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European Association of Urology

Brief Correspondence

Use of 29-MHz Micro-ultrasound for Local Staging of Prostate Cancer in Patients Scheduled for Radical Prostatectomy: A Feasibility Study

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Local staging is of paramount importance for risk stratification and surgical planning for patients diagnosed with prostate cancer (PCa). According to the European Association of Urology guidelines, local staging of PCa is mainly based on prostate-specific antigen values and digital rectal examination (DRE) [1]. Conventional transrectal ultrasound (TRUS), even when combined with three-dimensional reconstruction or functional images, has shown only limited performance in predicting the presence of extraprostatic extension (EPE) [1]. In recent years, several studies have evaluated the

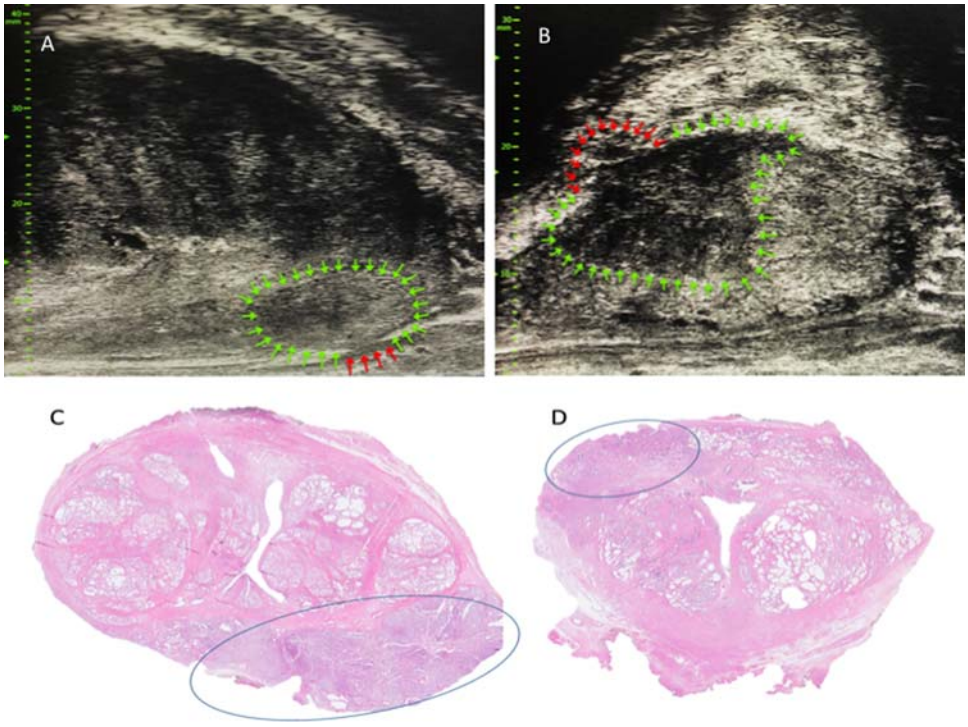

Fig. 1 – (A) Micro-ultrasound showing a mixed-echo (PRI-MUS 5) lesion with an irregular prostate border (red arrows) suspicious for extracapsular extension at the left apical region of the prostate. (B) Micro-ultrasound showing a mixed-echo (PRI-MUS 5) lesion with capsular bulging and the presence of a hypoechoic halo (red arrows) at the right base of the prostate. (C) Whole-mount section for (A) showing an index tumor with extraprostatic extension in the left lobe; the pathological diagnosis was grade group 4, pT3aN0 prostate cancer. (D) Whole-mount section for (B) with the index nodule bulging the capsule at the posterolateral base of the prostate. The pathological diagnosis was grade group 5, pT3aN0 prostate cancer. PRI-MUS = Prostate Risk Identification using Micro-Ultrasound score.

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Table 1 – Characteristics of patients scheduled for robot-assisted radical prostatectomy.

