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The added value of systematic biopsy in men with suspicion of prostate cancer undergoing multiparametric MRI-targeted biopsy

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Abstract

Purpose: Incorporation of multiparametric magnetic resonance imaging (mpMRI) and targeted biopsy (TBx) in the diagnostic pathway for prostate cancer (CaP) is rapidly becoming common practice. In men with a prebiopsy positive mpMRI a TBx only approach, thereby omitting transrectal ultrasound-guided systematic biopsy (SBx), has been postulated. In this study we evaluated the additional clinical relevance of SBx in men with a positive prebiopsy mpMRI (Prostate Imaging Reporting and Data System [PI-RADS] ≥ 3) undergoing TBx for CaP detection, Gleason grading and CaP localization.

Material and methods: Prospective data of 255 consecutive men with a prebiopsy positive mpMRI (PI-RADS ≥ 3) undergoing 12-core SBx and subsequent MRI-transrectal ultrasound fusion TBx in 2 institutions between 2015 and 2018 was obtained. The detection rate for significant CaP (Gleason score [GS] $\geq 3+4$) for TBx and SBx were compared. The rate of potentially missed significant CaP by a TBx only approach was determined and GS concordance and CaP localization by TBx and SBx was evaluated.

Results: TBx yielded significant CaP in 113 men (44%) while SBx yielded significant CaP in 110 men (43%) ($P = 0.856$). Insignificant CaP was found in 21 men (8%) by TBx, while SBx detected 34 men (13%) with insignificant CaP ($P = 0.035$). A TBx only approach, omitting SBx, would have missed significant CaP in 13 of the 126 men (10%) with significant CaP on biopsy. Ten of the 118 men (8%), both positive on TBx and SBx, were upgraded in GS by SBx while 11 men (9%) had higher maximum tumor core involvement on SBx. Nineteen of the 97 men (20%) with significant CaP in both TBx and SBx were diagnosed with unilateral significant CaP on mpMRI and TBx while SBx demonstrated bilateral significant CaP.

Conclusions: In men with a prebiopsy positive mpMRI, TBx detects high-GS CaP while reducing insignificant CaP detection as compared to SBx. SBx and TBx as stand-alone missed significant CaP in 13% and 10% of the men with significant CaP on biopsy, respectively. A combination of SBx and TBx remains necessary for the most accurate assessment of detection, grading, tumor core involvement, and localization of CaP.

Keywords: Prostate cancer; Magnetic resonance imaging; Biopsy; Early diagnosis; Grading

Abbreviations: CI, Confidence interval; DRE, Digital rectal examination; DWI, Diffusion-weighted imaging; DCE, Dynamic contrast-enhanced imaging; GS, Gleason score; (mp)MRI, (multiparametric) magnetic resonance imaging; NPV, negative predictive value; CaP, Prostate Cancer; PSA, Prostate Specific Antigen; RCT, Randomized controlled trial; SBx, Systematic biopsy; T, Tesla; T2W, T2-weighted imaging; TRUS, Transrectal ultrasound; TBx, Targeted fusion biopsy

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1. Introduction

Targeted biopsy (TBx) of suspicious lesions on multiparametric magnetic resonance imaging (mpMRI) has demonstrated favorable detection rates of significant prostate cancer (CaP) compared with transrectal ultrasound (TRUS)-guided systematic biopsy (SBx), especially in the repeat-biopsy setting [1,2]. Moreover, TBx of suspicious mpMRI lesions provides for a better Gleason score (GS) prediction of final histopathology compared to SBx. Consequently mpMRI in combination with TBx is increasingly being used [3–5]. Nevertheless, whether SBx can be safely omitted by performing only mpMRI and if necessary TBx is uncertain for now [6–9]. Although this uncertainty primarily focuses on men with a negative mpMRI thereby preventing biopsy at all, information on the necessity of SBx in men with a positive prebiopsy mpMRI undergoing TBx is still undetermined [10].

