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Clinical-Prostate cancer

The use of 29 MHz transrectal micro-ultrasound to stratify the prostate cancer risk in patients with PI-RADS III lesions at multiparametric MRI: A single institutional analysis

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Abstract

Introduction: Magnetic Resonance Imaging (MRI) has emerged as the most accurate diagnostic tool, showing a high sensitivity in the diagnosis of clinically significant prostate cancer (csCaP). However only a minority of patients with a PI-RADS 3 lesion at multiparametric magnetic resonance imaging (MRI) are diagnosed with csCaP. The aim of the current study was to assess whether high resolution micro-ultrasound (microUS) could help in sub-stratifying the risk of csCaP in this specific population.

Material and methods: We retrospectively analyzed the records of 111 consecutive patients scheduled for a prostate biopsy with at least 1 PI-RADS 3 lesions at MRI. We excluded patients with a PIRADS >3 lesion, even if they had a coexisting PIRADS 3 lesions. MicroUS was performed in all patients before prostate biopsy by an operator blind to MRI results. The Prostate Risk Identification using MicroUS (PRI-MUS) protocol was used to assess the risk of CaP and csCaP. All patients received both targeted and systematic biopsies. The primary endpoint was to determine the diagnostic accuracy of microUS in detection of csCaP in patients with a PI-RADS 3 lesion at MRI. Specifically, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of microUS were determined. Multivariable logistic regression models (MLRMs) were fitted to identify predictors of CaP. The diagnostic accuracy was reported as area under the receiver operator characteristic (ROC) curve.

Results: Overall, 43 patients (38.7%) harboured CaP and 22 (20%) csCaP. MicroUS showed a high sensitivity and negative predictive value (100%), while its specificity and positive predictive value were 33.7% and 27.2%, respectively. Among patients without lesions at microUS, 25 (83.3%) did not harbour CaP, while 5 (16.7%) patients were diagnosed with a Gleason score 6 CaP, with no patients harbouring csCaP. Using microUS, the csCaP detection would have remained 100%, while reducing the detection of insignificant CaP of a 23.8% extent (n = 5). In MLRMs, lesion identified at microUS and continuously-coded PSAd were independent predictors of CaP. The accuracy of a model including PRI-MUS score, digital rectal examination (DRE), PSA density, age and family history was 0.744 (95% CI: 0.645 − 0.843).

Conclusion: In our single-institutional retrospective study, microUS was potentially capable to stratify the presence of CaP in patients with an equivocal MRI. Further prospective studies on larger populations are needed to validate our results.

Keywords: Prostate cancer; Diagnosis; Pi-Rads 3; Prostate biopsy; Targeted biopsies; Multiparametric Mri; Micro-ultrasound

1. Introduction

Prostate cancer (CaP) is the most frequently diagnosed cancer and the third-ranked cause of cancer mortality among men [1,2]. In recent years, many efforts have been made to reduce the potential overdiagnosis and subsequent overtreatment of clinically insignificant prostate cancer (CaP). Several studies have investigated the potential impact of novel imaging modalities in the primary diagnosis

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of clinically significant CaP (csCaP) [3,4]. Magnetic Resonance Imaging (MRI) has emerged as the most accurate diagnostic tool, showing a high sensitivity in the diagnosis of csCaP [5]. The European Association of Urology (EAU) guidelines currently recommend MRI imaging prior to all prostate biopsies [6,7]. Nevertheless, the widespread adoption of MRI in the CaP diagnostic pathway is still affected by its limited availability outside of tertiary centers with experienced dedicated radiologists. In 2012, the Prostate Imaging-Reporting and Data System (PI-RADS) has been developed to determine the likelihood of csCaP presence, with the latest update (v2.1) published in 2019 [8]. PI-RADS is based on a 5-point Likert scale: Grades 4 and 5 are highly suspicious for csCaP and should prompt biopsy, while grade 1 and 2 can reliably exclude its presence. On the other hand, grade 3 is equivocal, thus questioning the need for a prostate biopsy in these cases [9,10].

To avoid unnecessary prostate biopsies in patients with PI-RADS 3 lesions, several traditional clinical parameters, biomarkers and nomograms have been proposed [11,12]. Micro-UltraSound (microUS), a novel ultrasound-based imaging modality operating at high frequency (29 MHz), has already been proposed as a valuable tool for csCaP diagnosis, showing a similar diagnostic performance to that of MRI [4,13,14].

