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Research article

Analysis of PI-RADS 4 cases: Management recommendations for negatively biopsied patients

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ABSTRACT

Purpose: To evaluate if subgroups of patients assigned to MRI category PI-RADS 4 regarding clinical and MRI imaging aspects have distinct risks of prostate cancer (PCa) to facilitate adequate clinical management of this population, especially after negative targeted biopsy.

Methods: This prospective, IRB approved single center cross-sectional study includes 931 consecutive patients after mp-MRI at 3 T for PCa detection. 193 patients with PI-RADS assessment category 4 received subsequent combined targeted MRI/US fusion-guided and systematic 12-core TRUS-guided biopsy as reference standard and were finally analyzed. The primary endpoint was PCa detection of PI-RADS 4 with MRI subgroup analyses. Secondary endpoints were analyses of clinical data, location of PCa, and detection of targeted biopsy cores.

Results: PCa was detected in 119 of 193 patients (62%) including clinically significant PCa (csPCa; Gleason score ≥3 + 4 = 7) in 92 patients (48%). MRI subgroup analysis revealed 95% PCa (73% csPCa) in unambiguous PI-RADS 4 index lesions without additional, interfering signs of prostatitis in the peripheral zone or overlaying signs of severe stromal hyperplasia in the transition zone according to PI-RADS v2. Transition zone confined PI-RADS-4-lesions with overlaying signs of stromal hyperplasia showed PCa only in 11% (4% csPCa). Targeted biopsy cores missed the csPCa index lesion in 7% of the patients. PSA density (PSAD) was significantly higher in PCa patients.

Conclusions: Small csPCa can reliably be detected with mp-MRI by experienced readers, but can be missed by targeted MR/US fusion biopsy alone. Targeted re-biopsy of unambiguous (peripheral) PI-RADS-4-lesions is recommended; whereas transition zone confined PI-RADS-4-lesions with overlaying signs of stromal hyperplasia might be followed-up by re-MRI primarily.

1. Introduction

Multiparametric magnetic resonance imaging (mp-MRI) is currently an essential part of prostate cancer (PCa) diagnostics [1,2]. Following the instructions of the PI-RADS guidelines (Prostate Imaging – Reporting and Data System: 2015, Version 2) [3] MRI lesions can be classified according to the risk of the presence of clinically significant (cs) PCa. In lesions with a final assessment category of 4, csPCa is by definition likely to be present and soon targeted biopsy is recommended. Although mp-MRI can detect csPCa with high sensitivity and specificity [4] there is a wide range of reported detection rates in this subgroup [5–8]. As a consequence there is, until now, uncertainty how to manage patients assigned to PI-RADS assessment category 4 if targeted biopsy is negative. These lesions are described as suspicious

Abbreviations: mp-MRI, multiparametric magnetic resonance imaging; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced imaging; PCa, prostate cancer; csPCa, clinically significant prostate cancer (Gleason score ≥3 + 4 = 7); GS, Gleason score; ESUR, European Society of Urogenital Radiology; ACR, American College of Radiology; PI-RADS, prostate imaging reporting and data system, version 2; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; US, ultrasound; TRUS-GB, transrectal ultrasound-guided prostate biopsy; FUS-GB, MRI/US fusion-guided prostate biopsy; IQR, interquartile range; IQ, image quality

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focal lesions in both peripheral (PZ) and transition zone with markedly focal diffusion restriction with low signal in ADC maps and corresponding high signal in the high-b-value images, focal enhancement and focal hypointense signal changes on axial T2WI. Thus PI-RADS-4-lesions can by definition possess the same MRI aspects as PI-RADS-5-lesions, suggesting malignancy and differ from the latter solely in a smaller size with a maximum diameter less than 15 mm, which in return complicates targeted biopsy and favors sampling errors. It is fact, however, that also small PCa can be higher-grade tumors and aggressively metastasize [9]. This circumstance is taken into account by PI-RADS which allows to categorize lesions smaller than 15 mm as category 5 if extraprostatic extensions or invasive behavior are apparent [1]. Hauth et al. revealed PCa in 69% of PI-RADS-4-lesions in re-biopsy after follow-up MRI and initial negative biopsy and generally recommend instant re-biopsy of PI-RADS-4-lesions with benign histopathology results [10]. This however, leads to a substantial increase of biopsies and potential complications [11,12].

