Research Article

Detection of prostate cancer using prostate imaging reporting and data system score and prostate-specific antigen density in biopsy-naive and prior biopsy-negative patients

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ABSTRACT

Background: Few studies report on indications for prostate biopsy using Prostate Imaging Reporting and Data System (PI-RADS) score and prostate-specific antigen density (PSAD). No study to date has included biopsy-naive and prior biopsy-negative patients. Therefore, we evaluated the predictive values of the PI-RADS, version 2 (v2) score combined with PSAD to decrease unnecessary biopsies in biopsy-naive and prior biopsy-negative patients.

Materials and methods: A total of 1,098 patients who underwent multiparametric magnetic resonance imaging at our hospital before a prostate biopsy and who underwent their second prostate biopsy with an initial benign negative prostatic biopsy were included. We found factors associated with clinically significant prostate cancer (csPca). We assessed negative predictive values by stratifying biopsy outcomes by prior biopsy history and PI-RADS score combined with PSAD.

Results: The median age was 65 years (interquartile range: 59–70), and the median PSA was 5.1 ng/mL (interquartile range: 3.8–7.1). Multivariate logistic regression analysis revealed that age, prostate volume, PSAD, and PI-RADS score were independent predictors of csPca. In a biopsy-naive group, 4% with PI-RADS score 1 or 2 had csPca; in a prior biopsy-negative group, 3% with PI-RADS score 1 or 2 had csPca. The csPca detection rate was 2.0% for PSA density <0.15 ng/mL/mL and 4.0% for PSA density 0.15–0.3 ng/mL/mL among patients with PI-RADS score 3 in a biopsy-naive group. The csPca detection rate was 1.8% for PSA density <0.15 ng/mL/mL and 0.15–0.3 ng/mL/mL among patients with PI-RADS score 3 in a prior biopsy-negative group.

Conclusion: Patients with PI-RADS v2 score 2, regardless of PSA density, may avoid unnecessary biopsy. Patients with PI-RADS score 3 may avoid unnecessary biopsy through PSA density results.

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1. Introduction

Prostate cancer (PCa) is the most common male malignancy and the second most common cause of male cancer-related death.1 Early detection of PCa is important, and diagnostic tools and methods have been improving for decades. One method, multiparametric magnetic resonance imaging (mpMRI), is increasingly used for PCa diagnosis because of its growing availability. Several studies report on the usefulness of mpMRI.2-10 Porpiglia et al.3 reported that a diagnostic pathway based on mpMRI had a higher detection rate than the standard approach for both PCa and clinically significant prostate cancer (csPCa). Several studies reported on the relationship between PCa detection and Prostate Imaging Reporting and Data System (PI-RADS) v2 score.5,11-13 Niu et al.12 reported that the new PI-RADS v2-based nomogram for forecasting high-grade PCa is effective and potentially reduces harm from unnecessary prostate biopsy. Several studies report on using prostate-specific antigen density (PSAD) for detecting Pca.14 A few studies investigated indications for prostate biopsy using PI-RADS score and PSAD.5,10 However, no study to date has included biopsy-naive and prior biopsy-negative patients. Therefore, we determined the predictive values of PI-RADS v2 scores combined

https://doi.org/10.1016/j.prnil.2020.03.003
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with PSAD to decrease the number of patients undergoing unnecessary prostatic biopsy with biopsy-naive and initial benign prostatic biopsy.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the Institutional Review Board of Samsung Medical Center. Included were 2,162 patients who underwent mpMRI at our hospital before a prostate biopsy, who had PSA value from 2.5 to 15 ng/mL and who underwent their second prostate biopsy with an initial benign negative prostatic biopsy or their first prostate biopsy between January 2016 and December 2018. In all, 1,064 patients who did not undergo prostate biopsy because no suspicious lesion was found on mpMRI were excluded. Finally, 1,098 patients were analyzed.

