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ORIGINAL ARTICLE

Use of high-resolution micro-ultrasound to predict extraprostatic extension of prostate cancer prior to surgery: a prospective single-institutional study

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Abstract

Purpose We aim to evaluate the accuracy of micro-ultrasound (microUS) in predicting extraprostatic extension (EPE) of Prostate Cancer (PCa) prior to surgery.

Methods Patients with biopsy-proven PCa scheduled for robot-assisted radical prostatectomy (RARP) were prospectively recruited. The following MRI-derived microUS features were evaluated: capsular bulging, visible breach of the prostate capsule (visible extracapsular extension; ECE), presence of hypoechoic halo, and obliteration of the vesicle-prostatic angle. The ability of each feature to predict EPE was determined.

Results Overall, data from 140 patients were examined. All predictors were associated with non-organ-confined disease ($p < 0.001$). Final pathology showed that 79 patients (56.4%) had a pT2 disease and 61 (43.3%) ≥ pT3. Rate of non-organ-confined disease increased from 44% in those individuals with only 1 predictor (OR 7.71) to 92.3% in those where 4 predictors (OR 72.00) were simultaneously observed. The multivariate logistic regression model including clinical parameters showed an area under the curve (AUC) of 82.3% as compared to an AUC of 87.6% for the model including both clinical and microUS parameters. Presence of ECE at microUS predicted EPE with a sensitivity of 72.1% and a specificity of 88%, a negative predictive value of 80.5% and positive predictive value of 83.0%, with an AUC of 80.4%.

Conclusions MicroUS can accurately predict EPE at the final pathology report in patients scheduled for RARP.

Keywords Prostate cancer · Micro-ultrasound · Diagnosis · Prostate biopsy · Local staging · mpMRI · Radical prostatectomy

Introduction

In men with localized prostate cancer (PCa), the goal of radical prostatectomy should be to completely remove PCa while warranting the lowest rate of side effects. For this reason, urologists aim to restrict surgical template to spare neurovascular-bundles and improve apical dissection, while ensuring negative surgical margins. Therefore, an accurate local staging is essential for treatment planning [1, 2]. Several studies have reported that extra-prostatic extension (EPE) is associated with higher rates of positive surgical margins and worse oncological outcomes [3]. The prediction of EPE is consequently of paramount importance, especially considering the recent trend in selecting higher risk PCa patients for surgery.

Conventional transrectal ultrasound (TRUS) imaging has demonstrated poor sensitivity for local staging of PCa and detection of EPE [4]. In recent years, several studies investigated the role of multiparametric-magnetic resonance imaging (mpMRI) for local staging of PCa, reporting a low sensitivity and a high specificity [5]. Therefore, current guidelines support the adoption of mpMRI for preoperative staging of PCa only in patients with intermediate

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to high-risk PCa, acknowledging the limitations of mpMRI for the detection of microscopic ECE and the paramount importance of an experienced radiologist for a correct image interpretation [1].

Recently, a high-resolution micro-ultrasound (microUS) system has been developed and several studies have shown promising results for PCa diagnosis, with good performance in terms of sensitivity and negative predictive value [6–10]. However, the role microUS for local staging has never been studied in an adequate cohort so far.

The aim of the current study was to investigate the clinical performance of microUS in the detection of EPE in patients with biopsy-proven PCa disease scheduled for robot assisted radical prostatectomy (RARP).

Materials and methods

Patient cohort and study design

All men with a biopsy-proven PCa who had been scheduled for a RARP between November 2019 and September 2020 were prospectively recruited. The study was approved by local authorities (Prot.n°2570-ICH-006) and all patients signed a written informed consent before enrollment.

Exclusion criteria were a total prostate specific antigen (PSA) > 20 ng/mL, prostate volume ≥ 100 ml, patients previously treated with radiation, focal therapy or androgen-deprivation therapy or patients unable/unwilling to undergo TRUS.

