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Adding systematic biopsy to magnetic resonance ultrasound fusion targeted biopsy of the prostate in men with previous negative biopsy or enrolled in active surveillance programs

A prospective single center, randomized study

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Abstract

Magnetic resonance imaging (MRI) targeted biopsy (TBx) of the prostate demonstrated to improve detection rate (DR) of clinically significant prostate cancer (csPCa) in biopsy-naive patients achieving strong level of evidence. Nevertheless, the csPCa yield for TBx alone versus TBx plus systematic biopsy (SBx) after accounting for overlapping of SBx cores with TBx cores, in prior-negative or active surveillance (AS) patients has not been well established.

The objective of the study was to investigate benefits in terms of detection rate and pathological stratification of prostate cancer (PCa) using contextual SBx during MRI-TBx.

Patients previously submitted to negative-SBx (cohort A) and those enrolled in an AS program (cohort B) who showed at least 1 suspicious area with a PIRADSv2 score ≥ 3 were prospectively and randomly assigned to only TBx strategy versus TBx plus SBx strategy. SBx locations could not encompass the TBx sites, so that the results of each type of biopsy were independent and did not overlap.

A total of 312 patients were included in the 2 cohorts (cohort A: 213 cases; cohort B: 99 cases). No significant differences were found in terms of overall PCa-DR (77.6% vs 69.6% respectively; $P = .36$) and csPCa-DR (48.2% vs 60.9 respectively; $P = .12$). The MRI-TBx alone cohort showed higher csPCa/PCa ratio (87.5% vs 62.2%; $P = .03$). The MRI-TBx plus SBx group subanalysis showed significantly higher csPCa-DR obtained at the MRI-TBx cores when compared with the SBx cores (43.7% vs 24.1%, respectively; $P = .01$). Independently to age, prostatic-specific antigen and prostate imaging-reporting and data system score, either in rebiopsy (OR 0.43, 0.21–0.97) or AS (OR 0.46, 0.32–0.89) setting, SBx cores were negatively associated with the csPCa-DR when combined to TBx cores.

MRI-TBx should be considered the elective method to perform prostate biopsy in patients with previous negative SBx and those considered for an AS program. Adding SBx samples to MRI-TBx did not improve detection rate of csPCa.

Abbreviations: AS = active surveillance, csPCa = clinically significant prostate cancer, DR = detection rate, FBx = fusion biopsy, MRI = magnetic resonance imaging, PCa = prostate cancer, SBx = systematic biopsy, TBx = targeted biopsy, TSE = turbo spin echo.

Keywords: biopsy, clinically significant, detection rate, magnetic resonance imaging, prostate biopsy, prostate cancer

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Prostate cancer (PCa) is the most common neoplasm diagnosed in men.[1,2] Magnetic resonance imaging (MRI) has shown a remarkable accuracy in the detection of clinical significant prostate cancer (csPCa).[3–5] A growing body of evidence suggests that multiparametric (mp) magnetic resonance imaging can improve prostate cancer risk group classification and could reduce false-negative rates and the necessity of repeat biopsies in both biopsy-naive patients and those with prior negative-biopsy;[6–9] not surprisingly, MRI targeted biopsies (TBx) should be strongly considered for any patient, biopsy naive or with a prior negative biopsy who has persistent clinical suspicion of PCa. Techniques for TBx include visual estimation TRUS-GB (cognitive technique), software coregistered MRI-ultrasound fusion (fusion technique), and in-bore MRI-guided biopsy.[10]

The use of MR-ultrasound fusion biopsy (FBx) in men with elevated serum prostate-specific antigen (PSA) is becoming increasingly widespread in clinical practice.[11] Prostatic MRI allows the identification of suspicious regions that may be missed by systematic biopsies (SBx) and direct sampling via FBx.[12] As stated by European Association of Urology (EAU) guidelines, MRI-TBx can be used in 2 different diagnostic pathways: the combined pathway in which patients with a positive mpMRI undergo combined SBx and TBx and patients with negative mpMRI undergo systematic biopsy; the MR pathway in which patients with a positive mpMRI undergo only TBx and patients with negative multiparametric MRI are not biopsied.[13]

Adding MRI TBx to SBx in biopsy naive patients increases the number of ISUP $\geq$ 2 PCa by approximately 20% whereas in the repeat-biopsy setting by approximately 40%. Therefore, it has been shown that TBx improves the detection of clinically significant prostate cancer.[14,15]

However, the csPCa yield for TBx alone versus TBx plus SBx after accounting for overlapping of SBx cores with TBx cores has not been well studied.

