PERSPECTIVE

Clinical Research

Prostatic high-resolution micro-ultrasound: an attractive step-forward in the management of prostate cancer patients

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Prostate Cancer and Prostatic Diseases; https://doi.org/10.1038/s41391-022-00611-9

Prostatic high resolution micro-ultrasound (MUS) was first described by Pavlovich et al. in 2014 [1]. Thanks to scanners operating at high frequency (29 MHz) and the resulting real-time spatial resolution up to 70 microns (near 300% higher than existing platforms) it allows to better evaluate the microstructures and tissue planes. Consequently, MUS is capable of highlighting the alterations of the prostatic histology that are typically associated with high-grade prostate cancer (PCa) such as loss of normal acinar lumen and tighter cellular packing. In 2016, Ghai et al. developed the Prostate Risk Identification using MUS (PRI-MUS), a 5-point grading system to stratify MUS images according to the risk of clinically significant PCa [2].

A number of potential benefits deriving from including MUS in the current management of patients with suspected PCa have been proposed. MUS can overcome some limitations of multi-parametric magnetic resonance imaging (mpMRI) such as availability, long procedural times, high costs, potential exclusion of patients with renal failure, pelvic prosthesis, claustrophobia or cardiac implants. Moreover, it can allow imaging and biopsy as a single procedure. Finally, it can represent a way to bring PCa imaging back to urology [3, 4]. However, despite the aforementioned premises and encouraging preliminary data, the supporting evidence is still limited.

A large-scale analysis from a prospective multicenter registry (1040 subjects at 11 sites in 7 countries) published in 2021 described sensitivity, specificity, positive and negative predictive values of MUS for clinically significant PCa [International Society of Urological Pathology (ISUP) Grade Group ≥ 2] of 94%, 22%, 44%, and 85%, respectively. Corresponding values for mpMRI were 90%, 22%, 43%, and 77%, respectively. *P* values (non-inferiority) were <0.001 for all parameters. Main limitations of this study included: incorporation of learning curves, variability in terms of biopsy protocols, exclusion of men with no previous mpMRI, lack of blinding with respect to mpMRI in most centers, lack of comparison to surgical pathology (gold standard) [3].

In the same year, Sountoulides et al. published the first meta-analysis comparing the detection rate of MUS vs. mpMRI imaging-targeted prostate biopsy (PB) [5]. Authors demonstrated similar detection rates between the techniques across all PCa grades. Overall detection rate for PCa was 0.99. In details, the pooled detection rates for ISUP 1, ISUP ≥ 2 and ISUP ≥ 3 PCa were 0.94, 1.05, and 1.25, respectively. Unfortunately, the strength of evidence was downgraded by the small number and not-randomized design of all included studies. In most cases data were collected retrospectively, broad eligibility criteria were applied across studies, in some cases operators were unblinded to the mpMRI findings at the time of MUS-guided PB. Finally, authors did not compare the detection rate of MUS-guided PB versus systematic TRUS-guided prostatic biopsy, the current standard recommended for all patients undergoing PB [6].

Of note, Rodríguez Socarrás et al. found that MUS sensitivity and negative predictive value to predict ISUP ≥ 2 PCa at the patient level were significantly higher than mpMRI (99.7 vs 84.3, and 99.2 vs 64.5, respectively) [4].

MUS has also been evaluated as a supplementary diagnostic tool for patients falling in the "grey zone" of PIRADS-3 lesions. In their single-institutional retrospective analysis on 111 consecutive patients with a PI-RADS 3 finding at mpMRI and scheduled for a PB, Avolio et al. aimed to assess whether MUS could help in sub-stratifying the risk of clinically significant PCa. Using MUS, the detection rate for clinically significant PCa would have remained 100%, while reducing the detection of insignificant PCa to 23.8%. Accuracy of these results were limited by small sample size. Moreover, the generalizability of findings was hampered by the very small number of urologists performing it [7].

Preliminary evidence exists hypothesizing a potential staging role for MUS. In 2022 Fasulo et al. published an exploratory retrospectively study evaluating the accuracy of MUS in predicting extraprostatic extension (EPE) in 140 patients scheduled for robot-assisted radical prostatectomy. Authors reported sensitivity, specificity, negative and positive predictive values of 72.1%, 88%, 80.5% and 83.0%, respectively. The most informative predictor of EPE was the presence of a visible capsular breach at MUS. Main limitations of the study were the small sample size, and risk of not generalizability of results due to the fact that procedures were performed at a highly specialized tertiary care center by the most experienced MUS practitioners [8].

