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ORIGINAL ARTICLE

Impact of using 29 MHz high-resolution micro-ultrasound in real-time targeting of transrectal prostate biopsies: initial experience

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Abstract

Purpose This report presents our early experience at Cleveland Clinic replacing conventional ultrasound with a novel 29 MHz high-resolution micro-ultrasound system for both systematic sampling and real-time targeting of suspicious regions during prostate biopsy. The added value of micro-ultrasound and MRI over systematic biopsy is presented.

Methods Sixty-seven consecutive subjects (January–August 2018) from our prospective database who underwent prostate biopsy using the micro-ultrasound system were included. 19/67 had prostate MRI imaging available. MRI targets were sampled using the UroNav fusion system. Patients had a median PSA of 5.37 ng/mL (IQR 4.13–8.74).

Results 38/67 (56.7%) subjects were positive for prostate cancer. In six of these cases, systematic biopsy was negative with only micro-ultrasound targeted samples detecting cancer. In two other cases, patients were upgraded from Grade Group 1 to Grade Groups 4 and 2 based on micro-ultrasound targets. Micro-ultrasound targets detected cancer in two subjects where MRI was negative (Grade Groups 3 and 2). MRI targets alone did not change the overall diagnosis of any subjects. Switching biopsy guidance to real-time micro-ultrasound increased detection rate on prostate biopsy from 44.8% (30/67) to 56.7% (38/67), a relative increase of 26.7%.

Conclusion High-resolution micro-ultrasound identified clinically significant cancer that would have, otherwise, been missed by both MRI fusion and systematic biopsy and was useful in both biopsy naïve and repeat negative patients. Early results from this small, single-center cohort are promising, particularly given the ease with which micro-ultrasound can replace the conventional ultrasound in standard prostate biopsy procedures.

Keywords Micro-ultrasound · Prostate cancer · TRUS · Biopsy · Systematic · Targeted · mpMRI · ExactVu

Introduction

The American Cancer Society estimates 174,650 new cases of prostate cancer (PCa) In the United States in 2019 [1]. PCa Diagnosis is complicated by the high false negative rate of transrectal ultrasound (TRUS) guided biopsies [2]. Recently, major clinical guidelines [3–5] have been amended to recommend multiparametric Magnetic Resonance Imaging (mpMRI) imaging targeted biopsy which improves PCa detection rates. However, this diagnostic pathway creates new challenges for access, excluding men with poor kidney function or prosthetic implants, adding additional cost of mpMRI, multispecialty nature of the pathway, and variability in expertise among radiologists.

High-resolution micro-ultrasound is a new imaging modality which allows practitioners to visualize prostate cancer and target suspicious areas in real time [6]. Micro-ultrasound operates at 29 MHz and provides a direct replacement for conventional ultrasound with a threefold improvement in spatial resolution. These micro-ultrasound systems can be used for standard systematic sampling as well as real-time targeting of suspicious regions during the same biopsy procedure.

This study reports on the utility of this new imaging modality during the first 8 months of use at our institution.

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The added value of high-resolution micro-ultrasound and MRI over systematic biopsy in increasing PCa detection rates during biopsy is presented with the goal of reducing false negatives and under-grading due to un-sampled lesions within the prostate.

Materials and methods

Patients

Sixty-seven consecutive patients underwent prostate biopsy using the ExactVu™ (Exact Imaging, Markham, Canada) 29 MHz micro-ultrasound system from January to August 2018. 19/67 patients presented with a recent mpMRI and underwent micro-ultrasound targeted biopsy and a standard 12 core systematic biopsy using the ExactVu system followed by an mpMRI targeted fusion biopsy using the UroNav system (Invivo, Gainesville).

All 67 subjects provided informed consent and were included in a prospective biopsy database maintained at the Cleveland Clinic (IRB study 12–118). Biopsies were performed by three urologists, who received a standardized training program prior to the start of this study. None of the urologists had any experience with micro-ultrasound prior to training, or outside of the data collection for this study. Each of the urologists had > 1 year experience using the UroNav system for MRI/US fusion.

MpMRI procedure

MpMRI imaging was performed on a 3 T Siemens Skyra without endorectal coil and marked by a team of 14 radiologists with 2 to > 10 years of experience in prostate MRI at the Cleveland Clinic according to the PI-RADS V2 protocol. Identification of regions of interest was performed in an offline workstation along with full contouring of the prostate and reviewed by the urologist prior to the biopsy procedure.

