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# Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next?

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**Abstract**

***Background:*** Multiparametric magnetic resonance imaging (mpMRI) of the prostate has excellent sensitivity in detecting clinically significant prostate cancer (csPCa). Nevertheless, the clinical utility of negative mpMRI (nMRI) is less clear.
***Objective:*** To assess outcomes of men with nMRI and clinical follow-up after 7 yr of activity at a reference center.
***Design, setting, and participants:*** All mpMRI performed from January 2010 to May 2015 were reviewed. We selected all patients with nMRI and divided them in group A (naïve patients) and group B (previous negative biopsy). All patients without a diagnosis of PCa had a minimum follow-up of 2 yr and at least two consecutive nMRI. Patients with positive mpMRI were also identified to assess their biopsy outcomes.
***Outcome measurements and statistical analysis:*** A Kaplan-Meier analysis was performed to assess both any-grade PCa and csPCa diagnosis-free survival probabilities. Univariable and multivariable Cox regression models were fitted to identify predictors of csPCa diagnosis.
***Results and limitations:*** We identified 1545 men with nMRI, and 1255 of them satisfied the inclusion criteria; 659 belonged to group A and 596 to group B. Any-grade PCa and csPCa diagnosis-free survival probabilities after 2 yr of follow-up were 94% and 95%, respectively, in group A; in group B, they were 96%. After 48 mo of follow-up, any-grade PCa diagnosis-free survival probability was 84% in group A and 96% in group B (log rank $p < 0.001$). Diagnosis-free survival probability for csPCa was unchanged after 48 mo of follow-up. On multivariable Cox regression analysis, increasing age ($p = 0.005$) was an independent predictor of lower csPCa diagnosis probability, while increasing prostate-specific antigen (PSA) and PSA density (<0.001) independently predicted higher csPCa diagnosis probability. The prevalence of and positive predictive value for csPCa were 31.6% and 45.5%, respectively. Limitations include limited follow-up and the inability to calculate true csPCa prevalence in the study population.
***Conclusions:*** mpMRI is highly reliable to exclude csPCa. Nevertheless, systematic biopsy should be recommended even after nMRI, especially in younger patients with high or raising PSA levels.
***Patient summary:*** It is a matter of debate whether patients with negative multiparametric magnetic resonance imaging (mpMRI) of the prostate could obviate the need to perform a systematic biopsy. In this report, we looked at the outcomes of patients with negative mpMRI and midterm clinical follow-up at a reference center. We found mpMRI to be highly reliable to exclude significant prostate cancer; nonetheless, systematic biopsy must still be recommended after negative mpMRI in patients with high clinical suspicion of prostate cancer.


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## 1. Introduction

The role of multiparametric magnetic resonance imaging (mpMRI) in prostate cancer (PCa) management has been constantly growing during the past decade. It is currently recommended to target lesions in men suspected of harboring PCa despite negative biopsies [1], and it is increasingly being used to guide biopsies, thanks to the high accuracy of mpMRI-targeted biopsy techniques [2,3]. Nonetheless, a systematic use of mpMRI as a triage test in patients with suspicion of PCa is still a matter of debate. The rationale of such a strategy lies on the limitations of PCa screening and diagnosis, which entails offering systematic transrectal ultrasound-guided biopsy (SB) to men presenting high levels of serum prostate-specific antigen (PSA) and/or a suspicious digital rectal examination (DRE). First, many men without PCa manifest elevated PSA levels and undergo unnecessary biopsies, which often detect clinically insignificant cancers [4]. In addition, SB may miss up to 20% of cancers [5]. Repeat biopsies are often needed to establish the diagnosis, but they can lead to overdetection and overtreatment of insignificant cancers, with a limited detection rate [6]. On the contrary, the risk of missing clinically significant PCa (csPCa) with SB may turn into undertreatment when active surveillance (AS) is considered [7]. In this context, mpMRI is potentially enticing as a triage test since it has been demonstrated to identify suspicious lesions that frequently results in the detection of a higher Gleason score (GS) on prostate biopsy [8,9]. Conversely, men with negative mpMRI (nMRI) findings appear to be at low risk of harboring significant prostatic disease. Several studies reported a high (>90%) negative predictive value (NPV) of mpMRI to exclude csPCa [10,11], and the PROMIS trial found an NPV of 89% for csPCa (which dropped to 72–76% when different definitions of csPCa were used) using template mapping biopsy as a reference standard [12], but there is paucity of data concerning the intermediate- and long-term follow-up of patients with nMRI. Moreover, according to a systematic review, no definitive conclusion about the NPV of mpMRI can be drawn at present, as several issues remain to be addressed. Above all, there is great variability in PCa prevalence in contemporary literature [13]. The aim of this study was, therefore, to assess the outcomes of patients with nMRI for PCa and clinical follow-up, after 7 yr of activity at our reference center.

