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# Usefulness of Biparametric Magnetic Resonance Imaging Combined With Prostate Specific Antigen Density in Pre-biopsy Detection of Clinically Insignificant Prostate Cancer

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**Abstract.** *Background/Aim: The aim of this study was to identify simple and reliable factors to detect clinically insignificant prostate cancer (PC) for avoiding immediate prostate biopsies using biparametric magnetic resonance imaging (MRI), which consists of T2-weighted and diffusion-weighted imaging. Patients and Methods: We retrospectively evaluated 427 men with suspected PC, who underwent biparametric MRI and standard 12-core transrectal prostate biopsy. MRI and prostate specific antigen density (PSAD) were analysed. To evaluate the combination of the two parameters, patients were divided into three groups (Group A: MRI negative and PSAD <0.23, Group B: MRI positive or PSAD ≥0.23, Group C: MRI positive and PSAD ≥0.23). A grade of ≥2 was defined as clinically significant PC. Results: Clinically significant PC was detected in 46.5% of men with positive MRI findings, and 60.0% of men with PSAD ≥0.23. When combining MRI and PSAD, detection rates of clinically significant PC were 10.0%, 28.4% and 65.3% in group A, B and, C, respectively. Conclusion: Negative biparametric MRI findings with PSAD <0.23 might be a reliable evidence for avoiding immediate prostate biopsies.*

Prostate biopsies are usually offered to men suspected of having prostate cancer (PC) due to elevated prostate-specific antigen (PSA) levels. However, men without PC or with clinically insignificant PC undergo unnecessary biopsies and overtreatment. The detection rate of PC is low in men who undergo a biopsy only because of elevated PSA levels (1). As PSA has a high false-positive rate, not only PSA but also other tools are needed for screening clinically significant PC. Multiparametric magnetic resonance imaging (mpMRI) has recently been widely used for the detection of significant prostate cancer. Using mpMRI as a triage test before a prostate biopsy would reduce unnecessary biopsies (2). However, mpMRI consists of T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and perfusion weighting imaging. The use of intravenous contrast medium can cause adverse effects, such as an acute reaction and nephrogenic systemic fibrosis, and is very time-consuming. In contrast, biparametric MRI (bpMRI) requires fewer scan sequences (T2WI and DWI), no intravenous contrast media, shorter image acquisition time, and has lower cost than mpMRI. Therefore, bpMRI would be adequate as a simple triage test before a prostate biopsy. The aim of the present study was to detect simple and reliable factors predicting clinically insignificant PC for avoiding unnecessary prostatic biopsies in clinical practice.

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*Key Words:* Biparametric magnetic resonance imaging, clinically significant prostate cancer, transrectal prostate biopsy.

## Patients and Methods

We retrospectively evaluated men with suspected PC who underwent prostate biopsy in our institution from August 2016 to April 2019. The exclusion criteria were PSA >20 ng/ml, have not performed bpMRI, and have not underwent 12 core biopsies. All patients underwent standard 12-core transrectal ultrasonography guided prostate biopsies. The final study population consisted of 427 men. In patients with bpMRI suspicious lesions, cognitive target biopsy near the individual standard biopsy area was performed. MRI images were acquired on a 1.5T MRI scanner (Sibna, GE Medical systems, Milwaukee, MI, USA). All patient examinations included T2WI, DWI and apparent diffusion coefficient (ADC). The prostate volume was acquired from the MRI (axial and coronal), and calculated according to the solid ellipse formula (length × width × height × π/6). MRI findings were analysed by three urologists. The histopathological examination was performed by a single pathologist. A grade of 2 or higher was defined as clinically significant prostate cancer.

Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatics (3).

