Detection of clinically significant prostate cancer in biopsy-naïve men

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DETECTION OF CLINICALLY SIGNIFICANT PROSTATE CANCER IN BIOPSY-NAÏVE MEN: DIRECT COMPARISON OF SYSTEMATIC BIOPSY, MULTIPARAMETRIC MRI- AND CONTRAST ULTRASOUND DISPERSION IMAGING-TARGETED BIOPSY

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ABBREVIATIONS

3D	Three dimensional
4M	Met prostaat MRI Meer Mans
CE(US)	Contrast-enhanced ultrasound/ultrasonography
(cs)PCa	(Clinically significant) prostate cancer
CR/IDC	Cribriform growth pattern and/or intraductal carcinoma
CUDI	Contrast ultrasound dispersion imaging
DCE	Dynamic contrast-enhanced imaging
ISUP	International Society of Urological Pathology
GG	Grade group
mpMRI	Multiparametric magnetic resonance imaging
PI-RADS	Prostate Imaging Reporting and Data System
PRECISION	Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not?
PZ	Peripheral zone
SBx	Systematic biopsy
TBx	Targeted biopsy

ABSTRACT

Objectives

To compare and evaluate a multiparametric magnetic resonance imaging (mpMRI)-targeted biopsy (TBx) strategy, contrast-ultrasound dispersion imaging (CUDI)-TBx strategy and systematic biopsy (SBx)-strategy for the detection of clinically significant prostate cancer (csPCa) in biopsy-naïve men.

Methods

A prospective, single-centre paired diagnostic study included 150 biopsy-naïve men, from November 2015 to November 2018. All men underwent pre-biopsy mpMRI and CUDI followed by a 12-core SBx taken by an operator blinded from the imaging results. Men with suspicious lesions on mpMRI and/or CUDI also underwent MRI- TRUS fusion-TBx and/or cognitive CUDI-TBx after SBx by a second operator. A non-inferiority analysis of the mpMRI- and CUDI-TBx strategies in comparison with SBx for International Society of Urological Pathology Grade Group [GG] ≥2 PCa in any core with a non-inferiority margin of 1 percentage point was performed. Additional analyses for GG ≥2 PCa with cribriform growth pattern and/or intraductal carcinoma (CR/IDC), and GG ≥3 PCa were performed. Differences in detection rates were tested using McNemar's test with adjusted Wald confidence intervals.

Results

After enrolment of 150 men, an interim analysis was performed. Both the mpMRI- and CUDI-TBx strategies were inferior to SBx for GG ≥2 PCa detection and the study was stopped. SBx found significantly more GG ≥2 PCa: 39% (56/ 142), as compared with 29% (41/142) and 28% (40/142) for mpMRI-TBx and CUDI-TBx, respectively ($P < 0.05$). SBx found significantly more GG = 1 PCa: 14% (20/142) compared to 1% (two of 142) and 3% (four of 142) with mpMRI-TBx and CUDI-TBx, respectively ($P < 0.05$). Detection of GG ≥2 PCa with CR/IDC and GG ≥3 PCa did not differ significantly between the strategies. The mpMRI- and CUDI-TBx strategies were comparable in detection but the mpMRI-TBx strategy had less false-positive findings (18% vs 53%).

Conclusions

In our study in biopsy-naïve men, the mpMRI- and CUDI- TBx strategies had comparable PCa detection rates, but the mpMRI-TBX strategy had the least false-positive findings.

Both strategies were inferior to SBx for the detection of GG ≥2 PCa, despite reduced detection of insignificant GG = 1 PCa. Both strategies did not significantly differ from SBx for the detection of GG ≥2 PCa with CR/IDC and GG ≥3 PCa.

Keywords

prostatic neoplasms; imaging; MRI; ultrasound; diagnosis; detection

INTRODUCTION

Multiparametric MRI (mpMRI) is increasingly being used for the detection of clinically significant prostate cancer (csPCa) and is currently recommended as the first-line investigation by the European Association of Urology (EAU) guidelines on PCa based on the results from three prospective multicentre trials [PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION), Assessment of Prostate MRI Before Prostate Biopsies (MRI- FIRST), Met Prostaat MRI Meer Mans (4M)] in biopsy-naïve men.[1-3] mpMRI-targeted biopsy (TBx) decreased the number of biopsy procedures, reduced the detection of insignificant PCa (International Society of Urological Pathology [ISUP] Grade group [GG] = 1), while maintaining the detection of csPCa (GG ≥2), as compared to TRUS- guided systematic biopsy (SBx).[1-3] However, moderate inter-reader reproducibility and non-negligible percentages of missed csPCa compromise the mpMRI-TBx strategy outside large-volume expert centres.[4-6] Furthermore, resources, such as radiological and urological expertise, and MRI gantry time, represent a logistic and financial challenge.[7]

Ultrasound (US), although widely available, cheaper to implement and familiar to the urologist, is currently recommended for prostate biopsy guidance only.[8] New US modalities including contrast-enhanced US (CEUS), micro-US and (shear wave) elastography have been introduced to improve US-based diagnosis of PCa.[9-11] In CEUS, a suspension of gas-filled microbubbles is used for visualisation of the perfusion of the prostate.[12] Algorithms for quantitative interpretation have been developed, as qualitative CEUS interpretation had limited value compared to SBx.[9,13,14] Particularly, contrast-US-dispersion imaging (CUDI), focussed on the detection of angiogenetic changes in the microvascular architecture, provides several parametric maps that can be used for PCa localization.[13,15,16] Despite its promise, there is no direct comparison on the performance of CUDI- and mpMRI-TBx in the identification of csPCa. Therefore, we conducted a prospective, paired diagnostic study comparing the detection rate of ISUP GG ≥2 PCa for the mpMRI-TBx, CUDI-TBx, and SBx strategies in biopsy-naïve men.

MATERIALS AND METHODS

Trial design and study population

This trial included consecutive biopsy-naïve men with an elevated serum PSA level (≥ 3.0 ng/mL) and/or suspicious DRE in the Amsterdam UMC, Amsterdam, the Netherlands between December 2015 and November 2018. Men were excluded if they had a PSA

level >20 ng/mL, a DRE suggestive for extracapsular disease or contra-indications for mpMRI and/or CEUS. The trial design was consistent with the Standards of Reporting for MRI-Targeted Biopsy Studies (START) recommendations.[17] After obtaining written informed consent, all men underwent mpMRI and CUDI and a prostate biopsy procedure (SBx in all men and TBx if the mpMRI and/or CUDI were suspicious). The study protocol was registered on Clinicaltrials.gov (NCT02831920) and published previously.[18] An independent data and safety monitoring board (DSMB) monitored the study.