## 2. Patients and methods

### 2.1. Study design and population

After institutional review board approval of this retrospective study, the reports of prostate mpMRI studies performed between January 2010 and May 2015 were reviewed. Standards for Reporting Diagnostic Accuracy guidelines were followed [14]. A proportion of the study population was included in a previous analysis [9]. Our patient selection criteria were the availability of mpMRI examinations of the prostate performed at our institution. Overall, 4952 consecutive patients with suspicion of PCa, based on elevated PSA levels, family history, or DRE, underwent mpMRI as per institution protocol. Among them, there were biopsy-naïve men, patients with previous negative biopsies, and patients on AS protocols. Reports of men with nMRI were reviewed and considered for this study. Two main subgroups were identified: group A included naïve men and group B included men with previous negative biopsy. A proportion of patents in group A underwent SB straight after imaging, while the remaining did not. All patients were followed with serial PSA measurements and DRE, under the supervision of a multidisciplinary team (MDT) and underwent repeat biopsy (group B and those in group A who underwent SB after the first nMRI) or SB (patients in group A who did not receive SB straight after imaging) when clinically indicated. In particular, patients in group A with no biopsy after the first nMRI underwent SB if there was still high clinical suspicion based on high or rising PSA/PSA density (PSAD) levels and/or other clinical features (family history, young age, and DRE). In absence of these concerns, patients were counseled about the potential risks of both under- and overdiagnosis. In most of the cases, the final decision to omit biopsy was a patient's preference. Patients in both groups were included in the analysis to assess the risks of developing any-grade PCa and csPCa after nMRI if they had at least a second nMRI (8–12 mo apart from the first) and a minimum MDT follow-up of 24 mo at our center, except for patients who were diagnosed with PCa after the first nMRI.

Reports of men with positive or uncertain mpMRI studies were also reviewed to assess PCa prevalence in our population, cancer detection rate of mpMRI, and its positive predictive value.

### 2.2. Multiparametric MRI imaging protocol

MRI of the pelvis, focused on the prostate gland, was performed using a 3-T magnet equipped with a phased-array coil and an endorectal coil (EC). The EC was progressively used less, in favor of a 32-channel phased-array coil, since images with comparable quality could be obtained [15]. Details about imaging protocol and use of EC are listed in Supplementary Table 1.

### 2.3. Multiparametric MRI interpretation

The images were evaluated in consensus by two genitourinary radiologists, with 13 and 2 yr of experience at the beginning of the study period. Starting from 2012, mpMRI studies were assessed using the Prostate Imaging Reporting and Data System (PI-RADS) score [16], according to which an examination is considered negative when assigned a score of 1 or 2. Examinations performed earlier were classified as negative when the report stated that no suspicious focus was found. Quantitative analysis was not considered as part of the definitive report since it was not performed in all patients.

### 2.4. Prostate biopsy and csPCa definition

Patients with nMRI in group A underwent standard SB, with 12–18 cores (median 14) biopsied for each patient, within 30 d from the first nMRI or as soon as indicated by MDT. Patients in group B underwent repeat saturation biopsy when indicated. Patients with uncertain or positive mpMRI results underwent SB with additional cognitive fusion-targeted biopsy cores on suspicious areas, mpMRI-targeted biopsy using a transrectal ultrasound/MRI fusion biopsy system or in-bore mpMRI-guided biopsy, within 30 d from mpMRI.

According to EAU-ESTRO-SIOG guidelines [1], selection criteria for insignificant cancer, eligible for AS, included the following: GS 6, clinical stage T1c or T2a, PSA <10 ng/ml, PSAD <0.15 ng/ml, and fewer than two to three positive cores with <50% cancer involvement on each positive core. After radical prostatectomy (RP), PCa was defined as low risk if stage was pT2c or lower, GS <7, and tumor volume <0.5 $cm^3$ [17].

