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ABSTRACT

Purpose: Patients with suspicion of clinically significant prostate cancer (csPC) on multiparametric prostate MRI (mpMRI) but negative or inconclusive MRI/US fusion-guided biopsy (FB) can be challenging in clinical practice. To assess the utility of MRI in-bore biopsy (IB) in patients with discordant imaging and histopathological findings after FB.

Methods: Consecutive patients with Prostate Imaging Reporting and Data System (PI-RADS) category 4 or 5 on mpMRI at 3T after FB without histologically confirmed csPC who underwent IB between 01/2014 and 05/2022, were retrospectively included. The primary objective was to assess the detection rate of csPC. Secondary objectives were to analyze clinical parameters, MRI parameters, and lesion localization.

Results: In the final cohort of 51 patients, the IB resulted in an overall detection rate of 71% for PC and 47% for csPC. Furthermore, in 55% of cases with initial low-grade PC, the Gleason score was upgraded after IB. CsPC was often detected apical and/or anterior. The detection rate for PC was 58% in PI-RADS category 4 and 94% in PI-RADS category 5 (csPC 39% and 61%, respectively). Patients with csPC had statistically significant smaller prostate volumes, a higher PI-RADS category, a higher prostate-specific antigen density (PSAD), and were older.

Conclusions: For a relevant proportion of patients with PI-RADS category 4 or 5 and negative or inconclusive findings on previous FB, but with persistent suspicion of csPC, a subsequent IB verified the presence of csPC. Therefore, IB can be a backup in cases of uncertainty.

1. Introduction

Multiparametric prostate MRI (mpMRI) and targeted biopsy have replaced primary or standalone systematic biopsy in many clinical settings due to the improved detection rates of clinically significant prostate cancer (csPC) and decreased diagnosis of low-grade tumors [1]. A targeted biopsy can be conducted in three ways: cognitive fusion, MRI/US fusion-guided biopsy, and MRI in-bore biopsy. The cognitive fusion requires the operator to mentally align the ultrasound and MRI images during the biopsy. MRI suspicious lesions are typically invisible on ultrasound; therefore, the operator must have experience in both techniques to successfully perform a valid fusion. In contrast, MRI/US fusion-guided biopsy uses software-assisted fusion to create either a firm or a flexible fusion pertaining to the borders of the prostate. MRI in-

Abbreviations: csPC, clinically significant prostate cancer; ISUP GG, International Society of Urological Pathology Grade Group; mpMRI, Multiparametric prostate MRI; PC, prostate cancer; PI-RADS, Prostate Imaging - Reporting and Data System; US, ultrasound.

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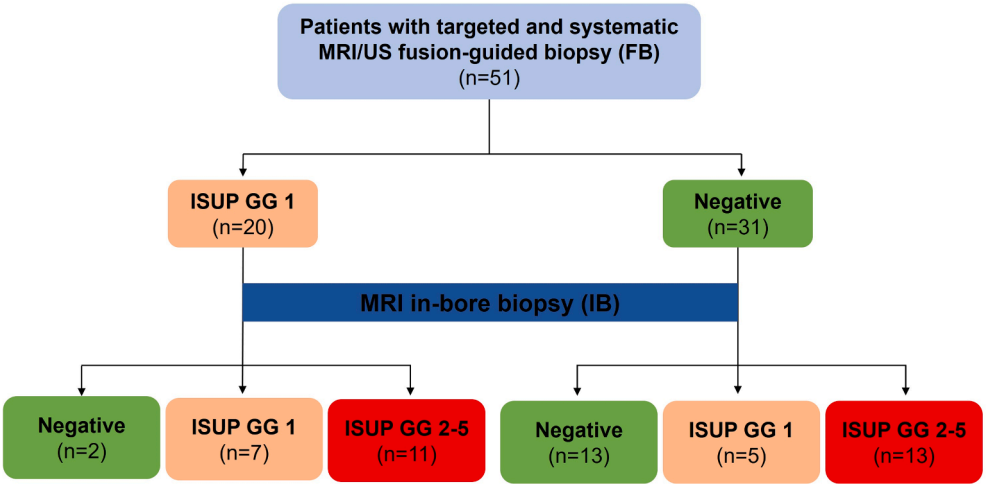

