Prospective PI-RADS v2.1 Atypical Benign Prostatic Hyperplasia Nodules With Marked Restricted Diffusion: Detection of Clinically Significant Prostate Cancer on Multiparametric MRI

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BACKGROUND. On the basis of expert consensus, PI-RADS version 2.1 (v2.1) introduced the transition zone (TZ) atypical benign prostatic hyperplasia (BPH) nodule, defined as a TZ lesion with an incomplete or absent capsule (T2 score, 2). PI-RADS v2.1 also included a revised scoring pathway whereby such nodules, if exhibiting marked restricted diffusion (DWI score, 4–5), are upgraded from overall PI-RADS category 2 to category 3 (2 + 1 TZ lesions).

OBJECTIVE. The purpose of this study was to compare the rates of detection of clinically significant prostate cancer (csPCa) in prospectively reported 2 + 1 TZ lesions, as defined by PI-RADS v2.1, and conventional 3 + 0 TZ lesions with targeted biopsy as the reference standard.

METHODS. This retrospective study included men with no known PCa or with treatment-naïve grade group (GG) 1 PCa who underwent 3-T multiparametric MRI of the prostate with prospective reporting by means of PI-RADS v2.1. Patients with at least one PI-RADS category 3 TZ lesion who underwent targeted biopsy formed the final sample. Biopsy results were summarized descriptively for 2 + 1 and 3 + 0 lesions. Generalized estimating equations were used to compare csPCa detection rates between groups. Associations between csPCa in 2 + 1 lesions and patient age, PSA level, prostate volume, PSA density, biopsy history, lesion size, and lesion ADC were tested with Kruskal-Wallis and Fisher exact tests.

RESULTS. Among 1238 eligible patients who underwent MRI reported with PI-RADS v2.1, 2 + 1 lesions were reported in 6% (n = 69) and 3 + 0 TZ lesions in 7% (n = 87) of patients. No PCa, GG1 PCa, or csPCa was found in 84% (n = 41), 10% (n = 5), and 6% (n = 3) of 49 patients with 2 + 1 lesions who underwent targeted biopsy. Nor were they found in 74% (n = 45), 15% (n = 9), and 11% (n = 7) of 61 patients with 3 + 0 lesions who underwent targeted biopsy. The csPCa detection rate was not significantly different between 2 + 1 and 3 + 0 lesions (p = .31). All cases of csPCa were GG2, except for one 3 + 0 lesion with a GG3 tumor. No clinical or imaging variable was associated with csPCa in 2 + 1 lesions.

CONCLUSION. The rate of csPCa in atypical BPH nodules with marked restricted diffusion was low (6%) and not significantly different from that of conventional 3 + 0 TZ lesions (11%).

CLINICAL IMPACT. The results provide prospective clinical data about the revised TZ scoring criterion and pathway in PI-RADS v2.1 for atypical BPH nodules with marked restricted diffusion.

Multiparametric MRI (mpMRI) of the prostate has become a cornerstone in the diagnosis and management of prostate cancer (PCa) [1]. In addition to technologic advances in mpMRI and MRI-guided targeted biopsy, the development of PI-RADS has contributed to adoption of this modality.

PI-RADS provides guidance on the use of mpMRI to detect and stratify findings in the prostate gland related to the risk of clinically significant PCa (csPCa). Developed from a combination of expert opinion and limited peer-reviewed data, the system entails use of a 5-point scale to indicate the likelihood that the integration of mpMRI findings on T2-weighted imaging, DWI, ADC maps, and dynamic contrast-enhanced MRI data correlates with the presence of csPCa [2]. The first version of the system, released in 2012 [3], included clinical guidelines for the performance of mpMRI along with a 15-point scor-

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ing system for image interpretation. A much wider adoption of the system occurred after PI-RADS version 2 (v2) was introduced in 2015. This revision introduced a simplified scoring algorithm with a dominant pulse sequence in each zone to improve diagnostic performance [2]. In 2019, recognizing the need to address limitations and inconsistencies of PI-RADS v2, the PI-RADS steering committee released PI-RADS version 2.1 (v2.1), which included minor changes to the scoring system while maintaining its overall construct [4].

A degree of benign prostatic hyperplasia (BPH) is present in almost every patient of advanced age and is consistently visible on MRI. Microscopically, nodular prostatic hyperplasia consists of nodules of glands and intervening stroma [5]. Although a capsule at the margin of BPH nodules is not described in the pathology literature [6], a well-defined demarcation of these nodules, referred to as a capsule, is a characteristic imaging feature on MRI, likely representing intervening stroma. Thus, on the basis of expert consensus, a visible complete capsule on MRI was introduced as a determining factor, and in PI-RADS v2.1 a transition zone (TZ) lesion with this feature is assessed as PI-RADS category 1. However, a relevant change in the revised scoring pathway introduced in PI-RADS v2.1 was the addition of atypical BPH nodules, defined as TZ nodules that do not have a complete or discernable MRI capsule [7]. These nodules, if markedly hypointense on ADC maps and markedly hyperintense on high-b-value DWI (DWI score, 4 or 5, depending on the size of the nodule), should be upgraded to an overall score of 3 (2 + 1) according to PI-RADS v2.1. This change recognizes that although BPH nodules are highly unlikely to harbor csPCa [8], restricted diffusion is a feature suggestive of malignancy. Typical suspicious lesions in the TZ appear as lenticular or noncircumscribed, homogeneous, moderately hypointense regions on T2-weighted images (score and overall PI-RADS category, 4 or 5, depending on size) [4].

