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ORIGINAL PAPER

Diagnostic accuracy of the Novel 29 MHz micro-ultrasound "ExactVu™" for the detection of clinically significant prostate cancer: A prospective single institutional study. A step forward in the diagnosis of prostate cancer

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Summary *Introduction and Objective: ExactVu™ is a real-time micro-ultrasound system which provides, according to the Prostate Risk Identification Using Micro-Ultrasound protocol (PRI-MUS), a 300% higher resolution compared to conventional transrectal ultrasound. To evaluate the performance of ExactVu™ in the detection of Clinically significant Prostate Cancer (CsPCa).*

Materials and methods: Patients with Prostate Cancer diagnosed at fusion biopsy were imaged with ExactVu™. CsPCa was defined as any Gleason Score ≥ 3+4. ExactVu™ examination was considered as positive when PRI-MUS score was ≥ 3. PRI-MUS scoring system was considered as correct when the fusion biopsy was positive for CsPCa. A transrectal fusion biopsy-proven CsPCa was considered as a gold standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the receiver operator characteristic (ROC) curve (AUC) were calculated.

Results: 57 patients out of 68 (84%) had a csPCa. PRI-MUS score was correctly assessed in 68% of cases. Regarding the detection of CsPCa, ExactVu™ 's sensitivity, specificity, PPV, and NPV was 68%, 73%, 93%, and 31%, respectively and the AUC was 0.7 (95% CI 0.5-0-8). For detecting CsPCa in the transition/anterior zone the sensitivity, specificity, PPV, and NPV was 45%, 66%, 83% and 25% respectively ant the AUC was 0.5 (95% CI 0.2-0.9). Accounting only the CsPCa located in the peripheral zone, sensitivity, specificity, PPV, and NPV raised up to 74%, 75%, 94%, 33%, respectively with AUC 0.75 (95% CI 0.5-0-9).

Conclusions: ExactVu™ provides high resolution of the prostatic peripheral zone and could represent a step forward in the detection of CsPCa as a triage tool. Further studies are needed to confirm these promising results.

KEY WORDS: *Prostate Cancer; Imaging; Detection rate; Microultrasound; PRI-MUS score.*

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer among men and represents the fifth cause of cancer death worldwide (1). The diagnosis of PCa represents a challenge for urologist as too many indolent tumors are still diagnosed after random or systematic prostate biopsy (2, 3). Thus, in the era of active surveillance, it is crucial to identify patients with *clinically significant PCa* (CsPCa) (4). Historically, standard *ultrasound* (US) has been utilized for the diagnosis of PCa with very low accuracy (5, 6). Advances in *multiparametric Magnetic Resonance Imaging* (mpMRI) techniques have improved the diagnostic accuracy of PCa and nowadays mpMRI represents the mainstay of PCa diagnosis (7). Recently, PRECISION study demonstrated that mpMRI-targeted biopsies increased diagnostic yield compared with systematic biopsies, particularly for CsPCa, and reduces overdetection of clinically insignificant PCa (8).

However, to date, high quality prostate MRI is not always available in all the centers and mpMRI still remain an expensive and time-consuming test: therefore, we are far to consider it as a triage test in the detection of CsPCa (9).

Over time, several enhanced ultrasound techniques such as the colour/power Doppler, and contrast-enhanced *transrectal ultrasound* (TRUS) have been used in an attempt to improve the accuracy of ultrasonography.

However, these techniques have showed modest improvements over conventional TRUS, and their clinical use is limited (10, 11).

Recently, a novel US technology based on 29 MHz, *ExactVu™* micro-ultrasound devices, has been proposed for the evaluation of prostatic gland for the diagnosis and staging of PCa and for the execution of fusion biopsy (12). *ExactVu™* is a new imaging modality that operates at high frequency (29 MHz). Throughout the *Prostate Risk*

No conflict of interest declared.

Identification Using Micro-Ultrasound (PRI-MUS) protocol, suspicious regions can be characterized, stratified, and targeted, similar to the *Prostate Imaging-Reporting and Data System* (PI-RADS) protocol for mpMRI (12, 13).
The aim of our study was to evaluate the diagnostic accuracy of *ExactVu™* ultrasound in the detection of CsPCa in a cohort of patients with PCa previously diagnosed with targeted mpMRI/Toshiba Aplio 500™ fusion biopsy.

