



Association Between Tumor Multifocality on Multi-parametric MRI and Detection of Clinically-Significant Prostate Cancer in Lesions with Prostate Imaging Reporting and Data System (PI-RADS) Score 4

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OBJECTIVE	To investigate whether presence of multifocality on multi-parametric magnetic resonance imaging would increase the likelihood of detecting clinically-significant prostate cancer in a PI-RADS 4 lesion.
METHODS	We identified patients with at least 1 PI-RADS 4 lesion who underwent multi-parametric magnetic resonance imaging-ultrasound fusion prostate biopsy. Patients were grouped into 1 of 4 cohorts—cohort 1 (a PI-RADS 4 index lesion and an additional PI-RADS 2 or 3 lesion), cohort 2 (single lesion with PI-RADS 4), cohort 3 (2 or more PI-RADS 4 lesions), or cohort 4 (a PI-RADS 4 lesion and an index lesion with PI-RADS 5). We compared the rate of grade group (GG) ≥ 2 pathology on targeted biopsy of PI-RADS 4 lesions between cohorts and evaluated clinical and radiological factors associated with cancer detection.
RESULTS	The overall rate of GG ≥ 2 pathology in the PI-RADS 4 lesions was 35.2%. The rate of GG ≥ 2 pathology in the cohorts 1, 2, 3, and 4 was 21.7%, 36.3%, 49.1%, and 42.7%, respectively ($P < .001$). On multivariable analysis, age (OR1.06, $P < .001$), clinical stage T2 (OR1.59, $P = .03$), prostate-specific antigen density (OR1.43, $P < .001$), peripheral zone lesion (OR1.62, $P = .04$), and study cohort (cohort 2 vs 1, OR1.93, $P = .006$; and cohort 3 vs 1, OR3.28, $P < .001$) were significantly associated with the risk of GG ≥ 2 in the PI-RADS 4 lesion.
CONCLUSION	On targeted biopsy of the PI-RADS 4 lesions, the proportion of GG ≥ 2 pathology is approximately 35%. Rate of GG ≥ 2 detection in PI-RADS 4 lesions might differ based on their location, multifocality, and PI-RADS classifications of other lesions identified. UROLOGY 134: 173–180, 2019. © 2019 Elsevier Inc.

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Conflicts of Interest: Soroush Rais-Bahrami serves as a consultant for Philips/InVivo Corp, Genomic Health Inc, and Blue Earth Diagnostics. Preston Sprenkle serves as a consultant for Boston Scientific and GenomeDx Biosciences.

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Multiparametric magnetic resonance imaging (mpMRI) of the prostate with subsequent targeted biopsy has now become an essential tool in the diagnostic armamentarium for prostate cancer detection and localization.^{1,2} Recent multi-center clinical trials have confirmed a superior diagnostic yield of mpMRI followed by targeted biopsy relative to standard transrectal ultrasound (TRUS) template biopsy in terms of identifying clinically-significant prostate cancer (csPCa) while reducing the total number of prostate biopsies.^{3,4} According to the Prostate Imaging-Reporting and Data System version 2, prostate lesions found on mpMRI are graded from 1 to 5, where higher imaging suspicion scores are associated with a higher risk of csPCa.⁵ Nonetheless, a high suspicious lesion

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of PI-RADS 4 has been associated with a substantial false-positive detection rate (60%-80%); this challenges the criteria for assigning lesions to this assessment category.^{6,7} Accordingly, some investigations have sought to identify the imaging characteristics within the PI-RADS 4 cohort to further risk stratify these lesions.⁸⁻¹⁰

Prostate cancer is often found to be multifocal when evaluating radical prostatectomy specimens. Although the literature reports that up to one-third of foci harboring csPCa can be invisible on mpMRI, the index lesion is typically able to be identified.¹¹ The largest and most dedifferentiated lesion on mpMRI with highest PI-RADS score (ie, index lesion) tends to be associated with the highest grade pathology and constitutes the source of metastasis.¹² This notion has constituted the rationale behind focal ablative therapies targeting the index lesion. However, efficacy of those focal therapies in patients with multifocality on mpMRI might be questionable.¹³ The clinical significance of satellite or nonindex lesions has been appreciated after recent reports showing a higher grade prostate cancer in these lesions.^{14,15} In addition, studies have shown nonindex lesions to be the clonal origin of lymph node metastasis in only one-quarter of radical prostatectomies for high-risk prostate cancer.¹⁶ Given that index lesions could harbor lower grade cancer than the nonindex foci on imaging in a fraction of patients, one could argue that the identification of csPCa within the index lesion is influenced by multifocality on mpMRI. We therefore investigated whether presence of multifocality on mpMRI would increase the likelihood of detecting csPCa in a PI-RADS 4 lesion.