As endorsed by the joint consensus statement by the Society of Abdominal Radiology and the American Urological Association, lesions assessed PI-RADS category 3 or higher should be strongly considered for biopsy [9]. This recent change in PI-RADS thus may result in an increase in the number of biopsies performed despite a lack of validating clinical data. The purpose of this study was to compare, with targeted biopsy as the reference standard, the rates of detection of csPCa in prospectively reported 2 + 1 TZ lesions defined by PI-RADS v2.1 (i.e., atypical BPH nodules [regions with an incomplete or undetectable capsule] with markedly restricted diffusion) and conventional (3 + 0) category 3 TZ lesions.

HIGHLIGHTS

Key Finding

- *In men who underwent prostate MRI prospectively interpreted with PI-RADS v2.1 and underwent subsequent targeted biopsy, clinically significant prostate cancer was detected in 6% of 2 + 1 transition zone lesions, as newly defined by PI-RADS v2.1, versus 11% of conventional 3 + 0 transition zone lesions (p = .31).*

Importance

- *These results from prospectively gathered clinical interpretations provide a real-world assessment of atypical BPH nodules with marked restricted diffusion, newly introduced in PI-RADS v2.1.*

Methods

Study Design

This HIPAA-compliant and institutional review board–approved study was a retrospective, observational, single-center analysis of prospectively generated data. No overlap existed between patients enrolled in this study and prior publications. The requirement for written informed consent was waived.

Patient Selection

A total of 1584 men underwent prostate mpMRI at our institution between April 2019 and April 2020 (Fig. 1). Among these men, patients were excluded because mpMRI findings were not prospectively reported with PI-RADS v2.1 (n = 257), they had undergone prior radiation therapy for PCa (n = 37), had undergone prior radical prostatectomy for PCa (n = 31), or had previously diagnosed csPCa when they underwent mpMRI (n = 21). These exclusions left 1238 eligible patients who either had no known PCa or had PCa in treatment-naïve grade group (GG) 1 at mpMRI prospectively reported with PI-RADS v2.1. A 2 + 1 TZ lesion was reported in 6% (69/1238) of these patients. A total of 71% (49/69) of these men with a total of 49 2 + 1 TZ lesions underwent subsequent targeted biopsy of these lesions. A 3 + 0 TZ lesion was reported in 7% (87/1238) of the eligible patients. A total of 62% (54/87) of these men, with a total of 61 3 + 0 TZ lesions, underwent subsequent targeted biopsy of these lesions. These two groups composed the final patient sample (Fig. 1).

Prebiopsy Multiparametric MRI

All MRI studies were performed with a 3-T MRI system (Ingenia, Philips Healthcare) with a phased-array surface coil and an endorectal coil. The PI-RADS–compliant mpMRI protocol included gapless 3-mm spin-echo axial (FOV, 18 × 18 cm), sagittal (FOV, 25 × 25 cm), and coronal (FOV, 16 × 16 cm) T2-weighted imaging; 3-mm axial echo-planar DWI (FOV, 16 × 16 cm) with acquired b values of 0, 100, 1000, 1500, and 2000 s/mm^2; ADC mapping with all b values of 1000 s/mm^2 or less; and dynamic contrast-enhanced imaging. The examinations were interpreted prospectively by one of 11 board-certified radiologists with 5–20 years of experience interpreting prostate mpMRI and each reading an average of more than 50 prostate MRI examinations annually. The radiologists independently assigned a lesion-specific PI-RADS v2.1 category [4], lesion size, and estimated volume of the prostate using a semiautomated segmentation tool (DynaCAD, version 4.0, Invivo). Radiologists had access to any clinical information available (e.g., PSA level, previous biopsy results).

Our structured clinical report includes a per-lesion description of size (measured as the largest dimension, usually on the axial T2-weighted images for TZ unless better delineated on images acquired with another sequence), location, mean ADC value, PI-RADS score for each pulse sequence (T2-weighted, DWI, and dynamic contrast-enhanced MRI), and overall PI-RADS category. Because these descriptors are routinely provided on a per-lesion basis, it is possible to discriminate TZ PI-RADS v2.1 category 3 le-