The aim of our study was to investigate the potential benefit in terms of Detection Rate and pathological stratification of prostate cancer using a contextual SBx during an MRI-TRUS TBx in a 2-cohort population: patients with previous negative SBx and patients considered for an active surveillance (AS) program.[16]

2. Methods

2.1. Study population

This is a prospective randomized single center study approved by our Internal Review Board of Policlinico Abano Terme, Abano Terme (PD), Italy, in accordance with good clinical practice guidelines and ethical principles of the Declaration of Helsinki. An informed consent was obtained from all patients enrolled in the study.

Two different cohorts were considered with the following inclusion criteria: a raised PSA serum level with a previous negative SBx; an enrollment in an AS program for low-risk PCa. In both 2 cohorts, all patients were submitted to mpMRI with at least 1 suspicious area with a PIRADSv2 score $\geq$3. Between April 2017 and July 2019, 213 consecutive patients were included in the cohort A and 99 consecutive patients in the cohort B.

Cohort A: all patients were previously submitted to SBx for clinical suspicion of prostate cancer based on raised PSA serum level, the histological examination resulted negative for PC and PSA levels continued to rise. All cases underwent mpMRI and showed at least 1 suspicious area with a PIRADS v2 score $\geq$3.

Cohort B: all patients were enrolled in an active surveillance program for diagnosis of low-risk (Gleason Score 3 + 3) PCa within the past year. The diagnosis was obtained by a standard ultrasound guided biopsy and all cases went mpMRI before confirmatory biopsy and showed at least 1 suspicious area with a PIRADS v2 score $\geq$3.

2.2. Multiparametric magnetic resonance imaging analysis

All multiparametric MRI examinations were performed with a 1.5 T whole body scanner (Achieva XR; Philips Medical Systems, Best, the Netherlands) with a 32-channels phased-array surface coil with endorectal coil. After local 3-plane acquisition, required for the correct positioning of the sequences, the morphological and functional studies were carried out. Morphological study of the prostate gland was obtained with Turbo Spin Echo (TSE) T2-weighted sequences (TE 100 msec, TR 4074 msec, slice thickness 3 mm, slice spacing 0.3 mm, field of view [FOV] 180 $\times$ 180 mm and matrix size 276 $\times$ 205) in the sagittal, axial, and coronal planes, including seminal vesicles and the entire prostate gland. For the functional study, DWI, DCE-MRI, and MRS acquisition were performed. The DWI acquisition was carried out in the axial plane, using a single-shot echo-planar imaging sequence, with 3 b-values (0, 600, and 1500 s/mm^2), slice thickness of 3 mm, FOV 180 $\times$ 180 mm and matrix size 80 $\times$ 71. The DCE-MRI was obtained using three-dimensional (3D) T1W high-resolution isotropic volume examination sequence during the intravenous injection of a contrast bolus of 0.1 mmol per kilogram of body weight of Meglumine gadobenate (Multihance, Bracco Diagnostics, Milan, Italy), at flow rate of 3.5 mL/s followed by 15 mL of saline solution. Twenty-three 3D data sets, 1 before and 22 after contrast administration, were acquired with 10 seconds temporal resolution and a total duration of 4 minutes (depending on the volume of the prostate gland). The first data set acquired before contrast agent administration can be used to detect residual blood of previous biopsy. The MRS was obtained with the use of 3D chemical shift imaging sequence and the following parameters: matrix $10 \times 10 \times 12$ phase-encoding steps with nominal voxel size < 0.5 cc; spectral selective suppression of water and lipid signals; interactive automatic shimming up to a line width at half height of the water resonance peak between 15 and 20 Hz. The volume of interest is aligned to axial T2WIs and centered on each prostate to maximize coverage of the whole gland, while minimizing contamination by surrounding tissue. Finally, a TSE T2-weighted sequence (TE 100 msec, TR 3445 msec, slice thickness 4 mm, slice spacing 0.4 mm, FOV 260 $\times$ 260 mm and matrix size 260 $\times$ 178) in the axial plane was acquired from the aortic bifurcation to the symphysis pubis to evaluate the pelvic lymph nodes and bone. All the multiparametric-MRI images were assessed by 1 reader (M.V.) with 10 years of specific experience on prostate MRI who was blinded to all patient information. The DWI and DCE-MRI images were processed on an independent workstation with dedicated software (View Forum, Philips Medical Systems, Best, the Netherlands). Regions of interest positioned on the suspected areas were used to calculate the corresponding value of the apparent diffusion coefficient for DWI. Semiquantitative MRI perfusion was performed on the same workstation with analysis of DCE datasets and signal intensity-time (I-T) curves generation. All lesions were scored using the PI-RADS-v2 according to the ESUR