We tested whether microUS could provide a sub-stratification of patients with PI-RADS 3 lesions at MRI, therefore reducing the number of biopsies without compromising the diagnosis of csCaP.

2. Materials and methods

2.1. Study design and data source

We retrospectively analysed data collected within a prospective ongoing clinical trial (Protocol ICH 003 v1.0 approved on September 27, 2017; study number 2004) aiming to compare microUS and MRI accuracy for the diagnosis of csCaP. Study design, setting, participants and overall results have already been reported [3,4]. All patients have provided informed consent before enrolment.

2.2. Study population

We analysed records of 468 patients with clinical suspicion of CaP, based on elevated PSA values, abnormal digital rectal examination, and MRI findings, who were referred to our Institution for targeted biopsies between October 2017 and March 2020. When MRI was performed at different centres, images were routinely reviewed and reassessed by our-hospital radiologists.

Inclusion criteria were: Patient age between 40 and 80 years, total PSA value <20 ng/ml, presence of cT1 or cT2 disease at digital rectal examination, and previous MRI (either with a 1.5-T scanner with an endorectal coil or with a 3.0-T scanner) showing at least 1 suspicious (PIRADS ≥3) lesion. Exclusion criteria included: patients with a PI-RADS >3 lesion (n = 307), patients with a PI-RADS 3 lesion coexisting with another highly suspicious lesion, namely PI-RADS 4 or 5 (n = 41), and patients with incomplete data (n = 9). Our final analysis included 111 patients (Fig.1.).

2.3. Biopsy procedure

Two urologists experienced in conventional US prostate imaging but without any previous experience with microUS performed the biopsies. Both received a standard online training on prostate microUS examination before the beginning of the study. The day before the procedure, the urologist not involved in the subsequent biopsy session was typically in charge of the contouring process. The day of the procedure, the second urologist performed the microUS examination and subsequent microUS-targeted biopsies in case of a positive microUS. Only after the completion of the microUS-guided procedure, the MRI/US fusion biopsy

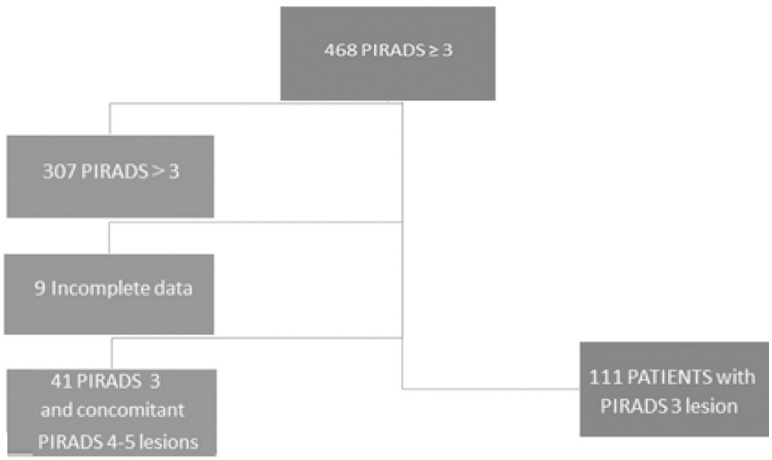

Fig. 1. Flowchart describing the patients selection process.

was performed, to make sure that the operator was blinded to the MRI results.

The images were categorized according to the Prostate Risk Identification Using Micro-Ultrasound (PRI-MUS) protocol that, similarly to PI-RADS, is a 5-point scale whose results stratify patients according to their risk of harbouring csCaP [15]. When a PRI-MUS ≥3 lesion was detected, targeted biopsies were obtained (≥2 cores/lesion). Subsequently, patients underwent either a transperineal or transrectal MRI/US fusion targeted biopsy according to MRI lesion location. A transperineal approach was used in case of apical or anterior/transitional zone lesions, while a transrectal approach was used in case of lesions located in the peripheral zone of the prostate mid portion/base. A software registration fusion approach (the BioJet fusion system, D&K technologies Gmbh, Barum, Germany) was used to perform MRI targeted biopsies. At least 2 targeted cores were also taken for each lesion detected by MRI. In case of topographically concordant lesions, targeted biopsies were obtained using both imaging modalities. Finally, each patient underwent a systematic biopsy consisting of at least 6 biopsy cores in the repeat biopsy setting and of at least 8 biopsy cores in the initial biopsy setting.