Micro-ultrasound, surgery, and pathological report

All patients underwent microUS the day prior to RARP using 29 MHz ExactVu™ (Exact Imaging, Markham, Canada) microUS system with a side-fire endorectal probe. MicroUS was performed by one of two experienced urologists who were blinded to both mpMRI and biopsy results.

All lesions detected by microUS were classified according to Prostate Risk Identification Using Micro-Ultrasound (PRI-MUS) score [11]. The dominant suspicious lesion was defined as the lesion with the highest PRI-MUS score or, in case of multiple lesions with the same PRI-MUS score, as the largest. Patients with a negative microUS (PRIMUS 2 with no visible lesions) were considered as patients with no risk factors for EPE.

The following MRI-derived potential risk factors of EPE were also evaluated: capsular contact length (CCL) ≥ 15 mm, capsular bulging, visible breach of the prostate capsule ("visible ECE"), presence of a hypoechoic halo and obliteration of the prostatic-seminal vesicle angle (Fig. 1 and Suppl. Figures 1, 2) [12, 13]. Obliteration of the vesicle-prostatic angle was considered only for basal lesions, while hypoechoic halo was usually observed in apical/anteriorly located lesions. The presence of each of these variables was determined to evaluate the most predictive of EPE. Overall, these variables were defined as "predictors". Moreover, clinical parameters such as age, family history of PCa, PSA value, digital rectal examination (DRE), prostate volume, and biopsy International Society of Urological Pathology (ISUP) score of the lesion were prospectively collected and evaluated [14].

RARP was performed by one of three experienced surgeons. Histopathological analyses were performed by dedicated experienced uropathologists according to the UICC and ISUP standards [14, 15]. The presence of EPE at the final pathology report was defined as the presence of extracapsular extension (ECE) or seminal vesicle invasion (SVI).

Statistical analysis

Means and standard deviations (SD), and medians and interquartile-range (IQR) and frequencies were reported when appropriate. Categorical variables were compared with chi-square tests; categorically and continuously coded variable with ANOVA. To test the relationship between number of predictors at microUS and final stage of disease the Cochran-Armitage-test for trend was applied. PRI-MUS 3 and 4 were pooled for the analysis due to the small sample. The diagnostic performance of all predictors was tested.

When evaluating the diagnostic performance of the predictors, side agreement was included by definition. Univariable and multivariable logistic regression models (LRMs) including both clinical and microUS-derived variables were fitted to test potential risk factor of EPE. A clinical model was tested alone and added by microUS parameters. The accuracy of the two models was determined with the ROC curve analysis. Finally, an n-fold cross-validation for the AUC was performed to provide cross-validated fitted probabilities for EPE. This method averages the AUCs corresponding to each fold and applies the bootstrap procedure to the cross-validated AUC to obtain statistical inference and 95% bias corrected CIs. Statistical significance was set at $p < 0.05$. All analyses were performed using STATA®16.1 (StataCorp, College Station, Texas).

Results

Characteristics of the study cohort

Of 230 patients who underwent RARP in the study period, 140 (60%) were included in the study (Suppl. Figure 3). Baseline characteristics, microUS and histopathological findings are summarized in Table1. The distribution of DRE,