guidelines for the evaluation and reporting of prostate multiparametric-MRI.[17,18]

2.3. Conduct of the biopsy

The biopsies were performed within 3 weeks from the diagnostic mpMRI study by a single urologist with a 5 years' experience in TRUS-guided SBx and TBx. In the cohort B, biopsies were performed at 1 year from inclusion in the AS program as confirmatory biopsies. All patients underwent an MRI-TRUS TBx on suspicious target lesions at mpMRI (PIRADSv2 score 3–5) using the Artemis platform. After TBx, a SBx was performed or not (based on randomization) with the Artemis-generated template, with 10/12-systematic cores throughout the prostate. SBx locations could not encompass the TBx sites, so that the results of each type of biopsy were independent and did not overlap.

Using the BK Ultrasound 5000 MRI-TRUS Fusion platform, fusion target biopsy was performed on the suspicious area previously identified on the multiparametric-MRI using a real-time alignment of the T2-weighted sequence to the TRUS image. MRI-TRUS images alignment was possible due to a tracking device consisted in a sensor coil on the TRUS probe paired with a magnetic field generator to register the location of the tracking device in the 3D space. At least 3 cores were taken for each lesion and the number of additional cores was based on the diameter of the lesion. The number of cores taken was related to the size of the lesions; the cores were carried out along the long axis of the lesion with a maximum of 2 biopsies taken for each needle. TRUS Standard Biopsy was a typical 12 cores double sextant template from lateral to medial of base, mid, and apex. Only the TRUS images, with no multiparametric-MRI target data available, were used for the standard biopsy portion of the case.

2.4. Pathologic analysis

Histopathologic examination was carried out by a single dedicated genitourinary pathologist with more than 20 years of experience, who was blinded to the origin (MRI-TRUS TBx or SBx) of each single core. Not indolent Prostate Cancer was defined by the presence of Gleason Score ≥7 (ISUP grade ≥2).

2.5. Study design and endpoints

After inclusion in each cohort A and B, cases were randomly assigned to an only TBx strategy versus a TBx + SBx strategy. Primary endpoints of this study were overall PCa-detection rate (DR), csPCa-DR, and pathologic results between MRI-TRUS TBx and SBx. Secondary endpoints were correlations between clinical characteristics of the population and csPCa detection on biopsy results.

2.6. Statistical analysis

Means, medians, and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables. The Mann–Whitney U test and χ^2 tests were used to compare the statistical significance of differences in medians and proportions, respectively. Multivariate logistic regression was performed to evaluate if age, PSA, or PIRADS categorization and type of cohort analyzed (ie, A vs B) were associated with the detection of csPCa at biopsies.

All analyses were carried out using SPSS IBM Statistics v. 22.0 (IBM Corp, Armonk, NY) with level of statistical significance set at $P < .05$.

3. Results

A total of 312 patients were included in the 2 cohorts (cohort A: 213 cases; cohort B: 99 cases). All cases were consecutively assigned to MRI-TRUS TBx alone or to a TBx + SBx strategy. The clinical, radiologic, and pathologic characteristics of the entire population are listed in Table 1. No statistically significant differences in terms of age, PSA, PIRADSv2 score distribution, biopsy cores taken per patient by SBx were present between the 2 biopsy strategy groups (Table 1). The 2 biopsy groups were homogeneous regarding most of clinical and radiological data, except for prostate volume (median value 50 vs 40 cc; IQR 39.5 – 61.25 vs 35–50, respectively) and radiological dimension of the index lesion (13 vs 10 mm; IQR 10–16, 25 vs 10–12, respectively).