MATERIALS AND METHODS

Patients

This multi-institutional review-board approved retrospective study was performed in prospective cohorts from Yale University and the University of Alabama at Birmingham (UAB). Each cohort was comprised of biopsy-naïve men, those with prior negative biopsy, or patients on active surveillance for prostate cancer, who underwent mpMRI and subsequent MRI-TRUS fusion targeted biopsy of the region(s) of interest (ROIs) visible on mpMRI between January 2015 and November 2017. mpMRI of the prostate was performed on patients without a prior diagnosis of prostate cancer due to concern for the disease based on elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE). Baseline data included age, race, biopsy status (active surveillance, biopsy-naïve, and prior negative biopsy), serum PSA, PSA density, prostate volume (measured on mpMRI), and the total number of ROIs on mpMRI.

mpMRI and Biopsy Protocols

mpMRIs were performed on 3.0T scanners (Philips Achieva, GE Signa, Siemens Verio, Siemens Trio, or Siemens Skyra). Interpreted by genitourinary MRI radiologists with 4-32 years of experience, each scan was assessed using PI-RADSv2 for T2-weighted, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) sequences. Prior to biopsy, each prostate was segmented on T2-weighted images and ROIs were contoured (ProFuse, Eigen, Grass Valley, CA at Yale and DynaCAD,

InVivo, Gainesville, FL at UAB). MRI-TRUS fusion targeted biopsy of ROIs and concurrent 12-core systematic biopsy was performed using Artemis (Eigen, Grass Valley, CA) and UroNav (Phillips/InVivo, Gainesville, FL) systems at Yale and UAB, respectively. Biopsies were performed by urologists with a range of 8-37 years of experience in urology.

Patient Selection and Study Cohorts

Patients were selected for analysis if they had at least 1 PI-RADS 4 lesion on mpMRI. Those men were categorized into 4 cohorts, including cohort 1—an index lesion with PI-RADS 4 and an additional PI-RADS 2 or 3 lesion), cohort 2—single ROI with PI-RADS 4, cohort 3—2 or more PI-RADS 4 lesions, or cohort 4—a lesion with PI-RADS 4, and an index lesion with PI-RADS 5. For patients in cohort 3 with multiple PI-RADS 4 lesions, the lesion with highest pathology (Grade Group [GG]) was included in the final statistical analysis.

Pathological Assessment

Biopsy cores were assessed by expert genitourinary pathologists with a range of 7-26.5 years and graded with a Gleason score and corresponding GG according to the World Health Organization and International Society of Urological Pathology recommendations as follows:¹⁷ Gleason score 3+3 (GG 1), Gleason score 3+4 (GG 2), Gleason score 4+3 (GG 3), Gleason score 4+4 (GG 4), and Gleason score 9 or 10 (GG 5). The presence of csPCa, defined as GG \geq 2 in each PI-RADS 4 lesion was evaluated by examining the pathology from the targeted biopsy cores from that lesion.

Study Outcomes

Outcomes of interest included the rate of csPCa detected in PI-RADS 4 lesions of the 4 study cohorts, the rates of negative, and GG 1 and 3 or greater cancers, and clinical and radiological factors associated with finding GG \geq 2 in PI-RADS 4 lesions. Subgroup analyses of patients based on the prior biopsy status (active surveillance, biopsy-naïve, and prior negative biopsy) and zonal location of the PI-RADS 4 lesion (peripheral versus transition) were performed as well.

Statistical Analysis

Continuous variables were reported as the median and interquartile range. Categorical variables were reported as count and proportion (%). *P* values were calculated using the Mann-Whitney test for continuous variables and the chi-squared or Fisher's exact tests for proportions. Logistic regression analysis was performed for the primary outcome of GG \geq 2 in PI-RADS 4 lesions of the studied cohorts. Variables demonstrating $\alpha < 0.05$ were retained on multivariable analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows version 24 (Armonk, NY: IBM Corp). Two-sided *P* values were calculated with $\alpha < 0.05$ considered statistically significant.

