6 channels). The prostate MRI protocol involved diffusion-weighted imaging in addition to T2-weighted imaging. T2-weighted turbo spin-echo MRI was acquired in 3 planes (axial, sagittal, and coronal). MRI datasets were obtained at identical slice locations, with a slice thickness of 3 mm and no intersection gap. Two b-values (0–1,400) were used, and diffusion restriction was quantified via apparent diffusion coefficient (ADC) mapping. Dynamic contrast-enhanced MRI was also performed.

Uroradiologists denoted regions of interest for suggested prostate cancer on the ADC maps examined using a Digital Imaging and Communications in Medicine workstation. The Prostate Imaging Reporting and Data System (PI-RADS) version 2 scoring system was used to describe the MRI findings.[8] The presence of visible lesions was defined as lesions with a PI-RADS score ≥3.

4. Prostate Biopsy Protocol

All patients underwent a prostate biopsy procedure performed by a urologist (LKS). One hour after an intravenous injection of third generation

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cephalosporin as a prophylactic antibiotic, all patients underwent prostate biopsy in the left lateral decubitus position. After povidone iodine rectal preparation, all patients received 10 cm^3 of 2% intrarectal lidocaine gel (Instillagel, FARCO-PHARMA, Köln, Germany). After 5 minutes, a transrectal probe was inserted and the prostate volume was measured. Then, local anesthesia was induced.

In patients with visible lesions on MRI, 4 MRI-targeted cores per target were initially performed. The targets were then obtained, and a 12-core biopsy was performed. MRI-targeted biopsy was performed with an MRI/transrectal ultrasound-fusion-targeted biopsy protocol using the BK3000 ultrasound system embedded side-fire method (BK Medical, Peabody, MA, USA) and an image-based fusion program (BioJet, D&K Technologies GmbH, Barum, Germany). In patients with nonvisible lesions, only a 12-core biopsy was performed.

5. Risk Factor Evaluation

Confounding factors among PSA levels, prostate volume, and PSA density were evaluated. The receiver operating characteristic (ROC) curve analysis for predicting the presence of visible lesions showed that the area under the ROC curve (AUC) values of PSA levels, prostate volume, and PSA density were 0.595 (0.542–0.648; p=0.0005), 0.574 (0.517–0.630; p=0.0108), and 0.639 (0.590–0.689, p<0.0001), respectively. For predicting cancer diagnosis and csPCa, the AUC values of PSA density (0.733 [0.692–0.773], p<0.0001; 0.743 [0.702–0.783], p<0.0001) were significantly higher than those of PSA levels (0.627 [0.582–0.673], p=0.0001; 0.664 [0.620–0.709], p=0.0001) and prostate volume (0.676 [0.632–0.720], p<0.0001; 0.647 [0.602–0.692], p<0.0001). Therefore, PSA level and prostate volume data were excluded from the multivariate analysis to avoid confounding (Fig. 1).

6. Statistical Analyses

Categorical variables were evaluated using the chi-square test and Fisher exact test. Differences in variables with a continuous distribution across categories were assessed using the Mann–Whitney U-test. Multivariate regression analyses were performed on the factors predicting visible lesion, cancer diagnosis, and csPCa (defined as a Gleason score sum ≥7 [3+4]) among target lesions that had a p-value <0.05 in the univariate analyses. ROC curves and AUCs were used to obtain the cutoff value. These optimal cutoff values were based on predefined values based on a sensitivity analysis using Youden index (sensitivity+specificity – 1).[9] The AUC was compared using the Delong method for statistical significance of differences in AUC. All reported p-values are 2-sided, and statistical significance was set at <0.05 Statistical analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA) and SAS ver. 9.3 (SAS Inc., Cary, NC, USA).

RESULTS

1. Demographic Data

The baseline clinical and demographic characteristics of the patients who underwent prostate biopsy are shown in Table 1. A total of 342 patients (59.6%) were diagnosed with prostate cancer (visible lesions=312 of 449 [69.5%]; nonvisible lesions=30 of 123 [24.0%]). Among them, the proportion of csPCa was 46.7% (visible lesions=312 of 449 [69.5%]; nonvisible lesions=30 of 125 [24.0%]). The individuals with visible lesions had a significantly higher frequency of prostate cancer and csPCa than those with nonvisible lesions (p<0.0001).

