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Use of Prostate Specific Antigen Density Combined with Multiparametric Magnetic Resonance Imaging Improves Triage for Prostate Biopsy

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Keywords
Biopsy · Fusion · Magnetic resonance imaging · Prostate cancer · Prostate specific antigen density

Abstract
Background: Multi-parametric magnetic resonance imaging (mpMRI)-directed biopsy for prostate cancer (PC) diagnosis improves the detection of clinically significant prostate cancer (CSPC) and decreases the rate of over-diagnosis of insignificant disease. The aim of this study was to investigate the value of mpMRI combined with prostate specific antigen density (PSAD) in the decision making related to the biopsy. ***Methods:*** mpMRI and mpMRI/transrectal ultrasound fusion targeted biopsies with subsequent systematic biopsies were performed in 397 patients (223 biopsy-naïve and 174 with a previous biopsy). Detection rates of (CSPC) and insignificant PC were stratified using the PIRADS score, and the number of avoidable biopsies and missed (CSPC) were plotted against PSAD values of 0.1–0.5 ng/mL^2. ***Results:*** PIRADS <3 and PSAD <0.2 ng/mL^2 were the safest criteria for not performing a biopsy. When applied to the biopsy-naïve group, 21.5% (48/223) of the biopsies could have been avoided and 3.7% (3/82) of CSPC would have been missed. In the repeat biopsy group, 12.6% (22/174) of biopsies could have been avoided and 6.9% (4/58) of (CSPC) would have been missed. ***Conclusions:*** A combination of mpMRI and PSAD might reduce the number of biopsies performed with the cost of missing <4% of CSPC.

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Introduction

Transrectal ultrasound (TRUS)-guided prostate biopsy based on an elevated prostate specific antigen (PSA) plasma level or on an abnormal digital rectal examination result has been the cornerstone of prostate cancer (PC) diagnosis for the last 30 years [1]. TRUS-guided prostate biopsy is performed according to a standard template on 10–12 samples, and it misses approximately 20–30% of cancers. At the same time, many of the lesions that are diagnosed using TRUS-guided prostate biopsy may be clinically insignificant PC [2].

A growing body of evidence on magnetic resonance imaging (MRI)-directed biopsy for PC diagnosis supports the value of multi-parametric magnetic resonance imaging (mpMRI) for the localization and detection of clinically significant PC. This approach also decreases the rate of over-diagnosis of insignificant disease and improves risk stratification in the diagnosed patients [3]. Some even suggest that mpMRI might be used as a front door examination in PC diagnostics that could significantly reduce the number of prostate biopsies that are performed [4].

Prostate specific antigen density (PSAD) is a derivative of PSA that is calculated as the PSA plasma level divided by the prostate gland volume in mL [5]. Although PSAD has not been established in the diagnostic algorithm of PC, there has been a revived interest in PSAD due to recent advances in PC imaging. In a subset of mpMRI findings that are indeterminate, especially PIRADS 3 lesions, it would be useful to have an adjunct measure to risk-stratify this group of patients and help make the biopsy decision. Several reports suggest that PSAD may be such a measure [3, 6].

The aim of this study was to investigate whether the combination of mpMRI and PSAD could decrease the number of prostate biopsies without missing too many clinically significant prostate cancers (CSPC). A secondary objective was to determine the ideal cutoff values to use to trigger a biopsy.

Materials and Methods

Study Design

The study population was recruited from patients scheduled for systematic TRUS-guided biopsy in 2 tertiary care centers. Inclusion criteria were as follows: age <80 years, elevated PSA above (age-specific) limit, negative digital rectal examination, no coagulopathy. Exclusion criteria were: previous prostate surgery, inability to undergo mpMRI examination (metal implants, pace-maker present, chronic renal failure [MDRD <60 mL/min], claustrophobia).

All demographic, clinical, and histopathological data were collected in one central database. The data were blinded and secured. The informed consent form was signed by all patients. The study has been reviewed and approved by a certified Ethical Board.