### 2.5. Follow-up outcomes and statistical analysis

To assess any-grade PCa and csPCa diagnosis-free survival probabilities in both groups, a Kaplan-Meier analysis was performed. Any-grade PCa and csPCa diagnosis-free survival was calculated from the date of mpMRI examination to the diagnosis of PCa or censored at the last follow-up evaluation (at least 24 mo after the first nMRI). Univariable and multivariable Cox regression models were used to identify independent predictors of subsequent diagnosis of csPCa.

All data were analyzed using the Statistical Package for Social Science (SPSS; ver. 22.0; SPSS Inc., IBM Corp; Armonk, NY, USA). All statistical analyses were two sided and statistical significance was defined as $p < 0.05$.

## 3. Results

### 3.1. Study population

During the study period, 1545 (31%) of all patients underwent nMRI; 290 (19%) of these were excluded for various reasons (Fig. 1). A total of 1255 men with nMRI were enrolled, 659 (53%) in group A, and 596 (47%) in group B. Table 1 summarizes clinical characteristics of each group.

As for the remaining mpMRI reviewed, 3407 had uncertain or positive findings at imaging; of these, 985 (29%) were not followed at our institution. The clinical characteristics and biopsy outcome of the remaining 2422 were collected in a START-consistent database [18] and are listed in Supplementary Table 2.

### 3.2. Biopsy and follow-up outcomes

In group A, 395/659 (60%) underwent SB within 30 d after initial nMRI and 12 patients were diagnosed with PCa, all being csPCa. After a median follow-up of 38 (interquartile range [IQR] 29–48) mo, 85 any-grade PCa cases were diagnosed in group A, with 36 being csPCa (Fig. 2). The 24 csPCa cases diagnosed in this subgroup during follow-up were found in the 264/659 (40%) men who did not undergo SB after the first nMRI in group A. After a median follow-up of 60 (IQR 48–70) mo, 78 any-grade PCa cases were diagnosed in group B, with 24 being csPCa.

Any-grade PCa diagnosis-free survival probability at 24 mo was 94% in group A and 96% in B; at 48 mo, it was 84% in group A and 96% in group B (Fig. 3A). CsPCa diagnosis-free