Materials and methods

Study population

After internal review board approval, between June 2018 and September 2018, 83 consecutive patients with biopsy proven PCa made by targeted mpMRI/TRUS fusion biopsy were registered into a prospective database and evaluated with *ExactVu™* ultrasound. In the absence of a validated learning curve, the first fifteen patients were excluded in order to reduce operator bias. Fusion biopsy was performed by one experienced urologist using the Toshiba Aplio 500™ system. Inclusion criteria were: 1) presence of one single index lesion on mpMRI according to the Prostate Imaging Reporting and Data system version 2 (PIRADS-v2) (14), 2) mpMRI/ultrasound fusion biopsy performed at our Department 3) diagnosis of PCa. Each patient included had complete demographic, clinical and pathologic parameters.

Study design

This prospectively recorded study included male patients referred to our tertiary center with diagnosis of PCa. First, patients underwent mpMRI which led to the identification of an index lesion defined as PIRADS-v2 score ≥ 3. Thereafter a fusion biopsy was carried out.
All patients with biopsy proven PCa at the level of the Index lesion were imaged with 29MHz *ExactVu™* transrectal micro-ultrasound.

Imaging

All the mpMRI examinations were performed before the biopsy, with a 1.5-T whole body scanner (*Signa HDxt; GE Healthcare, Milwaukee, WI, USA*) and a standard 8-channel pelvic phased-array surface coil combined with a disposable endorectal coil (*MedRad, Indianola, PA*). Parameters of mpMRI sequences and study acquisition were performed as previously reported in detail (15).
All MRI images were analysed by one expert uroradiologist, according to the 2012 *European Society of Urogenital Radiology* guidelines (16). The presence of PCa on mpMRI was defined as equivocal, likely or highly likely according to the PIRADS-v2 score.

Biopsy protocol

All men underwent transrectal fusion biopsy with the Toshiba Aplio™ 500 scanner (*Canon Medical Systems Corporation*) equipped with an end-fire 8-5.5 MHz transducer. After uploading the MRI images into the archive of the *ultrasound* machine (US), the registration between MRI and US images was done in the axial plane.
The fusion technique used an electromagnetic field tracking system, composed of an electromagnetic transmitter adjacent to the patient, as well as an electromagnetic sensors attached to the US transducer. After local anaesthesia with 10 mL of Lidocaine, a side by side images of US and MRI was obtained. Once that the index lesion was identified and marked, 3-5 cores were taken according to the size of the index lesion. Further random biopsy was taken in biopsy-naïve patients.

Histopathologic analysis

Histopathologic biopsy analysis was performed by a single experienced uro-pathologist according to *International Society of Urological Pathology* standards (17, 18).
Clinically significant prostate cancer was defined as any Gleason score ≥ 7.

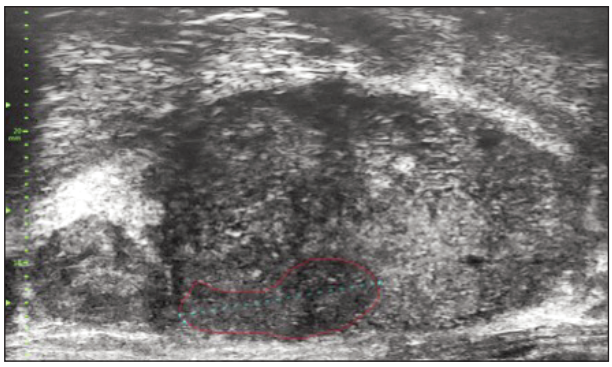
ExactVu™ micro-ultrasound Imaging

All patients underwent 29MHz *ExactVu™* transrectal micro-ultrasound at least 3 weeks after the fusion biopsy. One uro-radiologist and one urologist with extensive expertise in prostate imaging but naïve to micro-ultrasound, were trained by an experienced mentor to use the *ExactVu™* probes. Investigators and mentor were blinded to the mpMRI and to the pathologic report. *Prostate risk identification using micro-ultrasound* (PRIMUS) is an evidence-based scale for *ExactVu™*, developed to characterize tissue and stratify suspicious regions, as with PI-RADS for mpMRI (12). As previously described by *Ghai*, the echoic characteristics of the prostate gland were analysed and dichotomized in a 5 point-risk scale (Table 1) (12).

Table 1.
Echoic findings and corresponding PRIMUS risk assessment.