Multiparametric MRI was performed on 397 consecutive patients who were referred to our institution for a suspected diagnosis of PC. Of these, 223 patients were biopsy-naïve and 174 had one or more prostate biopsies in the past.

MpMRI examination was performed on a 1.5T MR scanner (Signa HDxT GE; General Electric, Milwaukee, WI, USA) with endorectal coil (Medrad, Pittsburgh, PA, USA) and 8-channel body array coil (General Electric, Milwaukee, WI, USA). All patients were examined using the standard protocol, which included multiplanar T2-weighted image (T2WI) sequences (in axial, coronal, and sagittal planes) and axial DWI of the prostate with b values of 0 and 1,500 s/mm^2 using the endorectal coil. ADC maps were reconstructed for qualitative and quantitative assessment of DWI using standard GE software, the AW 4.5 Workstation (General Electric, Milwaukee, WI, USA). T1WIs in the axial plane covering the whole pelvis were performed with a body array coil for evaluation of pelvic lymphadenopathy. DCE images were obtained using a fast three-dimensional T1W spoiled gradient echo in the same plane as the T2WIs; the 3D volume covered the entire prostate. DCE images were acquired before, during, and after fast injection of a bolus of paramagnetic contrast medium, gadobutrol. The images were acquired every 13 s for 4 min 30 s. Perfusion curves were generated using the commercial software on the GE AW 4.5.

All MR images were evaluated prospectively by 2 radiologists with 4 and 10 years of experience with prostate MRI respectively. All MRI lesions were categorized into 4 groups according to the PIRADS classification version 1 score: negative (PIRADS 1 or 2); PIRADS 3; PIRADS 4; or PIRADS 5 [7].

MRI/TRUS fusion-targeted biopsies were performed on patients with PIRADS 3–5 lesions followed by a systematic transrectal biopsy. Fusion-targeted biopsies consisted of 1–3 cores from each MRI suspicious lesion PIRADS ≥3 (mean of 2.2 cores per lesion). Systematic transrectal biopsy consisted of 12 cores.

Fusion-targeted biopsy was controlled by ultrasound system (Aplio 500, Toshiba Medical Systems, Japan) with software registration, as described previously [8].

Three examiners from 2 departments were involved with 18, 15, and 5 years of experience respectively.

All biopsy cores were labeled, examined, and reported separately by 2 pathologists with over 20 years of experience. Samples were evaluated according to the International Society of Urological Pathology Guidelines.

Roche PSA electrochemiluminescent immunoassay was used to determine the PSA level. Prostate volume was measured by TRUS during biopsy. PSAD was calculated as the serum PSA level (ng/mL) divided by the prostate volume (mL).

Overall detection rates and detection rates of CSPC were calculated for the biopsy-naïve and rebiopsy group and stratified according to the PIRADS category. Clinically insignificant PC was defined as Gleason score of 6, <3 positive biopsy cores, and <50% cancer in a biopsy core [9].

Our goal was to determine the optimal cutoff PSAD value and PIRADS score needed to maximize the number of avoided biopsies and minimize the number of missed significant cancers. The percentage of spared biopsies and missed significant cancers was calculated using PSAD cutoff values between 0.1 and 0.5 ng/mL^2.

Table 1. Clinical characteristics of the biopsy-naïve first biopsy and rebiopsy groups

	Age, years	PSA density, ng/mL/mL	PSA value, ng/mL	Prostate volume, mL	Trans. zone volume, mL
Biopsy-naïve group					
Mean	61.37	0.14	6.67	55.53	30.93
SD	8.09	0.13	6.24	25.54	18.58
Minimum	31.00	0.01	0.53	17.00	6.00
1. quartile	56.00	0.07	4.10	37.50	17.00
Median	62.00	0.10	5.40	50.00	27.00
3. quartile	67.00	0.15	7.25	69.00	41.00
Maximum	80.00	1.21	72.50	157.00	104.00
Rebiopsy group					
Mean	64.40	0.19	10.88	68.30	37.88
SD	6.14	0.17	7.80	32.13	21.54
Minimum	50.00	0.04	1.94	18.00	6.00
1. quartile	60.00	0.09	6.05	42.00	22.00
Median	65.00	0.13	8.31	63.00	34.00
3. quartile	69.00	0.23	13.46	88.75	50.00
Maximum	80.00	1.37	52.00	187.00	121.00
Paired *t* test					
p value	<0.0001	0.001	<0.0001	<0.0001	0.002

