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The Prevalence of Prostate Cancer in Biopsy Samples of Lesions with PI-RADS 2 Score in Multiparametric Magnetic Resonance Imaging: A Cross-sectional Study

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Abstract

Background: Prostate cancer (PC) is one of the most common cancers worldwide. Recently, multiparametric magnetic resonance imaging (mpMRI) has been used to diagnose PC in suspected patients. Prostate Imaging Reporting & Data System (PI-RADS) was developed and applied as a criterion for detecting lesions suspicious of PC. Various studies have been conducted to determine the negative predictive value of non-suspicious mpMRI (PI-RADS 1 or 2). However, the results of these studies have been limited and different.

Objectives: This study was conducted to determine the PC rate in patients with PI-RADS 2 lesions in mpMRI and the factors related to clinically significant prostate cancer (CsPC) diagnosis in these lesions.

Methods: By referring to the archive department of Shahada-e-Tajrish, Rasul-e-Akram, Treata, and Payambaran hospitals, among the patients suspected of PC who underwent biopsy and had elevated prostate-specific antigen (PSA) serum levels, the prostate biopsy samples of 330 patients were consecutively included in the study. Frequency of samples diagnosed with PC and its histological characteristics, including mass location, Gleason score (GS), Gleason group (GG), percentage of G4 and G5 cells, sample size, percentage of involvement of sample with cancer tissue, and invasion to the surrounding tissues were examined. Adenocarcinoma samples were divided into low-risk, intermediate-to-high-risk groups based on D'Amico criteria and the relationship between age, PSA total (PSAt), PSA density (PSAd), prostate volume, and the presence of a PI-RADS 3 or 4 lesion at the same time with the rate of diagnosed CsPCs were reviewed.

Results: The data from 709 tissue samples were collected, among which 249 were from the right inner part, 249 were from the left inner part, and 211 biopsy samples were from the peripheral portion of the prostate. Among these, 390 tissue samples in mpMRI studies were PI-RADS 2, and 319 were PI-RADS 3 or 4. The mean age of the patients was 64.78 ± 37.55. The mean PSAd, PSAt, and prostate volume were 0.15 ± 0.11, 8.73 ± 6.43, and 61.18 ± 25.76, respectively. Seventy-five samples were diagnosed with adenocarcinoma, of which 48% are in PI-RADS group 2, and 52% are in PI-RADS group 3 - 4 (P-value = 0.263). Comparing the histological characteristics of adenocarcinoma samples between the two groups showed that only the amount of GG was significantly higher in the samples with PI-RADS 3 and 4 (P-value = 0.035). Adenocarcinomas diagnosed in 72.2% of cases in PI-RADS 2 samples and 84.6% of PI-RADS 3 and 4 samples were clinically significant, and no significant difference was seen between the two groups (P-value = 0.38). The amount of PSAt in PI-RADS 2 adenocarcinoma samples was significantly higher in clinically significant carcinomas than in low-risk carcinomas (P-value = 0.045).

Conclusions: The results of the present study showed that PI-RADS 2 lesions should be considered for biopsy when there is clinical suspicion of PC. PSA levels can effectively determine the need for biopsy in PI-RADS 2 lesions.

Keywords: mpMRI, PI-RADS, MRI-Targeted Biopsy, Prostate Cancer

1. Background

Prostate cancer (PC) is one of the most common cancers among men and is considered one of the leading causes of cancer-related deaths in men (1). Prostate cancer has significant geographic variation in incidence and mortality rates (2). Meanwhile, in Iran, the burden of this cancer has been accompanied by an upward trend in the

past decades (3, 4).

Nowadays, the 12-core biopsy guided by transrectal ultrasound (TRUS) for men with elevated serum prostate-specific antigen (PSA) levels is the gold standard test for diagnosing this cancer (5). In recent years, multiparametric magnetic resonance imaging (mpMRI) has been used to diagnose PC in suspected patients. In 2012, Prostate Imaging Reporting & Data System (PI-RADS) was developed and applied as a set of standards to assign specific suspicion points to PC (6). In 2014, PI-RADS version 2 (PI-RADS v2) was released to overcome the shortcomings of PI-RADS version 1 (PI-RADS v1) (7, 8). Following the publication of PI-RADS v2, a meta-analysis conducted by Wu et al. was published to evaluate and compare the performance of mpMRI with PI-RADS v1 and v2. They suggested a PI-RADS score of 4 or more to be considered as a cut-off to indicate suspicious mpMRI results, while considering a PI-RADS score of $\geq$ 3 as a cut-off might be helpful in patients with previously negative prostate biopsies (8). Thus, lesions with a PI-RADS score of 1 or 2 were considered non-suspicious and preferred to be avoided for biopsy (9).

