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Not All Multiparametric Magnetic Resonance Imaging–targeted Biopsies Are Equal: The Impact of the Type of Approach and Operator Expertise on the Detection of Clinically Significant Prostate Cancer

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Abstract

Background: The extensive use of multiparametric magnetic resonance imaging (mpMRI) has led to an even more widespread use of different targeted biopsy techniques and approaches. The best way of performing targeted biopsies and the effect of operator expertise have still to be defined.
Objective: To compare the rate of detection of clinically significant prostate cancer (csPCa) of different mpMRI targeted approaches and to assess the role of operator expertise in the detection of csPCa.
Design, setting, and participants: We included 244 consecutive patients who underwent both 12-core transrectal ultrasound (TRUS) biopsy and mpMRI targeted biopsy with either a cognitive biopsy (CB) or fusion biopsy (FB) approach during the same session between 2013 and 2016 at a single tertiary referral centre.
Intervention: All men underwent 1.5-T mpMRI with an endorectal coil. All biopsies were performed by three operators as their first cases of targeted biopsy. Lesions with a Prostate Imaging Recording and Data System (PI-RADS) v.2 score of $\geq$3 detected at mpMRI were targeted.
Outcome measurements and statistical analysis: csPCa was defined as disease with a Gleason score at biopsy of $\geq$7. Operator expertise was coded as the progressive number of targeted biopsies performed by each physician. Multivariable logistic regression analyses (MVA) were used to assess the association between the targeted biopsy technique (FB vs CB) and operator expertise for detection of csPCa. Covariates consisted of prostate-specific antigen, prostate volume, PI-RADS v.2 (3 vs >3), number of targeted cores per MRI lesion, and digital rectal examination (negative vs positive). The same analyses were performed for patients undergoing FB only after accounting for the FB approach (transrectal vs transperineal). A lowess smoothing weighted function was used to graphically assess the effect of operator expertise on the probability of detecting csPCa, after accounting for all confounders.
Results and limitations: Overall, 157 patients (64%) underwent FB and 87 (36%) underwent CB. The overall csPCa detection rate was 58% for FB and 45% for CB ($p = 0.07$). A significantly higher rate of csPCa detection in targeted samples was observed for FB compared to CB (57% vs 36%; $p = 0.002$). On MVA, FB and operator expertise were significantly associated with a higher probability of csPCa detection in targeted samples (odds ratio [OR] 2.4 and 1.7, respectively; both $p \leq 0.03$). When the same analyses were repeated for patients undergoing FB, operator expertise remained an independent predictor of csPCa detection (OR 1.9; $p = 0.004$). An increase in the probability of detecting csPCa with the number of procedures performed was observed after accounting for all confounders.
Conclusions: We demonstrated that FB had higher detection rate than CB for csPCa. Moreover, operator expertise was significantly associated with higher detection rates for csPCa.
Patient summary: When different targeted biopsy techniques were compared, fusion biopsy provided a higher detection rate compared to cognitive biopsy for clinically significant prostate cancer (csPCa). Moreover, we found that operator expertise was an important predictor of the detection of csPCa, regardless of the procedure used.

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1. Introduction

Currently available guidelines suggest a 12-core transrectal ultrasound (TRUS)-guided prostate random biopsy as the standard of care for the initial diagnosis of prostate cancer (PCa) [1]. However, misdiagnosis of clinically significant PCa (csPCa), histologic upgrading at radical prostatectomy, and overdetection of clinically insignificant PCa are major drawbacks of this method [2–5]. In order to improve the PCa diagnostic pathway, multiparametric magnetic resonance imaging (mpMRI) of the prostate has the ability to identify csPCa lesions accurately [6,7]. In this context, recent studies have provided evidence of higher diagnostic accuracy of mpMRI in detecting csPCa when compared to TRUS-guided random biopsy in both the initial and repeat biopsy settings [8–10]. This has led to a trend towards greater use of targeted biopsy (TB) with a consequent reduction in overdiagnosis and overtreatment of clinically insignificant disease [11–13]. However, to date discordant data have been reported regarding the optimal technique (cognitive mpMRI/TRUS biopsy [CB] vs fusion mpMRI/TRUS biopsy [FB] vs in-bore mpMRI-guided biopsy) and approach (transrectal [TR] vs transperineal [TP]) for TB of the prostate [14–16]. For this reason, the best method for targeting mpMRI-detected suspicious lesions is still under debate [14,15,17–19]. Moreover, it is likely that besides the approach used, other operator-dependent variables such as physician expertise in TB can influence the performance characteristics. However, the impact of operator expertise on detection of csPCa has not been properly tested yet [20–22]. This is key, since the learning curve may influence the TB diagnostic performance and ultimately impact on correct patient management. To address these gaps, we compared the rate of csPCa detection for different TB approaches (visually registered TB, cognitive approach; TR and TP software-registered TB, fusion approach) and assessed the role of operator expertise in the detection of csPCa at a single tertiary referral centre.

2. Patients and methods

2.1. Study population

The study cohort consisted of 244 consecutive assessable patients who underwent mpMRI of the prostate with subsequent TB (FB or CB) and concomitant systematic biopsy in a single tertiary referral centre between January 2013 and December 2016. Data were prospectively collected from the first case performed.

