Prostate Mapping for Cancer Diagnosis—The Madrid Protocol: Transperineal Prostate Biopsies Using Multiparametric Magnetic Resonance Imaging Fusion and Micro-Ultrasound Guided Biopsies

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Purpose: We assessed the prostate cancer detection accuracy of transperineal prostate biopsy using multiparametric magnetic resonance imaging/ultrasound fusion targeted biopsy and micro-ultrasound during the same procedure. Micro-ultrasound is a new high-resolution imaging system that allows real-time targeted biopsy.

Materials and Methods: A total of 194 consecutive patients underwent transperineal prostate biopsies using real-time targeted micro-ultrasound (ExactVu™) and ultrasound fusion targeted biopsy (BiopSee®) in the same procedure, from February 2018 to September 2019. Biopsies were performed using a transperineal needle guide attached to the 29 MHz high resolution micro-ultrasound transducer.

Results: The overall positive rate was 56% (108) for prostate cancer and 42% (81) for clinically significant prostate cancer (Gleason Grade Group greater than 1), and adding micro-ultrasound and magnetic resonance imaging detected significantly more clinically significant prostate cancer than systematic biopsy ($p < 0.001$). Micro-ultrasound found 12 of 108 (11%) prostate cancers that were missed by all other techniques and 11 (92%) were clinically significant prostate cancer. PI-RADS and PRI-MUS were strong predictors of clinically significant prostate cancer in a logistic regression model (AUC 0.76). For prostate specific antigen greater than 4 ng/ml, PI-RADS greater than 3, there was an improvement in detection rate between PRI-MUS 4 and PRI-MUS 5 (52% Gleason Grade Group greater than 1 to 92% Gleason Grade Group greater than 1). No fever or clinical infection was observed and 17 (8.7%) patients presented with minor complications (Clavien Dindo I).

Conclusions: This is the first study using a transperineal approach for micro-ultrasound guided biopsy and multiparametric magnetic resonance imaging fusion biopsy. The results show a high accuracy for prostate cancer and clinically significant prostate cancer diagnosis, without infectious complications. The proposed method should be validated in large randomized clinical trials.

Key Words: prostatic neoplasms, biopsy, multiparametric magnetic resonance imaging, ultrasonography

Abbreviations and Acronyms

csPCa ▌ clinically significant prostate cancer
DRE ▌ digital rectal examination
GG ▌ Gleason Grade Group
iPCa ▌ insignificant prostate cancer
micro-US ▌ micro-ultrasound
mpMRI ▌ multiparametric magnetic resonance imaging
NPV ▌ negative predictive value
PCa ▌ prostate cancer
PI-RADS ▌ Prostate Imaging-Reporting and Data System
PPV ▌ positive predictive value
PRI-MUS ▌ Prostate Risk Identification Using Micro-Ultrasound
PSA ▌ prostate specific antigen
SBX ▌ systematic biopsy
TBX ▌ ultrasound fusion targeted biopsy
TRUS-BX ▌ transrectal ultrasound biopsy

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PROSTATE cancer is a significant health concern and it is the second most frequent cancer diagnosed in men.[1] The current standard for PCa diagnosis includes screening with PSA, digital rectal examination and transrectal ultrasound biopsy. This approach has a low specificity and sensitivity, leading to a high rate of unnecessary biopsies, underdiagnosis of clinically significant prostate cancer as well as over diagnosis and overtreatment of clinically insignificant prostate cancers.[2,3]

Multiparametric magnetic resonance imaging is a game changer in the PCa diagnosis pathway, as it allows image based identification of suspicious areas in the prostate, which may improve diagnostic accuracy for intermediate/high risk PCa. mpMRI and ultrasound fusion targeted biopsy is increasingly used as an alternative to randomized biopsies and is a useful tool to improve accuracy of PCa detection.[4e7] However, mpMRI may miss some csPCa,[8e11] as there is heterogeneity between PI-RADS scores and corresponding calibrations of biopsy yield. In addition, it cannot be used in certain patients with pacemakers, prostheses and severe claustrophobia.[9,12,13]

