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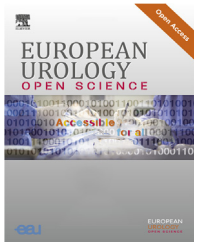

European Association of Urology

Prostatic Disease

Assessing the Role of High-resolution Microultrasound Among Naïve Patients with Negative Multiparametric Magnetic Resonance Imaging and a Persistently High Suspicion of Prostate Cancer

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Abstract

Background: Multiparametric magnetic resonance imaging (mpMRI) is an invaluable diagnostic tool in the decision-making for prostate biopsies (PBx). However, a non-negligible proportion of patients with negative MRI (nMRI) may still harbour prostate cancer (PCa).
Objective: To assess whether microultrasound (micro-US) can help in substratifying the presence of PCa and clinically significant PCa (csPCa; ie, any Gleason score $\geq$7 PCa) in patients with nMRI despite a persistently high clinical suspicion of PCa.
Design, setting, and participants: A total of 125 biopsy-naïve patients who underwent micro-US–guided PBx with the ExactVu system for a persistently high suspicion of PCa despite nMRI were prospectively enrolled.
Intervention: The Prostate Risk Identification using micro-US (PRI-MUS) protocol was used to identify suspicious areas; PBx included targeted sampling of PRI-MUS $\geq$3 areas and systematic sampling.
Outcome measurements and statistical analysis: The primary endpoint was the assessment of micro-US diagnostic accuracy in detecting csPCa. Secondary endpoints included determining the proportion of patients with nMRI who may avoid PBx after micro-US or transrectal US, presence of cribriform and intraductal patterns on biopsy core examination, predictors of csPCa in patients presenting with nMRI, and comparing micro-US–targeted and systematic PBx in identifying csPCa.
Results and limitations: Considering csPCa detection rate, micro-US showed optimal sensitivity and negative predictive value (respectively, 97.1% and 96.4%), while specificity and positive predictive value were 29.7% and 34.0%, respectively. Twenty-eight (22.4%) patients with a negative micro-US examination could have avoided PBx with one (2.9%) missed csPCa. Cribriform and intraductal patterns

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were found in 14 (41.2%) and four (11.8%) of csPCa patients, respectively. In multivariable logistic regression models, positive micro-US, age, digital rectal examination, and prostate-specific antigen density ≥0.15 emerged as independent predictors of PCa. Targeted and systematic sampling identified 33 (97.1%) and 26 (76.5%) csPCa cases, respectively. The main limitation of the current study is represented by its retrospective single-centre nature on an operator-dependent technology.

Conclusions: Micro-US represents a valuable tool to rule out the presence of csPCa among patients with a persistent clinical suspicion despite nMRI.

Patient summary: According to our results, microultrasound (micro-US) may represent an effective tool for the diagnosis of clinically significant prostate cancer in patients with negative magnetic resonance imaging (nMRI), providing high sensitivity and negative predictive value. Further randomised studies are needed to confirm the potential role of micro-US in the diagnostic pathway of patients with a persistent suspicion of prostate cancer despite nMRI.

1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) is an invaluable diagnostic tool in the decision-making process for prostate biopsies (PBx) [1,2]. The American Urology Association and European Association of Urology (EAU) currently recommend the use of mpMRI and mpMRI-guided PBx in order to improve the efficacy of systematic ultrasound-guided PBx for biopsy-naïve patients [3,4].

However, up to 20% of patients with negative mpMRI (nMRI) may still harbour prostate cancer (PCa) [2,5]. Additionally, magnetic resonance imaging (MRI) may not correctly identify tumours with extensive cribriform or intraductal patterns. In this setting, EAU Guidelines recommend using clinical data and liquid biomarkers to better select patients requiring biopsy [3]. However, while providing an estimate of PCa likelihood, risk calculators cannot localise PCa foci, which may be subsequently missed by systematic randomised biopsies. Additional imaging techniques able to identify and target suspicious areas may further increase the diagnostic yield of PBx [6,7].

Microultrasound (micro-US) is a high-resolution US-based imaging modality operating at higher frequencies (29 MHz) than conventional transrectal US systems (typically 6–8 MHz). Thus, micro-US allows visualisation of the alterations in the ductal anatomy that may be associated with clinically significant PCa (csPCa) [8].