A TBx only strategy would substantially decrease the number of biopsies, with its associated discomfort, and could reduce detection of insignificant CaP, often associated with overtreatment, as TBx predominantly detects GS ≥ 7 CaP [8,11,12]. Performing SBx, in addition to TBx, however seems to detect some significant CaP missed on mpMRI-TBx [9,13,14]. Current guidelines on CaP, therefore, still recommend to include systematic biopsies in men with a suspicious mpMRI undergoing TBx [8,15]. Proponents of a TBx only pathway, however, emphasize that missed significant tumors on mpMRI are low- to (limited volume) intermediate-risk tumors and are mainly caused by shortcomings in mpMRI and TBx quality. As most of the current studies have poor adherence to the Standards of Reporting for MRI-targeted Biopsy Studies (START) recommendations with widely diverging mpMRI performance, lesion targeting and biopsy procedures, it remains unclear whether SBx could potentially be omitted in men with a positive mpMRI undergoing TBx [10,16]. Moreover, the role of SBx for other meaningful factors that influence treatment decisions besides CaP detection and GS such as tumor focality and cancer core involvement is also unknown. In this study we evaluated the clinical usefulness of SBx, in addition to TBx, in men with a positive prebiopsy mpMRI (PI-RADS ≥ 3; Prostate Imaging Reporting and Data System v2.0) for CaP detection, Gleason grading and CaP localization.

2. Materials and methods

2.1. Study population

From November 2015 to June 2018, a total of 294 biopsy-naïve and 168 prior negative men ($n = 462$) with an elevated prostate-specific antigen (PSA) of ≥ 3.0 ng/ml and/or abnormal digital rectal examination (DRE), underwent mpMRI of the prostate in 2 institutions, the Amsterdam University Medical Centers, location AMC and Jeroen Bosch Hospital, the Netherlands. MpMRI was generally omitted for men with a PSA level of >25 ng/ml. Two hundred and sixty four out of 462 (57%) mpMRIs were classified as suspicious based on a PI-RADS score ≥3 or more. Out of these 264 men, 255 (97%) underwent both SBx and TBx and were included in the prospective database approved by the respective institutional review boards and reported according to the START criteria [16].

2.2. mpMRI protocol

Of the 255 men, 229 men (90%) underwent prebiopsy mpMRI at 3.0 T and 26 men (10%) at 1.5 T. One hundred and fourteen mpMRIs (45%) were performed with T2-weighted imaging, diffusion-weighted imaging and dynamic contrast-enhanced imaging (DCE) in 1 center, whereas 141 mpMRIs (55%) in the other center were biparametric without DCE imaging. Institutional mpMRI protocols are presented in Appendix 1. At least 1 uroradiologist (M.E., G.J.) with >8 years of experience in mpMRI of the prostate analyzed the images. Individual lesions were scored using PI-RADS v2 [17].

2.3. Biopsy protocols

Median time between mpMRI and biopsy was 20 days (interquartile range 13–33). SBx and TBx procedures were performed in 1 session and SBx was performed before TBx. In 156 out of 255 men (61%) the SBx operator was unaware of the mpMRI results and TBx procedure planning. Both centers performed a standard 12-core TRUS-guided SBx of the peripheral zone with additional cores of the transition zone included in prior-biopsy negative men, if deemed necessary. TBx was performed using MRI-TRUS fusion techniques: the Artemis system (Eigen, Grass Valley, CA) and the Navigo workstation (UC-Care Medical Systems, Yokneam, Israel) [18,19]. Suspicious lesions on mpMRI (PI-RADS ≥ 3) were generally targeted with 2 to 4 cores depending on lesion size. The biopsy procedures were all performed by experienced operators (>200 biopsy cases per year).

2.4. Histopathology

Biopsy cores were examined by an uropathologist in each center with ≥12 years of experience. The total number of (positive) cores, the tumor percentage of each biopsy core and GS were reported according to the 2014 International Society of Urological Pathology recommendations [20].

2.5. Statistical analyses

Descriptive statistics were used to describe patient characteristics and differences in variables were assessed with the χ^2 test for categorical variables and Mann-Whitney U test for continuous variables. Clinically significant CaP was

defined as GS ≥ 3 + 4 = 7 in a biopsy core. Detection rates were presented using cross-tabulations and compared using the McNemar test. We determined the number of missed and GS undergraded clinically significant CaP on TBx and evaluated the role of mpMRI reading and biopsy lesion targeting in men with missed significant CaP on TBx using mpMRI information and positive SBx locations. Last, we compared positive (significant) SBx and TBx core locations within each prostate lobe to assess the role of TBx and SBx in multifocality of CaP disease.

