

**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-naïve 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

**KEY MESSAGES**

- Despite its 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  $\geq 3$  systematic cores have a 3.5-fold increased risk of csPCa compared to PRI-MUS  $\leq 2$  cores.

identification using micro-ultrasound (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  $\geq 3$  and 795 cores were PRI-MUS  $\leq 2$ . csPCa was detected in 35% of the PRI-MUS  $\geq 3$  cores compared to 10% of the PRI-MUS  $\leq 2$  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  $\geq 3$  systematic cores having a 3.5-fold increased risk of csPCa compared to PRI-MUS  $\leq 2$  cores.

## INTRODUCTION

New imaging technologies have improved our ability to detect clinically significant prostate cancer (csPCa, defined as Gleason Grade Group  $\geq 2$ ). 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.<sup>2,3,4</sup> High resolution micro-ultrasound (microUS) is an imaging technique that may visualize csPCa (potentially including some missed by MRI) in real-time during biopsy.<sup>5</sup> Therefore, combined MRI/microUS-guided fusion prostate biopsy may be a novel technique used to increase detection of csPCa. The objective of our study is to determine the detection rate of csPCa during microUS-informed systematic biopsy when used in combination with MRI-guided biopsy for biopsy-naïve men.

## METHODS

All biopsy-naïve 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) 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 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.<sup>1</sup> If the patient had a PI-RADS  $\geq 3$  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 include 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.  $\geq 3$ ). 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 3 (IQR 3-3) targeted cores were taken within MRI-visible lesions per patient. A median of 12 (IQR 11-12) systematic cores were taken outside MRI-visible lesions. 70 (93%) patients had an MRI-visible lesion that was PI-RADS  $\geq 3$ . 66 (88%) patients had a systematic biopsy core that was assigned as PRI-MUS  $\geq 3$ . 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 (supplemental table 1). 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  $\geq 3$ , with 35% (37 cores) containing csPCa. The remaining 795 systematic biopsy cores were PRI-MUS  $\leq 2$ , 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). 15 (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 (Supplemental table 2). Within the 15 patients that were diagnosed on microUS-informed systematic biopsy only, all had at least one systematic biopsy core graded PRI-MUS  $\geq 3$ .

## DISCUSSION

The present study shows that for microUS-informed systematic prostate biopsies taken outside of MRI-visible lesions, PRI-MUS  $\geq 3$  cores have a 3.5-fold increased risk of csPCa detection, compared to PRI-MUS  $\leq 2$  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 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.<sup>3,6</sup> 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.<sup>2,7</sup> 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 which was missed by both targeted biopsy methods.<sup>8</sup> 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  $\leq 2$  detected csPCa in only 10% compared to 35% in PRI-MUS  $\geq 3$  cores. No man with a PRI-MUS score of 5 would have been falsely negative for csPCa, should PRI-MUS  $\leq 2$  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  $\leq 2$  cores be omitted from the systematic biopsy. In order to reduce cost and morbidity associated with prostate biopsies, one could consider omitting biopsying lesions that are PRI-MUS  $\leq 2$ , 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.<sup>9,10,11</sup>

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.<sup>12</sup>

## **CONCLUSIONS**

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

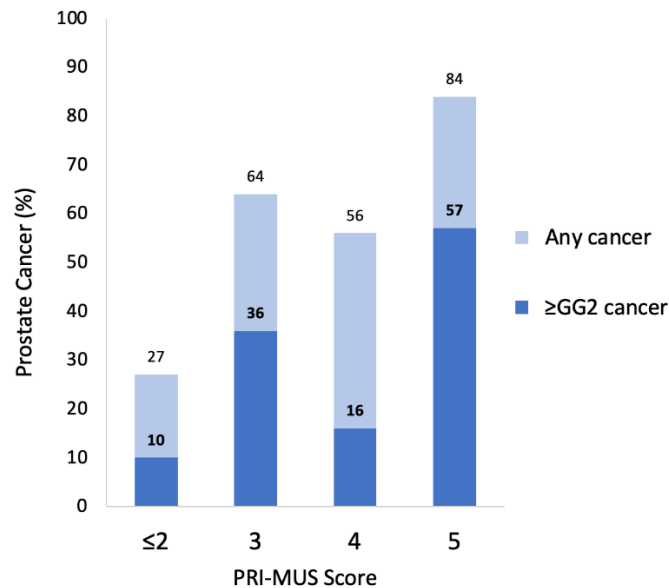
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## References

1. 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.
2. 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.
3. Rouvière O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019;20:100-9.
4. 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;154:811-8.
5. Lughezzani G, Maffei D, Saita A, et al. Diagnostic accuracy of microultrasound in patients with a suspicion of prostate cancer at magnetic resonance imaging: A single-institutional prospective study. *Eur Urol Focus* 2020;7:1019-26.
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.
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.
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.
9. Albers P, Wang B, Broomfield S, et al. Micro-ultrasound Versus Magnetic Resonance Imaging in Prostate Cancer Active Surveillance. *Eur Urol Open Sci* 2022;46:33-35.
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.
11. Kinnaird A, Sharma V, Chuang R, et al. Risk of Prostate Cancer after a Negative Magnetic Resonance Imaging Guided Biopsy. *J Urol* 2020;204:1180-86.
12. Klotz L, Andriole G, Cash H, et al. Optimization of prostate biopsy - Micro-Ultrasound versus 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.

## Figures and Tables

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



**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.



| <b>Table 2. Biopsy outcomes stratified by PI-RADS and PRI-MUS score</b> |          |                            |  |
|---|----------|----------------------------|--|
|   | <b>n</b> | <b>Any cancer detected</b> | <b>Grade group <math>\geq 2</math> cancer detected</b> |
| Overall (%)   | 75       | 63 (84%)                   | 39 (52%)   |
| PI-RADS score (%)   |          |                            |  |
| $\leq 2$  | 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 (%)   |          |                            |  |
| $\leq 2$  | 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.

| <b>Table 3. Cancer detection by core for micro-ultrasound in systematic biopsies</b> |                         |                            |  |
|--|-------------------------|----------------------------|--|
|  | <b># of cores taken</b> | <b>Any cancer detected</b> | <b>Grade group <math>\geq 2</math> cancer detected</b> |
| Overall (%)  | 900                     | 284 (32%)                  | 117 (13%)  |
| PRI-MUS score (%)  |                         |                            |  |
| $\leq 2$   | 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 identification using micro-ultrasound.