Furthermore, the individuals with visible lesions had more advanced age, higher PSA level, PSA density,

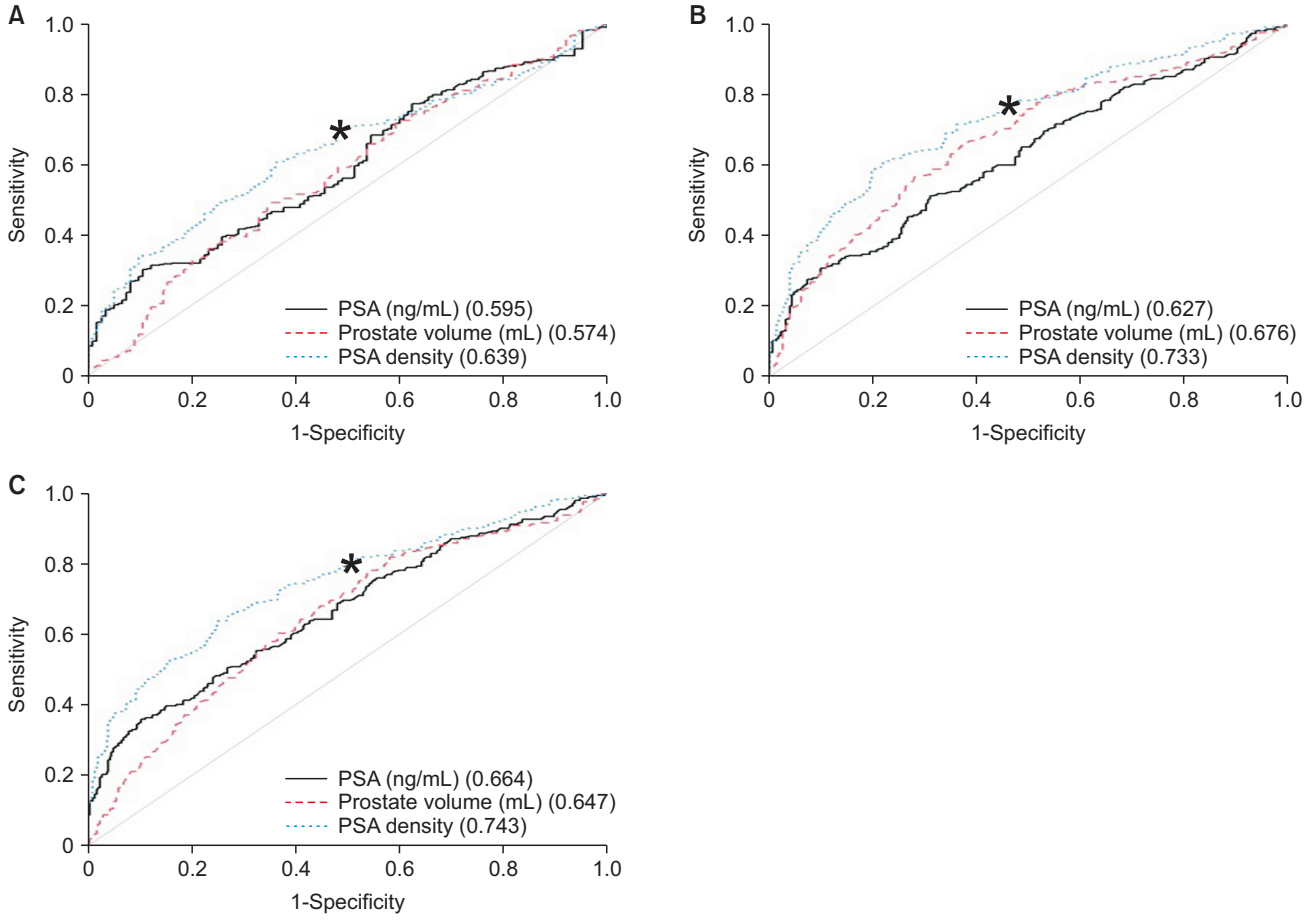

Fig. 1. Receiver operating characteristic curves. Prediction of the presence of visible lesions (A), cancer (B), and significant cancer (C). PSA: prostate-specific antigen. *Indicates the optimal cutoff point which is calculated by Youden index (Sensitivity+Specificity-1).

proportion of previous prostate biopsy history, and lower prostate volume than those with nonvisible lesions (n=449 vs. 125; median age, 69.0 vs. 65.7 years, p<0.001; median PSA levels, 25.07 ng/mL vs. 6.98 ng/mL, p=0.0002; PSA density, 0.75 ng/mL/cm^3 vs. 0.18 ng/mL/cm^3, p=0.0003; prostate volume, cm^3 38.0 vs. 42.1 cm^3, p=0.0139).

