Prostate Cancer Diagnosis with Micro-ultrasound

What We Know now and New Horizons

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KEYWORDS

• Prostate cancer • Micro-ultrasound • Cancer detection

KEY POINTS

- Micro-Ultrasound (MicroUS) is a novel high-resolution 29-MHz ultrasound with ~three times greater resolution compared to conventional transrectal ultrasound, potentially improving accuracy of targeted prostate biopsy.
- A growing body of literature is available supporting the use of MicroUS with comparable accuracy to multiparametric MRI, for guidance of targeted prostate biopsy.
- The ongoing OPTIMUM randomized controlled trial will help to establish the role of MicroUS in the diagnostic algorithm for the detection of clinically significant prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer diagnosed in men worldwide, accounting for 15% of the total new cancer cases in the male population and responsible for 375,000 deaths in 2020.[1] Population screening using prostate-specific antigen (PSA) and digital rectal examination is recommended by the NCCN, EAU and other clinical guidelines.[2,3] Over the past decade, the use of multiparametric magnetic resonance imaging (mpMRI) for the diagnosis of PCa has exponentially increased, with increased utilization in the PCa diagnosis pathway. Multiple level one evidence studies, including PRECISION, 4M, MRI-FIRST, PRECISE, and PROMIS, have confirmed MRI-targeted biopsy as being not inferior to (possible superiority) TRUS-guided systematic biopsies for clinically significant (cs) PCa detection with fewer core biopsies and substantially less insignificant PCa diagnosed[4–8] These studies have resulted in widespread acceptance of mpMRI prior to biopsy and inclusion of this method in most clinical guidelines.[2,3] Although mpMRI has improved detection rates, there are issues related to MRI cost, access, interpretation, fusion biopsy expertise and variability in scan quality.[9] Additionally, many patients within this population will have relative contraindications to mpMRI such as implanted devices, claustrophobia and impaired renal function.

More recently, high frequency Micro-Ultrasound (MicroUS) has emerged as a promising imaging technology for PCa diagnosis.[10] The most recent edition of the NCCN,[3] EAU[2] and AFU[11] guidelines mention the novel MicroUS imaging modality for the detection of PCa citing recent studies.[12–17] This modality has the potential to add value to mpMRI, in addition to easy access and a cost-effective tool for diagnosis of PCa, with the capability to improve sensitivity and negative predictive value (NPV) for csPCa, mainly due to its capacity of visualizing and targeting under real-time lesions suspicious for PCa.[18] The purpose of this review is to provide the reader an overview of the role of micro-US for diagnosis of PCa, discussing its diagnostic performance, technical considerations and limitations.

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HIGH RESOLUTION MICRO-ULTRASOUND

Overview

MicroUS is a novel imaging technique, developed by Exact Imaging (Toronto, Ontario, Canada), which has received regulatory approval in the European Union (CE Mark), the United States (FDA), and Canada (Health Canada medical device license) for visualization and biopsy of the prostate. MicroUS operates at frequencies of 29 MHz and allows for a roughly fourfold higher crystal density along the transducer (512 vs 128 crystals). The resolution of MicroUS is 70 microns, which is the diameter of a typical prostatic duct, as opposed to 200 microns or more of TRUS, which provides a threefold improvement in special resolution compared to conventional frequency TRUS.[18–20] The high resolution of the MicroUS system permits the visualization of the ductal anatomy and cellular density, resulting in a more detailed view of the prostate anatomy (**Fig. 1**). As a consequence, MicroUS has emerged as a promising new imaging device for targeted biopsy, with the potential to improve sensitivity for csPCa, due to its ability of visualizing and targeting under real-time lesions suspicious for PCa.[18] The first generation of MicroUS technology, the ExactVu 29 MHz system, was originally assessed in a pilot study in 2013 on a radical prostatectomy series.[10] Second generation high resolution MicroUS was released in 2017 and included additional advances in image quality and ergonomics, including redesign of the side fire transducer, which presents similar circumference (64 mm) as most of the TRUS transducers (58–74 mm),[21] and has been usually well tolerated by patients. For instance, in Klotz and colleagues,[12] a total of 1040 MicroUS procedures were performed with no drop-out for tolerability of the probe.