3. Results

3.1. Patient and procedure characteristics

Median age in the cohort of 255 men was 65 years (interquartile range 61–69) as seen in Table 1. Out of the 255 men, 160 (63%) had a CaP positive biopsy. Men with a positive biopsy were significantly older (66 vs. 64 years; $P = 0.04$), biopsy-naïve (78% vs. 38%) and had more often an abnormal DRE (53% vs. 7%; $P < 0.001$) compared with men with a negative biopsy. Men with a positive biopsy had a higher overall PI-RADS score ($P < 0.001$) while the amount of cores taken per procedure were comparable between both groups with a median of 3 TBx cores per procedure.

3.2. Detection of CaP

Of the 160 men with a positive biopsy, 126 (79%) were diagnosed with significant CaP (GS ≥ 3 + 4) and 34 (21%) with insignificant CaP (GS 3 + 3) as seen in Table 2. TBx revealed significant CaP in 113 men (44%) while SBx revealed significant CaP in 110 men (43%; $P = 0.856$). Insignificant CaP was found in 21 men (8%) by TBx and in 34 men by SBx (13%; $P = 0.035$). GS ≥4 + 3 CaP was found via TBx in 69 men (27%) compared to 56 men (22%) via SBx ($P = 0.019$). In men with PI-RADS 3, TBx detected 14 out of the 20 men (70%) with significant CaP on biopsy. For PI-RADS 4 and 5, 48 men and 58 men had significant CaP on biopsy with TBx, detecting significant CaP in 43 men (90%) and 56 men (97%), respectively. Detection results for TBx and SBx is presented separately for biopsy-naïve men and prior-negative men in Appendix 2.

3.3. Missed and GS undergraded significant CaP

TBx detected 16 out of 126 men (13%) with significant CaP (5 GS 3 + 4 = 7, 5 GS 4 + 3 = 7 and 6 GS ≥ 4 + 4 = 8) that were missed ($n = 10$) or GS undergraded insignificant ($n = 6$) on SBx as seen in Table 3. TBx would have omitted detection of insignificant CaP in 13 of the 34 men (38%). SBx detected 13 out of 126 men (10%) with significant CaP (9 GS 3 + 4 = 7, 3 GS 4 + 3 = 7 and 1 GS ≥ 4 + 4 = 8) that were missed (7%, $n = 9$) or GS undergraded insignificant (3%, $n = 4$) on TBx. Significant CaP on TBx was missed in 4 men with PI-RADS 3, 4 men with PI-RADS 4 and 1 man with PI-RADS 5, respectively. Data of these men is descriptively summarized in Appendix 3. Two men with PI-RADS 3 and 1 man for both PI-RADS 4 and 5 were diagnosed as GS 3 + 3 = 6 on TBx while SBx demonstrated significant CaP. Data of these men is descriptively summarized in Appendix 4.

3.4. GS concordance and maximum tumor core involvement

Of the 118 men both positive on SBx and TBx, 91 men (77%) had concordant GS, while 17 (14%) and 10 men (8%) were GS upgraded on TBx and SBx, respectively (Table 4). Of the 10 men upgraded on SBx, 4 men (3%) were upgraded from insignificant to significant CaP. One hundred and seven men (91%) had equal ($n = 91$) or higher ($n = 16$) maximum tumor core involvement in TBx compared to SBx. Eleven men (9%) had higher maximum tumor core involvement on SBx.

3.5. Focality of disease

As shown in Table 5, 75 out of the 118 men (64%) both positive on SBx and TBx, had CaP detected with concordant unilateral or bilateral disease on SBx and TBx. For significant CaP only, 72 out of the 97 men (74%) had significant CaP detected with concordant unilateral or bilateral disease as defined on SBx and TBx while 21 of the 97 men (22%) were diagnosed with unilateral significant CaP on TBx with SBx demonstrating significant CaP on the contralateral side ($n = 2$) or bilateral in the prostate ($n = 19$).

