Comparison of Initial Experience with Transrectal Magnetic Resonance Imaging Cognitive Guided Micro-Ultrasound Biopsies versus Established Transperineal Robotic Ultrasound Magnetic Resonance Imaging Fusion Biopsies for Prostate Cancer

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Abbreviations and Acronyms

CDR = cancer detection rate
csPCa = clinically significant prostate cancer
GS = Gleason score
MB = micro-ultrasound biopsy
mpMRI = multiparametric magnetic resonance imaging
MRI = magnetic resonance imaging
PCa = prostate cancer
PI-RADSv2 = Prostate Imaging Reporting and Data System version 2
PRI-MUS = Prostate Risk Identification Using Micro-Ultrasound
PSA = prostate specific antigen
RFB = robotic ultrasound-magnetic resonance imaging fusion biopsy
TRUS = transrectal ultrasound

Purpose: We compared cancer detection rates in patients who underwent magnetic resonance imaging cognitive guided micro-ultrasound biopsy vs robotic ultrasound magnetic resonance imaging fusion biopsy for prostate cancer.

Materials and Methods: Among 269 targeted biopsy procedures 222 men underwent robotic ultrasound magnetic resonance imaging fusion biopsy and 47 micro-ultrasound biopsy. Robotic ultrasound magnetic resonance imaging fusion biopsy was performed using the transperineal Artemis™ device while micro-ultrasound biopsy was performed transrectally with the high resolution ExactVu™ system. Random biopsies were performed in addition to targeted biopsy in both modalities. Prostate cancer detection rates and concordance between random and target biopsies were also assessed.

Results: Groups were comparable in terms of age, prostate specific antigen, prostate volume and magnetic resonance PI-RADS (Prostate Imaging Reporting and Data System) version 2 score. The micro-ultrasound biopsy group presented fewer biopsied cores in random and target approaches. In targeted biopsies micro-ultrasound biopsy cases presented higher detection of clinically significant disease (Gleason score greater than 6) than the robotic ultrasound magnetic resonance imaging fusion biopsy group (38% vs 23%, p=0.02). When considering prostate cancer detection regardless of Gleason score or prostate cancer detection by random+target biopsies, no difference was found between the groups. However, on a per core basis overall prostate cancer detection rates favored micro-ultrasound biopsy in random and targeted scenarios. In addition, the PRI-MUS (Prostate Risk Identification Using Micro-Ultrasound) score yielded by micro-ultrasound visualization was independently associated with improved cancer detection rates of clinically significant prostate cancer.

Conclusions: In our initial experience micro-ultrasound biopsy featured a higher clinically significant prostate cancer detection rate in target cores than robotic

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ultrasound magnetic resonance imaging fusion biopsy, which was associated with target features in micro-ultrasound (PRI-MUS score). These findings reinforce the role of micro-ultrasound technology in targeted biopsies.

Key Words: prostatic neoplasms; biopsy; magnetic resonance imaging; ultrasound, high-intensity focused, transrectal

PROSTATE cancer is the most commonly diagnosed cancer in men in the West.[1] The standard diagnostic procedure for men suspected of having PCa consists of digital rectal examination, prostate specific antigen screening and transrectal ultrasound biopsy or, more recently, transperineal biopsy.

The classical diagnostic approach with TRUS systematic biopsies uses conventional ultrasound guidance with low sensitivity and specificity, leading to under diagnosis of clinically significant PCa and over diagnosis of clinically insignificant PCa.[2] Recent studies suggest that guided biopsies (cognitive-targeted biopsy, multiparametric magnetic resonance imaging guided biopsy and mpMRI-TRUS fusion biopsy) improve detection rates of clinically significant PCa compared to conventional TRUS systematic biopsies.[3,4]

Fusion biopsy can be performed manually, using a software assisted platform (eg UroNav®, Koelis®) or by a robotic arm device, like Artemis. This technology consists of a 3-dimensional ultrasound guided prostate biopsy system, allowing biopsy needles to be guided into targets to improve accuracy.[4]

A new diagnostic tool using high resolution micro-ultrasound imaging improves image resolution over conventional ultrasound.[5–7] Based on imaging features the PRI-MUS protocol is applied in order to standardize suspicious findings and reproduce outcomes.[8] We compared cancer detection rates in patients who underwent mpMRI cognitive guided micro-ultrasound biopsy vs robotic ultrasound-magnetic resonance imaging fusion biopsies for PCa.

