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ORIGINAL PAPER

Do all patients with suspicious prostate cancer need Multiparametric Magnetic Resonance Imaging before prostate biopsy?

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Summary ***Objectives: Multiparametric magnetic resonance imaging (mpMRI) is a useful tool to diagnose prostate cancer (PCa) but its cost is not negligible. In order to reduce costs and minimize time to diagnosis, it is necessary to establish which patients benefit the most from doing mpMRI prior to prostate biopsy (PB). Our aim was to test if mpMRI still predicts PCa and clinically significant PCa (csPCa) in patients with high clinical suspicion of cancer, defined as prostate specific antigen (PSA) > 10 ng/ml, PSA-Density (PSAD) > 0.15 ng/ml/cc or suspicious digital rectal examination (DRE).***
Materials and methods: We retrospectively collected data on 206 patients who underwent mpMRI before PB at our Department from January 2017 to July 2018. mpMRI results were classified using Prostate Imaging Reporting and Data System (PI-RADS) version 2. In primary analysis, we evaluated the association of mpMRI with PCa and csPCa and stratified this model for low and high clinical suspicion of cancer.
In secondary analysis, we determined the rate of negative PB results in patients with high suspicion of cancer and compared theses rates with those obtained if only those with PI-RADS 3-5 would be biopsied.
Results: In primary analysis and overall, mpMRI was predictive of PCa and csPCa. In stratified analysis, mpMRI was still significantly associated with csPCa in patients with PSA > 10 ng/ml and PSAD > 0.15 ng/ml/cc, but not in those with suspicious DRE. In secondary analysis, negative result rates were lower if only patients with PI-RADS 3-5 were biopsied, even in subgroups with high suspicion of cancer based on PSA and PSAD. In patients with suspicious DRE, however, the rate of negative results did not change significantly if only patients with PI-RADS 3-5 were biopsied.
Conclusions: mpMRI is still useful in predicting csPCa in patients with PSA > 10 ng/mL and PSAD > 0.15 ng/ml/cc. If DRE is suspicious, though, mpMRI might be no longer useful in the prediction of PCa.

KEY WORDS: Prostate cancer; PSA; PSA density; Digital rectal examination; mpMRI; PI-RADS.

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer among men worldwide (1). Serum *prostate specific antigen* (PSA) and *digital rectal examination* (DRE) are the common initial assessments for detection. A suspicious DRE or a PSA higher than 4 ng/ml are generally considered an indication for *prostate biopsy* (PB) (2). In fact, a suspicious DRE is associated with a higher risk of PCa independently of the PSA levels (3).

The gold standard for PCa diagnosis is the *transrectal ultrasound* (TRUS)-guided PB. Nonetheless this technique has some limitations. TRUS-guided PB may miss up to 20% of cancers (4). Additionally, a large proportion of detected cancers are clinically insignificant (5), contributing to overdiagnosis and overtreatment of indolent tumors which may adversely impact quality of life without altering survival (6).

Multiparametric magnetic resonance imaging (mpMRI) promises to overcome these problems, distinguishing significant from insignificant disease and avoiding unnecessary PB (7, 8). Compared with radical prostatectomy specimens, mpMRI detects 85-95% of *clinically significant PCa* (csPCa) (9) and has negative predictive values of 83-94% (9, 10). Additionally, mpMRI preferentially detects csPCa and thus may help to avoid unnecessary PB for benign or insignificant lesions, reducing overtreatment (8, 11).

As a result, 64% of urologists consider mpMRI useful to detect PCa in biopsy-naïve men, while 97% consider it valuable in men with a prior negative biopsy (12). However, the systematic use of mpMRI as a triage test in patients with suspicion of PCa is still a matter of debate (13, 14). Moreover, mpMRI cost is not neglectable (8) and may delay PB.

In order to avoid unnecessary costs and minimize time to diagnosis, it is necessary to establish which patients benefit the most from doing mpMRI prior to TRUS-guided PB. We hypothesize that mpMRI may not add value to the detection of PCa in patients with a high clinical suspicion of cancer and mpMRI could be dispensable in this group of patients, saving costs and time to diagnosis.

The aim of this study is to determine if mpMRI prior to PB is still useful in predicting PCa and csPCa in patients with high clinical suspicion of cancer, defined as PSA > 10 ng/ml, *PSA-Density* (PSAD) > 0.15 ng/ml/cc or suspicious *digital rectal examination* (DRE).

No conflict of interest declared.

