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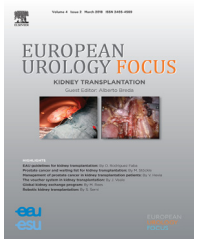

Review – Prostate Cancer

Can high resolution micro-ultrasound replace MRI in the diagnosis of prostate cancer?

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Article info

Article history:
Accepted November 3, 2019

Keywords:
Prostate cancer
Prostate ultrasound
High resolution micro ultrasound
Prostate imaging

Abstract

High resolution micro-ultrasound (micro-u/s) is a novel technology that permits visualization of lesions suspicious for prostate cancer. The resolution of 70 μ, that of a prostatic duct, means that alterations in ductal anatomy and cellular density are readily apparent. Initial experience in multiple centers comparing it to mpMRI suggests that the sensitivity for clinically significant prostate cancer is comparable or superior. Specificity is comparable or mildly reduced. Micro-u/s is an inexpensive, accessible and convenient alternative to mpMRI for imaging and diagnosing prostate cancer.

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Introduction

Multiparametric MRI has made dramatic inroads into the management of localized prostate cancer over the last 5 years. In particular, it has been widely incorporated into the diagnostic algorithm for men at risk for prostate cancer, and into the management of men with favorable risk disease on surveillance. International guidelines are increasingly promoting the use of MRI prior to biopsy. This represents a sea change in the management of localized prostate cancer, which historically has been guided by biopsy histology and not image guided.

Enthusiasm for MRI has reflected the fact that conventional ultrasound-based systematic transrectal biopsy has many limitations. Systematic biopsies are 'blind', and results reflect the vagaries of sampling. In about one third of men with known low grade prostate cancer, a subsequent biopsy is negative [1–3]. More importantly, co-existent higher grade cancer is missed in about a third of cases. This high false-negative rate highlights the insensitivity of the systematic biopsy procedure, which often results in men with aggressive disease being misattributed and encouraged to be managed conservatively instead of receiving appropriate treatment.

MpMRI represents a major advance in accurate imaging and targeting of prostate cancer. Multiple recent studies, including Precision [4], 4 M [5], MRI-FIRST [6], and PROMIS [7], a Cochrane analysis [8], and a recent meta-analysis [9], have confirmed the superiority of a targeted approach to systematic biopsies. However the diagnostic approach of MRI and targeted biopsies, has limitations. The technology is considerably more expensive than ultrasound. Accurate interpretation of the images requires a high degree of training. The Kappa for interobserver agreement between uro-radiologists is 0.55-0.80 [10]. There are numerous pitfalls of image interpretation and confounders including

https://doi.org/10.1016/j.euf.2019.11.006

prostatitis, BPH, and fibrosis [11]. MRI often occurs in the post-biopsy setting with a high burden of artefacts (hemorrhage, capsular irregularity). During biopsy, patient movement, prostate deformation by the US probe, and mismatch of image planes can lead to targeting error $>$ 4 mm. This is aggravated by MRI underestimation of the tumour volume compared with final pathology. Lesion targeting by needle guidance is highly dependent on dimensions of the primary lesion, numbers of relevant lesions, localization, and overall prostate volume. The result is aiming off the mark. Different technical fusion approaches provide different degrees of manual/automated adjustment tools. Targeted biopsy using a fusion targeted device has a considerable learning curve. The consequence is that MRI misses up to 23% (meta-analysis mean 12%) of GG $\geq$ 2 lesions. [12,13]. Other drawbacks to the utility of mpMRI include significant capital and operational costs, workflow complexity, reliance on expert radiological resources, patient inconvenience due to the necessity of two or more visits/procedures, and lack of MRI access. It therefore cannot yet be recommended as a replacement for systematic biopsy.

1. *Benefits of micro-ultrasound*

High resolution 29 MHz micro-u/s, a novel imaging modality, aims to improve the diagnostic accuracy of prostate biopsy while maintaining the affordability and convenience of ultrasound. This technical advance is based on two differences with conventional ultrasound: a 29 MHz system compared to 9-12 MHZ for conventional urologic ultrasound; and fabrication techniques allowing 4-fold higher crystal density along the transducer (512 vs 128 crystals). This results in dramatically improved resolution and allows for deep penetration. The resolution of this system is 70 microns, which is the diameter of a typical prostatic duct. Conventional ultrasound has a resolution of 200 microns or more. While some prostate cancers are visualized as a hypoechoic lesion at low resolution, the sensitivity is limited. The high resolution of the micro-u/s system allows visualization of the ductal anatomy and cellular density. Alteration of the ductal anatomy and cell density permits appreciation of additional tissue patterns related to prostate cancer resulting in improved sensitivity [14].