Fig. 1. Study population flow chart. *ISUP = International Society of Urological Pathology; GG = Grade Group.*

bore biopsy, conducted within the MRI scanner, is the only biopsy method that employs the same imaging modality for diagnosis and localization of lesions during biopsy. For many patients, MRI/US fusion-guided biopsy is the most clinically relevant method due to its higher availability, lower costs, and effort [2]. Simultaneous systematic biopsy can be easily combined with cognitive fusion or MRI/US fusion-guided biopsy in one session, but can also be combined with MRI in-bore biopsy. However, if prostate segmentation (prostate boundary correlation) is inadequate or lesion registration is inaccurate, csPC may be missed on MRI/US fusion-guided biopsy [3]. Additionally, the detection rates for csPC are significantly affected by the quality of the MRI and the operator's level of experience in conducting biopsies. Nevertheless, lesions that have a high or persistent suspicion for csPC followed by targeted biopsy without confirmation of csPC, can pose challenges in daily clinical practice [4]. In such cases, MRI in-bore biopsy provides an accurate documentation of biopsy specimens via needle-in-scan, making it a valuable substitute [5].

Thus, the objective of this study is to assess the significance of MRI in-bore biopsy for patients with a high suspicion of clinically significant prostate cancer on MRI but with negative or inconclusive results following MRI/US fusion-guided biopsy.

2. Materials and methods

2.1. Study design

The study was approved by our Institutional Review Board (Medical Faculty, Heinrich-Heine-University Düsseldorf; Study ID: 2020-1221). We retrospectively enrolled consecutive patients who underwent MRI in-bore biopsy after previous MRI/US fusion-guided biopsy without histologically proven csPC from 01/2014 to 05/2022. Inclusion criteria were suspected csPC on mpMRI (Prostate Imaging - Reporting and Data System PI-RADS category of 4 or 5), successful MRI in-bore biopsy, and previous MRI/US fusion-guided biopsy (targeted plus systematic). MRI in-bore biopsy was performed in 14 % of patients with suspicious mpMRI (PI-RADS category 4 or 5) and subsequent MRI/US fusion-guided biopsy without confirmation of csPC. The only exclusion criterion was previous treatment for PC (Fig. 1).

2.2. MR imaging

The mpMRI examinations were conducted in accordance with the PI-RADS recommendations [6]. The MRI protocol comprised T1-weighted imaging, high-resolution T2-weighted imaging (in three orthogonal planes; 3 mm slice thickness), diffusion-weighted imaging (including high b-value images and ADC-map calculation), and dynamic contrast-enhanced sequences. All scans were acquired using a 3T scanner.

2.3. MRI/US fusion-guided biopsy

Contouring of the prostate boundary (segmentation) and registration of the suspicious lesion with a 3D ROI, including a sub-ROI of the suspected most aggressive part of the tumor (lowest ADC value), were performed by a radiologist with at least 2 years of experience in mpMRI using DynaCAD software (version 3 or 4, Philips Healthcare, Invivo Corporation). All biopsies were performed transrectally by an experienced urologist with more than 5 years of experience, under periprostatic nerve block and oral antibiotic prophylaxis. All patients underwent MRI/US fusion-guided biopsy with combined targeted cores from the highly suspicious lesions and an additional 12 systematic cores using the UroNAV biopsy system (Philips Healthcare, Invivo Corporation). UroNAV uses elastic fusion of real-time ultrasound segmentation data for lesion targeting. A minimum of two adequate targeted biopsy cores were obtained from each suspicious lesion.