The clinical role and feasibility of a negative mpMRI strongly depend on its negative predictive value (NPV); thus, it is crucial for a negative mpMRI to reliably rule out the presence of a high-grade PC lesion. However, the findings of the previous studies have reported significant proportions of patients with Pi-RADS 1 or 2 lesions that underwent a systematic prostate biopsy and were diagnosed with clinically significant prostate cancer (CsPC). A meta-analysis that evaluated the NPV of negative mpMRI in 48 studies (including 9613 patients) found that CsPC was reported in more than 10% of patients with an unsuspicious lesion based on mpMRI (10). A study by the University of California comparing mpMRI of the prostate with the diagnostic gold standard of complete radical prostatectomy specimens found that mpMRI could potentially miss up to 35% of CsPCs and up to 20% of high-grade cancers. This study showed that 74% of undiagnosed tumors were clinically significant; So, 23% had a Gleason score (GS) higher than or equal to 7, and 38.7% were more than 1 cm in diameter (11). As such, these undiagnosed cancers were not all small, low-grade, and clinically insignificant. The Prostate MRI Imaging Study (PROMIS) reported an NPV of a negative mpMRI to be between 89% to 76% (12). The results of Hansen et al.'s study also showed that the NPV of a negative mpMRI to rule out PC with GS 7 - 10, regardless of the results of other laboratory tests, was 80% (13). Thus, the answer to the question of whether mpMRI with a PI-RADS score of 1 or 2 is a license to omit prostate biopsy, remains unknown (14-17).

Despite the development of various tools to stratify patients referred for biopsy, there are currently no recommendations on how to classify patients with non-suspicious mpMRI to determine the need for a biopsy. This hinders the improvement of diagnostic performance in mpMRI.

It is essential to investigate the predictive factors for CsPC diagnosis in patients with negative mpMRI to reduce the rate of undiagnosed CsPC, as well as futile biopsies.

2. Objectives

The current study was conducted to evaluate the PC rate in patients with PI-RADS 2 in mpMRI studies, the clinical significance of the diagnosed lesions, and the risk factors for the diagnosis of adenocarcinoma in samples with a mpMRI with a Pi-RADS score of 2.

3. Methods

In the current cross-sectional study, by referring to the medical archives of Rasul-e-Akram, Treata, Shohada-e-Tajrish, and Payambaran hospitals in Tehran, Iran, the patients suspected of PC were evaluated to be included in the present study. To find the required sample size using the proper Cochran's formula, an estimation of 95% confidence level, a precision of 5%, and an estimation of 20% of PI-RADS 2 lesion being diagnosed as PC, a minimum sample size of 245 was calculated. The patients suspected of PC who underwent biopsy and had elevated PSA serum levels were included in the current study. Finally, the prostate biopsy samples of 330 men were consecutively enrolled. The included patients had signed an informed consent form at the time of their admission to the hospitals. The selected participants were split into two groups according to their PI-RADS score: A group of samples with a PI-RADS-2 score and a group with a PI-RADS score of 3 or higher.

The incidence of prostate cancer (PC) and its characteristics, such as lesion location, GS, Grade group (GG), percentage of G4 and G5 cells, sample size, sample involvement percentage, and presence of invasion to surrounding tissues, were determined and compared between two groups based on biopsy results. The positive and negative predictive values for the diagnosis of PC were then calculated for each group using this comparison.

In addition, age, PSA levels, PSA density (PSAd) levels, PSA total (PSAt) levels, and prostate volume were recorded in two groups, and their relationship with cancer incidence was investigated. Adenocarcinoma samples were divided into low-risk and intermediate-to-high-risk

groups based on D'Amico criteria and the relationship between age, PSAt, PSAd, prostate volume, and the presence of a PI-RADS 3 or 4 lesion at the same time with the significance level of the lesion were also examined.