RESULTS

Our combined cohort included 645 patients with at least 1 mpMRI detected PI-RADS 4 lesion (345 at Yale and 300 at UAB). As illustrated in Table 1, the median age of the combined cohort was 65 years (interquartile range 60-70), and age was not statistically different between the Yale and UAB cohorts. Similarly, there were no significant differences in PSA and PSA density. The proportions of African-American men, men with abnormal DRE, patients with either biopsy status

Table 1. Patient demographic and clinical characteristics

	Yale	UAB	P value	Combined
No. pts	345	300	—	645
Age, y	65 (59-70)	66 (60-70)	.58	65 (60-70)
Race, n (%)			.001	
White	303 (87.8)	190 (77.2)		493 (83.4)
Non-white	42 (12.2)	56 (22.8)		98 (16.6)
Clinical stage T2, n (%)	111 (32.3)	12 (4.3)	<.001	123 (19.8)
Biopsy status, n (%)			<.001	
Active surveillance	115 (33.3)	131 (43.7)		246 (38.1)
Biopsy-naïve	149 (43.2)	46 (15.3)		195 (30.2)
Previous negative biopsy	81 (23.5)	123 (41)		204 (31.6)
PSA, ng/mL	6.4 (4.84-9.25)	6.54 (4.6-9.08)	.85	6.5 (4.7-9.1)
PSA density, ng/mL/mL	0.12 (0.08-0.18)	0.12 (0.08-0.20)	.78	0.12 (0.08-0.19)
Prostate volume, mm ³	49.67 (36-72.7)	47.32 (34.93-68.53)	.36	48.95 (35.58-70.64)
Location of lesion, n (%)			<.001	
Peripheral zone	293 (85.2)	211 (71.3)		504 (78.8)
Transition zone	51 (14.8)	85 (28.7)		136 (21.2)
Number of targeted cores	5.0 (5.0-5.0)	2.0 (2.0-3.0)	<.001	4.0 (2.0-5.0)
Study cohorts, n (%)			<.001	
Cohort 1	57 (16.5)	127 (42.3)		184 (28.5)
Cohort 2	179 (51.9)	88 (29.3)		267 (41.4)
Cohort 3	64 (18.6)	48 (16)		112 (17.4)
Cohort 4	45 (13)	37 (12.3)		82 (12.7)

PSA, prostate-specific antigen.

(biopsy-naïve, prior negative biopsy, or active surveillance), and men with PI-RADS 4 lesions located in the peripheral zone, however, were significantly different between the 2 institutes. Cohorts 1, 2, 3, and 4 included 184, 267, 112, and 82 men, respectively (Supplementary Table 1). Compared to patients in cohorts 1, 2, and 3, men in cohort 4 had higher PSA and PSA density ($P < .001$ for all; Supplementary Table 2).

The overall rate of GG ≥ 2 pathology in the PI-RADS 4 lesions was 35.2%. On targeted biopsy of the PI-RADS 4 lesion, the proportion of GG 2 or greater pathology findings in cohorts 1, 2, 3, and 4 was 21.7%, 36.3%, 49.1%, and 42.7%, respectively (cohort 1 vs 2, $P = .002$; cohort 1 vs 3, $P < .001$; and cohort 1 vs 4, $P = .001$; Fig. 1A). The rate of GG 3 or greater disease in cohorts 1, 2, 3, and 4 was 10.3%, 17.2%, 24.1%, and 22%, respectively (cohort 1 vs 3, $P < .001$; Supplementary Table 3).

Proportions of GG ≥ 2 pathology in each study cohort per biopsy status (biopsy-naïve, prior negative biopsy, and active surveillance) are listed in Supplementary Table 4. A subset analysis based on the patient's prior biopsy status was performed. When including only men who were on active surveillance (Fig. 1B) or biopsy-naïve (Fig. 1C), we found that rates of detecting GG 2 or greater pathology were higher for men in cohort 3 compared with those in cohort 1. In patients who had negative prior biopsy, the proportion of men with GG ≥ 2 was similar among the study cohorts (Fig. 1D).

Subgroup analysis of patients with PI-RADS 4 lesion located in the peripheral zone showed that the rate of GG ≥ 2 in cohorts 1, 2, 3, and 4 was 23.2%, 37.6%, 55.2%, and 43.5%, respectively ($P < .001$; Fig. 2A and Supplementary Table 5). However, the rate was similar among the study cohorts in men with the PI-RADS 4 lesion in the transition zone ($P = .33$; Fig. 2B).

On multivariable analysis, age (OR 1.06, 95%CI 1.03-1.09, $P < .001$), clinical stage T2 (OR 1.59, 95%CI 1.03-2.47, $P = .03$), PSA density (OR 1.43 per 0.1 unit, 95%CI 1.22-1.67, $P < .001$), peripheral zone lesion (OR 1.62, 95%CI 1.01-2.59, $P = .04$), and MRI lesion classification (cohort 2 vs 1, OR 1.93, 95%CI 1.21-3.08, $P = .006$; and cohort 3 vs 1, OR 3.28,

95%CI 1.88-5.72, $P < .001$) remained significantly associated with the risk of csPCa on targeted biopsy (Table 2).