2.2. Multiparametric magnetic resonance imaging

MpMRI was performed with a 3-Tesla magnetic resonance system (Intera Achieva TX; Philips Healthcare, Best, The Netherlands) before prostate biopsy using a phased array coil. MRI protocols included T1-weighted, T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging. After obtaining 3-plane localizer images, T2-weighted turbo spin-echo images were obtained in three orthogonal planes (axial, sagittal, and coronal). Axial T1-weighted turbo field echo sequences (3-mm slice thickness; FOV, 24 cm) were obtained. Apparent diffusion coefficient maps were automatically constructed on a pixel-by-pixel basis. Axial dynamic contrast-enhanced imaging was obtained from the prostate apex to base using a 3-D fast-field echo sequence.15

All images were evaluated by two genitourinary radiologists with 11 and 16 years of experience in prostate MRI using the validated PI-RADS v2. PI-RADS assessment categories were defined as score 1 (low) to score 5 (high) in accordance with the likelihood of significant PCa.11

2.3. Prostate biopsy

Systematic biopsy was performed using transrectal ultrasound guidance (IU22; Philips Healthcare, Andover, MA) in a standard paired sextant pattern by several urologists in our hospital.16

Two radiologists performed MRI/TRUS (transrectal ultrasound) fusion target biopsy and cognitive target biopsy on lesions with PI-RADS scores 1 to 5 on mpMRI. MRI/TRUS fusion target biopsy was performed using the UroNav Fusion Biopsy System (Invivo, Gainesville, FL) and a TRUS probe (Philips Healthcare; Amsterdam, The Netherlands).16

Gleason score \( \geq 3 + 4 \) was defined as csPca, and other scores were defined as clinically insignificant PCs.

2.4. Statistical analysis

Continuous variables were expressed as median (interquartile range [IQR]). Categorical variables were expressed as absolute values and percentages. Univariate and multivariate analyses were performed using logistic regression analysis 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 IBM SPSS Statistics, version 21.0 (IBM Co., Armonk, NY, USA).

3. Results

3.1. Patients who underwent mpMRI and prostate biopsy

Of the 2,162 patients with PSA value from 2.5 to 15 ng/mL who underwent mpMRI, 1,098 underwent prostate biopsy (Fig. 1). Among patients who underwent prostate biopsy, 472 (43%) had proven PCa, and 626 patients had no PCa. In addition, 318 patients had csPca, and 154 had nonsignificant PCs.

3.2. Patients characteristics

Clinical characteristics of the 1,098 patients who underwent mpMRI before prostate biopsy and had suspicious lesions on MRI examination are in Table 1. The median age was 65 years (IQR: 59-70), and the median PSA was 5.1 ng/mL (IQR: 3.8-7.1). The median prostate volume was 37.3 mL (IQR: 28.0-51.3), and the median PSAD was 0.14 ng/mL/mL (IQR: 0.10-0.20). The numbers of patients with PI-RADS 1-2, 3, 4, and 5 were 119 (10.8%), 210 (19.1%), 579 (52.7%), and 190 (17.3%), respectively. The number of patients in the biopsy-naive group was 601 (54.7%), and the number in the group with previous negative biopsy was 497 (45.3%).

3.3. Biopsy outcome stratified by prior biopsy history and PI-RADS v2 score

Of all patients, 119 (10.8%), 210 (19.1%), 579 (52.7%), and 190 (17.3%) were categorized with respective PI-RADS 1-2, 3, 4, and 5. Biopsy-proven PCa rates were 14.3%, 16.2%, 46.3%, and 80.5% in PI-RADS groups 1-2, 3, 4, and 5, respectively. Specific pathological outcomes stratified by prior biopsy history and PI-RADS v2 score are shown in Table 2. Of the 50 patients with PI-RADS score of 1 or 2 in a biopsy-naive group, 2 (4.0%) had csPca. Among 101 patients with PI-RADS score 3 in a biopsy-naive group, 7 (7.0%) had csPca. More than 30% of patients with PI-RADS score 4 in a biopsy-naive group were diagnosed with csPca. Of 69 patients with PI-RADS score 1 or 2 in a biopsy-negative group, 2 (3.0%) had csPca. Among 109 patients with PI-RADS score 3 in a biopsy-negative group, 7 (6.5%) had csPca. More than 20% of patients with PI-RADS score 4 in a biopsy-naive group were diagnosed with csPca.

