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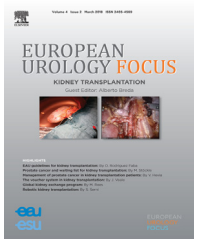

European Association of Urology
Prostate Cancer

Diagnostic Accuracy of Microultrasound in Patients with a Suspicion of Prostate Cancer at Magnetic Resonance Imaging: A Single-institutional Prospective Study

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Abstract

Background: Multiparametric magnetic resonance imaging (MRI) represents the gold standard for the diagnosis of clinically significant prostate cancer (csPCa). The search for alternative diagnostic techniques is still ongoing.
Objective: To determine the accuracy of microultrasound (microUS) for the diagnosis of csPCa within prospectively collected cohort of patients with a suspicion of prostate cancer (PCa) according to MRI.
Design, setting, and participants: A total of 320 consecutive patients with at least one Prostate Imaging Reporting and Data System (PIRADS) $\geq$3 lesion according to MRI were prospectively enrolled.
Intervention: All patients received microUS before prostate biopsy using the ExactVu system; the Prostate Risk Identification using microUS (PRI-MUS) protocol was used to identify targets. The urologists were blinded to MRI results until after the microUS targeting was completed. All patients received both targeted (based on either microUS or MRI findings) and randomized biopsies.
Outcome measurements and statistical analysis: The sensitivity and specificity of microUS to determine the presence of csPCa (defined as at least one core with a Gleason score $\geq$7 PCa) were determined. Multivariable logistic regression analysis was fitted to determine the predictors of csPCa.
Results and limitations: Clinically significant PCa was diagnosed in 116 (36.3%) patients. The sensitivity and negative predictive value of microUS for csPCa diagnosis were 89.7% and 81.5%, while specificity and positive predictive value were 26.0% and 40.8%, respectively. A combination of microUS-targeted and randomized biopsies would allow diagnosing the same proportion of csPCa as that diagnosed by an approach combining MRI-targeted and randomized biopsies (n = 113; 97.4%), with only three (2.6%) csPCa cases diagnosed by a microUS-targeted and three (2.6%) by an MRI-targeted approach. In a logistic regression model, an increasing PRI-MUS score was an independent predictor of csPCa ($p \leq 0.005$). The main limitation of the current study is represented by the fact that all patients had suspicious MRI.

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Conclusions: Microultrasound is a promising imaging modality for targeted prostate biopsies. Our results suggest that a microUS-based biopsy strategy may be capable of diagnosing the great majority of cancers, while missing only few patients with csPCa.
Patient summary: According to our results, microultrasound (microUS) may represent an effective diagnostic alternative to magnetic resonance imaging for the diagnosis of clinically significant prostate cancer, providing high sensitivity and a high negative predictive value. Further randomized studies are needed to confirm the potential role of microUS in the diagnostic pathway of patients with a suspicion of prostate cancer.

1. Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer among men and the third leading cause of cancer-related mortality [1,2]. The traditional diagnostic workup of patients suspected for PCa involved prostate-specific antigen (PSA) screening along with transrectal ultrasound (TRUS)-guided biopsy, where 10–12 cores are systematically taken per patient [3]. Unfortunately, this diagnostic pathway is insufficient due to its low sensitivity and specificity, resulting in both overdiagnosis of clinically insignificant PCa and underdiagnosis of clinically significant PCa (csPCa), with at least 28% of patients with an elevated PSA level who have had an initial negative biopsy and who are diagnosed with PCa in a following repeat biopsy [4].

As conventional gray-scale TRUS is not considered by current guidelines as a reliable tool to detect PCa, several imaging techniques enabling targeted biopsies of areas suspicious for malignancy have been investigated [5]. Among these, multiparametric magnetic resonance imaging (MRI) has emerged as an effective tool for the detection of csPCa [6–9]. Several prospective randomized studies have been reported providing high-level evidence supporting the adoption of an MRI-targeted approach both in the initial and in the repeat biopsy setting [10–12]. As a consequence, current guidelines recommend the use of MRI-targeted biopsies in these settings [5]. However, the consistent number of csPCa missed by the MRI-targeted biopsy approach still contraindicates the omission of systematic prostate biopsies [8,13]. In addition, the widespread adoption of MRI has been limited by its availability, increased costs, requirement for radiological expertise, and the complexity related to the MRI-targeted biopsies procedure [14,15].