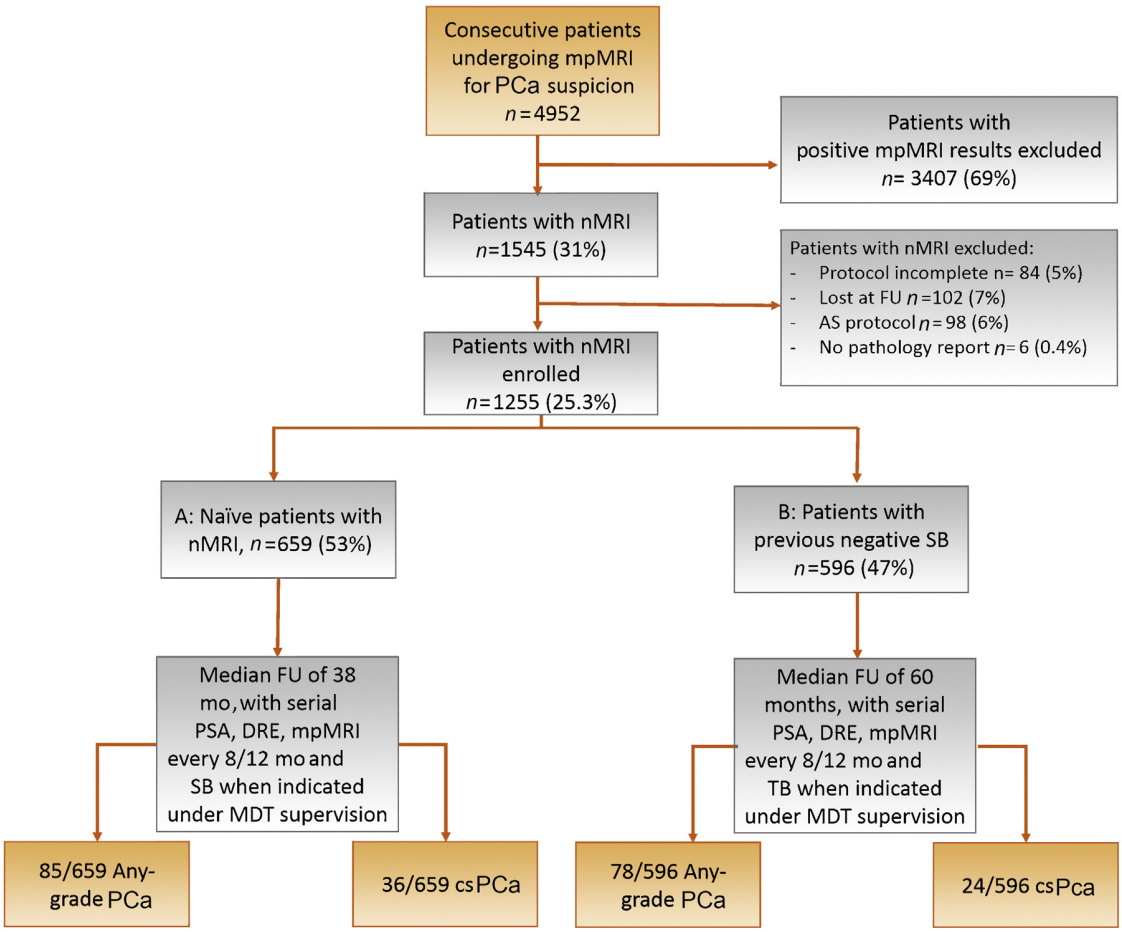


**Fig. 1 – Flowchart of study design. AS = active surveillance; csPCa = clinically significant prostate cancer; DRE = digital rectal examination; FU = follow-up; MDT = multidisciplinary team; mpMRI = multiparametric magnetic resonance imaging of the prostate; nMRI = negative mpMRI examination; NPV = negative predictive value; PCa = prostate cancer; PSA = prostate-specific antigen; SB = systematic transrectal ultrasound-guided biopsy; TB = template saturation biopsy.**

**Table 1 – Baseline clinical and demographic data, and follow-up length of the two subgroups**

| Variable | A: naïve patients ($n$ = 659) | B: patients with previous negative SB ($n$ = 596) |
|---|---|---|
| Age | 66 (62–69) | 68 (60–72) |
| PSA (ng/ml) | 5.9 (3.9–7.6) | 5.6 (3.2–7.8) |
| Prostate volume on MRI (ml) | 50 (42–68) | 60 (38–73) |
| PSA density | 0.11 (0.08–0.14) | 0.10 (0.08–0.15) |
| Family history, $n$ (%) | 71 (11) | 44 (7) |
| Positive DRE | 64 (10) | 54 (9) |
| Follow-up (mo) | 38 (29–48) | 60 (48–78) |

DRE = digital rectal examination; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; SB = systematic transrectal ultrasound-guided prostate biopsy.

