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Diagnostic accuracy and clinical utility of micro-ultrasound guided biopsies in patients with suspected prostate cancer

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Introduction New technologies to improve quality of prostate biopsies are appearing in clinical practice. We evaluate the performance of a micro-ultrasound device and the Prostate Risk Identification using MicroUltraSound (PRI-MUS) score in detecting clinically significant prostate cancer (csPCa).

Material and methods We retrospectively reviewed data of 139 biopsy- naïve patients with suspicion of prostate cancer, who underwent diagnostic MRI and micro-ultrasonography (microUS), followed by transrectal prostatic biopsy (systematic ±targeted) under local anesthetic. The main objective was to evaluate the performance of the Prostate Risk Identification using MicroUltraSound (PRI-MUS) score in detecting csPCa, defined as International Society of Urological Pathology (ISUP) ≥2.

Results Of all patients, 97 (70%) were found to have PCa, and 62 (45%) having csPCa.

Among 100 patients with positive microUS (PRI-MUS score ≥3), 23 (23%) had ncsPCa and 57 (57%) were diagnosed with csPCa (ISUP ≥2); and in 39 patients with negative microUS, 12 (31%) were diagnosed with ncsPCa and 5 (13%) with csPCa.

A PRI-MUS score ≥3 presented a sensitivity, specificity, positive predictive value and negative predictive value of 92%, 44%, 57% and 95%, respectively, for the detection of csPCa.

The PRI-MUS score had higher areas under the curve than Prostate Imaging Reporting & Data System (PI-RADS) both for targeted (AUC 0.801 vs 0.733) and systematic + targeted (AUC 0.776 vs 0.694) biopsies for csPCa detection.

Conclusions In our cohort, microUS performed well as a diagnostic tool through an easily implementable scale. MicroUS presented similar sensitivity and higher specificity than MRI in detecting csPCa. Further multicenter prospective studies may clarify its role in prostate cancer diagnosis.

Key Words: prostate cancer ‹› diagnosis ‹› ultrasonography

INTRODUCTION

Prostate cancer (PCa) is the second most common neoplasm in males and the fifth in terms of standardized mortality by cancer [1].

In men with elevated total prostate-specific antigen (PSA), a common strategy is to follow with a multiparametric magnetic resonance imaging (mpMRI) and the utilization of a risk calculator to estimate the probability of clinically significant prostate cancer (csPCa); with subsequent prostate biopsy, if the clinical risk justifies it [2].

The widespread use of mpMRI for identification of suspicious lesions and better selection of patients who need to have a biopsy allowed the traditional technique to evolve, with a Prostate Imaging

Reporting & Data System (PI-RADS) score ≥3 threshold for biopsy resulting in a reduction of the number of patients needing a biopsy of approximately 30%, while missing only 11% of ISUP (International Society of Urological Pathology) Grade ≥2 cancers [3], a good step for the reduction of overdiagnosis and overtreatment.

When performing a biopsy, micro-ultrasound (microUS) devices such as the ExactVu™ use very high frequencies of 29 MHz compared to the conventional 8–12 MHz, providing 3 times better special resolution, which allows for the identification of subtle changes in ductal anatomy occuring in prostate cancer, while maintaining a suitable imaging depth allowing visualization of the whole prostate and allowing to accurately target regions of interest in real time [4]. This has allowed for the development and validation of the PRI-MUS (Prostate Risk Identification using MicroUltraSound) protocol, with a 5 level scoring system where higher scores correlate with higher csPCa probability [4]. In addition, the improved ultrasound image can also be fused with MRI images with an appropriate software, like the FusionVu™, allowing mpMRI-microUS fusion biopsies.

Since the technique, either transrectal or transperineal, is the same as with conventional ultrasound, any clinician experienced in performing prostatic biopsies will be able to use this device without any difficulty, only needing to get familiar with the PRI-MUS classification, in order to correctly identify an increased risk of csPCa [4].

Our main goal was to evaluate the performance of the PRI-MUS score in detecting csPCa, in a cohort of patients with significant probability of having csPCa, who underwent previous mpMRI.

Other goals were to compare patient-level results between mpMRI and microUS targeted biopsy, to describe the performance of different biopsy strategies, and to evaluate microUS negative predictive value on finding csPCa in PI-RADS 3 patients.

