

# Analysis of the usefulness of magnetic resonance imaging and clinical parameters in the detection of prostate cancer in the first systematic biopsy combined with targeted cognitive biopsy

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**Citation:** Majchrzak N, Cieśliński P, Milecki T, Twardosz K, Głyda M, Karmelita-Katulska K. Analysis of the usefulness of magnetic resonance imaging and clinical parameters in the detection of prostate cancer in the first systematic biopsy combined with targeted cognitive biopsy. Cent European J Urol. 2021; doi: 10.5173/ceju.2021.3.R2.0111 [Epub ahead of print]

## Article history

Submitted: Apr. 15, 2021

Accepted: June 9, 2021

Published online: July 7, 2021

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**Introduction** The study aimed to assess the suitability of multiparametric magnetic resonance prostate imaging (mpMRI) in combination with clinical parameters [prostate-specific antigen (PSA), digital rectal examination (DRE)] in the identification of men at risk of the presence of prostate cancer (PCa) and clinically significant prostate cancer (csPCa, Gleason Score  $\geq 3+4$ ) in the cognitive fusion with systematic prostate biopsy.

**Material and methods** We retrospectively evaluated a population of 215 biopsy-naïve patients with a clinical suspicion of prostate cancer. The results of mpMRI, DRE, PSA and biopsy were analyzed. MpMRI of the prostate according to the Prostate Imaging Reporting and Data System (PI-RADS) v.2.0 scheme preceded cognitive fusion and systematic transrectal prostate biopsy. Uni- and multivariable logistic regression analysis (MVA) was used to identify the variables determining the risk of detecting PCa overall and csPCa.

**Results** In MVA, it was established that the combination of variables such as PSA level [odds ratio (OR) 1.195;  $p = 0.002$ ], PI-RADS  $\geq 3$  (OR 7.7;  $p = 0.002$ ), prostate volume (OR 0.98;  $p = 0.017$ ) significantly determines the probability of PCa detection in biopsy, while for csPCa it is PSA level (OR 1.14;  $p = 0.004$ ), DRE (+) (OR 5.75;  $p < 0.001$ ), PI-RADS  $\geq 4$  (OR 6.5;  $p < 0.001$ ). Analysis of mpMRI diagnostic value for PI-RADS  $\geq 4$  revealed better sensitivity (88.9% vs 82.6%) and better negative predictive value (NPV) (94.5% vs 82.4%) for detection of csPCa than for PCa overall.

**Conclusions** MpMRI results combining with DRE and PSA parameters help to identify men at high- or low-risk of csPCa detection in the first-time biopsy.

**Key Words:** prostate cancer ↔ prostate biopsy ↔ multiparametric magnetic resonance imaging ↔ PSA ↔ digital rectal examination

## INTRODUCTION

Multiparametric magnetic resonance imaging (mpMRI) has a proven role in the diagnostics of prostate diseases. Targeted prostate biopsy based

on mpMRI results, compared to standard transrectal biopsy, is characterized by a higher detection rate of clinically significant prostate cancer (csPCa) [1]. It has been proven that systematic biopsy combined with targeted prostate biopsy is the most effective

method of detecting prostate cancer (PCa), in particular csPCa [2].

As established, mpMRI is a tool with high sensitivity to detect csPCa and its high negative predictive value (NPV) (88.1% for csPCa) indicates patients, who can avoid unnecessary biopsy [3]. However, 'MRI-only' based biopsy strategy is limited by its low positive predictive value (PPV), especially for Prostate Imaging Reporting and Data System (PI-RADS) 3 lesions and its low to moderate inter-reader reproducibility [3–6]. Therefore, the important decision not to biopsy should consider clinical factors that determine the risk of PCa [e.g. PSA, PSA density, digital rectal exam (DRE)] [3].

Currently, the recommended strategy for qualifying patients with clinical suspicion of PCa for a prostate biopsy is based on an individual risk stratification. This stratification can be performed with the mpMRI result and calculators based on clinical variables [7, 8]. It has been proven that adding mpMRI result to the prediction clinical model can improve selection of patients at high risk of PCa with Gleason Score (GS)  $\geq 3+4$ , in whom prostate biopsy needs to be performed [9, 10]. The European Randomized Study of Screening for Prostate Cancer Risk Calculator (ERSPC – RC 3) with MRI have higher area under curve (AUC) for prediction high-grade PCa (GS $\geq 3+4$ ) compared to the original model based only on clinical variables (AUC 0.84 vs 0.76) [9]. Similarly, the addition of MRI results to the Prostate Biopsy Collaborative Group Calculator (PBCG – RC) and the Foggia Prostate Cancer Risk Calculator (FPC – RC) improved diagnostic accuracy of each calculators in predicting csPCa, AUC 0.73 vs 0.84 and 0.80 vs 0.87, respectively [10].