2.4. MRI in-bore biopsy

Transrectal MRI in-bore biopsy was performed and/or supervised by an uro- and interventional radiologist with more than 10 years of experience (L.S.), under local anesthesia and oral prophylactic antibiotics, on a 3T MRI scanner (Magnetom Prisma and Trio Tim, Siemens) using the DynaTRIM device (Invivo). Patients were placed in the prone position. An MR-compatible guide was inserted into the rectum and connected to the biopsy device (DynaTRIM device, Invivo). Biopsy planning was performed on the DynaCAD workstation (Invivo) using T2-weighted axial and sagittal images (T2 HASTE sequences: TR 2000 ms; TE 76 ms; FOV 28 cm; voxel size 1.4 × 1.1 × 3.0 mm). Two cores were taken from each suspicious lesion using an MR-compatible, fully automated 18-gauge biopsy gun (either 150- or 175-mm needle length, Invivo). Cores were taken from the most aggressive parts of the lesions (lowest ADC value) according to the previous mpMRI data. In unclear cases an additional DWI sequence was supplemented during biopsy. To ensure correct needle positioning within the lesion, needle-in control scans were obtained in axial and coronal orientations (T2 HASTE sequences: TR 1600 ms; TE 96 ms; FOV 38 cm; voxel size 1.5 × 1.2 × 4.0 mm; acquisition time 32 s).

2.5. Histopathology

All biopsy cores were histopathologically evaluated in accordance

Table 1
Baseline characteristics.

Variable		Value
Patients [n]		51
Age [y] mean ± SD		64 ± 8.4
PSA [ng/ml] median (IQR)		10.0 (6.2–12.8)
Prostate volume [ml] median (IQR)		42 (33–61)
PSAD [ng/ml/cm^3] median (IQR)		0.21 (0.13–0.36)
PI-RADS [n]	4	33
	5	18

PSA = prostate specific antigen; PSAD = PSA density; PI-RADS = Prostate Imaging – Reporting and Data System; SD = standard deviation; IQR = interquartile range.

Table 2
Detailed parameters of the MRI in-bore biopsy (IB).

Variable			Value
PC % (n)			71 (36)
csPC % (n)			47 (24)
csPC prior negative FB % (n)			42 (13)
csPC prior ISUP GG 1 PC in FB % (n)			55 (11)
No cancer % (n)			29 (15)
Time between IB and previous FB [month] median (IQR)			12 (2–20)
Biopsy time [min] median (IQR)			35 (30–40)
Number of cores median (IQR)			5 (5–6)
Maximum cancer percentage of core [%] median (IQR)			50 (29–70)
Gleason score distribution % (n)	3 + 3 = 6	ISUP GG 1	12 (33)
	3 + 4 = 7	ISUP GG 2	14 (39)
	4 + 3 = 7	ISUP GG 3	6 (17)
	4 + 4 = 8	ISUP GG 4	1 (3)
	4 + 5 = 9	ISUP GG 5	3 (8)

PC = prostate cancer; csPC = clinically significant PC (ISUP GG 2–5); IB = MRI in-bore guided prostate biopsy; ISUP = International Society of Urological Pathology; GG = Grade Group; IQR = interquartile range; FB = MRI/US fusion-guided biopsy.

with ISUP recommendations by an experienced pathologist with more than 10 years of experience. ISUP grade groups (ISUP GG) ≥ 2 were defined as csPC [7].

2.6. Image analysis

MpMRI studies were prospectively reviewed by experienced radiologists prior to the biopsy. All studies were reconfirmed according to PI-RADS v2.1 by two experienced, board-certified radiologists in consensus during subspecialty consultation (M.Q. and L.S., both with more than 10 years of experience reading prostate MRI). Images were reviewed for lesion localization. In accordance with PI-RADS v2.1 recommendations, the maximum diameter of each lesion was measured on the ADC-map for peripheral zone lesions and on T2-weighted images for transitional zone lesions; however, in cases of doubt, the sequence that best depicted the lesion was used [6]. Prostate volume was measured using volumetric software (DynaCAD, Philips Healthcare). Prostate-specific antigen density (PSAD) was calculated by dividing the blood PSA levels by prostate volume.