MATERIAL AND METHODS

Population

We performed a retrospective study, including 139 consecutive patients who underwent prostatic biopsy for suspected PCa performed by one of three urologists of a high-volume tertiary center, from January 2021 to June 2022. Inclusion criteria included being biopsy-naïve, a total PSA <20 ng/mL and having a mpMRI performed prior to the microUS and biopsy. Patients were excluded if they had any history of prostate cancer or prostate cancer related treatment.

All patients had a mpMRI, performed in the 6 months before biopsy, in different centers. Images were reported by radiologists in accordance to PI-RADS v2.1 system [5]. In case of classification discrepancy, in-house radiologist review was carried out.

Prostatic biopsy technique

The microUS system used was the ExactVu™ (Exact Imaging, Markham, Canada) equipped with a 29 MHz EV29L linear probe allowing for fusion with mpMRI images. Transrectal free hand technique was used at all cases.

Biopsies were performed by one of three urologists with more than 10 years of prostatic biopsy experience, after receiving a standardized online and hands-on training with the new system.

The ultrasound probe was inserted into the rectum and the prostatic gland was screened for suspect areas by sweeping from one side to the other and classified according to the PRI-MUS score. Suspicious findings included irregular shadowing, irregular prostate or peripheral zone border, heterogenous 'cauliflower' image, or mild heterogeneity or bright echoes in hyperechoic tissue [4]. Suspicious lesions identified on microUS were annotated and only then the pre-annotated mpMRI images were reviewed.

With a hand-held probe, 2–4 targeted cores were taken from regions of interest (PIRADS 3–5 and/or PRI-MUS 3–5) and then 12 systematic cores were sampled (6 from each prostatic side). The operator noted the provenience of each core; and if from a suspicious zone if it was visible on mpMRI, microUS or both. mpMRI lesions were obtained by cognitive fusion, with further aid from recognition on microUS when they overlapped.

Histology

All biopsy cores were analyses separately. The histological classification was performed by one of two experienced uropathologists, according to International Society of Urological Pathology (ISUP) standards [6], with csPCa being defined as any core with ISUP Grade Group ≥2.

Statistics

Descriptive statistics are reported using median and interquartile range (IQR).

Characteristics of patients with and without csPCa were compared using Chi-squared analysis or Fisher exact test for categorical variables and non-parametric Mann-Whitney U tests for continuous variables. Statistical significance in this study was set as $p < 0.05$. All reported p values are two-sided.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the area under the curve (AUC) for the receiver operator characteristics (ROC) curve were calculated for the PI-RADS and PRI-MUS classification systems.
For statistical analysis we used IBM® SPSS® v27 software. The study has received approval from the Institutional Ethics' Committee. All research was conducted respecting the latest version of Helsinki's declaration. Patients signed an informed consent before undergoing the procedure.

RESULTS

Study sample

We identified 139 patients who met our inclusion criteria.
Patients had a median age of 69 (IQR 64–73) years and a median PSA of 7.5 ng/mL (Table 1). Older age and abnormal digital rectal examination were associated with a higher probability of csPCa (p = 0.002 and p <0.001, respectively).
Median total PSA, presence of an anterior lesion and presence of family history were not statistically significantly different between patients with and without csPCa (p = 0.096, p = 0.34, p = 0.13; respectively).
Regarding mpMRI, 17 (12%) patients had unsuspicious (PI-RADS 1–2), 27 (19%) equivocal (PI-RADS 3), 65 (47%) suspicious (PI-RADS 4) and 30 (22%) highly suspicious (PI-RADS 5) evaluations.
In microUS, 39 (28%) of the evaluations were unsuspicious (PRI-MUS 1–2), 48 (35%) equivocal (PRI-MUS 3), 37 (27%) suspicious (PRI-MUS 4) and 15 (11%) highly suspicious (PRI-MUS 5).