PSA, prostate specific antigen.

Statistical Analyses

Statistical analyses were performed using the statistical software "R" version 3.4.3. Continuous variables were reported as means and SD and categorical variables were reported as proportions (%). Two-sample *t* tests or ANOVA were used to compare baseline characteristics between the biopsy-naïve group and the rebiopsy groups. All tests were performed using a level of significance of $\alpha = 0.05$.

Results

The characteristics of the study groups are shown in Table 1. In the biopsy-naïve group, the mean patient age was 61.4 years, the mean PSA was 6.67 ng/mL and the mean prostate volume was 55.5 mL. In the rebiopsy group, the mean patient age was 64.4 years, the mean PSA was 10.88 ng/mL, and the mean prostate volume was 68.3 mL. The average number of previous biopsies was 2.2 in the rebiopsy group.

Because of significant differences between the biopsy-naïve and rebiopsy groups for all variables (2-sample *t* test), all analyses were performed separately for each group.

The detection rates of PC were stratified according to PIRADS score in the biopsy-naïve group and the rebiopsy group (Table 2). Figures 1–4 show the percentages of potentially avoided (i.e., unnecessary) biopsies and the percentages of missed clinically significant PCs as a function of PSAD for all lesions with a PIRADS score <3 and for all lesions with a PIRADS score of 3 in the biopsy-naïve group and in the repeat biopsy group. We found that the safest criteria to use to decide not to perform a prostate biopsy were PIRADS <3 and PSAD <0.2 ng/mL[2]. When we used these criteria in the biopsy-naïve group, 21.52% (48/223) of the biopsies could have been avoided, 16.67% (5/30) of clinically insignificant PC would not have been diagnosed, and 3.66% (3/82) of clinically significant PC would have been missed. When we used these criteria for the repeat biopsy group, 12.64% (22/174) of biopsies could have been avoided, 4.35% (1/23) of clinically insignificant PC would not have been diagnosed, and 6.9% (4/58) of clinically significant PC would have been missed. Table 3 shows that as the biopsy criteria expand, the percentage of biopsies that could be avoided increased as did the number of clinically significant cancers that would be missed.

Receiver operating curves of MRI, PSA, and PSAD for biopsy-naïve and rebiopsy group are shown in Figures 5 and 6. Areas under curves are shown in Table 4.

Sensitivity, specificity, negative and positive predictive value of MRI and combination with PSAD in biopsy-naïve and rebiopsy group are shown in Table 5.

Table 2. Detection of prostate cancer according to PIRADS score in the biopsy-naïve and rebiopsy groups

PIRADS score	<3	3	4	5	Total
Biopsy-naïve group, *n* (%)					
Number of patients	53	73	78	19	223
Overall PC	12 (22.6)	31 (42.4)	51 (65.3)	18 (94.7)	112 (50.2)
Clinically significant PC	6 (11.3)	16 (21.9)	44 (56.4)	16 (84.2)	82 (36.7)
Insignificant PC	6 (11.3)	15 (20.5)	7 (8.9)	2 (10.5)	30 (13.4)
Rebiopsy group, *n* (%)					
Number of patients	25	67	65	17	174
Overall PC	8 (32.0)	25 (37.3)	32 (49.2)	16 (94.1)	81 (46.6)
Clinically significant PC	6 (24.0)	16 (23.9)	20 30.8)	16 94.1)	58 (33.3)
Insignificant PC	2 (8.0)	9 (13.4)	12 18.5)	0 (0.0)	23 (13.2)

PC, prostate cancer.

