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The FUTURE Trial: A Multicenter Randomised Controlled Trial on Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies

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Abstract

Background: Guidelines advise multiparametric magnetic resonance imaging (mpMRI) before repeat biopsy in patients with negative systematic biopsy (SB) and a suspicion of prostate cancer (PCa), enabling MRI targeted biopsy (TB). No consensus exists regarding which of the three available techniques of TB should be preferred.
Objective: To compare detection rates of overall PCa and clinically significant PCa (csPCa) for the three MRI-based TB techniques.
Design, setting, and participants: Multicenter randomised controlled trial, including 665 men with prior negative SB and a persistent suspicion of PCa, conducted between 2014 and 2017 in two nonacademic teaching hospitals and an academic hospital.
Intervention: All patients underwent 3-T mpMRI evaluated with Prostate Imaging Reporting and Data System (PIRADS) version 2. If imaging demonstrated PIRADS $\geq$3 lesions, patients were randomised 1:1:1 for one TB technique: MRI-transrectal ultrasound (TRUS) fusion TB (FUS-TB), cognitive registration TRUS TB (COG-TB), or in-bore MRI TB (MRI-TB).
Outcome measurements and statistical analysis: Primary (overall PCa detection) and secondary (csPCa detection [Gleason score $\geq$3 + 4]) outcomes were compared using Pearson chi-square test.
Results and limitations: On mpMRI, 234/665 (35%) patients had PIRADS $\geq$3 lesions and underwent TB. There were no significant differences in the detection rates of overall PCa (FUS-TB 49%, COG-TB 44%, MRI-TB 55%, p = 0.4). PCa detection rate differences were −5% between FUS-TB and MRI-TB (p = 0.5, 95% confidence interval [CI] −21% to 11%), 6%

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between FUS-TB and COG-TB (p = 0.5, 95% CI −10% to 21%), and −11% between COG-TB and MRI-TB (p = 0.17, 95% CI −26% to 5%). There were no significant differences in the detection rates of csPCa (FUS-TB 34%, COG-TB 33%, MRI-TB 33%, $p > 0.9$). Differences in csPCa detection rates were 2% between FUS-TB and MRI-TB (p = 0.8, 95% CI −13% to 16%), 1% between FUS-TB and COG-TB ($p > 0.9$, 95% CI −14% to 16%), and 1% between COG-TB and MRI-TB ($p > 0.9$, 95% CI −14% to 16%). The main study limitation was a low rate of PIRADS ≥3 lesions on mpMRI, causing underpowering for primary outcome.

Conclusions: We found no significant differences in the detection rates of (cs)PCa among the three MRI-based TB techniques.

Patient summary: In this study, we compared the detection rates of (aggressive) prostate cancer among men with prior negative biopsies and a persistent suspicion of cancer using three different techniques of targeted biopsy based on magnetic resonance imaging. We found no significant differences in the detection rates of (aggressive) prostate cancer among the three techniques.

1. Introduction

Prostate cancer (PCa) is the most common malignancy among European men [1]. The standard diagnostic procedure, transrectal ultrasound (TRUS)-guided systematic biopsy (SB), is limited by the inability to distinguish PCa from benign tissue using ultrasound [2]. Consequently, repeat TRUS-SB demonstrates PCa yields of 10–25% [3,4].

Guidelines advise performing multiparametric magnetic resonance imaging (mpMRI) when a suspicion of PCa persists despite negative TRUS-SB, followed by targeted biopsy (TB) of cancer suspicious regions (CSRs) [5,6]. Meta-analyses show that TB demonstrates higher detection rates of clinically significant PCa (csPCa) compared with TRUS-SB in a repeat biopsy setting [7–9]. The recently published PRECISION trial demonstrates similar advantages of TB in biopsy-naïve patients [10].

TB was introduced with in-bore MRI-TB, performed in the MRI scanner using real-time MRI guidance [11,12]. MRI-TB demonstrates a median PCa detection rate of 42% [12]. Nonetheless, MRI-TB remains challenging due to impracticalities (such as availability, required expertise, time-consuming and costly nature) forming barriers to widespread implementation, especially when prebiopsy MRI and TB for all patients with a suspicion of PCa might become the new standard [10]. Consequently, alternative techniques have been developed, as MRI-TRUS fusion TB (FUS-TB) [13,14] and cognitive registration TRUS TB (COG-TB) [15].