Imaging protocol

The conduct of the mpMRI and CUDI procedures are written in detail in the study protocol (Table S1).[18] mpMRI, consisting of T2-weighted, diffusion-weighted, and dynamic contrast-enhanced (DCE) sequences, was performed with the use of 1.5-T (n=39; 27%) or 3.0-T (n= 103; 73%) according to the Prostate Imaging-Reporting and Data System, version 2 (PI-RADSv2).[19] CUDI was based on four transrectal two-dimensional prostate plane CEUS recordings using a 2.4 mL bolus injection of SonoVue® (Bracco, Geneva, Switzerland) per plane. The CEUS recordings were subjected to CUDI quantification analyses based on the pharmacokinetic modelling of the contrast bolus transport through the microvasculature of the prostate as a convective-dispersion process.[13] Four different CUDI parametric maps were generated, representing spatiotemporal correlation, Péclet number, flow velocity and a combination of these parameters. We refer to earlier publications for an elaborate explanation of these individual parametric maps.[13,15,16]

Imaging evaluation

The mpMRI and CUDI were evaluated separately. A radiologist (M.E. with 12 years of prostate MRI experience) evaluated the mpMRIs according to PI-RADSv2. The CUDI was evaluated by a TRUS operator (C.K.M.: 87% and A.W.P.: 13%; both with 2 years of experience in TRUS]) using a Likert scale from 1 to 5 with higher numbers indicating a greater likelihood of csPCa. Likert score assessment categories are shown in Fig. S1.

Prostate biopsy and histopathology

All operators received education on TRUS and mpMRI and followed a biopsy training programme. The prostate biopsy procedures were performed in sequence in one session under local anaesthesia using a transrectal approach with a Phillips IU22 ultrasound scanner and C10-3V endocavity probe (Philips Healthcare, Bothell, WA, USA). First, an operator (with at least 6 months of TRUS experience) blinded from the mpMRI and CUDI, took a 12-core SBx in all men. The systematic sampling of the relevant prostate zones was done freehand and when a lesion was visible at TRUS, it was targeted using the

core for the relevant prostate zone (no additional TRUS-targeted cores were performed; Fig. S2). Thereafter, men with a suspicious CUDI (Likert score ≥3) underwent a cognitive CUDI-TBx, with a maximum of four cores, by a second operator (with at least 3 months of TBx experience). This operator also performed mpMRI-TBx in men with a suspicious mpMRI (PI-RADSv2 score ≥3) using an mpMRI-TRUS fusion system (Artemis®, Eigen, Grass Valley, CA, USA), with a maximum of four cores. A case example is shown in Fig. 1.

A uro-pathologist (C.D.S.H. with 15 years of experience), evaluated all biopsy cores separately for presence of PCa, GG, Gleason score, percentage tumour core involvement and morphological patterns of Gleason 4 including cribriform growth pattern and intraductal carcinoma (CR/IDC) in accordance with the ISUP criteria.[20]

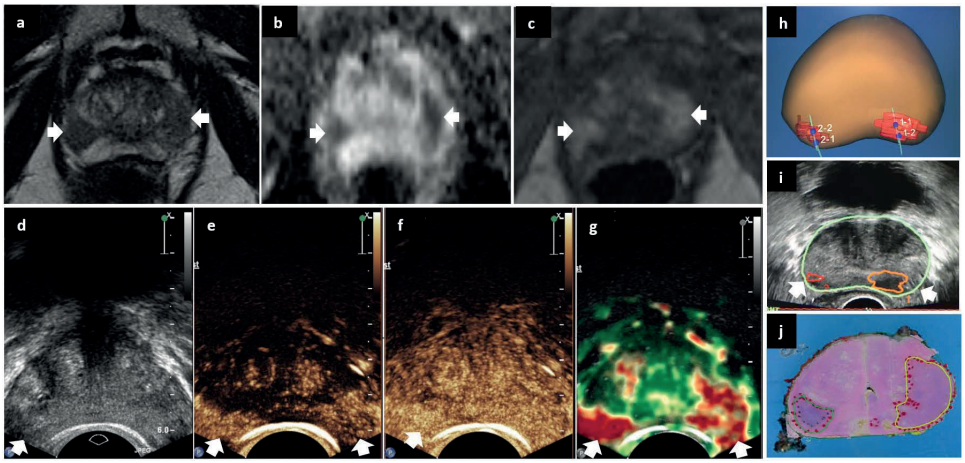

FIGURE 1. mpMRI and CUDI of the prostate in a 72-year old man with a PSA-value of 6.4 ng/mL. (**a-j**). (**a**) Hypo-intense areas on both sides of the peripheral zone (PZ) of the prostate on T2-weighted MRI (arrows). (**b**) The corresponding areas show restricted diffusion on the apparent diffusion coefficient image (arrows). **(c)** The corresponding areas show suspicious early contrast-enhancement on DCE MRI (arrows). A PI-RADS score of 5 (left side) and 4 (right side) were given. (**d**) A hypoechoic area in the right dorsolateral PZ of the prostate (arrow). (**e**) An early asymmetrical enhancement in the left and right PZ of the prostate in the first seconds of contrast-enhanced US (arrows) (**f**) The right PZ shows clear peak intensity at peak enhancement. (**g**): Both areas in the right and left PZ of the prostate are suspicious red-colored on the CUDI parametric map: Combination (arrows). A Likert score of 5 was given for both areas. (**h**): Transversal image of the MRI-TRUS fusion biopsy showing the two biopsied areas (red) and the biopsy cores (blue). (**i**): Real time TRUS image during MRI-TRUS fusion biopsy showing the lesions on both sides. (**j**) Both MRI-TBx and CUDI-TBx demonstrated a GG=3 PCa at biopsy; SBx demonstrated a GG=2 PCa at biopsy. Radical prostatectomy histopathology demonstrated a GG=3 PCa lesion in the right peripheral zone and a GG=2 PCa lesion in the left peripheral zone as demonstrated (prostate carcinoma delineated).

Outcomes

The primary outcome was the detection of GG ≥ 2 PCa in any core for each biopsy strategy and was designed to demonstrate the non-inferiority of the mpMRI-strategy or CUDI-strategy in comparison with SBx for the detection of GG ≥2 PCa with a pre-defined non-inferiority margin of 1 percentage point. Secondary outcomes included the detection of insignificant PCa (GG = 1), GG distribution, the number of men in whom biopsy could have been avoided after unsuspicious imaging and the number of GG ≥2 PCa missed for each strategy. Additional analyses for two other definitions of csPCa, GG ≥2 PCa with CR/IDC and GG ≥3 PCa were performed.