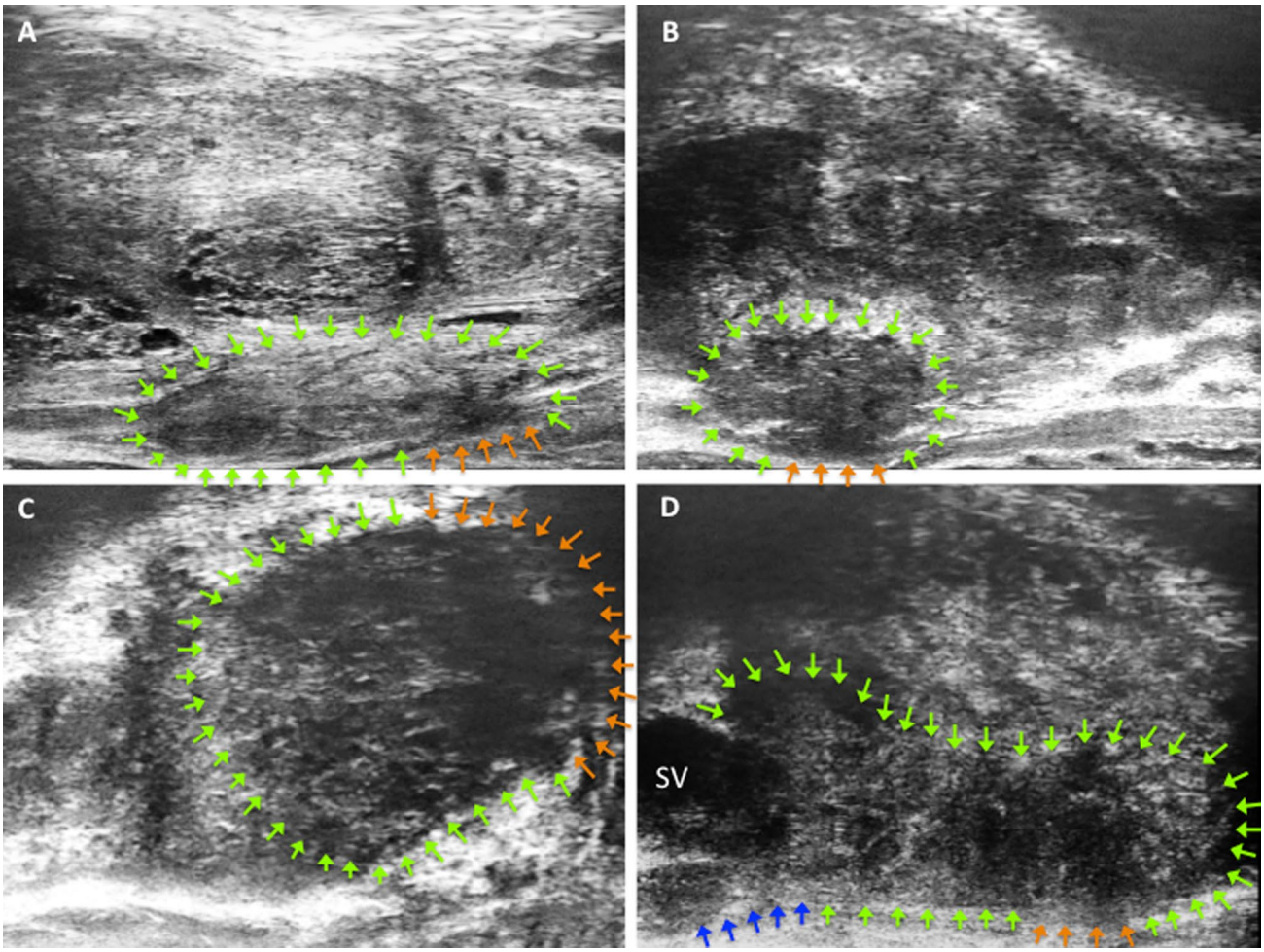

Fig. 1 Micro-ultrasound showing: **A** mixed-echo lesion (PRIMUS V; *green arrows*) and a visible capsular breach at the level of the apex (*orange arrows*); **B** smudgy lesion (PRIMUS IV; *green arrows*) with capsular bulging and visible capsular breach at the base of the prostate (*orange arrows*); **C** smudgy lesion (PRIMUS IV; *green arrows*) located at the anterior apex of the prostate with associated capsular bulging and hypoechoic halo (*orange arrows*); **D** large mixed-echo lesion (PRIMUS V; *green arrows*) showing both capsular breach (*orange arrows*) at the mid-prostate and obliteration of the prostate-seminal vesicle (SV) angle (*blue arrows*)

ISUP group, and PRI-MUS score was significantly different between patients with or without EPE (all $p < 0.001$).