MATERIALS AND METHODS

Study Population

RFB and MB were performed at our institution for PCa diagnosis after presenting information about advantages and disadvantages of the procedures. This was a retrospective study of prospectively collected data of patients with PCa who underwent MB or RFB from February 2017 to September 2018. Data were consecutively registered into an academic database. Biopsies were offered to men suspected of having PCa based on digital rectal examination and PSA values. Patients underwent MB or RFB depending on operating room availability, patient preference for anesthesia technique (local in MB, deep sedation for RFB) and history of biopsy related infections. A total of 451 biopsies (RFB or MB) were performed at our institution during this period. Patients without mpMRI suspected lesions were excluded from this study. A total of 269 patients underwent target + random biopsies through RFB (222) or MB (47).

Biopsy Protocols

Magnetic resonance imaging. Biopsies were performed after mpMRI for all patients at our institution. Target lesions were localized through 1.5 and 3.0T prostate mpMRI by an experienced radiologist incorporating T2-weighted images, dynamic contrast enhancement and diffusion weighted imaging. MpMRI findings were classified according to PI-RADSv2.

Biopsy modalities. Micro-ultrasound biopsy was performed in a transrectal approach using the high resolution ExactVu system on an outpatient basis. This cohort represents our initial experience with micro-ultrasound technology but each operator received a standardized online training program with hands-on training before participation. MpMRI was reviewed during biopsy to correlate with the real-time TRUS images as a cognitive-targeted approach. This approach may be called real-time visualization fusion as the fine adjustment of biopsy target was performed using the irregularities visualized on micro-ultrasound. Transperineal RFB was performed with the Artemis device in the operating room.

Biopsy samples were taken from targets in each modality, followed by systematic biopsy. Typically, 12 cores were taken in systematic biopsies and 3 cores from each target lesion. Slight technique variations were allowed in large prostates and large target lesions. All biopsies were performed by 4 staff urologists using a conventional spring-loaded gun and 18 gauge needle.

Outcomes

The primary outcome of this study was detection rate of clinically significant cancer (Gleason score 7 or higher) in patients who underwent RFB or MB. Secondary outcomes included PCa detection rates regardless of Gleason score and CDR in random or target biopsies. CDRs were also assessed on a per core basis.

We also evaluated the concordance between random and target biopsy in patients who underwent each biopsy modality. PCa concordance was defined as agreement between random and target in patients diagnosed with or without PCa. PCa GS concordance was defined as the proportion of patients accurately diagnosed with no PCa, GS 6 PCa or GS 7 or higher PCa by random as well as target biopsy.

Statistical Analysis

Continuous variables were reported with medians (interquartile ranges) and categorical variables with frequencies and proportions. A value of $p < 0.05$ was used to determine statistical significance. Statistical analysis was performed using Stata/SE® version 11.1.

