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The utility of in-bore multiparametric magnetic resonance-guided biopsy in men with negative multiparametric magnetic resonance-ultrasound software-based fusion targeted biopsy

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Abstract

Objectives: To evaluate the utility of in-bore multiparametric magnetic resonance-guided biopsy of the prostate (IB) in patients with visible lesion/s and previous negative software-based multiparametric magnetic resonance imaging/ultrasonography fusion-targeted biopsy of the prostate (FTB).

Patients and methods: We retrospectively analysed prospectively maintained database including consecutive men undergoing IB from March 2013 to October 2017 in 2 European centres expert in this procedure. We selected men with the following criteria: No previous treatment for prostate cancer (CaP), multiparametric magnetic resonance imaging (mpMRI) lesion(s) PIRADS score ≥ 3, FTB showing no clinically significant cancer (csCaP), and subsequent IB. Patient's characteristics, mpMRI findings, biopsy technique, and histopathological results were extracted. The primary outcome was to determine the detection rate of csCaP, defined as any Gleason pattern ≥ 4. A multivariable analysis was performed to identify predictors of positive findings at IB.

Results: Fifty-three men were included. Median age was 68 years (interquartile range [IQR] 64−68), median Prostate-Specific Antigen (PSA) was 7.6 ng/ml (IQR 5.2−10.9), and median prostate volume was 59 ml (IQR 44−84). Fifty-six lesions with PIRADS score 3 in 9 cases (16%), 4 in 30 cases (54%), and 5 in 17 cases (30%) were detected. FTB was performed in all cases using a transrectal approach with 3 different platforms (Toshiba, Koelis, and Artemis). Median time between FTB and IB was 3 months (IQR 1−7). A median of 2 cores per lesion were collected with IB (IQR 2−3). No cancer, clinically insignificant and clinically significant cancer were found in 33 (59%), 9 (16%), and 14 (25%) targeted lesions, respectively. Median maximum cancer core length and maximum positive percentage were 9 mm (3−13) and 55% (21%−80%). The only predictor of csCaP on IB was prostate volume ($P = 0.026$) with an ideal cut-off at 70 ml.

Conclusion: One in 4 patients with previous negative FTB, IB was able to detect csCaP. According to this study, IB would be of particularly useful in patients with large glands.

Keywords: Prostate cancer; Magnetic resonance imaging; Targeted biopsy; In-bore biopsy

1. Introduction

The standard procedure to obtain histological sampling of the prostate in cases of biochemical and/or clinical suspicion of localised prostate cancer (CaP) in the last 2 decades has been systematic transrectal ultrasound (TRUS)-guided biopsy of the prostate (SB) [1,2]. In this procedure, 10 to 12 cores are randomly sampled following a predetermined pattern from the area which is most likely

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to harbour CaP, namely the peripheral zone. This is usually performed under local anaesthesia and antibiotic prophylaxis in an outpatient setting with no pre-biopsy imaging. The downstream of such approach is, at present, evident to all of us. The disadvantages of this blind random approach are overdetection of clinically insignificant disease and underdetection of clinically significant disease (csCaP) [3].

This paradigm is about to change as a recent multicentre randomised controlled noninferiority trial has shown that an imaging-based pathway might overcome the limitations of SB [4,5]. The PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not) trial has demonstrated that an upfront multiparametric magnetic resonance imaging (mpMRI) prior to targeted biopsy was superior to SB in biopsy-naïve patients at risk for CaP, regardless the MR to TRUS fusion strategy used [4]. The detection rate of csCaP was superior in the targeted biopsy group (38%) as compared with the SB group (26%). In parallel, less clinically insignificant disease was diagnosed in the targeted biopsy group (9%) than in the SB group (22%).

This RCT has actually confirmed the findings of previous studies which have consistently reported the advantages of an imaging-based paradigm [5–12]. While at present few would argue with the utility of an imaging pathway, there is no consensus on the manner in which the MR phenotype is best used to guide targeted biopsy. Three MR-targeted biopsy techniques are available: Visual registration, software-assisted registration, and in-bore MR-guided biopsy (IB).