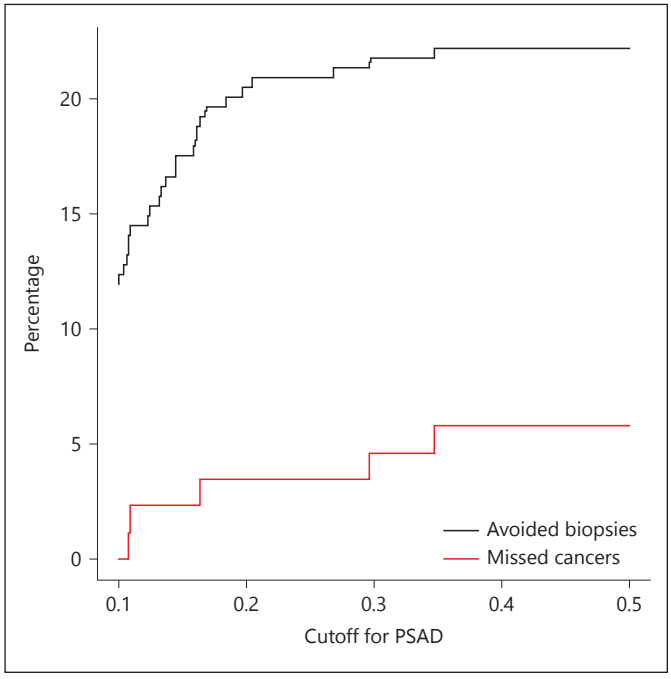

Fig. 1. Lesions with a PIRADS score <3 in the biopsy-naïve group. The percentage of biopsies that would be avoided and the percentage of CSPC that would be missed as a function of PSAD. PSAD, prostate specific antigen density.

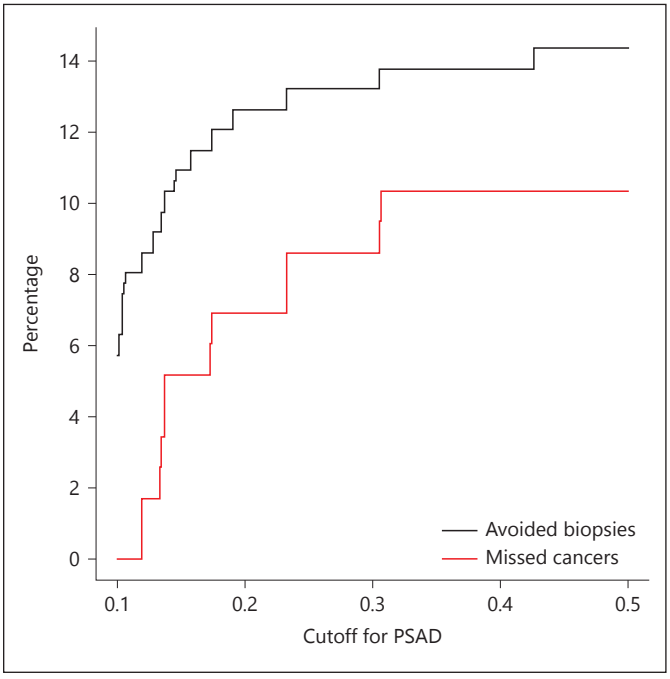

Fig. 2. Lesions with a PIRADS score <3 in the repeat biopsy group. The percentage of biopsies that would be avoided and the percentage of CSPC that would be missed as a function of PSAD. PSAD, prostate specific antigen density.

Discussion

Performing a pre-biopsy mpMRI of the prostate is an increasingly common approach at many centers. The goals are not only to stage the disease and to locate and target suspect lesions but also to guide decisions about whether to proceed with a biopsy [4, 10]. Unfortunately, the results of some mpMRI studies have been inconclusive, as discussed below. Therefore, investigators have recently sought to include additional variables, such as PSAD, into the diagnostic algorithm [11, 12].