Obviously, increasing usage of TB necessitates answering the question of which technique should be preferred. A meta-analysis of all three techniques demonstrated an advantage of MRI-TB compared with COG-TB for overall PCa detection, although this advantage was not apparent for csPCa [8]. However, comparative trials are few in number [17–21]. Consequently, little consensus exists on which technique should be preferred. This three-armed multicenter randomised controlled trial (RCT) compares overall PCa and csPCa detection rates of the three TB techniques and aims to identify whether there is a superior technique regarding diagnostic efficacy in a repeat biopsy setting.

2. Patients and methods

2.1. Recruitment

The trial protocol adheres to CONSORT, SPIRIT, and START recommendations [16–19]. The trial was conducted between December 2014 and November 2017 in two nonacademic teaching hospitals and an academic hospital. Institutional review board approval was granted. The protocol was registered in the Dutch Trial Register (NTR4988). All participants provided written informed consent.

Men were recruited with prior negative SB (<4 yr) and persistent suspicion of PCa (prostate-specific antigen [PSA] ≥4 (ng/ml) and/or suspicious digital rectal examination [DRE]). Exclusion criteria were prior diagnosed PCa, prior TB procedures, proven urinary tract infection (UTI), contraindication for mpMRI or TB, imaging or TB not performed according to protocol, or withdrawal of consent.

2.2. Magnetic resonance imaging

All participants underwent 3-T mpMRI according to Prostate Imaging Reporting and Data System (PIRADS) version 2 standards [20,21]. Sequences included T2-weighted (T2W) imaging, diffusion weighted imaging (DWI), and dynamic contrast enhanced imaging (Supplementary Table 1). Images were centrally evaluated by one of two expert radiologists (20 and 5 yr of experience in prostate MRI) using PIRADSv2 (Supplementary Table 2) [20,21]. Radiologists were not blinded for clinical data. Multiparametric MRI outcome was reported using a written record incorporating marked images.

2.3. Randomisation

Patients with PIRADS ≥3 lesions were randomised 1:1:1 to undergo TB using FUS-TB, COG-TB, or MRI-TB, using a block-randomisation tool, generating a random sequence. Investigators were blinded for randomisation sequence. Following randomisation, group allocation was revealed. If imaging demonstrated no CSR (PIRADS ≤2), the patients entered biochemical follow-up.

2.4. Biopsy

MRI-TB was performed in the MRI scanner (Magnetom Skyra, Siemens, Munich, Germany). CSR was reidentified using T2W and DWI. A rectally inserted needle guider was adjusted to aim towards the CSR. Transrectal biopsy was performed with an MR-compatible biopsy device [11]. After needle insertion, MRI verified its position. MRI-TB was performed by

10 expert-trained PhD candidates with at least 6 mo of experience at time of study commencement, including 3 mo of experience under expert supervision.

FUS-TB was performed in the operating room under (general/spinal) anaesthesia using transperineal MRI/TRUS fusion (BiopSee, Medcom, Darmstadt, Germany). Axial T2W images were imported, followed by prostate and CSR contouring. A biplane TRUS probe was inserted. Three-dimensional (3D) TRUS images were acquired. Using software, axial T2W and 3D ultrasound images were fused using rigid image fusion. Transperineal biopsy was performed using MRI/TRUS fusion guidance [13]. FUS-TB was performed by five urologists and expert-trained PhD candidates having at least 6 mo of experience, including 3 mo of experience under expert supervision.

COG-TB was performed in outpatient clinic using TRUS guidance (Hitachi Hi-Vision Preirus or BK Pro-Focus). Prior to biopsy, the mpMRI findings were reviewed. A biplane TRUS probe was inserted. The CSR was reidentified. Transrectal biopsy was performed using biplane TRUS guidance [15]. COG-TB was performed by five urologists and expert-trained PhD candidates with at least 6 mo of experience, including 3 mo of experience under expert supervision.

A minimum of two TB cores per CSR was required for adequate sampling of all the techniques.

2.5. Histopathology and definition of clinical significance

Biopsy cores were potted separately for each CSR and were evaluated by one uropathologist per centre (10, 11, and 17 yr of experience in PCa diagnosis). Cores were processed according to the International Society of Urological Pathology standards [22]. The pathologist was blinded for applied TB technique.