Previous studies demonstrated that subgroups of patients within assessment category PI-RADS 3, who differed in clinical conditions and MRI patterns, have different risks of PCa [13]. Proposals have already been made by other groups to further adjust or simplify the current PI-RADS system in order to improve the discriminatory power of mp-MRI [14,1].

Since patient management recommendations for the different PI-RADS categories – as they have been established by the American College of Radiology (ACR) for breast cancer [15] – are still lacking for prostate cancer this study evaluates if subgroups of patients assigned to MRI category PI-RADS 4 regarding clinical and MRI imaging aspects have distinct risks of prostate cancer (PCa) to facilitate adequate clinical management of this population, especially after negative targeted biopsy.

2. Material and methods

2.1. Study population and design

All consecutive patients with elevated PSA values or positive digital rectal examination and subsequent standardized mp-MRI for PCa detection were included in this single center cross-sectional study between January 2015 and September 2017.

Patients with PI-RADS assessment category 4 were finally analyzed and received combined targeted MRI/US fusion-guided and systematic 12-core TRUS-guided biopsy as reference standard with a mean interval of 32 ± 12 days between MRI and biopsy. Exclusion criteria were: 1. assignment to PI-RADS categories 1 to 3 or 5, insufficient imaging (no mp-MRI according to PI-RADS v2); 2. external, insufficient or refused subsequent targeted MRI/US fusion-guided (FUS-GB) plus systematic 12-core transrectal ultrasound-guided (TRUS-GB) biopsy; 3. known PCa. Parts of the patient population have been evaluated previously regarding the value of dynamic contrast-enhanced (DCE) MR imaging [Ullrich et al. 2018 under review]. Approval of the local ethics committee and written informed consent from all patients were obtained for this study.

2.2. Imaging

3 T MRI examinations with a phased-array-surface coil (8–60 channels) were performed (Magnetom TIM Trio™, Prisma™ or Skyra™; Siemens Healthcare GmbH, Erlangen, Germany). Imaging parameters were according to international recommendations [3,16] (Supp. 1). Image analyses were performed in consensus by two radiologists (T.U., L.S.) with 4 and 9 years of experience according to PI-RADS v2. Volumetric analysis and segmentation of the prostate gland was done using the DynaCAD software (Invivo, Gainsville, USA) by the same readers.

2.3. Biopsy

All patients received transrectal targeted MRI/US fusion-guided biopsy with elastic registration (two targeted cores from each lesion; Urostation, Koelis, La Tronche, France or UroNAV, Invivo, Gainsville, USA) and subsequent systematic 12-core TRUS-GB with an 18 G fully automatic biopsy gun (Bard Medical, Karlsruhe, Germany). Biopsies were conducted by two experienced urologists (C.A., A.H.) with 8 and 6 years of experience in MR-targeted transrectal prostate biopsy, respectively.

2.4. Data and image analysis

Demographic data (age), clinical data (PSA, PSAD), MRI data (prostate volume, longest lesion diameter), and biopsy data were analyzed and indicated according to the Standards of Reporting for MRI-targeted Biopsy Studies (START) [17]. For MRI subgroup analysis PCa detection was analyzed separately for all unambiguous clear PI-RADS-4-lesions according to PI-RADS v2 and for suchlike, focal, peripheral lesions that show every aspect of a PI-RADS-4-lesion but whose visibility is hindered by additional, overlaying, interfering signs of prostatitis in the whole peripheral zone and/or artifacts in DWI, as well as for focal, transitional PI-RADS-4-lesions whose visibility is hindered by overlaying, interfering signs of severe stromal hyperplasia in the whole transition zone according to PI-RADS v2. The definitions of the respective imaging criteria in the different sequences are described in detail in Supplementary Table 2 (Supp. 2). The division into the subgroups was done by the same two radiologists in consensus.