4. Discussion

SBx in men with an elevated PSA level and/or abnormal DRE has been the cornerstone of CaP diagnosis for decades. Due to its ability to detect significant CaP while reducing overdetection of indolent disease, mpMRI and TBx are rapidly becoming common practice in the diagnostic pathway and questions arise whether SBx can be fully replaced by this novel strategy [2,5,21,22]. Results of our study in 255 men with a prebiopsy positive mpMRI undergoing both SBx and TBx demonstrated that a TBx only approach would have missed significant CaP in 9 men (7%) and misclassified CaP as insignificant in 4 more men (3%). Using mpMRI information and positive SBx core locations, both inadequate CaP visualization on mpMRI ($n = 8$) and erroneous biopsy lesion targeting ($n = 5$) contributed to missed significant CaP in a mpMRI-TBx pathway. In addition, additional SBx for detection of significant CaP seems more useful in men with an intermediate suspicion on mpMRI as TBx detected 97% (56/58) of the significant CaP in men with a PI-RADS score 5 compared to 70% (14/20) in men with a PI-RADS score 3. For detection of significant CaP, one might consider to omit SBx in men with PI-RADS

Table 1
Clinical characteristics.

Variable	Total ($N = 255$)	Positive biopsy ($N = 160$)	Negative biopsy ($N = 95$)	P value
Patient				
Age at biopsy; y, median (IQR)	65 (61–69)	66 (62–71)	64 (59–68)	**0.044**
Ethnicity, *n* (%)				
• Caucasian	233 (91)	141 (88)	92 (97)	**0.017**
• Non-Caucasian	22 (9)	19 (12)	3 (3)	
Prebiopsy PSA; ng/ml, median (IQR)	8.1 (5.9–12.0)	8.1 (5.9–12.0)	8.3 (5.9–12.0)	0.781
PSA density; ng/ml/ml, median (IQR)	0.18 (0.12–0.28)	0.21 (0.13–0.30)	0.24 (0.20–0.23)	**<0.001**
DRE, *n* (%)				
• Normal	163 (64)	75 (47)	88 (93)	**<0.001**
• Abnormal	92 (36)	85 (53)	7 (7)	
TRUS prostate volume; cc, median (IQR)	45 (34–63)	40 (30–53)	54 (42–72)	**<0.001**
Biopsy type, *n* (%)				
• Biopsy-naïve	161 (63)	125 (78)	36 (38)	**<0.001**
• Prior negative	94 (37)	35 (22)	59 (62)	
Biopsy session, *n* (%)				
• 1	161 (63)	125 (78)	36 (38)	**<0.001**
• 2	56 (22)	27 (17)	29 (31)	
• ≥3	38 (15)	8 (5)	30 (31)	
mpMRI				
PI-RADS score per patient, *n* (%)[a]				
• 3	81 (32)	28 (18)	53 (56)	**<0.001**
• 4	94 (37)	63 (39)	31 (33)	
• 5	80 (31)	69 (43)	11 (12)	
MRI lesions per patient, *n* (%)				
• 1	186 (73)	114 (71)	72 (76)	0.742
• 2	62 (24)	41 (26)	21 (22)	
• ≥3	7 (3)	5 (3)	2 (2)	
Biopsy				
SBx cores in biopsy-naïve patients, n (%):				
• <12	8 (5)	7 (6)	1 (3)	0.649
• 12	147 (91)	114 (91)	33 (92)	
• >12	6 (4)	4 (3)	2 (6)	
SBx cores in prior-negative patients, *n* (%)				
• <12	9 (9)	3 (9)	6 (10)	0.596
• 12–16	56 (60)	17 (54)	37 (63)	
• 16	29 (31)	13 (37)	16 (27)	
MRI-TBx cores patient, median (range)	3 (2–4)	3 (2–4)	3 (2–4)	0.131
MRI-TBx cores per lesion, *n* (%)				
• 1, *n* (%)	22 (7)	13 (6)	9 (7)	0.279
• 2, *n* (%)	220 (67)	136 (65)	84 (70)	
• 3, *n* (%)	61 (18)	45 (21)	16 (13)	
• 4, *n* (%)	21 (6)	12 (6)	9 (7)	
• ≥5, *n* (%)	7 (2)	5 (2)	2 (2)	
Biopsy complication:				
Yes				0.574
• Prostatitis, *n* (%)	10 (4)	6 (4)	4 (4)	
• Urinary retention, *n* (%)	1 (0.4)	1 (0.5)	–	
• Gross rectal bleeding, *n* (%)	1 (0.4)	–	1 (1)	
• Gross hematuria	1 (0.4)	1 (0.5)	–	
No, *n* (%)	242 (95)	152 (95)	90 (95)	

DRE = digital rectal examination; IQR = interquartile range; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate specific antigen; SBx = systematic biopsy; TBx = targeted biopsy; TRUS = transrectal ultrasound.