Table 1. *Descriptive characteristics of patients undergoing prostate biopsy*

	Overall Population		RFB Group		MB Group		p Value
Total No. (%)	269	(100)	222	(82)	47	(18)	
Median age (IQR)	68	(62–72)	68	(62–72)	68	(65–72)	0.44
Median ng/ml PSA (IQR)	7.8	(5.5–10.2)	7.8	(5.5–10.0)	7.8	(5.6–11.4)	0.69
No. biopsy naïve (%)	69	(25.7)	55	(24.8)	14	(29.8)	0.48
Median gm prostate vol (IQR)	48.5	(36–65)	47	(36–65)	57	(37–69.3)	0.22
No. ng/ml/cm^3 PSA density (%):							
Less than 0.10	52	(19.3)	39	(17.6)	13	(27.7)	0.38
0.10–0.15	69	(25.7)	58	(26.1)	11	(23.4)	
More than 0.15	140	(52.0)	117	(52.7)	23	(48.9)	
Missing data	8	(3.0)	8	(3.6)	0	(0.0)	
No. PI-RADSv2 (%):							
3	21	(7.8)	17	(7.7)	4	(8.5)	0.16
4	155	(57.6)	132	(59.5)	23	(48.9)	
5	82	(30.5)	68	(30.6)	14	(29.8)	
Missing data	5	(1.9)	2	(0.9)	3	(6.4)	
% Prostate Biopsy Collaborative Group risk score (IQR)	24.6	(16.6–36.8)	24.7	(16.8–35.7)	23.9	(15.2–41.4)	0.98
Median MRI lesion size, mm (IQR)	12	(8–15)	12	(8–15)	12	(10–14)	0.98
Median No. biopsied cores (IQR)	15	(14–16)	15	(15–16)	12	(12–13.8)	<0.001
Median No. random cores (IQR)	11	(10–12)	11	(10–12)	10	(8–12)	<0.001
Median No. target cores (IQR)	4	(3–5)	4	(3–6)	3	(2–4)	<0.001

RESULTS

Patient Characteristics

Baseline data of 269 patients who underwent RFB or MB are reported in table 1. There were no significant differences in age, PSA, prostate volume or PI-RADSv2 score between the RFB and MB groups. The MB group presented fewer median biopsied cores in random (10 [8-12] vs 11 [10-12] cores, p <0.001) and target (3 [2-4] vs 4 [3-6], p <0.001) settings compared to the RFB group.

Cancer Detection Rates

The clinically significant PCa detection rate was slightly superior in the MB group but not statistically different (40% vs 32%, p=0.24). When considering only target biopsies the MB group presented a higher detection of clinically significant PCa than the RFB group (38% vs 23%, p=0.02; table 2, fig. 1).

We found no difference in overall CDR between the groups. PCa detection rate was 68% in the RFB vs 64% in the MB group (p=0.62). Random biopsies presented similar PCa detection in both methods (table 2, fig. 1).

On a per core basis CDR by MB was higher than by RFB in overall, random or target cores analysis. In random biopsies 19% vs 11% (p <0.001) of cores presented with PCa, while 38% vs 28% (p=0.04) of target lesion cores were positive in the MB vs RFB groups, respectively (table 3, fig. 2).

Table 2. *Prostate cancer detection rates*

	No. RFB Group (%)	No. MB Group (%)	p Value
Overall:			
Any PCa	150 (68)	30 (64)	0.62
GS 7 or greater	70 (32)	19 (40)	0.24
Random:			
Any PCa	119 (54)	24 (51)	0.75
GS 7 or greater	47 (21)	11 (23)	0.74
Target:			
Any PCa	115 (52)	26 (55)	0.66
GS 7 or greater	50 (23)	18 (38)	0.02

Concordance between Random and Target Biopsies

MB cases had a higher concordance rate between random and target biopsies in PCa diagnosis and GS classification, but statistical significance was not reached. Target and random biopsies agreed in PCa diagnosis in 79% vs 70% (p=0.2) of patients in the MB and RFB groups, respectively. GS concordance was found in 70% vs 61% (p=0.2) of those patients, respectively. Clinically significant PCa would be missed in at least 2% of patients in the MB and 9% in the RFB group if only target biopsy had been performed (table 4).

Real-Time Visualization of MRI Lesions in MB Group

Micro-ultrasound visualization of MRI lesions was evident from the PRI-MUS risk scores assigned during MB.[3] Of patients with PRI-MUS 4 targets 19% had csPCa detected through targeted samples (none through random samples), while 70% of patients with PRI-MUS 5 had csPCa detected through targeted samples vs only 45% through random samples (all of which were also detected in the targeted samples). PRI-MUS scores were assigned according to an extended sextant scheme and a clear increase in csPCa positive rate is evident at this level from 6.1% at PRI-MUS 1 to 69% at PRI-MUS 5 (table 5).