Similarly to the Prostate Imaging Reporting and Data System (PI-RADS) protocol for mpMRI, suspicious prostate lesions are characterised using micro-US through the Prostate Risk Identification Using micro-US (PRI-MUS) protocol [9]. According to recently published studies, micro-US has shown a similar diagnostic performance to that of mpMRI [10,11], while also providing an additional 1–17% detection of csPCa [12,13].

The aim of this study is to assess whether micro-US may help in identifying csPCa in patients with nMRI and a persistently high clinical suspicion of PCa.

2. Patients and methods

2.1. Study design and data source

Patients were prospectively enrolled between October 2019 and December 2021 within an on-going clinical trial (protocol ICH 003 v1.0 approved on September 27, 2017; study number 2004) aiming to compare micro-US and mpMRI accuracy for the diagnosis of csPCa.

The experimental protocol was approved by a local institutional review board in accordance with the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human individuals. For the scope of the current study, we included individuals who were screened for inclusion in the protocol, but who were subsequently excluded from further analysis for having nMRI (absence of a PI-RADS ≥3 lesion) confirmed after revision by experienced radiologists.

Despite having nMRI, these patients were referred to our centre for PBx for a persistently high suspicion of PCa based on either clinical (eg, digital rectal examination [DRE]) or laboratory findings. Study design, setting, participants, and overall results have already been reported [11,14]. All patients have provided informed consent before enrolment.

2.2. Study population

The inclusion criteria were patients in the initial biopsy setting, aged between 40 and 80 yr, with a total prostate-specific antigen (PSA) value of <20 ng/ml, and with at least one of the following criteria: persistently rising PSA (on more than two occasions of repeated testing); unexplained high PSA (asymptomatic, with a negative midstream specimen of urine culture), PSA density (PSAd) ≥0.15 ng/ml/ml, and presence of cT1 or cT2 disease at DRE. All patients had previous nMRI (either with a 1.5-T scanner with an endorectal coil or with a 3.0-T scanner) performed within 6 mo from biopsy. Negative MRI was defined as overall PI-RADS score <3 scans and no identifiable lesions for targeting. Patients' demographic, laboratory, MRI, and micro-US imaging and histopathological data were acquired; prebiopsy PSA value and prostate volume measured through MRI were recorded to obtain PSAd. Patients with incomplete clinical and pathological data were excluded from the study.

2.3. Biopsy procedure

All patients underwent a micro-US assessment by an expert urologist. The two urologists involved in micro-US examinations and biopsies had completed the training module developed by Exact Imaging for

micro-US reading. The PRI-MUS protocol, consisting of a five-point scale system capable of stratifying patients according to their risk of harbouring PCa, was used to identify suspicious lesions at micro-US. When a PRI-MUS ≥3 lesion was detected, micro-US–targeted biopsies were obtained (two or more cores per lesion).

All micro-US targeting was performed using a transrectal approach. After the administration of local anaesthesia, the operator sampled each of the PRI-MUS targets under real-time visualisation. After the completion of the micro-US–guided procedure, all patients received 12-core systematic biopsies.

All specimens were analysed by two dedicated uropathologists, according to the International Society of Urological Pathology (ISUP) 2014 recommendations. Clinically significant PCa was defined as any ISUP grade group ≥2 disease [15].

2.4. Study endpoints

The primary endpoint was to assess the diagnostic accuracy of micro-US for detecting csPCa in this subset of individuals. The secondary endpoints were the following: to assess how many nMRI patients could avoid PBx in case of negative micro-US and the proportion of missed csPCa, to assess the number of csPCa patients demonstrating cribriform and intraductal patterns at histopathological examination among patients with nMRI, to assess the predictors of csPCa in nMRI patients, and to compare the ability of micro-US–targeted and systematic biopsy approaches, both individually and combined, in diagnosing csPCa.

2.5. Statistical analysis

Medians with interquartile range and frequencies were reported for continuous and categorical variables, respectively. The Mann-Whitney U test and Pearson chi-square tests were applied to determine the statistical significance of differences in medians and proportions, respectively. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of micro-US were also determined.

The detection rates for PCa and csPCa were stratified according to PRI-MUS score. The potential impact of PSAd as a discriminatory factor in PBx decision-making was evaluated. Multivariable logistic regression models (MLRMs) were fitted to determine the predictors of csPCa. Covariates included lesions stratified by PRI-MUS score, DRE, PSAd, age, and family history. The diagnostic accuracy of an MLRM was reported as the area under the receiver operator characteristic curve. Statistical significance was set at $p < 0.05$. A statistical analysis was performed with STATA 16.1 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Patient characteristics

A total of 125 patients meeting the inclusion criteria were identified. Demographic and clinical characteristics for overall population and stratified according to PRI-MUS score are illustrated in Table 1. Interestingly, prostate volume, PSAd, PCa, csPCa, and ISUP grades were significantly different between individuals with a negative versus a positive micro-US examination ($p < 0.05$).