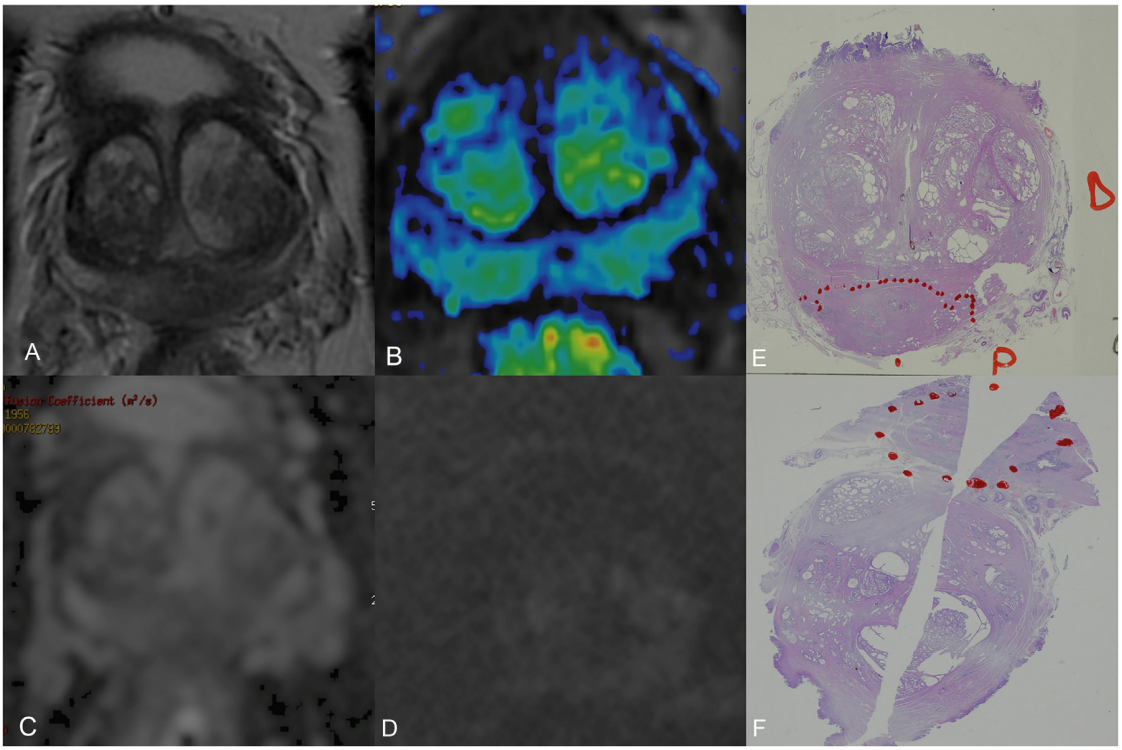


**Fig. 2 – Naïve 60-yr-old man with a PSA of 6.9 ng/ml. (A) T2-weighted sequence from mpMRI examination shows a circumscribed basal hypointense focus, which may be consistent with central zone appearance. (B) Perfusion color map does not show early enhancement corresponding to the focal finding on T2-weighted imaging. (C) Apparent diffusion coefficient map and (D) diffusion-weighted imaging with *b* value set at 2000 s/mm$^2$ failed to show suspicious areas at the same level. According to PI-RADS version 2, the overall score should be 2. This patient, because of rising PSA (7.8 after 3 mo), underwent standard systematic transrectal ultrasound-guided biopsy, which showed a left posterolateral paramedian microfocus of prostate cancer (Gleason score 4 + 4). (E and F) The patient underwent radical prostatectomy, which showed a paramedian posterior adenocarcinoma of the prostate with invasion of seminal vesicles, which corresponded to the suspicious area on T2-weighted imaging. Final diagnosis was as follows: adenocarcinoma of the prostate, Gleason score 9 (5 + 4), pT3b, pN1—group V. Plausible reason for false negative at mpMRI was predominant cribriform morphology. mpMRI = multiparametric magnetic resonance imaging of the prostate; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.**

survival probability at 24 mo was 95% in group A and 96% in group B; at 48 mo, the values remained unchanged (Fig. 3B).

After a median follow-up of 52 (IQR 37–68) mo (entire cohort), there were no cases of disease progression and no patient died because of PCa. Median follow-up for patients who were not diagnosed with any-grade PCa was 39 (IQR 30–48) mo in group A and 61 (IQR 49–71) mo in group B. Median follow-up for patients who were not diagnosed with csPCa was 39 (IQR 30–48) mo in group A and 60 (IQR 48–78) mo in group B.

Clinical and cancer characteristics of all patients diagnosed with csPCa, including possible reasons of nMRI in patients undergoing RP, are listed in Table 2.

On univariable analysis, age, PSA, PSAD, and previous negative biopsy were significant predictors of subsequent csPCa diagnosis in men with nMRI. On multivariable Cox regression analysis, all these variables except for the