Clinically significant PCa was defined as a Gleason score of $\geq$3 + 4. Owing to heterogeneity in its definition in the literature, a second definition for csPCa was also applied (Supplementary Table 3).

2.6. Outcomes, sample size calculation, and statistical analysis

The primary outcome was the detection rate of overall PCa for each TB technique. The secondary outcomes included csPCa detection rates, baseline clinical/mpMRI characteristics, procedural outcomes, and adverse events (Clavien-Dindo classification) [23,24]. Furthermore, exploratory subgroup analyses on (cs)PCa rates and a per-core analysis were performed.

We hypothesised that FUS-TB has an equivalent detection rate of PCa to that of MRI-TB, and that both MRI-TB and FUS-TB have a superior detection rate to that of COG-TB. Sample size was calculated using estimated PCa yields of TB techniques (40% FUS-TB, 25% COG-TB, and 40% MRI-TB) and 69% yield of CSR on mpMRI, based upon available literature at the time of trial design [4,7,12,13].

Two subinvestigations were formulated. Subinvestigation 1 is a superiority analysis comparing FUS-TB with COG-TB, and MRI-TB with COG-TB. A sample size of 152 per group was calculated to achieve 80% power to detect a difference of 15% between the null hypothesis (COG-TB) and alternative hypothesis (FUS-TB or MRI-TB) using a two-sided chi-square test without continuity correction and significance levels 5%,

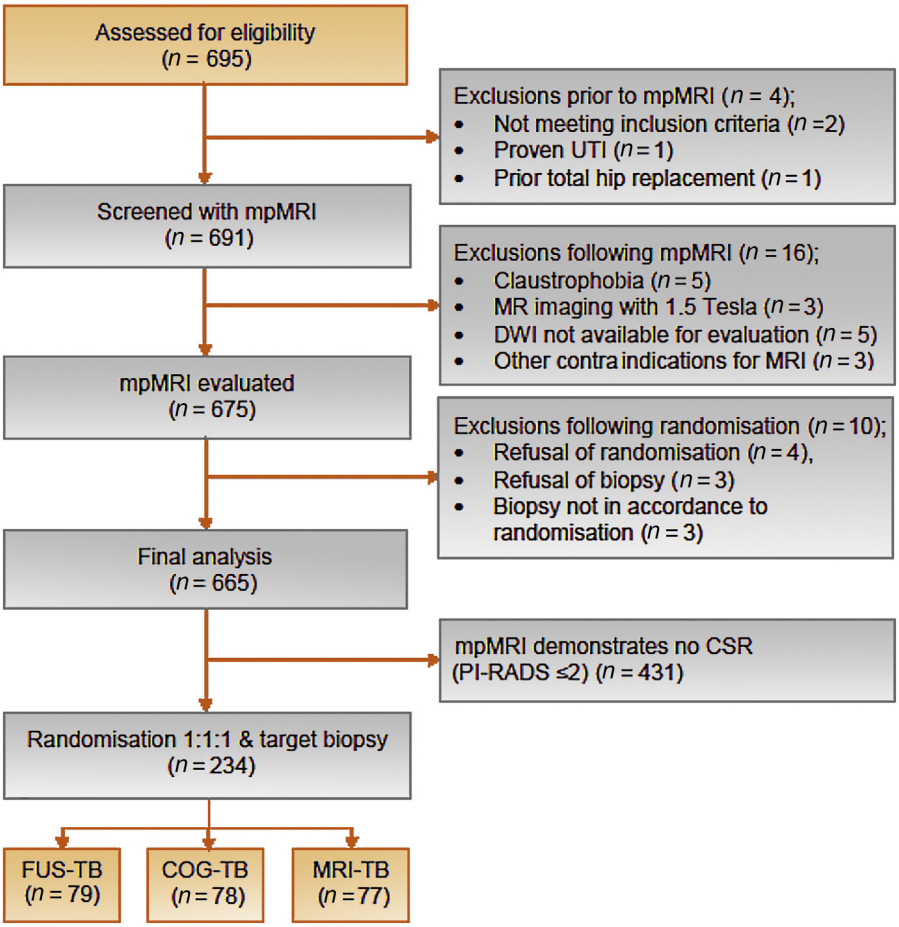

Fig. 1 – Flowchart of the study. COG-TB = cognitive registration TRUS TB; CSR = cancer suspicious region; DWI = diffusion weighted imaging; FUS-TB = MRI-TRUS fusion TB; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI TB; PI-RADS = Prostate Imaging Reporting and Data System; TB = targeted biopsy; TRUS = transrectal ultrasound; UTI = urinary tract infection.

assuming PCa yields of 25% for COG-TB and 40% for both FUS-TB and MRI-TB [11,13].

