Detection of clinically significant prostate cancer by micro-ultrasound-informed systematic biopsy during MRI/micro-ultrasound fusion biopsy

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ABSTRACT

INTRODUCTION: High-resolution micro-ultrasound (microUS) is a novel imaging technique that may visualize clinically significant prostate cancer (csPCa), including those missed by magnetic resonance imaging (MRI), in real time during prostate biopsy.

METHODS: From September 2021 to January 2022, 75 consecutive biopsy-naive men were entered into an observational cohort. All men underwent an MRI/microUS fusion prostate biopsy, completed by a single surgeon using the ExactVU device. At time of biopsy, each biopsy core was given a Prostate Risk Identification using MicroUS (PRI-MUS) score. Anonymized data were entered into a REDCap database. Cancer detection stratified by Prostate Imaging-Reporting & Data System (PI-RADS) and PRI-MUS score, and imaging modality was captured. Our primary outcome was the detection rate of csPCa in microUS-informed systematic biopsy cores, taken outside MRI-visible lesions, during MRI/microUS fusion prostate biopsy.

RESULTS: A median of three MRI-targeted and 12 microUS-informed systematic cores were taken per patient. MRI/microUS biopsy detected PCa in 84%, with csPCa detected in 52%. Of the 900 microUS-informed systematic cores, 105 cores were PRI-MUS ≥3 and 795 cores were PRI-MUS ≤2. csPCa was detected in 35% of the PRI-MUS ≥3 cores compared to 10% of the PRI-MUS ≤2 cores ($p<0.0001$). Detection of csPCa varied by core type: 8% of patients were diagnosed by MRI-targeted cores only, 38% were diagnosed by microUS-informed systematic cores only, and 54% were diagnosed by both.

CONCLUSIONS: MicroUS-informed systematic biopsy may be a useful adjunct to MRI, with PRI-MUS ≥3 systematic cores having a 3.5-fold increased risk of csPCa compared to PRI-MUS ≤2 cores.

INTRODUCTION

New imaging technologies have improved our ability to detect clinically significant prostate cancer (csPCa, defined as Gleason grade group ≥2). Magnetic resonance imaging (MRI)-guided prostate biopsy has become standard-of-care in many countries, however, it fails to detect up to 25% of csPCa, which are invisible on MRI, and thus systematic biopsy is still required.[1-3] High-resolution micro-ultrasound (microUS) is an imaging technique that may visualize csPCa (potentially including some missed by MRI) in real time during biopsy.[4] Therefore, combined MRI/microUS-guided fusion prostate biopsy may be a novel technique used to increase detection of csPCa. The objective of our study was to determine the detection rate of csPCa during microUS-informed systematic biopsy when used in combination with MRI-guided biopsy for biopsy-naive men.

METHODS

All biopsy-naive men undergoing combined MRI/microUS-guided fusion prostate biopsy at the University of Alberta between September 2021 and January 2022 were entered into an observational cohort. Patients were internally referred from a high-volume tertiary urology center for fusion prostate biopsy, with high clinical suspicion of localized prostate cancer. Human research ethics board approval was obtained (HREBA.CC-21-0388).

Subjects underwent an MRI/microUS device fusion (FusionVu)

KEY MESSAGES

- Despite it gaining popularity, MRI alone can still miss up to 25% of csPCa.
- High-resolution microUS is a novel imaging technique that may visualize csPCa missed by MRI in real time during prostate biopsies.
- MRI/microUS fusion biopsy detected any prostate cancer in 84%, with a csPCa detection rate of 52%.
- MicroUS-informed systematic biopsy cores with a PRI-MUS 5 score had an overall cancer detection rate of 84%, with a csPCa rate of 57%.
- PRI-MUS ≥3 systematic cores have a 3.5-fold increased risk of csPCa compared to PRI-MUS ≤2 cores.

transrectal prostate biopsy using the ExactVU MRI/microUS fusion device (Exact Imaging, Toronto, Canada). All biopsies were performed by a single surgeon, with a high-volume practice in focal therapy for prostate cancer and four years' experience performing transrectal ultrasound (TRUS) prostate biopsy. Prior to biopsy, a multiparametric prostate MRI (mpMRI) was completed, and all relevant lesions were assigned a Prostate Imaging Reporting & Data System version 2.1 (PI-RADS) score.