2.7. Statistical analysis

Descriptive statistical analysis was performed using IBM SPSS® Statistics (version 21, IBM). Patient characteristics were presented as mean ± standard deviation for normally distributed variables, or median with interquartile range (IQR) for nonparametric data. Detection rates were reported as both relative and absolute numbers. Subgroup analyses were conducted for patients with histologically confirmed low-grade tumors (ISUP GG 1), csPC (ISUP GG 2–5), and patients with negative biopsy results, using ANOVA. P values <= 0.05 were considered statistically significant.

Table 3
Analysis of PI-RADS and clinical parameter to final histopathology after MRI in-bore biopsy (IB).

		Negative	ISUP GG 1	ISUP GG 2–5	P value
all (n = 51)					
PI-RADS [n]	4	14	6	13	0.02
	5	1	6	11	
Age [y] mean ± SD		60 ± 7.7	66 ± 8.1	66 ± 8.3	0.05
Volume [ml] median (IQR)		61 (39–73)	53 (46–58)	38 (29–43)	0.01
PSA [ng/ml] median (IQR)		11 (7.5–19)	7.3 (4.6—10)	11 (8.0–13)	0.08
PSAD [ng/ml/cm^3] median (IQR)		0.17 (0.13–0.33)	0.15 (0.11–0.19)	0.25 (0.20–0.40)	0.09
		0.17 (0.11–0.29)			0.05

PSA = prostate specific antigen; PSAD = PSA density; PI-RADS = Prostate Imaging – Reporting and Data System; SD = standard deviation; IQR = interquartile range; IB = MRI in-bore guided prostate biopsy; ISUP = International Society of Urological Pathology; GG = Grade Group; IQR = interquartile range.

Table 4
Cross table of PI-RADS and histopathology divided by patients with prior ISUP GG 1 PC and negative biopsy.

		Negative	ISUP GG 1	ISUP GG 2–5	Total
Patients with prior ISUP GG 1 PC in FB					
PI-RADS [n]	4	2	4	6	12
	5	0	3	5	8
total		2	7	11	20
Patients with prior negative biopsy in FB					
PI-RADS [n]	4	12	2	7	21
	5	1	3	6	10
Total		13	5	13	31

PI-RADS = Prostate Imaging – Reporting and Data System; IB = MRI in-bore guided prostate biopsy; ISUP = International Society of Urological Pathology; GG = Grade Group; FB = MRI/US fusion-guided biopsy.

3. Results

3.1. Patients

A total of 51 patients, with a mean age of 64 years, a median PSA of 10 ng/ml, and a median prostate volume of 42 ml, were finally included in the analysis (Table 1). MRI/US fusion-guided biopsy revealed low-grade PC (ISUP GG 1) in 20 patients, while the remaining 31 patients had initially negative biopsy results. The persistent suspicion of csPC was confirmed in 33 patients with PI-RADS category 4 and in 18 patients with PI-RADS category 5.

3.2. PC detection

The PC detection rate after MRI in-bore biopsy was 71 % (36 out of 51), and for csPC, it was 47 % (24 out of 51). MRI in-bore biopsy resulted in a Gleason score upgrade in 55 % of cases with initial ISUP GG 1 PC (11 out of 20). The distribution of Gleason scores is presented in Table 2. The overall detection rate for PI-RADS category 4 was 58 %, and for PI-RADS category 5 it was 94 %; the detection rates for csPC were 39 % and 61 %, respectively (Table 3). Only one patient with PI-RADS category 5 showed no evidence of prostate cancer on MRI in-bore biopsy. CsPC was detected in 42 % of patients with prior negative biopsy results from MRI/US fusion-guided biopsy (13 out of 31) (Table 4).