3.2. Results of micro-US imaging

Overall, 28 patients (22.4%) did not show any micro-US suspicious lesion (PRI-MUS 1–2), while at least one target lesion (PRI-MUS ≥3) was identified in the remaining 97 (77.6%). Specifically, 34 (35.1%) patients had a PRI-MUS 3 lesion, 49 (50.5%) had a PRI-MUS 4 lesion, while 14 (14.4%) had a PRI-MUS 5 lesion.

3.3. PCa identification: biopsy results

A total of 47 (37.6%) and 34 (27.2%) patients harboured PCa and csPCa, respectively, with ISUP grade groups distributed as follows: 13 (10.4%) ISUP 1, 20 (16.0%) ISUP 2, eight (6.40%) ISUP 3, four (3.20%) ISUP 4, and two (1.60%) ISUP 5. Overall, 14 (11.2%) and four (3.2%) of nMRI individuals were found to harbour malignant cribriform and intraductal patterns on histological examination of PBx cores, corresponding to 41.2% and 11.8% of all the diagnosed csPCa, respectively.

Among patients with a negative micro-US examination, 26 (92.9%) did not harbour PCa, while one (3.6%) patient was diagnosed with an ISUP 1 disease and one (3.6%) harboured an ISUP 2 tumour. Among patients with at least one PRI-MUS ≥3 lesion, 52 (53.6%) had a negative biopsy, while 45 (46.4%) were diagnosed with PCa including 33 (34.0%) with csPCa. Full results of PCa and csPCa detection stratified according to PRI-MUS are depicted in Figure 1.

Considering csPCa detection rate, micro-US showed optimal sensitivity and an NPV (respectively, 97.1% and 96.4%), while the specificity and PPV were consistently lower (29.7% and 34.0%, respectively). A detailed comparison of the diagnostic accuracy of micro-US for both PCa and csPCa detection is reported in Table 2.

3.4. PCa identification: substratification by PRI-MUS score

Of those with nonsignificant PCa, five (14.7%) patients had a PRI-MUS 3 and seven (14.2%) had a PRI-MUS 4 lesion, while no patients had a PRI-MUS 5 lesion. Focusing on csPCa, this was detected in two (5.90%) men with a PRI-MUS 3, 21 (42.9%) men with a PRI-MUS 4, and ten (71.4%) individuals with a PRI-MUS 5 lesion

3.5. Results of targeted and systematic biopsies

Targeted and systematic sampling identified, respectively, 33 (97.1%) and 26 (76.5%) of the 34 csPCa patients diagnosed by their combined approach. Micro-US–targeted sampling was able to identify eight (23.5%) individuals missed by systematic sampling; conversely, systematic biopsy identified one additional csPCa patient. Full results of single and mixed biopsy approaches are provided in Supplementary Table 1.

The use of micro-US would have resulted in avoiding 28 (22.4%) unnecessary biopsies, while missing only one (2.9%) csPCa case. When adding a PSAd of ≥0.15 cut-off in the PBx decision-making, we found that 72 patients could have avoided PBx at the cost of missing five csPCa, while identifying 29 csPCa across 53 biopsies.

3.6. Results of logistic regression analysis

At MLRMs, positive micro-US, age, DRE, and PSAd ≥0.15 were identified as independent predictors of csPCa, as shown in Table 3. The accuracy of a model including PRI-MUS score, PSAd cut-off, age, family history, and DRE was 0.85 (95% confidence interval: 0.78–0.92; Fig. 2).