[a]The highest PI-RADS score is given if more than one lesion was present in a patient.

Statistically significant p-values ($p < 0.05$) are indicated in bold.

Table 2
Prostate cancer detection outcomes stratified according to the PI-RADS score.

Detection	Men with PI-RADS 3 ($n = 81$)	Men with PI-RADS 4 ($n = 94$)	Men with PI-RADS 5 ($n = 80$)	Total ($n = 255$)
All biopsy (TBx and SBx)				
No CaP, *n* (%)	53 (65)	31 (33)	11 (14)	95 (37)
Insignificant CaP, *n* (%)				
• GS 3 + 3	8 (10)	15 (16)	11 (14)	34 (13)
Significant CaP, *n* (%)				
• All	20 (25)	48 (51)	58 (72)	126 (49)
o GS 3 + 4	12 (15)	15 (16)	23 (29)	50 (20)
o GS 4 + 3	7 (9)	24 (25)	12 (15)	43 (17)
o GS ≥ 4 + 4	1 (1)	9 (10)	23 (29)	33 (13)
Total	81 (100)	94 (100)	80 (100)	255
TBx only				
No CaP, *n* (%)	61 (75)	44 (47)	16 (20)	121 (47)
o with significant CaP on SBx	4 (5)	4 (4)	1 (1)	9 (4)
Insignificant CaP, n (%)				
• GS 3 + 3	6 (7)	7 (7)	8 (10)	21 (8)
o with significant CaP on SBx	2 (2)	1 (1)	1 (1)	4 (2)
Significant CaP, *n* (%)				
• All:	14 (17)	43 (46)	56 (70)	113 (44)
o GS 3 + 4	7 (9)	15 (16)	22 (28)	44 (17)
o GS 4 + 3	7 (9)	20 (21)	13 (16)	40 (16)
o GS ≥ 4 + 4	0	8 (9)	21 (26)	29 (11)
Total, *n* (%)	81 (100)	94 (100)	80 (100)	255 (100)
SBx only				
No CaP, *n* (%)	56 (69)	35 (37)	20 (25)	111 (44)
o with significant CaP on TBx	1 (1)	2 (2)	7 (9)	10 (4)
Insignificant CaP, *n* (%)				
• GS 3 + 3	7 (9)	17 (18)	10 (13)	34 (13)
o with significant CaP on TBx	1 (1)	4 (4)	1 (1)	6 (2)
Significant CaP, *n* (%)				
• All	18 (22)	42 (45)	50 (63)	110 (44)
o GS 3 + 4	12 (15)	20 (21)	22 (28)	54 (21)
o GS 4 + 3	5 (6)	16 (17)	10 (13)	31 (12)
o GS ≥ 4 + 4	1 (1)	6 (6)	18 (23)	25 (10)
Total, *n* (%)	81 (100)	94 (100)	80 (100)	255 (100)

GS = Gleason score; MRI = magnetic resonance imaging; CaP = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; SBx = systematic biopsy; TBx = targeted biopsy.

score 5 as additional benefit of SBx is very low compared to the high amount of biopsies that need to be taken.

Our results are in line with a recent literature review that demonstrated that combination of both TBx and SBx improved significant CaP detection rates with 5% to 15% as compared with TBx alone [10]. Our study adds to this review other new important findings. First of all, maximum tumor core involvement is underestimated by TBx in 9% (11/118) of the men both positive on SBx and TBx while 5 more men (4%) had a higher significant GS in the SBx compared to the TBx. Although one could argue that TBx precision was insufficient in these cases, TBx fusion cores are also known for their 2 to 3 mm error margin while a recent systematic review did not demonstrate any additional value of in-bore MRI TBx compared to MRI-TRUS fusion TBx [23–25]. Moreover, 21 of the 97 men (22%) both positive for significant CaP on TBx and SBx were diagnosed with unilateral disease on mpMRI-TBx while SBx demonstrated bilateral significant disease. In line with the literature, TBx has a high sensitivity for index lesion characterization, but secondary lesions are often missed by imaging while disease progression is not always driven by the index lesion only [22,26–29]. Notwithstanding the fact that CaP detection and accurate GS determination are the cornerstone for decision making in CaP, secondary pathological features such as maximum tumor core involvement and multifocality are relevant for adequate risk stratification, prognosis, and treatment evaluation of CaP. Especially, for novel focal therapy techniques, aiming at selectively ablating CaP tumors while sparing functional and anatomical structures, mpMRI and TBx should be combined with SBx for adequate patient selection [30].

