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Bioptic prostatic inflammation correlates with false positive rates of multiparametric magnetic resonance imaging in detecting clinically significant prostate cancer

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Introduction The aim of this article was to determine the impact of bioptic prostatic inflammation (PI) on the false positive rate of multiparametric magnetic resonance imaging (mp-MRI) in detecting clinically significant prostate ancer (csPCa).

Material and methods Our prostate biopsy database was queried to identify patients who underwent mp-MRI before PB at our institution. A dedicated uropathologist prospectively assessed bioptic PI using the Irani scores. We evaluated the association between mp-MRI findings, bioptic Gleason grade (GG) and aggressiveness of PI, and PCa detection.

Results In total, 366 men were included. In patients with Prostate Imaging Reporting and Data System (PIRADS) 4-5 lesions, the csPCa (GG ≥2) rate was significantly higher in those with low-grade than in those with high-grade PI (36% vs 29.7%; p = 0.002), and in those with low-aggressive than in those with high-aggressive PI (37.7% vs 30.1%; p = 0.0003). The false positive rates of PIRADS 4–5 lesions for any PCa were 34.2% and 57.8% for low- and high-grade PI, respectively (p = 0.002); similarly, they were 29.5% and 59.4% for mildly and highly-aggressive PI (p = 0.0003). Potential study limitations include its retrospective analysis and single-center study and lack of assessment of the type of PI.

Conclusions Bioptic PI directly correlates with false positive rates of mp-MRI in detecting csPCa. Clinicians should be aware that PI remains the most common pitfall of mp-MRI.

Key Words: prostate cancer ‹› prostatic inflammation ‹› multiparametric magnetic resonance imaging ‹› prostate biopsy

INTRODUCTION

Prostate cancer (PCa) screening using prostate-specific antigen (PSA), has been shown to reduce PCa mortality [1] but PSA is not specific for PCa. Indeed, benign conditions such as prostatic inflammation (PI) and benign prostatic hyperplasia (BPH) can increase PSA levels leading to a large number of negative prostate biopsies (PBs) or to overdiagnosis of indolent cancers that may result in overtreatment with significant morbidity [2].

To reduce the rate of negative PBs as well as the risk of overdiagnosis and overtreatment of indolent PCa, current guidelines recommend using pre-biopsy multiparametric magnetic resonance imaging (mpMRI) [3].

Although level 1 evidence is now available supporting the use of mpMRI target biopsy to improve the

detection of clinically significant PCa (csPCa), defined as Gleason grade (GG) t2 according to International Society of Urological Pathology (ISUP) recommendations [4], in biopsy-naive and repeat-biopsy settings, mpMRI has some limitations. First, in a recent Cochrane meta-analysis which compared mpMRI to template biopsies (>20 cores) in biopsy-naive and repeat-biopsy settings, mpMRI had a pooled sensitivity of 0.91 (95% CI: 0.83–0.95) but a low pooled specificity of 0.37 (95% CI: 0.29–0.46) for ISUP grade t2 cancers with up to 44% (95% CI: 38 to 50%) of the patients being false positive [5]. Second, despite technological advances in MRI scanner technology, and the effort of the Prostate Imaging Reporting and Data System (PI-RADS) Steering Committee to standardize parameters for image acquisition and radiology reports [6], mpMRI's inter-reader reproducibility remains moderate at best, which currently limits its broad use by non-dedicated radiologists [7].

The intrinsic physical properties of the image formation process using mpMRI can explain some of the limitations of this technique. Because the mpMRI image is dependent upon the cellular distribution and the mobility of the water molecules, it can be easily understood that certain non-neoplastic conditions may be misdiagnosed as neoplastic lesions when they are characterized by sufficiently large accumulations of isolated cells in a liquid medium as occurs in inflammatory processes or glandular atrophy [8].