Microultrasound (microUS) is a new imaging modality that operates at high frequency (29 MHz), with the resulting microUS images having a resolution of up to 70 μm [16]. Microultrasound uses the Prostate Risk Identification using microUS (PRI-MUS) protocol to characterize and target suspicious regions for PCa, similar to the Prostate Imaging Reporting and Data System (PIRADS) protocol for MRI [17]. The microUS procedure is nearly identical to the standard conventional TRUS, with the additional benefit of enhanced imaging resolution and visualization of suspicious tissue that enables real-time targeted biopsies. The learning curve for microUS for operators already performing TRUS is expected to be short and is limited to simple technique issues and understanding of PRI-MUS characteristics [17]. The aims of the current study were to evaluate the effectiveness of microUS-guided biopsy in the detection of csPCa, defined as a Gleason score of ≥7, and to compare the diagnostic performance of MRI and microUS.

2. Patients and methods

2.1. Study population

The study population consisted of 320 consecutive men who were prospectively enrolled at our institution between October 2017 and September 2019. All patients were referred to our center for a suspicion of PCa based on elevated PSA values or abnormal digital rectal examination, and presented with at least one PIRADS ≥ 3 lesion (defined according to the PIRADSv2 protocol) after undergoing prostate multiparametric MRI (mpMRI; performed either with a 1.5-T scanner with an endorectal coil or with a 3.0-T scanner) [18]. Inclusion criteria were the following: patient age between 40 and 80 yr, total PSA value <20 ng/ml, presence of a cT1 or cT2 disease at digital rectal examination, and previous MRI showing at least one suspicious (PIRADS ≥ 3) lesion. Exclusion criteria were the following: acute or chronic bacterial prostatitis, and patients unable to undergo or with contraindications for MRI. The current study, which represents an extension of previously published experience, was approved by our institution's ethical committee, and all participants provided informed consent for the clinical trial (ICH 003 v1.0 27/09/2017; study number 2004) [19].

2.2. Biopsy procedure

Prior to biopsy procedure, all patients were imaged with the ExactVu system with an EV29 L 29 MHz side-fire transducer (Exact Imaging, Markham, Canada). The two urologists (G.L. and M.L.) performing biopsies were initially naïve to microUS and received a standardized online training program as well as hands-on training prior to the beginning of the study. The PRI-MUS grading system was used to assess the risk of PCa visualized under microUS and to locate targets in any prostatic region [17]. Images and video loops were saved during the biopsy procedure for a retrospective analysis. The biopsy workflow is reported in Supplementary Fig. 1. The urologist performing microUS was blinded to the MRI results; MRI images were uploaded on the Biojet system (D&K Medical, Barum, Germany) the day before the procedure by the other operator and were not available prior to the completion of the microUS scanning. Each lesion with a PRI-MUS score of ≥3 was subjected to at least one targeted biopsy using a transrectal approach. Subsequently, the urologist was unblinded to MRI results, and a MRI/US fusion targeted biopsy was performed obtaining at least two cores for each PIRADS ≥ 3 lesion using the Biojet software. A transperineal approach was used in case of lesions located at the level of the apex or in the anterior/transitional zone of the prostate, while a transrectal approach was used in case of lesions located in the mid portion or base of the prostate. In case of topographically concordant lesions at microUS and MRI, targeted biopsies were obtained using both imaging modalities. Finally, each patient was subjected to a

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systematic randomized biopsy consisting of at least six biopsy cores in the repeat biopsy setting and at least eight biopsy cores in the initial biopsy setting.

2.3. Statistical analysis

The primary endpoint was to assess the diagnostic accuracy of microUS-targeted biopsies to detect csPCa, defined as the presence of at least one biopsy core positive for a Gleason score (GS) ≥3 + 4 PCa. Secondary endpoints were to compare the diagnostic accuracy of microUS-targeted, MRI-targeted, and randomized biopsies; to determine the concordance/discordance between lesions identified by microUS and mpMRI; and to compare the histological findings of the microUS- and MRI-targeted biopsies.