This individual risk assessment whether or not to perform a biopsy is very important because of reducing harm caused by overdiagnosis and related overtreatment.

Our study aimed to assess how the MRI parameters: PI-RADS score, zonal location of the index lesion (IL), prostate volume and clinical factors: PSA (ng/ml) and DRE may help identify men at risk of PCa and csPCa (GS  $\geq 3+4$ ) detection during the cognitive targeted combined with systematic transrectal biopsy (T+SBx).

## MATERIAL AND METHODS

In total, 215 biopsy-naive men with clinical suspicion of PCa (PSA level  $\geq 4$  ng/ml and/or abnormal DRE results) were enrolled into the study. This was a single – center study, conducted in a specialized care hospital. The study was retrospective. Three urologists performed DRE.

## Imaging

The diagnostics began with mpMRI for which 1.5T (GE Healthcare Medical System Optima MR360, Chicago, IL, USA) and 3T equipment (Siemens HealthCare Magnetom Skyra, Erlangen, Germany) was utilized, using 12- and 18-channel body matrix coils. The mpMRI examination scheme followed the PI-RADS v. 2.0 - .1 recommendations [11, 12]. It included multiplanar assessment of the prostate in T1- and T2-weighted images, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging. Apparent diffusion coefficient (ADC) maps were developed automatically. The mpMRI examinations were evaluated by four radiologists with 4-5 years experience in prostate imaging, who knew the PSA levels and DRE results at the time of examination. For patients with more than one lesion in mpMRI, the IL criterion with the highest PI-RADS score was used.

## Biopsy technique

Transrectal ultrasound-guided biopsy was then performed using a biplane transducer with simultaneous imaging of both planes (BK Medical Flex 400, Herlev, Denmark).

Biopsy was performed based on mpMRI results, according to the scheme recommended by the European Association of Urology (EAU) [8].

All patients underwent systematic biopsy using a 12–16 core template.

Additionally, in patients with PI-RADS 3–5 lesions in mpMRI two to four extra target cores were taken from IL. MRI/ultrasound fusion technique was cognitive.

All patients with PI-RADS 1 and 2 lesions in mpMRI underwent systematic biopsy only. Three urologists performed the biopsy.

## Histopathology

Three pathologists examined the biopsy material in accordance with the guidelines of the International Society of Urological Pathology (ISUP) 2014 in the field of pathomorphological diagnosis of prostate cancer [13]. The definition of csPCa was used as established, Gleason Score  $\geq 3+4$  or ISUP Gleason Grade  $\geq 2$  [11, 12, 13].

## Statistical methods

The median and interquartile range were calculated for continuous variables and frequency and proportion for categorical variables. The following test was used: T-test, Mann-Whitney U for continuous vari-

ables, Chi-square for nominal variables, and Spearman rank correlation. Uni- and multivariable logistic regression analysis (UVA, MVA) was carried out to determine the factors affecting PCa and csPCa detection. Following variables were taken into account: age, PSA level, DRE result, PIRADS IL, zonal location of the IL, prostate volume. A p-value of  $<0.05$  was considered statistically significant. The calculations were made using IBM SPSS Statistics and PQStat by PQStat Software.

## RESULTS

The characteristics of the study group are included in Table 1.

The probability of PCa overall and csPCa detection for PIRADS  $\geq 4$  lesions is significantly higher than for PIRADS  $\leq 3$  lesions [PCa overall odds ratio (OR) 6.279, 95% confidence interval (CI) 3.290–11.986  $p < 0.001$ ; csCaP OR 8.190 95% CI 3.083–21.760  $p < 0.001$ ].

The percentage of insignificant PCa and csPCa detected for individual PI-RADS lesions is presented in Figure 1.

A correlation was found between higher PI-RADS scores and higher ISUP Gleason Grade obtained in prostate biopsy ( $p = 0.03$ ), and a positive correlation between PSA and PI-RADS values ( $p < 0.001$ ).

