RE: Comparison of micro-ultrasound and multiparametric magnetic resonance imaging for prostate cancer, *CUAJ*, Jan 2021

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Dear Editor,

We read with great interest the recent article from Klotz and colleagues, in which they propose an alternative imaging modality to aid prostate cancer diagnosis. In their study, they report superior diagnostic performance of prostate micro-ultrasound as defined by greater sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV), over multiparametric magnetic resonance imaging (mpMRI).[1] We applaud the authors for this innovative and progressive trial, however, we feel that there are methodological considerations require attention, particularly, if future evaluations of this technology are planned.

Firstly, the impact of tumour location is not fully considered. Eure et al. have previously highlighted the phenomenon of ultrasound signal loss in the deeper anterior zone of the prostate.[2] This is particularly relevant when we consider that the PRI-MUS protocol (Prostate Risk Identification using Micro-Ultrasound) is limited to peripheral zone evaluation, only. However, Eure and colleagues have recently demonstrated that the ExactVu micro-ultrasound system was able to effectively visualise prostate tumours across all mpMRI zones, which provides promise for further updates of the PRI-MUS protocol in the detection of anterior zone cancers.[2] In future, it would be valuable to see validation of diagnostic accuracies of micro-ultrasound in deeper prostatic zones, through the provision of more detailed information on tumour location.

Next, it appears that inter-observer variation in the present study is potentially under-reported for both PI-RADS (Prostate Imaging-Reporting and Data System) and PRI-MUS scores. Previous work has suggested that despite the complexity of mpMRI interpretation, PI-RADSv2.0 enables decent interobserver agreement, with the lowest Kappa Cohen coefficient being 0.57 between readers. [3] Insight into the interobserver variation in this study would be interesting, particularly for PRI-MUS scoring, as there is a paucity of literature in this field, at present. Indeed, reassuring levels of inter-observer variation would be of paramount importance to help strengthen the introduction of micro-ultrasound for prostate cancer diagnosis.

Other limitations may pertain to the micro-ultrasound technique itself. Whilst micro-ultrasound offers potential convenience by combining both imaging risk stratification, and biopsy guidance in the same setting, the does therefore unfortunately reduce the opportunity for multi-disciplinary pre-biopsy discussion (for example, between radiologists and urologists for difficult/uncertain cases). This factor is particularly important if micro-ultrasound is suggested as a replacement for mpMRI, as opposed to being a useful adjunctive modality.

Overall, we believe that this important paper has contributed to the development of imaging-based risk-stratification for suspected prostate cancer. The high value of NPV associated with micro-ultrasound could potentially reduce the number of biopsies required, and we are excited to see the future of this novel technology. However, considerations regarding full anatomic visualisation and intimate, user-dependent technique accuracy are crucial and must be addressed directly in future clinical evaluation.

References

1. Klotz L, Lughezzani G, Maffei D, et al. Comparison of micro-ultrasound and multiparametric magnetic resonance imaging for prostate cancer: A multicenter, prospective analysis. *Can Urol Assoc J.* 2021;15(1):E11–6.
2. Eure G, Fanney D, Lin J, et al. Comparison of conventional transrectal ultrasound, magnetic resonance imaging, and micro-ultrasound for visualizing prostate cancer in an active surveillance population: A feasibility study. *Can. Urol. Assoc. J.* 2019;13(3): E70–77.
3. Popita, C. *et al.* Interobserver agreement in prostate cancer detection using multiparametric MRI. *J. BUON Off. J. Balk. Union Oncol.* 2018;23:1061–69.