Statistical analysis

Detailed justification of sample size is provided in the protocol paper.[18] An interim analysis after 50% of the inclusion was performed by the DSMB to evaluate non-inferiority assumptions, with adjusted Wald CIs for differences of proportions with matched pairs. To compare proportions of csPCa and insignificant PCa in the biopsy strategies, the McNemar's test was used. All imaging cases of men with an unsuspicious MRI scan, but GG ≥ 2 PCa at biopsy were independently re-evaluated by two radiologists (with additional imaging cases to prevent biased reading). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS®) for Windows (version 25.0, SPSS Inc., IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

In November 2018, after inclusion of 150 men, an interim analysis was performed. As seen in the flow chart, 142 (95%) men were available for final analysis (Fig. S3). The DSMB concluded that presumed non-inferiority of the mpMRI- and CUDI-TBx strategies to SBx for GG ≥2 PCa detection would not be met based on conditional power computations and advised cessation of the study. Baseline characteristics are summarised in Table 1. The mpMRI (PI-RADS ≥3) and CUDI (Likert ≥3) were scored as suspicious in 50 men (35%) and 85 men (60%), respectively.

Table 1. Baseline characteristics (part 1 out of 2)

Variables	Value
Number of patients	142
Age, years, median (IQR)	65 (60 – 71)
Ethnicity, n (%)	
· Caucasian	100 (70)
· Non-Caucasian	42 (30)
Family history of PCa, n (%)	
· Yes	21 (15)
· No	121 (85)
PSA level, ng/mL, median (IQR)	6.2 (4.7 – 8.0)
DRE findings, n (%)	
· Normal	90 (63)
· Abnormal	52 (37)
TRUS prostate volume, mL, median (IQR)	50 (35 – 68)
TRUS findings, n (%)	
· Normal	87 (61)
· Abnormal	55 (39)
PSA density, ng/mL/mL, median (IQR)	0.12 (0.08 – 0.18)
mpMRI PI-RADS score assessment, n (%)	
· PI-RADS 1	2 (1)
· PI-RADS 2	90 (63)
· PI-RADS 3	8 (6)
· PI-RADS 4	22 (15)
· PI-RADS 5	20 (14)
CUDI Likert score assessment, n (%)	
· Likert 1	3 (2)
· Likert 2	54 (38)
· Likert 3	31 (22)
· Likert 4	40 (28)
· Likert 5	14 (10)
Biopsy strategy, n (%)	
· SBx	142 (100)
· mpMRI-TBx	50 (35)
· CUDI-TBx	85 (60)
Biopsy cores:	
· Combined strategies, median (IQR)	15 (12-17)

Table 1. Continued

Variables	Value
Biopsy cores per strategy:	
· SBx, median (IQR)	12 (12-12)
· mpMRI-TBx, median (IQR)	
· overall	3 (2-4)
· per lesion	2 (2-3)
· CUDI-TBx, median (IQR)	
· overall	3 (2-4)
· per lesion	2 (2-3)
Biopsy complications, n (%)	
· Complicated UTI/urosepsis	6 (3)
· Urinary retention	1 (1)
· Gross rectal bleeding	1 (1)

PCa detection

The overall PCa detection (all strategies) was 56% (80/142) with 43% (62/142) GG ≥2 PCa and 13% (18/142) GG = 1 PCa (Table 2). Both the mpMRI- and CUDI-TBx strategies were inferior to SBx for the detection of GG ≥2 PCa (absolute difference: 11%-points) (Fig. 2). SBx detected significantly more GG ≥2 PCa: 39% (56/142), compared to 29% (41/142) and 28% (40/142) for the mpMRI- and CUDI-TBx strategies, respectively ($P < 0.05$) (Table 3). SBx detected significantly more GG = 1 PCa: 14% (20/142), compared to 1% (two of 142) and 3% (four of 142) for the mpMRI- and CUDI-TBx strategies, respectively ($P < 0.05$). Cross-tabulations of the mpMRI- and CUDI-TBx strategies with the SBx outcome for each GG are presented in Table 4.

Detection rates of GG ≥2 PCa with CR/IDC were 25% (36/ 142) for SBx, compared to 22% (31/142) and 20% (28/142) for the mpMRI- and CUDI-TBx strategies, respectively (Table 2). Detection rates for GG ≥3 PCa were 14% (20/142) for SBx, compared to 16% (22/142) and 12% (17/142) for the mpMRI- and CUDI-TBx strategies, respectively. Detection rates for the combination of biopsy strategies are provided in Table 5.

TABLE 2. Detection rate and biopsy core analysis of biopsy strategies

	Biopsy strategy, n (%)			
	All	**TRUS-SBx**	**mpMRI-TBx**	**CUDI-TBx**
Biopsy performance				
Negative imaging; no biopsy	-	-	92 (65)	57 (40)
Biopsy performed	142 (100)	142 (100)	50 (35)	85 (60)
Biopsy outcome: clinically significant PCa if ≥ GG 2 / 3+4*				
No PCa	62 (44)	66 (46)	7 (5)	41 (29)
Insignificant PCa	18 (13)	20 (14)	2 (1)	4 (3)
csPCa	62 (44)	56 (39)	41 (29)	40 (28)
Biopsy outcome: clinically significant PCa if ≥ GG 2 / 3+4 with CR/IDC†				
No PCa	62 (44)	66 (46)	7 (5)	41 (29)
Insignificant PCa	39 (27)	40 (28)	12 (8)	16 (11)
csPCa	41 (29)	36 (25)	31 (22)	28 (20)
***Biopsy outcome:** clinically significant PCa if ≥ GG 3 / 4+3‡*				
No PCa	62 (44)	66 (46)	7 (5)	41 (29)
Insignificant PCa	53 (37)	56 (39)	21 (15)	27 (19)
csPCa	27 (19)	20 (14)	22 (16)	17 (12)
Grade group/Gleason score				
GG 1 / 3+3	18 (13)	20 (14)	2 (1)	4 (3)
GG 2 / 3+4	35 (25)	36 (25)	19 (13)	23 (16)
GG 3 / 4+3	17 (12)	13 (9)	14 (10)	8 (6)
GG 4 / 8	5 (4)	2 (1)	5 (4)	6 (4)
GG 5 / 9-10	5 (4)	5 (4)	3 (2)	3 (2)
Biopsy cores				
Total n. of cores	2118	1726	151	241
Total n. of positive cores	517	307	103	107
Ratio positive/total cores	0.24	0.18	0.68	0.44
Maximum tumor core involvement				
<10%	12 (15)	15 (20)	2 (5)	2 (5)
10-50%	24 (30)	22 (29)	6 (14)	11 (25)
>50%	44 (55)	39 (51)	35 (81)	31 (71)