Materials and methods

Patients demographics and variables

This study was performed in accordance with the Declaration of Helsinki and was approved by the *Ethics Committee of Hospital de Braga*.

We retrospectively collected data on 594 patients who underwent TRUS-guided PB at the *Urology Department* of *Hospital de Braga* from January 2017 to July 2018. 206 patients who underwent mpMRI before PB were included in our study. For patients who underwent repeated PB during this period, the last biopsy was taken as reference. Data on age, previous biopsies, DRE, PSA, prostate volume (assessed by TRUS), PSAD, PI-RADS and PB histological results were recorded. PSAD was determined only in patients who underwent TRUS before biopsy (PSAD = PSA/Prostate volume). DRE was described as unequivocal (normal and abnormal) or doubtful (if no definitive conclusions could be made).

mpMRI

mpMRI was performed using a 1.5 Tesla system. Three sequences were used: T2-weighted, dynamic contrast-enhanced and diffusion weighed images. For diffusion weighed images, b-values 0-1700 were used. Apparent diffusion coefficient-maps were calculated using diffusion weighed images. Suspicious lesions were scored according to the validated PI-RADS version 2.

In our study, the highest PI-RADS score of each mpMRI scan was used.

Taking into account the meaning of PI-RADS categories (15) and similarly to other studies (16), PI-RADS score was categorized in 1-2 (used as reference) and 3-5.

TRUS-guided PB

All men underwent randomized TRUS guided-PB. Twelve randomized cores (6 from right lobe and 6 from left lobe) were taken with no additional cores to suspicious lesions. Histopathological analysis was performed at our Hospital. PCa was classified according to the *International Society of Urological Pathology* standards and csPCa was defined as Gleason score ≥ 7 (3+4).

Statistical analysis

Variables analyzed were age, previous biopsy (yes/no), DRE, prostate volume, PSAD, PI-RADS, PCa and csPCa. Continuous variables were expressed as median and *interquartile range* (IQR). Categorical variables were expressed as absolute and relative frequencies.

For the primary analysis, the chi-squared test was performed to evaluate the association of mpMRI with PCa and csPCa. Thereafter, this model was stratified for different PSA and PSAD cutoffs as well as DRE.

When n was low, Fisher's-Exact Test was used to evaluate this association.

A $p < 0.05$ was considered to indicate statistical significance.

For the secondary analysis, negative PB result rates and false negative rates of mpMRI were also calculated.

Statistical analysis was performed using Stata version 15.

Results

Patients' demographics

206 patients underwent mpMRI and were included in our study. Patient's characteristics, PI-RADS scores and histological results are shown in Table 1. Median (IQR) age was 67 (61-72) years and median prostate volume was 45.9 (35-66) cc. Median PSA and PSAD were 8.55 (5.74-12.7) ng/ml and 0.17 (0.11-0.26) ng/ml/cc, respectively.

DRE was described as unequivocal for 130 patients, with 51 patients (24.76%) classified as suspicious. 79 patients (38.35%) patients had previously undergone PB for suspicious PSA or DRE. 34 patients (16.5%) had a normal mpMRI PI-RADS score (PI-RADS 1-2) and 172 patients (83.5%) had a suspicious PI-RADS (PI-RADS 3-5). PB result was normal in 78 (37.86%) patients, while 128 (62.14%) had PCa and 100 (48.54%) had csPCa.

Prediction of prostate cancer and clinically significant prostate cancer

As primary analysis, chi-squared test was used to test if PI-RADS was a predictor of PCa and csPCa, with results shown in Table 2.

After, we stratified these results for low *versus* high clinical suspicion of PCa, defined as PSA ≤ 10 *versus* PSA > 10 ng/ml, PSAD ≤ 0.15 *versus* PSAD > 0.15 ng/ml/cc and nor-

Table 1.
Patients' characteristics.

Variable	N	Value
Age (years) median (IQR)	206	67 (61-72)
Previous biopsy	206	
No n (%)		127 (61.65%)
Yes n (%)		79 (38.35%)
DRE	206	
Doubtful		76 (36.89%)
Unequivocal		
Normal		79 (38.35%)
Suspicious		51 (24.76%)
Prostate volume (cc) median (IQR)	138	45.9 (35-66)
PSA (ng/ml) median (IQR)	206	8.55 (5.74-12.7)
PSA density (ng/ml/cc) median (IQR)	138	0.17 (0.11-0.26)
PI-RADS	206	
1		18 (8.74%)
2		16 (7.77%)
3		38 (18.45%)
4		66 (32.04%)
5		68 (33.01%)
Prostate cancer	206	
No % (n)		78 (37.86%)
Yes % (n)		128 (62.14%)
Clinically significant prostate cancer	206	
No % (n)		106 (51.46%)
Yes % (n)		100 (48.54%)

Table 2.
Association of PI-RADS with PCa and csPCa.