Visual registration relies on expert operators able to cognitively fuse the pre-biopsy mpMRI with TRUS in order to direct needles toward the suspected lesion/s. Software-assisted registration relies on a fusion device overlapping in a rigid and/or an elastic manner mpMRI and TRUS in order to assist the operator in guiding his/her needles toward the relevant target, namely MRI-TRUS software-based fusion targeted biopsy (FTB). In-bore targeted biopsy seems the most intuitive and precise way to perform targeted biopsy as the needles are guided directly within the MR-suite [14,15].

At present, software-assisted registration is the most used technique to perform targeted biopsy in expert centres; however, there is no consensus regarding the management of patients with mpMRI-visible lesions who test negative at FTB. The question is to determine whether these are mpMRI false positives, or if the actual lesion was missed by targeted biopsy [6,7,9,16]. Evidence shows that performing a second FTB or even saturation biopsy in these cases has low utility as in most cases this systematic approach is not able to detect many additional csCaP [16–17]. Another strategy might be to switch the sampling strategy to a more direct one, namely IB. The objective of this study was to evaluate the utility of IB in men with previous negative FTB. This issue is relevant in an era in which we are changing our clinical pathway as there will be more and more patients in this novel scenario.

2. Material and methods

2.1. Study design

This is a retrospective analysis of a prospectively maintained database including consecutive men undergoing IB from March 2013 to October 2017 in 2 European centres expert in this procedure: The Department of Radiology, Klinik Hirslanden, Zurich, Switzerland, and the Department of Radiology and Nuclear Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands. Institutional ethics review board approval was obtained for both centres.

2.2. Participants

Inclusion criteria were the following: No previous treatment for CaP, suspicious mpMRI lesion/s PIRADS score ≥ 3, [13] previous FTB detecting no csCaP followed by subsequent IB. Patients' characteristics, mpMRI findings, and detailed pathological analysis of both FTB and IB were extracted from institutional database. We included only patients in which the same lesion/s was/ere targeted by FTB and IB.

2.3. mpMRI

MpMRI was conducted and interpreted following international standards [13]. The local protocol has been previously reported in other publications [18,19]. Briefly, a 3.0 Tesla MR-scanner with a pelvic phased-array coil was used (Skyra, Siemens Healthcare, Erlangen, Germany). T2-weighted images (T2W), dynamic contrast-enhanced images, and diffusion-weighted images (DW) were systematically obtained. In Zürich, endorectal coil was also used in addition to a pelvic external phased-array coil. A detailed description of the parameters is found in Table 1. Each suspicious lesion was scored PI-RADS 1 to 5 according to the likelihood of presenting csCaP [13].

2.4. FTB

Image fusion was obtained by importing axial T2 and Apparent Diffusion Coefficient (ADC) maps from Digital Imaging and Communications in Medicine (DICOM) to a specific external hardware. The images were then uploaded

Table 1
mpMRI parameters.

Sequences	Echo Time	Repetition Time	Slice-Thickness	Matrix	Field Of View
T2-weighted	110	3000	3 mm	960 × 960	190 × 190 mm
ADC	59	5378	3 mm	384 × 384	190 × 190 mm
DCE	1.4	5.5	3 mm	224 × 224	190 × 190 mm

DCE = dynamic contrast-enhanced images; mpMRI = multiparametric magnetic resonance imaging.

into the fusion device, and employed according to the specific platform software employed in each centre. In Nijmegen, the Aplio 500 Toshiba Medical Systems was used throughout the study timeframe whereas in Zurich 2 platform were used: up to the end of 2014, the Koelis system (Trinity, Auberndale, MA, USA) and afterwards the Artemis system (Eigen, Grass Valley, CA, USA). Two to 4 biopsy cores were obtained per lesion.

The biopsies were performed by expert operators under local anaesthesia with oral quinolones prophylaxis. Standard random 10 to 12 cores biopsy was performed at discretion of the operator; usually, these were performed only in biopsy naïve-men.

2.5. IB

IB was performed with the patient in ventral decubitus and a transrectal approach, as shown (Fig. 1), under local anaesthesia and prophylactic antibiotics. An MR-compatible needle guide was rectally inserted, associated to a biopsy device DynaTRIM (invivo corp., Gainesville, FL, USA). Median time procedure in our experience is approximately 35 minutes; a 45 minutes' slot is booked for each patient.