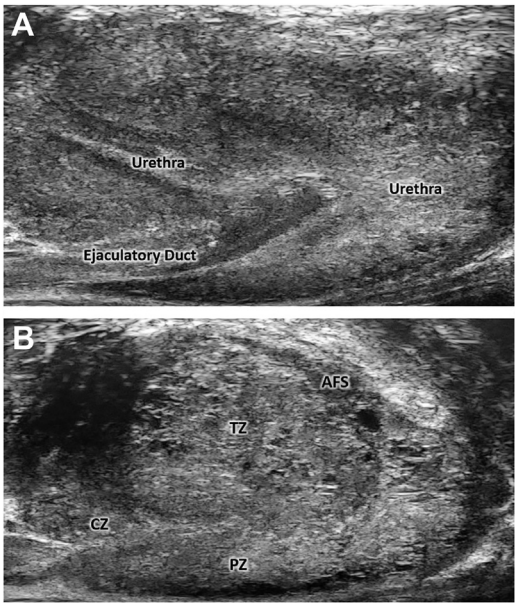

Fig. 1. Prostate MicroUS using a 29-MHz transducer showing the main anatomic landmarks of the prostate (sagittal plane). Midline view (*A*) showing clearly the urethra and ejaculatory duct. Paramedian view (*B*) demonstrating the four prostate zones: AFS, TZ, CZ and PZ. AFS, anterior fibromuscular stroma; CZ, central zone; PZ, peripheral zone; TZ, transition zone.

Prostate Risk Identification using Micro-Ulltrasound Grading System

In 2016, "Prostate Risk Identification using Micro-Ulltrasound" (PRI-MUS) grading system was proposed and validated to assess the risk of PCa for targeted biopsy with the MicroUS platform (**Table 1**).[22] The PRI-MUS scale ranges from 1 to 5, where a lesion ranked as a 1 implies a low risk for cancer while a lesion ranked as a 5 visualize a high risk for cancer. In contrast to PI-RADS (for mpMRI), PRI-MUS protocol is designed to take advantage of the real-time nature of ultrasound to be applied live during real-time TRUS biopsy. However, it refers to suspicious areas only in the peripheral zone of the prostate and the present version does not include a scoring system for the transition zone. Conversely, PI-RADS assesses lesions in the entire prostate gland. MicroUS paired with the PRI-MUS protocol can be used to inform biopsy decisions, guide prostate biopsy and aid in the detection of suspicious prostatic lesions in the same way as mpMRI. Furthermore, it also provides real-time visualization during the biopsy rather than requiring MRI/US fusion for targeting suspicious sites identified on mpMRI.

Technique

MicroUS-guided prostate biopsy can be performed by a transrectal or transperineal approach. Biopsy preparation and potential complications are similar to those related with TRUS-guided biopsy. Overall, recommendations concerning antibiotic prophylaxis, bowel preparation, anticoagulation withdrawal, and anesthesia delivery should follow the same local urologic guidelines.

The prostate is scanned in the parasagittal plane with MicroUS, since its high-resolution probe corresponds to a linear transducer. The first step of the study usually consists in measuring the prostate volume. For this assessment, initially a sweep is completed, which generates an axial view (**Fig. 2**A), and is used for the calculation of the maximum transverse diameter of the prostate. Subsequently, the midline sagittal plane is used for the measurement of the anteroposterior and

Table 1
PRI-MUS risk table

PRI-MUS Risk Score	Cancer Risk	Findings
1	Very Low	Small regular ducts, "Swiss cheese" with no other heterogeneity or bright echoes
2	Some	Hyperechoic with or without ductal patches (possible ectatic glands or cysts)
3	Indeterminate	Mild heterogeneity or bright echoes in hyperechoic tissue
4	Significant	Heterogeneous cauliflower/smudgy/mottled appearance or bright echoes (possible comedonecrosis)
5	Very High	Irregular shadowing (originating in prostate, not prostate border) or mixed echo lesions, or irregular prostate and/or peripheral zone border

craniocaudal diameters (Fig. 2B), which allows the estimation of the prostate volume. The second stage of the procedure consists in scanning carefully the entire prostate to depict morphologic abnormalities and lesions according to PRI-MUS score.