Descriptive analyses were performed using the Mann-Whitney *U* test to assess differences in mean between groups and using analysis of variance for distribution comparisons. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of microUS were calculated based on the underlying pathology results from any biopsy sample of the patient as reference. Definitions used to classify these patient outcomes are intended to reflect the use of microUS for screening before biopsy, as presented below:

1 A true positive individual was positive for csPCa and had at least one suspicious lesion identified on prebiopsy microUS.
2 A true negative individual had no suspicious microUS lesion, and all biopsy samples were negative for csPCa.
3 A false positive individual was negative for csPCa and had at least one suspicious microUS lesion.
4 A false negative individual had no suspicious microUS lesions, but had at least one biopsy sample positive for csPCa.

Finally, a multivariable logistic regression model was also fitted to determine the predictors of csPCa. Calculations were performed using SPSS v17.0 (IBM, Armonk, NY, USA).

Table 1 – Characteristics of the overall population and after stratification according to initial and repeat biopsy setting.

	All patients	Initial biopsy setting	Repeat biopsy setting	*p* value
No. of men (% total)	320 (100)	200 (62.5)	120 (37.5)	
Age (yr), median (IQR)	65 (59–70)	65 (58–70)	66 (60–71)	0.718
Family history of PCa, no. (%)				0.004
Yes	54 (16.9)	38 (19.0)	16 (13.3)	
No	158 (49.4)	108 (54.0)	50 (41.7)	
Missing	108 (33.8)	54 (27.0)	54 (45.0)	
tPSA (ng/ml), median (IQR)	7.3 (5.2–9.9)	6.8 (4.6–8.9)	8.8 (5.9–12.5)	0.001
DRE, no. (%)				0.325
Positive	72 (22.5)	49 (24.5)	23 (19.2)	
Negative	248 (77.5)	151 (75.5)	97 (80.8)	
Prostate volume (cc), median (IQR)	45 (30–70)	47.5 (31.1)	59.0 (45.3)	<0.001
Biopsy cores/patient, no. (IQR)				<0.002
Overall	13 (10–15)	14 (11–15)	10 (7–13)	
Targeted	4 (3–6)	4 (3–5)	5 (4–6)	
Positive biopsy cores, no. (IQR)				0.011
Overall	5 (3–7)	5 (3–8)	3 (1–6)	
Targeted	2 (1–3)	2 (1–3)	1.5 (1–2.2)	
Randomized	3 (1–5)	3 (1–5)	1 (0–2)	
Biopsy route for MRI-targeted biopsies, no. (%)				0.489
Transrectal	176 (55.0%)	113 (56.5%)	63 (52.5%)	
Transperineal	144 (45.0%)	87 (43.5%)	57 (47.5%)	
PIRADS score, no. (%)				0.845
3	56 (17.5)	34 (17.0)	22 (18.3)	
4	209 (65.3)	133 (66.5)	76 (63.3)	
5	55 (17.2)	33 (16.5)	22 (18.3)	
PRI-MUS score, no. (%)				0.544
1–2	65 (20.3)	42 (21.0)	23 (19.2)	
3	38 (11.9)	27 (13.5)	11 (9.2)	
4	159 (49.7)	98 (49.0)	61 (50.8)	
5	58 (18.1)	33 (16.5)	25 (20.8)	
PCa diagnosis, no. (%)				<0.001
Overall	156 (48.7)	107 (53.5)	49 (40.8)	
CsPCa	116 (36.3)	89 (44.5)	27 (22.5)	
Highest ISUP grade group, no. (%)				0.001
1	40 (25.6)	18 (16.8)	22 (44.9)	
2	54 (34.6)	44 (41.1)	10 (20.4)	
3	33 (21.1)	26 (24.3)	7 (14.3)	
4	12 (7.7)	8 (7.5)	4 (8.2)	
5	17 (10.9)	11 (10.3)	6 (12.2)	

ANOVA = analysis of variance; CsPCa = clinically significant PCa; DRE = digital rectal examination; IQR = interquartile range; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PCa = prostate cancer; PIRADS = Prostate Imaging Reporting and Data System; PRI-MUS = Prostate Risk Identification using Microultrasound; tPSA = total prostate-specific antigen.
All values are reported as median and interquartile range.
The ANOVA test was used to compare categorical variables, while the Mann-Whitney *U* test was used to compare continuous variables.