Table 5
Subgroup analysis of PC localization and IL diameter.

% (n)			ISUP GG 1 (n = 12)	ISUP GG 2–5 (n = 24)	P value
IL localization % (n)	Zonal	PZ	42 (5)	46 (11)	0.88
		TZ	33 (4)	25 (6)	
		AFS	17 (2)	29 (7)	
		CZ	8 (1)	0 (0)	
	Anatomical	apical	25 (3)	58 (14)	0.07
		mid	58 (7)	38 (9)	
		basal	17 (2)	4 (1)	
		anterior	42 (5)	71 (17)	0.17
		posterior	58 (7)	29 (7)	
		lateral	58 (7)	33 (8)	0.24
		medial	42 (5)	67 (16)	
IL diameter [mm] mean ± SD			15 ± 3.3	14 ± 4.6	0.20

IL = index lesion; ISUP = International Society of Urological Pathology; GG = Grade Group; PZ = peripheral zone; TZ = transition zone; AFS = anterior fibromuscular stroma; CZ = central zone; mid = middle gland; SD = standard deviation.

3.3. Subgroup analysis

Patients with csPC had statistically significantly smaller prostate volumes, higher PI-RADS categories, were older, and had higher prostate-specific antigen density (PSAD) compared to those with low-grade or no PC, as shown in Table 3. CsPC was predominantly located in the peripheral zone, mostly in the apical, anterior, and medial parts of the prostate (Table 5). There was no statistically significant difference in either the location or the diameter of the index lesion between low-grade PC and csPC.

4. Discussion

MRI-guided targeted biopsy is the standard approach for cases with suspicious findings for clinically significant prostate cancer (csPC) on mpMRI. This study showed that a proportion of patients with a negative or low-grade prostate cancer (ISUP GG 1) biopsy after systematic plus targeted MRI/US fusion-guided biopsy still had clinically significant prostate cancers (csPC), despite the high detection rates achieved by MRI/US fusion-guided biopsy in experienced settings.

The EAU guidelines recommend the use of MRI-guided targeted biopsy without expressing a clear preference for any specific method, such as cognitive fusion, MRI/US fusion-guided biopsy, or MRI in-bore biopsy. Although a review found no significant differences in the detection rates of csPC among the three methods [8], other literature indicated that MRI in-bore biopsy offers better detection rates compared to cognitive biopsy and similar results to MRI/US fusion-guided biopsy [9]. The variation in findings can likely be caused by heterogeneity of the included studies. However, MRI in-bore biopsy has shown a higher target-specific cancer detection rate than MRI/US fusion-guided biopsy [10,11]. It also enables direct visualization of the lesion-needle interaction, even in small lesions (Fig. 2). Therefore, a stepwise approach may be beneficial, using the less commonly available MRI in-bore biopsy as a backup method for cases with discordant histopathologic results after MRI/US fusion-guided biopsy.

This study found a csPC detection rate of near to 50 % in MRI in-bore biopsy, which is higher than the rates reported in the literature which range from 25 to 38 % [12,13]. Histopathologic upgrading was observed at a similar rate of 60 % [14]. Prostate cancer can be missed during MRI/US fusion-guided biopsy due to unexpected tissue displacement, suboptimal needle trajectory leading to inadequate MRI and/or US contouring of the prostate margin, or inaccurate registration of the index lesion [3]. However, there are significant differences among the available MRI/US fusion systems, ranging from basic rigid fusion platforms to advanced elastic fusion systems used in this study [2]. Direct comparison of the biopsy results is difficult due to distinct patient populations and varying csPC prevalence. Additionally, the accuracy of MRI/US fusion-guided biopsy significantly improves with experience, indicating a notable learning curve [15]. For patients with suspicious findings on mpMRI but negative systematic biopsy results, targeted biopsy alone is recommended [16]. However, systematic biopsy acts as a safety net when targeted biopsy cores are absent or inaccurate. Currently, the combined approach achieves the highest detection rates for csPC [17]. In this study, all patients underwent both systematic biopsy and targeted biopsy, suggesting the possibility of even higher csPC detection rates after targeted biopsy alone.