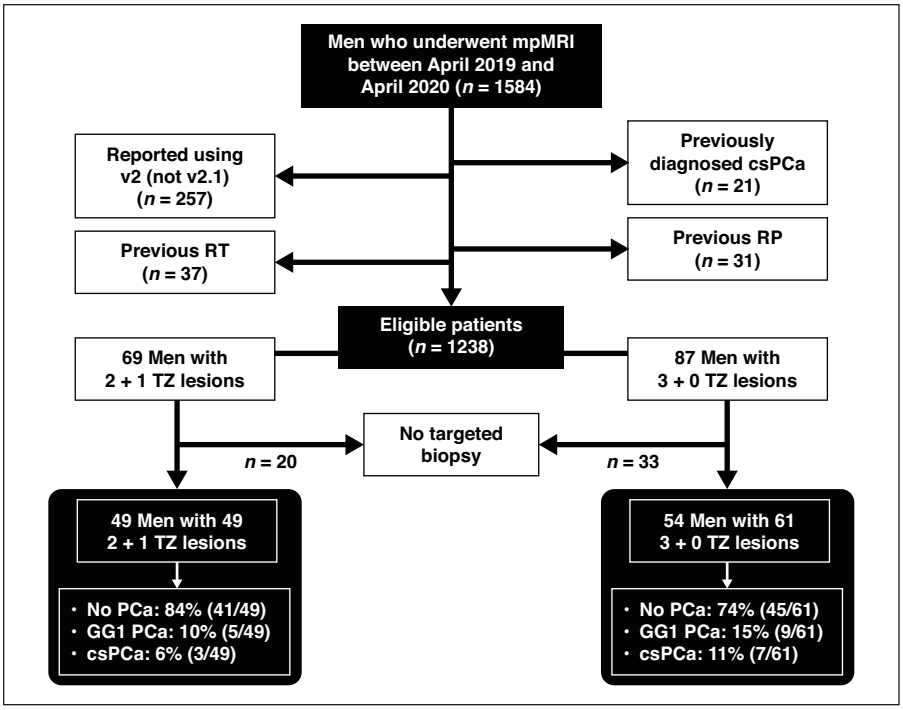

Fig. 1—Chart shows eligibility and patient sample. mpMRI = multiparametric MRI, v2 = PI-RADS version 2, v2.1 = PI-RADS version 2.1, csPCa = clinically significant prostate cancer, RT = radiation therapy, RP = radical prostatectomy, TZ = transition zone, GG1 = grade group 1.

sions assigned scores of 2 + 1 and 3 + 0. The lesion with the most concerning features (either the highest overall PI-RADS score or, in men with multiple lesions assigned the same PI-RADS score, the lesion with one or more of the following attributes: largest size, lowest ADC value, suspicion of having extraprostatic extension) was reported as the index lesion. The indications for mpMRI were either suspicion of PCa (e.g., elevated PSA level), with or without a previous negative biopsy result, or active surveillance of known PCa (either entering surveillance or as follow-up). Because PI-RADS v2.1 category 2 lesions are not routinely biopsied, these lesions are not consistently reported at our institution. Before the transition to PI-RADS v2.1 in March 2019, the 11 radiologists participated in a single group discussion of the changes implemented in the revised scoring system.

Biopsy Technique

One of the following biopsy techniques was used.

MRI-TRUS fusion biopsy—Fusion biopsies were performed by one of six urologists with at least 5 years of experience in targeted fusion biopsy using a reusable core biopsy system with an 18-gauge needle with the patient under periprostatic block anesthesia. Radiologists used postprocessing software (DynaCAD, version 4.0) during clinical interpretation for creation of 3D volumes of the prostate and for outlining the biopsy targets. These data were used by the MRI transrectal ultrasound (TRUS) fusion system (UroNav, version 2.0, Invivo) during the biopsy. In general, two or three cores were obtained from each target, and standard sextant-based systematic sampling was performed concurrently immediately after the targeted cores were obtained.

MRI-guided in-bore biopsy—Direct MRI-guided in-bore biopsies were performed with the patient under moderate sedation by one of two radiologists with 3 years of experience in targeted in-bore biopsy (D.N.C. and A.D.L.) using an MRI-compatible interventional device for transrectal prostate biopsy (DynaTRIM, Invivo) with an 18-gauge needle. These two radiologists were among the 11 radiologists who prospectively interpreted the MRI examinations. Biopsies were performed with a phased-array surface coil in a 3-T MRI unit (Ingenia, Philips Healthcare). The targeted biopsy did not include systematic sampling and usually consisted of three cores from each target.

Study Endpoints and Reference Standard

The primary endpoint of the study was detection of csPCa on a per-lesion basis. Genitourinary pathologists prospectively evaluated the biopsy specimens according to the standards recommended by the International Society of Urological Pathology [10]; their assigned histologic diagnoses served as the standard of reference. For this investigation, only the cores targeting the lesions of interest were considered. Possible biopsy outcomes included no cancer, indolent PCa (defined as GG1), and csPCa (defined as GG2–GG5) [11]. In men with more than one MRI-visible lesion, each lesion was targeted and labeled separately, allowing direct imaging-histology correlation. Given the focus of the study on 2 + 1 TZ lesions, in men with such lesions who underwent radical prostatectomy, the whole-mount radical prostatectomy specimens were reviewed to identify possible false-negative targeted biopsies or GG upgrades between biopsy and surgery. These whole-mount specimens were processed according to the recommended procedures by the International Society of Urological Pathology [12].

Statistical Analysis

Analyses were performed at the lesion level. Continuous measurements (age, PSA level, prostate volume, PSA density, lesion size, and lesion-specific mean ADC value) were reported as mean ± SD, and categoric measurements (whether the lesion of interest was the index lesion, previous biopsy status) were re-

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ported as counts and percentages. Kruskal-Wallis tests were used to test the difference in biopsy results for continuous variables, and Fisher exact tests were used for categoric variables. A generalized estimating equation was used to compare the csPCa detection rate in 2 + 1 versus 3 + 0 TZ lesions. Exchange covariance structure was used to adjust for a potential clustering effect from the presence of multiple lesions in the same patient. A value of $p < .05$ was considered statistically significant. All analyses were performed with the R program (version 4.0.2, R Foundation) [13].

Results

Among the 1238 eligible patients, a 2 + 1 TZ lesion was prospectively reported in 6% (69/1238). A total of 71% (49/69) of these men, with a total of 49 2 + 1 TZ lesions, underwent subsequent targeted biopsy of these lesions. A 3 + 0 TZ lesion was reported in 7% (87/1238) of the eligible patients. A total of 62% (54/87) of these men, with a total of 61 3 + 0 TZ lesions, underwent subsequent targeted biopsy of these lesions. These two groups composed the final patient sample (Fig. 1).