		Prostate cancer			Significant prostate cancer		
N		No cancer	PCa	P	No Cancer	csPCa	P
206	PI-RADS 1-2	22 (64.71%)	12 (35.29%)	< 0.001*	29 (85.29%)	5 (14.71%)	< 0.001*
	PI-RADS 3-5	56 (32.56%)	116 (67.44%)		76 (44.19%)	96 (55.81%)	

*P: p-value; *Chi-Squared Test.*

Table 3.
Association of PI-RADS with PCa and csPCa stratified for PSA ≤ 10 ng/ml and > 10 ng/ml and PSAD ≤ 0.15 ng/ml/cc and > 0.15 ng/ml/cc.

	N		Prostate cancer			Significant prostate cancer		
			No cancer	PCa	P	No Cancer	csPCa	P
PSA ≤ 10 ng/ml	127	PI-RADS 1-2	12 (60.0%)	8 (40.0%)	0.004*	16 (80.0%)	4 (20.0%)	0.018*
		PI-RADS 3-5	38 (35.51%)	69 (64.49%)		55 (51.40%)	52 (48.60%)	
PSA > 10 ng/ml	79	PI-RADS 1-2	10 (71.43%9	4 (28.57%)	0.004**	13 (92.86%)	1 (7.14%)	< 0.001**
		PI-RADS 3-5	18 (27.69%)	47 (72.31%)		21 (32.31%)	44 (67.69%)	
PSAD ≤ 0.15 ng/ml/cc	58	PI-RADS 1-2	10 (71.43%)	4 (28.57%)	0.139**	13 (92.86%)	1 (7.14%)	0.044**
		PI-RADS 3-5	21 (47.73%)	23 (52.27%)		27 (61.36%)	17 (38.64%)	
PSAD > 0.15 ng/ml/cc	80	PI-RADS 1-2	8 (66.67%)	4 (33.33%)	< 0.001**	10 (83.33%)	2 (16.67%)	< 0.001**
		PI-RADS 3-5	10 (14.71%)	58 (85.29%)		17 (25.0%)	51 (75.0%)	

*P: p-value; *Chi-Squared Test; **Fisher's Exact Test.*

Table 4.
Association of PI-RADS with PCa and csPCa stratified for normal and suspicious DRE.

	N		Prostate cancer			Significant prostate cancer		
			No cancer	PCa	P	No Cancer	csPCa	P
Normal DRE	79	PI-RADS 1-2	14 (70.0%)	6 (30.0%)	0.007*	18 (90.0%)	2 (10.0%)	0.004*
		PI-RADS 3-5	21 (35.59%)	38 (64.41%)		32 (54.24%)	27 (45.76%)	
Suspicious DRE	51	PI-RADS 1-2	2 (50.0%)	2 (50.0%)	0.168**	2 (50.0%)	2 (50.0%)	0.571**
		PI-RADS 3-5	8 (17.02%)	39 (82.98%)		13 (27.66%)	34 (72.34%)	

*P: p-value; *Chi-Squared Test; **Fisher's Exact Test.*

mal DRE versus suspicious DRE, respectively (Tables 3, 4). In our primary analysis, we found that PI-RADS 3-5 was a significant predictor of both PCa and csPCa (p < 0.001).

Low vs. high risk based on PSA
After stratification in low vs. high risk based on PSA, we found that in patients with low clinical suspicion of PCa (PSA ≤ 10 ng/ml), PI-RADS 3-5 was a significant predictor of PCa and csPCa (p = 0.004 and p = 0.018, respectively) and that in patients with high PSA levels (PSA > 10 ng/ml), PI-RADS 3-5 was also significantly associated with PCa and csPCa (p = 0.004 and p < 0.001, respectively).

Low vs. high risk based on PSAD
In stratified analysis by clinical suspicion based on PSAD, we found that in patients with low clinical suspicion of cancer (PSAD ≤ 0.15 ng/ml/cc), PI-RADS 3-5 was a predictor of csPCa (p = 0.044). However, in this group, PI-RADS 3-5 was not significantly associated with PCa (p = 0.139). In patients with high clinical suspicion of PCa (PSAD > 0.15 ng/ml/cc), PI-RADS 3-5 was significantly associated with both PCa and csPCa (p < 0.001).