It has been observed that MRI/US fusion-guided biopsy may not consistently detect csPC in patients with larger prostate volumes [18]. Additionally, the lesion's location significantly impacts detection rates. In this study, the majority of identified csPCs were situated anteriorly

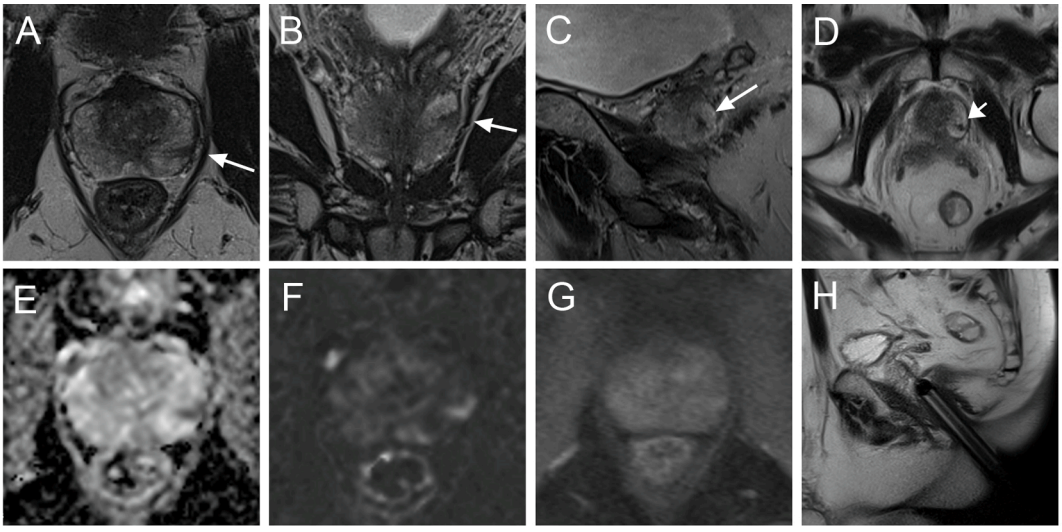

Fig. 2. Small lesion in the left, basal, posterolateral, peripheral zone (small arrow). Age 53; PSA 5.8 ng/ml; Volume 28 ml; PSAD 0.21 ng/ml/ml; PIRADS 4; ISUP GG 2. **A**: axial T2w; **B**: coronal T2w; **C**: sagittal T2w showing a hypointense lesion; **E**: ADC-map with reduced ADC-values; **F**: high b-value image with hyperintense signal; **G**: perfusion map with early asymmetric enhancement; **D, H**: axial and sagittal T2w needle-in scan with needle in the center of the posterolateral lesion (broad arrow).