All prostate biopsy specimens were analysed by 2 dedicated uropathologists, according to the International Society of Urological Pathology (ISUP) 2014 recommendations. Lesions with a Gleason score ≥ 7 were considered as csCaP, according to the definition used in the PROMIS study [16] Complete demographic, pre-operative and pathologic data were prospectively collected. PSA value and prostate volume measured by MRI were recorded to obtain PSA density (PSAd).

2.4. Study endpoints

The primary endpoint of this study was to assess the diagnostic accuracy of microUS for detecting csCaP in patients presenting with a PI-RADS 3 lesion at MRI. Specifically, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of microUS were determined. In addition, we calculated how many patients could potentially avoid a prostate biopsy without reducing csCaP detection. The secondary endpoint was to assess the predictors of CaP in patients presenting with PI-RADS 3 lesions. We also evaluated whether PSAd could be a helpful additional parameter to further stratify patients according to their risk of csCaP. Finally, we tested the accuracy of PSAd alone (i.e. without the microUS) for stratifying our population.

2.5. Statistical analysis

Median plus interquartile range and frequency were reported for continuous and categorical variables, respectively. The Pearson Chi-square and the Mann-Whitney *U* test were applied to determine the statistical significance of differences in proportions and medians respectively. The detection rates for CaP and csCaP were also reported and stratified according to PRI-MUS score. The potential impact of PSAd was evaluated.

Finally, multivariable logistic regression models (MLRMs) were fitted to identify predictors of CaP. Covariates included lesions stratified for PRI-MUS, digital rectal examination (DRE), PSAd, age and family history. In case of continuous variables, odds ratios were computed for are meant for an increment of 1 ng/ml^2 of PSAd and 1 year of age. The diagnostic accuracy of MLRM was reported as area under the receiver operator characteristic (ROC) curve.

All *P*-values were two-sided and statistical significance was assumed at $P \leq 0.05$. All analyses were performed using Stata (*Version Stata/IC 16.0, Stata Corp LLC, TX, USA*).

3. Results

Demographic and clinical characteristics are shown in Table 1. Of the 111 patients, 43 (38.7%) harboured CaP and 22 (20%) harboured csCaP. Of the twenty-two csCaP diagnoses, ISUP grade groups were distributed as follows: 15 (34.9%) ISUP 2, 5 (11.6%) ISUP 3, and 2 (4.7%) ISUP 5.

Thirty (27%) patients did not show any lesion at microUS (PRI-MUS 1−2) while in the remaining 81 (73%) patients at least 1 target lesion was identified (PRI-MUS ≥3). Specifically, 19 patients had a PRI-MUS 3 lesion, 54 patients had a PRI-MUS 4 lesion, while 8 patients had a PRI-MUS 5 lesion. The concordance between the lesions seen at MRI and at microUS, including a stratification according to prostate volume and location of the lesion, was described in the Table A.1.

Among patients without lesions at microUS, 25 (83.3%) did not harbour CaP, while 5 (16.7%) patients were diagnosed with a Gleason score 6 CaP, with no patients harbouring csCaP. Among patients with at least 1 PRI-MUS ≥3 lesion, 43 (53%) had a negative biopsy, while 38 (47%) and 22 (27%) were diagnosed with CaP and csCaP, respectively. CsCaP was detected in 4 (21.0%) of men with PRI-MUS 3, 15 (27.8%) of men with PRIMUS 4, and 3 (37.5%) of men with PRIMUS 5 (Fig. 2).

Considering csCaP detection rate, microUS showed high sensitivity and negative predictive values (100%), while its specificity and positive predictive value were 33.7% and 27.2%, respectively. Overall, 27% (n = 30) of the patients could have safely avoided a prostate biopsy. Using microUS as an additional test to decide whether or not perform the biopsy, the csCaP detection would have remained 100%, while reducing the detection of insignificant prostate cancer. Indeed, 23.8% (n = 5) of PRIMUS negative patients were diagnosed with ISUP GG 1 CaP.