The present study therefore aimed to determine whether grade and aggressiveness of PI, as histologically assessed by the Irani score [9], correlate with false positive rates of mpMRI in detecting csPCa at PB.

MATERIAL AND METHODS

Study population

After Institutional Review Board approval, we queried our prospectively maintained prostate biopsy database to identify patients who underwent mpMRI, PB, and Irani Scores assessment between April 2017 and February 2020. The study was part of a wider prospective, single center, observational study evaluating the role of intraprostatic inflammation in prostate cancer screening and treatment. The protocol was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent to take part was given by all participants.

mpMRI protocol and biopsy technique

Prostate mpMRI was performed in patients with PSA higher than 3.0 ng/ml and/or suspicious digital rectal examination (DRE). All exams were performed with a 1.5 Tesla MR scanner (Achieva, Philips Healthcare, Best, The Netherlands) using either a surface array coil (SENSE Flex surface), or an endorectal coil combined with a 16-channel surface coil (TORSO-XL coil). The mp-MRI protocol consisted of: A. T2-weighed images in axial, coronal and sagittal planes; B. T1-weighed images in axial plane; C. diffusion-weighted images in the axial plane (b-values 0–500–1000–1500/2000 sec/mm^2); D. dynamic contrast enhanced prostate MRI performed using a T1-weighted high resolution isotropic volume examination (THRIVE) on the axial plane with injection of 0.1 ml/kg of gadobutrol.

Two dedicated radiologists reported all the images according to PIRADS v2.0 recommendations [10].

PIRADS 1 and 2 lesions were considered to be negative. In these patients, a transrectal ultrasound guided standard PB was performed using our 18-core template [11].

Patients with a positive mpMRI (PIRADS 3,4,5 lesions) received additional three target cores from each mpMRI-suspicious lesion using an electromagnetic-tracked MRI/US fusion system (Navigo, UC-CARE, Yokneam, ISR) [12] followed by standard 18-core biopsy. All procedures were carried out by urologists using local non-infiltrative anesthesia [13, 14]. Additional information on mpMRI protocol and PB technique have been previously reported [15].

Pathology examination

A senior uropathologist (FS) prospectively reported all PB specimens according to the 2014 ISUP recommendations [4] and diagnostic criteria for high-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation of prostat [16]. ISUP Gleason-grade groups (GG) were reported per each core. Additionally, PI was assessed using the Irani Scores subsequently validated by Sciarra et al. [9, 17]. Specifically, the inflammatory infiltration grade was scored as 'G0' = no inflammatory cells, 'G1' = scattered inflammatory cell infiltrate within the stroma without lymphoid nodules, 'G2' = nonconfluent lymphoid nodules and 'G3' = large inflammatory areas with confluence of infiltrate. Inflammatory aggressiveness was graded as 'A0' = no contact between inflammatory cells and glandular epithelium (epithelium cells lining acini and ducts), 'A1' = contact between inflammatory cell infiltrate and glandular epithelium, 'A2' = interstitial inflammatory infiltrate associated with a clear but limited (less than 25% of the examined material) glandular epithelium disruption and 'A3' = glandular epithelium disruption on more than 25% of the examined material. Grading did not include the types of inflammatory cells (polymorpho-