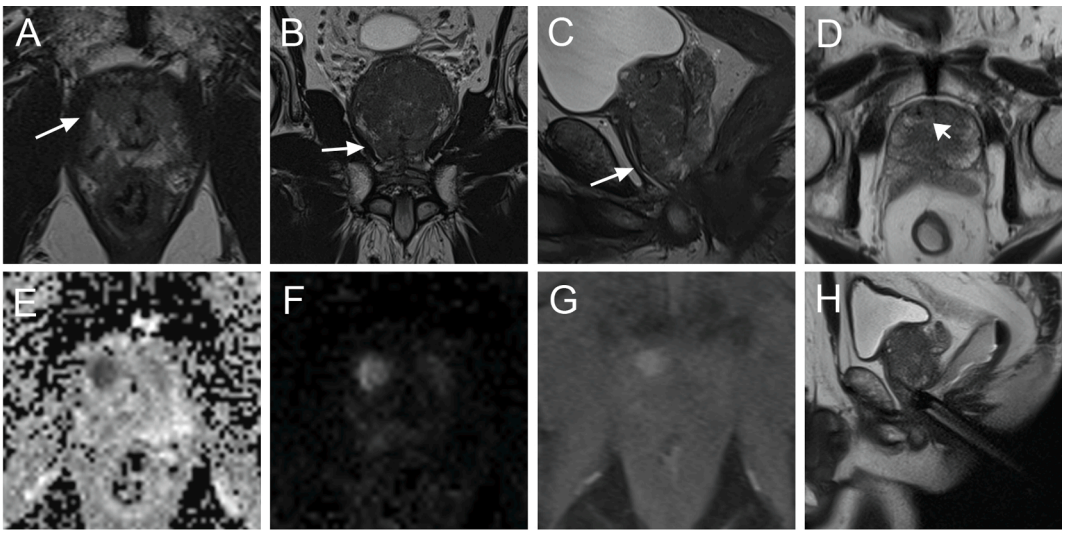

Fig. 3. Anterior apical lesion on the right side of the peripheral zone (small arrow). Age 78; PSA 11.0 ng/ml; Volume 53 ml; PSAD 0.21 ng/ml/ml; PI-RADS 4; ISUP GG 3. **A**: axial T2w; **B**: coronal T2w; **C**: sagittal T2w showing a hypointense lesion; **E**: ADC-map with reduced ADC-values; **F**: high b-value image with hyperintense signal; **G**: perfusion map with early asymmetric enhancement; **D, H**: axial and sagittal T2w needle-in scan with needle in the center of the anterior lesion (broad arrow).

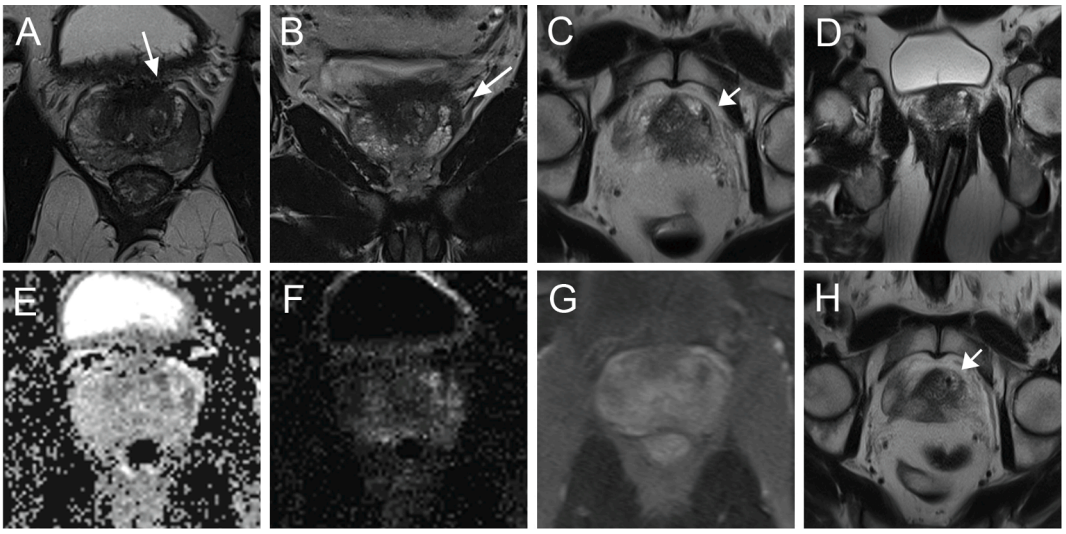

Fig. 4. Diffuse lesions in the anterolateral, basal, left, peripheral and transition zone (small arrow). Age 55; PSA 21.8 ng/ml; Volume 42 ml; PSAD 0.52 ng/ml/ml; PIRADS 4; ISUP GG 2. **A**: axial T2w; **B**: coronal T2w showing a hypointense lesion peripher anterior lateral and anterior medial in the transition zone; **E**: ADC-map with reduced ADC-values; **F**: high b-value image with slightly hyperintense signal; **G**: perfusion map with diffuse enhancement; **C, D**: axial and coronal T2w needle-in scan with needle in the center of the lateral lesion; **H**: axial T2w needle-in scan with needle in the center of the medial lesion (broad arrow).