Systematic biopsy is performed in the sagittal plane similar to conventional TRUS-guided biopsies. If MRI has been performed prior to biopsy, the prostate is initially assessed for visibility of MRI lesions and for additional areas based on PRI-MUS scoring system for the peripheral zone. For MRI lesions visible on MicroUS, visually directed real-time targeted biopsy (Fig. 3) is performed rather than requiring use of additional software fusion with conventional TRUS and thereby provides for accurate targeting.[13]

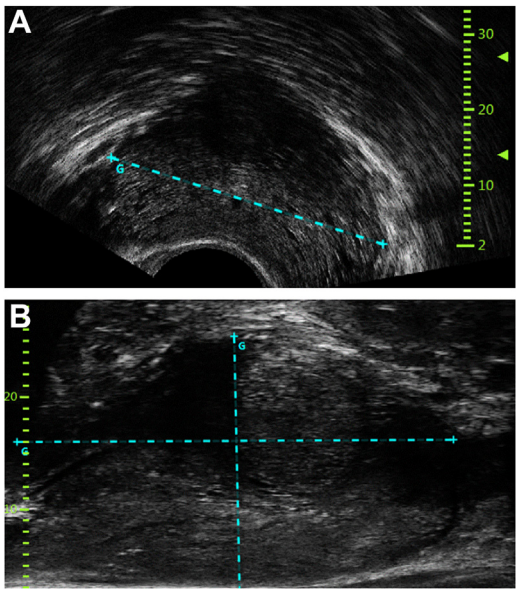

Fig. 2. Prostate volume calculation with MicroUS. Firstly, a sweep is performed with the probe and that generates an axial view (*A*) which is used for the measurement of the maximum transverse diameter of the prostate. Subsequently, the midline sagittal plane (*B*) is used for the calculation of the anteroposterior and craniocaudal diameters.

Multiparametric Magnetic Resonance Imaging/Micro-Ultrasound Fusion

The first commercial MicroUS device (ExactVu, Exact Imaging, Markham Canada) also includes the ability to perform mpMRI/microUS fusion (FusionVu). It has been shown that TRUS visibility of prostatic lesions facilitates targeted biopsy.[23] The capacity to visualize the abnormal tissue in the real-time on MicroUS may therefore improve the accuracy of mpMRI-targeted biopsy by obviating the need to rely upon elastic or rigid deformation calculations and frequent corrections for patient movement or capsule marking errors. MicroUS/MRI fusion (FusionVu) biopsies are performed using software platforms to combine the MRI data to the US for targeted biopsies if they are not visible on MicroUS imaging (Fig. 4). The software aligns the tumor boundary identified on MRI as an overlay on the real-time Micro-US image to enable a direct targeted biopsy.[13] This tool is especially useful for suspicious lesions in the anterior transition zone of the gland that may not be visible on MicroUS in real-time for biopsy.

Diagnostic Performance

MicroUS presents three times greater resolution as compared with conventional TRUS resolution, potentially resulting in improvement in accuracy of targeted prostate biopsy.[24] For example, a multicenter randomized controlled trial, previously showed that MicroUS is more sensitive than conventional TRUS in detecting PCa.[25]