PCa overall was detected in targeted IL biopsy in  $n = 86$  patients (40%). Positive systematic biopsy (outside the focus) was found in 35 patients (16.3%). In 6 patients (2.8%), the biopsy was positive despite the absence of the foci described in mpMRI, and in 6 (2.8%) patients, the biopsy confirmed cancer on the side opposite to the focus described in mpMRI. Among PIRADS  $\geq 4$  lesions, where no cancer was detected in a biopsy, in the case of 7 lesions (5.6%), the

**Table 1.** Group characteristic

	PCa overall detection	csPCa detection	no cancer	p value
Total n = 215, n (%) or median (IQR)	98 (45.6)	45 (20.9)	117 (54.4)	
Age (year)	66.00 (61.0–70.0)	66.0 (62.5–70)	64.0 (59.0–69.0)	0.547
PSA (ng/ml)	6.9 (5.2–11.2)	9 (6.1–15.1)	6.25 (4.9–8.5)	$<0.001$
Prostate volume (ml)	36.0 (30.0–51.3)	41.95 (32.0–54.0)	49.75 (38.0–67.6)	0.001
DRE				
Abnormal, 93 (43.3)	62(66.7)	36 (38.7)	31 (33.3)	$<0.001$
Normal, 122 (56.8)	36 (29.5)	9 (7.4)	86 (70.5)	
PIRADS				
1–3, 91 (42.3)	15 (16.5)	5 (5.5)	76 (83.5)	$<0.001$
4–5, 124 (57.7)	71 (57.3)	40 (32.3)	53 (42.7)	
IL PIRADS				
1–2 32 (14.9)	3 (9.4)	0	29 (90.6)	
3 59 (27.4)	12 (20.3)	5 (8.5)	47 (79.3)	$<0.001$
4 76 (35.3)	40 (52.6)	20 (26.3)	36 (47.4)	
5 48 (22.3)	31 (64.6)	20 (41.7)	17 (35.4)	
PIRADS score total n = 282 n (%)				
1–2 37 (13.2)				
3 84 (29.9)				
4 113 (40.2)				
5 48 (17.1)				

DRE – digital rectal exam; PI-RADS – Prostate Imaging Reporting and Data System; PCa – prostate cancer; csPCa – clinically significant prostate cancer (Gleason Score  $\geq 3+4$ ); IL – index lesion; PSA – prostate-specific antigen; IQR – interquartile range

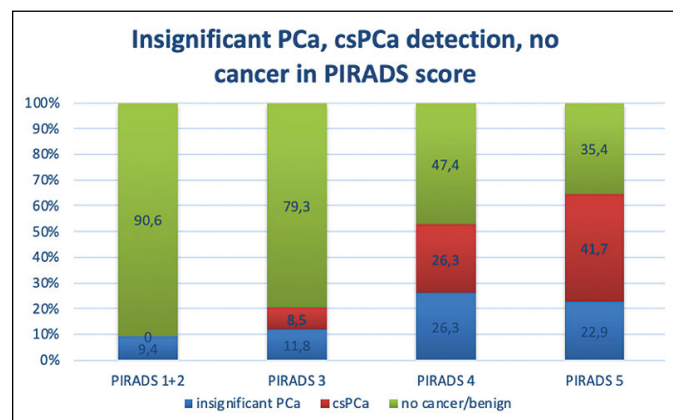
histopathological result indicated atypical small acinar proliferation (ASAP), while in 2 lesions (1.6%), inflammation was present.

Diagnostic test analysis for PIRADS  $\geq 4$  revealed better sensitivity (88.9% vs 82.6%) for detection of csPCa than for PCa overall and higher negative predictive value (NPV) (94.5% vs 82.4%) for csPCa than for PCa. Our findings showed low specificity (50.6%) and positive predictive value (PPV) (32.5%) for csPCa detection (shown in Table 2).

In a group of 93 DRE (+) patients, cancer was confirmed in 66.67% ( $n = 62$ ), while among 122 DRE (-) patients – in 29.5% ( $n = 36$ ). CsPCa was confirmed by prostate biopsy in 38.7% ( $n = 36$ ) of DRE (+) patients, and in 7.4% ( $n = 9$ ) of DRE (-) patients.

It was confirmed that in DRE (+) patients, foci are found in mpMRI 2.5 times more frequently (CI 95%, 1.434–4.354  $p < 0.001$ ) in the peripheral zone (PZ), compared to DRE (-) patients.

In 109 patients, the IL was located in the PZ, and T+SBx confirmed cancer in 70 patients (64.2%) and csPCa accounted for more than half of the neoplasms



**Figure 1.** Insignificant PCa (prostate cancer), csPCa (clinically significant prostate cancer) detection and no cancer in Prostate Imaging Reporting and Data System (PI-RADS) score.