3.1. Statistical Analysis

Quantitative data were described using the mean and standard deviation, while frequencies and percentages were used to describe qualitative data. To compare the data, statistical tests including chi-Square, independent *t*-test, and Fisher's exact test were utilized. All statistical analyses were performed using SPSS 26.0 software, and a significance level of 0.05 was used as the cutoff.

4. Results

A total of 721(249 samples taken from the inner right, 249 samples from the inner left, and 211 samples from the peripheral section of the prostate) pathology samples from 330 included patients were collected and divided into two groups according to the mpMRI score of each sample. The demographic records of the included patients are reported in Table 1. No significant differences were found between the groups regarding the demographic records (P-value > 0.05). The outcomes of the pathological assessment of biopsy samples are reported in Table 2. Likewise, no significant differences were found concerning the diagnosis of adenocarcinoma in the samples taken from the inner right, inner left, and peripheral sections of the prostate (inner right P-value = 0.222, inner left P-value = 0.436, peripheral P-value = 0.696).

In total, 17 patients in the PI-RADS 2 group and 16 in the PI-RADS 3 - 4 group had Adenocarcinoma (P-value = 0.696). When the samples were considered, 36 (48%) samples with the diagnosis of adenocarcinoma had PI-RADS 2 lesions, and 39 (52%) samples with the diagnosis of adenocarcinoma had PI-RADS 3 or 4 lesions. The difference between the groups regarding cancer diagnosis frequency was insignificant (P-value = 0.263).

Table 3 presents the characteristics of diagnosed adenocarcinoma among the groups. There were no significant differences observed in terms of GS, G4 cell percentage, G5 cell percentage, sample involvement, and perineural involvement between the samples diagnosed with adenocarcinoma in the groups. However, the GG was significantly higher in the adenocarcinoma samples with PI-RADS 3 - 4 compared to those with PI-RADS 2 (P-value = 0.035).

Based on D'Amico criteria, the study samples were divided into two groups: Low-risk (PSAt less than or equal to 10 and GS less than or equal to 6) and Intermediate-to-high-risk (PSAt greater than 10 and GS equal to or greater than 7). The frequency of each category is listed in Table 4.

The cancer risk rate differences among the groups were not statistically significant (P-value = 0.380). Comparing the demographic variables between the low-risk and intermediate-to-high-risk adenocarcinoma samples, no significant difference was found except for the PSA level, which was significantly higher in the intermediate-to-high-risk samples (age P-value = 0.057, PSA level P-value = 0.045, PSA density P-value = 0.074, Prostate volume P-value = 0.843).

By assessing the presence of PI-RADS 3 or 4 lesions at the same time as the risk of cancer in PI-RADS 2 lesions, it was found that 14 adenocarcinoma samples with a PI-RADS score of 2 did not have another lesion with a higher PI-RADS score, of which 8 (57.1%) of them were CsPCs. Additionally, 22 adenocarcinoma samples with a PI-RADS score of 2 had another lesion with a higher PI-RADS score, of which 18 (81.8%) of them were CsPC. The difference among these samples was not significant (P-value = 0.140).

5. Discussion

This study was performed to determine the rate of PC diagnosis and its clinical significance in patients with PI-RADS 2 lesions in mpMRI to see whether PI-RADS 2 lesions should be considered for biopsy. The present study's findings showed that 9.3% of PI-RADS 2 samples and 11.8% of PI-RADS 3 and 4 samples were diagnosed with adenocarcinoma, which did not have a statistically significant difference. Moreover, by comparing the characteristics of the investigated samples, except for the considerable difference between the two groups in the field of GG, no significant differences were detected concerning GS, the amount of G4 and G5 cells, the amount of the sample involvement with cancerous tissue and the involvement of peripheral nerves. By examining the clinical importance of adenocarcinoma samples in PI-RADS 2 and PI-RADS 3 - 4 lesions, no significant difference between the two groups was detected, as 72.2% of PI-RADS 2 adenocarcinoma lesions and 84.6% of PI-RADS 3-4 adenocarcinoma lesions were of moderate to high importance. The only factor associated with increased clinical significance of the detected cancer in PI-RADS 2 lesions was having a higher PSAt level. The presence of PI-RADS 3 - 4 lesions, regardless of their pathology survey results, did not predict the diagnosis of CsPC in PI-RADS 2 lesions.