Tables 1 and 2 summarize the lesion and patient characteristics. Among the 49 patients with 2 + 1 TZ lesions, 46 underwent MRI-TRUS fusion biopsy, and three underwent in-bore biopsy. Among the 61 3 + 1 TZ lesions, 56 were sampled by MRI-TRUS fusion biopsy and five by in-bore biopsy. The mean number of cores obtained per lesion was 2.2 (range, 2–4). The mean interval between mpMRI and biopsy was 36 days (range, 1–86 days).

Targeted biopsy of the 2 + 1 TZ lesions revealed PCa in 16% (8/49) of the lesions. No PCa, GG1 PCa, or csPCa was found in 84% (41/49), 10% (5/49), and 6% (3/49) of the lesions (Table 1). All cases of csPCa were GG2. The overall mean lesion size on MRI was 10 ± 5 (SD) mm (range, 4–28 mm). None of the patient-level or lesion-level variables analyzed had a statistically significant association with the presence of csPCa (Table 1). However, the mean sizes of 2 + 1 TZ lesions were 15 mm for GG2, 11 mm for GG1, and 9 mm for benign lesions ($p = .30$). The mean ADC values were 0.62×10^{-3} mm²/s for GG2, 0.66×10^{-3} mm²/s for GG1, and 0.71×10^{-3} mm²/s for benign lesions ($p = .43$). Examples of different lesion-specific biopsy outcomes are shown in Figures 2 and 3.

Targeted biopsy of the 3 + 0 TZ lesions revealed PCa in 26% (16/61) of the lesions. No PCa, GG1 PCa, or csPCa was found in 74% (45/61), 15% (9/61), and 11% (7/61) of the lesions (Table 2). Among the cases of csPCa, six were GG2 tumors, and one was a GG3 tumor. The mean lesion size on MRI was 10 ± 4 mm (range, 3–20 mm). The mean sizes of 3 + 0 TZ lesions were 11 mm for GG2 and greater, 9 mm for GG1, and 9 mm for benign lesions ($p = .72$). The mean ADC values were 0.62×10^{-3} mm²/s for GG2, 0.73×10^{-3} mm²/s for GG1, and 0.69×10^{-3} mm²/s for benign lesions ($p = .17$). PSA density was significantly higher ($p = .001$) and prostate volume was significantly lower ($p < .001$) in csPCa (Table 2).

The frequency of csPCa was not significantly different between 3 + 0 TZ lesions (11%) and 2 + 1 TZ lesions (6%) ($p = .31$). Similarly, the

TABLE 1: Clinical (Patient Level) and Imaging (Lesion Level) Characteristics and Biopsy Results for 2 + 1 Transition Zone (TZ) Lesions

Characteristic	Targeted Biopsy			All	p[a]
	Negative	Positive			
		Grade Group 1	Grade Group ≥ 2		
No. of lesions[b,c]	41 (84)	5 (10)	3 (6)	49 (100)	NA
Age (y)	65.4 ± 5.0	67.8 ± 5.8	59.3 ± 11.6	65.3 ± 5.7	.49
PSA level (ng/mL)	7.3 ± 3.5	8.6 ± 5.0	7.1 ± 3.4	7.4 ± 3.6	.95
Prostate volume (mL)	69.8 ± 32.7	44.4 ± 12.6	56.9 ± 8.8	66.4 ± 31.2	.15
PSA density (ng/mL/cm³)	0.13 ± 0.09	0.22 ± 0.16	0.13 ± 0.08	0.14 ± 0.1	.33
Index lesion size (mm)[d]	9 ± 4	11 ± 2	15 ± 15	10 ± 5	.30
Mean ADC value ($\times 10^{-3}$ mm²/s)[b]	0.71 ± 0.09	0.66 ± 0.07	0.62 ± 0.14	0.69 ± 0.10	.43
Is the 2 + 1 TZ lesion the index lesion?[b]					.13
No	81 (26/32)	16 (5/32)	3 (1/32)	65 (32/49)	
Yes	88 (15/17)	0 (0/17)	12 (2/17)	35 (17/49)	
Previous biopsy status[b]					.35
Biopsy-naïve	73 (16/22)	23 (5/22)	5 (1/22)	45 (22/49)	
Negative biopsy result	100 (13/13)	0 (0/13)	0 (0/13)	27 (13/49)	
Grade group 1 (AS)	86 (12/14)	7 (1/14)	7 (1/14)	29 (14/49)	

Note—Unless otherwise specified, values are mean ± SD or percentage with number with in parentheses. Some percentages do not total 100 owing to rounding. NA = not applicable, AS = active surveillance.

[a]Calculated for association with presence of grade group 2 or greater cancer by means of Kruskal-Wallis tests for continuous variables and Fisher exact tests for categoric variables.

[b]Lesion-level data.

[c]Values in parentheses are percentages.

[d]MRI-visible index lesion.