The first generation of this device, the ExactVu 29 MHz system (Exact Imaging, Toronto Canada) was initially evaluated in a pilot study in 2013 in a radical prostatectomy series [15]. It showed significantly improved accuracy in detecting foci of cancer compared to conventional ultrasound. Subsequently the '***Prostate Risk Identification using Micro-Ulltrasound***' (PRIMUS) grading system, analogous to PiRADS, was proposed to allow for more consistent interpretation of prostate images [14] (Fig. 1 and Table 1). This was followed by a randomized multicenter trial comparing micro-u/s to conventional ultrasound. There was a 19% improvement in the detection of clinically significant prostate cancer [16]. The second generation system was released in 2017 and incorporated further improvements in image quality and ergonomics. There are now reports from 13 groups totaling 1,644 cases Europe, the United States, and Canada. The current system has the capability of real-time orientation tracking of the imaging plane, allowing for longitudinal comparison of lesions, as well as MRI image fusion.

Results to Date

The critical question is, how does the sensitivity and specificity of high resolution u/s compare to MRI? There are 7 studies to date which compare the performance of these 2 modalities. Inclusion criteria were similar for 5 of the 7 studies. Patients in these 5 studies all had suspected prostate cancer based on an elevated PSA and/or abnormal DRE [18,20–23]. All men underwent an mpMRI. The patients were then biopsied using micro-u/s targeting, blinded to the MRI. Following this, results of the mpMRI were made available, and these targets were biopsied using cognitive fusion techniques. The other studies were in men on active surveillance with GG1 disease [17] or men with a documented positive MRI [19].

The results are striking and consistent. All 7 studies demonstrated comparable sensitivity of micro-u/s to mpMRI for GG $\geq$ 2 PC (Table 2). Several showed superior sensitivity compared to mpMRI [18,20]. In one study of 79 men, micro-u/s had a sensitivity of 98% vs 72% with mpMRI (95% CI, $p < 0.001$). Specificity micro-u/s was 40%, compared to 91% with mpMRI.

The Lughezzani study included 104 patients with at least one region of interest on MRI (Pirads $>$2) [19]. Micro-US sensitivity for GG $\geq$ 2 PC detection was 94%.

The sensitivity, specificity, NPV, and PPV for GG $\geq$ 2 Pca was 94%, 28%, 90%, and 40%. Discordant targeted lesions led to GG $\geq$ 2 PCa by micro-US in three cases and mpMRI in four cases. Both techniques missed one case found on systematic biopsy.

Micro-u/s is a new technology, and the data is preliminary. The studies are small, some were presented in abstract form and are still unpublished, and there is substantial heterogeneity between studies in terms of inclusion criteria. This stands in sharp contrast to the mpMRI data, which consists of multiple large randomized and prospective studies, and has now reached level 1 evidence. Nonetheless, this technology has a number of potential benefits over MRI including lower relative technology costs, convenience for the patient (one diagnostic test done contemporaneously with the biopsy), accessibility, ease of use, and fewer contraindications. The fact that a biopsy needle can be directed into a visible lesion, rather than relying on accurate MRI image fusion and targeting, is a major advantage and removes a substantial source of error. Based on the 5 studies summarized above, the sensitivity appears comparable to MRI. Validation is still required. However, based on this data, it is very plausible that, in a patient at intermediate risk for prostate cancer, a negative micro ultrasound would sufficiently lower the patient's risk of significant cancer so as to render both MRI and systematic biopsies unnecessary.

Like traditional ultrasound, micro-u/s and PRI-MUS grading seem to have a shorter learning curve than the MRI -based technique. This impression is mostly anecdotal; one abstract has reported a learning curve of 15 cases based

