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Diagnosis of clinically significant prostate cancer after negative multiparametric magnetic resonance imaging

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Introduction The diagnostic pathway after a negative magnetic resonance imaging (nMRI) exam is not clearly defined. The aim of the present study is to define the risk of prostate adenocarcinoma (PCa) at the prostate biopsy after a negative multiparametric magnetic resonance imaging (mpMRI) exam.
Material and methods Patients with nMRI Prostate Imaging Reporting & Data System (PI-RADS) ≤2 and without a previous diagnosis of PCa were identified among all patients undergoing mpMRI in a single referral center between 01/2016-12/2019. Detailed data about prostate biopsy after nMRI were collected, including any PCa diagnosis and clinically significant PCa diagnosis. [Gleason score (GS) ≥7]. In addition to descriptive statistics, uni and multivariable logistic regression assessed the potential predictors of any PCa and clinically significant prostate cancer (csPCa) at the biopsy after a negative mpMRI.
Results Of 410 patients with nMRI, 73 underwent saturation biopsy. Only prostate-specific antigen (PSA) levels were significantly higher in patients undergoing biopsy (5.2 ng/ml vs 6.4, p <0.001), while Prostate Cancer Research Foundation (SWOP – Stichting Wetenschappelijk Onderzoek Prostaatkanker) risk score and other variables did not differ. A total of 22 biopsies (30.1%) were positive for PCa, GS 6 was diagnosed in 14 patients, GS 7 in 3, GS 8 in 1 and GS 9–10 in 4. csPCa was found in 8 (11%) patients. No significant predictors of any PCa or csPCa were identified at multivariate regression analysis.
Conclusions Despite the good negative predictive value of mpMRI in the diagnosis of prostate cancer, 11% of the patients had csPCa. Specific predictive models addressing this setting would be useful.

Key Words: prostate cancer ‹› prostate multiparametric magnetic resonance imaging ‹› multiparametric magnetic resonance imaging ‹› negative magnetic resonance imaging ‹› clinically significant

INTRODUCTION

Multiparametric magnetic resonance imaging (mpMRI) has reached a central role in the diagnostic pathway of prostate cancer. The correlation between mpMRI and clinically significant prostatic cancer (csPCa) has been well described [1, 2, 3]. This association suggests that mpMRI could potentially serve as a prognostic biomarker for prostate adenocarcinoma (PCa) treatment selection and improve upon both the suboptimal accuracy and invasiveness of current risk stratification strategies. Currently, mpMRI is employed both to orient the decision-making for prostate biopsy and to target biopsy sampling in suspicious areas [4]. MRI pathway had the most favorable outcome in clinically significant and

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insignificant PCa detection compared with systematic biopsy [2]. As a result, the European Association of Urology (EAU) guidelines now recommend performing mpMRI before prostate biopsy, both in the biopsy-naïve and in the repeated biopsy settings. However, the controversial mpMRI negative predictive value (NPV), and the diagnostic pathway after a negative mpMRI (nMRI) is not clearly defined [5]. The number of expected false negatives per 1000 men assuming a baseline cancer prevalence of 30% is 84 (54–120). mpMRI has been included in multivariable models for individualized decision on biopsy; however, the definitive clinical reliability of these tools has not completely set [6]. Furthermore, a recent meta-analysis suggests that MRI is not accurate enough to replace prostate biopsy in patients suspected of having PCa, mainly because its accuracy is variable and influenced by the PCa risk [7]. The PROMIS trial [5] found an NPV of 89% for csPCa. However, these results dropped to 72–76% when different definitions of csPCa were used. Thus, there is paucity of data concerning the best strategy to use in the risk stratification for csPCa in patients with nMRI. Particularly, the way to identify patients with nMRI and a high risk of csPCa is not well defined. Associating MRI with predictive factors may increase the NPV of MRI and reduce the number of prostate biopsies in men whose risk of csPCa is low. nMRI performance could be enhanced if there were more accurate ways of determining the risk of having PCa [8, 9]. The aim of this study is to assess the risk of any PCa and clinically significant PCa in patients undergoing systematic biopsy after a negative mpMRI and to identify potential predictors of PCa in this specific setting.

MATERIAL AND METHODS

We collected data of all prostate mpMRI performed at our institution between 01/2016 and 12/2019 and identified negative scans. [Prostate Imaging Reporting and Data System (PI-RADS) ≤2]. All patients underwent mpMRI on a 1.5 T system (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany) with a 10-channel abdominal phased array coil.