Subinvestigation 2 is a noninferiority study comparing PCa detection rates of FUS-TB and MRI-TB. A sample size of 131 per group was calculated to achieve 80% power at 5% significance level using a one-sided equivalence test of proportions, when PCa yield in both the standard group (MRI-TB) and the alternative group (FUS-TB) tested for noninferiority is 40%, and the value of indifference still resulting in noninferiority is 15% [11–13].

To facilitate randomisation, identical groups of 152 individuals were chosen, resulting in 456 participants in all the groups combined. Ten additional individuals were included, correcting for calculated losses, resulting in 466 participants. Assuming that 69% has CSRs on mpMRI, 675 individuals are required for inclusion [7].

All analyses were conducted with SPSS version 21 (SPSS Inc., Chicago, IL, USA); 5% significance levels were adopted in all tests. To assess comparability between the groups, baseline characteristics were analysed using one-way analysis of variance or Kruskal-Wallis (for continuous variables) and Pearson chi-square tests (categorical variables). Detection rates of PCa and csPCa were compared using Pearson chi-square test [19].

3. Results

A total of 695 men were recruited. Thirty men were excluded following recruitment (Fig. 1), resulting in the inclusion of 665 individuals in the final per-protocol analysis.

The mean age was 64.7 (standard deviation [SD] 6.6), mean PSA 10.4 ng/ml (SD 7.3), mean prostate volume (TRUS) 56.9 ml (SD 24.0), median number of prior biopsies 1 (interquartile range [IQR] 1–2), and median interval between mpMRI and last SB 9 mo (IQR 4–22). Clinical stage (DRE) was cT1c in 80.9%, cT2a/b in 17.1%, cT2c in 0.8%, and cT3a in 1.2% of cases (Table 1).

In 234 individuals (35.2%), mpMRI demonstrated 263 PIRADS $\geq$3 lesions, with a mean CSR size of 13.5 mm (SD 7.0; Table 2). The remaining 431 individuals (64.8%) had PIRADS $\leq$2 and entered follow-up.

A total of 234 individuals with PIRADS $\geq$3 were randomised for TB: 79 for FUS-TB, 78 for COG-TB, and 77 for MRI-TB (Fig. 1). There were no significant differences in baseline characteristics or mpMRI outcomes among the groups (Table 3). Using TB, 115 PCa (49.1%) and 78 csPCa (33.3%) cases were detected.

There were no significant differences in the detection rates of overall PCa among the groups (FUS-TB 49.4%, COG-TB 43.6%, and MRI-TB 54.5%, $p = 0.4$; Table 4). The differences in PCa detection rates were −5.2% between FUS-TB and MRI-TB ($p = 0.5$, 95% confidence interval [CI] −20.6% to 10.5%), 5.8% between FUS-TB and COG-TB ($p = 0.5$, 95% CI −9.8% to 21.1%), and −11.0% between COG-TB and MRI-TB ($p = 0.17$, 95% CI–26.2% to 4.8%). Noninferiority analysis comparing overall PCa detection rates of FUS-TB and MRI-TB was inconclusive (lower limit 95% CI being −20.6%). Both FUS-TB and MRI-TB were not significantly superior to COG-TB for overall PCa detection ($p = 0.5$ and $p = 0.17$, respectively).

There were no significant differences in the detection rates of csPCa among the groups (FUS-TB 34.2%, COG-TB 33.3%, and MRI-TB 32.5%, $p > 0.9$; Table 4). The differences in csPCa detection rates were 1.7% between FUS-TB and MRI-TB ($p = 0.8$, 95% CI −13.1% to 16.4%), 0.8% between FUS-TB and COG-TB ($p > 0.9$, 95% CI −13.9% to 15.6%), and 0.9% between COG-TB and MRI-TB ($p > 0.9$, 95% CI −13.9% to 15.6%). FUS-TB was noninferior to MRI-TB for csPCa detection (lower limit 95% CI being −13.1%), and both FUS-TB and MRI-TB were not significantly superior to COG-TB for csPCa detection ($p > 0.9$ and $p > 0.9$, respectively).