	All patients	OC disease	Non-OC disease	*p* value
Patients, *n* (%)	54 (100)	30 (55.5)	24 (44.5)	–
Median age, yr (IQR)	64.0 (57.7–69.0)	65.0 (58.2–69.2)	63.5 (57.2–68.7)	0.595*
Median total PSA, ng/ml (IQR)	7.6 (5.5–10.1)	6.8 (5.4–9.4)	9.0 (5.9–11.8)	0.158*
Digital rectal examination, *n* (%)				0.016**
Negative	13 (24.1)	11 (36.7)	2 (8.3)	
Positive	41 (75.9)	19 (63.3)	22 (91.7)	
Median prostate volume, cm^3 (IQR)	46.0 (34.2–56.2)	50.0 (30.0–56.2)	40.0 (36.2–57.5)	0.739*
Biopsy ISUP grade group, *n* (%)				0.047**
1	9 (16.7)	7 (23.3)	2 (8.3)	
2	19 (35.2)	13 (43.3)	6 (25.0)	
3	15 (27.8)	9 (26.7)	7 (29.2)	
4	9 16.7)	2 (6.7)	7 (29.2)	
5	2 (3.7)	–	2 (8.3)	
PRI-MUS score, *n* (%)				0.001**
1–2	4 (7.4)	4 (13.3)	–	
3	1 (1.0)	1 (3.3)	–	
4	34 (63.0)	23 (76.7)	11 (45.8)	
5	15 (27.8)	2 (6.7)	13 (54.2)	
Extracapsular extension on mUS, *n* (%)				<0.001**
Absent	33 (61.1)	26 (86.7)	7 (29.2)	
Present	21 (38.9)	4 (13.3)	17 (70.8)	
Capsular bulge on mUS, *n* (%)				<0.001**
Absent	36 (66.7)	28 (93.3)	8 (33.3)	
Present	18 (33.3)	2 (6.7)	16 (66.7)	
Obliteration of the PSVA on mUS, *n* (%)				0.440**
Absent	13 (24.1)	6 (20.0)	7 (29.2)	
Present	4 (7.4)	1 (3.3)	3 (12.5)	
Not applicable[a]	37 (68.5)	23 (76.6)	14 (58.3)	
Hypoechoic halo on mUS, *n* (%)				0.016**
Absent	42 (77.8)	27 (90.0)	15 (62.5)	
Present	12 (22.2)	3 (10.0)	9 (37.5)	
Capsular contact length on mUS, *n* (%)				0.142**
<15 mm	45 (83.3)	27 (90.0)	18 (75.0)	
≥15 mm	9 (16.7)	3 (10.0)	6 (25.0)	
Pathologic T stage, *n* (%)				–
pT2	30 (55.5%)	30 (100)	–	
pT3a	17 (31.5%)	–	17 (70.8)	
pT3b	7 (13.0%)	–	7 (20.2)	
Pathologic N stage, *n* (%)				–
pN0	47 (87.0)	30 (100)	17 (70.8)	
pN1	7 (13.0)	–	7 (20.2)	
Median tumor volume, % (IQR)	15.0 (5.0–26.25)	10.0 (5.0–20.0)	20.0 (8.5–33.75)	0.040*
ISUP grade group at final pathology, *n* (%)				0.002**
1	4 (7.4)	4 (13.3)	–	
2	19 (35.2)	16 (53.3)	3 (12.5)	
3	18 (33.3)	6 (20.0)	12 (50.0)	
4	7 (13.0)	3 (6.7)	4 (16.7)	
5	6 (11.1)	1 (3.3)	5 (20.8)	

IQR = interquartile range; ISUP = International Society of Urological Pathology; mUS = micro-ultrasound; OC = organ-confined; PRI-MUS = Prostate Risk Identification using Micro-Ultrasound; PSA = prostate-specific antigen; PSVA = prostate-seminal vesicle angle

[a] Patients for whom obliteration of the PSVA was not assessable because of either tumor location or the absence of a clear lesion on mUS.

* Mann-Whitney *U* test.

** χ^2 test.

accuracy of multiparametric magnetic resonance imaging (mpMRI) in the prediction of ECE, showing high specificity (0.87–0.88) but low sensitivity (0.55–0.61) [2,3]. In addition, mpMRI is highly dependent on the radiologist's experience and the inter-reader agreement is moderate [1]. As a consequence, while mpMRI is currently recommended for local staging of PCa, the strength of this recommendation remains low. Therefore, the search for alternative imaging modalities is still ongoing.

The ExactVu micro-ultrasound (mUS) system is a novel imaging tool based on high-frequency TRUS that is capable of providing high-resolution images of prostatic tissue [4]. According to recent studies, this diagnostic strategy has shown promising results in the detection of clinically significant PCa [5,6]. The aim of the current study was to assess the feasibility of mUS for predicting the presence of non–organ-confined PCa before radical prostatectomy. We performed a retrospective analysis of data prospectively collected for 54 consecutive patients with PCa scheduled for robot-assisted radical prostatectomy (RARP) between November 2019 and February 2020 at our department. Patients with extracapsular (cT3) disease at DRE and prostate

volume ≥100 ml who were previously treated with radiation, focal therapy, or androgen deprivation therapy or who were unable or unwilling to undergo TRUS were excluded. Before surgery, all patients underwent mUS evaluation of the prostate performed by two urologists with extensive experience in mUS in the prebiopsy setting who were blinded both to clinical and pathological data. All lesions were classified using a Prostate Risk Identification using Micro-Ultrasound (PRI-MUS) score [7]. The presence of EPE at final histopathological evaluation was defined as the presence of either extracapsular extension (ECE) or seminal vesicle invasion (SVI). On the basis of previous studies on mpMRI and mUS, the following potential risk factors for EPE were assessed: visible breach of the prostate capsule; capsular irregularity or bulging; obliteration of the prostatic-seminal vesicle angle; presence of a hypoechoic halo as previously defined by Staerman [8]; and capsular contact length ≥15 mm [9] (Fig. 1 and Supplementary Fig. 1). The mUS results were compared to the histopathological results according to the International Society of Urological Pathology/World Health Organization standards [10].

