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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].

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