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Variable	Overall N = 366	Benign N = 203	GG 1 N = 84	GG ≥2 N = 79	P value
Age	67 (61, 71)	65 (59, 70)	68 (62, 71)	69 (64, 73)	0.0002
PSA	5.9 (4.5, 9.0)	5.9 (4.7, 8.8)	5.2 (4.1, 8.2)	6.9 (4.9, 13.4)	0.005
Biopsy history, n (%)					
Biopsy naive	206 (56.3%)	98 (48.3%)	55 (65.5%)	53 (67.1%)	0.003
Previous negative	160 (43.7%)	105 (51.7%)	29 (34.5%)	26 (32.9%)	
DRE, n (%)					
Negative	221 (60.4%)	138 (68.0%)	55 (65.5%)	28 (35.4%)	<0.0001
Suspicious	145 (39.6%)	65 (32.0%)	29 (34.5%)	51 (64.6%)	
Prostate volume	57 (40, 76)	64 (50, 87)	50 (39, 67)	41 (33, 58)	<0.0001
Irani G, n (%)					
0–1	251 (68.6%)	125 (61.6%)	67 (79.8%)	59 (74.7%)	0.004
2–3	115 (31.4%)	78 (38.4%)	17 (20.2%)	20 (25.3%)	
Irani A, n (%)					
0	189 (51.6%)	88 (43.3%)	54 (64.3%)	47 (59.5%)	0.002
≥1	177 (48.4%)	115 (56.7%)	30 (35.7%)	32 (40.5%)	

N – number; GG – Gleason grade; PSA – prostate-specific antigen; DRE – digital rectal examination

nuclear leukocytes, lymphocytes, monocytes or plasma cells). For the analysis, scores G 0–1 (low-grade inflammation) and G 2–3 (high-grade inflammation) were grouped whereas inflammatory aggressiveness was categorized as present (A t1) or absent (A 0).

Statistical analysis

The primary objective of the present study was to compare any PCa (GG t1) and csPC (GG t2) detection rates of mpMRI in patients with and without PI. Descriptive statistics was reported for the overall population and according to PB results. Continuous variables are reported as median and interquartile range and tested by the Mann-Whitney U-test, whereas categorical variables are reported as rates and tested by the Fisher's exact test or the chi-square test, as appropriate.

PCa detection rates were then reported according to PI-RADS score in the overall population and in patients with and without PI according to the IRANI A and G scores.

Statistical analyses were performed using Stata-SE 14 (StataCorp LP, College Station, TX, USA). All tests were 2-sided with a significance level set at $p < 0.05$.

RESULTS

A total of 366 men were eligible for the present analysis; 84 (23%) were diagnosed with GG 1 PCa and 79 (21.6%) with csPCa (GG t2). Their clinical characteristics are summarized in Table 1. Overall, patients with csPCa were older, had greater PSA and smaller prostate volume than those with benign prostate. In agreement with our previous findings [18], high-grade inflammation was significantly more common in patients with benign prostate than in those with ISUP 1 and ISUP t2 PCa (38%, 20% and 25% respectively; $p = 0.004$). Highly aggressive inflammation was significantly more common in patients with benign prostate than in those with GG 1 and GG t2 PCa (57%, 36% and 40% respectively; $p = 0.002$).

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Pathology n (%)	PI-RADS 1-2 (N = 57)	PI-RADS 3 (N = 84)	PI-RADS 4 (N = 182)	PI-RADS 5 (N = 43)
Benign	48 (84.2%)	63 (75.0%)	75 (41.2%)	17 (39.5%)
GG 1	8 (14.0%)	20 (23.8%)	48 (26.4%)	8 (18.6%)
GG ≥2	1 (1.8%)	1 (1.2%)	59 (32.4%)	18 (41.9%)

PIRADS – Prostate Imaging Reporting and Data System; N – number; GG – Gleason grade

The association between mpMRI findings and PB outcome is summarized in Table 2. Since the rates of csPCa were 32% and 42% for PIRADS 4 and 5, respectively, mpMRI was falsely positive in 68% and 58% of PIRADS 4 and 5 cases, respectively.

Figures 1 and 2 show the association between grade and aggressiveness of PI, mp-MRI findings and PB results. In patients with PIRADS 4 and 5 lesions, the csPCa rate was significantly higher in those with low-grade than in those with high-grade PI (36% vs 29.7%; $p = 0.002$), and in those with mildly aggressive than in those with highly aggressive PI (37.7% vs 30.1%; $p = 0.0003$). The false positive rates of PIRADS 4 and 5 lesions for any PCa were 34.2% and 57.8% for low- and high-grade PI, respectively ($p = 0.002$); similarly, they were 29.5% and 59.4% for mildly and highly aggressive PI ($p = 0.0003$).