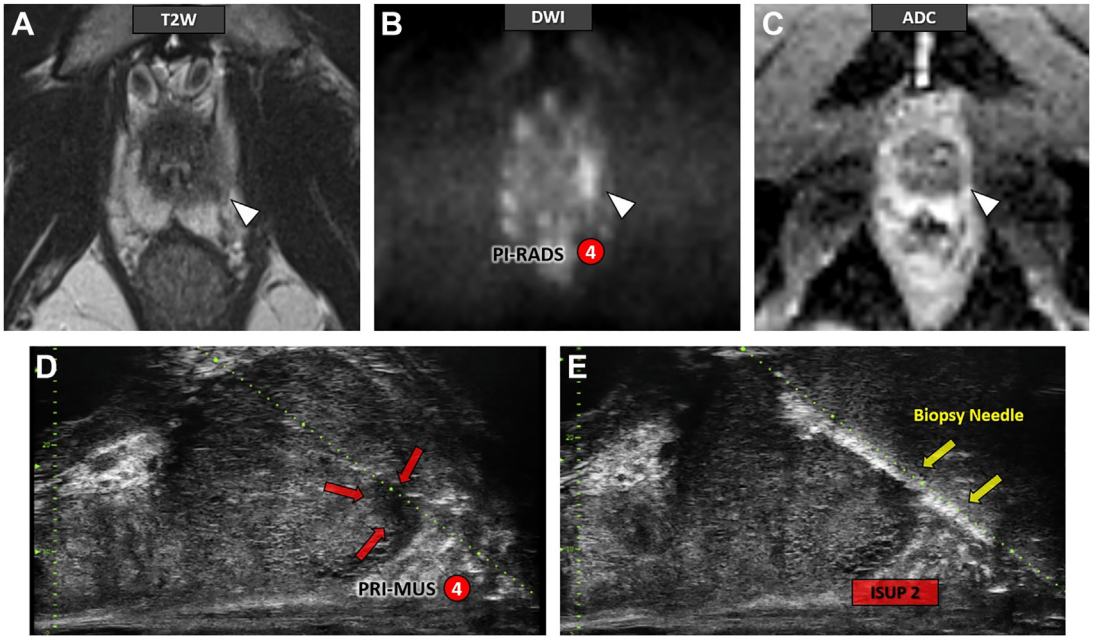

Fig. 3. Images in a 60-year-old man with prostate-specific antigen level of 4.5 ng/mL. Multiparametric MRI scans (axial T2-weighted image [*A*], diffusion-weighted image [*B* and ADC map [*C*]) show a PI-RADS 4 lesion in the left apex peripheral zone (*arrowheads*). MicroUS scan (*D*) shows the corresponding index lesion with smudgy pattern (PRI-MUS 4) (red *arrows*). Targeted biopsy revealed grade group 2 disease (*E*). PI-RADS, Prostate Imaging Reporting and Data System; PRI-MUS, Prostate Risk Identification Using Micro-Ultrasound.