3.4. Factors associated with csPca

Table 3 presents the univariable and multivariable logistic regression analyses for factors associated with csPca. Among the factors that were suspected of predicting csPca, age, PSA level, prostate volume, PSAD, and PI-RADS score more than 4 were

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**Fig. 1.** The number of patients who were proven clinically significant and non-significant prostate cancer by prostate biopsy.
significant factors correlated with csPca on univariate analyses. All of these factors except PSA level were significantly associated with csPca on multivariable analyses.

### 3.5. csPca detection rate stratified by PI-RADS score and PSAD

The rate of clinically significant Pca in the PI-RADS 1-2 group in biopsy-naive patients was 4% (Table 4). Among patients with PI-RADS score 3 in a biopsy-naive group, csPca detection rates were 2.0% for PSAD <0.15 ng/mL/mL, 4.0% for 0.15 ≤ PSAD < 0.3, and 1.0% for PSAD ≥ 0.3 ng/mL/mL. The csPca detection rate for the PI-RADS 1-2 group within prior biopsy-negative groups was 2.9%. Among patients with PI-RADS score 3 in prior biopsy-negative groups, csPca detection rates were 1.8% at PSAD <0.15 ng/mL/mL or 0.15 ≤ PSAD < 0.3 and 2.8% for PSAD ≥ 0.3 ng/mL/mL.

### 4. Discussion

With attention to diagnosis of PCa, especially early PCa detection, the number of prostate biopsy cases has increased. For many biopsy-negative cases, patients may undergo several biopsies. Therefore, criteria for avoiding unnecessary prostate biopsy are important. Patients who experience prior biopsy should get more attention than biopsy-naive patients when deciding to perform biopsy. Traditionally, the decision about whether a prostate biopsy should be performed has been based mainly on PSA, digital rectal examination findings, and age, which leads to inaccurate results.

PI-RADS score and PSAD are considered key factors to determine prostate biopsy. In this study, we found that PI-RADS score and PSAD were significant factors for csPca. Therefore, we determined indications for prostatic biopsy using PI-RADS score and PSAD in patients in a biopsy-naive group and a prior biopsy-benign group.

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### Table 1

The baseline characteristics of 1,098 patients.

| Variable                              | Value            |
|---------------------------------------|------------------|
| Median age, years (IQR)               | 65 (59–70)       |
| Median PSA, ng/mL (IQR)               | 5.1 (3.8–7.1)    |
| Median prostate volume, mL (IQR)      | 37.3 (28.0–51.3) |
| Median PSAD, ng/mL/mL (IQR)           | 0.14 (0.10–0.20) |
| PI-RADS score, n (%)                  | 1-2              |
|                                       | 119 (10.8)       |
|                                       | 210 (19.1)       |
|                                       | 579 (52.7)       |
|                                       | 190 (17.3)       |
| Prior biopsy history, n (%)           | Naive            |
|                                       | 601 (54.7)       |
|                                       | Prior biopsy-negative | 497 (45.3) |

PSA, prostate-specific antigen; PS AD, prostate-specific antigen density; PI-RADS, Prostate Imaging Reporting and Data System.