When evaluating a PSAd cutoff value of 0.15 in the substratification of patients with a positive microUS (PRI-MUS≥3), we showed a negligible impact of this variable on the presence of csCaP in our population, as 14 out of 54

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

	All patients	PRI–MUS 1–2	PRI–MUS 3–4– 5	*P*-value
No. of men (%)	111 (100)	30 (27)	81 (73)	
Median age, years (IQR)	63 (58 – 68)	65.5 (61 – 69)	62 (57 – 67)	0.085
Median BMI (IQR)	25.4 (23.6 – 26.6)	25.4 (23.1 – 26.5)	25.4 (24.6 – 26.6)	0.706
Family history of CaP, (%)				0.18
No	74 (66.7)	23 (76.7)	51 (63)	
Yes	19 (17.1)	3 (10)	16 (19.7)	
Missing	18 (16.2)	4 (13.3)	14 (17.3)	
Median total PSA, ng/ml (IQR)	6 (4.3 – 8.2)	5.3 (3.8 – 8.3)	6 (4.6 – 8)	0.241
Median PSA density (IQR)	0.11 (0.07 – 0.16)	0.09 (0.070. – 11)	0.12 (0.08 – 0.17)	0.063
Digital Rectal Examination, No. (%)				0.097
Positive	18 (16.2)	2 (6.7)	16 (19.8)	
Negative	93 (83.8)	28 (93.3)	65 (80.2)	
Prostate volume, cc (IQR)	50 (35 – 68)	55.5 (35 – 81)	50 (35 – 68)	0.298
Previous Biopsies, No (%)				0.221
Yes	55 (49.5)	12 (40)	43 (53)	
No	56 (50,5)	18 (60)	38 (47)	
Prostate Cancer, No (%)				0.004
Yes	43 (38.7)	5 (16.7)	38 (47)	
No	68 (61.2)	25 (83.3)	43 (53)	
Missing	–	–	–	
Significant Prostate Cancer, No (%)				0.001
Yes	22 (20)	0 (0)	22 (27)	
No	89 (80)	30 (100)	59 (73)	
Missing	–	–	–	
Highest ISUP Grade Group, No. (%)				0.115
1	21 (48.8)	5 (100)	16 (42.1)	
2	15 (34.9)	0 (0)	15 (39.5)	
3	5 (11.6)	0 (0)	5 (13.1)	
4	0 (0)	0 (0)	0 (0)	
5	2 (4.7)	0 (0)	2 (5.3)	

The Person chi square was used to compare categorical variables while the Mann-Whitney U test was used to compare continuous variables.

(25.9%) patients with a PSAd <0.15 still harbour csCaP as compared to 8 out of 27 (29.6%) in those individuals with a PSAd ≥0.15 (Fig. A.1). In a MRLM investigating factors associated with CaP, the presence of a lesion at microUS examination and continuously coded PSAd emerged as the independent predictors of CaP, with patients with at

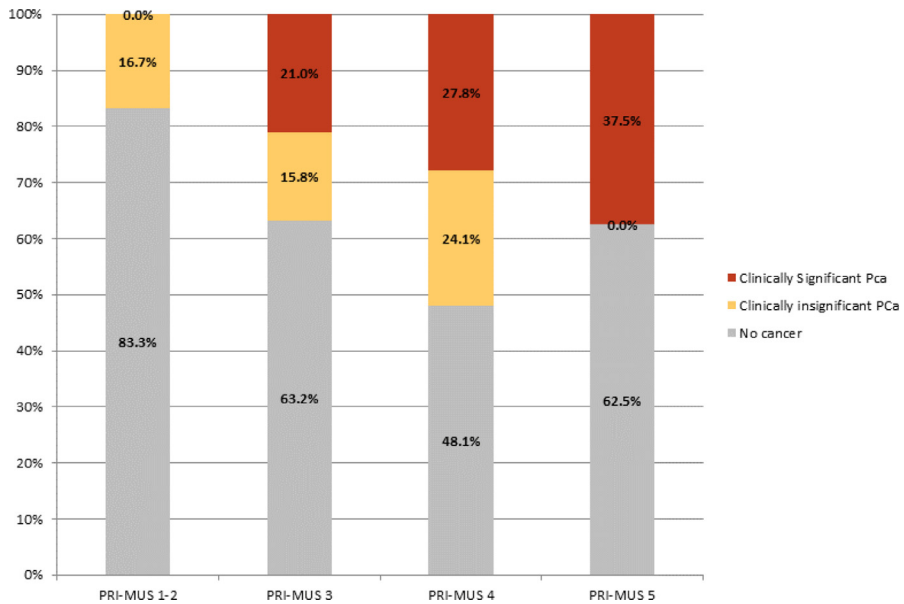

Fig. 2. Significant Prostate Cancer (csCAP) and Insignificant Prostate Cancer according to PRI-MUS Score.

least 1 PRI-MUS ≥3 showing a 4.22-fold higher risk of harbouring CaP as compared to their counterparts without any lesion at microUS (95%CI: 1.26−14.05; $P = 0.01$) (Table 2).