Micro-ultrasound (ExactVu) emerges as a promising new high-resolution imaging technology, which could be a potential alternative or complementary tool to MRI, to further improve csPCa yield.[14] The 29 MHz micro-US transducer provides a 70 μm resolution, which is a 300% improvement in resolution compared to conventional transrectal ultrasound.[15,16] Micro-US allows identification of suspicious lesions using the PRI-MUS™ scale (Prostate Risk Identification Using Micro-Ultrasound)[16] and performance of real-time targeted biopsies during the same procedure, with a short learning curve.[14,17] Moreover, it has been hypothesized that mpMRI and micro-US may be complementary in some patients as each technique may identify lesions missed by the other modality.[14]

On the other hand, TRUS-BX carries a significant risk of severe infections and sepsis.[18,19] The alternative transperineal approach offers advantages such as better access to the whole prostate and a lower infection rate.[20,21] Transperineal prostate biopsy is recommended as an alternative to prevent infections and limit antibiotic use side effects.[21,22] It is foreseeable that an increase in transperineal prostate biopsy will be observed in the coming years. This study aims to assess transperineal biopsy accuracy for PCa detection using the novel methods of micro-US guided biopsy and TBX during the same procedure.

MATERIAL AND METHODS

Patients

From February 2018 to September 2019, 194 consecutive patients with suspicion of PCa underwent transperineal prostate biopsy using micro-US (ExactVu) and TBX (BiopSee system) using the Ginsburg protocol. This was performed in a single center (ICUA-Clínica CEMTRO, Madrid-Spain). All patients received informed consent and biopsies were performed by 6 urologists who received training in transperineal biopsies using micro-US and TBX.

Criteria for suspicion of PCa and consequently for deciding to perform prostate biopsy included elevated PSA (4 ng/ml or greater) or suspicious DRE or visible lesion in mpMRI (PI-RADS 3 or greater). Both initial biopsy and repeat negative biopsy were permitted. However ,patients in whom micro-US or mpMRI was not performed or with a known diagnosis of prostate cancer were excluded from analysis.

Parameters assessed included age, PSA, prostate volume, MRI lesions, PCa and csPCa in targeted and systematic biopsies, number of cores, and Gleason Grade Group. CsPCa was defined as GG greater than 1 and complications are reported according to Clavien-Dindo classification.

Biopsy Protocol

Patients were positioned in a lithotomy position, prostate biopsy was performed with the patient under spinal short-term anesthesia with lidocaine. No Foley catheter was placed unless deemed necessary due to urethral bleeding and patients were discharged from the ambulatory center the same day of the procedure after a few hours. Careful asepsis and shaving of the perineal area as well as DRE were performed. All patients were initially submitted to real-time targeted transperineal prostate biopsies using micro-US while blinded to mpMRI findings. After that, patients with suspected mpMRI lesions (PI-RADS 3 or greater) were additionally subjected to TBX using the BiopSee system and SBX according to the Ginsburg protocol or using the "automatic placement" tool from BiopSee system. Patients without mpMRI suspicious lesions (PI-RADS less than 3) were submitted to real-time targeted biopsies using micro-US (ExactVu) and SBX (BiopSee system) by transperineal approach (fig. 1). [F1]

Micro-ultrasound Procedure. A transperineal guide was attached to the 29 MHz micro-US high-resolution transducer by ExactVu (fig. 2). The transducer with the [F2] attached transperineal guide was fixed on an articulated arm that allows stabilizing of the transducer and moving it conveniently. When the transducer was positioned transrectally, urologists identified suspicious prostate lesions according to PRI-MUS classification, and targeted biopsies using micro-US were performed. The software includes a navigation system that allows targeting suspicious areas according to the prostate zone and rotation angle with respect to the sagittal axis.

Fusion mpMRI Targeted and Systematic Biopsies. After finishing the biopsies using micro-US, the high resolution 29 MHz transducer was removed and the BiopSee system for TBX was positioned using a conventional biplanar transrectal ultrasound transducer. Lesions and prostate were marked on the MRI and then the fusion process with a 3-dimensional ultrasound capture was carried out using the BiopSee software. If fusion was satisfactory