A study of 1040 subjects by Distler et al. [13] showed that the negative predictive value of unsuspicious MRI for the presence of CSPC (PIRADS <3) increased from 79 to 89% when PSAD was 0.15 ng/mL/mL or less. In a

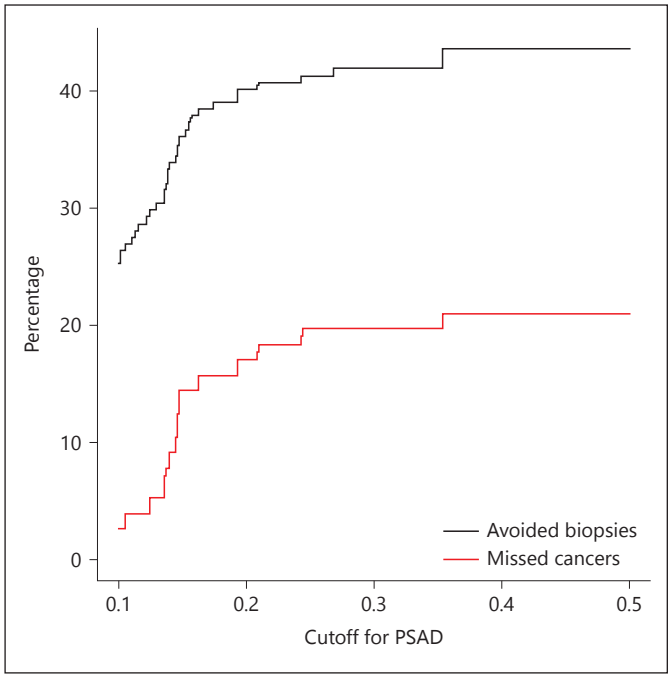

Fig. 3. Lesions with a PIRADS score of 3 in the biopsy-naïve group. The percentage of biopsies that would be avoided and the percentage of CSPC that would be missed as a function of PSAD. PSAD, prostate specific antigen density.

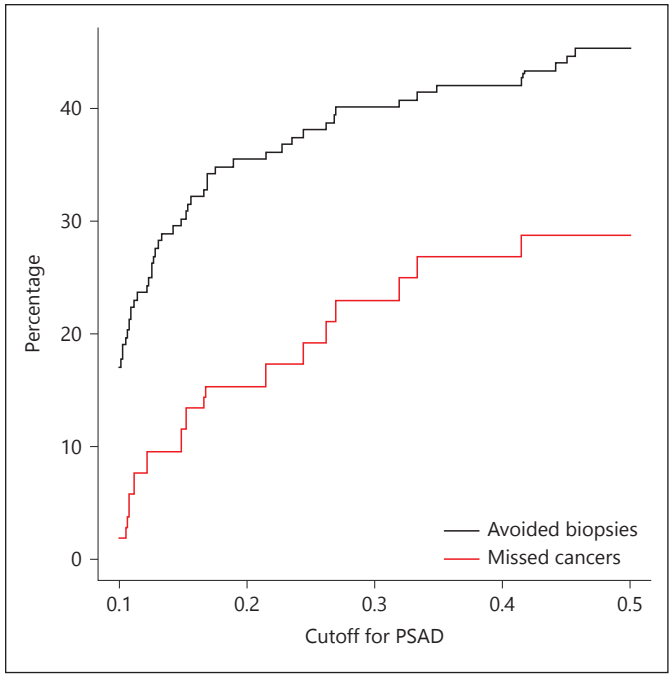

Fig. 4. Lesions with a PIRADS score of 3 in the repeat biopsy group. The percentage of biopsies that would be avoided and the percentage of CSPC that would be missed as a function of PSAD. PSAD, prostate specific antigen density.

