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ORIGINAL ARTICLE

Outcomes of magnetic resonance imaging fusion-targeted biopsy of prostate imaging reporting and data system 3 lesions

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Abstract

Purpose To evaluate the characteristics and histological outcomes in patients with Prostate Imaging Reporting and Data System (PI-RADS) 3 lesions undergoing magnetic resonance imaging-guided fusion-targeted biopsy (MRIFTB).

Methods We retrospectively reviewed 138 patients with PI-RADS category 3 lesions classified using multiparametric MRI who underwent MRIFTB between May 2016 and March 2018. The study population included biopsy-naïve and patients with prior negative biopsy. Univariate and multivariate analyzes were performed to determine significant predictors of prostate cancer (PCa) and clinically significant prostate cancer (csPCa). The definition of csPCa was set at Gleason score $\geq 3+4$.

Results Overall, 114 (82.6%) biopsied lesions were benign and 24 (17.4%) were identified as prostate cancer. Of these 24 lesions, 14 (58.3%) harbored csPCa. Peripheral zone (PZ) lesions were more likely to be associated with malignant disease than transition zone lesions (13.7 vs. 6.2%). Multivariate logistic analysis revealed that age, PZ location, and prostate-specific antigen (PSA) density ($P<0.05$) were independent predictors of both PCa and csPCa.

Conclusions A non-negligible number of PI-RADS 3 patients harbor csPCa. Moreover, age, lesion location, and PSA density could be potential clinical predictors of PCa and csPCa. Physicians should be aware of the cancer prevalence of PI-RADS 3 lesions, as the use of the aforementioned factors can help in the decision-making process for these patients.

Keywords Prostate cancer · PI-RADS score · PSA density · MRI · Prostate biopsy

Introduction

Prostate cancer (PCa) is the most common malignancy among men and the second most common cause of male cancer-related death [1]. Screening and diagnosis are based on digital rectal examination, prostate-specific antigen (PSA) values, transrectal ultrasound (TRUS), and TRUS-guided biopsy. TRUS is commonly used for prostate biopsy. Hypoechoic lesions are typically thought to be cancer but have a low sensitivity range of 0.17–0.5. Moreover, with conventional prostate biopsy methods, the cancer detection rate is 20–40% [2]. However, prostate biopsy is expensive and invasive, with a risk of hemorrhage and sepsis [3, 4]; therefore, a diagnostic procedure that can reduce the number of negative biopsies is needed.

The Prostate Imaging Reporting and Data System version 1 (PI-RADS v1), introduced in 2012, was designed to evaluate and classify multiparametric magnetic resonance imaging (mpMRI) findings [5, 6]. A meta-analysis that assessed PI-RADS v1 performance reported high accuracy for diagnosing PCa, although heterogeneity was detected because of differences in the use of PI-RADS [7]. Therefore, a standardized and globally acceptable second version (PI-RADS v2) was developed [8–10]. Comparison of the versions showed that PI-RADS v2 is more accurate in clinical practice [9] and has been validated in clinical studies [11–13].

Although patients with overall PI-RADS v2 category 4 or 5 lesions should generally undergo MRI-targeted biopsy, recommendations for further management of PI-RADS category 3 are lacking. Targeted biopsy may be the first choice, but monitoring lesion characteristics with follow-up MRI

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seems to be a practical and acceptable alternative, reducing the burden and risk of additional biopsies, especially when digital rectal examination and PSA density are stable.

This study examined the clinical characteristics of clinically significant prostate cancer (csPCa) in PI-RADS v2 category 3 lesions among patients undergoing MRI fusion-targeted biopsy (MRIFTB).