2.5. Histopathology

Histopathology evaluation (Gleason score and cancer involvement per biopsy core) was in accordance with the recommendations of the International Society of Urological Pathology (ISUP). Gleason score ≥3 + 4 = 7 (ISUP class ≥2) was defined as CsPCa [18].

2.6. Statistical analysis

IBM SPSS® Statistics (Version 21, IBM Deutschland GmbH, Ehningen, Germany) was used for statistical analyses. Descriptive statistics were expressed as mean ± SD and median + IQR). Not normally distributed data were tested with Mann–Whitney U test (MWU). McNemar test was applied to compare detection rates of systematic and targeted biopsies. Statistical significance was defined as p value < 0.05.

3. Results

3.1. Patients

931 consecutive patients with mp-MRI of the prostate were initially enrolled in the study. 193 patients (mean age 65 ± 9 years; median PSA 7.6 ng/ml, IQR 5.6–11 ng/ml; median prostate volume 45 ml, IQR 31–67 ml) with 326 PI-RADS-4-lesions on MRI finally met the inclusion criteria and were analyzed (see Flowchart; Fig. 1).

3.2. Clinical data

At the time of the biopsy, 101 patients were biopsy naïve (52%) and 92 patients had previously negative TRUS-guided biopsies (48%). Prostate volumes of biopsy naïve patients compared to patients with prior negative biopsy were significantly smaller (median 38 ml; IQR 29–54 ml vs. 55 ml, IQR 37–74 ml) ($p = 0.008$) and PSA values were significantly lower (6.3 ng/ml; IQR 4.8–8.8 ng/ml vs. 9.0 ng7ml, IQR 7.1–13 ng7ml) ($p = 0.009$). PCa was detected in 119 patients (62%; 131 PCa-positive lesions). 92 patients had csPCa with GS ≥3 + 4 = 7 (48%). Patients with PCa were significantly older ($p < 0.001$).

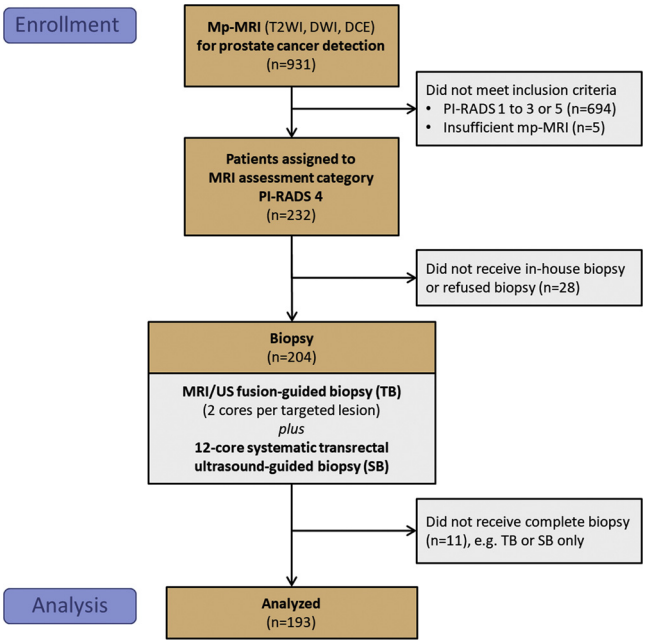

Fig. 1. Flowchart of patient enrollment and analysis.

Table 1
Prostate cancer (PCa) detection rates and Gleason score (GS) distribution.

