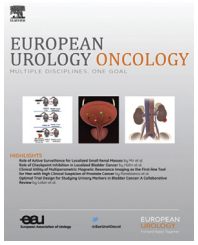
EUROPEAN UROLOGY ONCOLOGY XXX (2018) XXX–XXX

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com



European Association of Urology

Comparison of the Diagnostic Accuracy of Micro-ultrasound and Magnetic Resonance Imaging/Ultrasound Fusion Targeted Biopsies for the Diagnosis of Clinically Significant Prostate Cancer

Giovanni Lughezzani *, *Alberto Saita*, *Massimo Lazzeri*, *Marco Paciotti*, *Davide Maffei*, *Giuliana Lista*, *Rodolfo Hurle*, *Nicolò Maria Buffi*, *Giorgio Guazzoni*, *Paolo Casale*

Department of Urology, Humanitas Clinical and Research Center IRCCS, Rozzano, Italy

Article info

Article history:
Accepted October 1, 2018

Associate Editor:
Gianluca Giannarini

Keywords:
Prostate cancer
Diagnosis
Prostate biopsy
Multiparametric magnetic resonance imaging
Micro-ultrasound

Abstract

Multiparametric magnetic resonance imaging (mpMRI) and MRI/ultrasound (US) fusion targeted biopsies are an increasingly popular alternative to randomized biopsies, but adoption of this technique has been limited owing to its additional costs and complexity. High-resolution micro-ultrasound (micro-US) is a real-time US-based imaging modality that allows real-time targeted prostate biopsies using the Prostate Risk Identification Using Micro-Ultrasound risk identification protocol. We compared the diagnostic accuracy of micro-US targeted biopsies (index test) and MRI/US fusion targeted biopsies (reference standard test) in detecting clinically significant prostate cancer (csPC), defined as Gleason $\geq$7 disease, in a prospectively collected cohort of 104 patients with suspected PC defined according to prostate-specific antigen, digital rectal examination, and the presence of at least one Prostate Imaging-Reporting and Data System $\geq$3 lesion at mpMRI. PC was diagnosed in 56 patients (54%) and csPC in 35 (34%). Micro-US sensitivity for csPC detection was 94%, with 33/35 csPC cases correctly identified. The negative predictive value was 90%, while the positive predictive value was 40% and the specificity was 28%. Of the 61 targeted zones concordant between micro-US and mpMRI, 24 were csPC. Discordant targeted lesions led to csPC discovery by micro-US in three cases and mpMRI in four cases. Both techniques missed one case for which csPC was diagnosed by systematic biopsies only.

Patient summary: According to the results of our preliminary trial, micro-ultrasound may provide additional information regarding the presence or absence of clinically significant prostate cancer (PC) in patients with suspected PC. Further studies are warranted to investigate how this new imaging modality can best be leveraged within the PC diagnostic pathway.

* Corresponding author. Department of Urology, Humanitas Clinical and Research Center IRCCS, Via A. Manzoni 56, 20089, Rozzano (Milan), Italy. Tel.: +39 02 82247356.
E-mail address: giovanni.lughezzani@humanitas.it (G. Lughezzani).

https://doi.org/10.1016/j.euo.2018.10.001
2588-9311/

Please cite this article in press as: Lughezzani G, et al. Comparison of the Diagnostic Accuracy of Micro-ultrasound and Magnetic Resonance Imaging/Ultrasound Fusion Targeted Biopsies for the Diagnosis of Clinically Significant Prostate Cancer. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.10.001

Prostate cancer (PC) is the most frequently diagnosed cancer among men, and the second-ranked cause of cancer mortality [1]. The current standard of care involves prostate-specific antigen (PSA) screening and transrectal ultrasound (TRUS)-guided biopsy with 10–12 cores systematically taken per patient [2]. Unfortunately, this diagnostic pathway using conventional US guidance is insufficient because of its low sensitivity and specificity, resulting in both overdiagnosis of clinically insignificant PC and underdiagnosis because of a large proportion of false negative results.