Methods

With institutional review board approval, we retrospectively reviewed 412 patients who underwent mpMRI of the prostate and subsequent MRIFTB at our institute between May 2016 and March 2018. Indications for mpMRI included increased PSA based on interpretation by the attending physician, an abnormal increase in PSA, and a PSA density cutoff of ≥ 0.15 ng/mL^2, as this value has proven helpful in the differentiation of csPCa [14]. Six patients had previous prostate surgery and were excluded. Nine had inadequate medical records or MRI studies and seven were on anti-androgen therapy at the time of biopsy. Seven who did not undergo biopsy after MRI were excluded. For those with multiple biopsied lesions, the lesion with the highest category was included in the study. Among the remaining 383, 138 patients with PI-RADS 3 lesions were identified and biopsied.

mpMRI was performed using 3-T magnetic field strength and a pelvic phased-array coil. T1-weighted, T2-weighted, and diffusion-weighted and dynamic gadolinium contrast-enhanced imaging sequences were acquired. Each MRI scan was independently interpreted by a radiologist with experience in mpMRI of the prostate in a clinical practice setting and who was not blinded to the clinical context. Each lesion was assigned a score using the PI-RADS v2 category by the interpreting radiologist and all lesions with PI-RADS v2 scores of 1–5 were defined as targets for MRIFTB.

Transrectal prostate biopsies were obtained under local anesthesia using an automatic biopsy gun and an 18-G needle under TRUS guidance. In all, 12 cores (6 in the peripheral zone and 6 in the transitional zone) were taken in all patients. Two cognitive fusion-targeted biopsy cores were added for each lesion in patients with suspicious or equivocal lesions.

Factors evaluated for risk of a positive biopsy included age, PSA level, prostate volume, interval time between mpMRI and biopsy, PSA density, body mass index (BMI), and prostate zone. Univariate and multivariate analyzes using logistic regression identified significant predictors of PCa and csPCa. Hazard ratios and 95% confidence intervals (CIs) were determined. Analyses were performed using SPSS Version 23 (IBM Corporation, NY, USA). csPCa was defined as Gleason score (GS) $\geq 3+4$ in this study. $P<0.05$ indicated statistical significance.

Results

Study population and patient characteristics

The 138 PI-RADS 3 patients ranged from 55 to 72 years of age, with a mean of 63.9 years. Of the remaining 138 men, 130 had a solitary target lesion and 8 patients had multiple lesions biopsied, resulting in a total of 149 biopsied lesions. The pre-biopsy PSA level was 9.1 ng/mL, with a mean BMI of 24.9 kg/m^2, PSA density of 0.21 ng/mL, estimated prostate volume of 45.8 mL, and mean interval between MRI and biopsy of 24.7 days. PCa was diagnosed in 17.4% (24/138). In this subset, the median age was 67.2 years, with mean BMI, 25.6 kg/m^2; pre-biopsy PSA level, 9.7 ng/mL; PSA density, 0.25 ng/mL; estimated prostate volume, 39.0 mL; and mean interval between MRI and biopsy, 29.4 days (Table 1). Fifty-eight patients (42%) had previous prostate biopsies and 58% (80 of 138) were biopsy-naive (Table 2).

Characteristics of biopsied lesions

In the whole cohort, PI-RADS 3 lesions were the most commonly biopsied (36%, 138/383), followed by category 4 (31.6%, 121/383), category 5 lesions (16.7%, 64/383),

Table 1 Patient characteristics

Parameters	All patients ($n=138$)	Prostate cancer ($n=24$)	Benign ($n=114$)	P
Age, years, mean ± SD	63.9 ± 8.1	67.2 ± 7.3	63.4 ± 8.5	0.04
BMI, kg/m^2 mean ± SD	24.9 ± 2.4	25.6 ± 2.3	24.7 ± 2.4	0.08
PSA, ng/mL, median (range)	9.1 (7.6)	9.7 (8.4)	9.0 (7.4)	0.702
PSAD, ng/mL, median (range)	0.21 (0.19)	0.25 (0.2)	0.23 (0.2)	0.413
Interval time between MRI and FTB (days)	24.7	29.4	24.2	0.664
Prostate volume, cc mean±SD	45.8 ± 19.8	39.0 ± 16.7	47.5 ± 21.0	0.06

PSAD prostate-specific antigen density, *PSA* prostate-specific antigen, *MRI* magnetic resonance imaging, *FTB* fusion-targeted biopsy