	All patients (n = 193)	Biopsy naïve (n = 101)	Prior negative TRUS (n = 92)
Prostate cancer (PCa) detection rates			
Any cancer [% (n)]	62 (119)	73 (74)	49 (45)
GS ≥ 7	48 (92)	55 (56)	39 (36)
Gleason score (GS) distribution			
GS 3 + 3 = 6	14 (27)	18 (18)	9.8 (9)
GS 3 + 4 = 7a	26 (50)	31 (31)	21 (19)
GS 4 + 3 = 7b	12 (23)	15 (15)	8.7 (8)
GS 8	6.7 (13)	5.0 (5)	8.7 (8)
GS 9	2.6 (5)	4.0 (4)	1.1 (1)
GS 10	0.5 (1)	1.0 (1)	0

Note.- GS = Gleason score; PCa = prostate cancer.

Prostate volumes of PCa patients were significantly lower ($p < 0.001$) and calculated PSAD was significantly higher in PCa patients with a median of 0.19 ng/ml/ml (IQR 0.13-0.25) versus 0.14 ng/ml/ml (IQR 0.10-0.21; $p < 0.001$). Longest diameters of lesions did not differ significantly between patients with PCa (mean 12 ± 3 mm) and patients without PCa (mean 12 ± 4 mm; p = 029) (for detailed patient characteristic see Supp. 3). PCa detection rates and Gleason score distribution are illustrated in Table 1.

3.3. MRI subgroup analyses

Of all patients 57% (109/193) had unambiguous PI-RADS-4-lesions without artifacts or overlaying, interfering signs of peripheral prostatitis or transitional stromal hyperplasia, 20% (39/193) had focal, peripheral PI-RADS-4-lesion whose visibility is hindered by additional, overlaying, interfering signs of prostatitis in the whole peripheral zone and/or artifacts in DWI, and 23% (45/193) had focal, transitional PI-RADS-4-lesions whose visibility is hindered by overlaying, interfering signs of severe stromal hyperplasia in the whole transition zone. 95% (103/109) of the patients with clear PI-RADS 4 lesions had PCa, including 73% (80/109) csPCa. 28% (11/39) of the patients with overlaying signs of prostatitis had PCa, including 26% (10/39) csPCa. 11% (5%45) of the patients with overlaying signs of stromal hyperplasia had PCa, including 4.4% (2/45) csPCa. Examples of respective patients are shown in Fig. 2. Detailed data of subgroup analyses are illustrated in Table 2.

3.4. Prostate cancer location (lesion based)

200 of all 326 recorded PI-RADS-4-lesions (61%) were located in the PZ, 36% (n = 117) in TZ, and 2% (n = 7) in the anterior stroma (AS). Distribution and PCa detection based on the lesion localization is shown in Table 3. Overall PCa detection per lesion was significantly higher in the PZ (79%) compared to the TZ (18%) ($p < 0.001$), including csPCa ($p < 0.001$). 22% (24/109) of the clear PI-RADS 4 index lesions without overlaying signs of stromal hyperplasia or prostatitis were located in the TZ, 3% in the AS (3/109), and 75% in the PZ (82/109).

3.5. Detection of targeted biopsies

Targeted biopsy was falsely negative for PCa in 25 of 119 patients including 14 with a GS 3 + 4 = 7. Systematic biopsy missed PCa in 20 of 119 patients including 15 with GS 3 + 4 = 7. The combination of TB and SB detected significantly more PCa compared to each single biopsy method alone ($p < 0.001$). Detection rates of each biopsy method alone did not differ significantly (Table 4). All of the GS ≥ 7 PCa lesions (n = 14) solely detected in SB were located in the same region as initially described lesions in mp-MRI and could retrospectively be correlated using the information of the histopathologic report. 5 of 25 lesions, which were only detected in SB, could not be correlated in the MRI data but were low-volume GS 3 + 3 = 6.

4. Discussion

The management of patients with overall PI-RADS (v2) category 4 and subsequent negative targeted biopsy has not clearly been defined yet. In this study we found high overall PCa detection in PI-RADS-4-lesions and revealed distinct risks of PCa depending on clinical data, location of the lesion, and overlaying MRI aspects, allowing adapted management recommendations.