As previously mentioned, the clinical role and utility of a negative mpMRI (lesions with PI-RADS 1 or 2) are strongly related to its NPV; therefore, the possibility of

Table 1. The Demographic Variables of the Included Patients

Variables	Total Patients (324)	PI-RADS 2 (N = 198)	PI-RADS 3-4 (N = 126)	P-Value
Age	64.78 ± 7.55	62.54 ± 7.22	63.02 ± 7.96	0.100
PSA density	0.15 ± 0.11	0.15 ± 0.10	0.17 ± 0.13	0.064
PSA total	8.73 ± 6.43	8.57 ± 6.96	8.97 ± 5.81	0.110
Prostate volume	61.18 ± 25.76	63.14 ± 27.49	57.97 ± 22.69	0.140

Abbreviations: PSA, prostate-specific antigen.

Table 2. Pathological Evaluation Results of the Taken Samples

Variables	Inner Right Samples			Inner Left Samples			Peripheral Samples		
	PI-RADS 2 (N = 146)	PI-RADS 3-4 (N = 103)	P-Value	PI-RADS 2 (N = 126)	PI-RADS 3-4 (N = 123)	P-Value	PI-RADS 2 (N = 118)	PI-RADS 3-4 (N = 93)	P-Value
Benign	0	3	0.073	2	0	0.498	0	5	0.018
BPH	78	46	0.116	67	52	0.110	79	36	<0.001
CP	53	38	0.941	47	52	0.368	17	32	0.001
NH	37	27	0.981	29	29	0.863	15	23	0.041
HGPIN	10	5	0.480	13	13	0.915	10	18	0.031
AP	3	5	0.287	5	8	0.353	12	2	0.016
AG	9	7	0.888	12	11	0.906	17	7	0.091
ASAP	2	1	1.000	0	1	0.490	4	7	0.232
Adenocarcinoma	9	11	0.222	9	12	0.436	17	16	0.696

Abbreviations: BPH, benign prostate hyperplasia; CP, Chronic Prostatitis; NH, nodular hyperplasia, high-grade prostatic intraepithelial neoplasia; AP, acute prostatitis; AG, atrophic gland; ASAP, atypical small acinar proliferation.

Table 3. The Characteristics of the Diagnosed Adenocarcinoma Among the Groups [a]

Variables	PI-RADS 2	PI-RADS 3 - 4	P-Value
GS			0.194
4		2 (5.1)	
6	14 (38.9)	6 (15.4)	
7	18 (50)	26 (66.7)	
8	4 (11.1)	5 (12.8)	
GG			0.035
1	12 (33.3)	6 (15.4	
2	13 (36.1)	11 (28.2)	
3	5 (13.9)	13 (33.3)	
4	6 (16.7)	9 (23.1)	
G4 cells	22.17 ± 15.22	32.66 ± 28.03	0.104
G5 cells	0	2.33 ± 0.051	0.171
Sample involvement	26.35 ± 20.5	19.51 ± 14.79	0.733
Perineural involvement (PNI)			0.520
Yes	29 (80.6)	29 (74.4)	
No	7 (19.4)	10 (25.6)	

Abbreviation: GS, Gleason Score; GG, Gleason Grade Group.
[a] Values are presented as No. (%) or mean ± SD.

Table 4. The Risk Rate of the Adenocarcinoma Samples Among the Groups

Variables	No. (%)	P-Value
PI-RADS 2		0.38
Low	10 (27.8)	
Intermediate-high	26 (72.2)	
PI-RADS 3-4		
Low	6 (15.4)	
Intermediate-high	33 (84.6)	