Prostate cancer and clinically significant prostate cancer detection

In the 139 patients, 97 (69.8%) were found to have PCa, with 62 (44.6%) having csPCa.
Among the 35 patients with ncsPCa (ISUP 1), 7 (20%) had a negative MRI, 12 (34%) had a negative microUS, and 6 (17%) both images negative; 17 (49%) had a PI-RADS score of 4–5, while only 8 (23%) had a PRI-MUS score of 4–5.
Among the 39 patients with negative microUS, 22 (56%) had no prostate cancer, 12 (31%) had ncsPCa (ISUP 1) and only 5 (13%) were diagnosed with csPCa (ISUP 3).
Between the 100 patients with positive microUS (PRI-MUS ≥3), 20 (20%) had no prostate cancer, 23 (23%) had ncsPCa (ISUP 1) and 57 (57%) were diagnosed with csPCa (ISUP ≥2).
Thirteen patients (9%) had no suspected lesions both on mpMRI and microUS exams, but underwent biopsy due to suspicious digital rectal examination (n = 4) or high total PSA (n = 10), with only one (8%) of them having csPCa present on the randomized biopsy.

Table 1. *Patients' clinical characteristics*

	Total	Without csPCa	With csPCa	p*
N	139	77	62	
Age, Median (IQR)	69 (64–73)	66 (62–71)	71 (68–74)	0.002
Total PSA (ng/mL), Median (IQR)	7.5 (5.5–10.9)	7.2 (5.3–9.4)	8.2 (5.5–12.2)	0.096
Suspicious DRE, n (%)	27 (19)	7 (9)	20 (32)	<0.001
Family history, n (%)	27 (19)	11 (14)	16 (26)	0.13
Prostate volume (mL), Median (IQR)	47 (33–65)	53 (38–70)	40 (30–60)	0.059
Anterior lesion, n (%)	20 (14)	9 (12)	11 (18)	0.34
Number of targeted cores, Median (IQR)	3 (3–5)	3 (3–4)	4 (3–6)	0.03
PI-RADS score, n (%)				
1–2	17 (12)	15 (19)	2 (3)	
3	27 (19)	17 (22)	10 (16)	<0.001
4	65 (47)	38 (49)	27 (44)	
5	30 (22)	7 (9)	23 (37)	
PRI-MUS score, n (%)				
1–2	39 (28)	34 (44)	5 (8)	
3	48 (35)	27 (35)	21 (34)	<0.001
4	37 (27)	16 (21)	21 (34)	
5	15 (11)	0 (0)	15 (24)	

IQR – interquartile range (IQR); PSA – prostate-specific antigen; DRE – digital rectal examination; csPCa – clinically significant prostate cancer; PI-RADS – Prostate Imaging Reporting & Data System; PRI-MUS – Prostate Risk Identification using MicroUltraSound
* p values for comparisons between patients with and without csPCa

Targeted biopsy comparison

One-hundred and fifty (150) equivocal or suspicious lesions were identified on mpMRI imaging of 122 patients; while 128 equivocal or suspicious lesions were found on the micro-US imaging of 103 patients.
Eighty-four (60%) patients had the same suspicious lesions identified in both mpMRI and microUS, while 20 (14%) patients had different lesions identified in each imaging modality, 3 (2%) only had lesions identified on microUS, 18 (13%) only had lesions identified on mpMRI and 14 (10%) patients had no identified lesions.
When comparing targeted cores from mpMRI and microUS lesions, one hundred and twenty-six (91%) of the patients had a concordant ISUP. Comparing the mpMRI versus the microUS targeting only strategies, the first would have resulted in 7 (5%) patients being upgraded, with 4 (3%) being newly detected PCa and 5 (4%) being newly detected cases of csPCa; and 6/97 (6%) PCa diagnosis being missed, 2/62 (3%) of them being of csPCa (Figure 1).
Among the 62 patients with biopsy proven csPCa, 20 (32%) had a lower ISUP grade in systematic than microUS targeted cores, 22 (35%) had the same and 19 (31%) had a higher one. Compared to systematic biopsy alone, targeted microUS biopsy core analysis resulted in finding additional 9 cases of csPCa and 6 cases of high-risk PCa which were previously classified as low (n = 1) or intermediate risk (n = 5).
Among the 27 patients with PI-RADS 3, 11 (41%) had PRI-MUS 1 or 2, 13 (48%) had a PRI-MUS 3, 2 (7%) had a PRI-MUS 4 and 1 (4%) had a PRI-MUS 5 score. Among patients with PI-RADS 3 score, 10/27 (37%) had a biopsy proven csPCa, with 2 (7%) of them having a PRI-MUS <3.
This would mean the avoidance of biopsy among patients with PI-RADS 3 with a PRI-MUS <3 would result in 11 (41%) less biopsies while missing 2 (18%) of csPCa cases diagnosed.