**Table 2.** MpMRI diagnostic value for PI-RADS  $\geq 4$  lesions in PCa and csPCa detection

% (95% CI)	sensitivity	specificity	PPV	NPV	prevalence
PCa overall	82.6 (72.9–89.9)	58.9 (49.9–67.5)	57.3 (51.6–62.7)	82.4 (75.8–89.1)	40 (33.4–46.9)
csPCa	88.9 (76–96.3)	50.6 (42.8–58.3)	32.5 (28.4–36.4)	94.5 (88.1–97.6)	20.9 (15.7–27)

mpMRI – multiparametric resonance imaging; PI-RADS – Prostate Imaging Reporting and Data System; PCa – prostate cancer; csPCa – clinically significant prostate cancer (GS  $\geq 3+4$ ); CI – confidence interval

detected in this location (38 patients). The IL was located in the transition or central zones (non-PZ) in 84 patients, and T+SBx confirmed the presence of a PCa overall in 22 (26.2%), while csPCa was diagnosed in nearly 1/3 (6) of such patients.

Biopsy in DRE (-) patients was positive in 15.4% (n = 8) of patients with lesions located outside the PZ, while for lesions in the PZ, the biopsy confirmed PCa in 48% (n = 24) of cases.

### Factors influencing the detection of PCa overall and csPCa in T+SBx

In UVA it was shown that the level of PSA, abnormal DRE, PI-RADS  $\geq 3$ , location of the focus in the PZ, and smaller prostate volume are significant independent factors increasing the probability of total PCa detection in T+SBx.

The PSA, DRE (+) level, PIRADS  $\geq 4$ , and location of the lesion in the PZ are independent parameters

increasing the risk of csPCa. The results are presented in Table 3.

By consecutively combining various variables with MVA, we indicated which combination of variables is most significant in the detection of PCa overall and csPCa (shown in Table 3).

It has been shown that the probability of PCa overall detection in T+SBx increases significantly when taking into account higher PSA, smaller prostate volume, PIRADS  $\geq 3$ . Detection of csPCa depends significantly on the PSA level, abnormal DRE results, and the presence of a PIRADS  $\geq 4$  lesion. The location of the lesion in the non-PZ significantly reduces the probability of PCa and csPCa presence.

## DISCUSSION

Our study was conducted in 2017–2019, even before the appearance of the official EAU guidelines from 2019 regarding the inclusion of mpMRI in the diagnostic process for prostate cancer as the examination preceding first-time or repeat prostate biopsy [8].

In our study, we used a strategy of combining systematic and targeted biopsy.

Recent data revealed that up to 15% of csPCa are not detected in mpMRI and can be omitted in targeted biopsy only [2, 14]. The established factors, those determining csPCa detection in the systematic biopsy outside the IL are PI-RADS 4–5 and smaller prostate volume [2]. The probability of diagnosing csPCa in the systematic combined with targeted biopsy increase with the higher percentage of prostate involved by a suspicious lesion on MRI [15]. How-

**Table 3.** Uni- and multivariable analysis regression for risk of PCa and csPCa detection

OR (95% CI); p value	Univariable analysis		Multivariable analysis	
	PCa overall	csPCa	PCa overall	csPCa
Age	1.016 (0.977–1.057) p = 0.425	1.019 (0.97–1.07) p = 0.46	–	–
PSA	1.087 (1.018–1.161) p = 0.012	1.175 (1.09–1.27) p < 0.001	1.195 (1.07–1.338) p = 0.002	1.144 (1.043–1.254) p = 0.004
DRE (+)	4.778 (2.673–8.54) p < 0.001	7.93 (3.574–17.592) p < 0.001	–	5.753 (2.38–13.91) p < 0.001
IL PIRADS score	2.903 (1.24–6.799) p < 0.001 PIRADS $\leq 2$ – ref.	8.190 (3.083–21.76) p < 0.001 PIRADS $\leq 3$ – ref.	7.765 (2.157–27.956) p = 0.002 PIRADS $\leq 2$ – ref.	6.464 (2.2–19.015) p < 0.001 PIRADS $\leq 3$ – ref.
PZ	5 (2.791–8.967) p < 0.001	7.569 (3.197–17.921) p < 0.001	–	–
Non-PZ	0.257 (0.141–0.467) p < 0.001	0.181 (0.073–0.451) p < 0.001	0.155 (0.068–0.356) p < 0.001	0.175 (0.063–0.49) p < 0.001
Prostate Volume	0.97 (0.96–0.99) p = 0.002	0.99 (0.97–1.01) p = 0.37	0.977 (0.96–0.996) p = 0.017	–