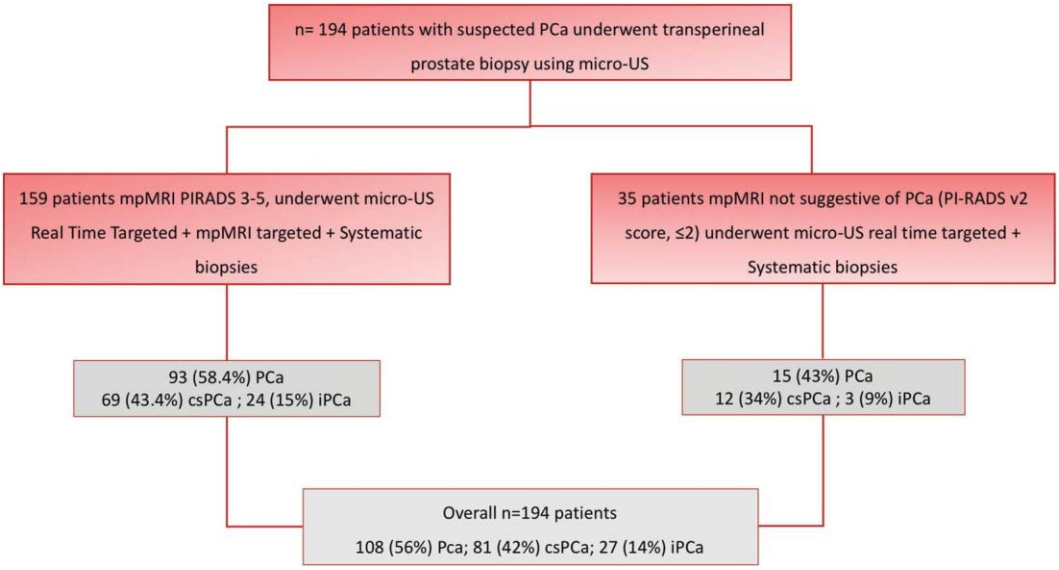


Figure 1. Diagnostic of PCa, iPCa and csPCa using micro-US real-time targeted biopsies and mpMRI targeted biopsies combined with systematic biopsies by transperineal approach.

the procedure followed, and if it was not satisfactory, additional marking of the contour of the prostate was performed on the ultrasound images and the elastic fusion feature was used. Subsequently TBX were first planned and then performed, taking up to 5 biopsies by lesion depending on the lesion's size and thereafter SBX according to Ginsburg protocol were taken. If the MRI was negative we used the automatic placement tool from the BiopSee system to achieve a similar number of biopsies.

Histopathological Analysis

Cores obtained from micro-US targeted biopsies and TBX transperineal biopsies were collected into cassettes for histopathological analysis. A uropathologist performed core analysis according to International Society of Urological Pathology classification and csPCa was defined as GG greater than 1.

Statistical Analysis

Data were collected in a prospective database and processed using SPSS® V21. McNemar's test and a Logistic Regression Model were conducted, with p ::;0.05 considered statistically significant.

Note that all sensitivities and specificities should be viewed as relative measures as no true reference standard was collected (ie prostatectomy specimens or template