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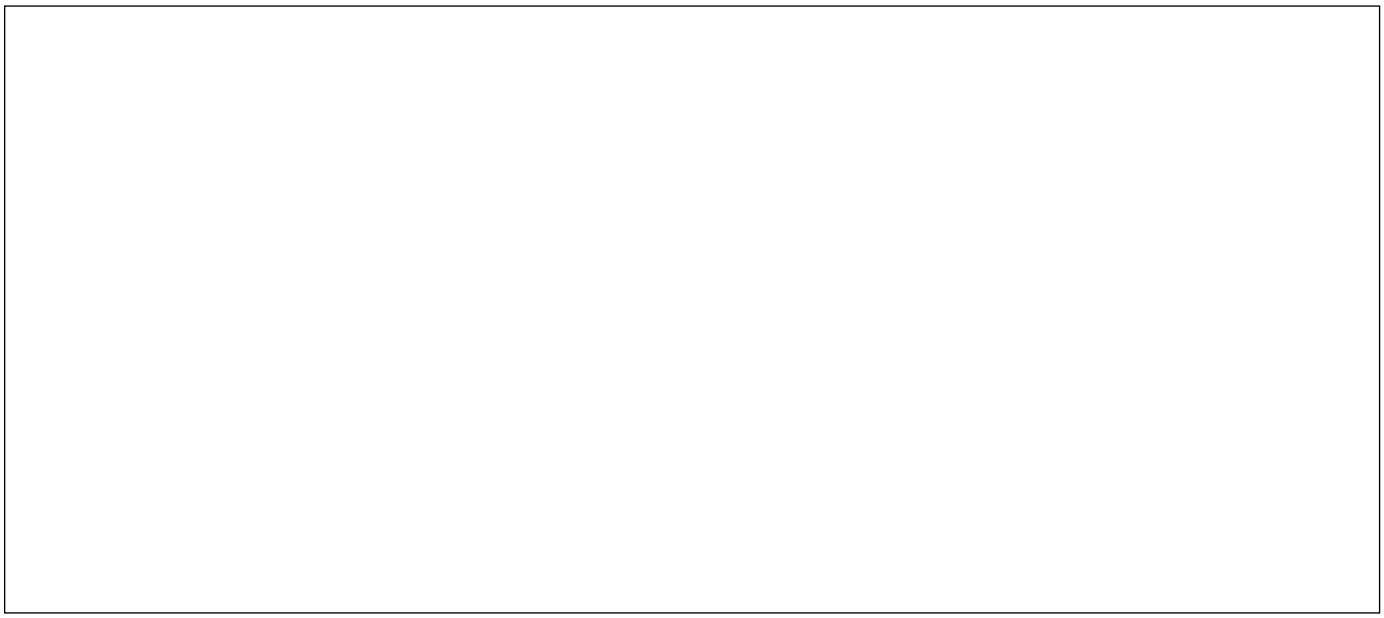

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DISCUSSION

Over the last years, mpMRI has gained popularity as the most efficient tool in predicting csPCa at PB [19]. Based on the results of the Cochrane metanalysis, the risk of missing csPCa in patients with a negative mp-MRI is very low [2.7% (95% CI: 1.5% to 5.1%)] [5]. If such a high sensitivity and negative predictive value (NPV) should allow clinicians to safely avoid or postpone PB in patients with a negative mp-MRI, its low specificity, nearly 44% (95% CI: 38 to 50%) of PIRADS 4 and 5 lesions are falsely positive, leads to a large number of unnecessary PBs [5].

There are two possible explanations for the latter finding. First, predictive values of a diagnostic test depend on disease prevalence; thus, mp-MRI in very low-risk patients would result in an inflation of false-positive findings and subsequent unnecessary biop-