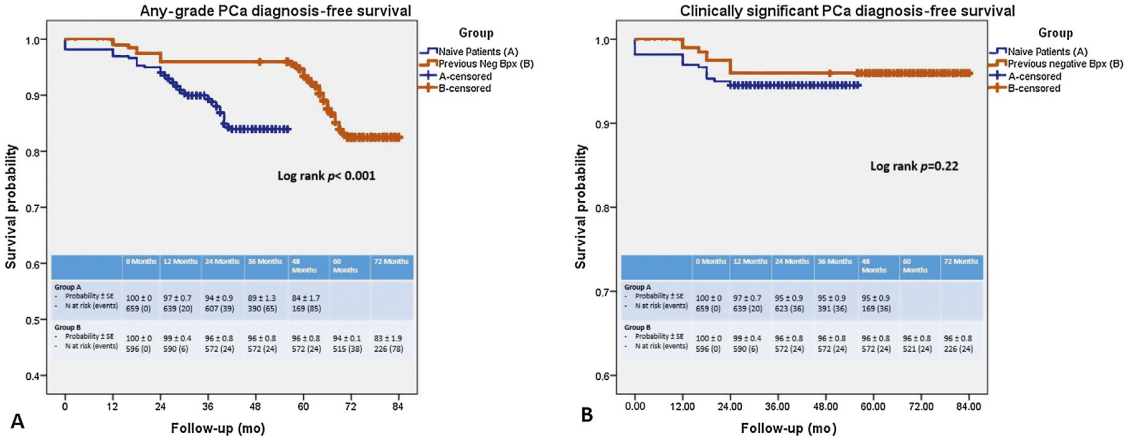


**Fig. 3 – Kaplan-Meier analysis for the two subgroups: (A) any-grade PCa diagnosis-free survival function and (B) clinically significant PCa diagnosis-free survival function. Bpx = biopsy; Neg = negative; PCa = prostate cancer; SE = standard error.**

**Table 2 – Clinical characteristics and biopsy or radical prostatectomy outcome of patients with clinically significant prostate cancer and negative multiparametric MRI**

| Patients with nMRI diagnosed with csPCa ($n$ = 60) | |
|---|---|
| Median (IQR) age (yr) | 64 (58–67) |
| Median (IQR) PSA level (ng/ml) | 7.3 (6.2–8.8) |
| Median (IQR) prostate volume on MRI (ml) | 48 (32–58) |
| Median (IQR) PSA density (ng/ml/ml) | 0.16 (0.13–0.27) |
| Gleason score, $n$ (%) | |
| 6 | 7 (12) |
| 3 + 4 | 25 (42) |
| 4 + 3 | 18 (30) |
| ≥8 | 10 (16) |
| Patients undergoing RP, $n$ (%) | 36 (60) |
| Reason for false negative, $n$ (%) | |
| BPH | 11 (31) |
| Prostatitis | 5 (14) |
| Small (≤0.5 ml) tumor in anterior horn | 11 (31) |
| Mucinous adenocarcinoma | 1 (2) |
| Predominant cribriform morphology | 8 (22) |

BPH = benign prostatic hyperplasia; csPCa = clinically significant prostate cancer; IQR = interquartile range; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; RP = radical prostatectomy.

**Table 3 – Multivariable Cox regression analysis to identify predictors of subsequent PCa diagnosis in patients with a previous negative mpMRI**

| Variables | HR | 95% CI | $p$ value |
|---|---|---|---|
| PSA | 1.21 | 1.1–1.32 | <0.001 |
| PSAD | 7.57 | 2.73–21 | <0.001 |
| Previous negative SB | 1.01 | 0.53–1.93 | 0.97 |
| Age | 0.93 | 0.89–0.98 | 0.005 |

CI = confidence interval; HR = hazard ratio; mpMRI = multiparametric magnetic resonance imaging of the prostate; PCa = prostate cancer; PSA = prostate-specific antigen; PSAD = PSA density; SB = systematic biopsy.

previous negative biopsy were independent predictors (Table 3).

### 3.3. *Positive mpMRI outcomes*

Of the 2422 patients with positive mpMRI results, 1827 (75%) were diagnosed with PCa and 1103 (46%) had csPCa. The prevalence of csPCa was 32%. Biopsy results are listed in Supplementary Table 2.

## 4. Discussion

Multiparametric MRI of the prostate has earned its role in the setting of targeting biopsy after a first negative SB [1] thanks to intense investigation [10,19,20] in the past decade. However, it is still unclear if its NPV is sufficiently high to possibly avoid biopsy in men with nMRI.

Several studies attempted to validate the clinical utility of nMRI. Villers et al [21] reported NPVs of 85% and 95% for foci >0.2 and >0.5 $cm^3$, respectively, compared with histopathology. Subsequent studies reported a "clinical NPV" for csPCa of 90% at 5-yr follow-up after initial nMRI and of 99% in men undergoing mpMRI before SB [11,22]. A recent meta-analysis showed that mpMRI has a median NPV of 88% for csPCa, for a median detection rate of csPCa of 33% [13]. Nevertheless, several crucial issues for a more definitive assessment of NPV remain to be addressed, with the great variability in csPCa prevalence among the different cohorts (which directly influences NPV), the lack of standardization of the population referred to prostate biopsy, and the variability of definitions of csPCa being most important.