Despite the drawbacks of performing only TBx, the TBx approach was more efficient on a per-core basis in the detection of significant CaP with higher rates of positive cores and 4 times fewer biopsy cores (median cores per session: 12 vs.

Table 3
Cross tabulation of the MRI-TBx and SBx protocol for detection and Gleason score.

Insignificant/Significant ($n = 255$)					
		MRI TBx protocol, *n* (%)			
		No cancer on biopsy	Insignificant CaP	Significant CaP	Total
SBx protocol, *n* (%)	No cancer on biopsy	95 (79)	6 (29)	10 (9)	111 (44)
	Insignificant CaP	17 (14)	11 (52)	6 (5)	34 (13)
	Significant CaP	9 (7)	4 (19)	97 (86)	110 (43)
	Total	121 (100)	21 (100)	113 (100)	255 (100)

Gleason Score (GS) ($n = 255$)							
		MRI TBx protocol, *n* (%)					
		No cancer on biopsy	GS 3 + 3	GS 3 + 4	GS 4 + 3	GS ≥ 4 + 4	Total
SBx protocol, *n* (%)	No cancer on biopsy	95 (78)	6 (29)	3 (6)	3 (8)	4 (14)	111 (44)
	GS 3 + 3	17 (14)	11 (52)	2 (4)	3 (8)	1 (3)	34 (13)
	GS 3 + 4	7 (6)	2 (10)	36 (77)	8 (22)	1 (3)	54 (21)
	GS 4 + 3	2 (2)	1 (5)	3 (7)	23 (59)	2 (7)	32 (13)
	GS ≥ 4 + 4	0	1 (5)	0	3 (8)	21 (72)	24 (9)
	Total	121 (100)	21 (100)	44 (100)	40 (100)	29 (100)	255 (100)

GS = Gleason score; MRI = magnetic resonance imaging; CaP = prostate cancer; SBx = systematic biopsy; TBx = targeted biopsy.

Table 4
GS concordance and biopsy core outcomes stratified according to the PI-RADS score.

	Men with PI-RADS 3 ($n = 81$)	Men with PI-RADS 4 ($n = 94$)	Men with PI-RADS 5 ($n = 80$)	Total ($n = 255$)
Gleason score (GS) concordance in men with TBx and SBx both CaP-positive ($n = 118$)				
Concordant, *n* (%)	12 (71)	31 (67)	48 (87)	91 (77)
Upgrading on TBx, *n* (%):	1 (6)	12 (26)	4 (7)	17 (14)
Upgrading on SBx, *n* (%):	4 (23)	3 (7)	3 (5)	10 (8)
Total, *n* (%)	17 (100)	46 (100)	55 (100)	118 (100)
MTCI in men with TBx and SBx both CaP-positive ($n = 118$)				
Equal MTCI in %, *n* (%)	13 (76)	33 (72)	45 (82)	91 (77)
Higher MTCI in % on TBx, *n* (%)	1 (6)	8 (17)	7 (13)	16 (14)
Higher MTCI in % on SBx, *n* (%)	3 (18)	5 (11)	3 (5)	11 (10)
Total, *n* (%)	17 (100)	46 (100)	55 (100)	118 (100)
Positive biopsy cores: TBx only				
Positive CaP cores, *n* (%):				
• GS 6 CaP	10 (4)	16 (5)	20 (8)	46 (6)
• GS ≥ 7 CaP	28 (13)	90 (31)	138 (55)	256 (33)
Total cores (*n*)	223 (100)	294 (100)	253 (100)	770 (100)
Positive biopsy cores: SBx only				
Positive CaP cores, *n* (%):				
• GS 6 CaP	38 (4)	63 (5)	74 (8)	175 (6)
• GS ≥7 CaP	52 (5)	191 (16)	281 (30)	524 (17)
Total cores, *n* (%)	1021 (100)	1178 (100)	940 (100)	3139 (100)
Number of cores per significant CaP diagnosis, mean [median] (IQR)				
TBx ($n = 113$)	2.8 [3] (2–3)	3.1 [3] (2–4)	3.2 [3] (2–4)	3.0 [3] (2–4)
SBx ($n = 110$)	12.6 [12] (12–12)	12.5 [12] (12–12)	11.8 [12] (12–12)	12.3 [12] (12–12)