All data were recorded in a prospectively maintained database. The characteristics of the study population are shown in Table 1. Of note, four patients did not have any lesion on mUS (PRI-MUS 1–2) and had organ-confined disease at final histopathological evaluation. For the scope of the analysis, these individuals were grouped with those not showing any risk factor for EPE. Of the 50 patients with detectable lesions, 49 (98.0%) showed topographic concordance between the main lesion detected by mUS and the index lesion observed at final pathology. Notably, all patients with non–organ-confined disease had at least one PRI-MUS 4 or 5 lesion. Histopathological examination showed 30 patients (55.5%) with pT2 disease, while 17 (31.5%) and seven (13.0%) harbored pT3a and pT3b disease, respectively. Notably, all the individuals with SVI also had EPE according to pathology. Among the factors taken into account, ECE, a capsular bulge, and a hypoechoic halo on mUS were significantly more frequent among patients with non–organ-confined disease ($p \leq 0.016$). Table 2 shows the relationship between the number of risk factors and EPE. We observed a statistically significant relationship between the number of risk factors detected by mUS and the presence of EPE. In detail, the proportion of patients with non–organ-confined disease was 77.8% if one or more risk factors were present and only 11.1% if no risk factor was found ($p < 0.001$). According to our results, six patients (11.1%) would be upstaged and three (5.5%) would be understaged by mUS, with one of the latter three patients showing focal (microscopic) ECE. mUS-based assessment for prediction of EPE would result in sensitivity of 87.5% (95% confidence interval [CI] 74.3–100%) and specificity of 80% (95% CI 65.7–94.3%), with a negative predictive value of 88.9% (95% CI 77.1–100%) and positive predictive value of 77.8% (95% CI 62.2–93.4%).

In summary, correct preoperative local staging of PCa is essential for a risk-tailored surgical strategy. The broad use of mpMRI in this setting is limited by its low sensitivity, high cost, moderate inter-reader reproducibility, and long learning curve [2,3,11]. Given the limited role of mpMRI in this setting, the search for accurate diagnostic alternatives is still ongoing. According to our preliminary results, mUS may represent an effective tool for determining the presence of EPE, with high sensitivity and good specificity. Specifically, we identified five parameters borrowed from previous experiences with mpMRI, and we observed a clear relationship between the number of risk factors and the presence of non–organ-confined disease. The main advantages of a mUS-based approach are that it can provide a real-time assessment of the presence of EPE and that it can be directly performed by urologists, who may pay more attention on the parameters needed during surgical planning.

Table 2 – Relationship between the number of risk factors according to mUS and the presence of non-OC disease.

Risk factors	Patients, *n* (%)		*p* value*
	OC disease	Non-OC disease	
0	24 (88.9)	3 (11.1)	<0.001
1	4 (40.0)	6 (60.0)	
2	1 (14.3)	6 (85.7)	
3	0 (0)	4 (100)	
4	1 (20.0)	4 (80.0)	
5	0 (0)	1 (100)	
mUS-based assessment for non-OC disease[a]			
0	24 (88.9)	3 (11.1)	<0.001
≥1	6 (22.2)	21 (77.8)	

CI = confidence interval; mUS = micro-ultrasound; OC = organ confined.
[a] Diagnostic performance of mUS-based assessment of non-OC disease: sensitivity 87.5% (95% CI 74.3–100.0%), specificity 80.0% (95% CI 65.7–94.3%); negative predictive value 88.9% (95% CI 77.1–100%), and positive predictive value 77.8% (95% CI 62.2–93.4%).
* χ^2 test.

The main limitation of our study is the small sample size, which is related to the exploratory nature of the study. Furthermore, previous experience with mUS and the learning curve for mUS interpretation may also affect the results. Large-scale studies to validate our results and determine the learning curve and interobserver agreement for mUS are warranted before implementation of this promising imaging tool in clinical practice. In addition, the real clinical impact of mUS on surgical planning (use of intraoperative frozen section analysis or proportion of nerve-sparing procedures) remains to be determined. Finally, a head-to-head comparison with mpMRI should also be performed to further corroborate the results.

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Analysis and interpretation of data: Regis, Persico, Lughezzani.
Drafting of the manuscript: Regis, Persico, Lughezzani.
Critical revision of the manuscript for important intellectual content: Casale, Buffi, Guazzoni.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euros.2020.05.002.

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