Low vs. high risk based on DRE
In stratified analysis by clinical suspicion based on DRE, we found that in patients with low clinical suspicion of cancer (normal DRE), PI-RADS 3-5 was a predictor of both PCa and csPCa (p = 0.007 and p = 0.004, respectively). Conversely, in patients with suspicious DRE, PI-RADS 3-5 was neither associated with PCa nor with csPCa (p = 0.168 and p = 0.571, respectively).
Noticeably, in this group of patients, only 4 patients (7.84%) with suspicious DRE had normal mpMRI findings (PI-RADS 1-2) and out of them 2 (50%) had csPCa.

Negative prostate biopsy (PB) result rates of prostate cancer and clinically significant prostate cancer
As secondary analysis, we evaluated the rate of negative PB in the subgroup of patients with PI-RADS 3-5. These results are shown in Table 5.
In total, 37.9% of patients biopsied had no PCa and 51% no csPCa.
If only patients with PI-RADS 3-5 were considered, negative PB rate dropped to 27.2% and 36.9% for PCa and csPCa respectively. The rate of patients with PCa and csPCa and PI-RADS 1-2 who would not be biopsied or diagnosed with this approach (false negative rate) would be 5.8% and 2.4%, respectively.

Patients with high risk based on PSA
Among patients with PSA > 10 ng/ml, the rate of negative PB was 35.4% for PCa and 43% for csPCa.
Patients with PSA > 10 ng/ml and PI-RADS 3-5 did not have PCa and csPCa in 22.8% and 26.6% respectively.
If among patients with PSA > 10 ng/m, only those with PI-RADS 3-5 were biopsied, the false negative rates would be 5.1% for PCa and 1.3% for csPCa.

Patients with high risk based on PSAD
Patients with PSAD > 0.15 ng/ml/cc had a negative PB result rate of 22.5% for PCa and of 33.8% for csPCa, respectively.
Patients with PSAD > 0.15 and PI-RADS 3-5 had no PCa in 12.5% and no csPCa in 21.3%. If only patients with PI-RADS 3-5 were biopsied, 5.0% of patients with PCa and 2.5% of patients with csPCa would be missed.

Patients with high risk based on DRE
Patients with suspicious DRE had no PCa in 19.6% and no csPCa in 29.4%.
If only patients with suspicious DRE and PI-RADS 3-5 had undergone biopsy, 15.7% would have no PCa and 25.5% would have no csPCa. According to this approach, 3.9% of patients with suspicious DRE and PI-RADS 1-2 bearing PCa or csPCa would be missed.

Table 5.
Negative PB result rates and false negative rates for PCa and csPCa globally and in patients with PI-RADS 3-5 in different subgroups.

	PCa			csPCa		
	Total	PI-RADS 3-5		Total	PI-RADS 3-5	
	NPBR	NPBR	FNR	NPBR	NPBR	FNR
Total	37.9%	27.2%	5.8%	51%	36.9%	2.4%
PSA > 10 ng/ml	35.4%	22.8%	5.1%	43%	26.6%	1.3%
PSAD > 0.15 ng/ml/cc	22.5%	12.5%	5.0%	33.8%	21.3%	2.5%
Suspicious DRE	19.6%	15.7%	3.9%	29.4%	25.5%	3.9%

NPBR: Negative PB result rates; FNR: False negative rates.

Discussion

To our knowledge, this is the first study to test mpMRI accuracy in detection of PCa stratified by clinical suspicion of cancer based on various clinical markers, including PSA, PSAD, and DRE.

According to the *European Association of Urology* guidelines, mpMRI before biopsy could improve the detection csPCa in two different ways. First it allows to target specific lesions visible on mpMRI. Secondly, mpMRI could be used as a triage test before biopsy, so that mpMRI-PB would be performed only in case of a positive mpMRI whereas patients with negative mpMRI findings would not undergo prostate biopsy at all. Based on this assumption most studies focused on using mpMRI to avoid PB and diagnosis of clinical insignificant PCa (17), rather than evaluating where mpMRI can add value compared to standard clinical tools alone.

The PROMIS trial showed high sensitivity and high negative predictive value of mpMRI for the detection of csPCa, defined as Gleason score ≥ 7 (4+3) or cancer core length ≥ 6 mm. However, the false-positive rate for mpMRI was 49%, needing follow-up biopsy sampling to confirm suspicious findings. Moreover, as negative and positive predictive values depend on prevalence, it becomes mandatory to pre-evaluate the risk of csPCa in patients with a suspicion of PCa (16). Biomarkers and nomograms are very helpful in this setting, but standard clinical examination should remain of pivotal importance (18).