referring to its results to ensure the absence of CsPC is very important. In the present study, the NPV rate in PI-RADS 2 lesions was 90.7% for all PC lesions and 93.3% for CsPC lesions. To the best of our knowledge, this is the first study aimed to determine the prevalence of PC and its characteristics in lesions with a PI-RADS score of 2, specifically; However, several studies have been conducted to evaluate the NPV of a negative mpMRI (PI-RADS 1 or 2 lesions). However, the results of these studies have been limited and different. A 2019 study by Vandrink et al. (18) suggested that a prostate biopsy could be avoided in more than half of the patients suspicious of PC. Additionally, like other researchers in this field, including the Profiling Early Breast Cancer for Radiotherapy Omission (PRECISION) (16) study, they hypothesized that the risk of CsPC in patients with PI-RADS 1 - 2 lesions is so low that biopsy does not seem unavoidable.In the study of Vandrink et al., out of 2281 patients with PI-RADS 1 - 2 lesions only 320 were followed up with mpMRI, a limited number of patients with PI-RADS $\geq$ 3 were sampled. Although it can be concluded from the study of Vandrink et al. that the lesions of 84% of men did not progress, it is also not possible to determine that the progression of the disease was undiagnosed in what proportion of these patients. A meta-analysis study investigating the NPV of mpMRI for PC diagnosis evaluated the data of 48 studies (including 9613 patients) and determined a median NPV of 82.4% for all PCs and 88.1% for CsPCs (10). In the study by Bogner et al., which was conducted in 2022 to assess and compare the biopsy results of PI-RADS 1 - 2 lesions according to the criteria defined in the first, second, and 2.1 versions of PI-RADS, 188 patients were biopsied. They reported that the NPV of negative and suspicious mpMRI was 93.2% and 89.1%, respectively, according to the old versions of PI-RADS. They concluded that by relying on mpMRI results without using other factors such as clinical suspicion and PSAd, some PC cases might not be diagnosed, so the doctor him/herself should choose to perform a biopsy according to the patient's medical condition (19). In another study published by Williams et al. in 2022 (20), to investigate the causes of some PCs being missed in mpMRI and MRI-targeted lesion biopsies, 2103 patients were subjected to biopsy using the mentioned method along with a systematic biopsy. Finally, 41 patients with PC were detected that could not be recognized using a sole MRI-targeted biopsy. The most important reasons for missing the proper diagnosis were failing to accurately locate the exact biopsy point during the action and refusing to biopsy lesions with low PI-RADS scores. In addition, the results of Williams et al. showed that a lower score in the mpMRI examination was associated with the non-diagnosis of CsPCs. They concluded that the presence of high PSA levels along with a low PI-RADS score in mpMRI indicates the existence of a malignant lesion (20), a statement that is in line with the findings of the current study.

It could be concluded from the mentioned studies, consistent with the findings of the current study, that relying on mpMRI results without considering other factors may hinder us from making a correct diagnosis and missing some patients with PC. According to the outcomes of the current study, the NPV of PI-RADS 2 lesions is not statistically different compared with the PI-RADS 3 - 4 lesions; thus, PI-RADS 2 lesions should not be simply neglected. However, for PC diagnosis, negative mpMRI could be considered more like a clinical means to help healthcare providers make their decisions. Prostate mpMRI is regarded as a significant advance in the diagnosis of PC, and nowadays, it is widely utilized worldwide; though it has limitations. It is suggested that a negative mpMRI should be regarded alongside nomograms that predict the existence of prostate malignancies and shared with the patient in decision-making to identify patients who may safely avoid biopsy (15). The outcomes of the current study showed that the PSAt serum level could help us and the patients make the proper decision on whether to consider taking a biopsy from PI-RADS 2 lesions. This finding is consistent with the results of previously published studies (21, 22). Furthermore, according to the literature, patients that decide not to be sampled with an insignificant mpMRI

of the prostate must be informed that CsPC may not be detected in 10% to 20% of cases, and a careful follow-up must be suggested (23).

To the best of our knowledge, the current study is the first study that attempted to specifically investigate the NVP of PI-RADS 2 lesions in prostate mpMRI studies and address the possible predictors of a CsPC diagnosis in these lesions. The evaluated data of the current study was collected from multiple health centers, which consist of two educational health centers affiliated with different medical universities and two private hospitals. This allowed us to gather sufficient samples and provide more generalizable results; however, the current study is not without limitations. First, the retrospective design of this study is considered one of its main limitations. Next, due to the study's retrospective design, we could not obtain sufficient data concerning the signs and symptoms of the patients. Another limitation of the present study was the lack of patient follow-up. Moreover, all patients underwent MR targeted biopsy, which could miss some PC patients and overestimate the NPV of mpMRIs with PI-RADS 2 lesions. Further prospective studies should address these issues.