2.2. mpMRI

All patients underwent a 1.5-T mpMRI study (Achieva and Achieva dStream; Philips Medical Systems, Best, The Netherlands) with a phased-array surface coil and an endorectal coil (BPX-15; Bayer Medical Care, Indianola, PA, USA). According to the European Society of Urogenital Radiology guidelines [6], the imaging protocol consisted of multiplanar T2-weighted images, diffusion-weighted imaging (with long *b* value and apparent diffusion coefficient map), dynamic contrast-enhanced MRI, and T1-weighted images with fat suppression. For patients who had previously received one or more sets of biopsies, all mpMRI scans were performed at least 4 wk after prostate biopsy, and precontrast T1-weighted images were recorded to rule out postbiopsy hemorrhagic artifacts. The mpMRI images were scored and reported according to Prostate Imaging Reporting and Data System (PI-RADS) v.2 [23] by three radiologists with at least 8 yr of experience in prostate mpMRI. Imaged lesions with a PI-RADS score of $\geq$3 were considered suspicious for PCa and were thus targeted.

2.3. Prostate biopsy technique and histopathology examination

Lesions visualized on mpMRI as suspicious for PCa were submitted to TB using either a software registration (FB) or a visual registration (CB) approach. Each patient also underwent a standard 12-core random biopsy during the same session, in accordance with current guidelines [1]. TRUS was performed using a Flex Focus 500 machine with a biplanar transducer (BK Medical, Herlev, Denmark). CBs and FBs were carried out by three urologists, each of whom had performed at least 200 prostate biopsies but were naïve for TB techniques. Each operator performed TB using one specific approach (operators 1, 2, and 3 performed CB, TR FB, and TP FB, respectively) regardless of any preferences. Operators 1, 2, and 3 performed 87, 70, and 87 TBs, respectively. Every biopsy was performed using an 18-gauge needle and a biopsy gun providing a specimen size of 18–22 mm using a TR approach only for CBs and either a TR or a TP approach for FBs.

For the FB technique, the patient's data and prostate mpMRI images were first entered into the BioJet fusion system (D&K Technologies, Barum, Germany) [24]. Then segmentation and contouring of the prostate and the suspicious lesion were performed by the urologist under the supervision of an experienced radiologist. For the TP approach, a standard brachytherapy grid with 5-mm spacing was also used. Technical data and use of the BioJet fusion system have previously been described [25]. The decision on the type of TB approach used was left to the discretion of each treating physician, regardless of the characteristics of the individual patient and the lesion being targeted. All prostate biopsy specimens were analyzed by two dedicated uropathologists.

2.4. Variable definition

Complete clinical data consisting of age at biopsy, prostate-specific antigen (PSA) values (ng/ml), digital rectal examination (DRE; negative vs positive), prostate volume defined at TRUS (ml), PI-RADS score (3 vs >3), biopsy technique (FB vs CB), biopsy approach (TR vs TP), number of target cores per MRI lesion, and previous biopsy (none vs prior negative biopsy) were available for all patients.

Operator expertise was coded as the progressive number of TBs performed by each physician. Each physician started from his own first TB case.

2.5. Outcomes

The study endpoint was comparison of the rate of csPCa detection for different TB techniques (FB vs CB) and approaches (TR vs TP) and to assess the role of operator expertise in csPCa detection in contemporary patients with a positive mpMRI. csPCa was defined as disease with a Gleason score at biopsy of $\geq$7.

2.6. Statistical analysis

Our statistical analysis consisted of four steps. First, the median and interquartile range and the frequency and proportion were reported for continuous and categorical variables, respectively. A Mann-Whitney *U* test and a χ^2 test were applied to assess the statistical significance of differences in medians and proportions, respectively.

Table 1 – Descriptive characteristics for 244 patients undergoing mpMRI of the prostate with subsequent targeted (fusion or cognitive) and concomitant systematic biopsy in a single tertiary care referral centre between 2013 and 2016

Variable	Overall (*n* = 244)	Fusion biopsy (*n* = 157, 64.3%)	Cognitive biopsy (*n* = 87, 35.7%)	*p* value
Median age at biopsy, yr (IQR)	66 (60–73)	67 (61–73)	62 (58–70)	0.002
Median PSA, ng/ml (IQR)	7 (4.8–10)	7.3 (5.2–10.5)	6 (4–9)	0.03
Digital rectal examination, *n* (%)				0.006
Negative	212 (86.9)	129 (82.2)	83 (95.4)	
Positive	32 (13.1)	28 (17.8)	4 (4.6)	
Median prostate volume, ml (IQR)	47 (37–65)	46 (37–62)	50 (37–75)	0.2
PI-RADS score				0.8
3	94 (38.5)	59 (37.6)	35 (40.2)	
>3	150 (61.5)	98 (62.4)	52 (59.8)	
Median target cores per MRI lesion, *n* (IQR)	3 (2–3)	3 (2–3)	2 (2–5)	<0.001
Median lesions at mpMRI, *n* (range)	1 (1–3)	1 (1–3)	1 (1–3)	0.6
Overall detection of PCa, *n* (%)				0.2
No	86 (35.2)	50 (31.8)	36 (41.4)	
Yes	158 (64.8)	107 (68.2)	51 (58.6)	
Overall detection of csPCa, *n* (%)				0.07
No	114 (46.7)	66 (42)	48 (55.2)	
Yes	130 (53.3)	91 (58)	39 (44.8)	
csPCa detection in target samples, *n* (%)				0.002
No	124 (50.8)	68 (43.3)	56 (64.4)	
Yes	120 (49.2)	89 (56.7)	31 (35.6)	
Previous biopsy, *n* (%)				0.04
No prior biopsy	131 (53.7)	76 (48.4)	55 (63.2)	
Prior negative biopsy	113 (46.3)	81 (51.6)	32 (36.8)	

IQR = interquartile range; PSA = prostate-specific antigen; PCa = prostate cancer; csPCa = clinically significant PCa; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Recording and Data System.