The detection rates of visible lesions stratified using the PI-RADS score (3 vs. 4 vs. 5) were 30.9% (54 of 175), 61.2% (150 of 245), and 91.1% (127 of 141), respectively. There is no significant difference in previous prostate biopsy history between the 2 groups (visible lesions=100 of 449 [22.3%]; nonvisible lesions=29 of 125 [23.2%], p=0.826).

2. Prediction of Cancer Diagnosis and Clinically Significant Prostate Cancer

Age and PSA density were identified as the significant factors for the presence of visible lesions. Univariate analysis was performed to predict cancer diagnosis and csPCa using several factors, including age, PSA density, and history of prostate biopsy. The multivariate logistic regression analyses identified that age, PSA density, and presence of visible lesions remained as independent predictors of prostate cancer diagnosis and csPCa (Table 2).

The diagnostic performance of PSA density using

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Table 1. Baseline clinical and demographic characteristics of patients suspected with prostate cancer who underwent prostate biopsy after magnetic resonance imaging

Characteristic	Visible lesions	Nonvisible lesions	p-value
No. of patients	449 (78.2)	125 (21.8)	
Age (yr)	68.9 (60.6–77.2)	65.7 (57.2–74.3)	0.0002
PSA level (ng/mL)	27.9 (15.5–40.3)	6.98 (2.88–7.01)	0.0004
Prostate volume (mL)	38.1 (20.8–55.3)	42.1 (23.8–60.4)	0.0229
PSA density	0.84 (0.43–1.25)	0.18 (0.07–0.30)	0.0008
Previous prostate biopsy history	100 (22.3)	29 (23.2)	0.8259
Diagnosis of prostate cancer	312 (69.5)	30 (24.0)	<0.0001
Gleason score			<0.0001
≤6	58 (18.6)	16 (53.3)	
≥7 (3+4)	254 (81.4)	30 (24.0)	
Positive systematic biopsy	286 (63.7)	30 (24.0)	<0.0001
Gleason score			0.0011
≤6	72 (25.2)	16 (53.3)	
≥7 (3+4)	214 (74.8)	30 (24.0)	
Positive target biopsy	331/561 (59.0)		
PI-RADS 3	54/175 (30.9)		
PI-RADS 4	150/245 (61.2)		
PI-RADS 5	127/141 (90.1)		

Values are presented as number (%) or median (range).
PSA: prostate-specific antigen, PI-RADS: Prostate Imaging Reporting And Data System.

Table 2. Multivariate analysis of factors predicting cancer and significant prostate cancer

Variable	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Presence of visible lesions				
Age (yr)	1.046 (1.022–1.072)	0.0002	1.044 (1.018–1.070)	0.0007
PSA (ng/mL)	1.068 (1.023–1.115)	0.0025	-	-
Prostate volume (mL)	0.988 (0.977–0.998)	0.0242	-	-
PSA density (0.1 unit)	1.401 (1.183–1.660)	<0.0001	1.398 (1.176–1.661)	0.0001
Previous prostate biopsy history	0.949 (0.592–1.519)	0.8260	0.962 (0.591–1.565)	0.8758
Cancer				
Age (yr)	1.070 (1.047–1.093)	<0.0001	1.069 (1.043–1.096)	<0.0001
PSA (ng/mL)	1.064 (1.032–1.097)	<0.0001	-	-
Prostate volume (mL)	0.972 (0.962–0.982)	<0.0001	-	-
PSA density (0.1 unit)	1.683 (1.437–1.972)	<0.0001	1.625 (1.372–1.925)	<0.0001
Previous prostate biopsy history	0.616 (0.415–0.914)	0.0161	0.538 (0.339–0.853)	0.0084
Presence of visible lesions	7.212 (4.566–11.389)	<0.0001	5.305 (3.244–8.674)	<0.0001
Significant prostate cancer				
Age (yr)	1.072 (1.049–1.096)	<0.0001	1.072 (1.045–1.100)	<0.0001
PSA (ng/mL)	1.083 (1.050–1.117)	<0.0001	-	-
Prostate volume (mL)	0.974 (0.964–0.985)	<0.0001	-	-
PSA density (0.1 unit)	1.691 (1.466–1.951)	<0.0001	1.632 (1.405–1.894)	<0.0001
Previous prostate biopsy history	0.746 (0.502–1.110)	0.1480	0.730 (0.457–1.165)	0.1869
Presence of visible lesions	10.327 (5.746–18.563)	<0.0001	7.413 (3.965–13.861)	<0.0001