The accuracy of the model including PRI-MUS score, PSAd, age, DRE, and family history, represented as area under the ROC curve (AUC) was 0.744 (95% CI: 0.645 −0.843), as shown in Fig. 3. Overall, 78 patients had a PSAd <0.15 while 33 had a PSAd ≥0.15. Using PSAd alone as a strategy to stratify patients according to csCAP risk would have resulted in a sensitivity of 36.4% (8/22 patients), specificity of 71.9% (64/89), PPV of 24.2% (8/33), and NPV of 82.1% (64/78).

4. Discussion

In recent years, the routine adoptions of MRI and MRI-targeted biopsies have significantly improved the ability to diagnose and characterize CaP [6,17,18]. However, there are still some partially unanswered issues. Patients with a PI-RADS 3 lesion represent a "gray area," where a prostatic biopsy is still advocated even though the proportion of CaP in this population is expected to be extremely low [19,20]. It has been shown that, outside of high-volume facilities, the quality of prostate MRI reports is often inadequate. More specifically, unexperienced radiologists may overestimate the proportion of patients classified as PIRADS 3 [19]. Since microUS is potentially adoptable by any size facility, it could be a practical solution to improve the risk-stratification of patients with a PIRADS 3 lesion at MRI in a real-life setting.

In the present study, we evaluated whether microUS could be used to further stratify the risk of harbouring csCaP among individuals with a PI-RADS 3 lesion. Furthermore, we evaluated the potential impact of clinical parameters, such as PSAd, on the diagnostic accuracy of microUS. Recent studies have shown that the prevalence of PI-RADS 3 index lesions ranges between 22% to 32% of men undergoing prostate MRI [19]. The prevalence of csCaP after targeted biopsy in PI-RADS 3 lesions is also highly variable ranging from 16-21% individuals, depending on previous biopsy history, as well as from clinical parameters such as PSAd [19,9]. As a consequence of this very low PPV, a non-negligible proportion of individuals still undergoes unnecessary invasive procedures, leading to negative biopsy or overdiagnosis of insignificant CaP. In our study, the overall detection of CaP in patients with ≥1 PI-RADS 3 lesions at MRI were 38.7%, while 20% of the patients had a csCaP. Our data confirm that PI-RADS 3 lesions may prompt unnecessary biopsies in a non-negligible proportion of patients and require integration with additional clinical and radiological parameters to guide biopsy decision.

Table 2
Multivariable logistic regression model testing the predictors of CaP

Predictors of CaP		Odds Ratio [95% CI]	*P*-value
Age		1.00 [0.94 − 1.08]	0.795
Family history	No	Reference	0.721
	Yes	1.24 [0.37 − 4.21]	
PRI-MUS score	Negative	Reference	0.001
	Positive	4.22 [1.26 − 14.05]	
Digital rectal examination			0.421
	Negative	Reference	
	Positive	0.59 [0.16 − 2.10]	
PSAd		1.08 [1.01 − 1.15]	0.01

Recently, some approaches to sub-differentiate PI-RADS 3 results and to identify patients who need immediate biopsy have been proposed [21,22]. Scialpi et al. proposed a subclassification of PI-RADS 3 lesions according to the lesion volume calculated in T2w and DWI. Two subgroups have been proposed: Low-risk lesions with volume <0.5 ml (3a) vs. high-risk lesions with a volume ≥0.5 ml (3b) [23]. Similarly, Rico et al showed that the association of the volume of PI-RADS 3 lesions and PSAd improves specificity and PPV in this patient population [24]. Additionally, Steinkohl et al demonstrated that performing follow-up MRI rather than immediate biopsy may be beneficial for patients with PI-RADS 3 lesions, suggesting an optimal interval for follow-up MRIs at 12.4 months [25]. Other innovative molecular based imaging, such as PSMA PET/CT, were also tested in this patient population, showing inconclusive results in patients with PI-RADS 3 lesions [26].

In our study, we showed that microUS could represent a helpful tool capable of discriminating patients harbouring csCaP among subjects with at least 1 PI-RADS 3 lesions at MRI. Indeed, microUS was able to correctly rule out the presence of csCaP in almost one third of patients. Of note; none out of 30 patients with a negative microUS were diagnosed with csCaP, with 16.7% receiving a GS6 diagnosis, thus yielding a NPV of 100%.