There were significant differences in the number of cores taken per technique: the median number of cores was four for FUS-TB (IQR 3–5), three for COG-TB (IQR 3–4), and two for MRI-TB (IQR 2–3; $p < 0.05$; Table 4). Furthermore, core positivity rate was significantly different among the groups (FUS-TB 31.3% [128/358], COG-TB 33.3% [88/275], and MRI-TB 47.7% [94/197], $p < 0.05$; Table 4). Various subanalyses did not demonstrate statistically significant differences in (cs)PCa detection rates among the groups (Table 5).

Among 234 individuals who underwent TB, 30.2% ($n = 70$) experienced no adverse events and 63.2% ($n = 148$) experienced grade I complications. Three patients required hospitalisation due to gross haematuria; 6.0% ($n = 14$)

Table 1 – Baseline characteristics

	Entire cohort ($n = 665$)	Cohort with CSR on mpMRI (PIRADS $\geq$3; $n = 234$)
Age, mean (SD)	64.7 (6.6)	65.7 (6.4)
PSA (ng/ml), mean (SD)	10.4 (7.3)	11.2 (8.5)
Volume on TRUS (ml), mean (SD)	56.9 (14.4)	47.4 (17.7)
Clinical stage (DRE), *n* (%)		
cT1c	538 (80.9)	188 (80.3)
cT2a/b	114 (17.1)	40 (17.1)
cT2c	5 (0.8)	3 (1.3)
cT3a	8 (1.2)	3 (1.3)
Clinical stage (TRUS), *n* (%)		
cT1c	535 (80.6)	189 (80.8)
cT2a/b	109 (16.4)	37 (15.8)
cT2c	10 (1.5)	4 (1.7)
cT3a	6 (0.9)	4 (1.7)
cT3b	4 (0.6)	–
Number of prior negative biopsies, median (IQR)	1 (1–2)	1 (1–2)
Months between mpMRI and previous biopsy, median (IQR)	9 (4–22)	8 (4–23)

Table 2 – Multiparametric MRI characteristics

Highest PIRADS grade on mpMRI (*n* = 665), *n* (%)	
1	31 (4.7)
2	400 (60.2)
3	64 (9.6)
4	101 (15.2)
5	69 (10.4)
CSRs per patient (*n* = 665), mean (SD)	1.1 (0.3)
CSR size (mm; *n* = 234), mean (SD)	13.5 (7.0)
CSR location (*n* = 234), *n* (%)	
Posterior	126 (53.8)
Anterior	90 (38.5)
Midline	18 (7.7)
CSR location (*n* = 234), *n* (%)	
Peripheral zone	137 (58.6)
Transition zone	29 (12.4)
Peripheral and transition	13 (5.6)
AFS	8 (3.4)
Transition and AFS	42 (17.9)
Central	5 (2.1)
Staging on mpMRI (*n* = 234), *n* (%)	
T2a/b	141 (60.1)
T2c	24 (10.3)
T3a	62 (26.5)
T3b	7 (3.0)

AFS = anterior fibromuscular stroma; CSR = cancer suspicious region; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; SD = standard deviation.

experienced grade 2 complications. Eight cases of UTIs occurred requiring antibiotics (four requiring hospitalisation), five individuals had lower urinary tract symptoms progression for which treatment was initiated, and one patient had atrial fibrillation. No grade 3, 4, or 5 events occurred [23,24].

4. Discussion

4.1. Main findings

This is the first multicenter RCT comparing all the three TB techniques based on mpMRI. There were no statistically significant differences in the detection rates of overall PCa or csPCa among the three techniques. Though the highest yield of overall PCa was achieved with MRI-TB, followed by FUS-TB, these results were not significantly superior to the yield achieved with COG-TB. This trend was not as apparent for csPCa, where the yields were very similar. The number of cores needed was lower for MRI-TB compared with other techniques, resulting in a higher core positivity rate. We expected an advantage of MRI-TB for small lesions and of transperineal FUS-TB for anterior lesions, but could not demonstrate such advantages in subanalyses. However, these subanalyses should be interpreted with caution due to small sample size per analysis.