GS = Gleason score; MTCI = maximum tumor core involvement, CaP = prostate cancer; PI-RADS = Prostate imaging reporting and data system; SBx = systematic biopsy; TBx = targeted biopsy.

3) per diagnosis. Moreover, a SBx only approach would have also missed a non-negligible amount (13%) of significant CaP while performing additional SBx on top of TBx, as expected, will come with an increased detection of insignificant CaP as a downside. This is demonstrated by the 38% additional insignificant CaP found by SBx alone in our cohort.

While reduced detection of insignificant CaP by TBx is demonstrated in almost all recent literature, results on

Table 5
Cross tabulation of the MRI-TBx and SBx protocol for (significant) CaP tumor localization.

Unilateral/bilateral disease (all CaP) ($n = 160$)						
		MRI TBx protocol, *n* (%)				
		No cancer on biopsy	Unilateral left	Unilateral right	Bilateral	Total
SBx protocol, *n* (%)	No cancer on biopsy	95 (79)	7 (13)	7 (15)	2 (6)	111 (44)
	Unilateral left	7 (6)	24 (43)	1 (2)	2 (6)	34 (13)
	Unilateral right	11 (9)	1 (2)	25 (54)	2 (6)	39 (15)
	Bilateral	8 (7)	24 (43)	13 (28)	26 (81)	71 (28)
	Total	121 (100)	56 (100)	46 (100)	32 (100)	255 (100)
Unilateral/bilateral disease (significant CaP) ($n = 160$)						
		MRI TBx protocol, *n* (%)				
		No cancer/insignificant	Unilateral left	Unilateral right	Bilateral	Total
SBx protocol, *n* (%)	No cancer /insignificant	129 (91)	7 (14)	6 (16)	3 (12)	145 (57)
	Unilateral left	5 (4)	29 (58)	1 (3)	3 (12)	38 (15)
	Unilateral right	7 (5)	2 (4)	24 (63)	0	33 (13)
	Bilateral	1 (1)	12 (24)	7 (18)	19 (76)	39 (15)
	Total	142 (100)	50 (100)	38 (100)	25 (100)	255 (100)

MRI = magnetic resonance imaging; CaP = prostate cancer; SBx = systematic biopsy; TBx = targeted biopsy.

increased detection of significant CaP by TBx are mixed [1,31]. In our study, high GS CaP (GS $\geq 4+3$) was more often found by TBx compared to SBx (27% vs. 22%; $P = 0.035$), but both techniques detected an equal amount of GS $\geq 3+4$ CaP (44% vs. 43%; $P = 0.856$). Two recently published prospective, multicenter, paired, diagnostic studies in biopsy-naïve men (MRI-FIRST and 4M study) demonstrated comparable detection of significant CaP for SBx and TBx while the multicenter PRECISION randomized controlled trial demonstrated that mpMRI with TBx detected more significant CaP compared to SBx [2,32,33]. Despite the differences in study design, comparison of results with these studies with fairly similar baseline characteristics illustrated some important findings (Appendix 5). Detection rates of significant CaP by TBx were higher in the PRECISION trial than in the biopsy-naïve men of the other studies: 38% vs. 32% (current study), 32% (MRI-FIRST) and 25% (4M study), respectively. However, significant CaP on SBx was detected in 35% and 30% of all biopsy-naïve men in our study and the MRI-FIRST study, while the PRECISION randomized controlled trial and 4M study detected only 26% and 23% of the men with significant CaP on SBx, respectively. Despite the clear difference in level of evidence, comparisons like these demonstrate that there is still room for improvement in attaining consistency in not only mpMRI with TBx but also in SBx since much higher detection rates of significant CaP were achieved with SBx in our study. Especially given the fact that biopsy sessions in biopsy-naïve men were performed by 2 operators in a complete blinded fashion in 86% (252/294) of the cases, mpMRI reading could have positively influenced the SBx performance only in a minority of the cases. Moreover, sensitivity analysis excluding these cases showed no impact on the detection rate of SBx indicating that these results most likely reflect the true clinical performance of SBx when performed by experienced TRUS operators.