Additional axial T2W and diffusion weighted images were obtained prior to biopsy in order to confirm target lesion position. The adjustable arm used to perform biopsies was guided by True fast imaging with steadystate free precession (TRUFI; Skyra, Siemens, Erlangen, Germany). This system also allowed to confirm needle position after each biopsy, the precision of which was assessed by a radiologist expert in prostate mpMRI. Only targeted biopsies were performed (Fig. 2).

All samples were analysed by dedicated uropathologists in each institution according to international standard [20]. For the purpose of the analysis, clinically significant disease was defined by the presence of any Gleason pattern ≥ 4.

2.6. Statistics

Descriptive statistics was used to summarise patients' and characteristics, FTB and IB performance. Continuous variables were displayed as median or mean and interquartile range (IQR) and standard deviation, respectively, according to their distribution. Categorical variables were displayed as frequencies and percentages. Univariable and multivariable logistic regression was performed to identify predictors of missed csCaP at FTB. The variables were selected a priori based on available literature suggesting their relevance in predicting detection of csCaP in similar cohorts of patients. For continuous relevant predictors, we tested different cut-offs considering their median value. The area under curve quantified the predictive accuracy of our model. The analysis was performed at a patient level. All statistical analyses were performed using STATA version 13 (StataCorp LP, College Station, TX, USA). Statistical significance was defined at a P-value < 0.05.

Fig. 1. Patient positioning for IB. IB = in-bore MR-guided biopsy.