Multiparametric magnetic resonance imaging (mpMRI) and MRI/US fusion targeted biopsies are currently recommended in the European Association of Urology guidelines as the standard diagnostic tool in patients with a prior negative biopsy and a persistent clinical suspicion of PC [2]. Recent evidence has convincingly shown that mpMRI-targeted biopsies may be a beneficial replacement for systematic biopsies, even in the first biopsy setting [3]. However, the applicability of mpMRI as a triage test in patients with a clinical suspicion of PC has been questioned because of resource consumption, procedural complexity, reproducibility, and cost considerations [4–6]. Moreover, a certain proportion of patients cannot undergo MRI for a number of reasons. As a consequence, significant efforts have been made to find alternative diagnostic strategies, such as computerized-supported TRUS, prostate-specific membrane antigen positron emission tomography/computed tomography, and micro-US [7–9].

Micro-US is a new imaging modality that operates at high frequency (29 MHz). The resulting images have a resolution of up to 70 μm and allow use of the Prostate Risk Identification Using Micro-Ultrasound (PRI-MUS) protocol to characterize, stratify, and target suspicious regions, similar to the Prostate Imaging-Reporting and Data System (PI-RADS) protocol for mpMRI [10]. The objective of the current study was to determine the diagnostic accuracy of micro-US in the detection of clinically significant PC (csPC).

Between October 2017 and March 2018, 104 consecutive patients with a clinical suspicion of PC defined according to PSA values, digital rectal examination results, and the presence of at least one PI-RADS $\geq$3 lesion on mpMRI were enrolled in a prospective single-institutional clinical trial (ICH 003 v1.0 27/09/2017; study number 2004). All procedures were approved by the local ethics board and all subjects provided informed consent. All patients underwent micro-US targeted biopsies performed by a urologist with extensive TRUS biopsy experience who was blinded to the mpMRI results, followed by MRI/US fusion targeted biopsies and 12-core systematic biopsies performed by another experienced urologist in the same biopsy session. The presence of csPC, defined as at least one biopsy core with Gleason $\geq$7 disease, was the outcome of interest. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated per subject per modality based on the targets (PRI-MUS or PI-RADS $\geq$3) from micro-US or mpMRI using the underlying pathology results from any biopsy sample from the patient as reference.

Descriptive characteristics for the study population are shown in Table 1. There were more lesions identified by mpMRI (138 vs 117 found by micro-US) because of the study design, as all subjects included had at least one PI-RADS $\geq$3 lesion. The majority of subjects had a PI-RADS 4 lesion (58%). Micro-US identified lesions in 83/104 (80%) subjects, with the majority having a PRI-MUS score 4 lesion (58%).

The diagnostic performance of mpMRI and micro-US targeted biopsies is summarized in Figure 1. Overall, PC was diagnosed in 56/104 individuals (54%, 95% confidence interval [CI] 44–63%) and csPC in 35/104 (34%, 95% CI 25–43%). Micro-US did not identify any suspicious lesion in 21/104 patients (20%, 95% CI 14–29%). Of those, 13 showed negative histology in both targeted and systematic biopsies, six were diagnosed with clinically insignificant PC, and two were diagnosed with csPC. On a per-patient basis, micro-US had sensitivity of 94% (95% CI 81–98%) and specificity of 28% (95% CI 18–39%) in predicting csPC, while the NPV was 90% (95% CI 70–97%). Sensitivity, specificity, and NPV values for mpMRI could not be determined as only mpMRI-positive subjects were included. The PPV was 40% (95% CI 30–51%) for micro-US and 34% (95% CI 25–43%) for mpMRI.