Second, multivariable logistic regression analyses were performed to assess the association of TB technique (FB vs CB) and operator expertise (modeled using a natural log function) with csPCa detection. Predictors included PSA, DRE (negative vs positive), prostate volume, PI-RADS score (3 vs >3), and number of targeted cores per MRI lesion.

Third, the same analyses were performed in the subgroup of patients undergoing FB to assess the association of approach (TR vs TP) and operator expertise (modeled using a natural log function) with csPCa detection. Covariates were the same as those included in the previous model.

Fourth, to produce the learning curve for the FB technique, lowess smoothing weighted functions were used to graphically assess the effect of operator expertise on the probability of detecting csPCa after accounting for all the variables included in the logistic model.

Finally, the same analyses were used in a multivariable approach to plot the learning curve effect for each operator.

All statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided with a significance level set at $p < 0.05$.

3. Results

Descriptive characteristics for the patient population are reported in Table 1. Overall, 157 patients (64%) underwent FB and 87 (36%) underwent CB. A TR approach was used for all patients who underwent CB. In the FB group, a TR approach was used for 70 men (45%) and a TP approach for 87 (55%). The overall PCa detection rate was 68% and 59% for FB and CB, respectively ($p = 0.2$). The overall csPCa detection rate was 58% and 45% for FB and CB, respectively ($p = 0.07$). A significantly higher csPCa detection rate in targeted samples was observed for FB relative to CB (57% vs 36%; $p = 0.002$).

On multivariable regression analyses, FB (odds ratio [OR] 2.4, 95% confidence interval [CI] 1.1–5.1; $p = 0.03$) and operator expertise (OR 1.7, 95% CI 1.2–2.3; $p = 0.001$) were significantly associated with a higher probability of detecting csPCa in targeted samples (Table 2). Furthermore, PSA (OR 1.07, 95% CI 1.01–1.14; $p = 0.03$), prostate volume (OR 0.98, 95% CI 0.97–0.99; $p = 0.01$), and PI-RADS score >3 (OR 4.5, 95% CI 2.4–8.5; $p < 0.001$) reached independent predictor status (Table 2).

Table 2 – Multivariable logistic regression model predicting clinical significant prostate cancer in 244 patients undergoing mpMRI of the prostate with subsequent targeted (fusion or cognitive) and concomitant systematic biopsy in a single tertiary care referral centre between 2013 and 2016

Predictor	Multivariable analysis	
	OR (95% CI)	*p* value
Prostate-specific antigen	1.07 (1.01–1.14)	0.03
Digital rectal examination		
Negative	Reference	–
Positive	1.2 (0.5–3.2)	0.5
Prostate volume [a]	0.98 (0.97–0.99)	0.01
PI-RADS score		
3	Reference	–
>3	4.5 (2.4–8.5)	<0.001
Number of target cores per MRI lesion	1.1 (0.8-1.5)	0.3
Targeted biopsy		
Cognitive	Reference	–
Fusion	2.4 (1.1–5.1)	0.03
Log operator expertise [b]	1.7 (1.2–2.3)	0.001

MRI = magnetic resonance imaging; OR = odds ratio; CI = confidence interval; PI-RADS = Prostate Imaging Recording and Data System.
[a] Prostate volume at transrectal ultrasonography.
[b] Logarithmic transformation of operator expertise.

Table 3 – Multivariable logistic regression model predicting clinically significant prostate cancer in 157 patients undergoing multiparametric MRI of the prostate with subsequent fusion and concomitant systematic biopsy in a single tertiary care referral centre between 2013 and 2016

Predictor	Multivariable analysis	
	OR (95% CI)	*p* value
Prostate-specific antigen	1.14 (1.04–1.28)	0.008
Digital rectal examination		
Negative	Reference	–
Positive	1.6 (0.6–4.7)	0.3
Prostate volume [a]	0.97 (0.95–0.99)	0.006
PI-RADS score		
3	Reference	–
>3	3.8 (1.7–8.7)	0.001
Number of target cores per MRI lesion	0.7 (0.5–1.1)	0.2
Biopsy approach		
Transrectal	Reference	–
Transperineal	4.1 (1.4–12.9)	0.01
Log operator expertise [b]	1.9 (1.2–2.8)	0.004

MRI = magnetic resonance imaging; OR = odds ratio; CI = confidence interval; PI-RADS = Prostate Imaging Recording and Data System.
[a] Prostate volume at transrectal ultrasonography.
[b] Logarithmic transformation of operator expertise.

On multivariable analyses for the group of patients undergoing FB, operator expertise remained an independent predictor of csPCa detection in targeted samples (OR 1.9, 95% CI 1.2–2.8; $p = 0.004$). Moreover, a TP approach (OR 4.1, 95% CI 1.4–12.9; $p = 0.01$), PSA (OR 1.14, 95% CI 1.04–1.28; $p = 0.008$), prostate volume (OR 0.97, 95% CI 0.95–0.99; $p = 0.006$), and PI-RADS score >3 (OR 3.8, 95% CI 1.7–8.7; $p = 0.001$) reached independent predictor status (Table 3).