The overall PCa detection rates of over 60% and almost 50% csPCa correspond to the results by other groups [19–21]. No csPCa was missed by mp-MRI in this study taking targeted and systematic 12-core TRUS-guided biopsy as reference standard. Nevertheless, PCa detection in the different PI-RADS categories varies widely among different centers [6]. The reasons for these diverse results are on MRI side differences in image acquisition, experience of the reader, subjective interpretation criteria and on biopsy side differences in targeted biopsy methods and techniques, experience of the biopsy performer and also the pathologist. In order to guarantee valid results standardized imaging protocols according to PI-RADS v2 must be used and reading as well as biopsy should be performed in experienced centers.

PI-RADS category 4 might be particularly difficult since PZ lesions are per definition smaller than 1.5 cm and therefore harder to detect than bigger and more obvious PI-RADS-5-lesions, also favoring sampling errors. The stated cutoff of 1.5 cm differentiating PI-RADS 4 and PI-RADS 5 is somehow arbitrary and questionable regarding the likelihood for csPCa in this subgroup [14]. Apart from the size, PCa detection in mp-MRI might be hampered by overlaying coincidental signs of prostatitis, especially in the PZ and signs of stromal hyperplasia in the TZ.

We demonstrated high likelihood (> 70%) of csPCa in unambiguous PI-RADS-4-lesions, analogously to easy detectable PI-RADS-5-lesions. These lesions were mostly localized in the PZ. Therefore soon re-biopsy might be recommended especially in these cases.

On the other hand, csPCa detection was much lower when coincidental signs of prostatitis were apparent in the PZ or overlaying signs of stromal hyperplasia in the TZ and PCa lesions were thus concealed. As the overall PCa detection is reduced by these cases, but still the risk of having PCa varies within PI-RADS category 4 subgroup analyses are