Test characteristics

For the PRI-MUS classification, the ≥3 cut-off entailed a higher sensitivity (92 vs 58%) and NPV

Table 2. *Performance characteristics of PI-RADS and PRI-MUS protocols in the detection of clinically significant prostate cancer*

	Sensitivity	Specificity	PPV	NPV
PI-RADS ≥3	60/62 97% (92–100)	15/77 19% (11–28)	60/122 49% (40–58)	15/17 88% (73–100)
PI-RADS ≥4	50/62 81% (71–90)	32/77 42% (31–53)	50/95 53% (43–63)	32/44 63% (60–86)
PRI-MUS ≥3	57/62 92% (85–99)	34/77 44% (33–55)	57/100 57% (47–67)	34/39 95% (87–100)
PRI-MUS ≥4	36/62 58% (46–70)	61/77 79% (70–88)	36/52 69% (57–82)	61/87 70% (60–80)

PI-RADS – Prostate Imaging Reporting & Data System; PRI-MUS – Prostate Risk Identification using MicroUltraSound; PPV – positive predictive value; NPV – negative predictive value

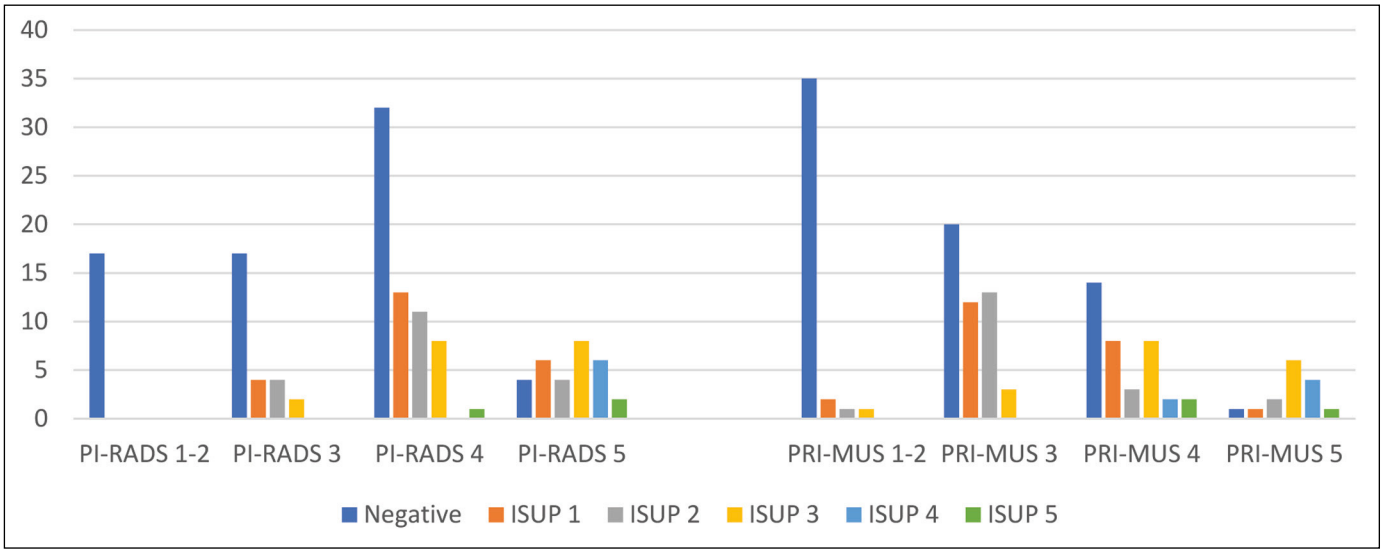

Figure 1. *Results of prostate targeted biopsy, stratified by imaging results.*
ISUP – International Society of Urological Pathology; PI-RADS – Prostate Imaging Reporting & Data System; PRI-MUS – Prostate Risk Identification using MicroUltraSound

(95 vs 70%), but a lower specificity (44 vs 79%) and PPV (57 vs 69%) when compared with a ≥4 cut-off (Table 2).
The rate of csPCa diagnosis on microUS targeted biopsies alone for PRI-MUS 1/2, 3, 4 or 5 was of 2/39 (5%), 15/47 (32%), 18/37 (49%) and 14/15 (93%), respectively.
Figures 2 and 3 presents the ROC curves for overall and targeted biopsy csPCa detection.
The PRI-MUS classification had higher AUC than PI-RADS, both for targeted (AUC 0.801 vs 0.733) and for systematic + targeted (AUC 0.776 vs 0.694) biopsies in csPCa detection.