Table 1 – Baseline characteristics of the overall population and after stratification according to PRI-MUS score at micro-US

		Total N = 125	PRI-MUS 1, 2 N = 28	PRI-MUS 3, 4, 5 N = 97	*p* value	Test
Age (yr), median (IQR)		59 (55–65)	58 (54.5–67)	60 (55–64)	0.91	Wilcoxon rank sum
BMI (kg/m^2), median (IQR)		24.7 (23–26)	23.5 (23–25.5)	25 (24–26)	0.21	Wilcoxon rank sum
PCa Family history, *n* (%)	No	85 (68)	18 (64.3)	67 (69.1)	0.96	Pearson's chi-square
	Yes	37 (29.6)	8 (28.6)	29 (29.9)		
	Missing	3 (2.4)	2 (7.14)	1 (1.03)		
Total PSA (ng/ml), median (IQR)		6 (5–8)	5.5 (4.75–7.20)	6 (5–8)	0.36	Wilcoxon rank sum
Prostate volume (ml), median (IQR)		48 (35–60)	52.5 (42.5–61.5)	46 (35–56)	0.04	Wilcoxon rank sum
PSA density (ng/ml/ml), median (IQR)		0.14 (0.09–0.18)	0.11 (0.08–0.17)	0.16 (0.09–0.18)	0.06	Wilcoxon rank sum *
PSA density cut–off (ng/ml/ml), *n* (%)	<0.15	63 (50.4)	19 (67.9)	44 (45.4)	0.04	Pearson's chi-squared
	≥0.15	62 (49.6)	9 (32.1)	53 (54.6)		
Digital rectal examination, *n* (%)	No	91 (72.8)	23 (82.1)	68 (70.1)	0.30	Pearson's chi-square
	Yes	31 (24.8)	5 (17.9)	26 (26.8)		
	Missing	3 (2.4)	0 (0)	3 (3.09)		
Prostate cancer, *n* (%)	No	78 (62.4)	26 (92.9)	52 (53.6)	<0.001	Pearson's chi-square
	Yes	47 (37.6)	2 (7.14)	45 (46.4)		
Clinically significant prostate cancer, *n* (%)	No	91 (72.8)	27 (96.4)	64 (66)	0.001	Pearson's chi-square
	Yes	34 (27.2)	1 (3.57)	33 (34)		
ISUP grade group overall, *n* (%)	Negative biopsies	78 (62.4)	26 (92.9)	52 (53.6)	0.01	Pearson's chi-square
	1	13 (10.4)	1 (3.57)	12 (12.3)		
	2	20 (16)	1 (3.57)	19 (19.6)		
	3	8 (6.4)	0 (0)	8 (8.25)		
	4	4 (3.2)	0 (0)	4 (4.12)		
	5	2 (1.6)	0 (0)	2 (2.06)		

BMI = body mass index; IQR = interquartile range; ISUP = International Society of Urological Pathology; PCa = prostate cancer; PRI-MUS = Prostate Risk Identification using micro-US; PSA = prostate-specific antigen; US = ultrasound.

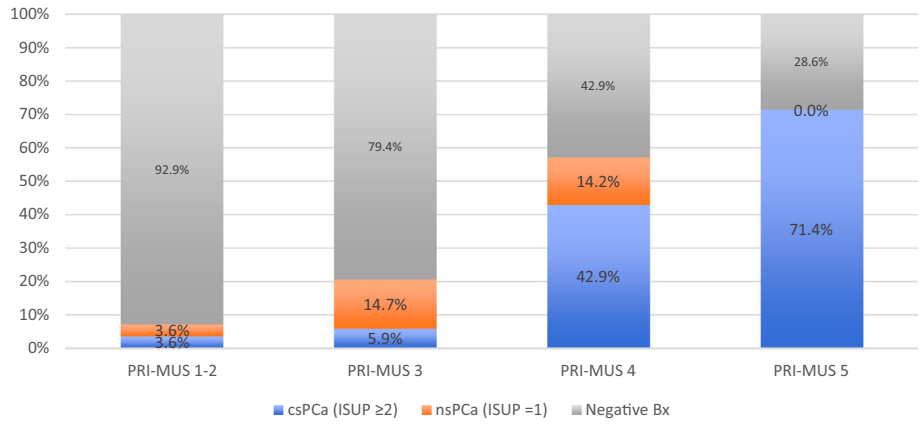

Fig. 1 – Significant prostate cancer (csPCa) and not significant (ns) prostate cancer according to PRI-MUS score. Bx = biopsy; ISUP = International Society of Urological Pathology; PRI-MUS = Prostate Risk Identification using Microultrasound.