DISCUSSION

To our knowledge, the present study is the first to demonstrate an association between multifocality on mpMRI and csPCa detection in PI-RADS 4 lesions. Our study revealed differences in rate of csPCa detection in PI-RADS 4 lesions based on their location, multifocality, and PI-RADS classifications of other lesions identified. We found that men with a PI-RADS 4 lesion and an additional lower suspicion MRI lesion (PI-RADS 2 or 3) showed the lowest rate of aggressive pathology (21.7%) in the PI-RADS 4 lesions. In fact, this rate is less than the overall probability of PI-RADS 4 lesions harboring csPCa in the present study (35.2%) and previous reports (22.1%-70.5%).^{4,6,15,18} Although this trend was generally seen in men with any prior biopsy status, the association did not reach conventional levels of statistical significance in patients with a history of a prior negative prostate biopsy. This might be in part explained by notably higher rates of benign findings in PI-RADS 4 lesions within this population, possibly due to prior sampling through TRUS with negative results.^{15,19-21} Given that only a minority of PI-RADS 4 lesions in cohort 1 (10%) contained GG 3 or greater pathology, targeted biopsy of the index lesion in this population can possibly be omitted without forfeiting the lesion risk classification. However, further confirmatory data in different cohorts are required prior to this recommendation.

Despite the multifocal nature of prostate cancer, the index lesion is often considered as a culprit focus emitting metastatic cells and therefore driving cancer progression.¹⁵

However, some studies have drawn attention to the clinical significance of MR nonindex lesions as well.^{14,15} In a recent study comparing preoperative mpMRI with radical prostatectomy specimens from men with intermediate- and high-risk disease, Hegde et al found that 11.3% of patients showed a higher grade prostate cancer in a nonindex versus

index lesion.¹⁴ Venderink et al noticed similar results with targeted biopsy of men with multiple lesions on mpMRI.¹⁵ In a similar fashion, we found that the presence of MR nonindex lesions with imaging characteristics of low to intermediate assessment categories (PI-RADS 2 or 3) was associated with lower likelihood of PI-RADS 4 index