Comparison between microUS findings and final pathology report

Visible ECE, presence of capsular bulge, obliteration of the vesicle-prostatic angle and hypoechoic halo were significantly more frequent among patients with non-organ-confined disease ($p < 0.001$) (Table 1). The mean lesion size was 17.4 mm (SD ± 5.8), and the median curvilinear contact length was 18.8 mm (SD ± 5.1). Of note, CCL ≥ 15 mm was not found to be a predictor of EPE ($p = 0.085$) and was excluded from further analyses.

Histopathological analysis showed that 79 (56.4%) patients had a pT2 disease, 42 (30.0%) pT3a and 19 (13.6%) pT3b disease, respectively. Among patients with PRI-MUS 1–2, 2 (16.8%) had a pT3 PCa. One patient was found with a single lesion PRI-MUS 3 and had an organ-confined disease. Conversely, 22 (28.2%) patients with PRI-MUS 4 and 36 (72.0%) patients with a PRI-MUS 5, had non-organ confined disease.

Relationship between microUS features and EPE

The risk of EPE increased proportionally with the number of predictors simultaneously detected by microUS ($p < 0.001$) (Table 2). Specifically, the proportion of patients with EPE increased from 44.0% in those individuals with only 1 predictor to 92.3% in those where 4 predictors were simultaneously observed. Similarly, at univariate LRM, the risk of harboring non-organ-confined disease was 7.7-fold higher in those having 1 microUS-derived predictors, increasing up to a 72.2-fold higher risk in those patients where

Table 1 Characteristics of patients underwent biopsy and robot-assisted radical prostatectomy

		All patients	Organ-confined disease	Non-organ-confined disease	*p*-value
		N = 140	*N* = 79	*N* = 61	
Age, median (IQR)		65 (60–70)	65 (60–69)	65 (59–71)	0.504*
Total PSA (ng\mL), median (IQR)		6.92 (5.10–9.75)	6.4 (4.60–8.80)	8 (5.60–12.0)	0.051*
DRE, *n* (%)	No Nodule	56 (100)	45 (80.4)	11 (19.6)	< 0.001§
	Nodule	83 (100)	33 (39.8)	50 (60.2)	
	Missing	1 (100)	1 (100)	0 (0)	
Prostate Volume (cc), median (IQR)		50 (35.5–60.0)	50 (40.0–60.0)	45 (35.0–60.0)	0.128*
Biopsy ISUP, *n* (%)	1	31 (100)	25 (80.7)	6 (19.4)	< 0.001§
	2	53 (100)	33 (62.4)	20 (37.7)	
	3	28 (100)	13 (46.4)	15 (53.6)	
	4	21 (100)	7 (33.3)	14 (66. 7)	
	5	7 (100)	1 (14.3)	6 (85.7)	
Overall PRI-MUS, *n* (%)	1–2	12 (100)	10 (83.3)	2 (16.7)	< 0.001§
	3	1 (100)	1 (100)	0 (0)	
	4	77 (100)	54 (70.2)	23 (29.9)	
	5	50 (100)	14 (28.0)	36 (72.0)	
microUS main lesion location	Apex	38 (100)	24 (63.2)	14 (36.8)	0.007§
	Margin	21 (100)	10 (47.6)	11 (52.4)	
	Base	7 (100)	0 (0)	7 (100)	
	Suburethral paramedian	6 (100)	3 (50.0)	3 (50.0)	
	Apex, margin	20 (100)	14 (70.0)	6 (30)	
	Margin, base	28 (100)	17 (60.7)	11 (39.3)	
	Apex, margin, and base	6 (100)	0 (0)	6 (100)	
	Apex, paramedian	2 (100)	1 (50.0)	1 (50.0)	
	No lesion viewed	12 (100)	10 (83.4)	2 (16.7)	
Visible breach of the prostatic capsule at microUS, *n* (%)	No	87 (100)	70 (80.5)	17 (19.5)	< 0.001§
	Yes	53 (100)	9 (17.0)	44 (83.1)	
Capsular bulge at microUS, *n* (%)	No	85 (100)	64 (75.3)	21 (24.7)	< 0.001§
	Yes	55 (100)	15 (27.3)	40 (72.7)	
Obliteration of the vesicle-prostatic angle at microUS, *n* (%)	No	64 (100)	44 (68.8)	20 (31.3)	< 0.001§
	Yes	18 (100)	2 (11.1)	16 (88.9)	
	Not app	58 (100)	33 (56.9)	25 (43.1)	
Hypoechoic halo or ring at microUS, *n* (%)	No	94 (100)	63 (67.1)	31 (33.0)	< 0.001§
	Yes	46 (100)	16 (34.8)	30 (65.2)	
Capsular Contact Length (CCL) at microUS, *n* (%)	< 15 mm	87 (100)	54 (62.1)	33 (37.9)	0.085§
	≥ 15 mm	53 (100)	25 (47.2)	28 (52.9)	
Pathologic T stage, *n* (%)	T2a	12 (100)	12 (100)	0 (0)	< 0.001§
	T2c	67 (100)	67 (100)	0 (0)	
	T3a	42 (100)	0 (0)	42 (100)	
	T3b	19 (100)	0 (0)	19 (100)	
Pathologic N stage, *n* (%)	N0	85 (100)	45 (53.0)	40 (47.1)	0.005§
	N1	15 (100)	2 (13.4)	13 (86.7)	
	Nx	40 (100)	32 (80.0)	8 (20.0)	
Margins at definitive pathology, *n* (%)	R0	114 (100)	69 (60.53	45 (39.47	0.041§
	R1	26 (100)	10 (38.46	16 (61.54	
Final pathology ISUP, *n* (%)	1	11 (100)	11 (100)	0 (0)	< 0.001§
	2	51 (100)	40 (78.4)	11 (21.6)	
	3	50 (100)	22 (44)	28 (56)	
	4	13 (100)	4 (30.8)	9 (69.2)	
	5	15 (100)	2 (13.3)	13 (86. 7)	