For every patient, T1/T2 weighted images, diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) sequences were obtained, the latter was acquired after i.v. administration of 0.1 ml/kg of gadobutrol (Gadavist, Bayer-Schering, Berlin, Germany), at an injection rate of 2–3 ml/s. The image acquisition was performed after i.v. administration of 40 mg hyoscine butylbromide (Buscopan, Boehringer Ingelheim GmbH, Ingelheim, Germany) as a spasmolytic agent.

The image analysis was performed by two experienced radiologists (A.L. and C.S.L.) both with an MRI experience longer than 10 years and who took part in a previous prostate MRI study involving more than 300 patients. The image analysis was conducted in accordance with the PI-RADS version 2 criteria. Every radiological report included the PI-RADS v2 score for each lesion, its dimension and the precise location using the 39-region map.

Patients with any previous diagnosis of PCa, as well as any previous prostatic surgery different from transurethral resection of the prostate (TURP) were excluded. For the present study, patients who underwent a prostate biopsy based on shared decision-making after negative mpMRI were identified and included. The number of cores on all post-MRI biopsies was extended to ≥24.

Complete pre-mpMRI data were collected, including age, prostate-specific antigen (PSA) and its derivatives (PSA density and velocity) when possible, previous prostate biopsy, pharmacological treatments including 5-alpha reductase inhibitors (5-ARIs), and previous TURP. Prostate volume at MRI was collected and the Prostate Cancer Research Foundation (SWOP) score [10] (any pCa risk and significant pCa risk) was calculated.

The results of post-MRI biopsy were recorded, including time from MRI to biopsy, detection rate of any PCa and detection rate of clinically significant PCa (GS ≥3+4) [11]. Post-MRI biopsy results were compared between biopsy-naïve patients and men with a previous negative biopsy. Moreover, post-biopsy management decisions were recorded; when radical prostatectomy was performed, complete information on definitive histopathology was collected. Finally, uni- and multivariable logistic regression analysis assessed the potential predictors of any PCa and csPCa at biopsy after negative mpMRI.

All statistical analysis was carried out using commercially available software (IBM SPSS version 26, NY, United States of America).

RESULTS

A total of 410 patients underwent mpMRI with negative results in the study period. After application of inclusion/exclusion criteria, 348 patients were left in the cohort. Of these, 73 (21%) were subjected to saturation prostate biopsy and included in the final analysis. Table 1 shows the comparison between patients who underwent biopsy and the rest of the cohort, where no obvious differences in age, digital rectal examination (DRE), PSA density (PSAD) or SWOP risk score for any PCa and csPCa were found, whereas median PSA was higher in the biopsy cohort (5.2 vs 6.4, $p < 0.001$).

A total of 73 patients underwent saturation biopsy after negative mpMRI (Table 1), with a median of 24 cores. Of these, 63/73 (86.3%) biopsies were performed via the transrectal route and 10/73 (13.7%) via the transperineal approach. Overall, 22/73 biopsies (30.1%) were positive for prostate cancer. GS 6 was diagnosed in 14/22 patients (63.6%); GS 7 in 3/22 (13.6%), GS 8 in 1/22 (4.6%) and GS 9–10 in 4/22 (18.2%) (Table 2). Therefore, csPCa was found in 8/73 (11%) patients who underwent biopsy after negative mpMRI. Table 3 shows the results stratified by previous biopsy status (biopsy naïve vs previous negative biopsy). Of note, no significant differences were found, in particular the detection of any PCa and csPCa did not differ between the two cohorts; SWOP risk calculator results were similar as well.
Finally, logistic regression analysis was carried out to assess possible predictors of biopsy positivity for any PCa and csPCa. The results of uni and multivariate models for any PCa are reported in Table 5. In particular, 5-ARI therapy was associated with an increased risk of any PCa diagnosis in this cohort.

Table 1. *Comparison between patients who underwent or did not undergo biopsy after negative multiparametric magnetic resonance imaging*