mpMRI targeted a total of 138 lesions, with PC present in 45/138 (33%). Of those, 13 lesions (9%) harbored clinically insignificant PC and 32 (23%) harbored csPC. Similarly, micro-US targeted 117 lesions in 83/104 subjects (80%). PC was present in 39/117 lesions (33%). Of those, six (5%) were clinically insignificant and 33 (28%) were csPC. Micro-US was concordant with mpMRI in 61/136 (45%) targeted regions (in two cases multiple lesions were targeted within the same anatomic region). Of these concordant lesions, 33 (54%) were benign, four (7%) were clinically insignificant PC, and 24 (39%) were csPC. Across all 104 subjects, there were 75 nonconcordant targeted zones identified by mpMRI without a matching micro-US lesion, and 55 nonconcordant targeted zones identified by micro-US without a matching mpMRI lesion. Of the 55 nonconcordant lesions found by micro-US, 9/55 (16%) were csPC and 2/55 (4%) were clinically insignificant PC. mpMRI found 8/75 (11%) nonconcordant lesions with csPC, of which two cases had csPC not identified by micro-US. Interestingly, both of these lesions were located in the transitional zone of the prostate. Finally, both mpMRI and micro-US missed one case for which csPC was diagnosed by systematic biopsies only. Details on how concordance between the modalities was determined are presented in the Supplementary material.

According to our preliminary experience in patients with suspected PC and positive mpMRI, micro-US appears to achieve high sensitivity and a high NPV in determining the presence of csPC, while its specificity and PPV were lower, which may be attributable in part to the initial phase of the learning curve. In the current population, the risk of csPC was 34% (95% CI 25–43%), but the risk of csPC among men with a negative micro-US was 9.5% (95% CI 3–29%), suggesting that negative micro-US represents a 72% lower risk of csPC ($p = 0.013$), missing only two cases of csPC. As a consequence, while further studies are needed to provide more evidence supporting its use in the PC diagnostic pathway, we believe that micro-US may represent a

Please cite this article in press as: Lughezzani G, et al. Comparison of the Diagnostic Accuracy of Micro-ultrasound and Magnetic Resonance Imaging/Ultrasound Fusion Targeted Biopsies for the Diagnosis of Clinically Significant Prostate Cancer. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.10.001

Table 1 – Descriptive characteristics for the study population.

	Overall	Patients without csPC	Patients with csPC	*p* value
Patients, *n* (%)	104	69 (66)	35 (34)	
Mean age, yr (range)	64.5 (46–78)	64.4 (46–78)	64.7 (51–75)	0.866
Mean total PSA, ng/ml (range)	7.9 (0.65–20.9)	8.1 (0.65–20.1)	7.4 (1.87–20.9)	0.341
Positive DRE, *n* (%)	20 (19)	9 (13)	11 (31)	0.037
Prior prostate biopsy, *n* (%)	62 (60)	45 (65)	17 (49)	0.105
Negative	37 (36)	28 (41)	9 (26)	0.138
Positive	25 (24)	17 (25)	8 (23)	0.845
Mean prostate volume, ml (range)	61.2 (18–178.5)	67.9 (18–178.5)	46.8 (18.9–99.0)	0.003
Biopsy cores, *n* (%)	1210	809	401	0.904
Random	735 (61)	481 (59)	254 (63)	0.712
Targeted	477 (39)	330 (41)	147 (37)	0.352
Targeted MRI lesions (*n*)	138	101	37	<0.001
Mean, *n* (range)	1.3 (1–3)	(1–3)	1.1 (1–2)	
PI-RADS score, *n* (%)				0.418
Not provided	3 (3)	2 (3)	1 (3)	
3	25 (24)	18 (26)	7 (20)	
4	61 (58)	41 (59)	20 (57)	
5	16 (15)	9 (13)	7 (20)	
Subjects identified with at least one micro-US lesion, *n* (%)	83 (80)	50 (72)	33 (94)	0.009
Targeted micro-US lesions (*n*)	117	72	45	0.090
Mean, *n* (range)	1.1 (0–3)	1.0 (0–3)	1.4 (1–3)	
PRI-MUS score, *n* (%)				0.003
1–2	21 (20)	19 (28)	2 (6)	
3	9 (9)	7 (10)	2 (6)	
4	48 (46)	30 (43)	18 (51)	
5	26 (25)	13 (19)	13 (37)	

csPC = clinically significant prostate cancer; PSA = prostate-specific antigen; DRE = digital rectal examination; MRI = magnetic resonance imaging; PI-RADS Prostate Imaging-Reporting and Data System; PRI-MUS = Prostate Risk Identification Using Micro-ultrasound.