Different biopsy strategies

The results for our cohort per different biopsy strategies are shown in Figure 4.
The analysis of cores from systematic biopsy + MRI target + microUS target identified 35 patients with ISUP 1 PCa and 62 patients with csPCa.
If only systematic biopsy + MRI targeted cores were obtained, 39 patients would be classified with ISUP 1 PCa and 57 with csPCa, missing 5 (8.1%) cases of csPCa in the current cohort.
If only systematic biopsy + microUS targeted cores were obtained, 34 patients would be classified with ISUP 1 PCa and 61 with csPCa, missing 1 (1.6%) case of csPCa in the current cohort.
Performing MRI targeted biopsies alone would classify 23 patients with ISUP 1 PCa and 46 with csPCa, missing 16 (25.8%) cases of csPCa in the current cohort.
Performing microUS targeted biopsies alone would classify 18 patients with ISUP 1 PCa and 47 with csPCa, missing 15 (24.2%) cases of csPCa in the current cohort.

DISCUSSION

Our results found that in a cohort of patients proposed to perform prostate biopsy, microUS was able to identify the patients without csPCa in 57/62 (92%) cases and, as such, may be an option to select patients that may and may not need biopsy performed after suspicious clinical data and/or mpMRI results.
In our experience, due to its higher specificity, the addition of microUS as a diagnostic and biopsy guiding method increased the AUC for csPCa detection versus PI-RADS classification only (AUC 0.776 vs 0.694) for all cores csPCa detection, respectively.
However, we recommend not to skip systematic biopsy, since it could result in additional missed csPCa.
Recent advances in prostate cancer pathways have tried to solve or at least ameliorate its overdiagnosis and overtreatment. Classically a patient with a high total PSA would undergo a randomized double sextant prostate biopsy with a conventional ultrasound probe.