DISCUSSION

Technologies to improve accuracy of prostate biopsy are rapidly emerging. Our study showed no difference in CDR in random or target plus random biopsies among patients who underwent RFB or high

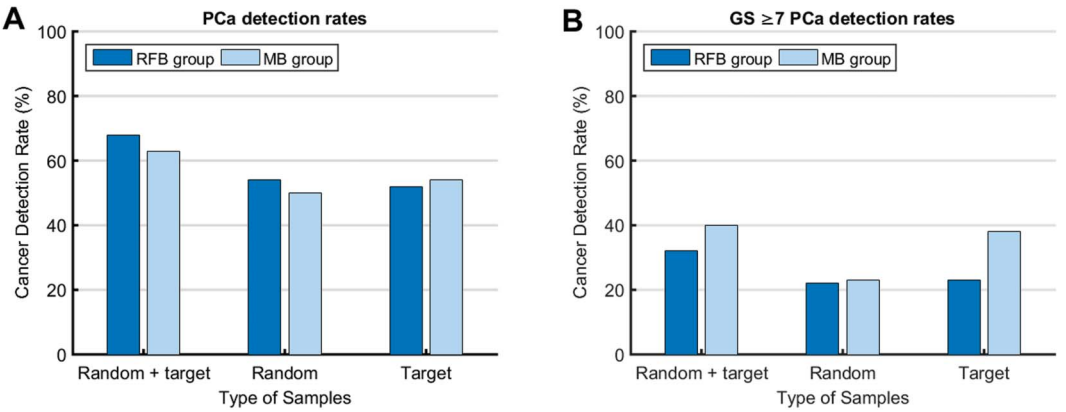

Figure 1. Cancer detection rates in random + target, random and target biopsies by biopsy modality (RFB or MB groups), showing PCa detection rates (*A*) and csPCa detection rates (*B*).

resolution micro-ultrasound imaging for PCa. However, we found higher detection of clinically significant PCa in the MB group when considering only target biopsies.

We performed RFB using the Artemis device, a 3-dimensional ultrasound guided prostate biopsy system that provides tracking of biopsy sites in the prostate using a robotic arm. The software provides fusion between mpMRI images and real-time ultrasound, allowing biopsy needles to be guided into targets, which has been demonstrated to improve the accuracy of prostate biopsy.[9] MB was performed using the ExactVu micro-ultrasound system after review of mpMRI performed before the procedure, a new alternative to mpMRI cognitive guided prostate diagnosis.[6,7] Resulting images of ExactVu high resolution micro-ultrasound (29 MHz) have a resolution up to 70 μm, an improvement of 300% over conventional ultrasound devices.[5,6]

TRUS-biopsy can lead to side effects including bleeding, pain and infection.[1,10] Multicenter prospective studies have shown that mpMRI used as a triage test might avoid unnecessary TRUS-biopsy, reducing biopsy related complications and improving diagnostic accuracy.[10–12] According to the PROMIS study mpMRI used as a triage test before first prostate biopsy could reduce unnecessary biopsies by a quarter. MpMRI could also reduce over diagnosis of clinically insignificant prostate cancer and improve detection of clinically significant cancer.[11] The PRECISION study found that the use of mpMRI before biopsy was superior to standard TRUS guided biopsy for PCa detection in biopsy naïve patients.[10] The Dutch trial "4M: Met Prostaat MRI Meer Mans" also provided evidence that the mpMRI pathway is noninferior to the TRUS systematic biopsy pathway in biopsy naïve men with regard to significant disease detection and supported the no immediate biopsy approach after nonsuspicious mpMRI.[12] Whether mpMRI precludes the need for systematic biopsy in biopsy naïve cases remains controversial. The MRI-FIRST trial found that obtaining mpMRI before biopsy does not seem to avoid the need for random biopsy.[13]