Biopsy procedure

All 67 patients were imaged and biopsied using the ExactVu micro-ultrasound system with the patient in left lateral decubitus position. The urologist inserted the transrectal micro-ultrasound transducer and first identified suspicious areas of the prostate according to the PRI-MUS™ scale [6]. PRI-MUS (prostate risk identification using micro-ultrasound) is an evidence-based scale for micro-ultrasound images developed to characterize tissue and stratify suspicious regions, as with PI-RADS™ for MRI. Local nerve block was then performed according to local standard of care and targeted biopsy samples taken from these regions followed by standard 12 core systematic biopsy using the ExactVu system. The micro-ultrasound transducer was then removed, and the MRI fusion procedure was immediately performed as has been described elsewhere [7] using the UroNav 3D tracking and elastic registration fusion system. As the UroNav system is not presently compatible with micro-ultrasound, this portion of the procedure utilized the conventional ultrasound. Two to three samples were taken per mpMRI target. Systematic samples were taken during the micro-ultrasound section of the procedure and were not repeated during the fusion portion of the biopsy.

All mpMRI targets were sampled using the UroNav system by the same urologist performing the ExactVu biopsy except in one case where mpMRI targets were sampled cognitively using the ExactVu system due to its obvious manifestation on micro-ultrasound.

Histopathological evaluation

Biopsy cores were submitted in individual cassettes categorized by prostate region and type of sample (systematic, micro-ultrasound target or mpMRI target). The cores were then evaluated by a genitourinary pathologist at the Cleveland Clinic according to the ISUP Gleason system.

Statistical analysis

Descriptive statistics are reported using mean and standard deviation for normally distributed continuous variables and median and interquartile range (IQR) for others. Clinically significant cancer was defined as any presence of Gleason pattern > 3 tissue (Gleason Sum > 6, Grade Group > 1). A one-way within-subjects ANOVA was conducted to compare the effect of the added micro-ultrasound targets on the pathology results.

Results

Demographics

Study demographics are summarized in Table 1. The median patient age was 66 years (IQR 59–69) and median PSA was 5.39 ng/mL (IQR 4.13–8.74). The median prostate volume based on the micro-ultrasound images was 38 cc (IQR 24–50). The median number of biopsy samples per target was 2 (IQR 2–3) for micro-ultrasound and 3 (IQR 2.5–3) for mpMRI.

Detection of prostate cancer

PCa was diagnosed in 38/67 (56.7%) of patients and clinically significant cancer (Gleason Sum of 7 or higher; Grade Group 2 or higher) was found in 21/38 cases. Adding

Table 1 Study demographics

Variable	Value
Number of patients	67
Age (years)	66 (IQR 59.5–68.5)
PSA (ng/mL)	5.39 (IQR 4.13–8.74)
Volume (cc) micro-US	38 (IQR 24–50)
Prior biopsies	19 (28%)
DRE findings	
Normal (cT1) *n* (%)	44 (65.67)
One half or less of one side (cT2a) *n* (%)	5 (7.46)
More than one half of one side (cT2b) *n* (%)	2 (2.99)
Unknown *n* (%)	16 (23.88)
Number of biopsy samples per target median (IQR)	
Micro-ultrasound target	2 (IQR 2–3)
mpMRI target	3 (IQR 2.5–3)

micro-ultrasound targets reduced under-grading by significantly increasing the median Grade Group of cancer detected ($F=7.52$, $p=0.009$). Pathology results are summarized in Table 2.

Micro-ultrasound targeted biopsy changed the subject diagnosis in 8/38 (21.1%) cases where cancer was diagnosed. In six of these cases, systematic biopsy was negative with only micro-ultrasound targeted samples detecting cancer (Grade Groups 4, 3, 2, 2, 1, 1), for a relative improvement of 26.7% ($p<0.09$). In two other cases, patients were upgraded from grade group 1 to grade groups 4 and 2 based on micro-ultrasound targets. For comparison, systematic biopsy diagnosed seven cancers not found on micro-ultrasound targeted biopsy, of which all but one was Grade Group 1. Three cases were also upgraded from Group 1 to Groups 2, 2, and 3. Cancer detection findings are stratified by biopsy protocol and displayed in Fig. 1.