** SBx/mpMRI-TBx/CUDI-TBx: csPCa: GG ≥2 (Gleason score ≥3+4) in any core. † SBx/mpMRI-TBx/CUDI-TBx: csPCa: GG ≥2 (Gleason score ≥3+4) with CR/IDC in any core. ‡ SBx/mpMRI-TBx/CUDI-TBx: csPCa: GG ≥3 (Gleason score ≥4+3) in any core.*

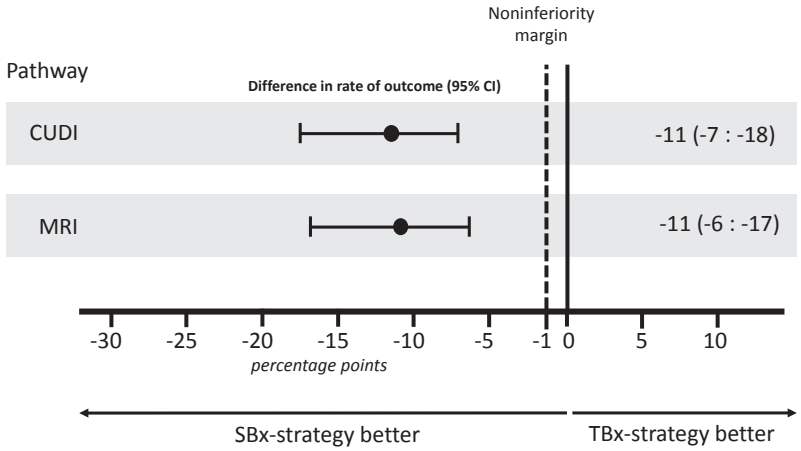

FIGURE 2. Non-inferiority analysis of the CUDI- and mpMRI-TBx strategies in comparison with SBx for detection of csPCa (GG ≥2). Non-inferiority analyses for primary outcome. Shown are the absolute differences between the TBx (CUDI and mpMRI) strategies and the SBx strategy in the rates of detection of csPCa (GG ≥2). The upper boundary of both two-sided 95% CIs for the difference (TBx strategy – SBx strategy) was lower than -1 percentage points, the non-inferiority margin (Δ) (dashed line), thus the CUDI- and mpMRI-TBx strategies were inferior to the SBx strategy for both PCa and csPCa.

Targeted biopsy outcome

Detection rates for the TBx outcome (overall score and individual lesions) are presented in Table S3. Detection rates of mpMRI-TBx for GG ≥2 PCa were 75% (six of eight), 73% (16/22) and 95% (19/20) for men with a PI-RADS score 3, 4 and 5, respectively. Detection rates of CUDI-TBx for GG ≥2 PCa were 19% (six of 31), 53% (21/40) and 93% (13/14) for men with a Likert score 3, 4 and 5, respectively.

Clinical performance of the mpMRI-strategy

Clinical performance of the mpMRI-TBx strategy is presented in Fig. 3. Performing SBx in the 92 men with PI-RADS 1–2 resulted in the diagnosis of 15 men (16%) with GG = 1 PCa and 18 men (20%) with a GG ≥2 PCa. Of these 18 men, five men were diagnosed with a GG = 2 PCa with CR/IDC and two men with a GG = 3 PCa. Of the 50 men with a PI-RADS ≥3, 82% (41/50) had GG ≥2 PCa on mpMRI-TBx. Two men (6%) with a PI-RADS ≥3 were diagnosed with GG ≥2 PCa only on SBx. The GG ≥2 PCa missed by the mpMRI-TBx strategy are reviewed in Table S4.

TABLE 3. Comparison of PCa detection yield and relative sensitivity for the different strategies

		Biopsy strategy								
	Prevalence of disease n (%, 95%-CI)	SBx-strategy Biopsy: n= 142 No biopsy: - n (%, 95%-CI)	mpMRI-strategy Biopsy: n= 50 No biopsy: n= 92 n (%, 95%-CI)	Relative sensitivity of mpMRI versus SBx	*P*	CUDI-strategy Biopsy: n= 85 No biopsy: n= 57 n (%, 95%-CI)	Relative sensitivity of CUDI versus SBx	*P*	Relative sensitivity of mpMRI versus CUDI	*P*
Biopsy outcome: csPCa if ≥ GG 2 / 3+4*										
Insignificant. PCa, n (%)	18 (12.7, 8-19)	20 (14.1, 9-21)	2 (1.4, 0.1-5)	0.10	**<0.001**	4 (2.8, 0.9-7)	0.22	**<0.001**	0.50	0.687
csPCa, n (%)	62 (43.7, 36-52)	56 (39.4, 32-48)	41 (28.9, 22-37)	0.73	**0.004**	40 (28.2, 21-36)	0.71	**0.002**	1.03	1.000
Biopsy outcome: csPCa if ≥ GG 2 / 3+4 with CR/IDC†										
Insignificant. PCa, n (%)	39 (27.5, 21-35)	40 (28.2, 21-36)	12 (8.5, 5-14)	0.30	**<0.001**	16 (11.3, 7-18)	0.40	**<0.001**	0.75	0.388
csPCa, n (%)	41 (28.9, 22-37)	36 (25.4, 18-33)	31 (21.8, 16-29)	0.86	0.302	28 (19.7, 14-27)	0.78	0.057	1.11	0.453
Biopsy outcome: csPCa if ≥ GG 3 / 4+3‡										
Insignificant. PCa, n (%)	53 (37.3, 30-46)	56 (39.4, 32-48)	21 (14.8, 10-22)	0.40	**<0.001**	27 (19.0, 13-26)	0.51	**<0.001**	0.78	0.263
csPCa, n (%)	27 (19.0, 13-26)	20 (14.1, 9-21)	22 (15.5, 10-22)	1.10	0.774	17 (12.0, 7-18)	0.85	0.508	1.29	0.063