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3. Results

3.1. Study demographics

Table 1 shows patients' characteristics and stratification according to biopsy setting. The majority of patients had a maximum PIRADS lesion score of 4 (65.3%). Microultrasound identified lesions in 265/320 (79.7%) patients, with the majority having a maximum PRI-MUS score of 4 (49.7%). Significant differences were observed in total PSA, prostate volume, number of biopsy cores taken, and number of positive biopsy cores between patients undergoing first or repeated biopsy. Of the 255 patients with at least one lesion detected by both microUS and mpMRI, 189 (74.1%) showed concordant lesions, while 66 (25.9%) individuals had discordant lesions according to the two imaging modalities. Among 189 patients with concordant lesions, a concordance between PRI-MUS and PIRADS score was observed in 117 (61.0%) cases (Supplementary Table 1). Conversely, in 40 (21.1%) patients, the lesion score was upgraded from a lower PIRADS to a higher PRI-MUS score, while in 32 (16.9%) patients, the lesion score was upgraded from a lower PRI-MUS to a higher PIRADS score. Finally, a substantial equivalence was observed between the diagnostic performance of microUS and that of MRI in 66 patients with topographically discordant lesions (Supplementary Table 2).

3.1.0.1. PCa and csPCa detection

A combined randomized and targeted biopsy approach diagnosed 256 (48.7%) patients with PCa overall and 116 (36.3%) with csPCa. Microultrasound showed high sensitivity (89.7%) and a high NPV (81.5%) for csPCa (Table 2). Conversely, specificity and PPV were lower at 26.0% and 40.8%, respectively. Similar figures were observed after stratification of patients according to the biopsy setting. A significant relationship between csPCa diagnosis and PRI-MUS score was observed (chi-square for trend: $p < 0.001$; Fig. 1). Fig. 2 shows a microUS image of a PRI-MUS 5 "mixed-echo" lesion, which pathology identified as GS 3 + 4 disease.

Table 2 – Patient-level sensitivity, specificity, PPV, and NPV for the prediction of csPCa in patients imaged with microUS.

Patient-level microUS outcomes	Sensitivity	Specificity	PPV	NPV
Overall	(104/116) 89.7% (84.2–94.2)	(53/204) 26.0% (20.0–32.0)	(104/255) 40.8% (34.8–46.8)	(53/65) 81.5% (71.8–91.2)
Initial biopsy setting	(77/89) 86.5% (79.4–93.6)	(30/111) 27.0% (18.2–35.8)	(77/158) 48.7 (41.1–56.5)	(30/42) 71.4% (57.8–85.0)
Repeat biopsy setting	(27/27) 100%	(23/93) 24.7% (15.9–33.5)	(27/97) 27.8% (18.1–35.9)	(23/23) 100%

CI = confidence interval; csPCa = clinically significant prostate cancer; microUS = microultrasound; NPV = negative predictive value; PPV = positive predictive value.
Values are expressed as (ratio) and percentage (95% CI).