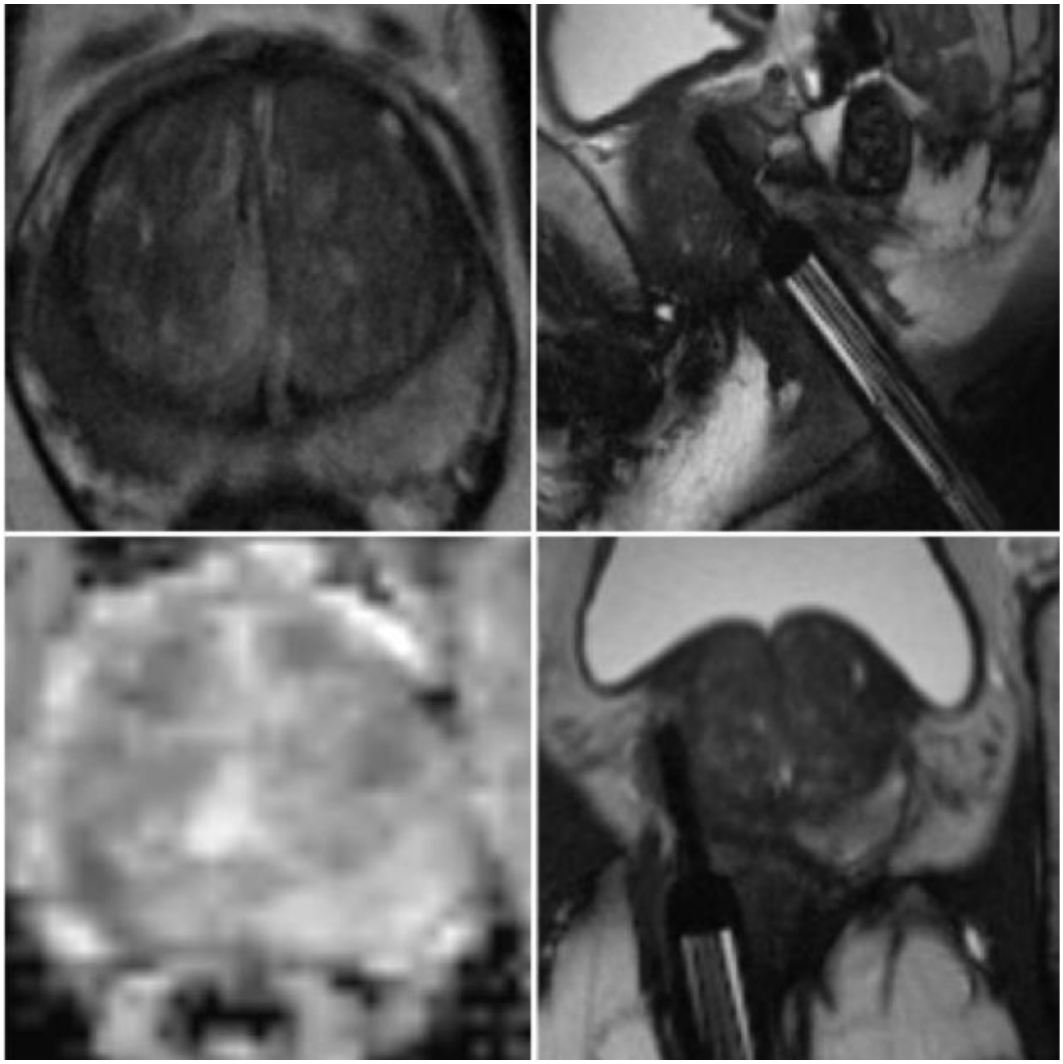

Fig. 2. Case study showing: (Left) Preoperative mpMRI showing a PIRADS 5 (T2 and ADC sequences are displayed) right peripheral lesion in a men with a large prostate. FTB and random biopsy showed no cancer. (Right) subsequent IB one month later showed Gleason 3+4 =7. Confirmation of needle position in the sagittal and axial view is displayed. FTB = fusion-targeted biopsy; mpMRI = multiparametric magnetic resonance imaging.

3. Results

3.1. Study population

After applying exclusion criteria, 53 patients were included in the quantitative analysis: 31 (58%) in Hirslanden, Zurich and 22 (42%) in Radboud UMC, Nijmegen. Patients' characteristics are summarized in Table 2. Median age was 68 years (IQR 64−68), median PSA was 7.6 ng/ml (IQR 5.2−10.9), and median prostate volume was 59 ml (IQR 44−84). Prior to any FTB, 30 (57%) participants underwent previous SB, whose 22 (74%) presented no cancer, 7 (23%) a clinically insignificant disease, and 1 (3%) a csCaP. Twenty-three patients had no previous SB before FTB.

MpMRI pre-FTB detected 56 lesions overall for a mean of 1.05 lesion per patient. The likelihood of presence of significant disease measured by the PI-RADS was 3 in 9 lesions (16%), 4 in 30 lesions (54%), and 5 in 17 lesions (30%). The mean maximum diameter of the lesions was 15.5 mm (IQR 4−40).

Fifty-six lesions were biopsied by FTB with a median of 4 cores per lesion (IQR 2−5) without any cancer found. Two patients underwent additional standard SB at the time of FTB: in one patient these were negative; in the other, insignificant Gleason 3+3 cancer was found in 1% of the core.

A median of 2 needles were deployed per lesion during IB. No cancer, clinically insignificant cancer and clinically significant cancer were found in 33 (59%), 9 (16%), and 14 (25%) lesions, respectively. The Gleason score was 3+3=6, 3+4=7, 4+3=7, 4+4=8, and 4+5=9 in 9 (16%), 8 (14%), 3 (5%), 2 (3%), and 1 (1%) lesions, respectively.

Table 2
Patients characteristics and biopsy findings.

Variable	Value
Patients (n)	53
Age (y), median (IQR)	68 (64−68)
PSA (ng/ml), median (IQR)	7.6 (5.2−10.9)
Prostate volume (ml), median (IQR)	59 (44−84)
Cores in FTB, median (IQR)	4 (2−5)
Lesions biopsied by FTB (n)	56
PI-RADS score	
3	9 (16%)
4	30 (54%)
5	17 (30%)
Previous SB ($n = 30$)	
no disease	22 (74%)
clinically insignificant disease	7 (23%)
clinically significant disease	1 (3%)
Time between biopsy sessions (months), median (IQR)	3 (1−7)
Cores in IB, median (IQR)	2 (2−3)
Lesions biopsied by IB	56
no cancer	33 (59%)
clinically insignificant cancer	9 (16%)
clinically significant cancer	14 (25%)
Gleason score	
3 + 3 = 6	9 (16%)
3 + 4 = 7	8 (14%)
4 + 3 = 7	3 (5%)
4 + 4 = 8	2 (3%)
4 + 5 = 9	1 (1%)
Maximum cancer core length (mm), median (IQR)	9 (3−13)
Maximum positive percentage (%), median (IQR)	55 (21−80)

FTB = fusion-targeted biopsy; IB = in-bore MR-guided biopsy; IQR = interquartile ratio.