*Statistically significant values denoted in bold. Relative sensitivity is the sensitivity (i.e., true positive rate) ratio between the MRI-, CUDI- and SBx-strategy for each definition of csPCa. A value of 1 shows equal sensitivity. Values >1 indicate greater sensitivity for the first strategy compared to the second strategy, whereas values <1 show lower sensitivity. Higher relative sensitivity is desirable for csPCa while lower relative sensitivity is desirable for insignificant PCa. The p values were calculated with McNemar's test for paired nominal data. Definitions of csPCa: * SBx/mpMRI-TBx/CUDI-TBx: clinically significant PCa: GG ≥2 (Gleason score ≥3 + 4) in any core. † SBx/mpMRI-TBx/CUDI-TBx: clinically significant PCa: GG ≥2 (Gleason score ≥3 + 4) with CR/IDC in any core. ‡ SBx/mpMRI-TBx/CUDI-TBx: clinically significant PCa: GG ≥3 (Gleason score ≥4+3) in any core.*

TABLE 4. Cross-tabulations of the mpMRI- (A) and CUDI strategy (B) outcome with the SBx outcome

A: Cross-tabulations of the mpMRI-TBx outcome and SBx outcome

		MRI-strategy, n (%)							
		No biopsy	No cancer on biopsy	GG=1 / 3+3	GG= 2 / 3+4	GG= 3 / 4+3	GG= 4 / 8	GG= 5 / 9-10	Total
SBx, n (%)	No cancer on biopsy	59 (64)	4 (57)	1 (50)	1 (5)	1 (7)	0	0	66 (46)
	GG=1 / 3+3	15 (16)	2 (29)	0	2 (11)	1 (7)	0	0	20 (14)
	GG= 2 / 3+4	16 (17)	1 (14)	1 (50)	13 (68)	5 (36)	0	0	36 (25)
	GG= 3 / 4+3	2 (2)	0	0	3 (16)	6 (43)	2 (40)	0	13 (9)
	GG= 4 / 8	0	0	0	0	0	2 (40)	0	2 (1)
	GG= 5 / 9-10	0	0	0	0	1 (7)	1 (20)	3 (100)	5 (4)
	Total	92 (100)	7 (100)	2 (100)	19 (100)	14 (100)	5 (100)	3 (100)	142 (100)

B: Cross-tabulations of the CUDI-TBx outcome and SBx outcome

		CUDI-strategy, n (%)							
		No biopsy	No cancer on biopsy	GG=1 / 3+3	GG= 2 / 3+4	GG= 3 / 4+3	GG= 4 / 8	GG= 5 / 9-10	Total
SBx, n (%)	No cancer on biopsy	41 (72)	24 (59)	0	1 (4)	0	0	0	66 (46)
	GG=1 / 3+3	8 (14)	7 (17)	2 (50)	3 (13)	0	0	0	20 (14)
	GG= 2 / 3+4	8 (14)	8 (20)	2 (50)	15 (65)	3 (38)	0	0	36 (25)
	GG= 3 / 4+3	0	2 (5)	0	4 (17)	4 (50)	3 (50)	0	13 (9)
	GG= 4 / 8	0	0	0	0	0	2 (33)	0	2 (1)
	GG= 5 / 9-10	0	0	0	0	1 (13)	1 (17)	3 (100)	5 (4)
	Total	57 (100)	41 (100)	4 (100)	23 (100)	8 (100)	6 (100)	3 (100)	142 (100)

TABLE 5. Detection rate and biopsy core analysis of combined biopsy strategies

	Biopsy strategy, n (%)			
	All	**SBx + mpMRI-TBx**	**SBx + CUDI-TBx**	**mpMRI-TBx + CUDI-TBx**
Biopsy performance				
Negative imaging; no biopsy	-	-	-	50 (35)
Biopsy performed	142 (100)	142 (100)	142 (100)	92 (65)
Biopsy outcome: *clinically significant PCa if ≥ GG 2 / 3+4**				
No PCa	62 (44)	63 (44)	65 (46)	39 (28)
Insignificant PCa	18 (13)	18 (13)	17 (12)	5 (4)
csPCa	62 (44)	61 (43)	60 (42)	48 (34)
Biopsy outcome: *clinically significant PCa if if ≥ GG 2 / 3+4 with CR/IDC†*				
No PCa	62 (44)	63 (44)	65 (46)	39 (28)
Insignificant PCa	39 (27)	38 (27)	38 (27)	20 (14)
csPCa	41 (29)	41 (29)	39 (27)	33 (23)
Biopsy outcome: *clinically significant PCa if ≥ GG 3 / 4+3‡*				
No PCa	62 (44)	63 (44)	65 (46)	39 (28)
Insignificant PCa	53 (37)	52 (37)	54 (38)	31 (22)
csPCa	27 (19)	27 (19)	23 (16)	22 (15)
Grade group/Gleason score				
GG 1 / 3+3	18 (13)	18 (13)	17 (12)	5 (4)
GG 2 / 3+4	35 (25)	34 (24)	37 (26)	26 (18)
GG 3 / 4+3	17 (12)	18 (13)	13 (9)	13 (9)
GG 4 / 8	5 (4)	4 (3)	5 (4)	6 (4)
GG 5 / 9-10	5 (4)	5 (4)	5 (4)	3 (2)
Biopsy cores				
Total n. of cores	2118	1877	1967	392
Total n. of positive cores	517	410	414	210
Ratio positive/total cores	0.24	0.22	0.21	0.54
Maximum tumor core involvement				
<10%	12 (15)	14 (18)	12 (16)	3 (6)
10-50%	24 (30)	21 (27)	24 (31)	11 (21)
>50%	44 (55)	44 (56)	41 (53)	39 (74)

** SBx/mpMRI-TBx/CUDI-TBx: csPCa: GG ≥2 (Gleason score ≥3+4) in any core. † SBx/mpMRI-TBx/CUDI-TBx: csPCa: GG ≥2 (Gleason score ≥3+4) with CR/IDC in any core. ‡ SBx/mpMRI-TBx/CUDI-TBx: csPCa: GG ≥3 (Gleason score ≥4+3) in any core.*