PSA: prostate-specific antigen, CI: confidence interval.

cutoff values calculated from the Youden index was determined. A PSA density of 0.15 ng/mL/cm^3 was identified as the optimal cutoff point, at which sensitivity is higher than 0.7 and the specificity is maximized, for predicting the presence of visible lesions on MRI as well as cancer diagnosis and

Table 3. Diagnostic performance of prostate-specific antigen density for the presence of visible lesions, cancer, and clinically significant prostate cancer

Outcome	Optimal cutoff point	Sensitivity (95% CI)	Specificity (95% CI)
Presence of visible lesion	≥0.15	0.695 (0.652–0.737)	0.520 (0.432–0.608)
Cancer	≥0.15	0.772 (0.727–0.816)	0.534 (0.470–0.599)
Clinically significant cancer	≥0.15	0.806 (0.759–0.853)	0.490 (0.434–0.546)

CI: confidence interval.

csPCa (Table 3).

3. Usefulness of PSA Density in Evaluating the Efficacy of Prebiopsy MRI

A subanalysis was performed for evaluating the efficacy of target biopsy in increasing prostate cancer detection rates compared with that of systematic biopsy. Among the 561 lesions detected, 27 (8.2%) were diagnosed as prostate cancer concomitant with negative systematic biopsy results. In contrast, 60 lesions (26.1%) were diagnosed as prostate cancer using systematic biopsy concomitant with negative target biopsy results.

In the groups with negative systematic biopsy results, a PSA density of 0.15 ng/mL/cm^3 was identified as the significant cutoff value for predicting a positive target biopsy (p=0.0019).

DISCUSSION

Age, PSA, prostate volume, PSA density, and previous biopsy history are well-known variables related to prostate cancer diagnosis.[10] In the ROC curve analysis for the prediction of visible lesions on MRI, prostate cancer, and csPCa, the AUC of PSA density showed superior probability than those of PSA level and prostate volume. Therefore, we chose PSA density for the analysis to avoid confounding factors. Interestingly, the cutoff value of 0.15 ng/mL/cm^3 for PSA density was significant for predicting the presence of visible lesions, cancer diagnosis, and csPCa. The presence of visible lesions has also been shown as related to the higher possibility of prostate cancer diagnosis, especially csPCa, consistent with the results of another study.[6] Furthermore, an increasing PI-RADS score of the visible lesions was positively related to PSA density. Therefore, we used the variables combining PSA density and presence of visible lesions for predicting the outcomes of the target lesions, instead of the PI-RADS score.

According to the American Urological Association and Society of Abdominal Radiology, at least 2 targeted cores should be obtained from each MRI-defined target lesion.[11] However, Lu et al.[12] revealed that sampling of 2 cores of the target lesion misses nearly one-quarter of csPCa detected on additional sampling. To improve grade group prediction and limit upgrading risk, a recent study showed that at least 4 targeted biopsy cores should be considered.[13] In this study, 4 MRI-targeted cores per target were performed. Owing to the invasiveness of a biopsy procedure, further study will be needed to decide the optimal number of targeted biopsy cores.

In the PAIREDCAP (Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer) study that compared targeted and systematic prostate biopsies for biopsy-naïve male patients, prostate cancer was detected up to 15% using systematic biopsy in the group without visible lesions, indicating a false-negative MRI result.[14] Moreover, Bryant et al.[15] reported that 15.1% of prostate cancer cases with a Gleason score ≥7 (3+4) and with negative multiparametric MRI (mpMRI) findings were underdetected with systematic biopsy. In our study, 24.0% of the

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patients without visible lesions under mpMRI were diagnosed with prostate cancer, and approximately 11.2% had csPCa with a Gleason score ≥7 (3+4). Generally, Asians have lower prostate volumes than Westerners; therefore, the PSA density is relatively high among Asians, resulting in higher cancer detection rates. In a previous study of 177 prostatectomy patients with nonvisible lesions, a nonvisible lesion was not a predictor for low-risk prostate cancer.[16] Therefore, these findings indicate that a negative mpMRI result cannot rule out the nonperformance of prostate biopsy.