Table 2 – Diagnostic accuracy of prostate cancer and clinically significant prostate cancer for overall population

	Value (%)	95% CI
Diagnostic accuracy of prostate cancer		
Sensitivity	95.7	85.5–99.5
Specificity	33.3	23.1–44.9
PPV	46.4	36.2–56.8
NPV	92.9	76.5–99.1
Diagnostic accuracy of clinically significant prostate cancer		
Sensitivity	97.1	84.7–99.9
Specificity	29.7	20.5–40.2
PPV	34	24.7–44.3
NPV	96.4	81.7–99.9

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

4. Discussion

MRI-targeted biopsies have been shown to detect more significant PCa than conventional transrectal ultrasonography–guided biopsies [16,17]. Despite the widespread implementation of mpMRI in PCa diagnostic pathway, its interobserver variability has shown suboptimal clinical test performance in daily practice, especially outside of high-volume centres of excellence, complying with quality assurance standards [18]. In a recent review, Sathianathen et al. [5] noted considerable heterogeneity in the diagnostic accuracy of mpMRI between studies. This variability reflects cancer prevalence, and institutional and individual differences in technique, skills, and experience. Indeed, the PRO-

Table 3 – Multivariable logistic regression model testing the predictors of clinically significant prostate cancer

Predictors of csPCa		Odds ratio (95% CI)	*p* value
Age		0.92 (0.86–0.99)	**0.031**
Family history	No	Reference	
	Yes	1.49 (0.51–4.36)	0.464
PSA density cut-off (ng/ml/ml)	<0.15	Reference	
	≥0.15	15.4 (4.15–57.2)	**<0.001**
PRI-MUS	1–2	Reference	
	≥3	13.0 (1.26–134)	**0.031**
Digital rectal examination	No	Reference	
	Yes	4.41 (1.31–14.9)	**0.017**
AUC (95% CI): 0.85 (0.78–0.92)			

AUC = area under the curve; CI = confidence interval; csPCa = clinically significant prostate cancer (any ISUP grade group ≥2 prostate cancer); ISUP = International Society of Urological Pathology; PRI-MUS = Prostate Risk Identification using microultrasound; PSA = prostate-specific antigen.

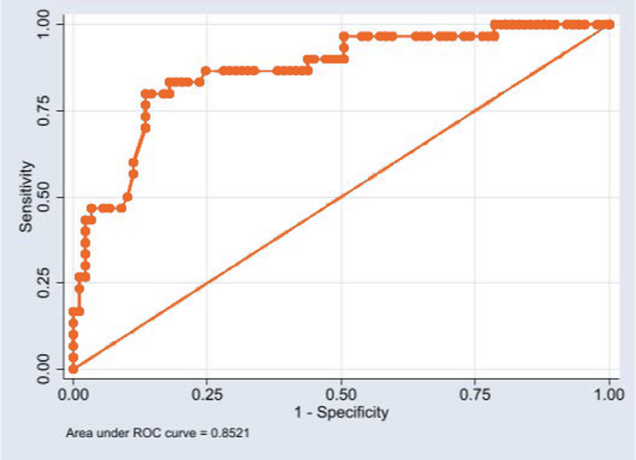

Fig. 2 – Diagnostic accuracy of the multivariate logistic regression model represented as area under the receiving operator characteristic (ROC) curve. Area under the ROC curve: 0.77 (95% CI: 0.66-0.88).

MIS trial had already demonstrated the importance of readers' experience in avoiding false negative results [16].

As suggested by Giganti et al., adherence to mpMRI technical parameters as outlined in PI-RADS v.2.1 guidelines could surely improve the quality of prostatic MRI.

Still, mpMRI achieves an NPV of >80% and a PPV of approximately 50% for the detection of csPCa [16,19]. These data indicate that every fifth case of csPCa is missed by MRI, and up to 50% of patients with positive MRI may undergo unnecessary PBx, with exposure to the potentially associated morbidities. Studies investigating the relationship between radiological and pathological findings have shown that smaller, low-grade, multifocal, nonindex tumours are more likely to be missed by mpMRI [20,21]. However, only few studies have investigated the reasons for MRI-targeted biopsy failures. Williams et al [22] observed that MRI-invisible lesions and MRI lesions missed by the radiologist represent, respectively, 41.5% and 7.3% of these failures.

Additionally, histopathological and molecular features associated with MRI invisibility may include cribriform architecture, more aggressive tumour microenvironments, and tumours with increased mutation density. Of interest, csPCa missed by mpMRI has been attributed to a "sparse" tumour intermixed with normal tissue, which may not be identified at diffusion-weighted imaging [23]. In such patients, a combined targeted and systematic biopsy approach may partially overcome PCa misdiagnosis. However, systematic biopsy alone is known to miss a significant proportion of csPCa cases [16,17,24].