Median number of targeted and random cores per patient were respectively 6 (IQR, 4–6) and 11.5 (IQR 10–12). Table 2 shows clinical characteristics of cases on the basis of the pathological diagnosis of csPCa and clinically insignificant PCa. csPCa showed a higher percentage of PI-RADS score 4/5 (73.2%) when compared with ciPC (33.3%).

3.1. Detection rate of PCa and csPCa

Table 3 shows the detection rate of all PCa, csPCa, and ratio csPCa/all PCa between patients assigned to MRI-TRUS TBx alone versus TBx + SBx. Between the 2 groups, no significant differences were found in terms of overall PCa detection rate (77.6% vs 69.6% respectively; $P = .36$) and csPCa detection rate (48.2% vs 60.9% respectively; $P = .12$). The MRI-TRUS TB alone cohort showed a higher csPCa/PCa ratio (87.5% vs 62.2%; $P = .03$) mainly due to the lower number of indolent (ISUP 1) tumor diagnosed.

Moreover, at the MRI-TRUS TB + SB group subanalysis, a significantly higher csPCa-DR was obtained at the MRI-TRUS TB cores when compared with the SBx cores (43.7% vs 24.1%, respectively; $P = .01$) (Table 2) with a concomitant more accurate Gleason Score stratification (Table 4). Twenty-four out of 81 cases (29.6%) were upgraded from benign at SBx cores to csPCa at TBx cores and 18 out of 51 (35.3%) were upgraded from ciPC at SBx cores to csPCa at TBx cores. On the contrary 5/65 cases (7.7%) benign and 3/33 (9.0%) with ciPC at TBx cores were upgraded to Gleason Score 3 + 4 at SBx cores (Table 4).

3.2. Multivariate analysis

In adjusted analyses, age, PSA levels, PIRADS score distribution were not significantly associated with csPCa detection at SBx (Table 5). Therefore, independently of these parameters, either in the rebiopsy (OR 0.43, 0.21–0.97) or active surveillance (OR 0.46, 0.32–0.89) setting, SBx cores were negatively associated with the csPCa-DR when combined to TBx cores.

4. Discussion

The advantage of magnetic resonance imaging TBx to SBx in increasing the detection rate of clinical significant prostate cancer, either in naive or in rebiopsy populations, has been well

Table 1

Clinical, radiologic, and pathological characteristics of the population.

	All (n = 312)	MRI-TRUS TBx + TRUS SBx cohort (n = 174)	MRI-TRUS TBx ALONE, cohort (n = 138)	*P* value	Previous negative (n = 213)	Active surveillance (n = 99)	*P* value
AGE [y]	68	67	68.5	.45	68	68	.84
Median (IQR)	(62–72)	(61–72)	(62.5–71.5)		(62–72)	(61–71.5)	
PSA [ng/mL]	7.36	7.36	7.39	0.95	7.89	6.90	*
Median (IQR)	(5.21 – 9.26)	(5.43–9.63)	(4.75–9.22)		(5.97–10.0)	(4.0–8.22)	**.02**
PSA density [ng/mL/cc]	0.15	0.14	0.18	.15	0.15	0.15	.75
Median (IQR)	(0.09 – 0.22)	(0.09–0.20)	(0.11–0.26)		(0.10–0.22)	(0.08–0.21)	
Volume [cc]	45	50	40	*	50	38	*
Median (IQR)	(35–57)	(39.5 – 61.25)	(35–50)	**.008**	(40–60)	(32.5–50)	**.01**
Susp. area	11.5	13	10	*	12	10	*
Diameter [mm]	(10–15)	(10–16.25)	(10–12)	**.01**	(10–17)	(8.5–12)	**.001**
Median (IQR)							
PI-RADS-v2 n (%)							
3/5	156 (50%)	93 (53.4%)	63 (45.6%)	.71	105 (49.3%)	51 (51.5%)	
4/5	129 (41.3%)	72 (41.4%)	57 (41.3%)		87 (40.8%)	42 (42.4%)	.72
5/5	27 (8.7%)	9 (5.2%)	18 (13.0%)		21 (9.9%)	6 (6.1%)	
Median (IQR)	3.5 (3–4)	3 (3–4)	4 (3–4)		4 (3–4)	3 (3–4)	
cores taken per pts							
Median (IQR)							
Total	16 (15–18)	16 (15–18)	—	—	16 (15–18)	16 (15–18)	.92
Fusion	6 (4–6)	6 (4–6)	6 (6–7)	.91	6 (4–7)	6 (6–6.5)	.87
Random	11.5 (10–12)	11.5 (10–12)	—	—	11 (10–12)	12 (10–12)	.95