The surgeon was not blinded to results of the mpMRI prior to the biopsy procedure. At time of biopsy, each biopsy core was given a Prostate Risk Identification using Micro-Ultrasound (PRI-MUS) score.[5] If the patient had a PI-RADS ≥3 lesion(s) on MRI, then three MRI-targeted cores were first obtained per lesion, followed by microUS-informed systematic biopsy (12 cores). If a suspicious PRI-MUS lesion was identified as part of the systematic biopsy, the surgeon may alter his biopsy angle to preferentially target that lesion; however, only a single core is taken per lesion as part of the sextant template systematic biopsy. During the MRI-targeted biopsy, if the lesion also happens to have a high PRI-MUS score, only three cores would be taken, but the cores would be labeled with both the MRI-reported PI-RADS score, as well as the surgeon-assigned PRI-MUS score.

The primary outcome was the detection rate of csPCa in microUS-scored systematic biopsy cores taken outside the MRI-visible regions of interest. Secondary outcomes included overall and csPCa detection rates stratified by PI-RADS and PRI-MUS scores, as well as cancer detection rate in targeted biopsy cores, also stratified by PRI-MUS score.

Fisher's exact test was used to compare csPCa detection in systematic cores stratified by PRI-MUS scores (<3 vs. ≥3). A two-sided p-value of <0.05 was considered significant.

RESULTS

A total of 900 microUS-informed systematic cores were obtained from 75 consecutive men undergoing MRI/microUS fusion prostate biopsy (Table 1). A median of three (interquartile range [IQR] 3–3) targeted cores were

Table 1. Baseline patient characteristics (N=75)

Age, mean (SD)	63 (7.1)
Ethnicity, n (%)	
Asian	10 (13)
Black	3 (4)
Caucasian	57 (76)
Hispanic	2 (3)
Indigenous	3 (4)
Family history of prostate cancer, n (%)	23 (31)
Digital rectal exam (DRE), n (%)	
Normal	65 (87)
Abnormal	10 (13)
Unknown/DRE not done	0 (0)
PSA [ng/mL], median (IQR)	7.1 (5.1–8.7)
Prostate volume (cc), median (IQR)	40 (32–52)
PSA density [ng/mL/cc], n (%)	
<0.15	34 (45)
≥0.15	41 (55)
Unknown	0 (0)
PRI-MUS score, n (%)	
≤2	8 (11)
3	20 (27)
4	28 (37)
5	18 (24)
Not scored for technical reasons	1 (1)
PI-RADS score, n (%)	
≤2	3 (4)
3	5 (7)
4	52 (69)
5	13 (17)
Contraindication to MRI	2 (3)
Number of targeted cores, median (IQR)	3 (3-3)
Number of systematic cores, median (IQR)	12 (11–12)

IQR: interquartile range; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting & Data System; PRI-MUS: Prostate Risk Identification using Micro-Ultrasound; PSA: prostate-specific antigen; SD: standard deviation.

Table 2. Biopsy outcomes stratified by PI-RADS and PRI-MUS score

	n	Any cancer detected	Grade group ≥2 cancer detected
Overall (%)	75	63 (84%)	39 (52%)
PI-RADS score (%)			
≤2	3	2 (67%)	1 (33%)
3	5	3 (60%)	2 (40%)
4	52	43 (83%)	24 (46%)
5	13	13 (100%)	10 (77%)
Contraindication to MRI	2	2 (100%)	2 (100%)
PRI-MUS score (%)			
≤2	8	6 (75%)	3 (38%)
3	20	15 (75%)	10 (50%)
4	28	25 (89%)	14 (50%)
5	18	16 (89%)	12 (67%)

MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting & Data System; PRI-MUS: Prostate Risk Identification using Micro-Ultrasound.

Table 3. Cancer detection by core for micro-ultrasound in systematic biopsies

	# of cores taken	Any cancer detected	Grade group ≥2 cancer detected
Overall (%)	900	284 (32%)	117 (13%)
PRI-MUS score (%)			
≤2	795	213 (27%)	80 (10%)
>2	105	71 (68%)	37 (35%)
3	25	16 (64%)	9 (36%)
4	43	24 (56%)	7 (16%)
5	37	31 (84%)	21 (57%)

PRI-MUS: Prostate Risk Identifica tion using Micro-Ultrasound.