TABLE 2: Clinical (Patient-Level) and Imaging (Lesion-Level) Characteristics and Biopsy Results for 3 + 0 Transition Zone (TZ) Lesions

Characteristic	Targeted Biopsy			All	p[a]
	Negative	Positive			
		Grade Group 1	Grade Group ≥ 2		
No. of lesions[b,c]	45 (74)	9 (15)	7 (11)	61 (100)	NA
Age (y)	66.1 ± 7.1	65.1 ± 5.9	61.4 ± 9.2	66.1 ± 7.1	.28
PSA level (ng/mL)	8.9 ± 5.1	6.7 ± 1.3	9.4 ± 4.7	8.9 ± 5.1	.51
Prostate volume (mL)	73.0 ± 43.4	35.3 ± 16.2	32.2 ± 9.2	73.0 ± 43.4	< .001
PSA density (ng/mL/cm^3)	0.14 ± 0.09	0.21 ± 0.07	0.31 ± 0.17	0.14 ± 0.09	.001
Index lesion size (mm)[d]	9 ± 4	9 ± 3	11 ± 6	10 ± 4	.72
Mean ADC value (× 10^{-3} mm^2/s)[b]	0.69 ± 0.11	0.73 ± 0.10	0.62 ± 0.1	0.69 ± 0.11	.17
Is the 2 + 1 TZ lesion the index lesion?[b]					.50
No	73 (29/40)	13 (5/40)	15 (6/40)	66 (40/61)	
Yes	76 (16/21)	19 (4/21)	5 (1/21)	34 (21/61)	
Previous biopsy status[b]					.93
Biopsy-naïve	69 (18/26)	15 (4/26)	15 (4/26)	43 (26/61)	
Negative biopsy	79 (19/24)	13 (3/24)	8 (2/24)	39 (24/61)	
Grade group 1 (AS)	73 (8/11)	18 (2/11)	9 (1/11)	18 (11/61)	

Note—Unless otherwise specified, values are mean ± SD or percentage with number with in parentheses. Some percentages do not total 100 owing to rounding. NA = not applicable, AS = active surveillance.
[a]Calculated for association with presence of grade group 2 or greater cancer by means of Kruskal-Wallis tests for continuous variables and Fisher exact tests for categoric variables.
[b]Lesion-level data.
[c]Values in parentheses are percentages.
[d]MRI-visible index lesion.

frequency of any cancer was not significantly different between 3 + 0 TZ lesions (26%) and 2 + 1 TZ lesions (16%) (p = .20).

A total of 18% (9/49) of the men with 2 + 1 TZ lesions underwent prostatectomy, including 12% (5/41) of those with negative, 40% (2/5) of those with GG1 PCa, and 67% (2/3) of those with GG2 PCa biopsy results. The mean interval between biopsy and prostatectomy in this subgroup was 38 days (range, 28–64 days). The men with negative biopsy or GG1 PCa results of biopsy of the 2 + 1 TZ lesion were treated with prostatectomy because csPCa was found in lesions in other locations in the prostate. Among patients with negative results of biopsy of the 2 + 1 TZ lesion, histopathologic assessment of the prostatectomy specimen did not reveal any tumor in the region of the 2 + 1 TZ lesion that was missed by targeted biopsy. In all patients with GG1 and GG2 PCa results of biopsy of the 2 + 1 TZ lesion, histopathologic assessment of the prostatectomy specimen confirmed both the presence and the GG of cancer in the region of the 2 + 1 TZ lesion diagnosed with preoperative MRI and targeted biopsy (Fig. 3).

Discussion

Using the most recent modification of PI-RADS to include both atypical BPH nodules with marked restricted diffusion (2 + 1 lesions) in the TZ, we prospectively reported PI-RADS v2.1 category 2 + 1 lesions in 6% and 3 + 0 TZ lesions in 7% of the prostate MRI examinations in our clinical practice. We found PCa in 16% of the 2 + 1 TZ lesions, approximately one-third of which (6% of all 2 + 1 TZ lesions) were clinically significant cancer. Although the 6% was lower than our 11% rate of detection of csPCa in 3 + 0 TZ lesions, the difference was not statistically significant. The 6% rate of detection of csPCa in 2 + 1 TZ lesions is also slightly lower than previously reported [14–16] for PI-RADS category 3 TZ lesions.

In a retrospective validation of PI-RADS v2 in a study that included 457 men with 352 TZ lesions assigned category 3 by two readers in consensus, Thai et al. [14] found cancer in 22% of the patients, one-half of which were csPCa. This is similar to the findings by Hofbauer et al. [15], who observed detection rates of 26% and 11% for PCa and csPCa in TZ lesions prospectively classified as PI-RADS v2 category 3. In a retrospective comparison of PI-RADS v2 and v2.1 for the assessment of TZ lesions, Byun et al. [16] reported a high (50%) rate of csPCa in 2 + 1 TZ lesions. However, their preliminary retrospective study included only eight 2 + 1 TZ lesions. Their higher prevalence of csPCa may be explained in part by the inclusion of only patients who underwent radical prostatectomy, leading to a higher level of risk in their sample than the average population risk, and by a more liberal definition of csPCa, which included tumors with a volume of 0.5 cm^3 or greater in addition to any GG2 or higher PCa.

Although evaluation of peripheral zone lesions is fairly straightforward, heterogeneity due to BPH is almost always present in the TZ, creating additional challenges for assessment. Referred to as organized chaos by Weinreb [17], this appearance is frequently used to explain the inferior diagnostic performance [18] and re-