Figure 1 shows the learning curve for FB. The probability of detecting csPCa was plotted against operator expertise after accounting for several confounders. We observed a sharp increase in the probability of detecting csPCa, from 53% during the first procedures to 83% when reaching 60 procedures. Thereafter, the detection rate showed a slow nonsignificant increase up to 85% at 80 procedures without reaching any plateau.

Finally, when we assessed the learning curve effect for each operator in a multivariable fashion, operator expertise remained an independent predictor of csPCa detection in targeted cores (OR 1.03, 1.06, and 1.01 for operators 1, 2, and 3, respectively; all $p < 0.04$). Figures 2–4 show the learning curve effect for the three operators. The number of procedures performed influenced the probability of detecting csPCa in targeted cores for each operator. Specifically, csPCa detection ranged from 30% during the first procedure to 57% when reaching 60 procedures for operator 1 (who performed CB), from 15% to 78% for operator 2 (who performed TR FB), and from 70% to 83% for operator 3 (who performed TP FB). The effect of operator expertise on csPCa detection was more pronounced for operator 2 than for operators 1 and 3.

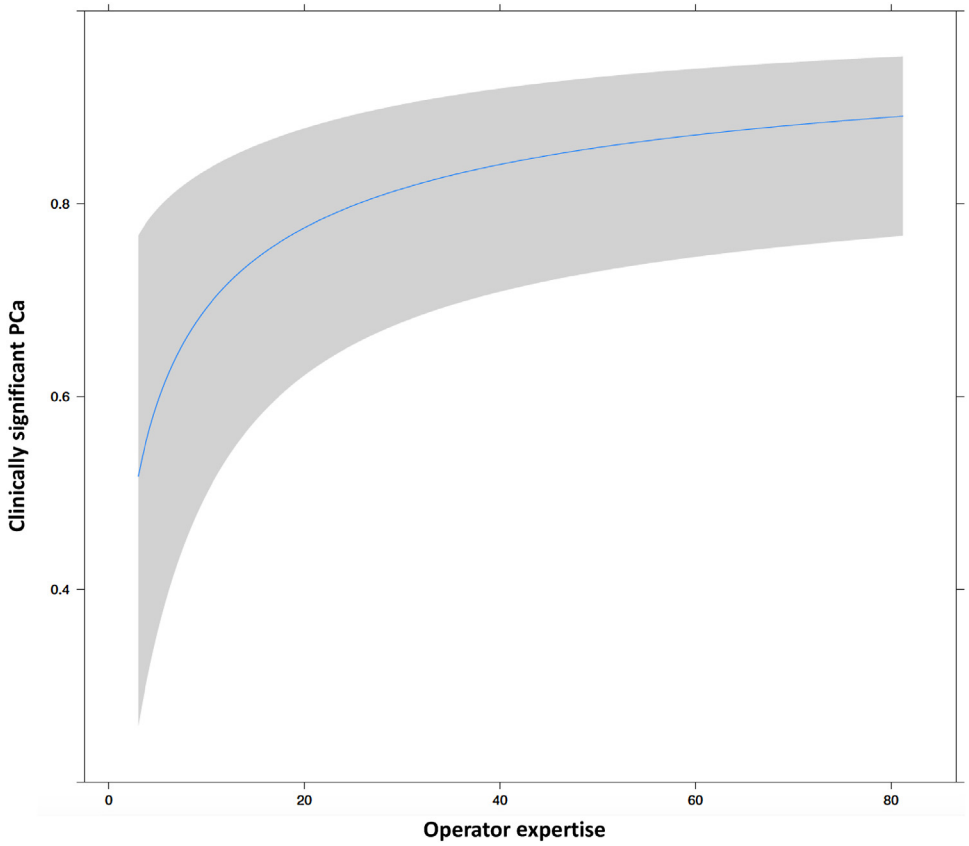

Fig. 1 – The operator learning curve for fusion biopsy. Probability of detecting clinically significant prostate cancer (PCa) after accounting for prostate-specific antigen, prostate volume, PI-RADS v.2 score, number of targeted cores per magnetic resonance imaging–detected lesion, digital rectal examination, and fusion biopsy approach (transrectal vs transperineal).
PI-RADS = Prostate Imaging Recording and Data System.