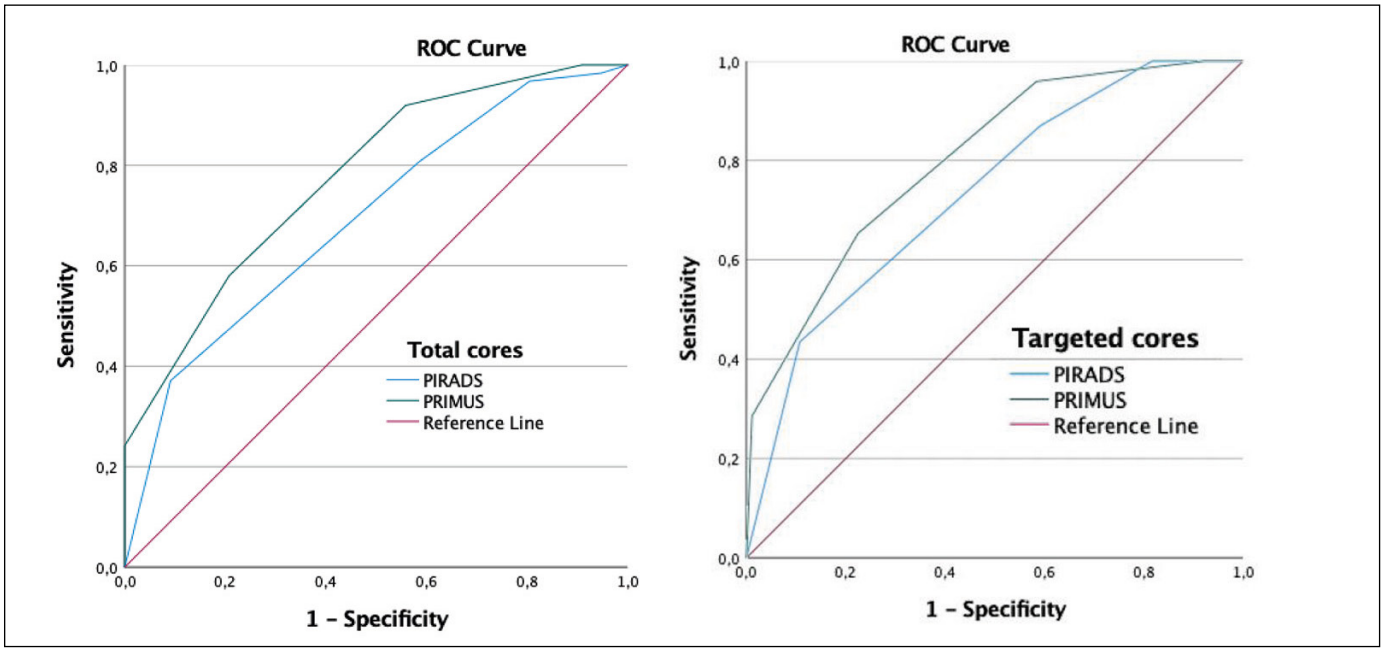

Figure 2 and 3. *Receiver operating characteristics curves of the ExactVu™ for the detections of clinically significant prostate cancer. Left, for overall biopsy detection [AUC PI-RADS 0.694 (0.607–0.782), PRI-MUS 0.776 (0.700–0.852)]; Right, for targeted biopsy detection [AUC PI-RADS 0.733 (0.646–0.819), PRI-MUS 0.801 (0.726–0.875)].*

ExactVu™ – Exact Imaging, Markham, Canada; AUC – area under curve; ROC Curve – receiver operating characteristic curve; PI-RADS – Prostate Imaging Reporting & Data System; PRI-MUS – Prostate Risk Identification using MicroUltraSound

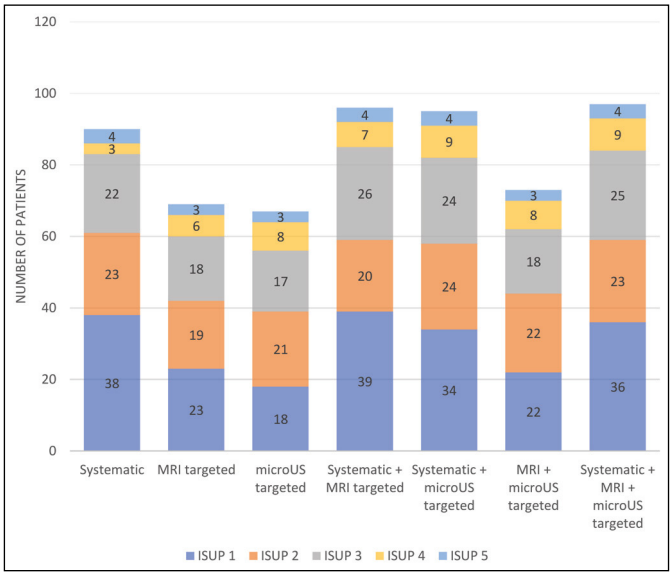

Figure 4. *Report of different biopsy strategies' results by ISUP grading.*

ISUP – International Society of Urological Pathology; microUS – micro-ultrasonography; MRI – magnetic resonance imaging

The implementation of mpMRI for prostate cancer diagnosis has made possible for clinicians to reduce the number of patients undergoing biopsy and being diagnosed with non-clinically significant prostate cancer (ncsPCa) [3].

However, its clinical application may be hindered by the exam costs and availability, additional cost of acquiring fusion devices (even though those have been found to be cost effective) [7], the need for additional radiologist training, only moderate interobserver agreement [8], the longer procedure time before completing an adequate learning curve [9], or the potential toxicity of gadolinium.

The microUS systems are comparatively simpler to use and free from toxicities; although they may be less suited for active surveillance since image comparison would be more difficult.

With their real-time superior resolution, they may be suitable as (a) diagnostic tools on their own or (b) further refinement of the biopsy pathway as diagnostic and targeting tool after mpMRI.

The PRI-MUS system has been validated as a diagnostic tool per se, achieving good performance in detecting csPCa [4]. Although all urologists are familiar with ultrasound guided biopsies, the recognition of microUS validated suspicious patterns may take some practice to get used to. Some studies have focused on this topic, with a multi-institutional study involving 9 clinicians who completed a pre-determined training program suggesting that with proper mentoring and advice from experts, expert sensitivity may be reached within the first 20 to 40 cases and expert specificity after 40 to 90 cases [10], which in dedicated practices may be easy to reach.