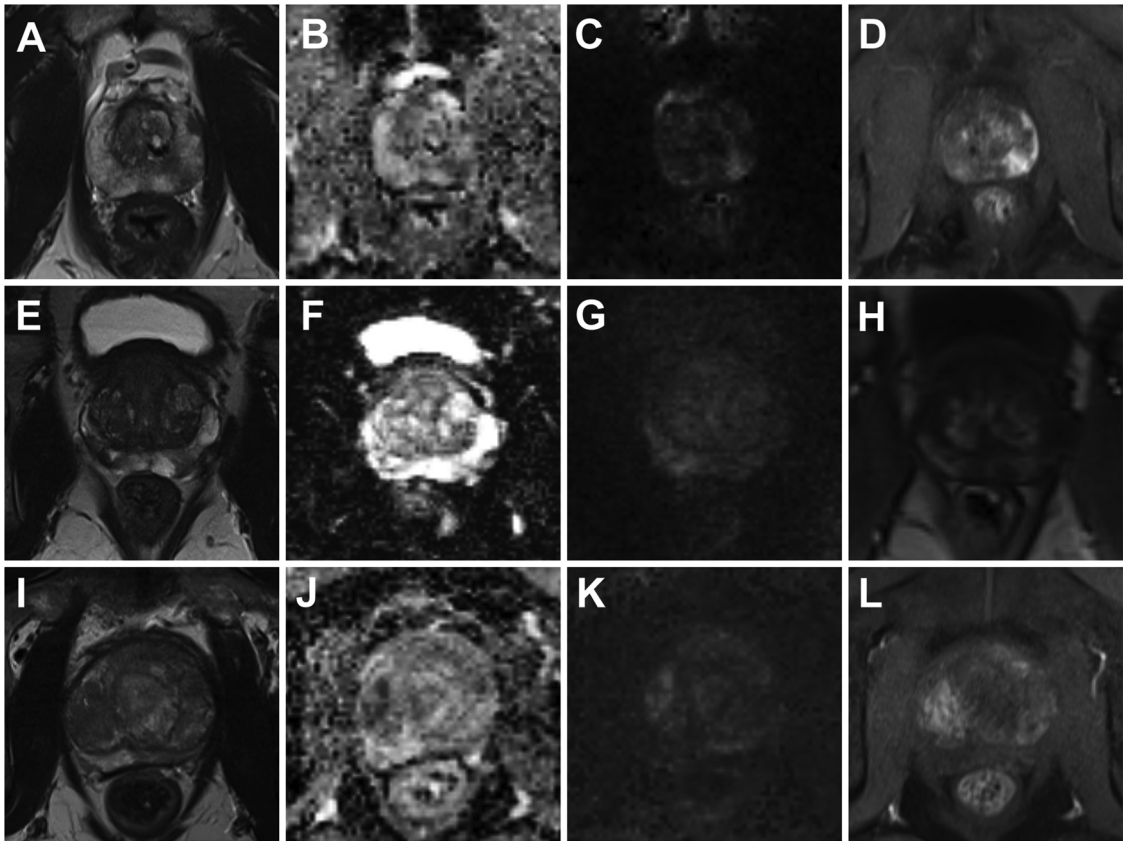

Fig. 2. Examples of PI-RADS-4-patients with different MRI appearance.
Case 1: 66-year-old man, PSA 6.3 ng/ml, PSAD 0.25 ng/ml/ml – Clear PI-RADS-4-lesion in mid left peripheral zone, markedly hypointens in T2WI (A), focal diffusion restriction (B,C) and hyperperfusion (D). 10 of 18 positive cores (GS 4 + 5 = 9; PZpl mid left; up to 60%).
Case 2: 58-year-old man, 10.4 ng/ml, PSAD 1.68 ng/ml/ml – Focal PI-RADS-4-lesion with coincidental prostatitis in right basal peripheral zone, wedge shaped moderately hypointens in T2WI (E), only mild diffusion restriction on ADC (F,G) but focal pronounced hyperperfusion (H). 5 of 18 positive cores (GS 3 + 4 = 7a; PZpl basal right; 20–40%; other cores revealed prostatitis).
Case 3: 68-year-old man, 20.2 ng/ml, PSAD 0.24 ng/ml/ml – Focal PI-RADS-4-lesion within stromal hyperplasia in left mid transition zone, ill-defined moderately hypointens in T2WI (I), focal diffusion restriction (J,K) and pronounced hyperperfusion (L). Negative histopathology of 18 biopsy cores.

Table 2
: PCa detection rates of PI-RADS 4 lesions depending on different visual and technical aspects on MRI associated with prostate cancer.

MRI subgroup characteristics per patient			
Imaging aspect		Patients with PCa	Patients with GS ≥ 7 PCa
Unambiguous PI-RADS 4 lesions w/o artifacts or inflammatory/stromal overlay*	% (n)	95 (103/109)	73 (80/109)
Focal PI-RADS 4 lesions w overlaying prostatitis in the PZ and/or artifacts in DWI**	% (n)	28 (11/39)	26 (10/39)
Focal PI-RADS 4 lesions w overlaying (severe) stromal hyperplasia in the TZ***	% (n)	11 (5/45)	4.4 (2/45)

Note.- PCa = prostate cancer; GS = Gleason score; * patients showed clear aspects of PCa; ** patients showed coincidental diffuse alterations peripheral; *** patients showed coincidental diffuse alterations in the transition zone; [a] Mann-Whitney U test; **Boldface** indicates statistically significant difference.

Table 3
Lesion distribution and location of MRI detected Prostate cancer (PCa) lesions.