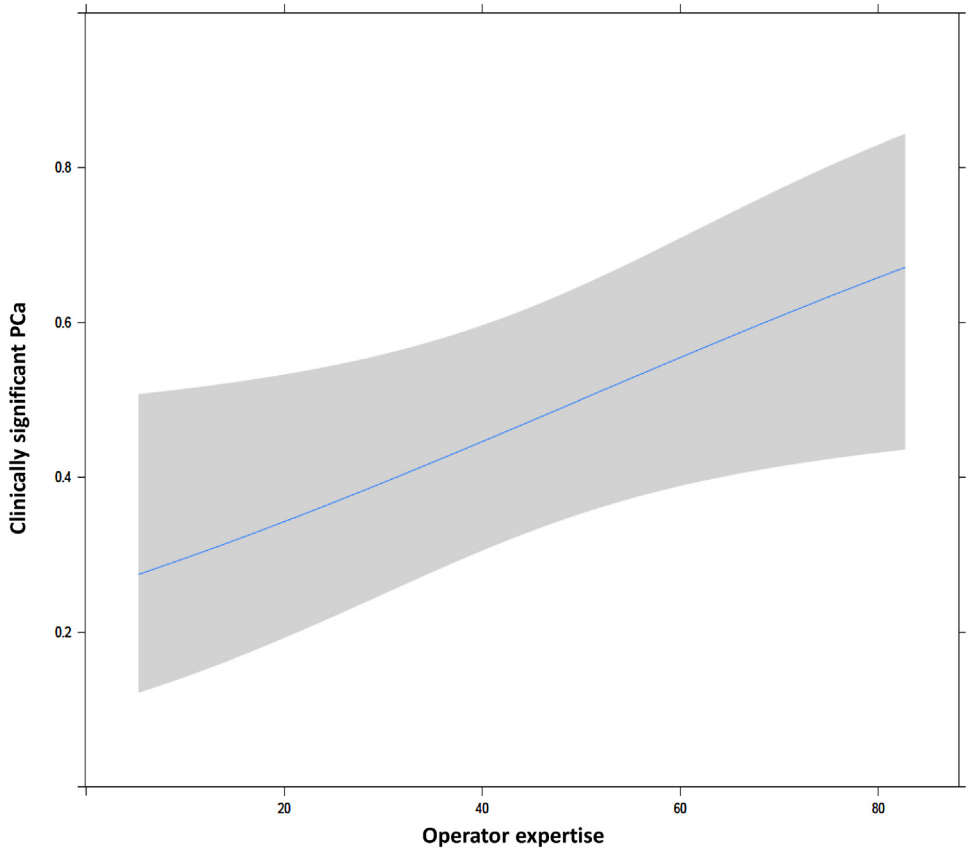

Fig. 2 – Learning curve for operator 1 (cognitive targeted biopsy). Probability of detecting clinically significant prostate cancer (PCa) after accounting for prostate-specific antigen, prostate volume, PI-RADS v.2 score, number of targeted cores per magnetic resonance imaging–detected lesion, and digital rectal examination.
PI-RADS = Prostate Imaging Recording and Data System.

4. Discussion

The widespread use of mpMRI of the prostate to detect PCa has led to increasing utilization of TB [11–13]. To date, the optimal technique (FB vs CB) and the optimal approach (TR vs TP) for performing mpMRI-guided TB of the prostate remain unclear and existing data on this topic are contradictory [14,15,17–19]. To try to solve this issue, we used a cohort of consecutive patients who underwent mpMRI-guided TB at a single tertiary referral centre and compared csPCa detection rates for different TB approaches. We hypothesized that FB could significantly improve the csPCa detection rate relative to CB. Moreover, we compared the TP and TR approaches in the FB setting. Furthermore, given the fact that prostate biopsy outcomes are multifactorial, we hypothesized that operator expertise might influence TB performance, regardless of the technique used.

Our findings confirmed our three hypotheses and are noteworthy. First, we observed that the FB technique was a significant predictor of csPCa detection. Specifically, FB had 2.4-fold higher probability of detecting csPCa relative to CB (95% CI 1.1–5.1; $p = 0.03$). The added value of software-registered TB compared to visually registered TB is the software visualization of prostate and lesions contours, which helps the physician in accurate deployment of the needle in the prostate. Nonetheless, most mpMRI lesions are visible on ultrasound. Van de Ven et al [26] reported that 43% and 62% of PI-RADS 4 and 5 lesions, respectively, appear as hypoechoic areas in ultrasound images. According to our results, use of a software registration approach (FB), together with the ultrasound image interpretation, yielded higher accuracy in the diagnosis of csPCa. To date there is no strong evidence suggesting that one technique is better than the other. In the context of CB in a randomized study, Panebianco et al [27] reported exceptional and promising data regarding PCa detection rates in biopsy-naïve patients with PI-RADS $\geq$3 lesions on mpMRI who underwent 12-core TRUS biopsy combined with CB TB. Among patients randomized to the TRUS biopsy group, 215/570 (38%) were diagnosed with PCa. Conversely, among 440 patients with positive mpMRI, 417 (95%) were found to have PCa [27]. In the present study, 51/87 patients (59%) in the CB cohort were diagnosed with PCa (Table 1). Despite the existence of different studies comparing CB and FB with different conclusions, the main meta-analysis [19] evaluating different TB techniques failed to demonstrate a significant advantage of any of them with regard to PCa and csPCa detection. It is of note that the studies comparing FB and CB that were included in this meta-analysis were limited by a small sample size [17,28,29] or the use of nonstandardized