One of the limitations of the classification was only being suited for the peripheral zone diagnosis. A further study [11] found that the PRI-MUS score could be applied also to transition and anterior zones, maintaining a good performance, however the PRI-MUS classification for anterior zone is slightly modified and its validation is yet to be determined.

During the last years some institutions [11–16] have reported their initial experiences, reporting sensitivities for csPCa from 65–100%, specificities between 15-73%, positive predictive values 35–93% and negative predictive values of 31–100%. The range of values highlights that results can be operator-dependent and affected by patients' selection.

Klotz et al. [17] analyzed the performance of the ExactVu™ system in detecting csPCa in 1040 patients from 11 centers in their initial experiences, with microUS showing a better sensitivity than mpMRI for predicting ISUP ≥2 PCa (94 vs 90%, p = 0.03), with non-inferior specificity (22 vs 22%, p <0.001 for non-inferiority). In our experience both methods revealed sensitivities above 90%, with micro-ultrasound having a higher specificity [44% (CI 95%: 33–55%) vs 19% (CI 95%: 11–28%); for PRI-MUS ≥3 and PI-RADS ≥3, respectively].

In our previous experience [18], targeted biopsies presented higher rates of csPCa detection when biopsy was performed with microUS using the technique described in this article than with the Artemis robotic arm fusion system with mpMRI fused images (38 vs 23%, p = 0.02), in similar patient populations.

In a recent multicenter trial [19] comparing csPCa detection between mpMRI and microUS, microUS targeted biopsy was non-inferior to mpMRI targeted biopsy, detecting 97% of cases of the latter (95% CI 80–116%, p = 0.023). This is consistent with the results from our study, where microUS detected 57/62 (with 39 negative results) and mpMRI 60/62 (with 17 negative results) cases of csPCa.

Evaluating the role of the microUS as a stratification tool in 111 patients with a PI-RADS 3 score, Avolio et al. [20], reported that among 30 patients without suspicious lesions (PRI-MUS 1–2), 25 (83.3%) had no PCa, 5 (16.7%) had ISUP 1 PCa and none (0%) had csPCa. These results support the role for the microUS as a stratification tool in the presence of an equivocal mpMRI. In our study, we had 11 patients with a PI-RADS 3 and PRI-MUS 2 scores, with 2 (18%) of them having a csPCa that would have been missed by suppressing their biopsies.

We view microUS as a valuable technology, that is fast to learn and easy to implement, that may be

useful in diagnosis (as a cheaper MRI replacement) and stratification (following MRI) due to maintaining high sensitivity with better specificity in identifying csPCa. Its role in active surveillance is less clear by now, as ultrasound obtained images are more difficult to compare. It will be interesting to see if these kinds of devices develop higher clinical adoption in the future and if our and other institutions' results are reproducible in multicenter studies. In the future the addition of artificial intelligence visualization tools may provide further guidance in recognizing areas of interest, which could prove an additional improvement.

Our study has certain limitations, those being: it has a small sample, from a small number of practicians, from a single center; not all patients had a single region of interest; no real gold standard was used (gold standard for comparison would be the specimen from radical prostatectomy); since mpMRI was performed first in all patients and was one of the main factors for deciding whether to pursue or not with a biopsy, we also were unable to compare in a real life scenario the test characteristics of mpMRI and microUS for csPCa detection.

CONCLUSIONS

In our single center study, the new biopsy system was easily implemented into the clinical routine. MicroUS had a very good sensitivity and negative predictive value in detecting clinically significant prostate cancer, with acceptable specificity and positive predictive values; with better AUC than mpMRI.

In our population, the use of microUS for stratification of patients with a PI-RADS 3 would have reduced biopsy numbers in this cohort by 40% while missing 18% of csPCa diagnosis.

With its good performance and some technical advantages over mpMRI, we believe microUS biopsy has great potential and may soon find a place as a diagnostic tool in addition to MRI or instead of mpMRI in regions where its availability is limited.

Further studies may also further expand its role in equivocal mpMRI results, patients with suspected prostate cancer and previous negative biopsies, local staging and active surveillance.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DECLARATIONS

Petr Macek has received payment of honoraria for presentations by Exact Imaging.

ETHICS APPROVAL

Study has received approval from the Institutional Ethic's Committee. Patients provided written consent for all procedures and study inclusion.

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