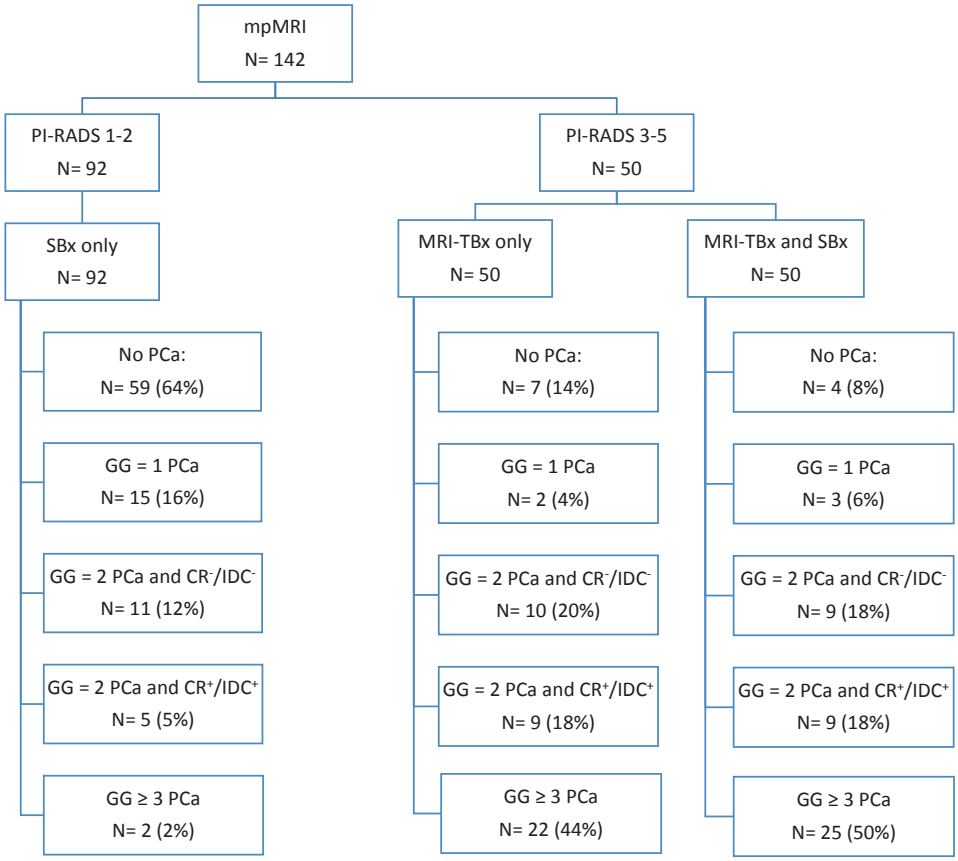

FIGURE 3. Clinical performance of the mpMRI-strategy. Detection of the mpMRI-strategy (B) for GG = 1 PCa, GG = 2 PCa (with and without CR/IDC) and GG = 3 PCa.

Clinical performance of the CUDI-strategy

Clinical performance of the CUDI-strategy is presented in Fig. 4. Performing SBx in the 57 men with a Likert 1-2 resulted in the diagnosis of seven men (12%) with a GG = 1 PCa and eight men (14%) with a GG = 2 PCa. Of these eight men, two men were diagnosed with a GG = 2 PCa with CR/IDC. A total of 40 of the 85 men (47%) with a Likert ≥3 had GG ≥2 PCa on CUDI-TBx. SBx in men with a Likert ≥3 detected an additional 12 men (14%) with GG ≥2 PCa. The GG ≥2 PCa missed by the CUDI-TBx strategy are reviewed in Table S5.

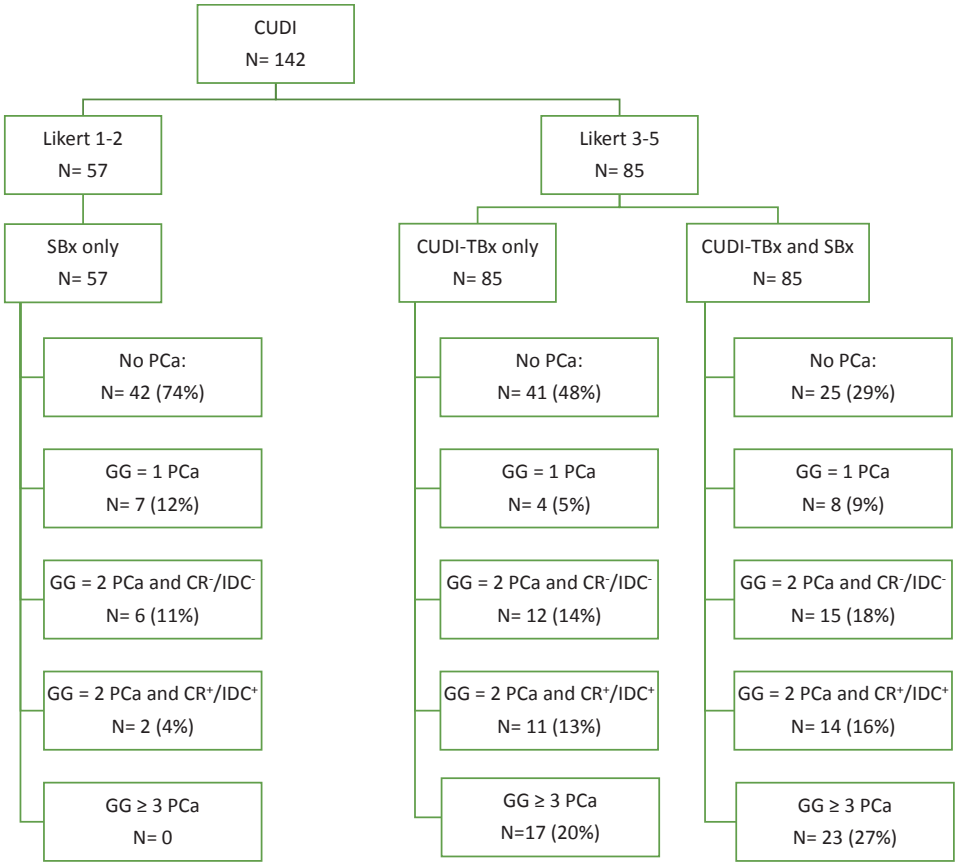

FIGURE 4. Clinical performance of the CUDI-strategy. Detection of the CUDI-strategy (B) for GG = 1 PCa, GG = 2 PCa (with and without CR/IDC) and GG = 3 PCa.

Follow-up and MRI re-reading

Follow-up data are presented in Table S6. None of the 62 men with a benign biopsy session had a GG ≥2 PCa at follow-up [median (interquartile range): 16 (11–23) months].

Two radiologists performed a blinded re-reading of the mpMRIs of the 18 men with PI-RADS 1–2 and missed GG ≥2 PCa. Correct mpMRI re-reading of the GG ≥2 PCa biopsy location occurred in seven (M.E.: 39%) and six (33%: C.H.) of the cases, respectively.