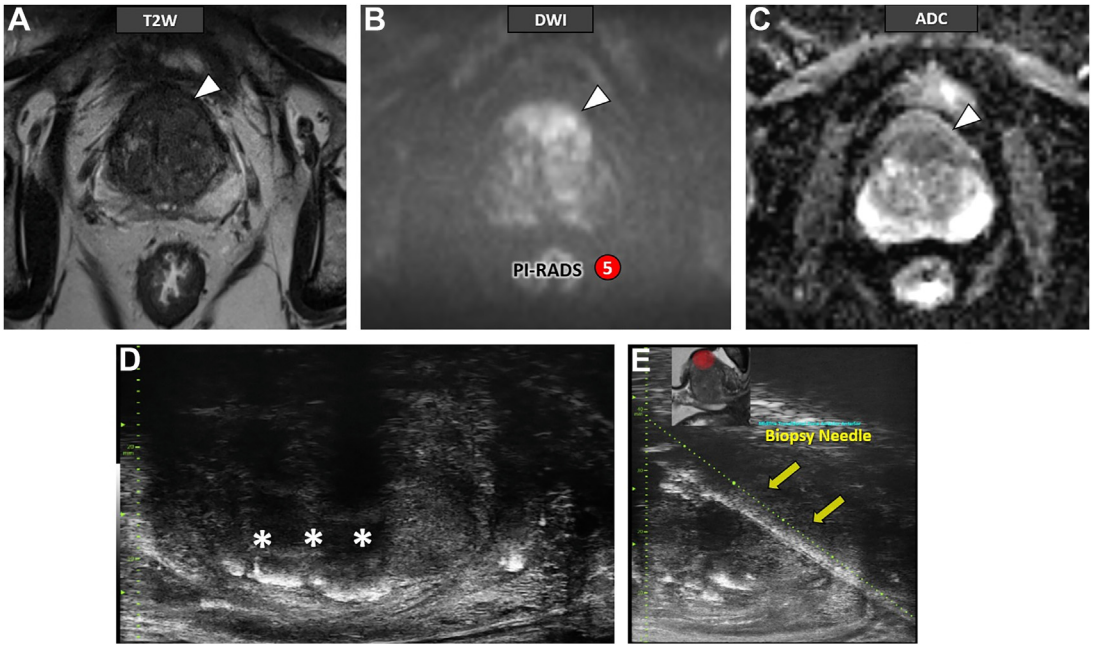

Fig. 4. Images in a 71-year-old man with prostate-specific antigen level of 12.3 ng/mL. Multiparametric MRI scans (T2-weighted [*A*], diffusion-weighted imaging [*B*] and ADC map [*C*] show a 2-cm PI-RADS 5 lesion (*arrowheads*) in the anterior transition zone. (*C*) MicroUS scan (*D*) failed to detect the site of the tumor, due to shadowing from calcification in corpora amylacea (*asterisks*), limiting the assessment of anterior gland. Targeted MicroUS/MRI fusion (FusionVu) (*E*) biopsies (using software platforms to integrate the MRI and ultrasound data) revealed grade group 2 disease. PI-RADS, Prostate Imaging Reporting and Data System.

More recently, multiple studies have also shown that the sensitivity of MicroUs is comparable to that of mpMRI for PCa detection (Fig. 5). The first study comparing MicroUS and mpMRI was published in 2018 by Eure and colleagues,[26] and showed that MicroUS could potentially be as sensitive to csPCa as mpMRI in the active surveillance cohort. This feasibility study had many limitations including small sample size, however it demonstrated that blinding between the two modalities was possible and that a within-patient comparison was feasible. Subsequently, multiple studies highlighting the similarities of csPCa detection rates between mpMRI and microUS have been published since 2019.[13]

In 2020, Socarras and colleagues performed a single center prospective trial where 194 patients first underwent microUS targeted biopsy while the operator was blinded to the mpMRI results.[27] While multiple studies have demonstrated the benefit of adding mpMRI to systematic biopsies for the detection of csPCa,[28] Socarras and colleagues showed additional benefit of adding MicroUS to mpMRI and systematic mapping, owing to its potential to detect csPCa that may be invisible on mpMRI. MicroUS detected 11% additional cancers not detected by MRI or systematic biopsy in their study. Likewise, Lughezzani and colleagues assessed diagnosis of csPCa with MicroUS in a cohort of 320 patients with a positive MRI (PI-RADS $\geq$3).[29] This study showed a 2.6% improvement in csPCa detection by adding MicroUS targets to that of MRI targets and systematic biopsy. Furthermore, they concluded that these two modalities (MicroUS and MRI) appear to provide complementary information that could be combined to maximize the detection of csPCa. This may additionally have implications for patients being considered for focal therapy.

In 2021, Klotz and colleagues published the first multi-center prospective registry trial (11 institutions; 1040 patients) to compare the diagnostic performance of mpMRI targeted biopsy to microUS targeted biopsy.[12] Any man with an indication for prostate biopsy (elevated PSA or abnormal DRE) was included in the study. The authors concluded that MicroUS had comparable or higher sensitivity for csPCa compared to mpMRI. In this study, MicroUS and mpMRI sensitivity were 94% versus 90%, respectively ($P = .03$), and negative predictive value (NPV) for the two modalities was 85% versus 77%, respectively. An important limitation of this study was the methodological differences between sites. For example, 7 of the 11 sites were unblinded