Table 2 Positive correlations and histological outcomes of PI-RADS 3 lesions

Parameters	Overall incidence ($n=138$)	Prostate cancer ($n=24$)	csPCa ($n=14$)	Benign ($n=114$)
Location of PCa detection % (n)				
PZ	52.9% (73/138)	21.9% (16/73)	13.7% (10/73)	78.1% (57/73)
TZ	47.1% (65/138)	12.3% (8/65)	6.2% (4/65)	87.7% (57/65)
Prior biopsy % (n)				
None	58.0% (80/138)	16.3% (13/80)	11.3% (9/80)	83.8% (67/80)
Negative	42.0% (58/138)	19.0% (11/58)	8.6% (5/58)	81.0% (47/58)
Targeted biopsy results % (n)				
3+3		41.7% (10)		
3+4		33.3% (8)		
4+3		16.7% (4)		
3+5				
4+4		8.3% (2)		
4+5				
5+3				
5+4				
5+5				

csPCa clinically significant prostate cancer, *PCa* prostate cancer, *PZ* peripheral zone, *TZ* transitional zone

category 1 lesions (13.8%, 53/383) and category 2 lesions (1.8%, 7/383). Prostate biopsy of PIRADS 1–5 lesions yielded prostate cancer in 20.8% (11/53), 28.6% (2/7), 17.4% (24/138), 34% (41/121) and 86% (55/64), respectively. The detection rate of csPCa was 7.5% (4/53), 14.3% (1/7), 10.1% (14/138), 24% (29/121) and 75% (48/64) in each PI-RADS category.

Of the total patients with PCa, systemic biopsy detection rates for PI-RADS 1–5 categories were 13.2% (7/53), 14.3% (1/7), 7.9% (11/138), 13.2% (16/121) and 10.9% (7/64). Systemic biopsy revealed csPCa in 3.8% (2/53), 0% (0/7), 2.9% (4/138), 5% (6/121) and 6.3% (4/64) for each PI-RADS group. Targeted biopsies detected any carcinoma in 7.5% (4/53), 14.3% (1/7), 9.4% (13/138), 20.7% (25/121), and 75% (48/64). The detection rate for csPCa in targeted PI-RADS 1–5 lesions was 3.8% (2/53), 14.3% (1/7), 7.2% (10/138), 19% (23/121) and 68.8% (44/64), respectively.

Peripheral zone (PZ) biopsies accounted for 52.9% of cases. In PI-RADS 3 lesions, csPCa was more common in the PZ (10 of 73, 13.7%) than in the transitional zone (TZ) (4 of 65, 6.2%), with a higher proportion of biopsy-negative TZ lesions (88%) than PZ lesions (78%).

The prevalence of csPCa in PI-RADS 3 lesions with targeted biopsies was 11.3% (9/80) in men with first biopsies and 8.6% (5/58) in those with previously negative biopsies (Table 2).

Risk factor evaluation

Multiple logistic regression analysis for predictors of PCa and csPCa is summarized in Table 3. Univariate logistic regression analysis showed that age ($P=0.045$ and $P=0.012$), PSA density ($P=0.025$ and $P=0.049$), and PZ location ($P=0.028$ and $P=0.045$) were significant predictors of total PCa and csPCa. PSA and prostate volume data were excluded from multivariate analysis to avoid confounding. Multivariate logistic regression analysis revealed that age ($P=0.038$ and $P=0.007$), PSA density ($P=0.033$ and $P=0.043$), and PZ location ($P=0.030$ and $P=0.047$) were independent predictors of both total PCa and csPCa.

Discussion

Although most PI-RADS 3 lesions are benign or clinically insignificant, the approximately 11% rate of csPCa demonstrated in this study reinforces the need for intervention and tissue biopsy. A prior PI-RADS v2 study revealed an 11.4–27.1% detection rate of PI-RADS category 3 lesions [15], which is consistent with our findings. Our study showed that lesions in patients with previously negative biopsies represent a significant group with equivocal suspicion of csPCa and sufficient management should be implemented. In the ongoing debate of the necessity for a biopsy of category 3 lesions, a modified threshold for proceeding to tissue diagnosis is needed for prior biopsy-negative patients. However, only 4.3% of category 3 lesions yielded high-grade disease (Table 2). When patients present with low-grade disease that is unlikely to require intervention, the minimal yield of higher-grade carcinoma should be weighed when considering benefits and risks of biopsy.