In our study all biopsies were performed after suspicious lesions were found at mpMRI (PI-RADSv2 score 3-5). This justifies the high CDR (68% in RFB vs 63% in MB, p=0.5) and it emphasizes the relevance of mpMRI in the pre-biopsy setting. The clinically significant PCa detection rate was slightly superior in the MB group, but not statistically different (40% vs 32%, p=0.24). Note that this csPCa

Table 3. *Cancer detection rate on a per biopsy basis, number of positive/total cores*

	No. RFB Group (%)	No. MB Group (%)	p Value
Overall:			
No Ca	2,883 (84)	448 (78)	<0.001
PCa	538 (16)	128 (22)	
Random:			
No Ca	2,169 (89)	360 (81)	<0.001
PCa	269 (11)	82 (19)	
Target:			
No Ca	711 (72)	81 (62)	0.04
PCa	270 (28)	49 (38)	

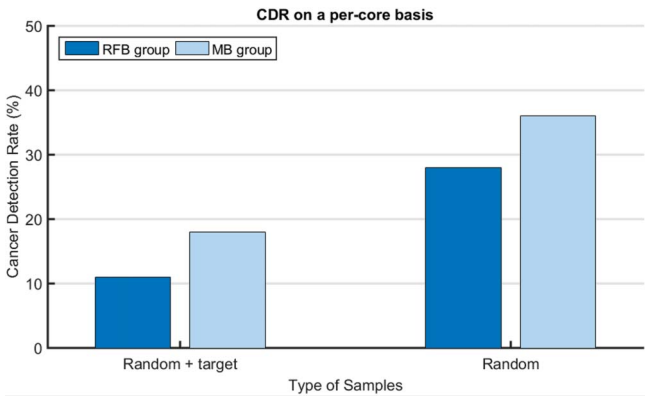

Figure 2. CDR on per core basis in random and targeted biopsies by biopsy modality.

Table 4. *Concordance of prostate cancer detection in random vs target*

Random / Target	No. RFB Group (%)			No. MB Group (%)		
	No PCa	PCa GS 6	PCa GS 7 or Greater	No PCa	PCa GS 6	PCa GS 7 or Greater
No PCa	72 (32)	26 (12)	9 (4.0)	17 (36)	4 (8.5)	0 (0)
PCa GS 6	18 (8.1)	36 (16)	11 (4.9)	1 (2.1)	6 (13)	1 (2.1)
PCa GS 7 or greater	13 (5.8)	10 (4.5)	27 (12)	5 (11)	3 (6.4)	10 (21)
PCa concordance*		156 (70)			37 (79)	
PCa GS concordance†		135 (61)			33 (70)	

* p=0.22
† p=0.20

rate is consistent not only with risk calculator estimates, but also in comparison with similar cohorts in the literature.[13] A fundamental limitation of this study is that patients were not randomized between the 2 groups. While no selection bias was evident in the clinical indicators assessed, we cannot exclude this possibility without further randomized evidence. Furthermore, the RFB arm used a transperineal biopsy approach while the MB arm used transrectal. While the transperineal route has yielded an accuracy similar to that of the transrectal approach in most of the published studies, this is a potential source of bias.[14]

Current evidence on PCa detection between cognitive and fusion based target biopsy is conflicting.[15–17] A systematic review suggested that software based targeted biopsy detects more clinically significant disease than cognitive targeted biopsy (20% vs 15%, p=0.05).[16] However, a meta-analysis by Schoots et al did not show any difference in overall and clinically significant PCa detection between cognitive and fusion based target biopsy.[17] In a recent series with cognitive biopsy using high resolution micro-ultrasound, authors reported 31% clinically significant PCa detection, with improvement in overall PCa detection from 45% to 57%.[18] However, from the additional 7 patients diagnosed with PCa due to micro-ultrasound technology in this group, only 1 had clinically significant PCa.

MB appears to be a powerful tool for performing cognitive biopsy. In our series those patients who underwent MB had greater detection of clinically significant tumors in target biopsies compared to RFB (38% vs 23%, p = 0.02). Concordance between target-random biopsies in PCa and in csPCa detection was also slightly greater in the MB group but not statistically significant (p=0.2).