and apically (Fig. 3). These regions are more challenging to access via a transrectal approach [19]. To address this challenge, Bajeot et al. suggest supplementing transrectal MRI/US fusion-guided biopsy with transperineal targeted biopsy in cases of discordance between imaging and pathological findings [20]. However, the optimal biopsy route remains undetermined. Consequently, the PERFECT trial, a multicenter randomized controlled clinical study, is currently underway to compare the efficacy and safety of transperineal and transrectal targeted biopsy approaches for csPC [21]. However, the identification of diffuse lesions, which may be challenging to discern on multiparametric MRI (Fig. 4), can present a notable obstacle.

Consistent with the findings of this study, PI-RADS category 5 has demonstrated cancer detection rates exceeding 90 % [22]. In cases of significant discordance between imaging and histopathologic results, a thorough re-evaluation of the diagnostic pathway, from MRI to biopsy and subsequent histopathologic analysis is crucial. This re-evaluation should include consideration of an additional biopsy, particularly for patients with smaller prostate volumes [4]. Numerous clinical studies, aligning with our investigation, have reported an inverse correlation between prostate size and both the incidence and aggressiveness of prostate cancer. Some evidence even suggesting a protective effect of larger prostate size against prostate cancer [23].

The study has limitations due to its retrospective design and single-center approach. Furthermore, MRI in-bore biopsy was not available for all cases with PI-RADS category of 4 or higher, despite the absence of evidence of csPC in prior MRI/US fusion-guided biopsy. Therefore, it is possible that the proportion of patients without evidence of csPC on MRI/US fusion-guided biopsy may have been underestimated. Furthermore, this study did not include postoperative outcomes or long-term follow-up of the enrolled patients. As a result, patients who tested negative on biopsy after negative MRI/US fusion-guided biopsy and MRI in-bore biopsy may still have undetected tumors.

5. Conclusions

Our findings suggest a sequential strategy, using MRI in-bore biopsy as a backup for men with a strong suspicion of clinically significant prostate cancer on mpMRI but without confirmation from MRI/US fusion-guided biopsy. This approach is supported by the fact that almost half of this patients were diagnosed with clinically significant prostate cancer by MRI in-bore biopsy. The MRI in-bore biopsy proved to be particularly beneficial in such a pathway for patients with PI-RADS category 5 or ISUP GG 1 prostate cancer, as well as for those presenting with apical and/or anterior clear MRI-lesions (may differ depending on the initial biopsy approach), and smaller prostate volumes with higher PSA density (PSAD).

CRediT authorship contribution statement

M. Quentin: Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **M. Boschheidgen:** Writing – review & editing, Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **J.P. Radtke:** Writing – review & editing, Supervision, Resources, Investigation, Conceptualization. **F. Spohn:** Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **T. Ullrich:** Writing – review & editing, Validation, Formal analysis, Data curation, Conceptualization. **L. Drewes:** Validation, Resources, Investigation. **B. Valentin:** Investigation, Data curation. **J. Lakes:** Validation, Investigation. **Al-Monajjed:** . **C. Arsov:** Writing – review & editing, Conceptualization. **I. Esposito:** Writing – review & editing, Data curation. **P. Albers:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization. **G. Antoch:** Writing – review & editing, Supervision, Resources, Conceptualization. **L. Schimmöller:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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