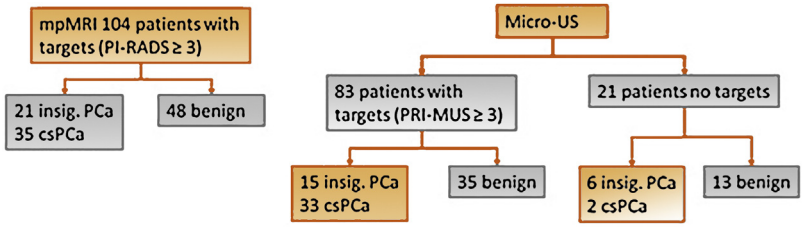


Fig. 1 – Diagnostic performance of multiparametric magnetic resonance imaging (mpMRI) and micro-ultrasound (micro-US) in the diagnosis of clinically insignificant (Gleason 6) and clinically significant (Gleason ≥7) prostate cancer.

potentially cost-effective and easy-to-learn imaging technique for effective "real-time" targeting of prostatic lesions (see the example in Supplementary Fig. 1).

Several limitations of the current study should be noted. First, since the study only included patients with positive mpMRI, we could not perform a head-to-head comparison of the two imaging techniques. Specifically, this limits the possible sensitivity of micro-US to at most equal that of mpMRI and does not allow comparison of the specificity. In addition, the fact that only patients with a potential cancerous lesion on mpMRI were included may have affected the micro-US interpretation. Second, the limited sample size in our preliminary study prevented us from determining independent predictors of csPC in multivariable models. Third, our definition of csPC is not universal. While many definitions exist, to keep our analysis as simple as possible we only presented a single definition consistent with the third (and simplest) definition from PROMIS [4]. Finally, given the low number of cases, we could not address the impact of tumor location and prostate size on the micro-US diagnostic performance, as lesions in the transitional zone and/or within large prostates may be more difficult to diagnose using this imaging modality.

Author contributions: Giovanni Lughezzani had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lughezzani, Saita, Lazzeri.
Acquisition of data: Paciotti, Maffei, Lista.
Analysis and interpretation of data: Lughezzani.
Drafting of the manuscript: Lughezzani.
Critical revision of the manuscript for important intellectual content: Saita, Lazzeri, Hurle, Buffi, Guazzoni, Casale.
Statistical analysis: Lughezzani.

Please cite this article in press as: Lughezzani G, et al. Comparison of the Diagnostic Accuracy of Micro-ultrasound and Magnetic Resonance Imaging/Ultrasound Fusion Targeted Biopsies for the Diagnosis of Clinically Significant Prostate Cancer. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.10.001

Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Guazzoni, Casale.
Other: None.

Financial disclosures: Giovanni Lughezzani certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2018.10.001.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
[2] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–29.
[3] 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.
[4] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.
[5] Walz J. The "PROMIS" of magnetic resonance imaging cost effectiveness in prostate cancer diagnosis? Eur Urol 2018;73:31–2.
[6] Lughezzani G, Buffi NM, Lazzeri M. Diagnostic pathway of patients with a clinical suspicion of prostate cancer: does one size fit all? Eur Urol 2018;74:400–1.
[7] Tokas T, Grabski B, Paul U, Baurle L, Loch T. A 12-year follow-up of ANNA/C-TRUS image-targeted biopsies in patients suspicious for prostate cancer. World J Urol 2018;36:699–704.
[8] Lopci E, Saita A, Lazzeri M, et al. ^{68}Ga-PSMA PET/CT for primary diagnosis of prostate cancer in men with contraindications to or negative mpMRI: a prospective observational study. J Urol 2018;199(4 Suppl):e155.
[9] Pavlovich CP, Cornish TC, Mullins JK, 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.
[10] 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.

Supplementary Fig. 1 – Micro-ultrasound image of a PRI-MUS 5 lesion (suspicious mixed-echo lesion). Orange arrows indicate previous biopsy needle tracks that missed the lesion. The targeted cores showed a Gleason score 4 + 3 cancer, which was confirmed at final pathology.