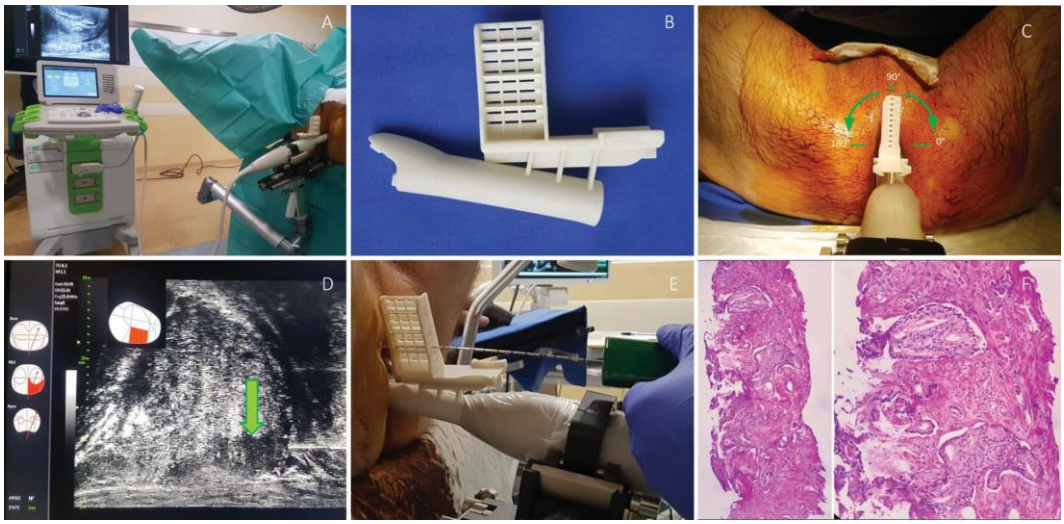


Figure 2. Transperineal prostate biopsies using micro-US. A, high resolution 29 MHz micro-US transducer, transperineal guide, stepper and console. B, transperineal guide. C, schema of movements and degrees in transperineal approach. D and E, suspect area according to PRI-MUS scale, identified and biopsied in real time using micro-US and navigation system. F, csPCa findings in cores obtained from transperineal micro-US guided biopsy.

Table 1. Demographics

Mean age (IQR)	62.0 (58.0–68.0)
Mean ng/ml PSA (IQR)	6.5 (4.7–9.2)
Mean cc US prostate vol (IQR)	47.0 (32.0–67.0)
Mean cc MRI prostate vol (IQR)	58.1 (36.6–81.5)
No. pos DRE (%)	31 (16.5)
No. previous biopsy (%)	65 (33.9)
No. other test (Select MDx, PCA3, 4k score) (%)	19 (9.5)
No. mpMRI lesions/mode (range)	258/1 (0–4)
No. anticoagulant therapy (%)	19 (9.8)
No. previous prostate surgery (%)	13 (6.7)

biopsy) to confirm that patients with benign micro-US, MRI and SBX were indeed benign.

RESULTS

Demographic characteristics of 194 patients are [T1] summarized in table 1. Median patient age was 62 years (IQR 58–68), PSA 6.5 ng/ml (IQR 4.7–9.2) and prostate volume by MRI 58.1 cc (IQR 36.6–81.5). In 34 patients mpMRI was not suggestive of PCa (PI-RADS v2 score, 2 or less). Overall 65 (33.9%) had a previous biopsy and in 19 (9.5%) some additional tests like SelectMDx, PCA3 or 4k score were available. Transperineal guide and stepper were used in 141 (73%) patients, and the remaining biopsies were performed freehand without the stabilization of stepper or needle guide.

The overall positive rate was 56% (108) for PCa and 42% (81) for csPCa, adding micro-US and TBX detected significantly more PCa than SBX alone ($p < 0.001$), and significantly more csPCa ($p < 0.001$, [T2] table 2). TBX compared with micro-US targeted biopsies did not reach statistical difference for PCa or csPCa diagnosis (McNemar test $p = 0.24$ and 0.15). Both PI-RADS and PRI-MUS were strong predictors of csPCa in a Logistic Regression Model (AUC for model with leave-one-out validation 0.76). For PSA greater than 4 ng/ml PI-RADS greater than 3 there was an improvement in csPCa detection rate between [F3] PRI-MUS 4 and PRI-MUS 5 of 51% to 92% (fig. 3).

PCa and csPCa findings according to PRI-MUS scale and PI-RADS classification using micro-US, TBX, SBX and combining all techniques ("Mapping") are shown in supplementary table 1 (https://www.jurology.com). In 35 cases mpMRI was not suggestive of PCa (PI-RADS v2 score 2 or less), but with clinical suspicion or some additional positive test like SelectMDx, PCA3 or 4k, underwent micro-US biopsies + SBX, we found 15 (43%) PCa and 12 (34%) csPCa (fig. 1).

Micro-US found 12 of 108 (11%) PCa that were missed by all other techniques and 11 (92%) were csPCa. On the other hand, SBX found 8 (4%) csPCa missed by TBX and micro-US, while TBX found just 1 (0.5%) csPCa missed by micro-US and SBX.

Of 13 patients with previous prostatic surgery 9 were positive for csPCa with no additional PCa. Interestingly, in these 9 the PRI-MUS score was 4-5 while the PRI-MUS score for the remaining 4 of 13 negative cases was 3 or less.