Targeted biopsy results in mpMRI subgroup

Biopsy-confirmed prostate cancer in 10 of 19 patients who presented for biopsy with a prostate MRI available for review. Histopathology results are presented in Table 2. A direct comparison of the highest Grade Group found by each biopsy technique for these ten cases is presented in Fig. 2. Systematic biopsy performed surprisingly well in this group, identifying the highest grade disease in 8/10 and leaving little room for adding value through targeted biopsy.

Table 2 Patient-level prostate cancer detection findings stratified by sampling method

Variable	Systematic biopsy ($n=67$)	Micro-ultrasound targets ($n=67$)	Systematic + micro-ultrasound targeted biopsy ($n=67$)
Benign	35 (52.24)	39 (58.21)	29 (43.28)
GS 6, GG 1	17 (25.37)	14 (20.9)	17 (25.37)
GS 7 (3 + 4), GG 2	8 (11.94)	8 (11.94)	11 (16.42)
GS 7 (4 + 3), GG 3	5 (7.46)	3 (4.48)	6 (8.96)
GS 8, GG 4	1 (1.49)	2 (2.98)	3 (4.48)
GS 9–10, GG 5	1 (1.49)	1 (1.49)	1 (1.49)

mpMRI subgroup ($n=19$)

Variable	Systematic samples	mpMRI targets	Micro-ultrasound targets	Highest patient level result
Benign	10 (52.63)	14 (73.68)	11 (57.89)	8 (42.11)
GS 6, GG 1	6 (31.58)	2 (10.53)	4 (21.1)	6 (31.58)
GS 7 (3 + 4), GG 2	1 (5.26)	1 (5.26)	2 (10.53)	2 (10.53)
GS 7 (4 + 3), GG 3	1 (5.26)	1 (5.26)	2 (10.53)	2 (10.53)
GS 8, GG 4	1 (5.26)	1 (5.26)	0 (0)	1 (5.26)
GS 9–10, GG 5	0 (0)	0 (0)	0 (0)	0 (0)

Adding micro-ultrasound targets to the biopsy procedure confirmed cancer in six additional patients and upgraded the diagnosis from low-grade disease (Gleason Sum of 6: Grade Group 1) in two other cases. Adding micro-ultrasound targeted samples significantly increased the median Grade Group found at the patient level [one-way within-subjects ANOVA $F=7.52$, $p=0.009$]. Pathology results per targeting modality used within the mpMRI subgroup are also presented

Values are presented as number (%)

GS Gleason Sum; *GG* Grade Group

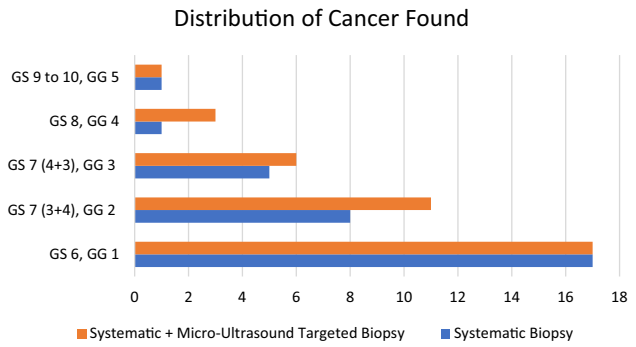

Fig. 1 Distribution of cancer found stratified by biopsy protocol: systematic and targeted. Micro-ultrasound targets identified more cancers in every Gleason Sum, Grade Group tier except for Gleason Sum 6/Grade Group 1 and Gleason Sum 9/Grade Group 5 where micro-ultrasound targets did not make a difference in the diagnosis

These issues are exacerbated by the relatively low specificity in the PSA blood test, and high morbidity associated with transrectal prostate biopsy [9]. This study suggests that the small change of replacing conventional TRUS with high-resolution micro-ultrasound TRUS may improve prostate biopsy outcomes and change the risk–benefit profile of prostate screening.

In this cohort, systematic biopsy alone would have underdiagnosed 8/38 subjects, missing clinically significant cancer in six patients and low-grade cancer in two, all of whom were diagnosed based on micro-ultrasound targets. Switching biopsy guidance from conventional to high-resolution micro-ultrasound targeting increased the detection rate on prostate biopsy from 44.8% (30/67) to 56.7% (38/67), a relative increase of 26.7% ($p < 0.09$), and significantly increased the average grade group of cancer detected ($p < 0.01$).