4.2. Negative mpMRI and follow-up

Compared with published literature, the yield of mpMRI was relatively low (35.2%). This can partially be explained by the threshold applied for recruitment (persisting suspicion on PCa defined as PSA $\geq$4 ng/ml and/or suspicious DRE), accurately reflecting clinical thresholds for noninvasive diagnostic tools such as mpMRI. Furthermore, expert reading of mpMRI possibly contributes to low yields.

In 431 individuals with negative mpMRI (PIRADS $\leq$2), nine (2.1%) PCa cases were detected during limited follow-up (median 12 mo) including two (0.5%) cases of csPCa. An

Table 3 – Baseline characteristics and mpMRI outcomes of three groups of TB

	FUS-TB (*n* = 79)	COG-TB (*n* = 78)	MRI-TB (*n* = 77)
Baseline characteristics			
Age, mean (SD)	64.6 (6.9)	66.5 (6.3)	66.0 (5.9)
PSA (ng/ml), mean (SD)	11.6 (9.0)	11.0 (7.1)	11.0 (9.4)
Volume on TRUS (ml), mean (SD)	45.4 (14.4)	48.5 (18.1)	48.3 (20.2)
Clinical stage (DRE), *n* (%)			
cT1c	62 (78.5)	64 (82.1)	62 (80.5)
cT2a/b	16 (20.3)	12 (15.4)	12 (15.6)
cT2c	0 (0)	2 (2.6)	1 (1.3)
cT3a	1 (1.3)	0 (0)	2 (2.6)
Number of prior negative biopsies, median (IQR)	1 (1–1)	1 (1–2)	1 (1–2)
Months between mpMRI and previous biopsy, median (IQR)	8 (3–23)	7 (4–23)	9 (4–25)
mpMRI outcome			
PIRADS score, *n* (%)			
3	23 (29.1)	21 (26.9)	20 (26.0)
4	34 (43.0)	32 (41.0)	35 (45.5)
5	22 (27.8)	25 (32.1)	22 (28.6)
CSR size (mm), mean (SD)	13.9 (7.6)	12.9 (6.1)	13.6 (7.1)
Number of CSRs, mean (SD)	1.1 (0.3)	1.1 (0.3)	1.1 (0.4)
CSR location, *n* (%)			
Posterior	35 (44.3)	46 (59.0)	45 (58.4)
Anterior	37 (46.8)	25 (32.1)	28 (36.4)
Midline	7 (8.9)	7 (9.0)	4 (5.2)

COG-TB = cognitive registration TRUS TB; CSR = cancer suspicious region; DRE = digital rectal examination; FUS-TB = MRI-TRUS fusion TB; IQR = interquartile range; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI TB; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; SD = standard deviation; TB = targeted biopsy; TRUS = transrectal ultrasound.

Table 4 – Biopsy outcome of three groups of TB

	FUS-TB (n = 79)	COG-TB (n = 78)	MRI-TB (n = 77)	p value
Days between mpMRI and biopsy, median (IQR)	53 (41–70)	27 (20–35)	39 (27–53)	<0.05[a]
Biopsy cores				
Total TB cores, n	358	275	197	
Per subject, median (IQR)	4 (3–5)	3 (3–4)	2 (2–3)	<0.05[a]
Per CSR, median (IQR)	4 (3–5)	3 (3–3)	2 (2–3)	<0.05[a]
PCa-positive cores, n	128	88	94	
Positivity rate, mean (SD)	31.3% (37.8)	33.3% (42.1)	47.7% (46.4)	<0.05[b]
Detection rate of PCa, n (%)	39 (49.4)	34 (43.6)	42 (54.5)	0.4[c]
Detection rate of csPCa[d], n (%)	27 (34.2	26 (33.3)	25 (32.5)	>0.9[c]

ANOVA = analysis of variance; COG-TB = cognitive registration TRUS TB; csPCa = clinically significant PCa; CSR = cancer suspicious region; FUS-TB = MRI-TRUS fusion TB; IQR = interquartile range; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI TB; SD = standard deviation; PCa = prostate cancer; TB = targeted biopsy; TRUS = transrectal ultrasound.
[a] Kruskal-Wallis.
[b] One-way ANOVA.
[c] Pearson chi-square.
[d] Gleason ≥3 + 4.