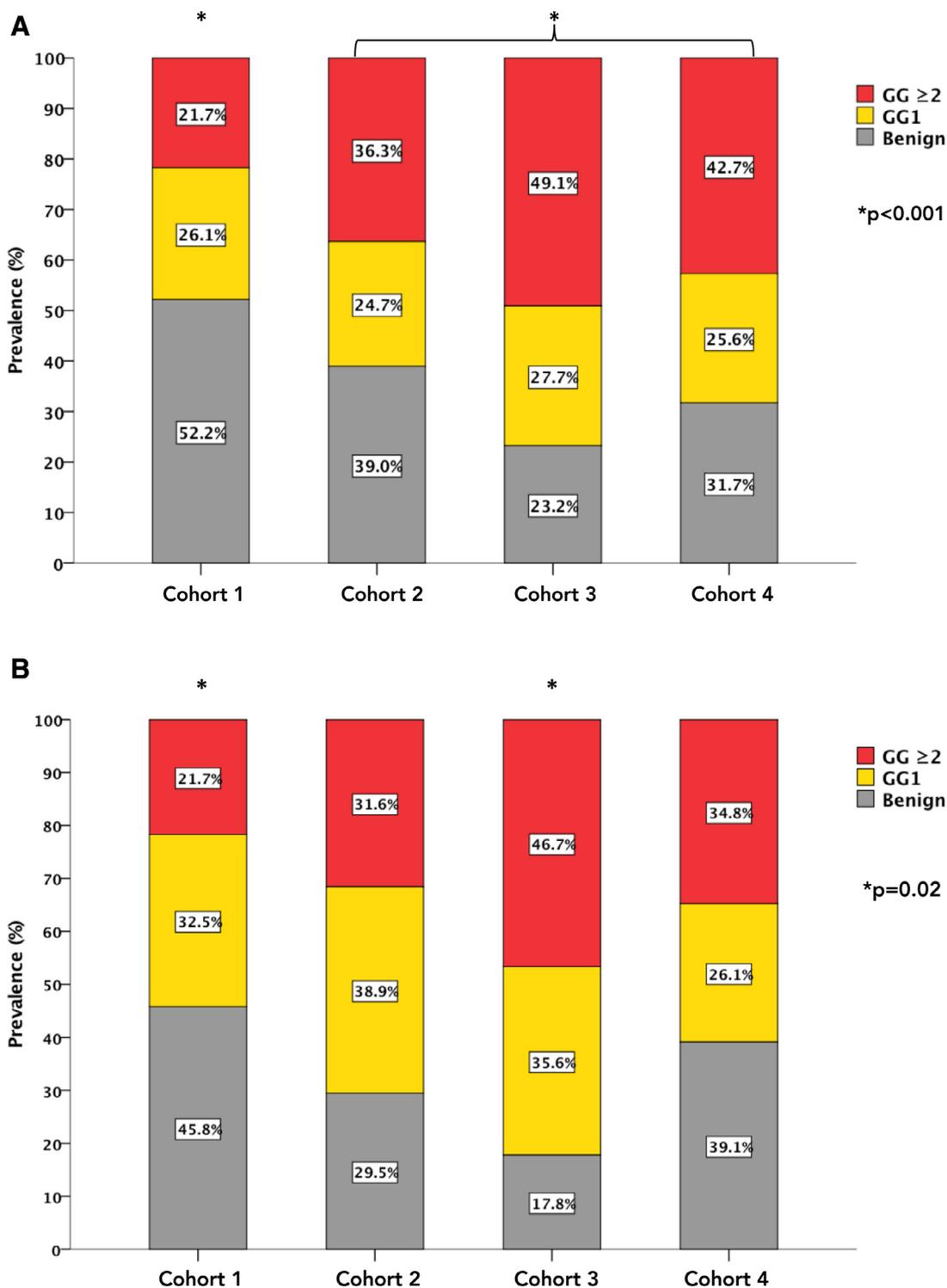


Figure 1. Biopsy pathology by (A) total combined cohort; (B) patients on active surveillance; (C) biopsy-naïve