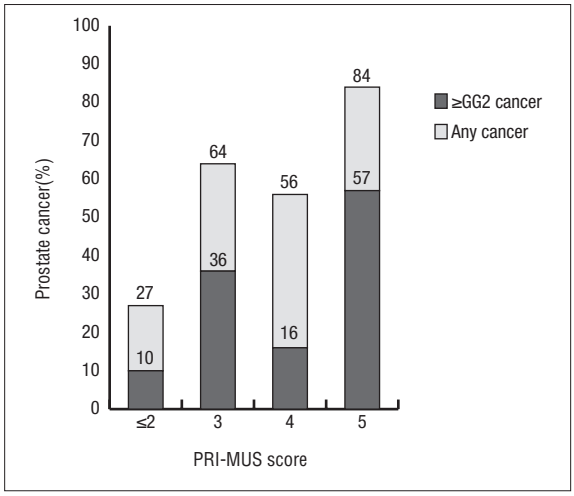

Figure 1. Cancer detection rates per core by micro-ultrasound (US)-informed systematic biopsies. Overall (light grey) and clinically significant (Gleason grade group [GG] ≥2; dark grey) prostate cancer detection rates per core stratified by prostate risk identification using micro-ultrasound scores (PRI-MUS) during microUS-informed systematic prostate biopsy.

taken within MRI-visible lesions per patient. A median of 12 (IQR 11–12) systematic cores were taken outside MRI-visible lesions. Seventy (93%) patients had an MRI-visible lesion that was PI-RADS ≥3. Sixty-six (88%) patients had a systematic biopsy core that was assigned as PRI-MUS ≥3. On a per-patient analysis, combined MRI/microUS fusion biopsy detected any prostate cancer in 84%, with a csPCa detection rate of 52% (Table 2).

On a per-biopsy core analysis, in total, 204 cores were taken from MRI-visible lesions, with any cancer detected in 54% of the cores and csPCa detected in 28% of the cores (Supplementary Table 1; available in the Appendix at *cuaj.ca*). In the microUS-informed systematic cores, any cancer was found in 32% of the cores, with csPCa detected in 13% of the cores (Table 3). Within 900 systematic biopsy cores, 105 cores were PRI-MUS ≥3, with 35% (37 cores) containing csPCa. The remaining 795 systematic biopsy cores were PRI-MUS ≤2, with 10% (80 cores) containing csPCa ($p<0.0001$) (Figure 1, Table 3). Systematic biopsy cores with a PRI-MUS 5 score had an overall cancer detection rate of 84%, with a csPCa rate of 57%.

Detection of csPCa varied by biopsy core type. Three (8%) patients were diagnosed by targeted biopsy only (within MRI-visible lesions). Fifteen (38%) patients were diagnosed by microUS-informed systematic biopsy only (outside of MRI-visible lesions), while the remaining 21 (54%) patients were diagnosed with csPCa by both targeted and systematic biopsies (Supplementary Table 2; available in the Appendix at *cuaj.ca*). Within the 15 patients that were diagnosed on microUS-informed systematic biopsy only, all had at least one systematic biopsy core graded PRI-MUS ≥3.

DISCUSSION

The present study shows that for microUS-informed systematic prostate biopsies taken outside of MRI-visible lesions, PRI-MUS ≥3 cores have a 3.5-fold increased risk of csPCa detection compared to PRI-MUS ≤2 cores. When broken down by biopsy core type, 8% of patients were diagnosed with csPCa on MRI-targeted biopsy only, 38% were diagnosed with microUS-informed

> “To reduce cost and morbidity associated with prostate biopsies, one could consider omitting biopsying lesions that are PRI-MUS ≤2, as the rate of csPCa is low.”

systematic biopsy only, and the remaining 54% were diagnosed with both biopsy techniques.

The detection of csPCa in this study using combined MRI/microUS fusion biopsy is higher than in previously published reports using MRI-targeted only or combined MRI and conventional ultrasound-guided systematic cores. In the PRECISION and MRI-FIRST trials, the rates of csPCa diagnosed in biopsy-naive men were 38% and 37%, respectively.[2,6] In this study, using MRI/microUS fusion prostate biopsy, we found a 52% csPCa detection rate in biopsy-naive men. Our data suggest that MRI can potentially miss 38% of csPCa, higher than the 25% previously shown in the literature.[1,7] It is possible that microUS improves the quality of 'blind' systematic biopsies, and contributes to the increased rate of csPCa detection observed in this study. In a recent prospective study, when comparing mpMRI and microUS-directed biopsies for detecting csPCa, mpMRI targeted biopsy detected 9% of csPCa cases missed by micro-US, whereas microUS targeted biopsy detected 6% of csPCa missed by mpMRI, and systematic biopsy detected 5% of csPCa that was missed by both targeted biopsy methods.[8] Furthermore, targeted microUS prostate biopsy was shown to be non-inferior to targeted biopsy by mpMRI. Taken together, our results suggest that microUS may be highly valuable for both targeted and systematic biopsies.