	No biopsy after MRI	Biopsy after MRI	P value
N. of patients	275 (79%)	73 (21%)	n/a
Age at 1st MRI, years (median, IQR)	65.1 (59.7–70.2)	65.2 (57.9–69.7)	0.67
DRE equivocal positive negative	19 (17.3%) 5 (4.5%) 86 (78.2%)	8 (21.1%) 1 (5.3%) 28 (73.7%)	0.85
PSA at 1st MRI (ng/dL) (median, IQR)	5.2 (3.3; 7.3)	6.4 (4.9; 9.6)	0.001
PSAD before 1st MRI (median, IQR)	0.08 (0.05–0.11)	0.09 (0.07–0.13)	0.068
PSAD after 1st MRI (median, IQR)	0.07 (0.04–0.12)	0.10 (0.06–0.13)	0.066
PSAD (1st MRI) >0.15 (median, IQR)	23 (13.6%)	9 (15.8%)	0.68
PSA DT (month) (median, IQR)	10 (62.5–54.5)	26 (73.5–104.5)	0.95
PSA velocity (ng/dL/y) (median, IQR)	1.3 (1.03–0.405)	0.23 (0.43–1.08)	0.084
Prostate volume (median, IQR)	65 (46–88.8)	72 (50; 97)	0.35
SWOP any PCa risk 1 (median, IQR)	0.06 (0.05–0.092)	0.07 (0.06–0.10)	0.20
SWOP csPCA risk 1 (median, IQR)	0.01 (0.01–0.012)	0.01 (0.01–0.02)	0.23

N – number; MRI – magnetic resonance imaging; IQR – interquartile range; DRE – digital rectal examination; PSA – prostate-specific antigen; PSAD – PSA density; PSA DT – PSA doubling time; PCa – prostate cancer; csPCa – clinically significant prostate cancer; SWOP – Prostate Cancer Research Foundation Score

Table 2. *Baseline features of patients who underwent biopsy after negative mpMRI*

Variables	
N. of patients	73
Previous Biopsy before first MRI	36 (49.3%)
Age at 1st MRI, years (median, IQR)	65.2 (57.9–69.7)
N. of previous MRI (median, IQR)	1 (1–2)
N. of patients with previous negative TURP	22 (30.1%)
DRE equivocal positive negative	 8 (21.1%) 1 (5.3%) 28 (73.7%)
PSA at 1st MRI (ng/dL) (median, IQR)	6.4 (4.9–9.6)
PSAD before 1st MRI (ng/ml^2) (median, IQR)	0.09 (0.07–0.13)
PSAD after 1st MRI (ng/ml^2) (median, IQR)	0.10 (0.06–0.13)
PSAD (1st MRI) >0.15 (ng/ml^2)	9 (15.8%)
PSA DT (months) (median, IQR)	26 (73.5–104.5)
PSA velocity (ng/dL/y) (median, IQR)	0.23 (0.43–1.08)
Prostate volume (ml) (median, IQR)	72 (50–97)
SWOP (median, IQR) any PCa risk 1 csPCA risk 1 any PCa risk 2 csPCA risk 2	 0.07 (0.06–0.10) 0.01 (0.01–0.02) 0.065 (0.06–0.20) 0.02 (0.01–0.08)

N – number; MRI – magnetic resonance imaging; IQR – interquartile range; DRE – digital rectal examination; PSA – prostate-specific antigen; PSAD – PSA density; PSA DT – PSA doubling time; PCa – prostate cancer; csPCa – clinically significant prostate cancer; SWOP – Prostate Cancer Research Foundation Score

Table 3. *Post MRI prostate biopsy features*

Variables	
Biopsy type transperineal transrectal	 10 (13.7%) 63 (86.3%)
N. of cores (median, IQR)	24 (14–24)
Positive biopsy	22 (30.1%)
GS 6 7 8 9 10	 14 (63.6%) 3 (13.6%) 1 (4.5%) 3 (13.6%) 1 (4.5)
any PCa	22 (30.6%)
csPCa	8 (11%)
SWOP any PCa risk after MRI csPCa risk after MRI	 0.07 (0.06; 0.10) 0.01 (0.01; 0.02)

N – number; IQR – interquartile range; GS – Gleason score; PCa – prostate cancer; csPCa – clinically significant prostate cancer; MRI – magnetic resonance imaging; RARP – robot-assisted radical prostatectomy

Table 4. *Post-mpMRI biopsy results stratified by indication*

	Biopsy naive – 0	Previous biopsy – 1	P value
Time between MRI and biopsy, days (median, IQR)	150 (59.5–346)	313.5 (176–389.8)	0.067
Biopsy type transperineal transrectal	 30 (81.1%) 6 (16.2%)	 4 (11.1%) 32 (88.9%)	 0.48
Positive biopsy	13 (35.1%)	10 (27.8%)	0.50
GS 6 7 8 9 10	 8 (61.5%) 2 (15.4%) 1 (7.7%) 2 (15.4%) 0 (0%)	 6 (66.7%) 1 (11.1%) 0 (0%) 1 (11.1%) 1 (11.1%)	 0.68
any PCa	13 (35.1%)	9 (25.7%)	0.94
csPCa	5 (13.5%)	3 (8.3%)	0.52
SWOP any PCa risk after MRI (median, IQR)	0.09 (0.07–0.15)	0.06 (0.06–0.08)	0.08
SWOP csPCa risk after MRI (median, IQR)	0.02 (0.01–0.02)	0.01 (0.01–0.01)	0.21

mpMRI – multiparametric magnetic resonance imaging; IQR – interquartile range; GS – Gleason score; PCa – prostate cancer; csPCa – clinically significant prostate cancer; SWOP – Prostate Cancer Research Foundation Score

Table 6 shows the results of uni- and multivariate models for clinically significant PCa. No significant predictors of csPCa diagnosis were found, in particular SWOP risk scores were not useful to predict csPCa diagnosis in this cohort.