3.2. Predictive factors for a csCaP missed at the FTB

At multivariable analysis, a large prostate volume was the only relevant predictor of missed csCaP in IB (Table 3), with a best cut-off at 70 ml ($P = 0.026$; odds ratio 0.134; 95% conflict of interest 0.02−0.78).

Addition of prostate volume to a base model for predicting csCaP including PSA, age, and PIRADS score, improved the area under the curve from 64.9% to 75.9% (Fig. 3).

We performed an alternative logistic regression considering PSA density as a derived variable instead of PSA value and prostate volume. This analysis showed that also PSA density is a significant predictor of detected csCaP with a best cut-off at 0.1 (supplementary Table 1).

Table 3
Univariable and multivariable analysis to evaluate predictors of clinically significant disease at IB.

Variable	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
PSA	1.09	0.98−1.21	0.125	1.12	0.98−1.29	0.100
Age at latest biopsy	1.03	0.92−1.15	0.618	1.07	0.93−1.21	0.338
PI-RADS score	1.77	0.66−5.80	0.260	2.04	0.62−6.65	0.285
Prostate volume 70 ml	0.97	0.94−0.99	0.027	0.13	0.02−0.78	0.026

CI = conflict of interest; OR = odds ratio.

4. Discussion

In summary, this study shows that in men with mpMRI visible lesion/s and previous negative FTB, the use of IB is useful, and might be highly recommended in some cases. Around one-fourth of these patients harboured clinically significant disease that was missed by previous FTB. As expected, FTB was more likely to fail in men with large glands.

There is an intense debate around which strategy to adopt to perform targeted biopsy directed toward MR-positive lesions. A recent large multicentre randomised trial has shown that no statistically significant difference could be observed in terms of detection of clinically insignificant and significant disease, regardless which strategy was used: Visual registration, FTB, or IB. However, the study population was represented exclusively by men with previous negative biopsy. Also, in light of low percentage of men with lesion/s PIRADS ≥ 3, the study was deemed underpowered by the investigators to test the primary outcome, namely the detection on any CaP [21].

There are numerous reports exploring the detection rate of clinically significant disease of one strategy against another [12,14,18,22−25]. Visual registration has been consistently shown to be inferior to FTB and IB, although the difference is not enormous and not always statistically significant [22,25,26]. Conversely, there is no evidence in head-to-head comparative study suggesting that any of FTB or IB is superior to the other [27]. A recent RCT assigned a group of 210 men either to IB or to FTB plus random biopsy. There was no difference amongst the 2 strategies in terms of detection of any cancer (37% vs. 39%; $P = 0.7$), significant cancer (29% vs. 32%; $P = 0.7$) or highest percentage of cancer involvement per core (48% vs. 42%; $P = 0.4$). However, this RCT also enrolled only men with at least one previous negative random biopsy session. Overall, while there is substantial evidence that FTB and IB are superior to visual registration across the board, there is no evidence suggesting that FTB is superior to IB although the opposite might seem intuitively possible.

Indeed, FTB is more likely to miss cancer in particular situations. As suggested in our study, this strategy is most likely to fail in men with large glands with a best cut-off at 70 ml. This is probably the consequence of missed registration and/or greater deformation with transrectal ultrasound. This issue is well known and has been consistently reported in the literature [28−30].

This study should be regarded as an attempt to explore the utility of IB in a subgroup of men with previous negative FTB. Few studies have addressed these questions: The optimal management of this new class of men. One retrospective study analysed the fate of men with Likert lesions