A goal of image-guided prostate biopsy is to minimize unnecessary biopsies, as well as any incidental detection of clinically insignificant prostate cancer. In this study, microUS-informed systematic cores assigned PRI-MUS ≤2 detected csPCa in only 10% compared to 35% in PRI-MUS ≥3 cores. No man with a PRI-MUS score of 5 would have been falsely negative for csPCa should PRI-MUS ≤2 cores be omitted from the systematic biopsy. Furthermore, only 9% of patients in the entire study would have been falsely negative for csPCa should all PRI-MUS ≤2 cores be omitted from the systematic biopsy. To reduce cost and morbidity associated with prostate biopsies, one could consider omitting biopsying lesions that are PRI-MUS ≤2, as the rate of csPCa is low. This combination of negative MRI and microUS may be an important diagnostic tool in determining risk of occult csPCa and when to perform biopsies during active surveillance. [9-11]

Limitations

The current study is limited by the retrospective design and lack of comparator using conventional ultrasound-guided systematic biopsies. These limitations will be addressed in the ongoing OPTIMUM randomized controlled trial, with its three-arm design comparing microUS, microUS/mpMRI, and US/mpMRI fusion biopsies.[12]

CONCLUSIONS

MicroUS-guided prostate biopsy could be a useful adjunct to MRI to help detect MRI-invisible csPCa, with PRI-MUS ≥3 biopsy cores having a 3.5-fold increased risk of csPCa compared to PRI-MUS ≤2 cores.

COMPETING INTERESTS: Dr. Fung is a shareholder in Mikata Health and is currently a councillor (elected physician member) for the College of Physicians and Surgeons of Alberta. Dr. Kinnaird has participated in a clinical trial supported by Exact Imaging (with no overlap with the current paper). The remaining authors do not report any competing personal or financial interests related to this work.

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REFERENCES

1. Lovegrove CE, Miah S, El-Shater Bosaily A, et al. Comparison of transrectal ultrasound biopsy to transperineal template mapping biopsies stratified by multiparametric magnetic resonance imaging score in the PROMIS trial. *J Urol* 2019;203:100-7. https://doi.org/10.1097/JU.0000000000000455
2. 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, multicenter, paired diagnostic study. *Lancet Oncol* 2019;20:100-9. https://doi.org/10.1016/S1470-2045(18)30569-2
3. Elkhoury FF, Felker ER, Kwan L, et al. Comparison of targeted vs. systematic prostate biopsy in men who are biopsy naive: The prospective assessment of image registration in the diagnosis of prostate cancer (PAIREDCAP) study. *JAMA Surg* 2019;154:811-8. https://doi.org/10.1001/jamasurg.2019.1734
4. Lughezzani G, Maffei D, Saita A, et al. Diagnostic accuracy of micro-ultrasound in patients with a suspicion of prostate cancer at magnetic resonance imaging: A single-institutional prospective study. *Eur Urol Focus* 2020;7:1019-26. https://doi.org/10.1016/j.euf.2020.09.013
5. 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. https://doi.org/10.1016/j.juro.2015.12.093
6. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;378:1767-77. https://doi.org/10.1056/NEJMoa1801993
7. Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *N Engl J Med* 2020;382:917-28. https://doi.org/10.1056/NEJMoa1910038
8. Hofbauer SL, Luger F, Harland N, et al. A non-inferiority comparative analysis of micro-ultrasonography and MRI-targeted biopsy in men at risk of prostate cancer. *BJU Int* 2022;129:648-54. https://doi.org/10.1111/bju.15635
9. Albers P, Wang B, Broomfield S, et al. Micro-ultrasound vs. magnetic resonance imaging in prostate cancer active surveillance. *Eur Urol Open Sci* 2022;46:33-5. https://doi.org/10.1016/j.euros.2022.09.019
10. Kinnaird A, Yerram NK, O'Connor L, et al. Magnetic resonance imaging-guided biopsy in active surveillance of prostate cancer. *J Urol* 2022;207:823-31. https://doi.org/10.1097/JU.0000000000002343
11. Kinnaird A, Sharma V, Chuang R, et al. Risk of prostate cancer after a negative magnetic resonance imaging-guided biopsy. *J Urol* 2020;204:1180-6. https://doi.org/10.1097/JU.0000000000001232
12. Klotz L, Andriole G, Cash H, et al. Optimization of prostate biopsy — micro-ultrasound vs. MRI (OPTIMUM): A 3-arm randomized controlled trial evaluating the role of 29 MHz micro-ultrasound in guiding prostate biopsy in men with clinical suspicion of prostate cancer. *Contemp Clin Trials* 2022;112:106618. https://doi.org/10.1016/j.cct.2021.106618

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