patients; (D) patients with prior negative biopsy. (Color version available online.)

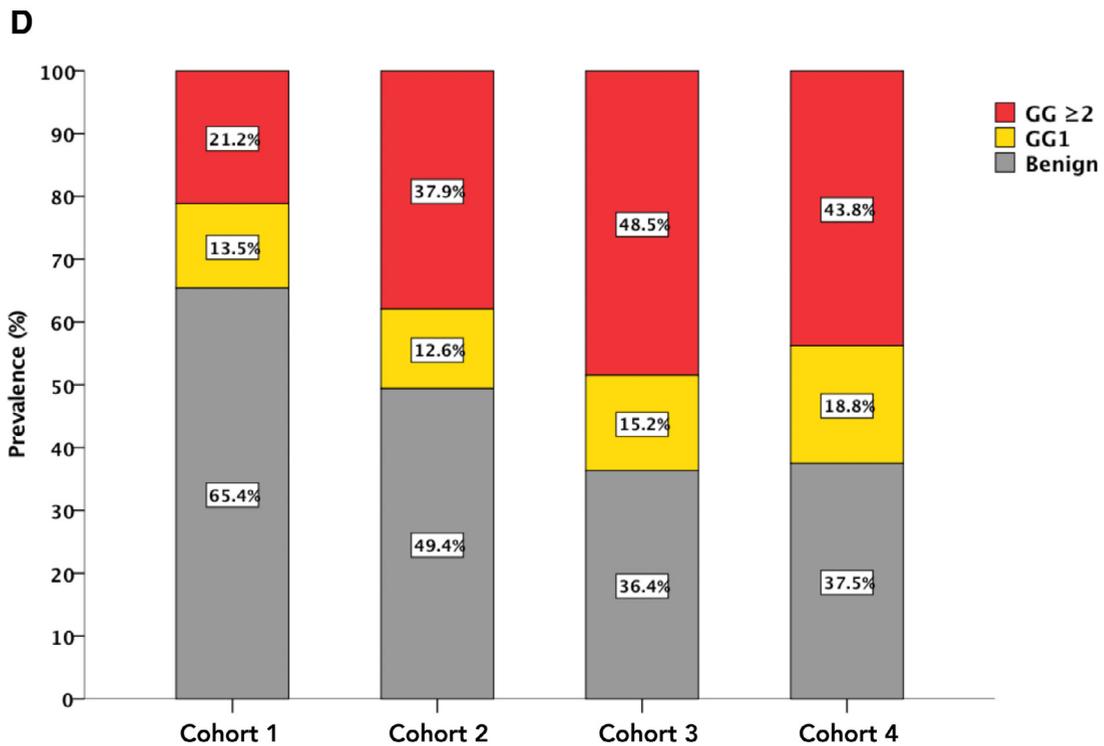
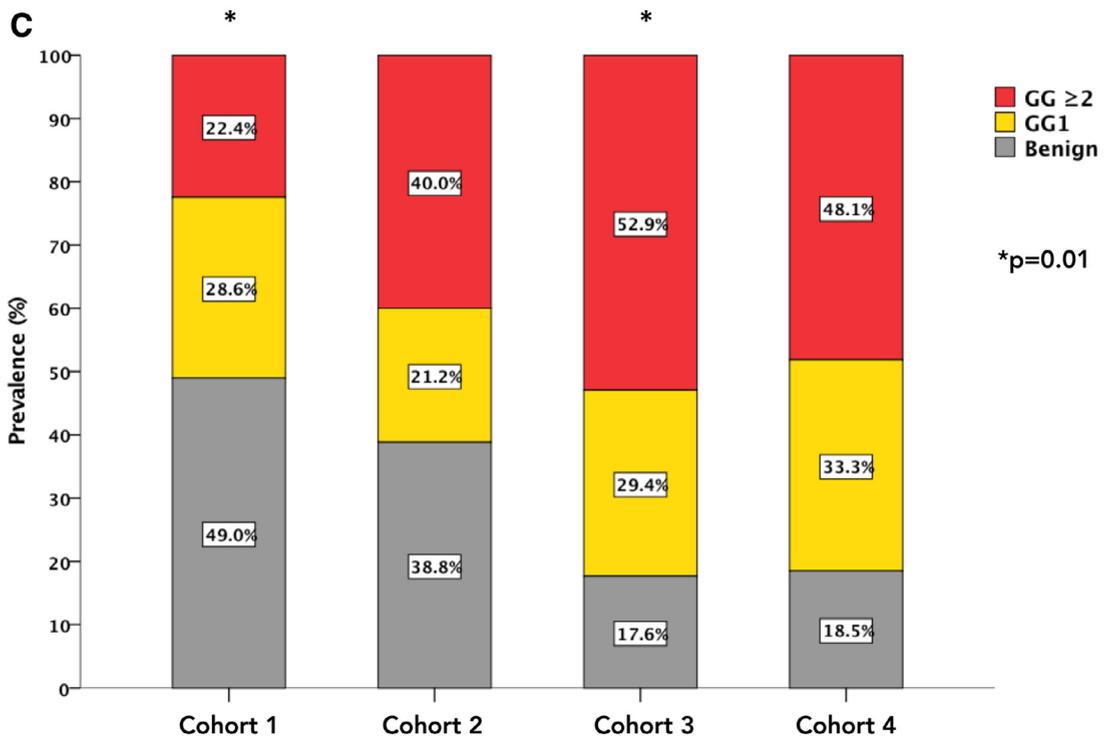