Micro-US sensitivity, specificity, PPV and NPV to predict csPCa at the patient level were uniformly higher than mpMRI (table 3). Sensitivity and NPV [T3] achieved statistical significance with $p < 0.001$. However, the implication of this is unclear given the clear patient selection and small number of mpMRI negative cases. Performance of micro-ultrasound differed with prostate volume, finding more csPCa than mpMRI in smaller glands (50 cc or less, 34 vs 33) and less in larger glands (greater than 50 cc, 9 vs 19).

No fever or clinical infection was observed, nor any Clavien-Dindo greater than II complications. Overall 17 (8.5%) patients presented with minor complications (Clavien Dindo I-II), mainly acute urinary retention (supplementary table 2, https://www.jurology.com).

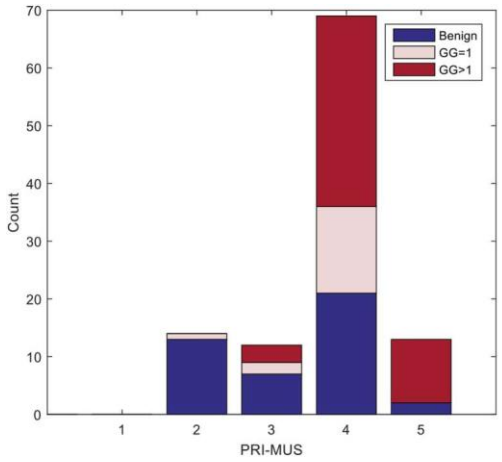
DISCUSSION

PCa is classically suspected based on a suspicious DRE and/or high PSA levels. Definitive diagnosis depends on pathological verification in prostate biopsy cores with ultrasound guided biopsy still standard of care.[1] A prostate biopsy can be performed by the transrectal or the transperineal approach.[20,21] The conventional TRUS-BX approach based on patient selection with PSA/DRE and blind

Table 2. Transperineal prostate biopsy findings

	Micro-US	mpMRI Targeted*	Systematic	Mapping(micro-US + mpMRI-T + systematic)
No. benign (%)	121 (63)	90 (45)	82 (42)	67 (34)
No. prostatic intraepithelial neoplasia (%)	8 (4)	5 (2.5)	7 (3.6)	10 (5)
No. atypical small acinar proliferation (%)	7 (3.6)	2 (1)	12 (6)	12 (6)
No. PCa (%)	60 (31)	67 (35)	97 (50)	108 (56)
No. csPCa (%)	47 (24)	55 (28)	64 (33)	81 (42)
Median No. lesions (IQR)	407; 2 (1–5)†	258; 1 (0–4)‡	-	-
Mean No. biopsy cores (IQR)	911; 5 (3–6)	1,269; 6 (5–9)	6,340; 32 (30–37)	8,520; 44 (38–48)
Mean No. cores involved (IQR)	2 (1–3)	2 (1–4)	3 (1–5)	5 (1–8)

* In 40 patients negative mpMRI PI-RADS 2 (no lesions) = 34 (17%).
† PRI-MUS 3 or greater.
†‡PI-RADS 3 or greater.



Factor	OR	p-value	VIF
Log10(PSA)	2.49 [10.26 - 0.61]	0.21	1.05
Age/10	1.42 [2.20 - 0.92]	0.11	1.13
DRE	1.42 [3.65 - 0.55]	0.47	1.03
Previous biopsy	0.67 [1.40 - 0.32]	0.28	1.06
PI-RADS 2	3.17 [9.59 - 1.05]	0.04	1.42
PI-RADS 3	Reference	-	-
PI-RADS 4	2.04 [5.00 - 0.84]	0.12	1.63
PI-RADS 5	6.37 [23.26 - 1.75]	0.01	1.65
PRI-MUS 2	0.00 [Inf - 0.00]	1	1.58
PRI-MUS 3	Reference	-	-
PRI-MUS 4	3.10 [8.40 - 1.14]	0.03	1.93
PRI-MUS 5	8.60 [41.39 - 1.79]	0.01	1.7

Figure 3. Logistic regression model (AUC for model with leave one out validation ▮ 0.76)

targeting has proven to be an inadequate diagnostic procedure due to a high rate of false-negatives, misgrading and over diagnosis of low risk disease.[3]

Our study recommends a change in the clinical pathway of PCa diagnosis. The detection rate of prostate mapping by transperineal approach was 56% for all PCa and 42% for csPCa. Adding micro-US and TBX detected significantly more csPCa than SBX. Interestingly, micro-US found 11% PCa missed by all other techniques and a high percentage of those (92%) were csPCa.