Table 5 – Biopsy outcome of three groups of TB per subanalysis

Biopsy outcomes per subanalysis						p value
			FUS-TB (n = 23)	COG-TB (n = 21)	MRI-TB (n = 20)	
mpMRI outcome, n (%)	PIRADS 3 (n = 64)	PCa	6 (26.1)	5 (23.8)	5 (25.0)	>0.9[b]
		csPCa[a]	2 (8.7)	5 (23.8)	4 (20.0)	0.4[b]
			FUS-TB (n = 34)	COG-TB (n = 32)	MRI-TB (n = 35)	
	PIRADS 4 (n = 101)	PCa	12 (35.3)	7 (21.9)	17 (48.6)	0.07[b]
		csPCa[a]	7 (20.6)	5 (15.6)	9 (25.7)	0.6[b]
			FUS-TB (n = 22)	COG-TB (n = 25)	MRI-TB (n = 22)	
	PIRADS 5 (n = 69)	PCa	21 (95.5)	22 (88.0)	20 (90.9)	0.7[b]
		csPCa[a]	18 (81.8)	16 (64.0)	12 (54.5)	0.15[b]
Small CSR (≤10 mm; n = 91), n (%)			FUS-TB (n = 29)	COG-TB (n = 31)	MRI-TB (n = 31)	
		PCa	7 (24.1)	6 (19.4)	9 (29.0)	0.7[b]
		csPCa[a]	3 (10.3)	6 (19.4)	5 (16.1)	0.6[b]
Anterior located CSR (n = 90), n (%)			FUS-TB (n =37)	COG-TB (n = 25)	MRI-TB (n = 28)	
		PCa	23 (62.2)	15 (60.0)	18 (64.3)	>0.9[b]
		csPCa[a]	18 (48.6)	11 (44.0)	10 (35.7)	0.6[b]
Posterior located CSR (n = 126), n (%)			FUS-TB (n = 35)	COG-TB (n = 46)	MRI-TB (n = 45)	
		PCa	14 (40.0)	12 (26.1)	21 (46.7)	0.12[b]
		csPCa[a]	7 (20.0)	12 (26.1)	13 (28.9)	0.7[b]
Peripheral zone CSR (n = 130), n (%)			FUS-TB (n = 39)	COG-TB (n = 44)	MRI-TB (n = 47)	
		PCa	16 (41.0)	14 (31.8)	23 (48.9)	0.3[b]
		csPCa[a]	8 (20.5)	12 (27.3)	15 (31.9)	0.5[b]
Transition zone CSR (n = 29), n (%)			FUS-TB (n = 10)	COG-TB (n = 14)	MRI-TB (n = 5)	
		PCa	6 (60.0)	10 (71.4)	5 (100.0)	0.3[b]
		csPCa[a]	5 (50.0)	7 (50.0)	3 (60.0)	>0.9[b]
Small prostate volume (<50 ml; n = 100), n (%)			FUS-TB (n =38)	COG-TB (n = 33)	MRI-TB (n = 29)	
		PCa	20 (52.6)	21 (63.6)	23 (79.3)	0.08[b]
		csPCa[a]	13 (34.2)	17 (51.5)	13 (44.8)	0.3[b]
Large prostate volume (≥50 ml; n = 134), n (%)			FUS-TB (n = 41)	COG-TB (n = 45)	MRI-TB (n = 48)	
		PCa	19 (46.3)	13 (28.9)	19 (39.6)	0.2[b]
		csPCa[a]	14 (34.1)	9 (20.0)	12 (25.0)	0.3[b]

COG-TB = cognitive registration TRUS TB; csPCa = clinically significant PCa; CSR = cancer suspicious region; FUS-TB = MRI-TRUS fusion TB; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI TB; PCa = prostate cancer; PIRADS = Prostate Imaging Reporting and Data System; TB = targeted biopsy; TRUS = transrectal ultrasound.
[a] Gleason ≥3 + 4.
[b] Pearson chi-square.

elaborate analysis will be presented after completion of 2- and 5-yr follow-up.