Table 1 (continued)

*ANOVA test; §: chi squared test, *DRE* digital rectal examination, *ECE* extracapsular extension, *IQR* interquartile range, *ISUP* International Society of Urological Pathology, *microUS* micro ultrasound, *PRI-MUS* prostate risk identification using micro-ultrasound

Table 2 Relationship between number of predictors according to micro-ultrasound and presence of non-organ confined disease

Factor	Level	Organ-confined disease	Non-organ confined disease	*p*-value§	Univariate analysis OR (95%CI); *p*-value*
N (%)		79 (54.4)	61 (43.6)	–	–
N° of predictors, *n* (%)	0	54 (85.7)	9 (14.3)	< 0.0001	Reference
	1	14 (56.0)	11 (44.0)		4.71 (1.63–13.6) $p = 0.004$
	2	6 (27.3)	16 (72.7)		16.0 (4.95–51.8) $p < 0.0001$
	3	4 (23.5)	13 (76.5)		19.5 (5.18–73.3) $p < 0.0001$
	4	1 (7.70)	12 (92.3)		72.0 (8.31–623) $p < 0.0001$
MicroUS-based assessment, *n* (%)	0	54 (85.7)	9 (14.3)	< 0.0001	Reference
	≥ 1	25 (32.5)	52 (67.5)		12.5 (5.32–29.3) $p < 0.0001$

§Cochran–Armitage test for trend, *logistic regression model, *CI* confidence interval, *microUS* micro ultrasound, *OR* odd ratio

4 predictors were present ($p \leq 0.004$). The percentage of patients with non-organ confined disease with no predictors was 14.3% versus 67.5% if one or more were present ($p < 0.001$) (Table 2).

A staging concordance between EPE at microUS and final histopathology was found in 114 (81.4%) patients. Conversely, 25 patients (17.9%) were upstaged and 9 (6.42%) were under-staged by microUS (Table 2).