PCa detection rates with transperineal or TRUS-BX approach were comparable before the MRI era.[20] However, transperineal biopsies are recommended as an alternative to TRUS biopsies to avoid serious infections.[18,22] In our series no infection was observed in any of the 194 patients as a result of the biopsy.

The need for a more accurate diagnosis pathway for PCa has involved imaging tools such as mpMRI and micro-US. Micro-US has emerged as a relatively inexpensive technique to capture images at higher frequencies and is used in various applications in cancer, developmental biology, and cardiovascular disease.[15] In urology this technology has been applied to prostate cancer and more recently in bladder cancer.[16,17,23e26] Lughezzani et al compared the diagnostic accuracy of micro-US targeted biopsies and TBX in detecting csPCa in a cohort of 104 patients where micro-US relative sensitivity for csPC detection was 94%.[17] Of note, the technique used in that study was a TRUS-BX approach. Our study is the first describing a transperineal approach, with the benefit of a very low rate of infection.

Another application of micro-US that has been is studied is the active surveillance of PCa.[24,27,28] Eure et al enrolled 9 patients on active surveillance.[24] MpMRI and micro-ultrasound both demonstrated superior sensitivity to Gleason 7 or higher cancer compared to TRUS.

Level 1 evidence leading to changes in the PCa diagnostic paradigm with mpMRI has emerged in the last decade, including PRECISION,[4] MRI 1st,[6] 4M,[7] BIDOC and systematic reviews.[5] While mpMRI is not a perfect solution, due to a percentage of MRI invisible csPCa, and other limitations like reader variability and the imprecision of current targeting methods, TBX substantially improves the detection of csPCa. Thus, there is a need to standardize MRI interpretation and prostate biopsy technique.

In addition, 29 MHz micro-US can be complementary to mpMRI in the same way as conventional US, with the advantage that micro-US also identifies targets, especially in those cases of negative

Table 3. Relative sensitivity, specificity, PPV and NPV for PRI-MUS and PI-RADS

	PRI-MUS		PI-RADS		
	PCa	csPCa	PCa	csPCa	p Value for csPCa Comparison
Sensitivity	98.9 (95.5e99.9)	99.7 (96.8e100.0)	85.5% (77.9e91.3)	84.3% (75.2e91.1)	<0.001
Specificity	29.3 (20.5e39.2)	23.1 (16.2e31.4)	21.4% (13.8e30.6)	18.8% (12.7e26.8)	0.21
PPV	62.3 (54.7e69.2)	46.0 (38.7e53.7)	56.3% (48.5e63.8)	40.7% (33.3e48.4)	0.16
NPV	95.6 (83.7e99.6)	99.2 (91.4e100.0)	55.8% (38.9e71.6)	64.5% (47.7e79.0)	<0.001

No reference standard was available to distinguish false-negative cases, although these may exist due to incomplete sampling of the prostate despite all 3 approaches. Therefore, all values here should be considered relative to the other methods used rather than absolute for the population.

MRI with high suspicion of PCa or indeterminate (PI-RADS 3) lesions.[4e7,29] In our study PI-RADS and PRI-MUS were strong predictors of csPCa. mpMRI appears to perform better in larger prostates, perhaps due to limited penetration of micro-US. Imaging enhancements to improve image quality in the anterior prostate and a modified PRI-MUS scale addressing regions outside the peripheral zone should address this discrepancy and provide further improvement to micro-US performance.

The limitations of our study are similar to those of previous single center studies. We did not complete a proper learning curve and had no prior experience with micro-US other than the training received before the study. The lack of randomization and a control arm may have caused bias due to knowledge of mpMRI results and target location despite the micro-US sampling occurring first before MRI review. Further, micro-US systematic sampling was not performed and the BiopSee automated placement system was used for systematic spacing. It is not certain that SBX taken using micro-US would behave the same way as the sample size is small. However, this is the first study using the transperineal approach. The reported NPV for MRI was lower here than in other studies, but this may be due to the effect of additional cancers detected by micro-US.[30] An analysis of the data with micro-US cores removed shows a MRI NPV of 80.2% (95% CI 66.6e90.4), which is much closer to values from the literature for this definition of csPCa.[4,5]

CONCLUSION

This is the first study using micro-ultrasound guided biopsy and mpMRI fusion biopsy for PCa detection by transperineal approach. The results show a high accuracy for PCa and csPCA diagnosis, avoiding infectious complications due to biopsy. The proposed method should be validated in large randomized clinical trials.