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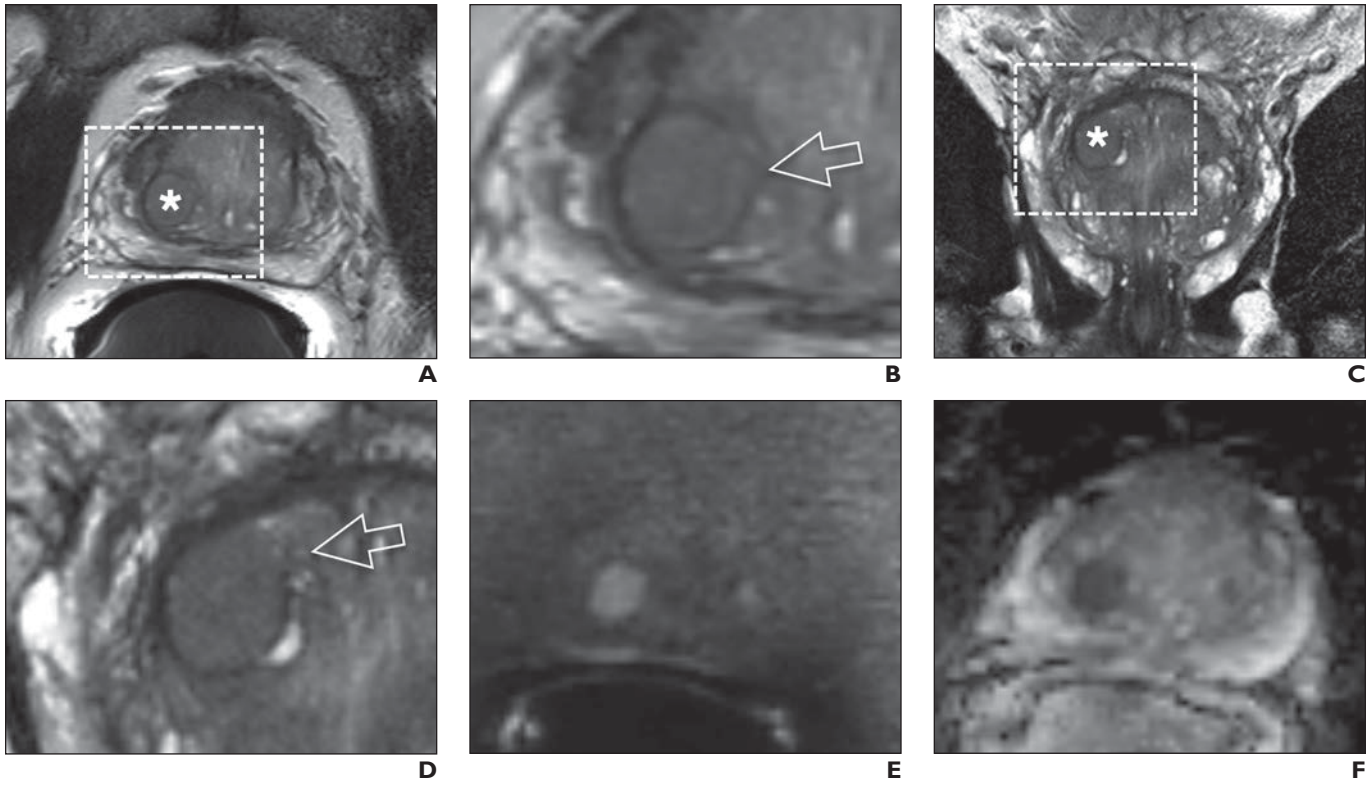

Fig. 2—60-year-old biopsy-naïve man with increasing PSA levels (most recent, 3.8 ng/mL) undergoing multiparametric MRI for biopsy planning. Example of atypical benign prostatic hyperplasia nodule with marked restricted diffusion (2 + 1 transition zone lesion) and negative result of targeted biopsy.
A and **B,** Axial T2-weighted MR images show 10-mm lesion (*asterisk*, **A**) in right base transition zone. Lesion was interpreted as nodule with incomplete capsule (*arrow*, **B**). Dashed rectangle in **A** indicates detail in **B**.
C and **D,** Coronal T2-weighted images more clearly delineate area (*arrow*, **D**) where capsule is not evident in **A** and **B,** therefore representing lesion with T2 score of 2. Asterisk (**C**) indicates 10-mm lesion**.** Dashed rectangle in **C** indicates detail in **D**.
E, High-b-value DWI (b = 2000 s/mm^2) shows lesion is markedly hyperintense. DWI score is 4; thus, PI-RADS version 2.1 assessment is category 3 (2 + 1). Targeted biopsy revealed benign prostatic tissue.
F, ADC map shows lesion is markedly hypointense.

producibility [19] of PI-RADS in the assessment of TZ lesions compared with peripheral zone lesions. In a retrospective review of 120 mpMRI examinations by six experienced readers before and after a training session to assess the interobserver reproducibility of the lexicon proposed by PI-RADS v2, Rosenkrantz et al. [19] found lower agreement for TZ than for peripheral zone lesions. Those authors reported kappa values ranging from 0.453 to 0.529 for assessment of the features closely related to 2 + 1 TZ lesions (i.e., presence of capsule and markedly hyperintense appearance on high-b-value DWI and hypointense appearance on ADC maps) in optimal circumstances in which all readers were presented with the location of the lesion to evaluate. Although they did not report separate cancer detection rates for 2 + 1 TZ lesions and 3 + 0 TZ lesions, Tamada et al. [20] retrospectively compared PI-RADS v2 and v2.1 in imaging of 58 patients who underwent mpMRI followed by MRI-TRUS fusion biopsy. Although reporting similar diagnostic sensitivity for both PI-RADS versions, the authors found that higher interobserver agreement between the two experienced readers was achieved with PI-RADS v2.1 (κ = 0.645) than with PI-RADS v2 (κ = 0.580).