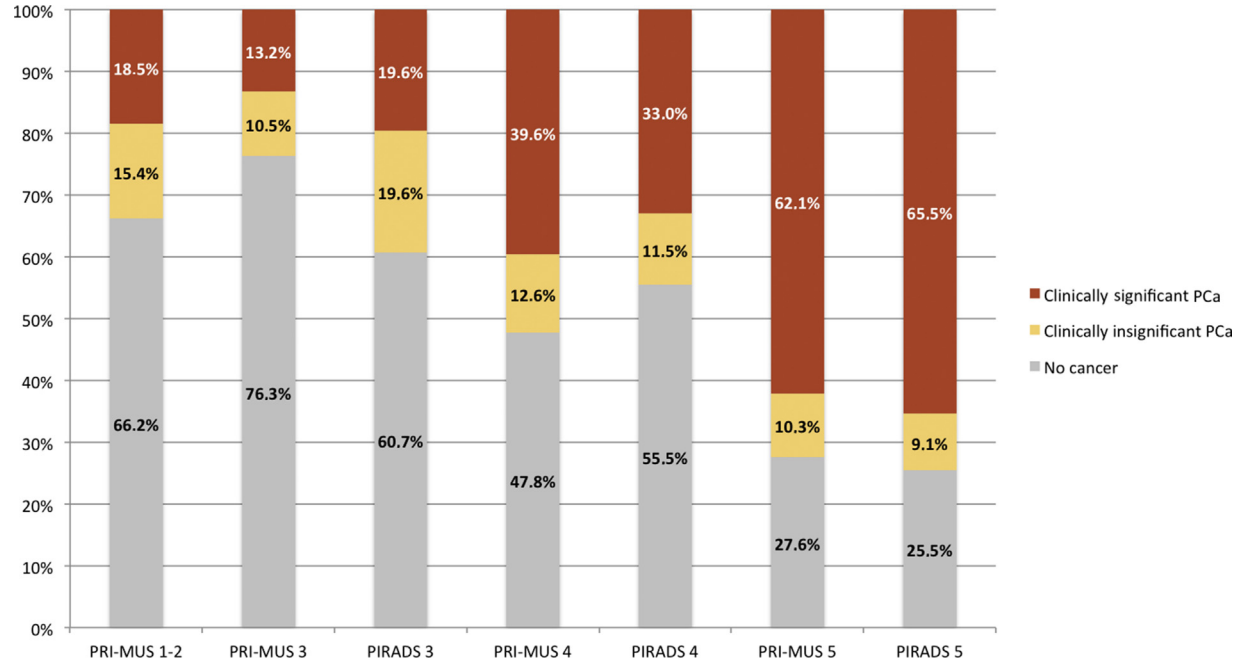

Fig. 1 – Stratification of overall and csPCa diagnosis according to different PRI-MUS scores. csPCa = clinically significant prostate cancer; PCa = prostate cancer; PRI-MUS = Prostate Risk Identification using Microultrasound.

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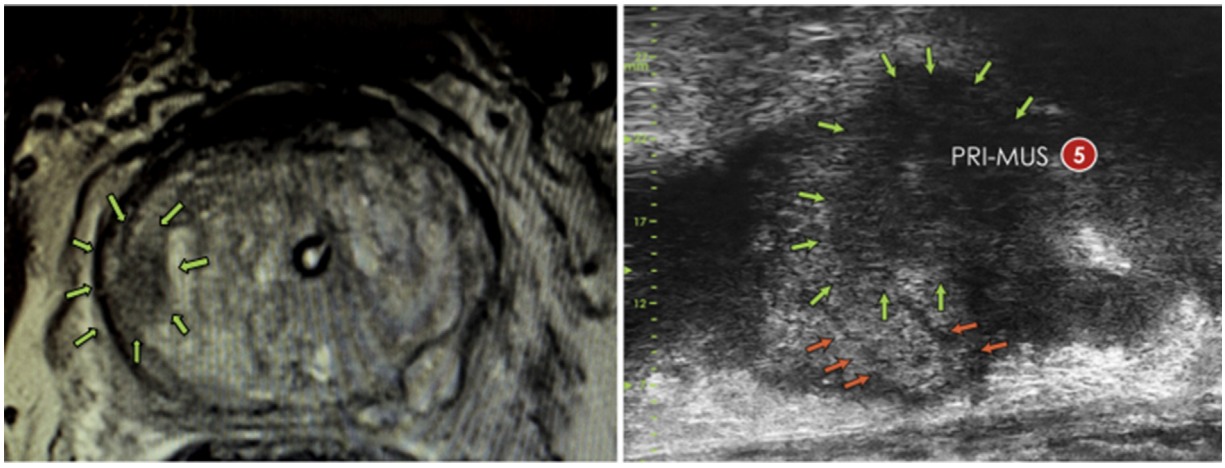

Fig. 2 – MRI and microUS showing, respectively, a PIRADS 4 and a PRI-MUS 5 (suspicious mixed-echo lesion) on the right lateral side of the prostate. Orange arrows indicate previous biopsy needle tracks that may have grazed the side of the lesion, resulting in GS 6 underdiagnosis. Pathology reports this core as GS 7 PCa. GS = Gleason score; microUS = microultrasound; MRI = magnetic resonance imaging; PCa = prostate cancer; PIRADS = Prostate Imaging Reporting and Data System; PRI-MUS = Prostate Risk Identification using Microultrasound.