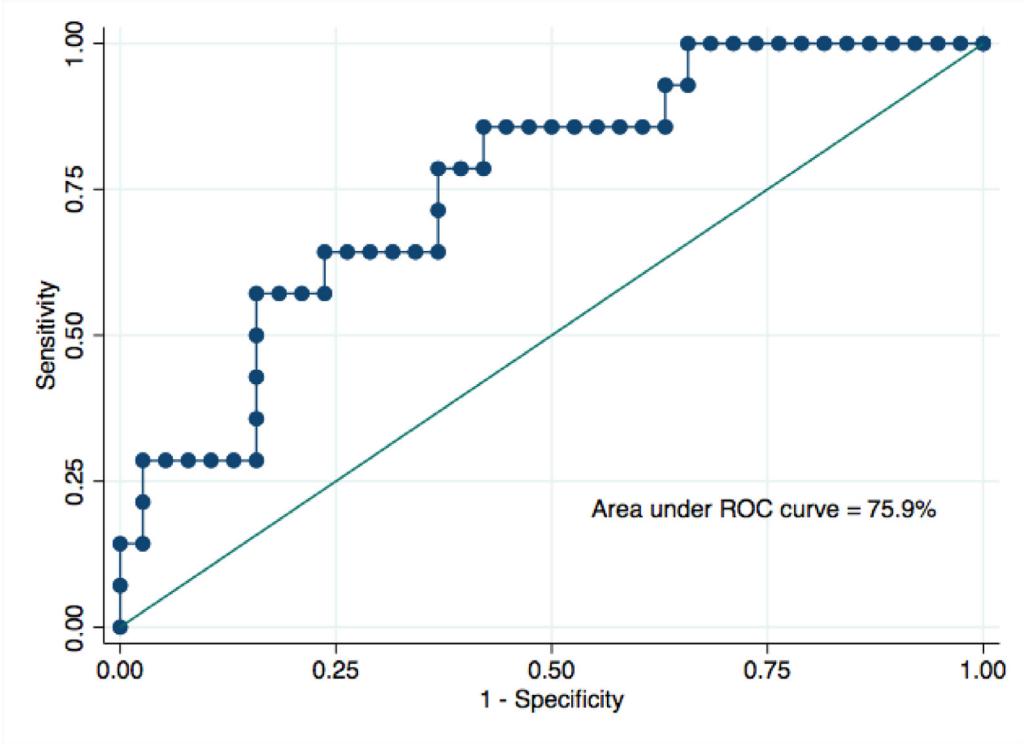

Fig. 3. Receiver Operating Characteristic curve based on variables for prediction of detecting clinically significant cancer at IB. IB = in-bore MR-guided biopsy.

5 and previous negative FTB [29]. This study showed that almost half of the 32 selected men has missed csCaP on further biopsy or radical prostatectomy; however, this study should be regarded with caution as these men were highly selected – more likely to have high grade cancer - and most of these cancers were verified by radical prostatectomy. Another study assessed the utility of repeat FTB in men with previous negative FTB and persistent suspicion of CaP. In this study, of the 130 rebiopsied lesions, the utility of repeat sampling was substantially lower than in our study with insignificant and significant cancer detected only in 10% and 6% cases, respectively. This compares to 16% insignificant and 25% significant CaP in our series. Patients and lesions characteristics were similar across the 2 studies. Based on these findings, IB could be suggested to this subgroup of men as a reasonable option to characterise visible mpMRI lesions negative on FTB, although further evidence in larger cohorts is needed to release more definitive recommendations.

This study has some inherent limitations. This is a retrospective analysis on a limited sample size observed over a short period of time. The population was homogeneous in terms of indication to IB, although 43% did not have initial SB. There is now level 1 evidence showing that SB combined to FTB improves the detection rate of csCaP; therefore, combination biopsy should be contemplated, at least in biopsy naïve-men. In this retrospective analysis including a cohort of men referred to 2 expert radiological centers from different urological units we were not able to ensure, neither to control the initial biopsy procedure. A certain selection bias is to be expected, and is difficult to be absolutely quantified. Further research in large cohorts is needed to explore whether these findings can be applicable to men with these characteristics. Further, while all patients had a consistent imaging-based clinical pathway including mpMRI prior to biopsy and negative FTB followed by IB, imaging, and all biopsy were performed in 2 different centers. Albeit the 2 centers had a similar IB protocol, we accept this might have had an impact on the validity of the results; external validity might be enhanced though. Finally, lesion location was not taken into account in this analysis as this variable was not available. It has been well demonstrated that some locations – such as anterior and apical regions – are more challenging than others to be targeted with FTB, especially, when these are performed through a transrectal approach, as in this cohort [31].

5. Conclusion

IB in men with previous negative FTB should be considered as in around 1 patient out of 4 clinically significant disease is detected. Based on this study, IB is more useful in men with large glands as in these cases FTB is more likely to fail. Further studies are needed to confirm these findings in larger cohorts.

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Declaration of competing interest

No conflict of interest was declared by the authors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.11.041.

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