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EDITORIAL COMMENTS

We would like to congratulate the authors for their important contribution on micro-ultrasound, a promising new high-resolution imaging system for prostate cancer. The outcomes of this well designed retrospective study need to be interpreted with an understanding of some challenges of prostate cancer imaging, like variation of imaging quality in different areas of the prostate, effect of MRI performance on diagnostic outcomes and benchmarking.

Patient selection and prostate size may influence the findings of these analyses. In patients undergoing repeat biopsies, anterior are more common.[1] The anterior prostate and larger prostates are a challenge for all imaging techniques, in that ultrasound resolution is influenced by the wave length and depth of ultrasound penetration.

The reported negative predictive value of mpMRI for clinically significant prostate cancer of 66% is lower than commonly reported in the literature.[2] The quality of MRI targeted biopsies heavily depends on the quality of the MRI reading. In a comparison to another technique, quality control methods (eg double reading) ought to be applied

Finally, benchmarking to allow insight into the false-negative rate of a diagnostic technique is often cumbersome. Correlation with state-of-the-art comparators, like comprehensive prostate mapping biopsy or prostatectomy specimen, would not be feasible in this scenario.

To make a distinct statement of the quality of the described diagnostic technique, outcomes should be assessed in a homogenous cohort, using quality assurance and recognized benchmarking. This will require further formalised prospective research.

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Recently, micro-ultrasound has emerged as a promising new imaging device for prostate cancer detection. Rodriguez Socarras et al highlight the Madrid protocol, which includes addition of micro-US targeting to mpMRI and transperineal mapping biopsy for the detection of csPCa. While multiple studies have shown the benefit of adding mpMRI to systematic biopsies for the detection of

csPCa,[1] this study highlights additional benefits of adding micro-US to mpMRI targets and systematic mapping, thereby improving the accuracy in assessing patient risk profile for disease management. The results show that micro-US has the potential to detect csPCa that may be invisible on mpMRI. Other studies have also highlighted the benefit of targeting under real-time visualization using micro-US rather than relying on cognitive/fusion software.[2] Given the known variability in mpMRI acquisition and interpretation, prospective trials with well established mpMRI readers or RCT studies are the need of the hour to confirm the potential of micro-US to decrease the ever increasing burden on mpMRI. Studies looking at the combined NPV of micro-US and mpMRI targets in an attempt to avoid or reduce the need of systematic sampling would be another scope for future research.

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REPLY BY AUTHORS

We appreciate these constructive editorial comments. Multiparametric magnetic resonance imaging was the first imaging modality that allowed us to see localized prostate cancer, and this has led to viewing it as a panacea. Although its negative predictive value is high, it is variable despite standardization. The PROMIS study defined clinically significant disease as Gleason 4 D 3 or greater, or core length of 6 mm or greater in any location, and found a NPV of 89% (83-94), but when adjusted to Gleason 3D4 or greater, or core length 4 mm or greater, dropped to 72% (65-79).[1] These results are in accordance with our findings. Moreover, the higher value in PROMIS is still lower than that achieved by micro-ultrasound. As Dr. Ghai points out, studies looking at the combined NPV of micro-US and mpMRI targets would be another scope for future research.

This real-world cohort includes a proportion of cases submitted to prior biopsies that often present with anterior disease. This bias against micro-ultrasound in our study is reassuring if we consider the generalizability of the technique, given the promising performance demonstrated.

Micro-ultrasound and mpMRI are not competitive, as they more likely constitute a symbiotic pair, or complementary tools, in what we called "The Madrid protocol," as another manifestation that the PCa diagnosis pathway is continuously evolving. We should no longer rely only on PSA or digital rectal examination. The combination of clinical information, novel markers and imaging tools will allow us to avoid unnecessary biopsies and, thus, reduce PCa over diagnosis and overtreatment.

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