5.1. Conclusions

The current study was conducted to determine the detection rate of PC and its clinical significance in patients with PI-RADS 2 lesions in mpMRI and to see whether PI-RADS 2 lesions should be considered for biopsy. In the present study, the NPV rate in PI-RADS 2 lesions was 90.7% for all adenocarcinoma lesions and 93.3% for clinically significant adenocarcinoma lesions. No statistically significant difference was seen by comparing the NPV of PI-RADS 2 and PI-RADS 3 - 4. The present study showed that PI-RADS 2 lesions ought to be considered for biopsy when there is clinical suspicion of PC. PSA levels can effectively determine the need for biopsy in PI-RADS 2 lesions. Conducting prospective studies with a larger number of samples and a multicenter design can determine the minimum PSA level and other risk factors related to the clinical significance of PCs diagnosed in PI-RADS 2 lesion samples, increasing the NPV of mpMRI with PI-RADS 2 lesions, making biopsies more targeted in non-suspicious mpMRI lesions and reducing the rate of biopsy.

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Footnotes

Authors' Contribution: R. D. collected the clinical data, interpreted them, performed the statistical analysis, and drafted the manuscript. H. K. conceived and designed the evaluation and revised the manuscript. M. G. conceived and designed the evaluation, interpreted the clinical data, and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interests: We have been operating in the urology ward at Shohada-e-Tajrish Hospital for the last five years. We have no personal financial interest, patents, or stocks in profitable companies regarding this article. We are not members of the editorial board or reviewers of this journal.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: All procedures performed in this study involving human participants were by the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and were approved by the Research Ethics Committee of the Faculty of Medicine, Shahid Beheshti University of Medical Sciences. This study is approved under the ethical approval code of IR.SBMU.MSP.REC.1400.500.

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References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: Cancer today. *Lyon, France: Inter Agency Res Cancer*. 2018;**3**(20):2019.
2. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The epidemiology of prostate cancer. *Cold Spring Harb Perspect Med*. 2018;**8**(12). [PubMed ID: 29311132]. [PubMed Central ID: PMC6280714]. https://doi.org/10.1101/cshperspect.a030361.
3. Jamshidi M, Aliramaji A, Khafri S, Moudi E. Relationship between the breast cancer history and prostate cancer in relatives with prostate cancer. *J Babol Univ Med Sci*. 2017;**19**(8):7–11.
4. KOLAH DS, Sajadi AR, Radmard AR, KHADEMI HOUMAN. [Five common cancers in Iran]. *Arch Iran Med*. 2010. Persian.
5. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*. 2017;**71**(4):618–29. [PubMed ID: 27568654]. https://doi.org/10.1016/j.eururo.2016.08.003.
6. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol*. 2012;**22**(4):746–57. [PubMed ID: 22322308]. [PubMed Central ID: PMC3297750]. https://doi.org/10.1007/s00330-011-2377-y.
7. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. *Eur Urol*. 2016;**69**(1):16–40.