Table 5. *PRI-MUS scores in MB group based on extended sextant (12-region) scheme*

PRI-MUS score	1	2	3	4	5
No. regions	132	275	20	43	70
Region pos predictive value (%)	6.1	4.7	15.0	67.4	68.6
No. pts	0	8	2	16	20
csPCa by targeted samples	0	0	0	3	14
csPCa by random samples	0	1	0	0	9
csPCa by either samples	0	1	0	3	14

MB uses the PRI-MUS protocol to characterize and grade suspicious tissue based on micro-ultrasound findings, aiming to improve targeting accuracy and reduce false-negative results.[6–8] The PRI-MUS protocol was previously suggested to be associated with PCa incidence and severity.[19] Recently published studies have confirmed micro-ultrasound and PRI-MUS as useful tools for PCa detection with strong correlation with clinically significant PCa.[7] Some authors concluded that it can provide sensitivity similar to that of multiparametric magnetic resonance imaging targeting clinically significant PCa.[6,7] In our study, patients and individual lesions were more likely to be diagnosed with csPCa by targeted samples when the PRI-MUS score was high. In a multivariate logistic regression model (leave-one-out AUC 0.75) only age, PSA density and the appearance of PRI-MUS 5 predicted csPCa on targeted samples with p <0.1. Group assignment to MB was not an independent predictor when combined with PRI-MUS score (p=0.86), suggesting that PRI-MUS score (and, thus, micro-ultrasound visualization) is sufficient to explain the improved targeted detection rate of csPCa.

Considering that the physicians had access to mpMRI and micro-ultrasound imaging for characterizing suspicious lesions in the MB group, it was expected that there would be a higher number of biopsied cores in this group. Surprisingly, we found fewer biopsied cores in the MB group and, thus, the number of cores cannot justify the improved diagnostic accuracy found in those patients. Furthermore, on a per core analysis the MB group presented a higher CDR for target or random biopsies.

To our knowledge, this is the largest comparative analysis of high resolution micro-ultrasound vs mpMRI/TRUS fusion biopsy in PCa diagnosis. However, this study has several limitations. We presented a retrospective analysis of 2 different modalities of prostate biopsy. The lack of prospective biopsies with RFB and MB makes comparison more difficult in relation to the accuracy of each modality. This cohort represents the initial deployment of micro-ultrasound imaging at our

center and the learning curve of the urologists who performed the biopsies was not measurable. Lastly, micro-ultrasound holds promise for improving the clinically significant PCa detection rate, but the association with mpMRI in our study precludes us from generalizing the results for the use of micro-ultrasound alone.

CONCLUSIONS

MB has shown a higher CDR of clinically significant lesions in targeted cores than RFB. When random biopsy is included with targeted cores PCa overall CDRs are comparable. The findings of our study reaffirm the role of micro-ultrasound visualization and PRI-MUS score as reliable tools in csPCa targeted detection.