Category 3 lesions situated in the PZ were also more likely to harbor csPCa than those in the TZ, with a greater proportion of benign TZ category 3 lesions compared with

Table 3 Univariate and multivariate logistic regression analyzes to detect total prostate cancer (A) and clinically significant prostate cancer (B)

Parameters	(A) Total prostate cancer				(B) Clinically significant prostate cancer			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.061 (1.001–1.124)	0.045	1.069 (1.005–1.136)	0.038	1.106 (1.023–1.196)	0.012	1.174 (1.057–1.303)	0.007
PSA	1.010 (0.959–1.065)	0.700	Not assessed		1.041 (0.988–1.097)	0.133	Not assessed	
PSAD	1.700 (0.680–4.249)	0.025	1.672 (0.628–4.450)	0.033	3.257 (0.877–12.103)	0.049	4.301 (1.047–17.661)	0.043
BMI	1.169 (0.979–1.396)	0.085			1.354 (0.997–1.838)	0.155		
Interval between MRI and FTB	1.002 (0.994–1.009)	0.663			0.995 (0.974–1.017)	0.664		
Location of lesion								
Peripheral zone	2.750 (1.116–6.777)	0.028	3.069 (1.207–7.800)	0.030	2.469 (0.808–7.545)	0.045	2.962 (0.872–10.091)	0.047
Transitional zone	0.216 (0.084–0.555)	0.214			0.314 (0.101–0.974)	0.113		
Prostate volume	0.974 (0.947–1.002)	0.056	Not assessed		0.992 (0.964–1.036)	0.058	Not assessed	

BMI body mass index, *PSAD* prostate-specific antigen density, *PSA* prostate-specific antigen, *MRI* magnetic resonance imaging, *FTB* fusion-targeted biopsy

those in the PZ. The assessment of the TZ is more challenging than that of the PZ because of the heterogeneous and multinodular characteristics encountered in TZ hypertrophy. Even when there is a suspicion that a TZ lesion represents benign prostatic hyperplasia (BPH), due to the obscured margins caused by the mass effect within a multinodular TZ, a PI-RADS category 3 score is given. Diagnostic performance of MRI in the TZ is variable across studies, with accuracies of 66–84% [16, 17]. Moreover, TZ tumors remain difficult to detect, mostly because of the hypointense and homogeneous appearance of stromal nodules, which often show restricted diffusion [17]. Future PI-RADS versions must clarify and refine the rules for interpreting TZ lesions, particularly in the differentiation of BPH nodules. Rosenkrantz et al. [15] proposed morphological dynamic contrast-enhanced criteria for the differentiation of equivocal TZ lesions, where encapsulated swirled or popcorn-like enhancement was more suggestive of BPH than were the more suspicious finding of unencapsulated, sheet-like confluent enhancement.

PSA density helps predict biopsy outcome [18, 19]. In the present study, PSA density was an independent predictor of total PCa and csPCa. When the threshold of PSA density is set to 0.15 ng/mL, the detection rate for PCa has reported a specificity of 0.63–0.74 and sensitivity of 0.70–0.79 [18, 19]. PSA density is useful for determining csPCa and progression of PCa [18–20]. PSA density is used in the updated Epstein criteria for prediction of csPCa, as follows: PSA density of < 0.15 ng/mL/mL, GS ≤ 6, fewer than 3 positive cores, and $< 50\%$ cancer involvement in any core [21]. Moreover, PSA density was reportedly very effective in predicting prognosis of csPCa in men aged ≤ 50 years [22]. Kundu et al. [20] reported a strong correlation between PSA density with higher pathological staging and PCa aggressiveness, based on GS and tumor volume, resulting in decreased progression-free survival rate after radical prostatectomy. PSA density is useful for the prediction of biopsy outcomes, as well as for the prediction of outcomes in csPCa and aggressive PCa.