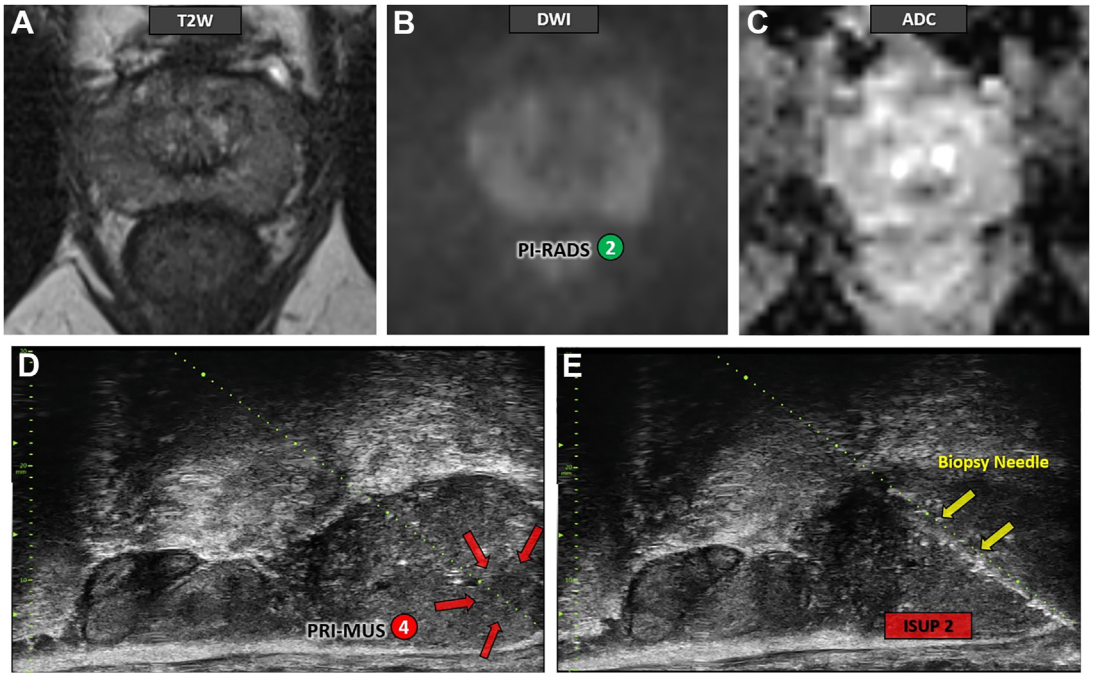

Fig. 5. Images in a 49-year-old man with prostate-specific antigen level of 8.26 ng/mL. Multiparametric MRI scans (T2-weighted [*A*], diffusion-weighted imaging [*B*] and ADC map [*C*] did not show any suspicious lesion (PI-RADS 2). MicroUS scan (*D*) showed a 6mm-hypoechoic lesion with smudgy pattern (PRI-MUS 4) in the left midgland peripheral zone (red *arrows*). Targeted biopsy revealed grade group 2 disease (*E*). PI-RADS, Prostate Imaging Reporting and Data System; PRI-MUS, Prostate Risk Identification Using Micro-Ultrasound.

to the mpMRI before using microUS; however, the results between blinded and unblinded groups were similar.

In 2022, Ghai and colleagues[15] and Hofbauer and colleagues[16] compared detection rate of csPCa using microUS targeted biopsy and mpMRI targeted biopsy. In Hofbauer and colleagues's multi-center prospective study, microUS found 73% of csPCa cases and mpMRI found 76%. MicroUS was non-inferior to mpMRI (P = .023) for detecting csPCa on biopsy. In Ghai and colleagues's single-center prospective trial, of the 94 men biopsied, mpMRI targeted biopsy found csPCa (GG $\geq$ 2) in 37 (39%) of the men and microUS found csPCa in 33 (35%) of the men. This study showed that the two modalities had comparable detection rates, nevertheless MicroUS would not have permitted avoidance of biopsy in as many cases as mpMRI. Interestingly, the detection of high-risk pathologic features (intraductal carcinoma and cribriform subtypes) was nearly equal between modalities. The combination of the two modalities, mpMRI targeted and microUS guided biopsy, allowed the detection of csPCa in 39 (40%) of the men in the trial. This study in particular suggests the potential added benefit of using mpMRI combined with microUS and reinforced that there was no value in adding systematic biopsies to mpMRI and microUS targeted biopsies.