	PZ	TZ	AS	p-value [b]
Distribution of all lesions [%]	61 (200/326)	36 (117/326)	2.1 (7/326)	< **0.001**
PCa lesion distribution				
Distribution of all PCa lesions [%]	79 (103/131)	18 (24/131)	3.1 (4/131)	< **0.001**
Distribution of all GS ≥ 7 lesions [%]	82 (77/94)	17 (16/94)	1.1 (1/94)	< **0.001**
PCa detection per lesion				
PCa detection per lesion [%]	52 (103/200)	21 (24/117)	57 (4/7)	< **0.001**
GS ≥ 7 PCa detection per lesion [%]	39 (77/200)	14 (16/117)	14 (1/7)	< **0.001**

Note.- TZ = transition zone; PZ = peripheral zone; PCa = prostate cancer; anterior stroma; GS = Gleason score; [b]ANOVA test was used to calculate differences in proportions of TZ, PZ and AS; **Boldface** indicates statistically significant difference.

Table 4
: Comparison of prostate cancer (PCa) detection in targeted MRI/US fusion-guided biopsy (FUS-GB) and 12-core systematic transrectal ultrasound-guided biopsy (TRUS-GB).

		N	Detection rates [%]	p-value [b]
TB vs SB	**Any cancer**	94 vs 99	49 vs 51	0.06
TB vs combination		94 vs 119	49 vs 62	< **0.001**
SB vs combination		99 vs 119	51 vs 62	< **0.001**
TB vs SB	**GS ≥ 7 PCa**	78 vs 77	40 vs 40	1.0
TB vs combination		78 vs 92	40 vs 48	< **0.001**
SB vs combination		77 vs 92	40 vs 48	< **0.001**
Gleason upgrade by TB [%]				
Higher Gleason score on TB compared to SB		40	34	**n.a.**
Described MRI lesion detected only on corresponding SB cores [%]				
All PCa		20	80	**n.a.**
GS ≥ 7 PCa		14	100	**n.a.**

Note.- TB = targeted biopsy (MR/US FUS-GB); SB = systematic biopsy; PCa = prostate cancer; GS = Gleason score; [b]McNemar test was used to test for statistical significance; **Boldface** indicates statistically significant difference.

important to design adapted management recommendations.

Immediate re-biopsy might not be crucial if the respective index lesion is located in the TZ with overlaying severe stromal hyperplasia, considering the fact that less than 5% of these lesions finally contain csPCa. Therefore, the general recommendation of instant re-biopsy of all negative PI-RADS-4-lesions by Hauth et al. could be optimized in experienced centers to prevent overdiagnostic and overtreatment, considering that overall mortality in patients with initial benign biopsy results seems to be low [10,22].

Even though PCa detection rates tend to decrease in re-biopsies [23,24] we previously revealed high detection rates in secondary biopsy settings using targeted MRI-guided in-bore biopsy [8]. The combination of FUS-GB and systematic TRUS-guided biopsy detected significantly more PCa including csPCa than each biopsy method alone which is in accordance with other studies [25,26].

PSAD as clinical parameter was significantly higher in PCa patients, which is in line with previous studies that suggested PSAD as independent risk factor for PCa [27–29].

Limitations of this study are the single center design and lack of patient follow-up analyses. Second, we used targeted MRI/US fusion-guided plus systematic 12-core TRUS-guided biopsy as reference standard, but did not compare the detected lesion with whole mounted radical prostatectomy specimens. No inter- or intra-reader agreement analysis has been performed since assessment of overlying signs of prostatitis and/stromal hyperplasia has been done in consensus. As different definitions of clinical significance of PCa exist, results might vary depending on the respective definition.

In conclusion, patients assigned to final PI-RADS assessment category 4 possess a high likelihood of PCa and initially have to be biopsied. Given the high overall risk of PCa in this PI-RADS category, targeted re-biopsy of unambiguous, especially peripheral PI-RADS-4-lesions is recommended after initial negative MR/US fusion biopsy. Transition zone confined PI-RADS-4-lesions with overlaying signs of stromal hyperplasia might be followed-up by re-MRI primarily. In uncertain cases PSAD should be considered for biopsy decision. In 7% of patients targeted MR/US fusion biopsy cores alone missed the csPCa lesion and therefore additional systematic TRUS-GB should primarily be performed.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.01.030.

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