3.2. *Added value of targeted biopsies*

Overall, 27 (23.2%) patients were diagnosed only on target cores and missed by random ones. Of these, 21 (18.1%) csPCa cases were detected by both microUS and MRI-targeted biopsies. The remaining six cases of csPCa were diagnosed on microUS-targeted (n = 3; 2.6%) and MRI-targeted (n = 3; 2.6%) biopsies only. Conversely, systematic randomized biopsies detected additional 12 (10.3%) cases of csPCa that were missed by targeted biopsies. Of these, 11 patients were in the initial biopsy setting and only one case in the repeat biopsy setting. Full comparative results between microUS and MRI-targeted biopsies are provided in Table 3. Overall, 20 (17.2%) patients with a negative MRI-targeted biopsy showed csPCa on microUS-targeted biopsies. Similarly, 14 (12.1%) patients with a negative microUS-targeted biopsy had csPCa at MRI-targeted biopsies. Fig. 3 shows a concordant lesion found in left base-lateral zone of the prostate that was identified on MRI as PIRADS 3, while it was marked as a PRI-MUS 4 (likely suspicious) lesion with microUS. The targeted biopsies revealed a GS 3 + 4 PCa.

3.3. *Multivariate logistic regression modeling*

A logistic regression model was constructed to determine the extent to which microUS risk assessment impacted csPCa detection rates. The parameters used and resulting fit are shown in Table 4. Prostate volume, age, and initial biopsy setting were all significant predictors of csPCa. The presence of a PRI-MUS 4 or a PRI-MUS 5 lesion was associated with a 3.1- or a 6.2-fold higher risk of being diagnosed with csPCa ($p < 0.005$). Similarly, the presence of a PIRADS 5 lesion also emerged as an independent predictor of csPCa (odds ratio: 4.4; p = 0.007). The model provided strong predictive accuracy with a leave-one-out validation area under the curve of 81.2%, compared with 77.0% of the model including only clinical predictors.

4. Discussion

In the current prospective study, we evaluated the role of microUS in the detection of csPCa. Our findings showed a similar improvement in csPCa detection by adding microUS targets to that by adding MRI targets. Furthermore, these two modalities appear to provide complementary

Table 3 – Comparison of mpMRI and microUS-targeted biopsy results.

		ISUP Gleason grade on mpMRI-targeted biopsies						
		0	1	2	3	4	5	Total
ISUP Gleason grade on microUS-targeted biopsy	0	194	10	16	3	0	0	223
	1	4	8	1	0	0	0	13
	2	5	0	25	0	0	0	30
	3	1	0	0	27	0	0	28
	4	2	0	0	0	9	0	11
	5	4	1	0	0	0	10	15
	Total	210	19	42	30	9	10	320

ISUP = International Society of Urological Pathology; microUS = microultrasound; mpMRI = multiparametric magnetic resonance imaging.