Two recent metanalyses have also compared MicroUS and mpMRI for PCa detection. In Sountoulides and colleagues[17] study (13 studies and 1125 patients), the detection rate of csPCa and insignificant PCa, as well as the overall detection rate of PCa were similar between MicroUS-guided and mpMRI-targeted prostate biopsy. The pooled detection ratio for Grade group (GG) $\geq$ 2 PCa was 1.05 (95% CI 0.93–1.19, I^2 = 0%), and 0.94 (95% CI 0.73–1.22, I^2 = 0%) for GG1 PCa. The overall detection ratio for PCa was 0.99 (95% CI 0.89–1.11, I^2 = 0%). You and colleagues (11 studies and 1081 patients)[30] also concluded that there was no significant difference between MicroUS and mpMRI in the detection of csPCa, showing an odds ratio of 1.01 (95% CI: 0.83–1.22, P = .92) for csPCa detection.

In 2023, Avolio and colleagues[31] assessed the performance of MicroUS for predicting csPCa in patients with a persistent clinical suspicion of PCa despite negative mpMRI. The authors concluded that MicroUS may represent an effective tool for the diagnosis of csPCa in men with negative mpMRI, providing high sensitivity and NPV (respectively, 97.1% and 96.4%), despite low specificity and positive predictive value (29.7% and 34.0%, respectively).

Overall, available evidence has demonstrated that MicroUS detection rates for csPCa diagnosis are comparable to the detection rates of mpMRI guided biopsy procedures. The conclusions presented are uniform and include three studies providing level 1a evidence (per the OCEBM criteria for diagnostics tests)[32]; however, scarce randomized controlled trial data is available and some of the studies mentioned in this review have limitations with risk of bias. The OPTIMUM trial (ClinicalTrials.gov Identifier: NCT05220501) will address this unmet need. This is a 3-arm multi-center randomized controlled trial (n = 1200) comparing MicroUS guided biopsy with MRI/US fusion and MRI/MicroUS "contour-less" fusion. This trial will investigate whether MicroUS alone, or in combination with mpMRI, provides effective guidance during prostate biopsy for the detection of clinically significant prostate cancer (csPCa) for biopsy naïve subjects. This study will also allow several secondary outcomes of interest to be assessed. These include the difference in the detection of csPCa with MRI/US fusion versus MRI/MicroUS fusion biopsy and the added value of each biopsy technique (MicroUS targeted, mpMRI targeted, and systematic). Additionally, economic health data will be collected as a part of the study to assess cost and time savings compared to mpMRI targeted biopsy.

Limitations

While MicroUS may enable the detection of some lesions not identified on mpMRI, it may have some limitations. First, increased the attenuation of the ultrasound beam at higher frequency can lead to limited depth of penetration, and this can therefore limit the diagnostic performance of the current generation MicroUS device in the assessment of the anterior prostate gland including the transition zone especially in large prostates. In addition, shadowing from the corpora amylacea when calcified can also limit the assessment of the anterior gland (see **Fig. 4**). 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 in MicroUS performance.

Second, robust studies aiming to determine the learning curve of MicroUS and the interobserver agreement in the PRI-MUS score are still needed. Finally, despite presenting similar sensitivity to mpMRI for csPCa detection, MicroUS has been shown to be inferior to mpMRI for avoiding biopsy, due to lower specificity; nevertheless, most lesions visible on mpMRI are also visible on MicroUS, allowing real-time targeted biopsy.[15] Therefore, it may be best suited for use in conjunction with

mpMRI, but results of the multicenter OPTIMUM trial will provide evidence on how best to utilize this new technology.

Future Perspectives

MicroUS has been proposed to address other challenging indications in prostate imaging, including the local staging of PCa and active surveillance of PCa. MicroUS has also the potential to add value to biparametric (bp) MRI, and may represent a promising guidance for focal therapy in the near future.

Knowledge of the existence and location of extraprostatic extension (EPE) allows for more confident decisions on treatment margin. A few studies have investigated MicroUS' ability to predict non-organ-confined disease and EPE of PCa. In 2020, Regis and colleagues first investigated MicroUS' ability to predict the presence of EPE before radical prostatectomy.[33] This study showed that a MicroUS based assessment for the prediction of EPE would yield a sensitivity of 87.5% (95% CI 74.3%–100%) and a specificity of 80.0% (95% CI 65.7%–94.3%). In 2022, Fasulo and colleagues also investigated MicroUS' ability to predict EPE of PCa prior to radical prostatectomy.[34] MicroUS correctly predicted the presence of EPE in 80% of the cases with confirmed EPE on surgery.