On the other hand, about half of the patients with a PRI-MUS ≥3 lesion at microUS had a negative biopsy, while 38 (47%) harboured CaP and 22 (20%) csCaP. Our findings are in line with the literature, showing that microUS had a high sensitivity and NPV, with a relatively low specificity and positive predictive value when compared with other imaging modalities [27,3,4].

The addition of a PSAd cutoff value of 0.15 to further stratify patients with PRI-MUS ≥3 lesions would have spared 54 additional biopsies at the cost of missing 14 csCaP diagnoses. Of note, if we used PSAd alone to stratify our population, we would have a lower accuracy compared to the microUS. To the best of our knowledge, this is the first study showing that microUS can potentially be used as a complementary tool supporting urologists in the selection of patients with equivocal MRI lesions requiring prostate biopsies.

Our study is not devoid of limitations. The small sample size limits the accuracy of our results. Having only 2 urologists performing microUS in a single center may hinder the generalizability of our findings. Indeed, microUS represents

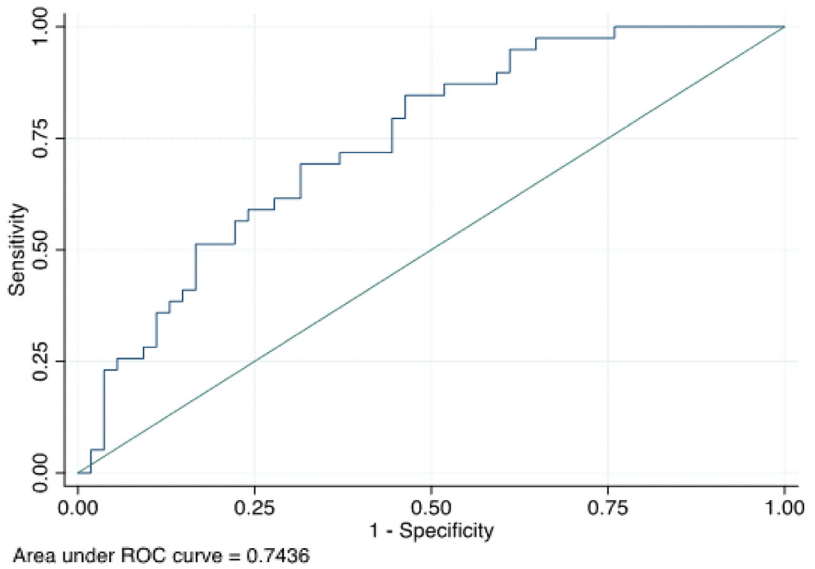

Fig. 3. Diagnostic accuracy of the multivariate logistic regression model represented as area under Receiving Operator Characteristics curve (ROC). Area under the ROC curve: 0.744 (95% CI: 0.645 − 0.843). After stratification according to PRI-MUS score, 4 (21.0%) csCaP were diagnosed in those with a PRI-MUS 3 lesion, as compared to 15 (27.8%) csCaP in those having a PRI-MUS 4 lesion, and 3 (37.5%) in those having a PRI-MUS 5 lesion.

an operator-dependent technology, whose learning curve is still under investigation, even though it is expected to be quite short. In addition, we did not evaluate the application of other clinical features that were not routinely available in our population such as PSA kinetics or MRI lesion diameter could help in the risk stratification [28]. Moreover, the number of systematic biopsy cores was not standardized across the whole population and this may have negatively affected the CaP detection rate. More specifically, the number of systematic cores may have been reduced in case of a frankly negative microUS and/or depending on patient's characteristics, therefore potentially increasing the false negative rate.

No ideal reference standard, such as transperineal template mapping biopsies, was used and some cancers may have been missed despite the adoption of 2 imaging techniques. In addition, while we did not consider prostate volume as an exclusion criterion, the diagnostic accuracy of microUS may indeed be negatively affected by an excessively large volume, especially when lesions are located in the anterior/transitional part of the gland. Finally, there may be an operational selection bias as all of these patients had a suspicious MRI and, therefore, clinicians may have been prone to consider microUS findings as suspicious. Similarly, as during microUS examination urologists were blinded to MRI results, we could not determine how many MRI-visible lesions were also directly observed during microUS scanning of the prostate.

5. Conclusion

In our single-institutional retrospective study, microUS was potentially capable to stratify the presence of CaP in patients with an equivocal MRI. Further prospective studies on larger populations are needed to determine whether microUS could be adopted as a supplementary diagnostic tool in patients with an equivocal MRI result.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2021.05.030.

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