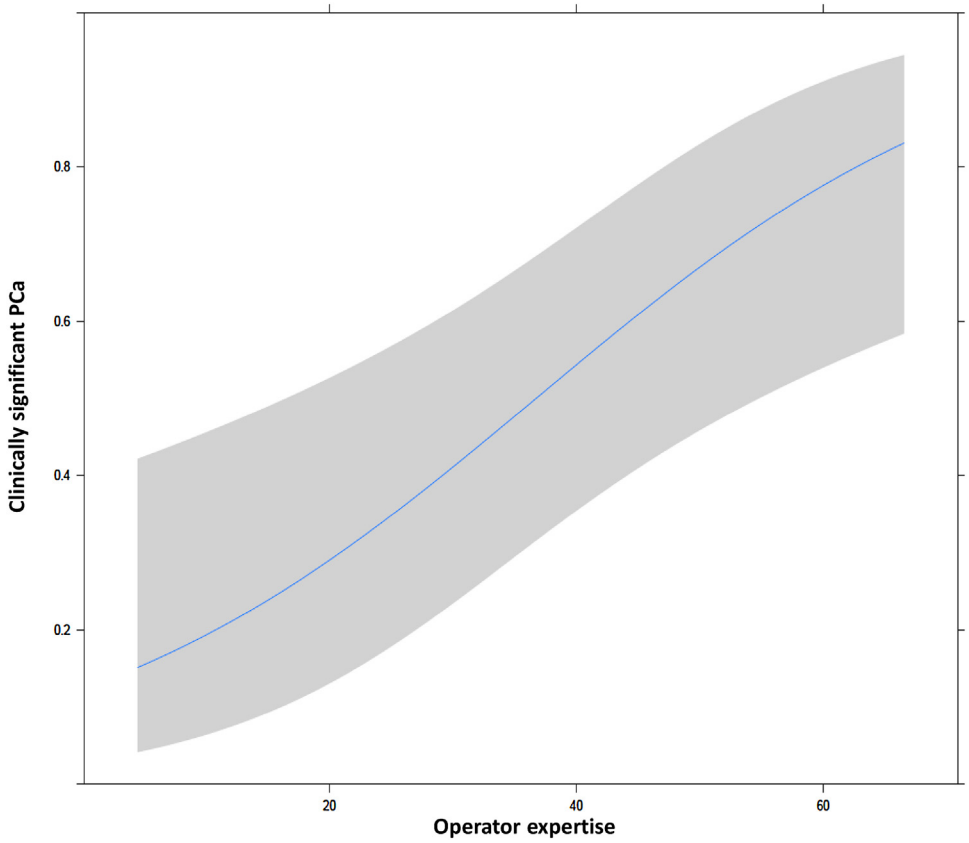

Fig. 3 – Learning curve for operator 2 (transrectal fusion targeted biopsy). Probability of detecting clinically significant prostate cancer (PCa) after accounting for prostate-specific antigen, prostate volume, PI-RADS v.2 score, number of targeted cores per magnetic resonance imaging–detected lesion, and digital rectal examination.
PI-RADS = Prostate Imaging Recording and Data System.

mpMRI reporting systems [16]. Therefore, further prospective and especially randomized studies are needed to definitively and reliably assess whether FB has a significantly higher csPCa detection rate relative to CB.

Second, the subgroup analysis for patients undergoing FB revealed that the TP approach had a higher csPCa detection rate compared to the TR approach. Specifically, TP FB had a 4.1-fold higher probability of detecting csPCa relative to the TR approach (95% CI 1.4–12.9; $p = 0.01$). Unfortunately, our findings cannot be directly compared to other cohorts, since to the best of our knowledge our study represents the first attempt to compare TR versus TP in the specific setting of FB. The same topic was addressed in the standard biopsy setting, although no significant differences in the PCa detection rate were found between the two approaches [14,15]. One might argue that patients undergoing TP rather than TR FB are more likely to present with different characteristics, especially for lesion localization, given the fact that anterior lesions are more likely to be targeted using a TP approach. Nonetheless, our data provide no evidence of a statistically significant difference between the TR and TP FB cohorts, especially in terms of lesion localization (anterior lesions in 30/70 [42%] of the TR group vs 30/87 [29%] of the TP group; $p = 0.18$). A possible explanation of our findings may reside in the different transducers used for the two approaches. Specifically, sagittal sections were performed using a convex transducer in the TR approach, which led to deformation of the prostate. Conversely, sagittal sections were performed using a linear transducer in the TP approach. This could result in more accurate synchronization between mpMRI and ultrasound images of the prostate in the TP approach.

Third, we observed that operator expertise significantly affected the probability of csPCa detection in a cohort of patients submitted to TB, after accounting for several confounders (OR 1.7, 95% CI 1.2–2.3; $p = 0.001$). To the best of our knowledge, the current study represents the first report to provide this evidence using a multivariable approach and taking into account different TB techniques.

Fourth, the positive impact of operator expertise on detection of csPCa was confirmed in subgroup analyses for the FB cohort after accounting for several confounders (OR 1.9, 95% CI 1.2–2.8; $p = 0.004$). To the best of our knowledge, we are the first to assess the learning curve for FB in a multivariable fashion. Other authors have previously demonstrated the presence of a learning curve effect in the TB field, describing an increase over time in the PCa detection rate [20–22]. Gaziev and colleagues [20] demonstrated the existence of a learning curve for PCa detection in the FB setting. However, these authors exclusively focused on the TP approach and did not account for several confounders such as PSA, DRE, prostate volume, PI-RADS