REFERENCES

1. Mottet N, Bellmunt J, Bolla M et al: EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017; **71:** 618.
2. Diamand R, Oderda M, Al Hajj Obeid W et al: A multicentric study on accurate grading of prostate cancer with systematic and MRI/US fusion targeted biopsies: comparison with final histopatology after radical prostatectomy. World J Urol 2019; **37:** 2109.
3. Kam J, Yuminaga Y, Kim R et al: Does magnetic resonance imaging-guided biopsy improve prostate cancer detection? A comparison of systematic, cognitive fusion and ultrasound fusion prostate biopsy. Prostate Int 2018; **6:** 88.
4. Natarajan S, Marks LS, Margolis D et al: Clinical application of a 3D ultrasound-guided prostate biopsy system. Urol Oncol 2011; **29:** 334.
5. Pavlovich CP, Cornish TC, Mullins JK et al: High-resolution transrectal ultrasound: pilot study of a novel technique for imaging clinically localized prostate cancer. Urol Oncol 2014; **32:** 34.
6. Eure G, Fanney D, Lin J et al: Comparison of conventional transrectal ultrasound, magnetic resonance imaging, and micro-ultrasound for visualizing prostate cancer in an active surveillance population: a feasibility study. Can Urol Assoc J 2019; **13:** 70.
7. Lughezzani G, Saita A, Lazzeri M et al: Comparison of the diagnostic accuracy of micro-ultrasound and magnetic resonance imaging/ultrasound fusion targeted biopsies for the diagnosis of clinically significant prostate cancer. Eur Urol Oncol 2019; **2:** 329.
8. Ghai S, Eure G, Fradet V et al: Assessing cancer risk on novel 29 MHz micro-ultrasound images of the prostate: creation of the micro-ultrasound protocol for prostate risk identification. J Urol 2016; **196:** 562.
9. 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.
10. Kasivisvanathan V, Rannikko AS, Borghi M et al: MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018; **378:** 1767.
11. Ahmed HU, El-Shater Bosaily A, Brown LC et al: Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017; **389:** 815.
12. van der Leest M, Cornel E, Israël B et al: Head-to-head comparison of transrectal ultrasound guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol 2019; **75:** 570.
13. Rouvière O, Puech P, Renard-Penna R et al: Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019; **20:** 100.
14. Xiang J, Yan H, Li J et al: Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. World J Surg Oncol 2019; **17:** 31.
15. Marra G, Ploussard G, Futterer J et al: Controversies in MR targeted biopsy: alone or combined, cognitive versus software-based fusion, transrectal versus transperineal approach? World J Urol 2019; **37:** 277.
16. Valerio M, Donaldson I, Emberton M et al: Detection of clinically signifcant prostate cancer using magnetic resonance imaging—ultrasound fusion targeted biopsy: a systematic review. Eur Urol 2014; **68:** 8.
17. 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 2014; **68:** 438.
18. Abouassaly R, Klein EA, El-Shefai A et al: Impact of using 29MHz high-resolution micro-ultrasound in real-time targeting of transrectal prostate biopsies: initial experience. World J Urol 2019; doi: 10.1007/s00345-019-02863-y.
19. Ghai S and Van de Kwast T: Suspicious findings on micro-ultrasound imaging and early detection of prostate cancer. Urol Case Rep 2017; **21:** 98.

EDITORIAL COMMENTS

Micro-ultrasound, operating at 29 MHz frequency, is a promising new imaging device which has the potential to improve accuracy of prostate biopsy. The authors show that micro-ultrasound targeting detected more csPCa than the software fusion assisted targeted biopsies. This is based on the ability of micro-ultrasound to visualize the MRI targets in real time, rather than relying on MRI-TRUS fusion coupled with conventional TRUS (6 to 9 MHz) for targeting. Also, fewer samples were obtained in the micro-ultrasound arm, suggesting improved confidence in lesion identification and targeting. Other studies have shown that there may be substantial differences in the quality of software based fusion assisted targeting, which confirms the benefit of targeting under real-time visualization obtained with micro-ultrasound.[1] Reported negative predictive values of mpMRI have been in the range of 67% to 88%[2] while the PRECISION study group reported a positive predictive value of mpMRI for csPCa at 52% (reference 10 in article). These results highlight the benefit of mpMRI, although the probability of inaccurate sampling and reliability on cognitive/software fusion exists. Lughezzani et al

reported real-time visualization of most (24 of 28) csPCa cancer identified on mpMRI by micro-ultrasound (reference 7 in article) and, therefore, it has the potential to enhance the accuracy of mpMRI in detecting csPCa when used in conjunction.

This article adds to the preliminary existing data of the benefit of micro-ultrasound over conventional TRUS. However, results of prospective ongoing trials (ClinicalTrials.gov Identifier: NCT03938376) are awaited to confirm that this emerging technique will decrease the ever increasing burden on prostate mpMRI and the need for fusion MRI-TRUS technology.