Microscopically, BPH, which is not a precursor to PCa, consists of nodules of glands and intervening stroma. Most of the hyperplasia is composed of glandular proliferation, but the stroma is also increased and in some cases may predominate. This variability in histologic presentation likely explains the signal intensity heterogeneity observed in BPH nodules on MRI. In our study, no analyzed imaging or clinical parameter was significantly associated with the prevalence of csPCa in 2 + 1 TZ lesions. These included parameters commonly associated with the prevalence of csPCa, such as PSA density [21]. The lack of significant associations may have been influenced by the small sample size. However, 2 + 1 TZ lesions exhibited nonsignificant increases in lesion size and nonsignificant decreases in lesion ADC as they progressed from benign to GG1 to GG2 histologic features.

Limitations

Certain limitations of our study should be recognized. First, our data were based solely on prospectively generated radiology reports and did not incorporate a retrospective assessment of interreader agreement. Our aim was to assess the performance of real-world data collected as part of routine clinical interpretations. PI-RADS assessments assigned retrospectively by readers informed of the location of target lesions may not reflect performance in standard clinical practice. In addition, potential additional lesions identified by further retrospective review would have lacked a histologic reference standard.

Second, this was not a hypothesis-driven study, and no power analysis was performed. The sample size was small, in part reflec-

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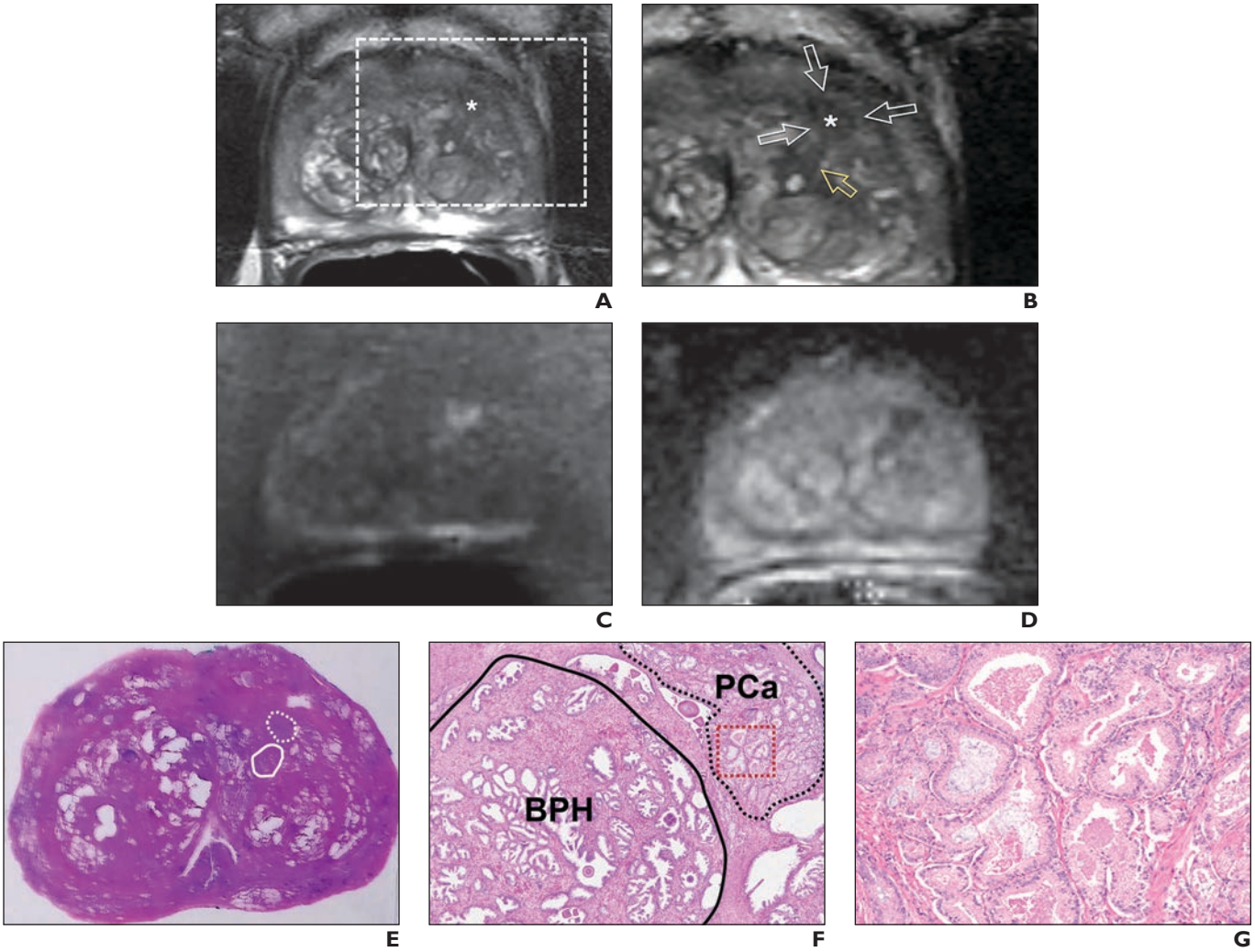