DISCUSSION

This prospective, paired diagnostic study is the first to compare both an mpMRI-TBx and CUDI-TBx strategy with SBx in biopsy-naïve men in a blinded fashion. At interim analysis, SBx detected 39% of GG ≥2 PCa, compared to 29% for the mpMRI-TBx strategy and 28% for the CUDI-TBx strategy, respectively. The study was halted at interim analysis, as conditional power computation by the DSMB demonstrated that presumed non-inferiority of the mpMRI- and CUDI-TBx strategies to SBx would not be met for the detection of GG ≥2 PCa. Despite early cessation of accrual, the present study makes multiple contributions to existing literature regarding the optimal prostate biopsy regimen in biopsy-naïve men. Consistent with the PRECISION, 4M and MRI-FIRST trials on mpMRI-TBx, detection of GG = 1 PCa was significantly lower with mpMRI-TBx compared to SBx, demonstrating its potential to selectively detect GG ≥2 PCa.[1-3] Likewise, addition of SBx to mpMRI-TBx led to higher detection rates of GG ≥2 PCa, but also significantly increased detection of insignificant GG = 1 PCa.[1-3,21]

However, in these trials the mpMRI-TBx strategy maintained its detection for GG ≥2 PCa, while in our present study the mpMRI-TBx strategy had inferior detection rates in comparison with SBx.[1-3] The reason for this controversial result may be twofold. Firstly, our present SBx achieved a high detection rate of 39% for GG ≥2 PCa and only 10% (six of 62) of all GG ≥2 PCa were missed on SBx, while these numbers were 23% (44/190) and 20% (19/94) for the 4M and MRI-FIRST trial, respectively. Consequently, SBx in our present study detected 9–16% more GG ≥2 PCa than the SBx in the other three trials, while baseline characteristics of the study populations where fairly similar (Table S7). Albeit, the high proportion of men with an abnormal DRE (37%) or TRUS (39%) could have contributed to a high detection rate of SBx in comparison with mpMRI-TBx within our present study. After all, csPCa lesions found with SBx, but missed with mpMRI often involve the palpable dorsolateral segments of the prostate.[22,23] Another, important explanation may be the fact that biopsy operators received an extensive education and training programme. A systematic 12-core sampling of all the relevant prostate zones was performed including needle targeting of TRUS abnormalities if deemed necessary. In all, 27 of the 55 men (49%) with a TRUS abnormality had a GG ≥2 PCa in the SBx core(s) of the suspicious hypoechoic region, while the remaining 51% (29/ 56) of GG ≥2 PCa in the SBx strategy was found in unsuspicious prostate zones.

Secondly, our present mpMRI-TBx strategy, performed by a dedicated MRI radiologist, had a lower sensitivity for GG ≥2 PCa compared with the current literature and, as a consequence, led to a lower detection rate (i.e., true-positive rate) of GG ≥2 PCa in comparison with SBx. Of all men with a GG ≥2 PCa, 34% (21/62) were not found using

the mpMRI-TBx strategy, while this was 16% (31/190) and 14% (13/94) for the 4M and MRI-FIRST trial, respectively.[3,4] The number of missed cases in our present study was not directly related to the use of 1.5-T MRI, as the percentages of PI-RADS 1–2 cases with GG ≥2 PCa found at SBx were comparable for 1.5-T MRI (13%) and 3-T MRI (13%). Meanwhile, contrary to what is presented in the current literature, our present mpMRI-TBx strategy was very specific for GG ≥2 PCa.[4,6] Of the men with a positive mpMRI, 82% had GG ≥2 PCa on mpMRI-TBx, with a median of two TBx cores per PI-RADS lesion. In comparison, only 39%, 50% and 55% of the men with a positive mpMRI had GG ≥2 PCa on mpMRI-TBx in the MRI-FIRST, 4M and PRECISION trial, respectively.[1,3] As shown in Table S7, receiver operating characteristic curve analysis of the mpMRI-TBx strategy for GG ≥2 PCa at biopsy had an area under the curve (AUC) of 0.82 for our present study, while the 4M- study and MRI-First study had an AUC of 0.82 and 0.60, respectively. Although we acknowledge that higher sensitivity for GG ≥2 PCa is essential to the use of mpMRI as a triage test, a too low specificity significantly reduces the value of mpMRI-TBx as most patients will be positive, regardless of having GG ≥2 PCa or not.

Our present study reinforces the evidence that high-quality clinical expertise and standardisation ofmpMRI and the biopsy regimen are essential in PCa diagnostics. The variability in diagnostic performance ofmpMRI readings and TBx techniques clearly emphasise the necessity to standardise mpMRI acquisition, inter-reader and inter-operator reproducibility of the mpMRI-TBx strategy to prevent suboptimal care outside large-volume expert centres.[4] Despite the use of the PIRADSv2 scoring system, mpMRI inter- reader reproducibility remains moderate at best.[24,25] In our present study, about one-third of the missed cases on mpMRI were retrospectively recognised by the two radiologists. In the 4M study, GG ≥2 PCa was only missed in 4% of the cases, but prostate mpMRI readings were centrally reviewed by two experienced radiologists before biopsy, with 12% of the first mpMRI readings being discordant.[2] Systematic double reading could potentially reduce the number of missed csPCa and increase the detection of the mpMRI-TBx strategy.[26] Hopefully, significant improvements in the mpMRI-TBx pathway in our own institution will be observed over time by implementation of the recently published PI-RADSv2.1, systematic mpMRI double reading before biopsy, and multidisciplinary meetings using pathological correlation and feedback.[27] However, it remains to be seen whether such an intensive programme can be organised in every healthcare system. Advances in artificial intelligence, particularly deep- learning techniques, as well as registration and segmentation, might alleviate problems in inter- and intra-observer variability, as well as the long learning curves associated with PI-RADS.[28] However, full implementation of computer- aided diagnostic systems, either as a supportive tool or as part of the pathway, is still awaited.[29]

One other particular question relates to the sampling efficiency and the number of cores needed for accurate targeting of the MRI region-of-interest. The optimal number of TBx cores remains controversial, which may be partly a result of various MRI-TBx techniques (cognitive guidance, MRI-TRUS fusion software or direct in-bore guidance) and the indication for the biopsy. Additional focal perilesional saturation with four cores has been suggested to reduce the risk of missing or undersampling the lesion.[2] Consistent with two recently published studies by Porpiglia et al. and Kenigsberg et al., our present study showed that a high diagnostic yield can be achieved for all different PI- RADS lesions with a median of two TBx cores per lesion.[30,31] Rather than adhering to a fixed number of biopsy cores, we believe that individual biopsy operators should critically evaluate their own TBx outcomes with imaging and pathological feedback to determine how to optimise MRI-TRUS-fusion biopsy in their own hands.