Finally, complete data was available for those patients who underwent radical prostatectomy in the present cohort (n = 13), as shown in Table 7. A total of 5/13 patients (38.5%) were found to have non-organ confined disease with extraprostatic extension at definitive histopathology; while 6/13 patients (46.2%) had a Grade Group 4.

DISCUSSION

In the present study, 73 men underwent 24-core biopsy after a negative mpMRI, with 30.1% (22/73) of overall pCa detection and 11% (8/73) of csPCa. In this single institution study patients were included if there were no suspicious lesions on pre-biopsy mpMRI as defined by PI-RADS v2 criteria (PI-RADS ≤2). Patients with prior PCa or surgi-

Table 5. *Uni- and multivariate regression for any PCa diagnosis at biopsy*

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age at 1st MRI	1.06	0.99–1.15	0.11	1.09	0.98–1.2	0.11
5-ARI (yes vs no)	2.47	0.46–13.36	0.29	7.67	0.97–60.7	0.053
PSAD (≥0.15 vs <0.15)	0.83	0.15–4.57	0.83	0.47	0.06–3.47	0.46
PSA velocity	1.07	0.82–1.41	0.62	/	/	/
PSA DT	1.00	0.99–1.001	0.88	/	/	/
Prostate volume	0.99	0.98–1.01	0.86	0.98	0.96- 1.01	0.19
Previous biopsy	0.64	0.23–1.76	0.39	0.52	0.13- 2.04	0.34
Time between MRI and biopsy	1.001	0.99; 1.003	0.44	/	/	/

OR – odds ratio; 95% CI – 95% confidence level; MRI – magnetic resonance imaging; 5-ARI – 5-alpha reductase inhibitors; PSAD – prostate-specific antigen density; PSA DT – prostate-specific antigen doubling time

Table 6. *Uni and multivariate regression for clinically significant PCa diagnosis at biopsy*

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age at 1st MRI	1.08	0.97–1.21	0.17	1.16	0.97–1.38	0.11
5-ARI (yes vs no)	1.71	0.17; 16.85	0.64	/	/	/
PSAD (≥0.15 vs <0.15)	1.38	0.14–13.9	0.79	0.72	0.05–11.04	.81
PSA velocity	1.03	0.63- 1.69	0.89	/	/	/
PSA DT	1.001	1–1.002	0.21	/	/	/
Prostate volume	0.97	0.94–1.00	0.048	0.98	0.94–1.02	0.33
Previous biopsy (yes vs no)	0.58	0.13–2.64	0.48	0.37	0.05–2.78	0.33
Time between MRI and biopsy	1.002	0.99–1.005	0.26	/	/	/

OR – odds ratio; 95% CI – 95% confidence level; MRI – magnetic resonance imaging; 5-ARI – 5-alpha reductase inhibitors; PSAD – prostate-specific antigen density; PSA DT – prostate-specific antigen doubling time

Table 7. *Features of the patients who underwent radical prostatectomy*

Variables	
RARP	13 (100%)
pT	
1b	1 (7.7%)
2a	5 (38.5%)
2c	2 (15.4%)
3a	4 (30.8%)
3b	1 (7.7%)
pN	
0	12 (92.3%)
1	1 (7.7%)
EPE	5 (41.7%)
PSM	6 (46.2%)
Grade Group	
1	2 (15.4%)
2	5 (38.5%)
4	6 (46.2%)

RARP – robot assisted radical prostatectomy; EPE – extraprostatic extension; PSM – positive surgical margins; RARP – robot-assisted radical prostatectomy

cal benign prostatic hyperplasia (BPH) treatment were excluded because that could alter PSA levels and/or MRI findings, introducing potential confounders. Patients with mpMRI performed elsewhere were also excluded to maintain MRI protocol uniformity and enhance the internal validity of the findings.