Individually, PI-RADS category and PSA density are useful for predicting biopsy outcomes. However, due to relatively low negative predictive value [23], decision making solely based on PI-RADS v2 category is difficult. A recent study in men with first biopsies investigated PSA density in PI-RADS 3 lesions and further categorized these by values of < 0.10, 0.10–0.20, and > 0.20. The detection rate of GS $\geq 3 + 4$ and GS $\geq 4 + 3$ was 18%, 31%, and 46%, and 3%, 9%, and 4%, respectively [24]. In an updated study of men on active surveillance, detection rates for GS $\geq 3 + 4$ and GS $\geq 4 + 3$ in PI-RADS 3 lesions using a PSA-density cutoff of ≥ 0.15 ng/mL^2 were 47% and 13%, without missing any upgrade to GS 3 + 4 or higher [25]. Thus, active surveillance patients with a PI-RADS 3 index lesion and PSA density of < 0.15 ng/mL^2 may not benefit from follow-up biopsy. Therefore, combined PI-RADS v2 score and PSA density are considered useful for the prediction of biopsy outcome and determination of follow-up strategy in patients with negative biopsies.

Some studies have shown that MRI fusion-targeted biopsies result in higher csPCa detection rates than those of standard TRUS biopsy and may improve assessment of tumor grade [26, 27]. Targeted biopsy techniques include MRI-guided core biopsy, MRI-TRUS fusion-guided biopsy, and cognitive registration technique. Few studies have compared outcomes among techniques. Wysock et al. [28] reported that the cancer detection rates were not significantly different between MRI-TRUS fusion- and cognitive fusion-targeted biopsy. However, Delongchamps et al. [26] found that compared to cognitive

fusion biopsy, MRI-TRUS fusion significantly increased cancer detection rates over random biopsies whereas cognitive fusion did not. All patients in this study underwent MRI-TRUS fusion-guided biopsy. Detection rates for all PCa and csPCa in the present study were comparable to those of MRI-guided core and MRI-TRUS fusion-guided biopsy series.

A limitation of this study was its retrospective design, which is associated with a risk of selection bias. Second, the definition we used to indicate csPCa is open to debate, because no universally accepted definition exists. Third, the number of patients in our study was small, possibly causing underestimation of predictive value. Therefore, larger cohort studies are needed to validate our findings. Moreover, our reference standard was a biopsy rather than a final prostatectomy specimen, so we cannot completely validate our scoring accuracy and determine the actual significance of a negative biopsy. In studies where whole mount radical prostatectomy has been used as the reference standard, only patients who underwent surgery were evaluated and there was verification bias. Therefore, we selected to use MRIFTB as our reference standard. Our analysis excluded patients without any visible lesions on MRI, so we cannot assess the detection of csPCa in such patients. Lastly, PI-RADS v2 scores were assigned by a single radiologist, and inter-observer reliability could not be assessed.

Conclusions

The prevalence of PI-RADS 3 index lesions detected during diagnostic work-up is considerable. Management strategies should be developed for this group of men with an indeterminate suspicion of having csPCa. However, the results have to be interpreted carefully considering the low number of patients. Clinicians should be aware of category 3 lesion rates, with greater emphasis placed on those in the PZ and in patients with prior negative biopsies. Furthermore, our study suggests that the addition of PSA density as a clinical predictor is helpful in diagnosing PCa and csPCa. As no management recommendations have been assigned to PI-RADS categories, further research is needed on the use of mpMRI and prostate fusion biopsy.

Author contributions TJK and SKH contributed to protocol/project development; MSL, SIH, and HJL were involved in data collection or management; TJK, MSL, and SKH analyzed the data; TJK and SKH contributed to manuscript writing/editing; TJK, HJL, and SKH were involved in critical review; SKH supervised the study.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest, including specific financial interests, relationships, and affiliations relevant to the subject materials described in this manuscript.

Ethical statements All study protocols were in accordance with the principles of the Helsinki Declaration. We removed personal identifiers and anonymized all data, which exempted the study from the need to obtain informed consent from patients.

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