Fig. 3—66-year-old biopsy-naïve man with PSA level of 5.0 ng/mL undergoing multiparametric MRI for biopsy planning. Example of atypical benign prostatic hyperplasia (BPH) nodule with marked restricted diffusion (2 + 1 transition zone lesion) proven to represent clinically significant (grade group 2) prostate cancer.
A and **B,** Axial T2-weighted MR images show 8-mm ovoid lesion (*asterisk*; *white arrows*, **B**) in left mid gland anterior transition zone interpreted as nodular area without discernible capsule and therefore representing lesion with T2 score of 2. Yellow arrow (**B**) indicates adjacent BPH nodule without capsule (T2 score, 2) and with lower degree of restricted diffusion (DWI score, 3). Dashed rectangle in **A** indicates detail in **B**.
C, High-b-value DWI (b = 2000 s/mm^2) shows lesion was markedly hyperintense (DWI score, 4); thus, PI-RADS version 2.1 assessment is category 3 (2 + 1). Also evident is adjacent BPH nodule (*yellow arrow*, **B**) without capsule (T2 score, 2) and with lower degree of restricted diffusion (DWI score, 3). Targeted biopsy revealed grade group 2 prostate cancer, and patient was referred for radical prostatectomy.
D, ADC map image shows lesion is markedly hypointense.
E, Photomicrograph (H and E, ×1) of whole-mount slide shows cancer (*dotted line*) and adjacent BPH nodule (*solid line*).
F, Photomicrograph at low magnification (H and E, ×40) shows enlarged benign glands in area of hyperplasia (*solid line*) in contrast to adjacent densely packed atypical cancerous cells (*dotted line*) better visualized at high magnification in **G.** PCa = prostate cancer. Dashed rectangle indicates detail in **G**.
G, Photomicrograph at high magnification (H and E, ×100) more clearly shows area within rectangle in **F**.

tive of the low prevalence of 2 + 1 TZ lesions. Nonetheless, our data provide valuable insights to aid sample size calculations in future studies. Moreover, some patients (for instance, 29% [20/69] of the men with 2 + 1 TZ lesions) who had abnormal mpMRI findings chose not to undergo subsequent targeted biopsy, introducing potential patient selection bias.

In this study, targeted biopsy was used as the reference standard, and whole-mount histopathologic data were available for only a limited number of patients. However, radical prostatectomy is currently performed predominantly for patients with csPCa and thus would not be expected to be available to all patients.

Targeted biopsy, regardless of the technique used, may be affected by misregistration, which can introduce sampling error. Absence of csPCa in the very small number of patients with negative results of targeted biopsy of a 2 + 1 TZ lesion who later underwent prostatectomy because cancer was present in a different anatomic location is nonetheless reassuring.

Conclusion

Clinically significant PCa was diagnosed by means of targeted biopsy in only 6% of the prospectively reported atypical BPH nodules with markedly restricted diffusion (2 + 1 TZ lesions introduced

in PI-RADS v2.1), which is not significantly different from the 11% rate of diagnosis of csPCa in conventional 3 + 0 TZ lesions. These lesions were reported in 6% (2 + 1) and 7% (3 + 0) of all men without known csPCa who underwent prostate mpMRI. Although the broad PI-RADS categories indicate the likelihood of csPCa, knowledge of the exact percentage of csPCa within a given PI-RADS category is a useful refinement. Such information may enhance risk stratification, enable more informed discussions with patients, and facilitate management decisions (e.g., avoiding a low-yield biopsy in a man with a favorable clinical risk profile). Future studies with larger prospective samples are warranted.

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Editorial Comment on "Prospective PI-RADS v2.1 Atypical Benign Prostatic Hyperplasia Nodules With Marked Restricted Diffusion: Detection of Clinically Significant Prostate Cancer on Multiparametric MRI"

Many studies have confirmed that PI-RADS version 2 (v2) accurately identifies prostate cancer, though limitations are well documented [1]. A chief challenge is classifying difficult transition zone (TZ) lesions, on which there is fairly low interobserver agreement in PI-RADS v2. PI-RADS version 2.1 (v2.1) addresses this with incremental changes [1]. Among these changes, typical encapsulated nodules are now PI-RADS category 1 (benign), and nodules without encapsulation are PI-RADS 2 (probably benign), unless marked restricted diffusion is present (2 + 1 lesion), which upgrades these lesions to PI-RADS 3 (indeterminate).

Timely validation studies of these changes are critical to ensure appropriateness for clinical practice. Early publications suggest slightly improved accuracy and interobserver variability of PI-RADS v2.1 for TZ assessment. The largest study to date [2] showed that PI-RADS v2.1, compared with v2, achieves statistically significant small improvements in interobserver variability (weighted $\kappa = 0.70$ vs 0.62) and diagnostic accuracy for clinically significant prostate cancer (pooled AUC, 0.87 vs 0.83).

The current study adds to this validation literature by evaluating PI-RADS v2.1 TZ lesions in 1238 prospectively issued reports in a clinical practice environment. The absolute number of patients affected by the 2 + 1 TZ reporting change was only 6% (69/1238). The detection rate of clinically significant prostate cancer in 2 + 1 lesions at targeted biopsy was 6% (3/49), similar to previously published results for PI-RADS v2 category 3 lesions (4–33%) and PI-RADS v2.1 category 3 lesions (7%) [3].

The findings in this article indicate that the new 2 + 1 category should not be expected to profoundly affect overall accuracy; only three clinically significant cancers were detected in 1238 patients. Nevertheless, 2 + 1 categorization and other TZ reporting changes in PI-RADS v2.1 appear to provide small incremental improvements. Aided by such studies, debate will continue re-

(Editorial Comment continues on next page)

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Editorial Comment on "Prospective PI-RADS v2.1 Atypical Benign Prostatic Hyperplasia Nodules With Marked Restricted Diffusion: Detection of Clinically Significant Prostate Cancer on Multiparametric MRI" (continued)

garding how best to change reporting to optimize accuracy and reproducibility. For now, as the international interpretation standard, PI-RADS v2.1 can be implemented in radiology practices wherever prostate MRI is performed.

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