Improved risk management with better identification of csPCa may lead to more specific and individualised treatment options and less overtreatment of indolent disease [25]. Therefore, alternative imaging techniques capable of ruling out the presence of csPCa in individuals with nMRI but a persistent clinical suspicion of PCa are still needed.

To the best of our knowledge, this is the first study evaluating the performance of micro-US for predicting PCa and csPCa in patients with a persistent clinical suspicion of PCa despite nMRI. We found that micro-US–guided biopsies had a significant impact on our ability to detect csPCa compared with systematic biopsies. Specifically, the addition of micro-US as a supplementary diagnostic tool improved the diagnosis of csPCa by 8/34 (23.5%), while reducing the diagnosis of non-csPCa by 83%. In addition, micro-US can be used to avoid unnecessary biopsies without significantly compromising the detection of csPCa.

We also observed that up to 41.2% and 11.8% of csPCa missed by mpMRI had a cribriform and intraductal pattern, respectively. This finding is consistent with a previous study by Truong et al. [26] who observed that, despite being a well-established predictor of distant metastasis and cancer-specific mortality, mpMRI overlooked the majority (82.6%) of tumours with cribriform and intraductal patterns.

Nonetheless, it should be stressed that the diagnostic accuracy of micro-US may be limited by large prostate volumes and specific tumour location, such as the transitional zone, even if a recent software update (increasing US penetration up to 60 mm) and a second version of PRI-MUS-score may partially overcome these limitations [18]. Other innovative molecular-based imaging, such as prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography, were also tested in this patient population [27]. In cases of malignancy, PSMA expression is significantly increased and associated with PCa stage and grade [28]. Lopci et al. [29] found that a maximum standardised uptake value of 5.4 and a maximum-to-background standardised uptake value ratio of 2 detect 100% of ISUP ≥2 tumours. In a recent meta-analysis, Kawada et al. [30] demonstrate that PSMA-PET-TB appears to have favourable diagnostic accuracy for csPCa detection, achieving an NPV of 85%. Nevertheless, before broad implementation of PSMA-PET-TB in the diagnostic setting, standardisation and assessment of its cost effectiveness are required.

Introduction of micro-US in the biopsy pathway has been shown to improve the accuracy of mpMRI-targeted sampling, making the fusion procedure easier and finding additional targets that may have been missed by mpMRI [12]. Of course, both micro-US and mpMRI have the potential to detect csPCa cases that were missed by the other modality. We can expect a synergistic effect when mpMRI and micro-US are combined for imaging-targeted biopsy of lesions.

We recognise that our study has some limitations. First, the sample size and the number of events in this study are limited, thus affecting the significance of our results.

Second, this is a retrospective, single-centre study on an operator-dependent technology, and as a consequence, the observed outcomes may not be generalisable. Third, all mpMRI studies were reviewed internally, but these were not homogeneous due to different magnetic fields (1.5 vs 3 T), diffusion-weighted imaging protocols (*b* values 1000–1500 s/mm^2), acquisition and reconstruction software, and endorectal coil use in 1.5-T scanners. Additionally, systematic biopsies on the same side of the prostate could partially overlap with the micro-US–targeted biopsies. Moreover, transperineal template biopsies were not used, which may have led to some cancers going undetected.

Finally, we have no data that relate the biopsy findings with final whole mount pathology findings, which obviously represent the "gold standard" for the correct topographical and malignity characterisation of PCa.

5. Conclusions

Our findings indicate that micro-US could represent a helpful tool capable of discriminating patients harbouring csPCa among those with nMRI but a persistent suspicion of PCa.

Therefore, micro-US may be applied as an additional decision-making tool for PBx, allowing for a more accurate identification of csPCa. Further studies are still needed to corroborate our findings and to better establish the role of this promising strategy within the diagnostic workup of PCa 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: Avolio, Lughezzani.
Acquisition of data: Avolio, Fasulo, Maffei, De Carne, Saitta.
Analysis and interpretation of data: Fasulo, Avolio, Lughezzani.
Drafting of the manuscript: Avolio.
Critical revision of the manuscript for important intellectual content: Lughezzani, Lazzeri, Casale, Buffi, Sanchez-Salas, Guazzoni.
Statistical analysis: Fasulo, Avolio.
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Supervision: Lughezzani, Lazzeri, Casale, Buffi, Sanchez-Salas, Saita, Hurle, Guazzoni.
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Appendix A. Supplementary data

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