Results from the 3-arm multicenter RCT OPTIMUM are awaited to determine whether MUS alone is non-inferior to MRI/ultrasound fusion with respect to the diagnosis of clinically significant PCa

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Received: 6 October 2022 Revised: 18 October 2022 Accepted: 31 October 2022
Published online: 12 December 2022

and whether the MRI/MUS "contour-less" fusion biopsy is a reliable alternative to MRI/ultrasound fusion biopsy [9].

Other potential fields of application of MUS deserve investigations. Results from the NCT05326282 trial will shed light on the potential role of MUS in the assessment and monitoring of localized PCa in men under active surveillance.

Although the skills to perform an ultrasound examination are widely diffused in the urological and radiological community, and the execution and interpretation of the MUS could be simpler than the mpMRI, interobserver agreement for PRI-MUS scoring is still under investigation. Preliminary data about the learning curve for MUS suggests that expert sensitivity is achieved within the first 20–40 cases, while expert specificity generally takes 40–90 cases to develop [10]. However, it should be noted that MUS is an operator-dependent technique and this could limit its reliability in the clinical practice. Furthermore, impact of tumor location on MUS performances is under debate as some authors have highlighted the possible phenomenon of ultrasound signal loss in the deeper anterior zone of the prostate, mainly in patients with large prostates [3, 9, 10].

In conclusion, MUS could represent an attractive step-forward in the management of PCa as a supplementary or alternative tool compared to mpMRI. However, evidence is still preliminary and their strength suboptimal to provide clear recommendations in everyday clinical practice.

DATA AVAILABILITY

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Pavlovich CP, Cornish TC, Mullins JK, Fradin J, Mettee LZ, Connor JT, et al. High-resolution transrectal ultrasound: pilot study of a novel technique for imaging clinically localized prostate cancer. Urol Oncol. 2014;32:34.e27–32. https://doi.org/10.1016/j.urolonc.2013.01.006
2. Ghai S, Eure G, Fradet V, Hyndman ME, McGrath T, Wodlinger B, 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
3. Klotz L, Lughezzani G, Maffei D, Sánchez A, Pereira JG, Staerman F, et al. Comparison of micro-ultrasound and multiparametric magnetic resonance imaging for prostate cancer: a multicenter, prospective analysis. Can Urol Assoc J. 2021;15:E11–E16. https://doi.org/10.5489/cuaj.6712.
4. Rodríguez Socarrás ME, Gomez Rivas J, Cuadros Rivera V, Reinoso Elbers J, Llanes González L, Michel Mercado I, et al. Prostate mapping for cancer diagnosis: the madrid protocol. transperineal prostate biopsies using multiparametric magnetic resonance imaging fusion and micro-ultrasound guided biopsies. J Urol. 2020;204:726–33. https://doi.org/10.1097/JU.0000000000001083.
5. Sountoulides P, Pyrgidis N, Polyzos SA, Mykoniatis I, Asouhidou E, Papatsoris A, et al. Micro-ultrasound-guided vs multiparametric magnetic resonance imaging-targeted biopsy in the detection of prostate cancer: a systematic review and meta-analysis. J Urol 2021;205:1254–62. https://doi.org/10.1097/JU.0000000000001639
6. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU guidelines on prostate cancer. Paper presented at the EAU annual congress, Amsterdam 2022. ISBN 978-94-92671-16-5.
7. Avolio PP, Lughezzani G, Paciotti M, Maffei D, Uleri A, Frego N, et al. The use of 29 MHz transrectal micro-ultrasound to stratify the prostate cancer risk in patients with PI-RADS III lesions at multiparametric MRI: a single institutional analysis. Urol Oncol. 2021;39:832.e1–832.e7. https://doi.org/10.1016/j.urolonc.2021.05.030.
8. Fasulo V, Buffi NM, Regis F, Paciotti M, Persico F, Maffei D, et al. Use of high-resolution micro-ultrasound to predict extraprostatic extension of prostate cancer prior to surgery: a prospective single-institutional study. World J Urol 2022;40:435–42. https://doi.org/10.1007/s00345-021-03890-4
9. Klotz L, Andriole G, Cash H, Cooperberg M, Crawford ED, Emberton M, 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 https://doi.org/10.1016/j.cct.2021.106618.
10. Cash H, Hofbauer S, Shore N, Pavlovich CP, Bulang S, Schostak M, et al. Prostate cancer detection by novice micro-ultrasound users enrolled in a training program. Soc Int Urol J. 2022;3:62–8. https://siuj.org/index.php/siuj/article/view/172. Accessed 18 Oct 2022.

AUTHOR CONTRIBUTIONS

FF and MC: conceptualization and supervision, MH, CDN, CM and DA: writing.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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