Diagnostic performance of all predictors was tested and visible ECE at microUS resulted to be the best predictor with a sensitivity of 72.1% and a specificity of 88.6%, negative predictive value of 80.5% and positive predictive value of 83.0%; moreover, it had the highest accuracy with an AUC 0.804 (95%CI 0.74–0.87). The AUCs of the other predictors ranged from 0.63 to 0.73 (Suppl. Table 1).

At univariate-LRM, DRE (OR 6.20, 95%CI 2.81–13.7), ISUP score at biopsy (OR 2.05, 95%CI 1.45–2.88), PRI-MUS (OR 4.98, 95%CI 2.52–9.87), presence of a visible breach of the prostatic capsule (OR 20.1, 95%CI 8.25–49.1), capsular bulge (OR 8.13, 95%CI 3.76–17.6) and hypoechoic halo or ring at microUS (OR 1.02, 95%CI 1.002–1.021) were all associated with EPE ($p \leq 0.019$) (Suppl Table 2). A multivariate-LRM (MLRM) including clinical variables only, DRE (OR 3.01, 95%CI 1.33–8.89) and PRI-MUS (OR 3.78, 95%CI 1.79–7.99) resulted to be predictors of EPE, showing an AUC of 0.820 (95%CI 0.750–0.890). In the MLRM including both clinical and microUS predictors, DRE (OR 3.16, 95%CI 1.12–8.88), visible ECE (OR 8.07, 95%CI 2.71–24.1), and capsular bulge (OR 3.80, 95%CI 1.25–11.6) were predictors of EPE with an AUC of 0.877 (95%CI 0.812–0.938) (Suppl. Table 2, Suppl. Figure 4). N-folds cross-validation resulted in an AUC of 0.795 (95%CI 0.675–0.851) for the clinical model versus 0.881 (95%CI 0.715–0.888) for the model with also microUS parameters.

Discussion

Our study aimed to assess the diagnostic performance of microUS in the detection of EPE in patients with biopsy-proven PCa scheduled for RARP. First, we assessed the feasibility of this tool for local staging of PCa. Presence of the predictors was significantly more frequent in patients with EPE. Furthermore, we confirmed that microUS was capable to correctly assess the presence of EPE in more than 80% of cases.

Several studies demonstrated that the presence of EPE, defined as extension of PCa beyond the boundaries of the prostate is an important risk factor for adverse oncological outcomes after surgery [16]. For this reason, the detection of non-organ confined disease plays an important role in surgical planning, in order to avoid positive surgical margins, especially in case of preservation of the neurovascular bundle [1, 3, 4]. Specifically, current guidelines contraindicate the adoption of a nerve-sparing approach in those cases where the risk of EPE is not negligible [1]. Therefore, a reliable tool capable of accurately determining the likelihood of a non-organ confined disease is required.

A growing body of evidence supports the use of mpMRI as the most accurate imaging tool both for PCa localization and staging purposes [17, 18]. Recent studies have shown

that the addition of preoperative mpMRI may increase the ability of clinical parameters and nomograms to predict EPE[19–21]. On the other hand, a large meta-analysis published in 2016 showed that mpMRI has a high specificity but heterogeneous sensitivity to detect EPE. Specifically, the sensitivity of mpMRI ranged between 38 and 58% with a specificity ranging between 90 and 95%. These differences are probably related to radiologist experience, location of the lesion and type of mpMRI utilized [20, 22]. Combination of high magnetic field strength (3 T) and functional imaging in addition to T2-weighted imaging, as well as experienced readers, may further improve mpMRI sensitivity [22]. However, these requirements increase costs and hinder the widespread adoption of this technology. Moreover, the real impact of mpMRI on the decision-making process (e.g., its ability to tailor the individual template of dissection during RARP) is still poorly understood. Improving imaging for pre-surgical planning can lead to a new scenario where the surgery can be tailored to suit both patient and tumor features, therefore, maximizing the oncological and functional outcomes.