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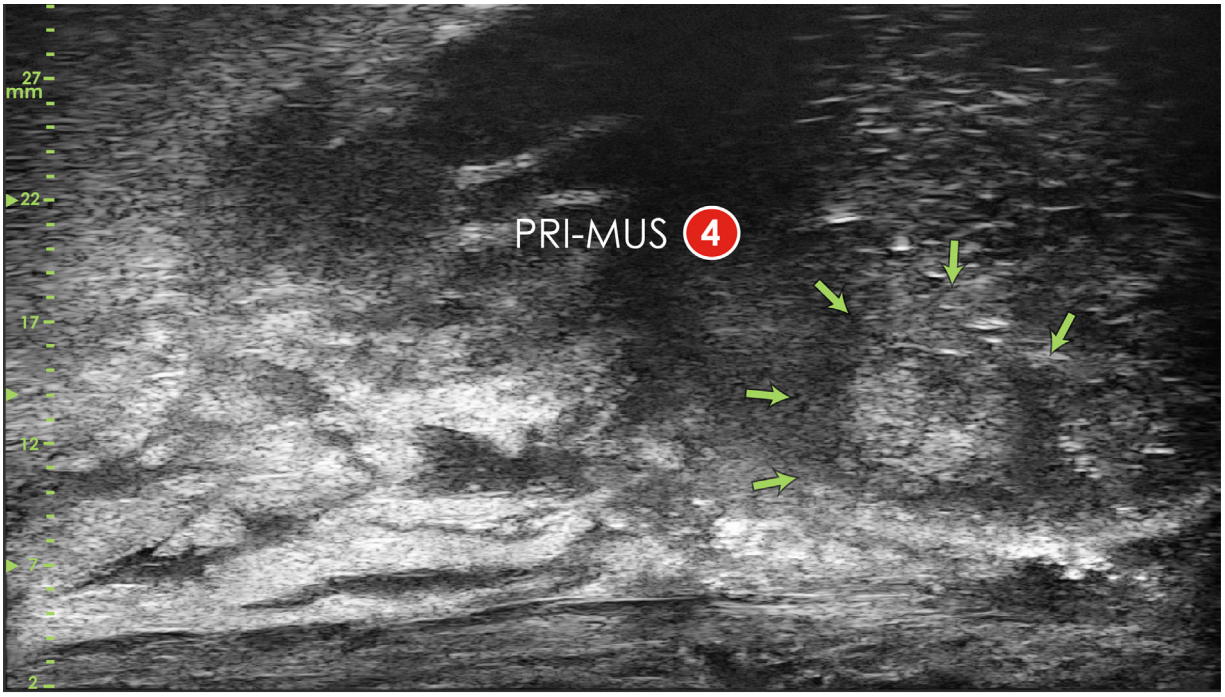

Fig. 3 – Microultrasound image of the left-base-lateral PRI-MUS 4 (likely suspicious) lesion, in concordance with mpMRI, although risk levels differed between the modalities, with mpMRI assigning an equivocal PIRADS 3 grade. Targeted biopsies resulted in a GS 7 PCa. GS = Gleason score; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PIRADS = Prostate Imaging Reporting and Data System; PRI-MUS = Prostate Risk Identification using Microultrasound.

Table 4 – Multivariate logistic regression model assessing the predictors of csPCa.

Predictors of csPCa	Odds ratio (95% CI)	*p* value
Age	1.07 (1.03–1.11)	0.001
Biopsy setting	Reference	<0.001
Repeat	Reference	
Initial	5.70 (2.91–11.16)	<0.001
Log10(tPSA)	4.25 (1.41–12.74)	0.010
Prostate volume	0.98 (0.97–0.99)	0.001
DRE		
Negative	Reference	NA
Positive	1.75 (0.87–3.55)	0.118
PIRADS score		
3	Reference	NA
4	1.82 (0.78–4.19)	0.162
5	4.41 (1.51–12.90)	0.007
PRI-MUS score		
Negative (1 or 2)	Reference	NA
3	0.53 (0.15–1.92)	0.335
4	3.08 (1.39–6.78)	0.005
5	6.18 (2.22–17.20)	<0.001

CI = confidence interval; csPCa = clinically significant prostate cancer; DRE = digital rectal examination; NA = not applicable; PIRADS = Prostate Imaging Reporting and Data System; PRI-MUS = Prostate Risk Identification using Microultrasound; tPSA = total prostate-specific antigen.

information that could easily be combined into a single procedure in order to maximize the detection of csPCa.

The role of conventional TRUS in the diagnosis of PCa, at least when only the b-mode imaging is considered, is suboptimal, and as a consequence, this diagnostic tool is not currently recommended by European Association of Urology guidelines for targeting biopsies, but only for performing systematic biopsies [5]. As a consequence, efforts have been made to identify an imaging technique allowing both visualization and targeting of suspicious areas within the prostate. In this context, MRI and MRI-targeted biopsies have emerged as modalities with substantial improvement compared with systematic biopsies for the detection of csPCa. While initially reserved for individuals with at least one previous negative prostate biopsy, MRI is currently recommended also in the initial biopsy setting, as confirmed by several prospective randomized studies [5,10–12]. Nevertheless, the large-scale adoption of a MRI-first approach is still limited by considerations related to its availability, costs, learning curve, and the need for high-quality images and dedicated uroradiologists, as well as the complexity related to the MRI-targeted biopsy procedure [14]. Biparametric MRI may represent a contrast-free, cheaper, and faster alternative to mpMRI, but further prospective studies are still needed to evaluate its diagnostic accuracy [20,21]. Furthermore, the suboptimal NPV of MRI makes it impossible to avoid systematic biopsies, at least in the initial biopsy setting or in patients under active surveillance [8,13,22,23]. Finally, a non-negligible proportion of patients may be unable to undergo MRI, due to either medical contraindications (ie, presence of pacemaker or prosthetic implants) or claustrophobia.