MRI = magnetic resonance imaging, TRUS = trans rectal ultrasound, TBx = targeted biopsy, SBx = systematic biopsy, PSA = prostatic-specific antigen, IQR = interquartile range, n = number.
In bold values that are statistically significant

demonstrated by multicenter studies and stated by international guidelines.[13–15] However, the csPCa yield for TBx alone versus TBx plus SBx after accounting for overlapping of SBx cores with TBx cores, has not been well studied. EAU guidelines in a naive population, when multiparametric magnetic resonance imaging is performed and its PIRADS is ≥ 3, recommend with a strong level of evidence to combine targeted and systematic biopsies. On the contrary in a prior negative biopsy, when mpMRI is PIRADS ≥ 3, the recommendation to perform targeted biopsy only, reaches a weak level of evidence.[13] In active surveillance strategy, TBx and SBx appear to be complementary to each other, both missing a significant proportion of cancer upgrading or

Table 2

Characteristics of the entire PCa population in relation to niPC and iPC pathologic diagnosis.

	Total PCa population (n = 231)	csPCa (n = 168)	ciPCa (n = 63)	*P* value
AGE, y	68	68	68	.90
Median (IQR)	(62–71.2)	(62–71.2)	(62–72)	
PSA, ng/mL	7.37	7.36	7.37	.12
Median (IQR)	(5.2–9.36)	(5.25–9.22)	(5.16–9.2)	
PSA density, ng/mL/cc	0.15	0.15	0,16	.43
Median (IQR)	(0.08–0.2)	(0.09–0.22)	(0.1–0.23)	
PROSTATE VOLUME, cc	50	45	43	.88
Median (IQR)	(37–60)	(35.7–57.2)	(33–54)	
DIAMETER Susp. Areas, mm	12	11.5	11	.12
Median (IQR)	(10–16)	(10–15)	(10–15)	
SITES of Susp. Areas, n (%)				
Anterior	108 (47.5%)	72 (42.8%)	36 (57.1%)	.28
Posterior	123 (53.2%)	96 (58.2%)	27 (42.8%)	
PI-RADS-v2, n (%)				
3/5	81 (35%)	42 (25%)	39 (61.9%)	
4/5	120 (51.9%)	105 (62.5%)	15 (23.8%)	.14
5/5	24 (10.4%)	18 (10.7%)	6 (9.5%)	
Median (IQR)	3.5 (3–4)	3.5 (3–4)	4 (3–4)	
CORES TAKEN per pts, n				
Median (IQR)				
TOTAL	16 (15–18)	16 (15–18)	15 (15–18)	.79
FUSION	6 (5–7)	6 (5–7)	4 (5–7)	.10
RANDOM	11.5 (10–12)	11.5 (10–12)	12 (10–12)	.58

ciPCa = clinical indolent prostate cancer, csPCa = clinically significant prostate cancer, IQR = interquartile range, n = number, PSA = prostatic-specific antigen.

Table 3

Detection rate and histological results.

	Entire population (n = 312)			MRI-TRUS TBx + TRUS SBx cohort (n = 174)		
	MRI-TRUS TBx + TRUS SBx (n = 174)	MRI-TRUS TBx (n = 138)	*P* value	MRI-TRUS TBx	TRUS SBx	*P* value
Detection rate PCa n (%)	135/174 (77.6%)	96/138 (69.6%)	.36	109/174 (62.6%)	93/174 (53.4%)	.46
Detection rate csPCa n (%)	84/174 (48.2%)	84/138 (60.9%)	.12	76/174 (43.7%)	42/174 (24.1%)	**.01**
Ratio of detection rate csPCa/PCa n (%)	84/135 (62.2%)	84/96 (87.5%)	**.03**	76/109 (69.7%)	42/93 (45.2%)	**.01**
ISUP grade (Gleason score) n (%)						
Negative	39 (22.4%)	42 (30.4%)	**.009**	65 (37.3%)	81 (46.6%)	**.007**
1 (3 + 3)	51 (29.3%)	12 (8.7%)		33 (19.0%)	51 (29.3%)	
2 (3 + 4)	51 (29.3%)	21 (15.2%)		43 (24.7%)	33 (19.0%)	
3 (4 + 3)	9 (5.2%)	24 (17.4%)		12 (6.9%)	0 (0%)	
4 (4 + 4/3 + 5/5 + 3)	12 (6.9%)	27 (19.6%)		12 (6.9%)	3 (1.7%)	
5 (4 + 5/5 + 4/5 + 5)	12 (6.9%)	12 (8.7%)		9 (5.2%)	6 (3.4%)	