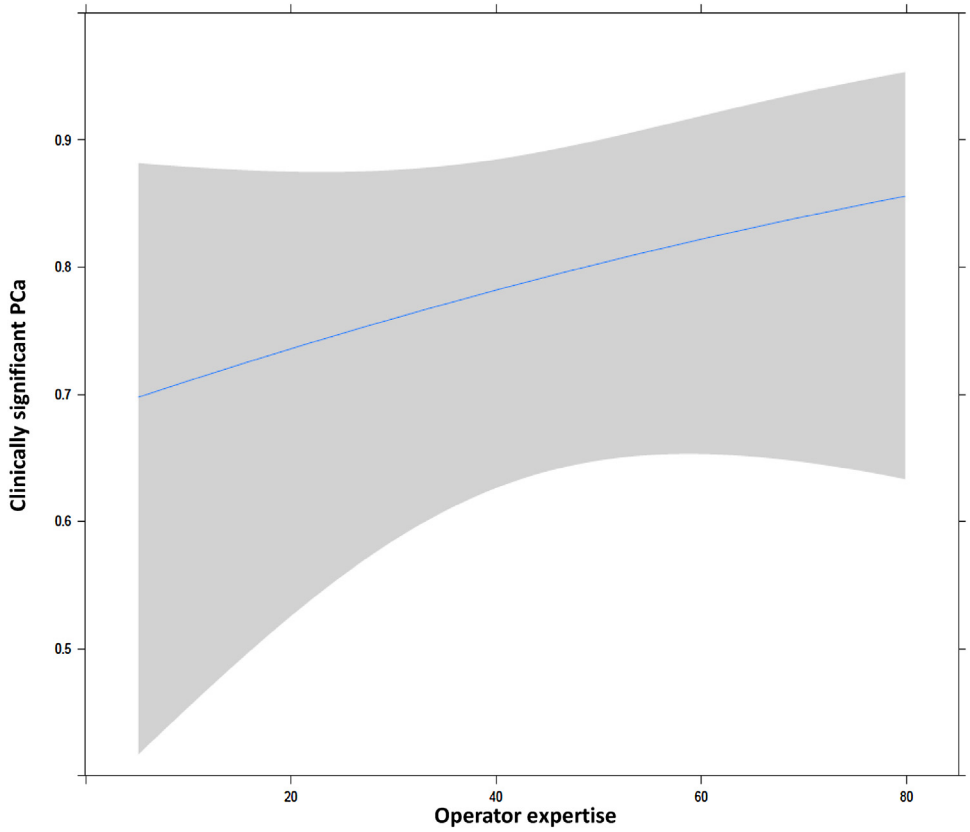

Fig. 4 – Learning curve for operator 3 (transperineal fusion targeted biopsy). Probability of detecting clinically significant prostate cancer (PCa) after accounting for prostate-specific antigen, prostate volume, PI-RADS v.2 score, number of targeted cores per magnetic resonance imaging–detected lesion, and digital rectal examination.
PI-RADS = Prostate Imaging Recording and Data System.

score, and number of target cores per mpMRI lesion, which may all influence prostate biopsy outcomes. By accounting for these related factors we could provide a more realistic assessment of the impact of operator expertise on the ability to detect csPCa. Calio et al [21] reported data for three large consecutive cohorts of biopsy-naïve patients undergoing FB. They identified a learning curve effect via multivariable association, whereby a higher csPCa detection rate was observed for their most recent cohort. By contrast, we observed a learning curve effect for each consecutive TB for both CB and FB. When we graphically assessed the overall effect of operator expertise for the FB subgroup of patients after accounting for several confounders (Fig. 1), we observed that csPCa detection probability increased with the number of procedures performed. Specifically, there was a sharp increase in the csPCa detection probability from 53% initially to 83% when 60 procedures were reached. Thereafter, the learning curve appeared quite long, with a maximum detection rate of 85%. These findings seem to suggest that in the early phase of the learning curve there may be a certain probability of misdiagnosing csPCa and that at least 60 procedures are needed to reach an acceptable csPCa detection rate. It is of note that even after 60 procedures we failed to observe a plateau in the learning curve, which implies that a training program is needed to ensure a high probability of success in this specific biopsy setting.

Finally, assessment of the learning curve effect for each operator confirmed that operator expertise is an independent predictor of csPCa detection in targeted cores (Figs. 2–4). For each operator we observed that the higher the number of TBs performed, the greater was the probability of detecting csPCa. It is of note that the learning curve effect was more pronounced for operator 2, who performed TR FB, in comparison to operators 1 and 3, who performed CB and TP FB, respectively. Specifically, the probability of detecting csPCa in targeted cores during the initial cases was inferior to that for the other operators. This suggests that initial familiarization with the software and the synchronization process might be more complicated for TR FB. Nonetheless, after approximately 60 cases, operator 2 reached a csPCa detection probability of ~80%, which is higher than the rate achieved by operator 1 (CB) and slightly lower than that of operator 3 (transperineal FB). Thus, FB resulted in a higher csPCa detection rate relative to CB (Table 2). Operator 3, who performed TP FB, had the weakest learning curve effect. Specifically, the probability of detecting csPCa was approximately 70% for the initial case and increased to ~85% for the last cases. The present data therefore suggest that a TP FB approach

seems to be the easiest technique for performing TBs and the one with the highest csPCa detection rate.

Our study is not devoid of limitations. First, our findings originated from observational data. As a consequence, they should be interpreted with caution. It should be noted that the reliability of observational data in comparison to data originating from randomized controlled trials (RCTs) is still a controversial topic. Anglemyer et al [30], in a meta-analysis assessing the impact of study design (RCT vs observational) on the effect of measures estimated, concluded that there is a little difference between the results obtained from RCTs and observational studies, and no significant differences between effects of the study design [30]. Second, the small size of our cohort means that our findings need to be confirmed in a larger cohort. Third, our cohort is heterogeneous. Specifically, it comprised both biopsy-naïve and prior negative-biopsy patients submitted to different techniques without any randomization, and thus there is a risk of selection bias. However, the results from this study still represent real clinical practice and therefore must be considered generalizable. Finally, TBs were performed with a unique fusion software system, so our data might not be applicable to patients undergoing FB with other fusion software systems or with different synchronization methods (ie, elastic and rigid fusion registration) [31].