## Results

Median age was 70 years old (range=42-86 years), median PSA levels were 7.3 ng/ml (range=1.4-20.0 ng/ml), median prostate volume was 30 ml (range=10-120 ml). Three hundred and sixty-one, 55 and 11 men underwent a first, second and third biopsy, respectively. PC was detected in 260 of 427 men (60.9%), and 173 of 427 men (40.5%) had clinically significant PC (Table I). Clinically significant PC was detected in 46.5% of men with positive MRI findings, and 21.0% of men with negative MRI findings. Median PSAD was 0.24. Using ROC analysis, the optimal cut-off value for PSAD was 0.23 with a sensitivity of 66.9% and specificity of 73.4% [AUC=0.73 (95%CI=0.684-0.781)]. In multivariate analysis, MRI findings [odds ratio (OR)=2.9; $p$=0.0002] and PSAD (OR=3.4; $p$<0.0001) were revealed as independent predictors of clinically significant PC (Table II). We divided men into three groups in accordance with the combination of the two parameters (Group A: MRI negative and PSAD <0.23, Group B: MRI positive or PSAD ≥0.23, Group C: MRI positive and PSAD ≥0.23). When combining MRI and PSAD, detection rates of clinically significant PC were 10.0%, 28.4% and 65.3% in group A, B and C, respectively (Table III).

Table I. *Participant characteristics*.

| | Total (n=332) |
|---|---|
| Age (median): years old | 42-86 (70) |
| PSA (median): ng/ml | 1.4-20.0 (7.3) |
| Prostate volume (median): ml | 10-120 (30) |
| Number of prostatic Biopsy | |
| 1 | 361 |
| 2 | 55 |
| 3 | 11 |
| Prostate cancer | 260 (60.9%) |
| Clinically significant prostate cancer | 173 (40.5%) |
| Grade group (n=260) | |
| 1 | 86 (33.1%) |
| 2 | 51 (19.6%) |
| 3 | 44 (16.9%) |
| 4 | 57 (21.9%) |
| 5 | 22 (8.4%) |
| Clinical T stage (n=260) | |
| 1c | 47 (18.1%) |
| 2a | 163 (62.7%) |
| 2b | 4 (1.5%) |
| 2c | 21 (8.1%) |
| 3a | 20 (7.7%) |
| 3b | 5 (1.9%) |

## Discussion

There has been a development of certain predictive models to predict the existence of PC. These models consider factors including PSA, age, family history, ethnicity, digital rectal examination, % free PSA, transrectal ultrasonography, prostate volume and PSAD. However, there remains no consensus whether predictive models could improve long-term PC risk (4).

In the present study, age, PSA, PSAD and MRI findings were independent factors in multivariate analysis. On the contrary, prostate volume was not an independent predictive factor for the detection of clinically significant PC.

PSAD has been demonstrated to be a simple and valuable predictor of clinically significant PC (5, 6). Nordstrom *et al*. reported that among men with a PSAD of <0.1, 0.15-0.19 and >0.2 ng/ml/cc, 6.2%, 27.7%, and 46.2% had clinically significant PC, respectively (5). In our study, the detection rates of clinically significant PC were 21.7% and 60.0% in men with a PSAD of <0.23 and ≥0.23, respectively.

Prebiopsy mpMRI has emerged as a tool to detect clinically significant PC. Its detection rate is higher than that of ultrasound (7). Therefore, target biopsy with mpMRI could be useful for detecting significant prostate cancer. On the other hand, the negative predictive value ranged from 63% to 98% (8). It is not sufficient to use only mpMRI as a triage test. Several reports have shown the diagnostic accuracy of mpMRI in combination with other parameters including PSA, PSAD and age (9, 10). Kobt *et al*. reported that clinically significant PC was diagnosed in 7% men with both PSAD <0.15 and low suspicion of mpMRI (10).

Regarding prostate MRI, mpMRI is recommended according to guidelines (11, 12), however, it requires intravenous contrast media, is time-consuming and has higher cost. Therefore, it might be difficult to apply to all biopsy-naïve men with elevated PSA levels.