4.3. *Current knowledge*

The literature directly comparing TB techniques is limited; nonetheless, conclusions drawn support the findings of this RCT. Puech et al. [15] could not demonstrate an advantage of FUS-TB compared with COG-TB in 68 individuals undergoing both techniques, with a concordance of 84%. Wysock et al. [25] performed both FUS-TB and COG-TB in 125 men and found PCa detection rates of 32.0% for FUS-TB versus 26.7% for COG-TB (p = 0.14), and csPCa rates of 20.3% for FUS-TB versus 15.1% for COG-TB (p = 0.05). An RCT by Arsov

et al. [26] compared MRI-TB with FUS-TB (+SB) in 210 patients. They found PCa detection rates of 37% for MRI-TB versus 39% for FUS-TB ($p = 0.7$), and csPCa rates of 29% for MRI-TB versus 32% for FUS-TB ($p = 0.7$). Yaxley et al. [27] reported on COG-TB and MRI-TB in 483 men, and found no advantage of any technique—neither for overall PCa (81.6% for COG-TB vs 74.2% for MRI-TB, $p = 0.53$), nor for csPCa detection (75.5% for COG-TB vs 68.1% for MRI-TB, $p = 0.40$). Finally, Kaufmann et al. [28] compared detection rates of (cs)PCa between COG-TB, MRI-TB, and FUS-TB in a nonrandomised cohort of 156 men, and found no significant differences in the detection rates of csPCa (COG-TB 23.7%, MRI-TB 40.0%, and FUS-TB 25.6%, $p = 0.27$), although they found a significant advantage of MRI-TB and FUS-TB over COG-TB for overall PCa detection (COG-TB 29.0%, MRI-TB 51.1%, and FUS-TB 52.4%, $p = 0.04$).

4.4. Limitations

The main limitation of the study is powering, primarily due to a lower yield of PIRADS $\geq$3 on mpMRI (50% lower than anticipated) and thus low availability of TB, causing underpowering for the primary endpoint. This is partially counterbalanced by higher PCa detection rates (44–55%) than the anticipated yields (25–40%). Although no statistically significant differences were found among the groups with the current sample size, clinically relevant differences cannot be ruled out definitively based on broad 95% CIs. A larger trial might give more definitive results, although a post hoc power analysis (based on the established yield of mpMRI and TB in this study) demonstrated that an overwhelming 9886 individuals would need to undergo mpMRI using the current study design. More importantly, the differences in csPCa detection rates ranged between 0.8% and 1.7%, and as such even larger sample sizes would be necessary to find statistically significant differences among the groups. Future studies could search for superior techniques for specific lesions (size and location).

The absence of a consensus on csPCa definition limits any study on TB. We applied a commonly used definition of csPCa [10,25]. Furthermore, an additional analysis was included using an alternative definition of csPCa [29,30]. With this conservative definition of csPCa (incorporating Gleason grade, tumour volume, PSA density, and stage), there were also no significant differences in detection rates (FUS-TB 43.0%, COG-TB 39.7%, and MRI-TB 46.8%, $p = 0.68$; Supplementary Table 3).

Interobserver variability is a factor in PCa diagnosis impacting the quality and reliability of MRI evaluation, accuracy of biopsy procedures, and histopathological evaluation. Owing to logistical restrictions and institutional regulation, we were not able to implement double readings of MRI or histopathology, which would have increased the reliability. However, our group represents an expert team of urologists and radiologists regarding PCa diagnosis. Consequently, the generalisability of this paper with regard to common practice might be limited and should be implemented with caution. Nonetheless, expertise and experience were similar in all the groups and cannot explain the absence of statistical differences between techniques.

Finally, each technique has its own strengths and limitations. FUS-TB was performed under anaesthesia, reducing movement potentially resulting in better targeting, while being invasive, expensive, and time consuming. COG-TB enables real-time correction for movement, but requires experience with both TRUS and mpMRI. With MRI-TB, postbiopsy scan with needle in situ can confirm adequate sampling, although it is limited by availability, required expertise, and time-consuming and costly nature.

5. Conclusions

In men with prior negative prostate biopsies and a persistent suspicion of prostate cancer, the rate of CSRs (PIRADS $\geq$3) on mpMRI was 35%. If TB of these regions is performed, the detection rate would be 49% for PCa and 33% for csPCa. Based on this multicenter RCT, there were no significant differences in the detection rates of (cs)PCa among the three techniques of mpMRI-based TB. Consequently, other factors (such as local experience, availability, and costs) should be evaluated when determining which technique(s) to implement.

Author contributions: Olivier Wegelin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Wegelin, Exterkate, Somford, van Melick, Barentsz, Bosch.
Drafting of the manuscript: Wegelin.
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Supervision: Somford, van Melick, Barentsz, Bosch.
Other: Statistical analysis was performed with the help of Dr. E. Tromp and Dr. J.C. Kelder (see the Acknowledgements section).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.11.040.

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