Besides this limitation our study has other limitations. One being the fact that our study does not address the full diagnostic pathway of mpMRI and TBx, but only the clinical relevance of SBx in men with a positive prebiopsy mpMRI undergoing TBx. Second, SBx harbors both random and systematic errors as shown in studies as the PROMIS trial with transperineal template mapping biopsy as reference standard and studies in the repeat biopsy setting showing non-negligible rates of significant CaP after a negative SBx.[6,34,35] Consequently, the use of SBx as reference standard comes with limitations. Comparison with radical prostatectomy pathology, however, was also not possible, as only a selected group underwent surgery and partial embedding was performed in the majority of these patients. Furthermore, our study addressed the more clinical question as to whether TBx is adequate as a standalone approach for CaP detection and localization in mpMRI positive men as in practice men with a positive mpMRI result could then avoid the need for SBx. Third, SBx was performed before TBx to evaluate the unbiased performance of SBx. This may have resulted in nonuniform prostate swelling making image registration and TBx less accurate. The diagnostic yield of TBx in men with a positive prebiopsy mpMRI, however, was on average comparable with current literature as shown in Appendix 5. Fourth, 1 center did not perform DCE MRI while 10% of all mpMRI scans were performed on 1.5 T. Both could have negatively affected TBx outcome. Recent studies, however, demonstrated comparable diagnostic accuracy of PI-RADS v2 using a biparametric protocol while mpMRI on 1.5 T is capable of yielding adequate diagnostic scans [17,36,37]. Lastly, our chosen definition of clinically significant CaP is

debatable. Although it is common to define GS ≥ 3 + 4 disease on biopsy as significant CaP, GS 3 + 4 = 7 disease shows considerable heterogeneity in pathological features and clinical outcome [38]. In the future, addition of histopathological parameters such as cribriform growth pattern and percentage Gleason grade 4 could improve risk stratification of GS 3 + 4 disease and possibly aid in reaching a more definitive answer to the question whether TBx could safely replace SBx as the majority (69%) of missed tumors with a TBx only pathway were tumors with a GS 3 + 4 = 7.

Findings of this study highlight that for now, both TBx and SBx are important in the detection, grading and localization of CaP. Due to the major implications for broader use of mpMRI such as additional equipment, trained personnel, and total costs, findings like these should be extended. There is a well-known variation in biopsy targeting and a substantial portion of false positives is reported in literature [10]. Comparison of detection rates between our 2 centers also demonstrated significantly different detection rates for CaP on TBx (76% vs. 41%, $P < 0.05$). Although this is partly explained by difference in prevalence of CaP disease due to a difference in biopsy population (relatively more prior negative men in the center with lower CaP detection), our results also demonstrate that there is still a need to achieve higher consistency in the reporting of mpMRI and targeting of suspicious lesions. Given the fact that both centers had a comparable amount of missed significant CaP on TBx (4% vs. 6%), SBx should not be considered as redundant for the time being and should be performed, just as MRI reading and TBx, by dedicated operators with experience in TRUS. A combination of both SBx as TBx seems necessary in the detection of significant CaP as both techniques detect non-negligible significant CaP missed in a stand-alone approach.

5. Conclusions

In men with a prebiopsy positive mpMRI, TBx detects high-GS CaP while reducing insignificant CaP detection as compared to SBx. SBx and TBx as stand-alone missed significant CaP in 13% and 10% of the men with significant CaP on biopsy, respectively. A combination of SBx and TBx remains necessary for the most accurate assessment of detection, grading and localization of CaP.

Author disclosure statement

All authors declare no conflicts of interests.

Acknowledgments

None.

Ethical considerations

The medical ethics review committee of each participating center granted a waiver for the collection and analysis of the clinical data in a prospective database. The trial was conducted in accordance to the Good Clinical Practice.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi:10.1016/j.urolonc.2019.01.005.

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