PCa – prostate cancer; csPCa – clinically significant prostate cancer (GS  $\geq 3+4$ ); PSA – prostate-specific antigen; DRE (+) – digital rectal examination abnormal; IL PIRADS score – index lesion Prostate Imaging Reporting and Data System; PZ – peripheral zone; non-PZ – transition or central zone /other than peripheral; OR – odds ratio; CI – confidence interval; ref. – reference

ever, at the moment there is no safely clinical model to select patient who can avoid systematic biopsy, due to limitations of mpMRI reading and targeting of the suspicious lesion [2, 5, 14]. Therefore, the biopsy combination strategy we used is the best option for PCa diagnosis.

As established, mpMRI is a tool with high sensitivity to detect csPCa [3]. We compared our assessment of the diagnostic value of mpMRI in PCa overall and csPCa detection to the results of the Moldovan meta-analysis [3]. We confirmed the excellent sensitivity of mpMRI in PCa and csPCa diagnosis. In the analysis of NPV we obtained results consistent with the cited meta-analysis, for PCa overall, the median mpMRI NPV is 82.4% (IQR 69.0–92.5%) vs 82.4% in our study and for csPCa 88.1% (IQR 85.7–92.3%) vs 94.5% in our study [3]. Thus, as did Moldovan et al., we confirmed that mpMRI is a useful tool to select patients at low risk of PCa overall and csPCa, in whom biopsy can be omitted.

However, other clinical factors should be considered in the decision for prostate biopsy, as we demonstrated in our MVA.

The available and most common calculator, the European Randomized Study of Screening for Prostate Cancer Risk Calculator (ERSPC-RC3), assessing prostate cancer risk, is based mainly on the combined analysis of PSA level, DRE and prostate volume [16]. Additionally, it was found that the calculator's quality can be improved by taking into account mpMRI results and patient age [9]. We indicated the significance of abnormal rectal examination with a coexisting PI-RADS  $\geq 4$  lesion in csPCa detection. Concerning these variables and their importance in assessing the risk of csPCa, we confirmed the correlations shown in the literature [17, 18]. Similarly, to the available calculators, we demonstrated the PSA and prostate volume parameters' statistical significance in overall PCa detection [9, 15, 18]. We also indicated that the location of the IL in the peripheral zone is an independent predictor of the risk of total PCa and csPCa. Therefore, this variable may help decide to perform a biopsy on suspicious lesions in biopsy naive patients.

The effectiveness assessment of the initially created model went beyond the scope of the study. The above analysis may be helpful but not determinative for deciding whether or not to perform a biopsy. It enables the identification of people from the group of increased or low risk of PCa and csPCa.

It should be mentioned that the rate of csPCa detected in PI-RADS 4 in our study was lower than we expected. It may be due to the lesion's location in the anterior region of the prostate, false-positive results resulting from incorrect interpretation of foci coex-

isting with benign prostatic hyperplasia, biopsy technique and image fusion method. It has been proven that computer fusion biopsy compared to cognitive fusion is characterized by a higher cancer confirmation rate for lesions located in the anterior part or in the transition zone of the prostate [19–22].

Our study has several limitations: its single-center study design, one biopsy technique was performed (transrectal with cognitive fusion), different levels of experience of urologists performing T+SBx and different radiologists' experience describing the tests, lack of follow-up for negative biopsy patients. In the meta-analysis, Stabile et al. indicated that the level of experience of the radiologist describing the mpMRI examination and the urologist performing the prostate biopsy are the most important variables affecting the percentage of PCa and csPCa diagnoses based on mpMRI [23].

## CONCLUSIONS

MpMRI and DRE should precede prostate biopsy in all patients with a suspicion of PCa. MpMRI results combine with DRE and PSA parameters may help identify men at high or low risk of csPCa detection during the first biopsy. The low-risk patients (PI-RADS  $\leq 3$  in the non-peripheral zone, normal DRE) can avoid unnecessary biopsy. However, this decision, whether or not to perform a biopsy, should be taken very carefully. In low-risk patients, the risk of csPCa is lower, but it cannot not be totally excluded.

## LEGAL ASPECTS

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere. All authors approved the manuscript and this submission.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

## FUNDING SOURCES

The authors did not receive financial support.

## STATEMENT OF ETHICS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The Bioethics Committee at the Poznań University of Medical Sciences decided that the conducted study does not bear any characteristics of a medical experiment.

Final approval of manuscript done by all authors.

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