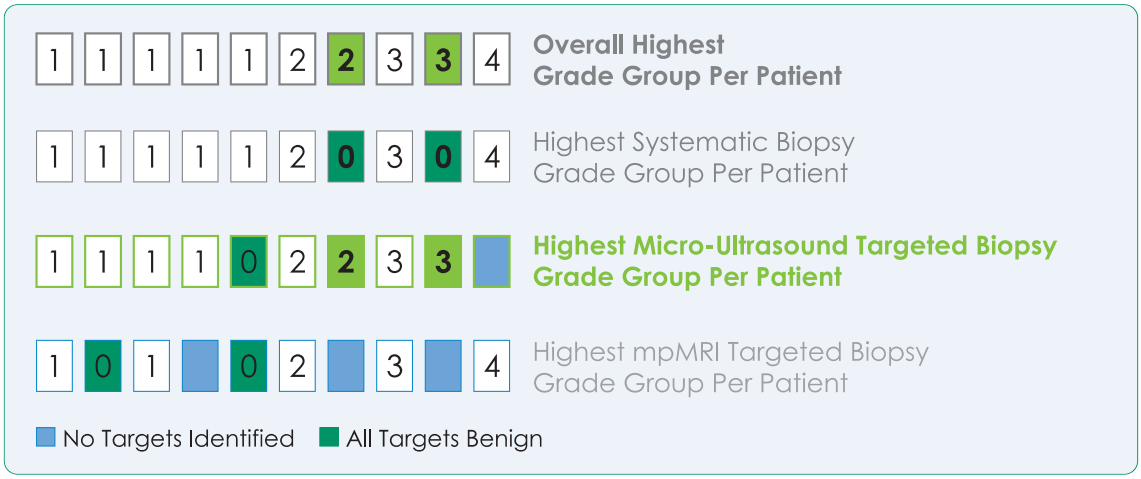

Fig. 2 Pathology results for the ten subjects with biopsy-confirmed prostate cancer. The top row shows the highest Grade Group found using any technique, while subsequent rows break down the highest Grade Group found through each biopsy type: systematic, micro-ultrasound targeted or mpMRI targeted

Micro-ultrasound targeted biopsy found additional clinically significant cancer in two subjects (Grade Group 3 and 2) where mpMRI was negative and all systematic samples were benign. As shown in Fig. 3, MRI did not identify additional cancer in any cases not already identified by systematic biopsy; however, the difference in added value between micro-ultrasound and MRI is not statistically significant and may represent random chance ($p = 0.11$) .

Discussion

The conventional TRUS prostate biopsy is an inefficient diagnostic procedure due to its high rate of false negatives requiring re-biopsy and the frequency of under-grading, which requires confirmatory biopsy in many men [2, 8].

Micro-ultrasound is not the only technique which has been proposed to improve outcomes in prostate biopsy. Multiparametric MRI has produced level 1 evidence from PROMIS [10], PRECISION [11], large cohorts [12] and compelling systematic reviews [13–15]. Despite slow adoption due to reader variability, accessibility, and cost, MRI has made a considerable difference in many urology practices. In this study, 29 MHz micro-ultrasound was used as an adjunct to MRI in the same way as conventional ultrasound; however, instead of only systematic biopsies, micro-ultrasound also identified targets.

In this small series, the value of MRI was largely obscured by systematic biopsy, while micro-ultrasound targets were responsible for detecting 2/5 additional clinically significant cancers. It is not clear whether this benefit is related to