In contrast, bpMRI requires fewer sequences, less image acquisition time, and has a lower cost. Previous reports showed that the value of dynamic contrast-enhanced imaging is controversial. Wang *et al*. reported that DWI PIRADS score 3 lesions in peripheral zone dynamic contrast-enhanced imaging has not improved for the detection of clinically significant PC (13). DWI is the most promising image for evaluating prostate cancer in mpMRI (14). Pepe *et al*. reported that apparent diffusion coefficient value is significantly correlated with the presence of clinically significant PC (15). Some studies evaluated the accuracy of bpMRI compared with mpMRI (16-18). Di Campil *et al*. reported that there was no significant difference regarding the evaluation of clinically significant PC among three radiologists between bpMRI and mpMRI (16). Scialpi *et al*. also reported that bpMRI has the same sensitivity for detecting clinically significant PC compared to mpMRI, both in the peripheral zone and in the transitional zone (17). Furthermore, Mussi TC *et al*. showed that the use of contrast enhancement in mpMRI did not increase the detection of clinically significant PC, and had similar sensitivity,

Table II. *Factors to predict clinically significant prostate cancer.*

| Variable | Univariate *p*-Value | Multivariate odds ratio (95%CI) *p*-Value |
|---|---|---|
| Age (years) (≥70 years *vs*. <70 years) | 0.0011 | 1.6 (1.0-2.4) 0.048 |
| PSA (ng/dl) (≥7.3 *vs*. <7.3) | <0.0001 | 1.7 (1.0-2.9) 0.033 |
| Prostate volume (ml) (≥30 *vs*. <30) | <0.0001 | 0.7 (0.4-1.2) 0.157 |
| Number of prostatic biopsy (1 *vs*. 2, 3) | 0.134 | |
| PSAD (≥0.23 *vs*. <0.23) | <0.0001 | 3.4(1.9-6.2) <0.0001 |
| MRI findings (positive *vs*. negative) | <0.0001 | 2.9 (1.7-5.2) 0.0002 |

specificity, positive predictive value and negative predictive value as compared to a non-contrast protocol (18). In this study, clinically significant PC were detected in 46.5% of men with positive MRI findings, and in 21.0% of men with negative MRI findings. That is comparable to the previous studies using mpMRI (2, 8).

Several reports have been published that the combination with bpMRI and PSAD improves diagnostic accuracy of detecting clinically significant PC (19-21). Bossen *et al*. reported that only 5% of biopsy naive men with low or equivocal suspicion bpMRI findings and a PSAD value of <0.15 ng/ml/cc had clinically significant PC (19). Our study also demonstrated that 10% men with negative MRI findings and PSAD of <0.23 had clinically significant PC. Thus, the men with negative MRI findings and PSAD of <0.23 could be candidates to avoid immediate prostate biopsy.

This study has several limitations. This is a retrospective, single institution study. The real-time fusion technique was not used for prostate cancer suspicious regions on MRI. However, our study is necessary in terms of practicing only transrectal 12 core biopsy with the cognitive target technique when real-time fusion or trans-perineal biopsy is not available.

In conclusion, the combination of negative MRI findings with low PSAD is a simple and reliable tool for helping decision making of prostate biopsy and avoiding unnecessary biopsy for men without clinically significant PC.

## Conflicts of Interest

The Authors have stated that they have no conflicts of interest in relation to this study.

## Authors' Contributions

S Sekito: Data collection, Data analysis, Manuscript writing; T Terabe: Data collection; T Shibahara: Data collection; T Onishi: Data collection, Data analysis, Manuscript revision. All Authors read and approved the final manuscript.

Table III. *Parameters to detect clinically significant prostate cancer.*

| | csPC (%) | *p*-Value |
|---|---|---|
| bpMRI findings Negative (n=100) | 21 (21.0) | <0.001 |
| bpMRI findings Positive (n=327) | 152 (46.5) | |
| PSAD <0.23 (n=217) | 47 (21.7) | <0.001 |
| PSAD ≥0.23 (n=210) | 126 (60.0) | |
| Group A (n=60) | 6 (10.0) | <0.001 |
| Group B (n=197) | 56 (28.4) | |
| Group C (n=170) | 111 (65.3) | |

csPC: Clinically significant prostate cancer; Group A: MRI negative and PSAD <0.23; Group B: either MRI positive or PSAD≥0.23; Group C: MRI positive and PSAD≥0.23.

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