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As a consequence, the quest for alternative imaging techniques allowing easier application while maintaining higher quality than randomized systematic biopsies continues. Multiparametric ultrasound, which combines the information derived from B-mode, shear wave elastography, and contrast-enhanced ultrasound, has shown promising results in the detection of index lesions before radical prostatectomy, but its applicability in clinical practice and its use as a targeting modality to detect csPCa have not been determined yet [24–26]. Preliminary studies on a limited number of patients have shown that microUS may warrant substantial improvement compared with systematic biopsies for the detection of csPCa and are summarized in Supplementary Table 3. The current study, which represents the largest prospective effort that has been published to date, further supports this evidence, showing a similar improvement in csPCa detection by adding microUS targets to that by adding MRI targets. Of note, the overall PCa and csPCa detection rates in the current population are similar to those reported by previous studies on the same topic [8,11]. Similarly, the added value for csPCa detection by microUS-targeted biopsies was comparable with what has been described previously in other recent MRI series, suggesting that the diagnostic accuracy of microUS is similar to that of MRI at expert European centers [8,12]. More importantly, some patients with csPCa were diagnosed only by microUS or MRI-targeted biopsies. These two modalities hence appear to provide complementary information that could be used in conjunction to maximize the detection of csPCa, as suggested by two recently published studies [27,28]. Nevertheless, the non-negligible proportion of patients with csPCa diagnosed by systematic biopsies in the initial biopsy setting supports the need to include this approach in biopsy-naïve individuals.

There are several limitations of our study that warrant mention. First, an observer bias may be present as all patients included in the current study had suspicious MRI. Although blinded to MRI lesion location, the two urologists may have been led to consider a higher number of microUS lesions as suspicious. In addition, the inclusion of patients with suspicious MRI makes it impossible to assess fully the diagnostic performance of MRI and to provide a comparison of the accuracy of the two diagnostic tools. Second, MRI results did not routinely undergo internal re-evaluation by the institutions' radiologists and were performed with both 1.5- and 3.0-T scanners. While this reflects common urological practice, it may lower the diagnostic performance of MRI in the study population. Third, the number of randomized and targeted biopsy cores that were taken per patient was not standardized. Therefore, some cases of csPCa may have been missed in patients with fewer cores taken from both targeted and systematic biopsies. Fourth, an ideal reference standard such as transperineal template mapping biopsies was not used, and, as a consequence, some cancers may have been missed. Lastly, the interpretation of microUS is highly operator dependent. While all images and cine loops were systematically saved for a retrospective review, formal determination of the interobserver agreement between different clinicians was not performed. However, it should be taken into consideration that both operators had similar experience with conventional TRUS and were novice in microUS. In addition, given the relatively low number of patients included, the impact of the learning curve on the diagnostic performance of microUS remains to be determined, and further studies are warranted to explore how the operator's experience may impact these results.

5. Conclusions

Microultrasound demonstrated a considerable potential as a targeted biopsy modality, providing high sensitivity and an acceptable NPV for csPCa. In consequence, microUS may improve the detection rate of csPCa compared with systematic randomized biopsies. In addition, microUS and MRI may be used as complementary imaging techniques, as they appear to provide independent information in a non-negligible proportion of patients.

***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.
Acquisition of data: Lughezzani, Maffei, Lazzeri, Colombo, Elefante.
Analysis and interpretation of data: Lughezzani, Maffei.
Drafting of the manuscript: Lughezzani, Maffei.
Critical revision of the manuscript for important intellectual content: Saita, Paciotti, Diana, Buffi, Hurle, Lazzeri Guazzoni, Casale.
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Appendix A. Supplementary data

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