[PubMed ID: 26427566]. [PubMed Central ID: PMC6467207]. https://doi.org/10.1016/j.eururo.2015.08.052.
8. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic performance of prostate imaging reporting and data system version 2 for detection of prostate cancer: A systematic review and diagnostic meta-analysis. *Eur Urol*. 2017;**72**(2):177–88. [PubMed ID: 28196723]. https://doi.org/10.1016/j.eururo.2017.01.042.
9. Drost FH, Osses D, Nieboer D, Bangma CH, Steyerberg EW, Roobol MJ, et al. Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: A cochrane systematic review and meta-analysis. *Eur Urol*. 2020;**77**(1):78–94. [PubMed ID: 31326219]. https://doi.org/10.1016/j.eururo.2019.06.023.
10. Moldovan PC, Van den Broeck T, Sylvester R, Marconi L, Bellmunt J, van den Bergh RCN, et al. What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the european association of urology prostate cancer guidelines panel. *Eur Urol*. 2017;**72**(2):250–66. [PubMed ID: 28336078]. https://doi.org/10.1016/j.eururo.2017.02.026.
11. Johnson DC, Raman SS, Mirak SA, Kwan L, Bajgiran AM, Hsu W, et al. Detection of individual prostate cancer foci via multiparametric magnetic resonance imaging. *Eur Urol*. 2019;**75**(5):712–20. [PubMed ID: 30509763]. https://doi.org/10.1016/j.eururo.2018.11.031.
12. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): A paired validating confirmatory study. *Lancet*. 2017;**389**(10071):815–22. [PubMed ID: 28110982]. https://doi.org/10.1016/S0140-6736(16)32401-1.
13. Hansen NL, Barrett T, Kesch C, Pepdjonovic L, Bonekamp D, O'Sullivan R, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naive men with suspicion of prostate cancer. *BJU Int*. 2018;**122**(1):40–9. [PubMed ID: 29024425]. https://doi.org/10.1111/bju.14049.
14. Panebianco V, Barchetti G, Simone G, Del Monte M, Ciardi A, Grompone MD, et al. Negative multiparametric magnetic resonance imaging for prostate cancer: What's next? *Eur Urol*. 2018;**74**(1):48–54. [PubMed ID: 29566957]. https://doi.org/10.1016/j.eururo.2018.03.007.
15. Stabile A, Giganti F, Rosenkrantz AB, Taneja SS, Villeirs G, Gill IS, et al. Multiparametric MRI for prostate cancer diagnosis: Current status and future directions. *Nat Rev Urol*. 2020;**17**(1):41–61. [PubMed ID: 31316185]. https://doi.org/10.1038/s41585-019-0212-4.
16. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med*. 2018;**378**(19):1767–77. [PubMed ID: 29552975]. [PubMed Central ID: PMC9084630]. https://doi.org/10.1056/NEJMoa1801993.
17. Stabile A, Dell'Oglio P, De Cobelli F, Esposito A, Gandaglia G, Fossati N, et al. Association between prostate imaging reporting and data system (PI-RADS) score for the index lesion and multifocal, clinically significant prostate cancer. *Eur Urol Oncol*. 2018;**1**(1):29–36. [PubMed ID: 31100225]. https://doi.org/10.1016/j.euo.2018.01.002.
18. Venderink W, van Luijtelaar A, van der Leest M, Barentsz JO, Jenniskens SFM, Sedelaar MJP, et al. Multiparametric magnetic resonance imaging and follow-up to avoid prostate biopsy in 4259 men. *BJU Int*. 2019;**124**(5):775–84. [PubMed ID: 31237388]. https://doi.org/10.1111/bju.14853.
19. Bogner K, Engelhard K, Wuest W, Hamel S. Prostate cancer in PI-RADS scores 1 and 2 version 2.1: A comparison to previous PI-RADS versions. *Abdom Radiol (NY)*. 2022;**47**(6):2187–96. [PubMed ID: 35312821]. https://doi.org/10.1007/s00261-022-03444-1.
20. Williams C, Ahdoot M, Daneshvar MA, Hague C, Wilbur AR, Gomella PT, et al. Why does magnetic resonance imaging-targeted biopsy miss clinically significant cancer? *J Urol*. 2022;**207**(1):95–107. [PubMed ID: 34433302]. [PubMed Central ID: PMC8665000]. https://doi.org/10.1097/JU.0000000000002182.
21. Abd-Alazeez M, Ahmed HU, Arya M, Charman SC, Anastasiadis E, Freeman A, et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level–can it rule out clinically significant prostate cancer? *Urol Oncol*. 2014;**32**(1):45 e17–22. [PubMed ID: 24055430]. [PubMed Central ID: PMC4082533]. https://doi.org/10.1016/j.urolonc.2013.06.007.
22. Thompson JE, van Leeuwen PJ, Moses D, Shnier R, Brenner P, Delprado W, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. *J Urol*. 2016;**195**(5):1428–35. [PubMed ID: 26529298]. https://doi.org/10.1016/j.juro.2015.10.140.
23. Frydenberg M. Avoiding biopsy in men with PI-RADS scores 1 and 2 on multiparametric MRI of the prostate, ready for prime time? *BJU Int*. 2019;**124**(5):715–6. [PubMed ID: 31646757]. https://doi.org/10.1111/bju.14901.