Table 3. Avoided biopsies and missed cancers using the indicated criteria to decide not to perform a prostate biopsy

Criteria for not performing a biopsy	Biopsies avoided, *n* (%)	Undiagnosed insignificant PC, *n* (%)	Missed significant PC, *n* (%)
Biopsy-naïve group			
PIRADS <3 and PSAD <0.2	48/223 (21.5)	5/30 (16.7)	3/82 (3.7)
PIRADS <3	53/223 (23.7)	6/30 (20.0)	6/82 (7.3)
(PIRADS <3 and PSAD <0.2) or (PIRADS 3 and PSAD <0.15)	108/223 (48.4)	18/30 (60.0)	14/82 (17.1)
PIRADS <3 or (PIRADS 3 and PSAD <0.15)	113/223 (50.7)	19/30 (63.3)	17/82 (20.7)
PIRADS <4	126/223 (56.5)	21/30 (70.0)	22/82 (26.8)
Rebiopsy group			
PIRADS <3 and PSAD <0.2	22/174 (12.6)	1/23 (4.3)	4/58 (6.9)
PIRADS <3	25/174 (14.4)	2/23 (8.7)	6/58 (10.3)
(PIRADS <3 and PSAD <0.2) or (PIRADS 3 and PSAD <0.15)	65/174 (37.7)	5/23 (21.7)	10/58 (17.2)
PIRADS <3 or (PIRADS 3 and PSAD <0.15)	68/174 (39.1)	7/23 (30.4)	12/58 (20.6)
PIRADS <4	92/174 (52.9)	11/23 (47.8)	22/58 (37.9)

PC, prostate cancer; PSAD, prostate specific antigen density.

Table 4. Area under curve calculated for MRI, PSA and PSAD for biopsy-naïve and rebiopsy group

Indicator	AUC	SE	*p* value	95% CI
Biopsy-naïve group				
MRI (PIRADS score)	0.770	0.033	0.000	0.706–0.835
PSA value, ng/mL	0.657	0.037	0.000	0.584–0.731
PSA density, ng/mL^2	0.733	0.036	0.000	0.662–0.804
Rebiopsy group				
MRI (PIRADS score)	0.664	0.046	0.000	0.573–0.755
PSA value, ng/mL	0.593	0.046	0.046	0.502–0.684
PSA density, ng/mL^2	0.721	0.041	0.000	0.641–0.802

MRI, magnetic resonance imaging; PSA, prostate specific antigen; PSAD, prostate specific antigen density.

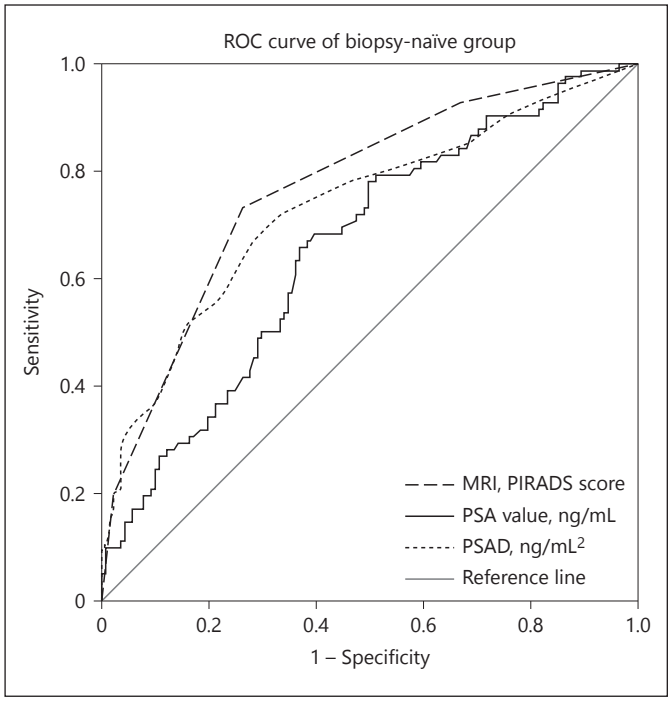

Fig. 5. ROC of MRI, PSA and PSAD for biopsy-naïve group. ROC, receiver operating curve; MRI, magnetic resonance imaging; PSA, prostate specific antigen; PSAD, prostate specific antigen density.