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### Table 2

Biopsy outcome based on MRI finding (PI-RADS v2) in accordance with prior biopsy history

| Biopsy state                  | PI-RADS v2 | Negative | Insignificant Pca | Significant Pca |
|-------------------------------|------------|----------|------------------|-----------------|
|                               |            |          | GS 6             | GS 3 + 4 = 7    | GS ≥ 4 + 3 = 7  |
| Biopsy-naive (n = 601)        | 1-2 (n = 50)| 43 (86.0%)| 5 (10.0%)        | 2 (4.0%)        | 0 (0%)          |
|                               | 3 (n = 101)| 84 (83.2%)| 10 (9.9%)        | 3 (3.0%)        | 4 (4.0%)        |
|                               | 4 (n = 330)| 151 (45.8%)| 60 (18.2%) | 51 (15.5%) | 68 (20.6%)      |
|                               | 5 (n = 120)| 18 (15.0%)| 15 (12.5%) | 28 (23.3%) | 59 (49.2%)      |
| Prior biopsy-negative (n = 497)| 1-2 (n = 69)| 59 (85.5%)| 8 (11.6%) | 1 (1.5%) | 1 (1.5%)        |
|                               | 3 (n = 109)| 92 (84.4%)| 10 (9.2%) | 4 (3.7%) | 3 (2.8%)        |
|                               | 4 (n = 249)| 160 (64.3%)| 37 (14.9%)| 20 (8.0%) | 32 (12.9%)      |
|                               | 5 (n = 70)| 19 (27.1%)| 9 (12.9%) | 19 (27.1%) | 23 (32.9%)      |

PI-RADS v2, Prostate Imaging Reporting and Data System, version 2; GS, Gleason score.

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### Table 3

Multivariate logistic regression analysis of factors associated with clinically significant Pca in patients with biopsy-naive and prior benign prostatic biopsy.

| Variables                  | Univariate | Multivariate |
|----------------------------|------------|--------------|
|                            | HR (95% CI) | P            | HR (95% CI) | P            |
| Age                       | 1.08 (1.06–1.10) | <0.001 | 1.11 (1.08–1.13) | <0.001 |
| PSA                       | 1.13 (1.08–1.18) | <0.001 | 1.11 (1.00–1.24) | 0.062 |
| Prostate volume            | 0.95 (0.94–0.96) | <0.001 | 0.95 (0.93–0.97) | <0.001 |
| PSAD <0.15                 | -           | -            | -           | -            |
| PSAD 0.15–0.29             | 3.38 (2.51–4.55) | <0.001 | 1.86 (1.11–3.14) | 0.020 |
| PSAD ≥ 0.30                | 11.86 (7.41–18.97) | <0.001 | 3.19 (1.19–8.59) | 0.022 |
| PI-RADS 1 or 3             | -           | -            | -           | -            |
| Prior biopsy history       | -           | -            | -           | -            |
| Naive                      | -           | -            | -           | -            |
| Prior biopsy-negative      | -           | -            | -           | -            |

Bold letters indicate significance (P < 0.05).

With attention to diagnosis of PCa, especially early PCa detection, the number of prostate biopsy cases has increased. For many biopsy-negative cases, patients may undergo several biopsies. Therefore, criteria for avoiding unnecessary prostate biopsy are important. Patients who experience prior biopsy should get more attention than biopsy-naive patients when deciding to perform biopsy. Traditionally, the decision about whether a prostate biopsy should be performed has been based mainly on PSA, digital rectal examination findings, and age, which leads to inaccurate results.

PI-RADS score and PSAD are considered key factors to determine prostate biopsy. In this study, we found that PI-RADS score and PSAD were significant factors for csPca. Therefore, we determined indications for prostatic biopsy using PI-RADS score and PSAD in patients in a biopsy-naive group and a prior biopsy-benign group.