5. Conclusions

We demonstrated that FB had higher rate of csPCa detection relative to CB. In particular, within the FB setting a TP approach was superior to a TR approach in detecting csPCa. Moreover, we found that operator expertise was an important predictor of detection of csPCa, regardless of the procedure used.

Author contributions: Armando Stabile 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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References

[1] Mottet N, Bellmunt J, Briers E, et al. EAU guidelines on prostate cancer 2016. European Urology Association. http://uroweb.org/guideline/prostate-cancer/.
[2] Roehl KA, Antenor JA, Catalona WJ. Serial biopsy results in prostate cancer screening study. J Urol 2002;167:2435–9.
[3] Epstein JI, Feng Z, Trock BJ, et al. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012;61:1019–24.
[4] Arnsrud Godtman R, Holmberg E, Khatami A, et al. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Göteborg randomised population-based prostate cancer screening trial. Eur Urol 2013;63:101–7.
[5] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8.
[6] Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. Eur Radiol 2012;22:746–57.
[7] Ahmed HU, Bosaily AE, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;6736:815–22.
[8] Futterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging?. A systematic review of the literature. Eur Urol 2015;68:1045–53.
[9] Baco E, Ukimura O, Rud E, et al. Magnetic resonance imaging-transectal ultrasound image-fusion biopsies accurately characterize the index tumor: correlation with step-sectioned radical prostatectomy specimens in 135 patients. Eur Urol 2015;67:787–94.
[10] Radtke JP, Schwab C, Wolf MB, et al. Multiparametric magnetic resonance imaging (MRI) and MRI–transrectal ultrasound fusion biopsy for index tumor detection: correlation with radical prostatectomy specimen. Eur Urol 2016;70:846–53.
[11] Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging–derived targets: a systematic review. Eur Urol 2013;63:125–40.
[12] Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. Eur Urol 2015;68:8–19.
[13] Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015;68:438–50.
[14] Takenaka A, Hara R, Ishimura T, et al. A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer Prostatic Dis 2008;11:134–8.
[15] Hara R, Jo Y, Fujii T, Kondo N, et al. Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. Urology 2008;71:191–5.
[16] Delongchamps NB, Peyromaure M, Schull A, et al. Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. J Urol 2013;189:493–9.

[17] Wysock JS, Rosenkrantz AB, Huang WC, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. Eur Urol 2014;66:343–51.
[18] Oberlin DT, Casalino DD, Miller FH, et al. Diagnostic value of guided biopsies: fusion and cognitive-registration magnetic resonance imaging versus conventional ultrasound biopsy of the prostate. Urology 2016;92:75–9.
[19] Wegelin O, van Melick HHE, Hooft L, et al. Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: a systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? Eur Urol 2016;71:517–31.
[20] Gaziev G, Wadhwa K, Barrett T, et al. Defining the learning curve for multiparametric magnetic resonance imaging (MRI) of the prostate using MRI-transrectal ultrasonography (TRUS) fusion-guided transperineal prostate biopsies as a validation tool. BJU Int 2016;117:80–6.
[21] Calio B, Sidana A, Sugano D, et al. Changes in prostate cancer detection rate of MRI-TRUS fusion vs systematic biopsy over time: evidence of a learning curve. Prostate Cancer Prostatic Dis 2017;20:436–41.
[22] Mager R, Brandt MP, Borgmann H, et al. From novice to expert: analyzing the learning curve for MRI-transrectal ultrasonography fusion-guided transrectal prostate biopsy. Int Urol Nephrol 2017;49:1537–44.
[23] Barentsz JO, Weinreb JC, Verma S, et al. Synopsis of the PI-RADS v2 guidelines for multiparametric prostate magnetic resonance imaging and recommendations for use. Eur Urol 2015;69:41–9.
[24] Tewes S, Hueper K, Hartung D, et al. Targeted MRI/TRUS fusion-guided biopsy in men with previous prostate biopsies using a novel registration software and multiparametric MRI PI-RADS scores: first results. World J Urol 2015;33:1707–14.
[25] Shoji S, Hiraiwa S, Endo J, et al. Manually controlled targeted prostate biopsy with real-time fusion imaging of multiparametric magnetic resonance imaging and transrectal ultrasound: an early experience. Int J Urol 2015;22:173–8.
[26] Van de Ven WJM, Sedelaar JPM, van der Leest MMG, et al. Visibility of prostate cancer on transrectal ultrasound during fusion with multiparametric magnetic resonance imaging for biopsy. Clin Imaging 2016;40:745–50.
[27] Panebianco V, Barchetti F, Sciarra A, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol Oncol Semin Orig Investig 2015;33, 17.e1–17.e7.
[28] Puech P, Rouvière O, Renard-Penna R. Prostate cancer diagnosis: multiparametric MR-targeted biopsy with cognitive and transrectal US–MR fusion guidance versus systematic biopsy—prospective multicenter study. Radiology 2013;268:461–9.
[29] Thompson JE, Moses D, Shnier R, et al. Multiparametric magnetic resonance imaging guided diagnostic biopsy detects significant prostate cancer and could reduce unnecessary biopsies and over detection: a prospective study. J Urol 2014;192:67–74.
[30] Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev 2014 2014;4.
[31] Logan JK, Rais-Bahrami S, Turkbey B, et al. Current status of MRI and ultrasound fusion software platforms for guidance of prostate biopsies. BJU Int 2015;114:641–52.