Figure 1. Continued

lesion harboring csPCa. This finding could explain to some extent the unexpectedly low sensitivity of PI-RADS 4 for csPCa in a number of previous studies.^{6,22} In other words, MR characteristics of PI-RADS 4 lesions in this context could be mimicked by adjacent benign elements of nonindex PI-RADS 2 or 3 lesions.

We found that detection of csPCa in PI-RADS 4 lesions varied by clinical and imaging features. Patients with a solitary PI-RADS 4 lesion or multiple PI-RADS 4 foci had higher odds of harboring csPCa. The present series is unique in that it integrated the MR multifocality status into the multivariate model. In addition, older men, and

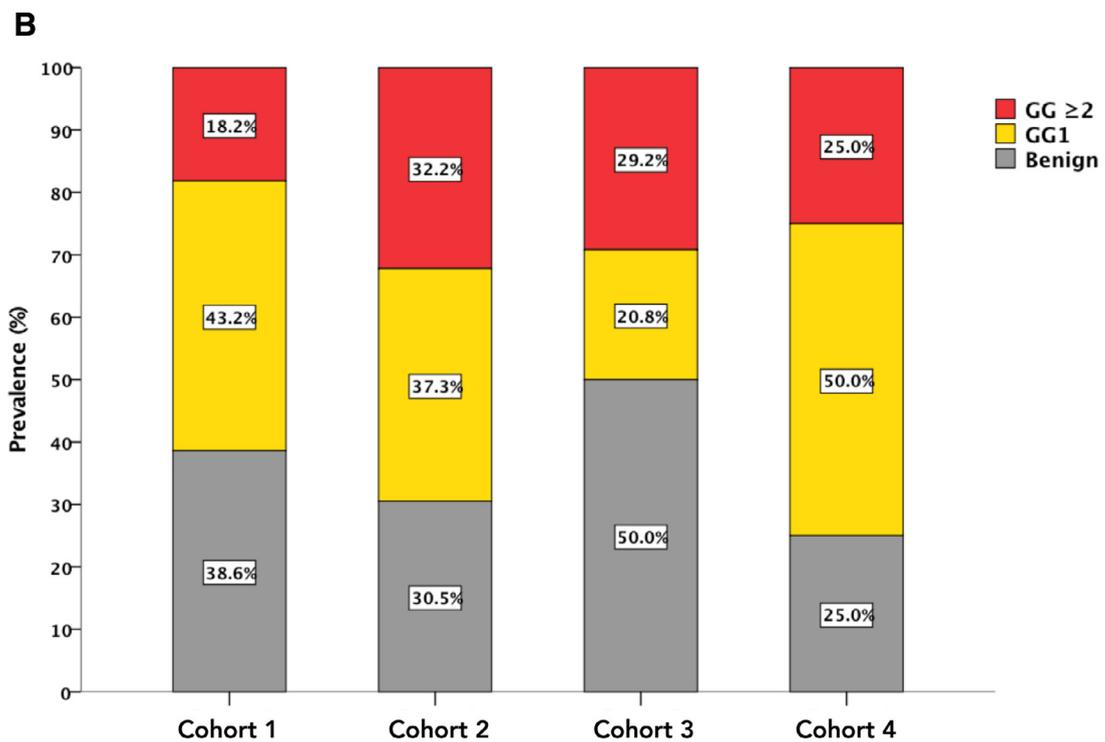
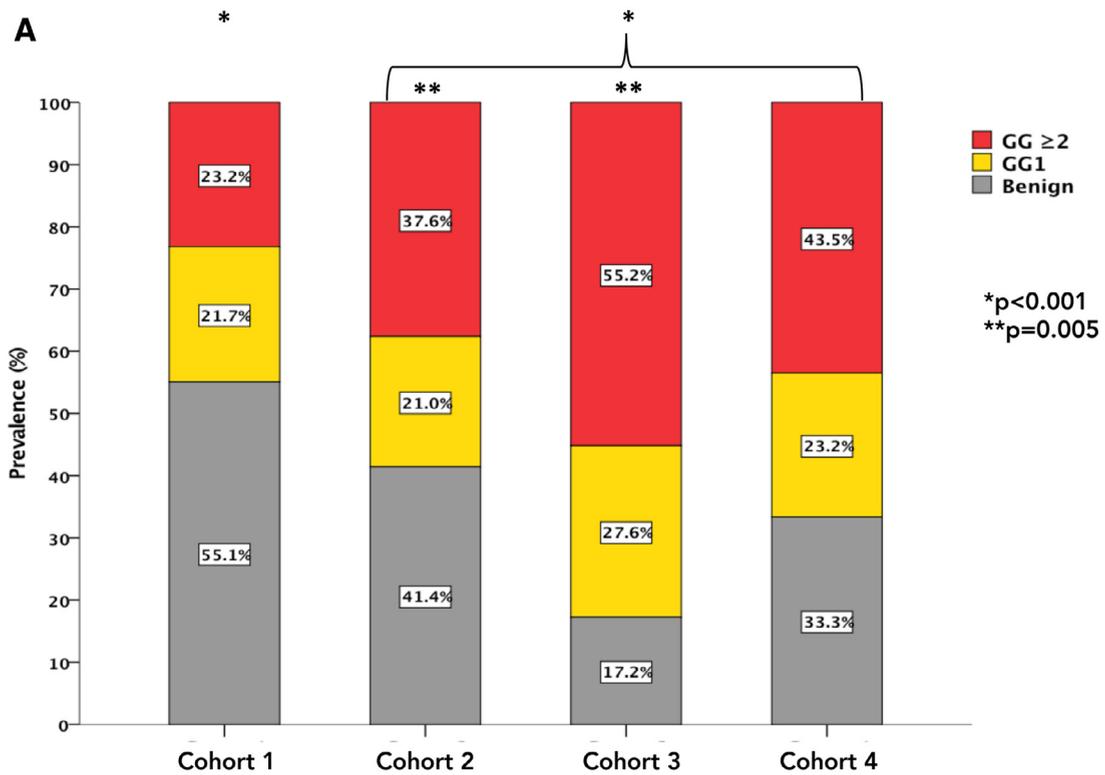


Figure 2. Biopsy pathology by location in (A) peripheral zone; (B) transition zone. (Color version available online.)