In the last decades, ultrasonography (US) has become a routine examination during the work-up for PCa. The potential advantages of US are related to real-time information, portability, and low costs. These advantages prompted us to evaluate whether a model based on microUS could represent an effective tool for determining the presence of EPE. In a preliminary proof of concept study on 54 patients, we demonstrated that microUS had a sensitivity of 87.5% and a specificity of 80% for detection of EPE [23]. Based on the previous report, we identified five empirical parameters: four were borrowed from previous experiences with mpMRI (capsular bulge, capsular contact length, visible ECE and obliteration of the vesicle-prostatic angle), with the addition of the presence of the hypoechoic halo as a microUS-only related feature. Interestingly, a clear relationship between the number of risk factors and the presence of EPE was confirmed also in this larger series. Our data showed that the single variables (visible ECE, capsular bulge, obliteration of the vesicle-prostatic angle and hypoechoic halo or ring) at microUS were statistically significantly associated with non-organ-confined disease ($p < 0.001$). Only CCL > 15 mm was not found to be a predictor of EPE, and this was confirmed even when a different cut-off value (> 20 mm) was tested. This is in contrast with the recent literature on mpMRI. As an example, Rosenkrantz et al. demonstrated on 90 patients that length of capsular contact of dominant lesion at mpMRI had higher sensitivity, yet lower specificity, than subjective interpretations for EPE detection [24].

In our series, the most informative predictor of EPE was the presence of a visible capsular breach at microUS. These results were in line with our previous findings. Moreover, the risk of extracapsular disease increased with the number of risk factors. Furthermore, a model including both clinical and microUS-derived parameters achieved an accuracy of 0.871.

The main limitation of our study is the small sample size, related to the exploratory nature of the study. Furthermore, the researchers were aware that enrolled patients had to undergo RARP, which could have biased microUS interpretations, leading to over-detection of lesions. Moreover, the high-rate of positive DRE increased the likelihood of clinically detectable disease. Additionally, the procedures were performed at a highly specialized tertiary care center and by the most experienced microUS practitioners, and the results may not be generalizable. Furthermore, since inclusion and exclusion criteria were arbitrarily determined, a selection bias may be operational and may limit the generalizability of our findings. Moreover, the learning curve for microUS interpretation and interobserver variability in determining EPE, limit and may affect the results, although this is equally true for mpMRI interpretation. It is also important to note that high prostate volume and tumor localization could affect the results, as lesions located anteriorly or in the transitional zone may have been missed or misinterpreted by microUS [25]. Lastly, no head-to-head comparison with conventional TRUS or mpMRI was performed. Another limitation is represented by the fact that not all patients enrolled in the current study had a visible tumor at microUS and, therefore, a proper evaluation of EPE parameters was not performed in these individuals. However, the false negative rate of microUS in the current population (8.6%) was consistent with the false negative rate observed by previously published microUS series [26]. Finally, to validate our findings and promote the adoption of this promising imaging tool in clinical practice multicenter studies, and a head-to-head comparison with mpMRI s should be performed [27–30]. In addition, a prospective study should be conducted to assess the impact of preoperative evaluation of EPE both on functional and oncological outcomes.

Conclusions

Our findings suggest that microUS could represent an accurate tool for the evaluation of EPE. Moreover, having a positive DRE, visible ECE or the presence of a capsular bulging at microUS may be used together to accurately predict non-organ confined disease. Considering the current limitations of mpMRI, microUS could represent a viable, safe, and cost-effective device for imaging-based PCa local staging. Further prospective studies are needed to assess the real utility of this cutting-edge technology.

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Availability of data, materials, and code Data, code, and analysis are available upon request.

Declarations

Conflicts of interest The authors have no relevant financial or non-financial interests to disclose.

Research involving human participants, their data or biological material The study was approved by local authorities (Prot.n°2570-ICH-006) and all patients signed a written informed consent before enrollment.

Informed consent Informed consent was obtained from all individual participants included in the study.

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