According to other authors, mpMRI does not have a very high NPV. Filson et al [23] reported an NPV of nMRI of 54%, with 16% of men in their cohort (38/244) being diagnosed with csPCa. However, 48% (116/244) of their patients had a history of positive biopsy. Another report showed that 60% of patients with nMRI studies had unfavorable pathology after RP [24]. Nonetheless, all patients in that cohort underwent RP, with possible selection bias.

Our retrospective study after 7 yr of clinical experience showed that any-grade PCa and csPCa diagnosis-free survival were both 96% in men with nMRI and previous

negative SB (group B) after 48 mo of follow-up. This outcome strengthens previous findings [8,11,22] that showed mpMRI to be highly reliable in excluding significant disease in men with previous negative biopsy and are in accordance with the findings of the more recent papers by Ahmed et al [12] and Schouten et al [25]. On the contrary, in naïve patients (group A), all PCa and csPCa diagnosis-free probabilities at 48 mo were 84% and 95%, respectively, showing that the addition of SB improves all PCa and csPCa diagnosis-free survival from 84% to 96% and from 95% to 96%, respectively. However, on multivariable analysis, a previous negative SB was not an independent predictor of subsequent csPCa diagnosis, while age, PSA, and PSAD were all independent predictors, with PSAD being the strongest (hazard ratio: 7.57). Moreover, csPCa diagnosis-free survival probabilities were not significantly different in the two groups. From a clinical standpoint, an SB can be considered after an nMRI in patients with high PSA and PSAD; this is consistent with the findings of a previous research [26]. Besides, a 5% risk of developing a csPCa during follow-up, compared with a reported NPV of SB of 74% or lower[12], might be considered acceptable and clinically appropriate, and would prompt PSA monitoring rather than biopsy as a reasonable argument for patients' counseling.

With regard to clinical and pathologic features of csPCa developed after nMRI in patients who underwent RP, we found, as previously reported, that prostatitis and benign prostatic hyperplasia can mask PCa [22] and that small tumors near the anterior horn can be missed at mpMRI [27], possibly indicating that the reader experience is extremely important to avoid false negative, as also shown by the PROMIS trial, which was based on quality control of mpMRI and systematic training of radiologists [12].

Finally, the relatively high frequency of high-grade PCa with cribriform morphology in patients with nMRI who underwent RP highlights the limitations of current prostate mpMRI. According to recent reports [28], PCa with predominant cribriform morphology is often invisible at imaging, and mucinous adenocarcinoma, although rarer, is also not readily visible on diffusion-weighted imaging [29], which is considered the "dominant sequence" by PI-RADSv2. In this regard, quantitative analysis, although not considered in the present study, has shown promising results in peripheral zone tumor characterization [30].

The major strengths of our study are the large patient population included in the analysis and the "real-life" setting, since our data are based on image interpretation performed during clinical routine. The use of at least one confirmatory nMRI is also pivotal, as without it a substantial proportion of men (at least 20%) would have undergone repeat biopsy, with limited csPCa detection rate (12%), according to a contemporary series [6].

This study has several limitations. First of all, a "true" NPV could not be calculated because of the inherent limits of this approach: where no whole mount of the prostate was done, in the majority of patients, no true negative can exist.

Besides, not all patients underwent prostate biopsy, this decision being supported by an MDT, which is not always available in clinical routine. A possible selection bias in this sense could have maximized the detection of csPCa. Second, as not all patients with positive mpMRI were followed at our center, the true prevalence of PCa of the original cohort could not be assessed. Finally, in populations with a higher prevalence of csPCa, in cohorts with longer follow-up, and when other definitions of csPCa are applied, the risk of csPCa development may be underestimated.

## 5. Conclusions

In our study, we demonstrated that csPCa diagnosis-free survival probability after 48 mo of follow-up was 95% and 96% in naïve men and patients with previous negative biopsy, respectively. As a result, after an nMRI, a noninvasive follow-up based on confirmatory MRI and PSA measurements is a viable option for selected patients. Nevertheless, SB cannot be routinely omitted after nMRI, especially in younger patients with strong clinical suspicion of PCa (rising PSAD), given the possibility of missing clinically significant, MRI-silent tumors.

***Author contributions:*** Valeria Panebianco had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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*Acquisition of data:* Campa, Grompone.
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*Drafting of the manuscript:* Barchetti.
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*Statistical analysis:* Indino, Del Monte, Barchetti.
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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.03.007.

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