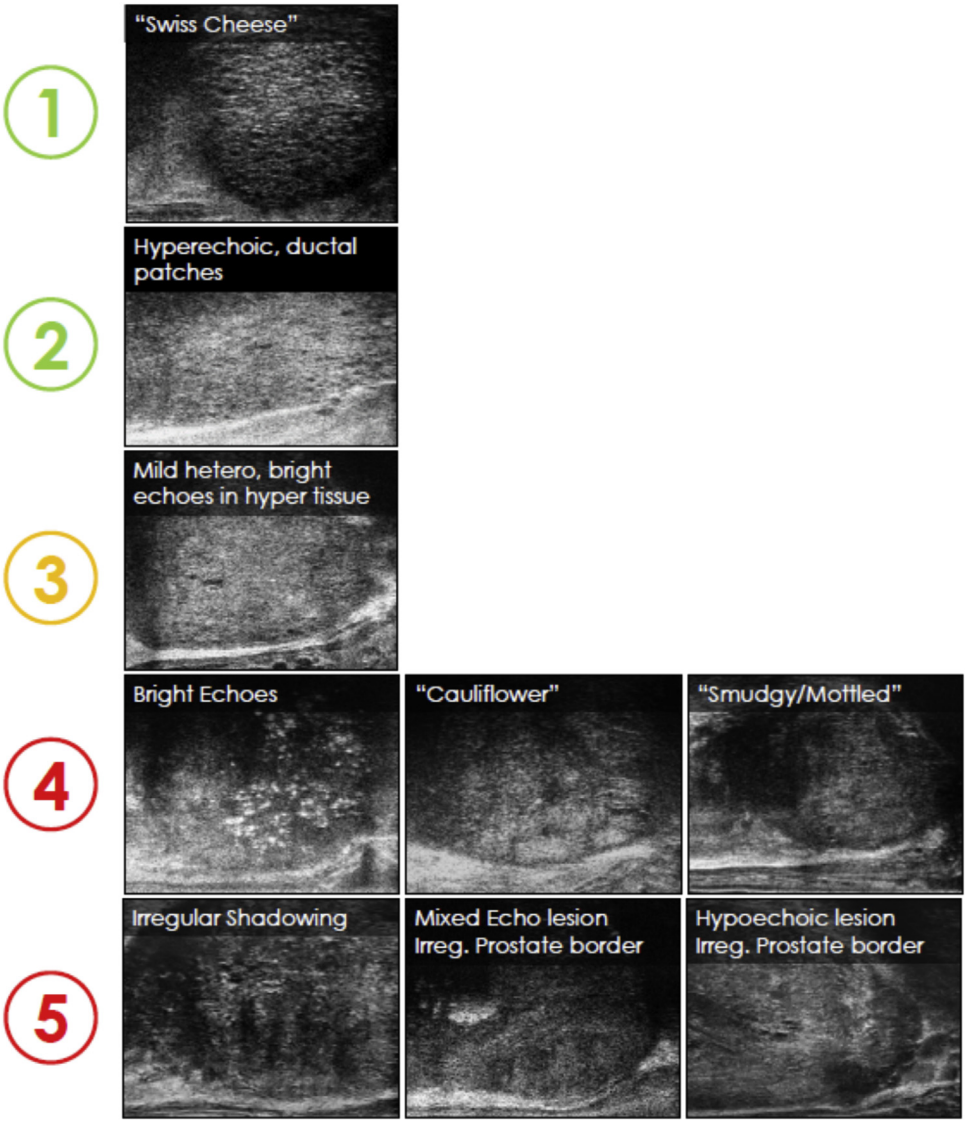

Fig. 1 – Examples of PRIMUS grades.

Table 1 – Prostate risk identification for Micro-U/S (PRIMUS) criteria [14].

Grade	Characteristics	Relative risk for cancer
1	Small regular ducts, "Swiss cheese"	0.28
2	Hyperechoic with or without ductal patches	0.49
3	Bright echoes in hyperechoic tissue	1.2
4	Heterogeneous cauliflower/smudgy/mottled appearance Bright echoes ('starry sky' appearance)	1.5
5	Irregular peripheral zone border Mixed echo lesions, Irregular shadowing	2.0

Table 2 – List of studies comparing MRI with Micro-Ultrasound.

Study	Year	N	Population	Result
Eure et al [17]	2018	9	Active Surveillance	8/9 lesions found by micro-ultrasound. 5/9 found by MRI
Astobieta et al [18]	2018	79	All prostate biopsy	98% Sensitive vs. 68% MRI
Staerman [20]	2018	87	All prostate biopsy	Micro-ultrasound more sensitive than mpMRI (82% vs 76%)
Lughezzani G et al [19]	2019	179	MRI positive	91% relative sensitivity to MRI
Lopez [21]	2019	22	All prostate biopsy	100% sensitivity by micro-ultrasound for csPCa
Perez [22]	2019	43	All prostate biopsy	Highly concordant with mpMRI, equal sensitivity
Abouassaly [23]	2019	67 (19 MRI)	All prostate biopsy	20% of cancers detected by micro-ultrasound targets rather than MRI targets

on an ROC analysis [24]. Targeted biopsies with micro-u/s can be performed by a urologist in an outpatient setting. Once learned, the procedure requires approximately an additional 5 minutes for target identification compared to conventional TRUS biopsy.

As with MRI, some significant cancers may not be visible. In the high risk patient, systematic biopsies are warranted even in the absence of a region of interest on micro u/s, and systematic as well as targeted biopsies are appropriate in this setting.

MRI and micro u/s may be complementary in some patients. Both approaches identify lesions missed by the other imaging modality. Further research into the marginal utility of each modality is warranted.

Conclusion

Micro U/S is a less expensive, accessible and convenient alternative to mpMRI for imaging and diagnosing prostate cancer. Based on preliminary data, it has comparable and sensitivity; the specificity appears to be somewhat less, likely depending on user experience. It represents an appealing approach to men at risk for prostate cancer, and has the potential to solve many of the problems of access, lack of expertise, learning curve of fusion targeted biopsies, and cost associated with an 'MRI first' approach. In high risk or complex patients the two modalities are likely complementary. Conversely, in the common scenario of a patient with a moderate risk of prostate cancer based on PSA and other risk factors, micro-u/s with targeted biopsies if a region of interest is identified is a compelling approach with advantages of cost, availability, convenience, fewer sources of error, and a short learning curve. Further studies will be required to validate this promising technology.

Conflicts of interest

The author has received clinical research funding from Exact Imaging Inc.

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