The PI-RADS v2 score was developed to assess csPCa, and the use of MRI for detecting prostate cancer has increased with the emergence of the PI-RADS.[17] Mehralivand et al.[18] reported that the cancer detection rates of 1, 2, 3, 4, and 5 categories in PI-RADS were 25.0%, 20.2%, 24.8%, 39.1%, and 86.9% for all prostate cancers and 0%, 9.6%, 12%, 22.1%, and 72.4% for csPCa, respectively. Our institution interpreted the presence of visible lesions on MRI as lesions with a PI-RADS score ≥ 3 (clinically significant cancer is equivocal). In our study, the PI-RADS score 3 vs. 4 vs. 5 for prostate cancer and csPCa were 30.9% vs. 61.2% vs. 90.1% and 14.9% vs. 44.9% vs. 83.7%, respectively, which is similar to previous studies' results.

For MRI-target biopsy, a systematic biopsy in addition to target biopsy is recommended to achieve the best detection results. Targeted biopsy or systematic biopsy alone does not cover the overall detection rates. In a recent study, the overall cancer detection rates and those of target and systematic biopsies were 70%, 60%, and 60%, respectively,[14] and we had comparable results in the present study, at 59.6%, 59.0%, and 55.1%, respectively.

MRI yields a 5%–16% additional detection rate compared with systematic biopsy alone. Fourcade et al. reported that systematic biopsy alone would have missed the detection of prostate cancer in 12% of patients.[19] In our study, 27 of 331 positive lesions (8.2%) would have been missed if the targeted biopsy was not performed because of the false-negative MRI findings. In contrast, 60 of the negative lesions (26.1%) would not have been diagnosed by targeted biopsy alone, which is similar to results of a previous study.[20] Therefore, to maximize cancer detection rates, both targeted and systematic biopsies should be implemented. The present study also reported that the PSA density of 0.15 ng/mL/cm^3 was a useful indicator for recommending MRI to patients suspected with prostate cancer to prevent missed diagnoses in cases without targeted biopsy (Table 4).

Patients with prior negative biopsy results receiving a PI-RADS assessment category of 3 to 5 require a repeat biopsy with image guided targeting.[11] In this setting, Exterkate et al.[21] reported that the value of adding systematic biopsy to targeted biopsy is limited because only 1.3% csPCa would be missed if systematic biopsy had been omitted. In this study, however, 8% csPCa would be missed without systematic biopsy. Therefore, we cannot confirm that repeat biopsy

Table 4. Stratifying outcomes of the target and systematic biopsies according to prostate-specific antigen (PSA) density

Variable	Target biopsy benign	Target biopsy cancer	p-value
Systematic biopsy			<0.0001
Benign	170 (73.91)	27 (8.16)	
Cancer	60 (26.09)	304 (91.84)	
Systematic biopsy (benign)			0.0019
PSA density <0.15 ng/mL/cm^3	86 (50.59)	5 (18.52)	
PSA density ≥0.15 ng/mL/cm^3	84 (49.41)	22 (81.48)	

could be safely omitted despite prior biopsy negative history.

Washino et al.[22] reported that a PI-RADS v2 score ≤3 and PSA density <0.15 ng/mL/cm^3 does not yield csPCa. Oishi et al.[6] suggested that repeat biopsy could be omitted in cases with a negative MRI finding and those with a PSA density <0.15 ng/mL/cm^3. As in previous studies, this study reconfirmed that the PSA density has a potential role in compensating for the low negative predictive value of mpMRI for prostate cancer. In other words, a PSA density ≥0.15 ng/mL/cm^3 is a useful indicator for detecting prostate cancer in target lesions concomitant with negative systematic biopsy results. Therefore, we recommend that patients with a PSA density ≥0.15 ng/mL/cm^3 should consider prebiopsy MRI.

Nevertheless, this study has some limitations. Several characteristics could account for the heterogeneity in the results, including the small cohort size, having multiple physicians in the study, and the variability of the clinical decision-making regarding performance of prebiopsy MRI. To increase the cost-effectiveness of prebiopsy MRI, the indicators to reduce false-positive MRI findings should be investigated. Despite these limitations, we demonstrated the indication for preventing missed prostate cancer diagnosis in cases without prebiopsy MRI.

CONCLUSIONS

A PSA density ≥0.15 ng/mL/cm^3 is a useful indicator for recommending prebiopsy MRI and for predicting cancer and csPCa. Therefore, patients with a PSA density ≥0.15 ng/mL/cm^3 should consider MRI to avoid a missed cancer diagnosis.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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