The use of SWOP risk score and the 24-core biopsy protocol are distinctive features of the present study. A nMRI has the potential to lower suspicion of aggressive prostate cancer and to avoid unnecessary biopsies. However, csPCa undetected by mpMRI are still a large portion (10–15%) of the total MRI examinations [12, 13, 14]. Therefore, the interpretation of a nMRI demands the awareness of missing csPCa in a certain number of patients.

Several reports in the literature have attempted to validate the predictive value of a nMRI. In a cohort of 75 men, nMRI was highly predictive of the absence of cancer on systematic biopsy, and only one man (1.3%) had GS 3+4 cancer on biopsy [15].

These findings are in contradiction with our results since the 11% of the nMRI had a csPCa requiring a definitive treatment of the primary tumor. Of note, the study by Wysock et al. differs from ours in several aspects. First, 28% of the included patients were under active surveillance (and most GS 6 cancers were detected in this subgroup), whereas all patients with any previous diagnosis of pCa were excluded from the present study. Moreover, median PSA levels were lower in Wysock et al. (4.7 vs 6.4 in our cohort) and SWOP PCa risk score was not taken into account.

On the same issue, Panebianco et al. [16] reported on 1255 patients with negative mpMRI, either biopsy naïve or with previous negative biopsy. Overall, a 4.8% of csPCa were detected during follow-up. While clinical variables (PSA and PSAD) are comparable to the present report, only a fraction of the patients included in the cited study underwent prostate biopsy, therefore a direct comparison is not possible.

A recent systematic review analyzed the negative predictive value of mpMRI [12]. With the same definitions of nMRI and csPCa used in our study, the results show a 7–10% risk of clinically significant PCa after nMRI, although the data might be significantly variable depending on clinical setting, local situation and approach to post-MRI biopsy. However, this risk is certainly comparable to the 11% seen in the present study.

One advantage of the present study is that, besides the PCa diagnosis at prostate biopsy, a considerable percentage of patients received radical prostatectomy and whole-mount pathology was available for comparison.

Comparable findings were not reported in men specifically with nMRI, but rather in men with significant cancer detected on biopsy who underwent definitive treatment. In a recent meta-analysis by Goel et al., targeted biopsy was upgraded in 23.3% of the cases, whereas systematic biopsy had an upgrade rate of 42.7% at radical prostatectomy. The odds of GS upgrading at radical prostatectomy (RP) after systematic biopsy compared with fusion biopsy were 1.75 [17]. These results suggest that there is a real, but small, rate of higher-risk disease that is difficult to detect by mpMRI, potentially related to low tumor volume. Although mpMRI-targeted prostate biopsy may better predict pathology at radical prostatectomy than systematic prostate biopsy [17], these small, yet significant, cancer foci would be difficult to detect with the available biopsy technology and remain a topic of further investigation.

The main limitations of our study are due to the retrospective nature of the data collection. In particular, there is a possible selection bias for the men included in the study; patients included in the study may present with elevated clinical suspicion of csPCa who eventually underwent a prostate biopsy. In fact, not all men with negative MRI at our institution underwent a biopsy. However, complete clinical information was available for all patients (including those who did not undergo biopsy) and direct comparison of the biopsy and non-biopsy group found differences only in the absolute PSA value, while all the other variables, including the PSAD, PSA velocity (PSAV) and SWOP risk score did not show any significant difference.

Most saturation biopsies were transrectal. A potential limitation is the superior detection of csPCa of transperineal template-based saturation biopsy

to transrectal in the MRI target setting, when adjusted for number of cores and prostate volume [18]. Possible missing lesions in certain parts of the prostate (even with random 24 cores) cannot be excluded, especially in larger glands [18, 19]. However, the hypothesized advantage in PCa detection for random transperineal biopsies is unclear [20], especially in the MRI era.

Our ability to assess the true NPV of nMRI for csPCa is inherently limited by the sensitivity of systematic saturation biopsy to detect PCa. However, all patients of the included patients had a systematic 24-core biopsy, therefore reducing the sampling error in comparison to 12-core biopsy, which was used in the majority of the studies present in the current literature.

CONCLUSIONS

Our study reports approximately 11% (8/73) chance of detecting clinically significant prostate cancer with a systematic 24-core biopsy in patients with negative mpMRI.

The use of prostate-specific antigen, prostate-specific antigen density and suspicious DRE in the presence of prebiopsy negative magnetic resonance imaging could be useful factors to identify men with clinically significant prostate cancer who should undergo systematic biopsy. Specific predictive models addressing this setting would be useful.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

All procedures 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 standards.

DISCLAIMER

All included patients undergoing radical treatment provided written informed consent for surgery. 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. Institutional review board number was not required due to observational and retrospective nature of the study.

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