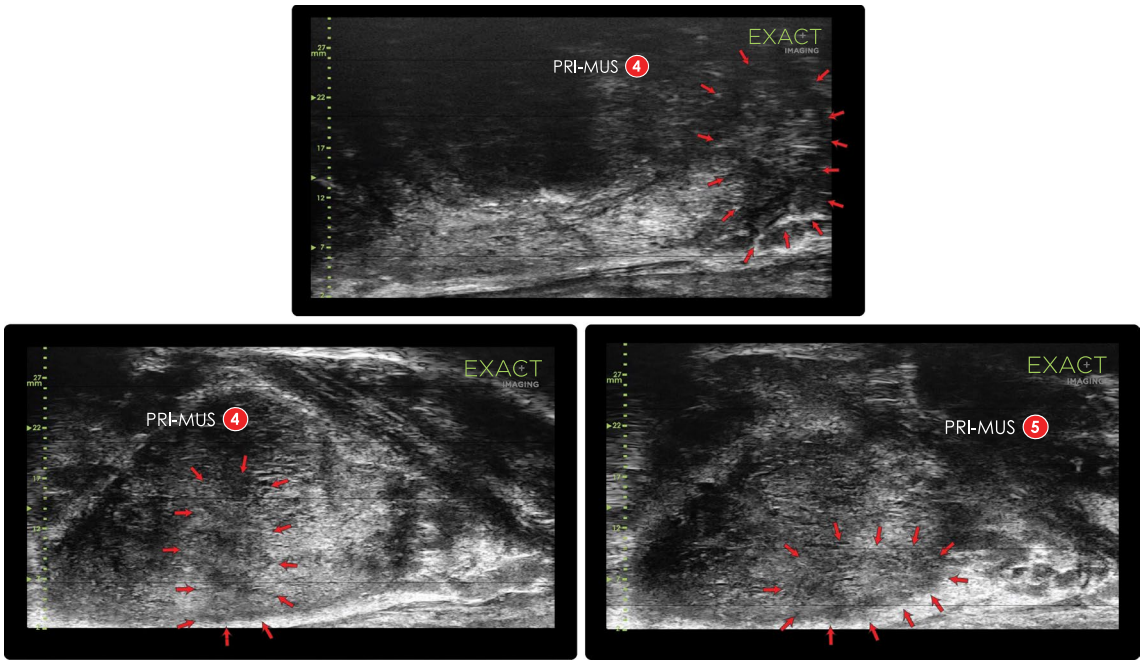

Fig. 3 (Top) micro-ultrasound target (PRI-MUS 4) identified in left lobe of the prostate near the apex, characterized with smudgy and hypoechoic features, and confirmed by pathology as a Gleason Sum 7/Grade Group 2 cancer. The patient had a PSA of 4.05 ng/mL, a previous negative biopsy, a negative MRI, and all systematic biopsy samples were benign. (Bottom) micro-ultrasound targets for a patient with PSA 4.8 ng/mL with negative MRI. (Left) PRI-MUS 4 identified in the middle of the peripheral zone in the right lobe of the prostate and characterized with smudgy and hypoechoic features. (Right) PRI-MUS 5 in the right lobe of the prostate near the apex and characterized as mixed-echo lesion. Both targets were confirmed by pathology as Gleason Sum 7/Grade Group 3 cancer, while all systematic biopsies were benign

lesion size (with the higher resolution of micro-ultrasound leading to detection of smaller significant cancers) or some other difference between the imaging modalities; however, the previous work on high-resolution micro-ultrasound has suggested some independence in location and type of cancers found [16].

This study was limited by the single-center design, and though three independent operators performed cases, none had prior experience with micro-ultrasound outside of training. This suggests that even though learning curve was rapid, familiarity with the modality may further improve results. The lack of blinding and randomization may have caused bias due to knowledge of previous biopsy results or in MRI sampling due to knowledge of the micro-ultrasound target location. We note that such biases represent the real-world use case as these data are commonly used by both urologists and radiologists in interpreting ultrasound and MRI images.

The sample size is too small to draw statistical conclusions around the relative value of micro-ultrasound and mpMRI; however, it is clear that micro-ultrasound added value in this cohort even in the context of mpMRI fusion biopsy in a center of excellence. Finally, at the time of the study, the PRI-MUS protocol for micro-ultrasound only described identification of suspicious areas in the peripheral zone. The updated PRI-MUS v2 protocol is validated for the entire prostate and may have improved detection rates for cancers in the anterior and transition zones.

Conclusion

Prostate cancer is the second leading cause of cancer death among men, primarily driven by late discovery of advanced disease. As such, there is a need to improve the accuracy of cancer detection and imaging overall. During our initial experience replacing conventional TRUS with 29 MHz micro-ultrasound, we demonstrated an improved cancer detection rate ($p < 0.09$) and reduced under-grading ($p < 0.01$) compared to systematic biopsy, and in some cases, mpMRI, although this subgroup did not achieve statistical significance ($p = 0.11$). Replacing the conventional ultrasound guidance with high-resolution micro-ultrasound guidance in our prostate biopsy workflow was straightforward and did not present logistical or workflow impediments. While this was a small, single-center study, these promising early results suggest that micro-ultrasound may improve outcomes throughout the general urological community.

Author contributions RA: protocol/project development, manuscript writing/editing, and data collection. EAK: data collection and management, and protocol development. AE: data analysis and manuscript writing/editing. AS: data collection.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and ethical approval was obtained from the Cleveland Clinic's Institutional Review Board (IRB study 12-118).

Informed consent Informed consent was obtained from all individual participants included in the study.

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