Active Surveillance is recommended by the main urologic clinical guidelines to manage patients with low-risk PCa.[2,3] Albers and colleagues has recently evaluated the potential role of MicroUS in active surveillance.[35] This study compared MicroUS' ability to detect disease progression for men within an active surveillance program from GG = 1 to GG $\geq$ 2, as compared to mpMRI. No difference between MicroUS and mpMRI was found in detecting GG $\geq$ 2 lesions. MicroUS (with PRI-MUS $\geq$ 3) had a higher sensitivity than mpMRI (with PI-RADS $\geq$ 3) in detecting GG $\geq$ 2 cancer (97% vs 85% respectively). The study concluded that microUS may be more sensitive than mpMRI in this patient population. More recently, Maffei and colleagues also evaluated the adoption of MicroUS in patients with low-risk PCa undergoing confirmatory biopsies at 1 year from AS initiation, and compared diagnostic performance of MicroUS to that of mpMRI-targeted biopsies.[36] In this study, MicroUS and mpMRI showed a sensitivity of 94.1% and 100% and an NPV of 88.9% and 100% respectively in detecting ISUP$\geq$2 patients, concluding that both modalities represent valuable imaging technologies with high sensitivity and NPV in detecting csPCa, thus allowing their use for event-triggered confirmatory biopsies in active surveillance patients. Further studies are warranted to support the use of MicroUS in the field of local staging and active surveillance.

Micro-US has also the potential to be an adjunct to bpMRI for PCa detection. Two metanalyses have shown no significant difference between bpMRI and mpMRI in performance.[37,38] The ongoing prospective PRIME Trial (ClinicalTrials.gov Identifier: NCT04571840) will answer whether bpMRI is non-inferior to mpMRI and will help to establish the role of bpMRI in the diagnostic pathway for the detection of csPCa. MicroUS has high sensitivity in detecting PCa in peripheral zone and the role of DCE (dynamic contrast-enhanced) sequence in mpMRI is limited to lesions in the peripheral zone. Therefore, MicroUS imaging and biopsy may complement bpMRI and provide for an ideal tool for the detection of csPCa.

Moreover, given the ability of precise and real-time visualization of the prostate lesions (especially in the peripheral zone), MicroUS may represent a promising tool for focal therapy guidance, and our Institution is initiating a pilot study testing MicroUS guided focal laser ablation.

SUMMARY

Available evidence has demonstrated MicroUS to be a potentially cost and time saving novel technology with comparable cancer detection rates to mpMRI, which allows real-time visualization for accurate targeted biopsy. It remains uncertain whether MicroUS should be used as a stand-alone modality or in combination with mpMRI for PCa detection. The ongoing OPTIMUM randomized controlled trial will provide further evidence for the best utilization of this novel technology in the diagnostic pathway for cancer detection. Early data also suggest this imaging technique may also have a role in local staging and active surveillance of PCa. MicroUS has also the potential to add value to bpMRI, and may represent a promising guidance for focal therapy.

CLINICS CARE POINTS

- Micro-Ultrasound (MicroUS) is a promising novel high-resolution ultrasound technology for prostate cancer detection and targeted biopsy.
- While existing literature supports MicroUS replacing conventional TRUS for prostate imaging and biopsy, its optimal use remains unclear, whether as a standalone method or in combination with multiparametric MRI to enhance prostate cancer detection.

- Early data indicates that this new imaging modality may also be valuable for local staging and active surveillance of prostate cancer.

CONFLICTS OF INTEREST

A.B. Dias has nothing to disclose. S. Ghai was Institutional PI for the initial multi-institutional randomized controlled trial comparing first-generation transrectal high-resolution micro-ultrasound with conventional frequency transrectal ultrasound for prostate biopsy. The trial was funded by Exact Imaging.

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