Our primary analysis among all included patients unsurprisingly demonstrated that mpMRI PI-RADS 3-5 was associated both with PCa and csPCa, as previously described (7-10). After stratification by clinical suspicion of PCa, also as expected, in patients with low clinical suspicion of PCa, defined as PSA ≤ 10 ng/ml, PSAD ≤ 0.15 ng/ml/cc and normal DRE, mpMRI PI-RADS 3-5 was significantly associated with PCa in most evaluations (except for lowest PSAD values ≤ 0.15 ng/ml/cc) and with diagnosis of csPCa in all evaluations.

However, importantly we observed that among patients with high clinical suspicion of PCa, defined as PSA > 10 ng/ml and PSAD > 0.15 ng/ml/cc, mpMRI PI-RADS 3-5 remained significantly associated with csPCa and PCa.

However, in patients with high clinical suspicion of PCa based on DRE, mpMRI PI-RADS 3-5 was not significantly associated with PCa or csPCa. The main explanation of this finding is that almost all patients with an unequivocal abnormal DRE have a mpMRI PI-RADS of 3-5. Altogether, these findings demonstrate an added value of mpMRI even among patients with PSA > 10 ng/ml and PSAD > 0.15 ng/ml/cc. Patients with suspicious DRE, however, might not benefit from mpMRI for the PB diagnosis of cancer.

Our secondary analysis showed that the rate of negative PB results would drop significantly if PB was only performed in patients with PI-RADS 3-5. The rate of negative PB results was 37.9% vs 27.2% for PCa and 51% *vs* 36.9% for csPCa when the total rate was compared with the rate in patients with PI-RADS 3-5. Even in subgroups with high clinical suspicion of cancer, defined as PSA > 10ng/ml and PSAD > 0.15 ng/ml/cc, mpMRI would be useful to avoid unnecessary PB. The rate of negative PB results was 35.4% *vs* 22.8% for PCa and 43% *vs* 26.6% for csPCa when total rate was compared with the rate in patients with PI-RADS 3-5 and PSA > 10 ng/ml and 22.5% *vs* 12.5% for PCa and 33.8% *vs* 21.3% for csPCa when total rate was compared with the rate in patients with PI-RADS 3-5 and PSAD > 0.15 ng/ml/cc. mpMRI was thus helpful in selecting patients with PCa and csPCa who needed to undergo PB even in the subgroup with high clinical suspicion of cancer, defined as PSA > 10 ng/ml and PSAD > 0.15 ng/ml/cc.

However, in patients with suspicious DRE performing PB only in those with PI-RADS 3-5 would not change significantly the rate of negative PB results. The negative PB result rate was 19.6% *vs* 15.7% for PCa and 29.4% *vs* 25.5% for csPCa when total rate was compared with the rate in patients with PI-RADS 3-5. In addition, this 4% reduction was obtained at the cost of a false negative rate of 3.9%. Therefore, in line with primary analysis' findings, patients with suspicious DRE do not benefit from mpMRI before PB. For the first time, we specifically report the utility of mpMRI in patients with high clinical suspicion of cancer. Contrary to our hypothesis, when PSA was > 10 ng/ml and PSAD > 0.15 ng/ml/cc, mpMRI was still useful in discriminating PCa and csPCa. However, according to our hypothesis, if DRE is suspicious, mpMRI might no longer be necessary to aid in the PB diagnosis of cancer.

It is true that omitting mpMRI, many PCas of anterior gland could be undetected to the standard TRUS guided-PB (19), but several studies assessed the importance to detect anterior PCa with discordant findings (20).

The optimization of the TRUS guided-PB technique is, anyway, decisive.

This study has some limitations. Firstly, our gold standard was systematic PB and not targeted PB or final prostatectomy specimens and therefore some men with negative PB result may have had PCa. Secondly, mpMRI images were reviewed by different radiologists, which may weaken internal validity, although this condition could represent better every day clinical practice.

Conclusions

We think to report the first study to evaluate the accuracy of mpMRI in patients with different clinical suspicion of PCa. PI-RADS 3-5 was predictive of csPCa even when PSA was > 10 ng/ml and PSAD > 0.15 ng/ml/cc. Therefore, mpMRI should be performed also in this set of patients with high clinical suspicion of cancer. In patients with suspicious DRE, mpMRI seems not to be significantly associated with cancer and it may be avoided to reduce costs and save time to diagnosis in this particular group of patients.

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