csPCa = clinically significant prostate cancer, n = number, MRI = magnetic resonance imaging, SBx = systematic biopsy, TBx = targeted biopsy, TRUS = trans rectal ultrasound.
In bold values that are statistically significant

Table 4

Histological contingency table in the MRI-TRUS TB + TRUS SB cohort.

		MRI-TRUS TBx						SBx Total
		Negative	GS 3+3	GS 3+4	GS 4+3	GS 4+4	GS 4+5	
SBx	Negative	39	18	6	9	3	6	81
	GS 3+3	21	12	15	0	3	0	51
	GS 3+4	5	3	22	0	3	0	33
	GS 4+3	0	0	0	0	0	0	0
	GS 4+4	0	0	0	0	3	0	3
	GS 4+5	0	0	0	3	0	3	6
MRI-TRUS TBx Total		65	33	43	12	12	9	174

GS = Gleason score, MRI = magnetic resonance imaging, SBx = systematic biopsy, TBx = targeted biopsy, TRUS = trans rectal ultrasound.

Table 5

Multivariate logistic regression predicting the presence of niPC on SBx cores.

Variable	OR (95%)	*P* value
Age	1.03 (0.99–1.15)	.068
PSA	1.06 (1.01–1.13)	.124
PIRADSv2 score	0.99 (0.96–1.01)	.059
Re-biopsy cohort	0.43 (0.21–0.97)	.041
AS cohort	0.46 (0.32–0.89)	.039

AS = active surveillance, OR = odds ratio, PSA = prostatic-specific antigen, PI-RADS = prostate imaging-reporting and data system, v2 = version 2.

reclassification. Thus, combining the 2 biopsy techniques seems to be the best way to select patients for AS or to monitoring them.[19,20] However, EAU guidelines recommend to perform mpMRI before confirmatory biopsy with a strong level of evidence, but the recommendation to perform the combination of TBx and SBx at confirmatory biopsy reaches a weak level of evidence.

For these reasons we decided to consider for our study 2 different populations (prior negative biopsy and active surveillance) in which the level of evidence to combine SBx and TBx is weak. In addition, we excluded the naive biopsy population, in which this level of evidence is strong.

The purpose of our study was to investigate the potential benefit in terms of Detection Rate and pathological stratification of prostate cancer using a contextual SBx during an MRI-TRUS TBx.

In our experience, independently of other clinical parameters, either in the rebiopsy or in the active surveillance setting, SBx cores were negatively associated with the csPCa detection rate when combined to TBx cores. In fact, in both populations, the MRI-TRUS TBx alone cohort showed a higher csPCa/PC ratio (87.5% vs 62.2%; $P = .03$) mainly due to the lower number of indolent (ISUP 1) tumor diagnosed.

Considering the group of patients submitted to a combination of MRI-TRUS targeted and systematic cores, SBx upgraded TBx only in 7.7% with benign and 9.0% with ciPC at TBx cores and the upgrade was to a Gleason score 3 + 4 (ISUP 2).

Main limitation of our study is not equally distributed population among the 2 cohort enrolled; therefore, we were not able to establish a clear difference in the outcomes reached.

Our analysis was prospective, and the 2 cohorts are representative of the normal clinical practice. Our findings suggest that MRI-TRUS TBx represents the elective method to perform prostate biopsy in these 2 settings and the combination

of a SBx does not improve the detection rate of csPCa nether in a population of prior negative biopsy nor in AS confirmatory biopsy.

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