Most studies found little possibility of detecting cancer for PI-RADS score 2 or less with a tendency to decide that PI-RADS scores more than 2 are positive results.17-23

For lesions with PI-RADS score 3, many studies recommend not performing prostate Bx because of low possibility of Pca. However, several studies report that we should not ignore the possibility of Pca for PI-RADS 3 lesions. In clinical settings, we usually do not perform prostate Bx for PI-RADS 2 lesions. However, opinions about PI-RADS 3 lesions are diverse. In this study, we found that, for patients with PI-RADS score 1 or 2, 4% in a biopsy-naive group and 2.9% in prior biopsy-negative group had csPca. We also found that, for patients with PI-RADS score 3, 7% in a biopsy-naive group and 6.5% in a prior biopsy-negative group had csPca. These results are comparable with previous studies. Based on these results, we decided to not perform biopsy for patients with PI-RADS 2 lesion regardless of biopsy history because of a smaller than 5% possibility of Pca. However, deciding whether to perform biopsy or not for PI-RADS 3 lesions is still difficult. Consideration of PSAD with PI-RADS category would be helpful for deciding whether to perform biopsy. In most studies, the PSA density threshold value is set from 0.10 to 0.30 ng/mL/mL. In this study, we set PSAD values as 0.15 and 0.3 ng/mL/mL.

Some studies evaluated detection of Pca using a combination of PI-RADS v2 score and PSA density. Washino et al. reported that biopsy-naive patients with PI-RADS v2 score < 3 and PSA density <0.15 ng/mL/mL may avoid unnecessary biopsies because these patients showed no csPca and no additional detection of Pca on further biopsies.9 Kotb et al.10 reported that men with benign prostatic biopsy and PSA density <0.15 combined with low PI-RADS score (<3) may...
avoid second prostatic biopsy, knowing the risk of missing a clinically significant prostatic cancer is 7%.

In this study, for PI-RADS <2, detection rates of csPca were 4% in 8x-naive and 2.9% in prior biopsy-negative patients regardless of PSAD values. csPca detection rates were 2.0% at PSA density <0.15 ng/mL/mL and 6.0% at <0.3 ng/mL/mL among patients with PI-RADS score 3 who were biopsy-naive. Also, csPca detection rates were 1.8% at PSA density <0.15 ng/mL/mL and 3.7% at <0.3 ng/mL/mL among patients with PI-RADS score 3 in a prior biopsy-negative group. However, we found that the risk of missing csPca at PSA density <0.15 ng/mL/mL is 2%.

Based on these results, we believe an NPV of 95% or above is acceptable. In our study, patients with PI-RADS v2 score <2 may avoid unnecessary biopsy regardless of PSAD value. For PI-RADS score 3, patients with PSAD <0.15 in a biopsy-naive group and PSAD <0.3 in a prior biopsy-negative group may avoid unnecessary biopsies. Similar to this, cancer detection rates differ in accordance with prior biopsy status (biopsy-naive and prior biopsy-negative). Rates of missing csPca in patients with prior benign prostatic biopsy are lower than in patients who are biopsy-naive when PI-RADS score 3 is same and PSAD values are in same category. In clinical settings, clinicians are more reluctant to perform rebiopsy in patients with prior negative biopsy owing to patient discomfort, complications, and costs. We could consider more strict indications for prostate biopsy in these patients, and the results of this study may be helpful in these cases.

This study has some limitations. The analysis was retrospective, and patient selection bias will be present. Second, no widespread accepted definition exists of csPca. Last, MRI interpretation and PI-RADS scoring were conducted by two radiologists with different levels of skill.

Nevertheless, our study has a large sample size. Furthermore, this is the first study to evaluate prostatic biopsy outcomes using PI-RADS v2 score combined with PSAD in patients who are biopsy-naive or had a prior negative biopsy result.

5. Conclusion

The combination of PI-RADS v2 score and PSA density could be helpful to practitioners deciding whether to perform prostatic biopsy or not. Patients with PI-RADS v2 score <2, regardless of PSA density, may avoid unnecessary biopsies. Patients with prior benign prostatic biopsy and both PI-RADS score 3 and PSA density <0.30 ng/mL/mL may avoid second prostatic biopsy, as the risk of missing csPca is 3.6%. In biopsy-naive patients, we could avoid prostatic biopsies when patients have PI-RADS score 3 and PSA density <0.15 ng/mL/mL, as the risk of missing csPca is 2%.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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