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REFERENCES

1. Klotz L, Loblaw A, Sugar L et al: Active surveillance magnetic resonance imaging study (ASIST): results of a randomized multi-center prospective trial. Eur Urol 2019; **75:** 300.

2. Moldovan PC, Van den Broeck T, Sylvester R et al: What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol 2017; **72:** 250.

Micro-ultrasound is a promising new technology for prostate imaging. Micro-ultrasound (29 MHz) is used like conventional ultrasound (approximately 7 MHz), ie similar transrectal probes, but the resolving power of micro-ultrasound (70 microns) is far superior to conventional ultrasound. Early on Pavlovich et al showed that, compared with conventional TRUS, micro-ultrasound has increased sensitivity and specificity for detection of cancer foci (reference 5 in article). In this study men with MRI visible lesions were studied to determine the cancer detection rate comparing biopsies obtained via micro-ultrasound guidance vs MRI/ultrasound fusion. The key finding was that micro-ultrasound compared favorably with MRI/ultrasound fusion.

A tantalizing implication is that use of micro-ultrasound, if sufficiently reliable, might lead to decreased dependence on MRI. Unfortunately this study does not allow collection of that sort of evidence. The authors deserve credit for bringing this interesting new technology to attention, but in this retrospective piece the study design precludes firm conclusions. Among the issues, group assignments were determined by convenience and patient preference rather than by any scientific method. Concordance of MRI and micro-ultrasound lesions by size (volume or diameter) is not reported. In addition, no "ground truth" (prostatectomy or template mapping biopsy) was available, the negative predictive value was questionable and accuracy of perineal fusion biopsy using the Artemis device, which is the comparator, has not yet been established.

On a positive note, performing and interpreting micro-ultrasound were quick and easy to learn. Thus, in the near future we look for prospective studies of micro-ultrasound, which could become a disruptive technology.

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REPLY BY AUTHORS

"Whatever we accomplish is due to the combined effort." - Walt Disney

MRI targeted prostate biopsy has undeniable value in the current approach to PCa diagnosis. Software based image fusion has been proposed as a possible new standard over systematic or cognitive biopsies. While a software guided approach seems to improve accuracy over cognitive fusion for clinically significant PCa detection in particular cases of anteriorly located and small lesions,[1] an improved ultrasound image might provide sound information to make a cognitive approach more reliable in PCa diagnosis.

The micro-ultrasound platform provides high resolution images assisting us in overcoming traditional ultrasound limitations for PCa detection (reference 6 in article). Of the utmost importance, micro-ultrasound is not intended to challenge or dismiss the benefits achieved with MRI. Instead, it aims to add useful information during targeted biopsy in order to help overcome MRI limitations, such as lack of real-time visualization and

underestimation of tumor boundaries.[2] Our initial experience (with the acknowledgement of its limitations) with prostate targeted biopsy combining real-time micro-ultrasound visualization for MRI cognitive guidance has provided better detection of clinically significant PCa than MRI ultrasound fusion. Importantly, after a short period of training, physicians have been able to perform biopsies on an outpatient basis with an easy to learn, compact platform. We were able to deploy and profit from MRI information for prostate biopsies and the latter was combined with a highly detailed view of prostatic soft tissue, provided by micro-ultrasound imaging.

Our findings shine a spotlight on this novel imaging technology, with prospective data expected in the near future. We certainly agree that further research should clarify the role of micro-ultrasound in prostate biopsies, ideally to confirm that symbiosis of both technologies further improves detection of those PCa lesions needing treatment and avoids over detection of indolent tumors.

REFERENCES

1. Elkhoury FF, Felker ER, Kwan L et al: Comparison of targeted vs systematic prostate biopsy in men who are biopsy naïve: the Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) study. JAMA Surg 2019; https://doi.org/10.1001/jamasurg.2019.1734.

2. Priester A, Natarajan S, Khoshnoodi P et al: Magnetic resonance imaging underestimation of prostate cancer geometry: use of patient specific molds to correlate images with whole mount pathology. J Urol 2017; **197:** 320.