patients with abnormal DRE and higher PSA density were more likely to show csPCa in their PI-RADS 4 lesions. These nonspecific findings are consistent with other reports concerning clinical predictors of significant disease in lesions with PI-RADS 3-5.^{10,23,24} Nonetheless,

avoiding targeted biopsy of PI-RADS 4 lesions in the clinical setting of low PSA density has not been recommended due to high prevalence of csPCa in these patients.¹⁵ Consistent with previous studies, we also observed that patients with PI-RADS 4 lesions located

Table 2. Univariable and multivariable logistic regression models for the prediction of GG \geq 2 prostate cancer

	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, y	1.05 (1.03-1.08)	<.001	1.06 (1.03-1.09)	<.001
Race				
White	1.00 (Ref)	—		
Non-white	0.74 (0.46-1.18)	.20		
Clinical stage T2	1.89 (1.26-2.82)	.002	1.59 (1.03-2.47)	.03
Biopsy status				
Active surveillance	1.00 (Ref)	—	1.00 (Ref)	—
Biopsy-naïve	1.40 (0.94-2.07)	.09	1.11 (0.72-1.73)	.62
Prior negative biopsy	1.24 (0.84-1.85)	.26	0.86 (0.54-1.35)	.51
PSA density (per 0.1 unit)	1.38 (1.20-1.59)	<.001	1.43 (1.22-1.67)	<.001
Peripheral zone lesion	1.65 (1.10-2.49)	.01	1.62 (1.01-2.59)	.04
Study cohort				
Cohort 1	1.00 (Ref)	—	1.00 (Ref)	—
Cohort 2	2.05 (1.33-3.15)	.001	1.93 (1.21-3.08)	.006
Cohort 3	3.47 (2.08-5.78)	<.001	3.28 (1.88-5.72)	<.001
Cohort 4	2.68 (1.53-4.69)	.001	1.46 (0.76-2.78)	.24

PSA, prostate-specific antigen.

at peripheral zone had higher likelihood of harboring csPCa.¹⁹ An arguable diagnostic accuracy of mpMRI in detecting csPCa within the transition zone compared with the peripheral zone along with the inherent limited number of csPCa in the transition zone may shed light on the lack of association between multifocality on imaging and likelihood of transition zone confined PI-RADS 4 lesions harboring csPCa.⁵

There are several limitations of this study. First, our results were based on targeted biopsy rather than gold-standard whole-mount prostatectomy specimen which may lead to increased false positive or negative rates. Nonetheless, focusing on radical prostatectomy cases would limit the studied patients to those with aggressive pathology, leaving out men with low-risk or no prostate cancer found on targeted biopsy.²⁵ Second, we counted the pathology findings of only targeted biopsy from the PI-RADS 4 lesion. Lack of pathology information from the systematic biopsy cores from the sextant containing the lesion might result in potential inaccuracy of biopsy pathology for each MRI-targeted lesion.²⁶ Nonetheless, the recent PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02380027) Identifier: NCT02380027) trial showed that the rates of csPCa detection were higher when MRI-targeted biopsy rather than systematic biopsy was performed.⁴ Third, institutional biases including an MRI interpretation bias might exist since significant differences were noted in the distribution of study cohorts 1 and 2 and the peripheral zone lesions between the 2 institutions. These could be seen across academic centers as radiologists' experience in prostate mpMRI reporting varies. Although accuracy of PI-RADS scoring in terms of the associated pathological findings on targeted biopsies was reviewed in meetings at both centers, the institutes were not blinded. Fourth, PI-RADS 4 lesions in the peripheral zone were determined based on their appearances on DWI sequences and DCE positivity (if DWI assessment category was 3). Apart from a continued debate surrounding whether DCE affects

identification of csPCa,^{1,6,25} inter-reader variations exist in DCE imaging interpretations.²⁷ This may potentially account for a difference noted in the rate of csPCa within the study cohort 1 between 2 cohorts in the present study. Therefore, studies of PI-RADS 4 lesions with assessment categories according to a recently released PI-RADS version 2.1 will be valuable in the future.²⁸ Lastly, 2 software-based fusion registration platforms (Artemis and UroNav) with 2 different primary methods of image registration for fusion (elastic versus rigid) were used in 2 institutions.²⁹ Although a recent meta-analysis did not find any difference in the detection of csPCa between rigid and elastic registrations,³⁰ the heterogeneity which was seen among the included studies in this systematic review warrants a further multi-center study controlled for the registration technique to confirm our present findings.

CONCLUSION

Based on this retrospective study, on targeted biopsies of the PI-RADS 4 lesions, the proportion of GG \geq 2 pathology is approximately 35%. Moreover, our data revealed differences in rate of csPCa detection in PI-RADS 4 lesions based on their location, multifocality, and PI-RADS classifications of other lesions identified.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2019.08.008>.

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