CUDI is a less expensive, accessible and convenient US-based alternative to mpMRI for the diagnosis of PCa. The strategy showed promising results in this first clinical evaluation with similar detection rates for GG ≥2 PCa and GG = 1 PCa as the mpMRI-TBx strategy. At the same time, the CUDI-TBx strategy had more false positives than the mpMRI-TBx strategy (53% vs 18%) and the AUC of the CUDI-TBx strategy for GG ≥2 PCa was 0.71. These false-positive findings were mainly caused by the fact that CUDI, like DCE MRI, demonstrated difficulties in distinguishing prostatitis and BPH from csPCa.[32] Future research on CUDI is therefore foreseen. Three-dimensional (3D) CEUS, shortening the procedure time with full 3D modelling of the kinetic behaviour of microbubbles can potentially reduce the risk of missing a lesion outside the pre-defined imaging plane(s).[33] Furthermore, the exploration of different US modalities in a multiparametric fashion, like mpMRI, seems important to accurately distinguish malignant from benign conditions, such as prostatitis and BPH on CUDI.[34] Although CUDI has the potential to solve many of the problems associated with MRI such as cost, availability, convenience and MRI- TRUS registration error; large-scale, multicentre evaluation of the CUDI-TBx strategy, either alone or combined in so-called multiparametric US, will be required before proceeding to clinical implementation of this technique.

An optimal imaging strategy for PCa diagnosis is based on the balance of adequate detection of csPCa, assuredness regarding the accuracy of negative imaging, and limited detection of insignificant PCa.[35] The highest detection rate for GG ≥2 PCa was achieved by a combination of lesion targeting (mpMRI or CUDI) and zonal biopsy (SBx). The combination of mpMRI-TBx with SBx performed slightly better than CUDI-TBx with SBx for GG ≥2 PCa detection and had less false-positive findings. There was no additional value in performing all three biopsy strategies. As expected, a combination of SBx and TBx also significantly increased the detection of insignificant GG = 1 PCa. As stand-alone,

both the mpMRI- and CUDI-TBx strategies showed reduced detection of insignificant (GG = 1) PCa, but detection and accuracy of negative imaging for GG ≥2 PCa was also insufficient. Although at present it is common to define GG ≥2 PCa on biopsy as 'csPCa', this definition is probably too stringent.[36] Particularly, GG = 2 PCa shows considerable heterogeneity in clinical outcome, as recent studies suggest that survival rates for GG = 2 PCa in the absence of CR/IDC is similar to those for GG = 1 PCa.[37,38] Therefore, these men carry a risk of being overdiagnosed and overtreated.[39] Of the men with GG ≥2 PCa missed by mpMRI and CUDI, 61% (11/18) and 75% (six of eight) were men with a GG = 2 PCa without these adverse pathological features, respectively. Defining 'csPCa' is a dynamic process but now more important than ever, as with the increased acceptance of active surveillance the number of men deferring therapy and living with the disease is increasing. Incorporation of these additional morphological subtypes of Gleason pattern 4 seems to better reflect clinically significant disease burden than solely the presence of a GG ≥2 PCa. Incorporation of these criteria in the future will probably also aid in reaching a more definitive answer to the question of whether SBx can be safely omitted in men with negative imaging.

Altogether, these results and those of the previous trials strongly suggest that the mpMRI-TBx strategy has added value in biopsy-naive men, especially considering its detection of more aggressive PCa. We therefore recommend performing a pre-biopsy mpMRI of the prostate in biopsy- naive men. For now, results of our present study suggest the incorporation of the mpMRI-TBx strategy in a combined pathway, in which patients with a positive mpMRI undergo combined SBx and TBx, and patients with a negative mpMRI undergo SBx alone. Although, the added value of SBx depends on the definition of csPCa, and the combined pathway comes with an increase in GG = 1 PCa detection, 10 additional men (24%) with GG ≥2 PCa with CR/IDC were detected with combined mpMRI-TBx and SBx in comparison with mpMRI-TBx only. Conditions therefore remain to be defined under which SBx can be safely avoided in men with negative imaging. If only performed in men with a negative mpMRI and PSA density ≥0.15 ng/mL/mL (n = 23), SBx would have detected eight out of the 18 missed GG ≥2 PCa cases (five out of 10 cases with GG ≥2 PCa with CR/IDC) at the cost of two more men with GG = 1 PCa. If the prostate biopsy is omitted based on shared decision-making, it thus requires a robust follow-up regimen to potentially diagnose 'initially missed' csPCa in a curable timeframe. Risk-calculators combining imaging findings with clinical data can hopefully select those men who may still benefit from biopsy if the imaging is negative even more accurately.[40] In the future, the decision to perform a prostate biopsy should not be based solely on imaging, but on the combination of all relevant PCa diagnostics including the patient's demographics and clinical findings.

Besides the early cessation of accrual, some other limitations should be mentioned. First of all, the present study was performed in one centre and local preferences could limit the generalisability of our results. However, it also reflects daily practice in a tertiary care centre, while results from randomised controlled trials in (large-volume) expert centres seem difficult to reproduce in the real-life setting.[41] Second, PCa might have been missed by all strategies in some patients. We did not use template prostate mapping biopsy, as we were interested in the comparison of the mpMRI- and CUDI-TBx strategies with the current standard of care. In addition, none of the men with a benign biopsy had a GG ≥2 PCa at the most recent follow-up. Third, all biopsy strategies were performed in sequence on the same day; to prevent visibility of TBx needle tracks, SBx was performed first. Biopsy haemorrhage and gland swelling may have negatively affected the TBx procedure. However, these artefacts are mild at such a short interval and the mpMRI-TBx (last in sequence) had high targeting accuracy (Table S3). Last, cost- effectiveness and patient-reported outcomes of obtaining pre- biopsy mpMRI, CUDI and prostate biopsy were beyond the scope of the present study.

CONCLUSIONS

In our study with biopsy-naïve men, the mpMRI- and CUDI- TBX strategies had similar PCa detection rates, but the mpMRI-TBx strategy had less false-positive findings. Both strategies had inferior detection rates for GG ≥2 PCa than SBx. Both strategies did not significantly differ to SBx in the detection of GG ≥2 PCa with CR/IDC and GG ≥3 PCa. Despite the fact that both imaging strategies reduced the detection of insignificant GG = 1 PCa, SBx cannot be omitted in biopsy-naïve men for GG ≥2 PCa based on negative imaging alone.

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Conflict of interest

Dr M. Mischi reports a patent US20130182933A1 licensed to CUDI bv and a patent WO2017/042280A1 licensed to CUDI bv. The other authors report no conflict of interest.

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