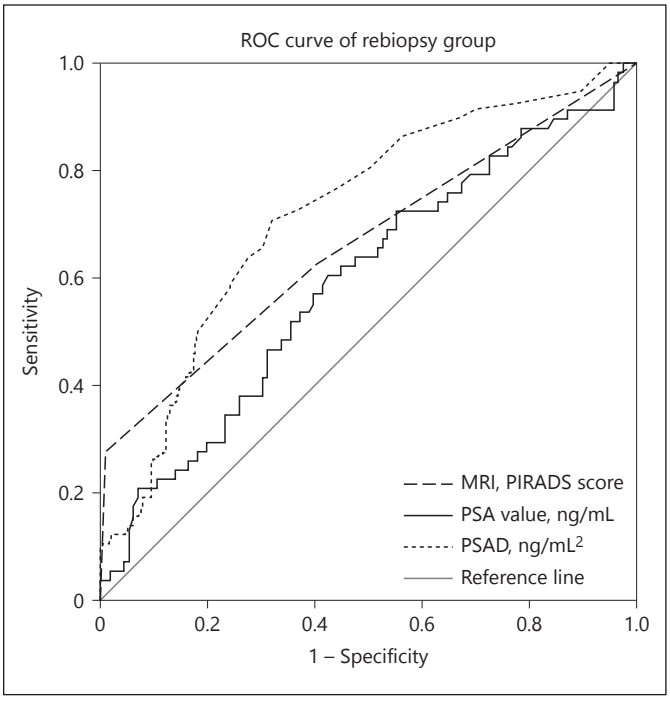

Fig. 6. ROC of MRI, PSA and PSAD for rebiopsy group. ROC, receiver operating curve; MRI, magnetic resonance imaging; PSA, prostate specific antigen; PSAD, prostate specific antigen density.

repeat biopsy setting, the negative predictive value of significant PC increased from 83 to 93%. By increasing the probability of ruling out CSPC, approximately 20% of unnecessary biopsies could have safely been avoided [13]. This is similar to our finding that 21% of biopsies could have been avoided using PIRADS <3 and PSAD <0.2 as the criteria for deciding not to perform a biopsy.

Washino et al. [14] reported that PIRADS ≤3 and PSAD <0.15 ng/mL^2 identified no clinically significant PC on biopsy. They found that the PIRADS score and PSAD were both independent predictors of PC and of CSPC. When the PIRADS score and PSAD were combined, PIRADS ≥4 and PSAD ≥0.15 ng/m/mL or PIRADS 3 and PSAD ≥0.30 ng/mL/mL were both associated with the highest clinically significant PC detection rates (76–97%) in the biopsy-naïve group. PIRADS ≤3 and PSAD < 0.15 ng/mL/mL were never associated with CSPC.

Hansen et al. [15] reported in a repeat biopsy setting that PSAD ≤0.2 is associated with a low detection of Glea-

Table 5. Sensitivity, specificity, negative, and positive predictive value of MRI and combination with PSAD in biopsy-naïve and rebiopsy group

	Value, %	95% CI
Biopsy-naïve group		
PIRADS <3		
Sensitivity	92.68	84.75–97.27
Specificity	33.33	25.63–41.76
PPV	44.71	41.48–47.98
NPV	88.68	77.79–94.60
PIRADS <3 and PSAD <0.2		
Sensitivity	96.34	89.68–99.24
Specificity	31.21	23.67–39.55
PPV	44.89	41.97–47.84
NPV	93.62	82.46–97.86
Rebiopsy group		
PIRADS <3		
Sensitivity	89.66	78.83–96.11
Specificity	16.38	10.16–24.39
PPV	34.90	32.25–37.65
NPV	76.00	57.22–88.23
PIRADS <3 and PSAD <0.2		
Sensitivity	93.10	83.27–98.09
Specificity	15.52	9.46–23.41
PPV	35.53	33.16–37.96
NPV	81.82	61.48–92.69

MRI, magnetic resonance imaging; PSAD, prostate specific antigen density.

son score ≥7 PC, not only in men with a negative mpMRI but also in men with equivocal imaging (PIRADS = 3). They suggested that surveillance rather than repeat biopsy may be appropriate for these men. Conversely, biopsies were suggested for men with a high PSAD, even if the mpMRI shows no suspicious lesion, and for men with a suspicions mpMRI, even is their PSAD was low.

In our study, the number of potentially avoidable biopsies increased sharply in the biopsy-naïve group as a function of PSAD up to 0.2 ng/mL^2 and then stabilized. At the same time, the number of missed clinically significant cancers remained under 5% (Fig. 1). In the rebiopsy group, this favorable trade-off between avoidable biopsies and the number of missed significant PC was less clear. Table 3 shows the relationship between different criteria (PIRADS score and PSAD) that could be used to decide not to perform a prostate biopsy as well as the number of biopsies that could be avoided and the number of significant cancers that would be missed.

We suggest that PIRADS <3 and PSAD <0.2 ng/mL^2 be used as criteria to decide not to perform a prostate biopsy in biopsy-naïve patients. In our study population, this would have resulted in a 20% decrease in the number of biopsies performed, and only 4% of significant cancers would have escaped diagnosis. If slightly different criteria suggested by other authors were applied to our cohort (i.e., PIRADS = 3 and PSAD <0.15) [14, 16, 17], it would result in a 50% reduction in the number of biopsies but would also miss 21% of significant cancers. We speculate that the discrepancy between this finding and those reported in other papers might be explained by the performance of the mpMRI [3, 18, 19]. This study has some limitations. The main limitation is that we used PIRADS version 1. This study was designed when PIRADS version 2 was not yet available. However, the mpMRI classification used in studies has varied until recently, and published reports use several different systems (PIRADS version 1, PIRADS version 2, Likert scores, and others). Other limitations include using prostate biopsy as reference standard and not prostatectomy specimens. Another limitation is that mpMRI was performed on multiple external devices in the repeat biopsy group, and the protocols may have varied for the different devices. To eliminate this potential source of bias, we used a second reading by our study radiologist in this group of patients.

Conclusion

The use of a combination of mpMRI and PSAD values might reduce the number of biopsies performed without compromising safety by missing too many significant cancers. It is essential to determine the best PIRADS score and PSAD cut-off value that will trigger a biopsy. In our group of patients, mpMRI with PSAD performed better in biopsy-naïve patients, reducing the number of biopsies by 20% and missing only 4% of significant cancers. Results in the repeat biopsy group were less compelling.

Statement of Ethics

Subjects have given their written informed consent. The study has been reviewed and approved by a certified Ethical Board. The number of the approval document is: G-14-08-64; August 13, 2014.

Disclosure Statement

The authors declare that they have no conflict of interests to disclose.

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Authors Contribution

M.Z. performed the work related to conception and design of study, acquisition, analyzing and interpretation of data and drafting of the manuscript. J.S. performed the work related to conception and design of study, acquisition, analyzing and interpretation of data and critical revision of the manuscript. V.A. performed the task of acquisition, analyzing and interpretation of data and critical revision of the manuscript. J.H. performed the work of conception and design of study and drafting of the manuscript. I.M. performed the work of conception and design of study, acquisition of data. A.P. was responsible for acquisition of data. J.V. performed the work related to the conception and design of study, acquisition of data and supervision. M.B. performed the tasks of conception and design of study, supervision and critical revision of the manuscript. R.Z. was involved in the work related to the conception and design of study, analyzing and interpretation of data, supervision and critical revision of the manuscript.

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