PRIMUS risk score	ExactVu microultrasound findings
PRIMUS 1	Small regular ducts, "Swiss cheese" with nother heterogeneity or bright echoes
PRIMUS 2	Some hyperechoic with or without ductal patches (possible ectatic glands or cysts)
PRIMUS 3	Mild heterogeneity or bright echoes in hyperechoic tissue
PRIMUS 4	Hetereogeneous cauliflower/smudgy/mottled appearance or bright echoes (possible comedonecrosis)
PRIMUS 5	Irregular shadowing (originating in prostate, not prostate border) or mixed echo lesions, or irregular prostate and/or peripheral zone border

Figure 1.
Parasagittal micro-ultrasound of the right lateral edge of the prostate. The ExactVu™ shows mottled tissue consistent with PRI-MUS grade 4 on the base of the prostate (red line underlines the lesion).



According to PRI-MUS protocol, *ExactVu*^{TM} imaging consisted of a five steps procedure: 1) identifying the prostate border; 2) identifying the peripheral zone; 3) identifying the transition/anterior zone; 4) identifying any suspicious features in the peripheral (Figure 1), transition (Figure 2) and anterior zone (Figure 3) and their nearness to the prostatic capsule (Figure 4); 5) assign a PRI-MUS risk score based on previously reported features 12. *ExactVu*^{TM} imaging was considered positive when the PRI-MUS score was ≥ 3.

Figure 2.
The ExactVu^{TM} *shows bright Echoes and "Cauliflower" area (arrow) consistent with PRI-MUS grade 4 on the transition zone of the prostate.*

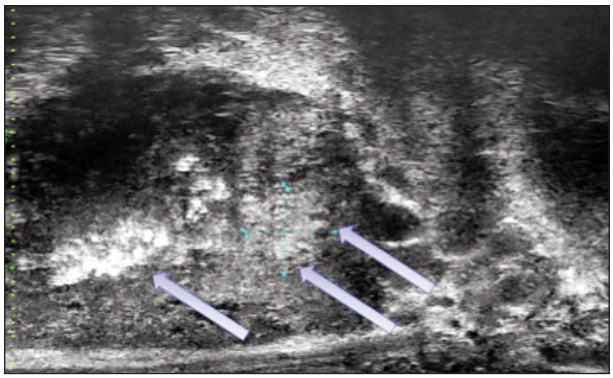


Figure 3.
"Smudgy/Mottled" tissue consistent with PRI-MUS 4 in the anterior part of the prostate (red line underlines the lesion).

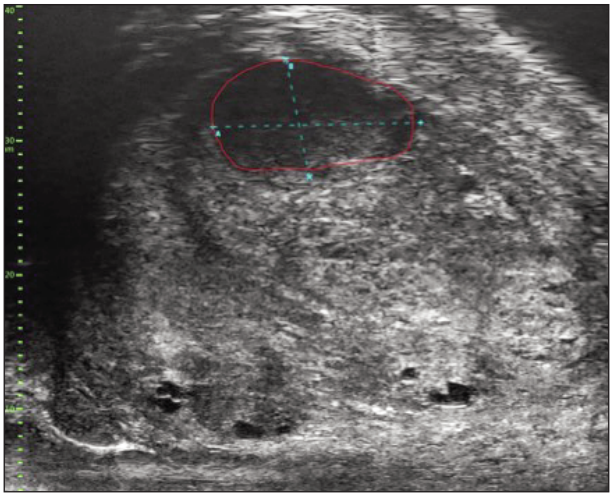
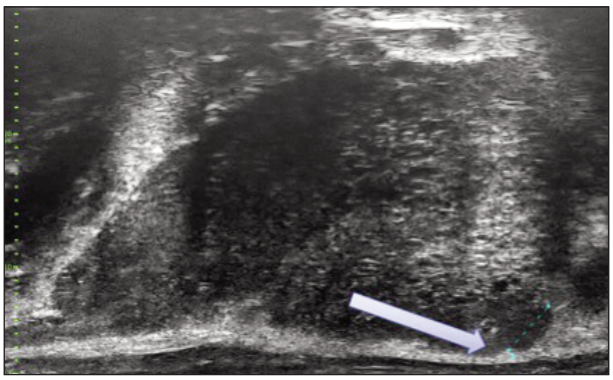


Figure 4.
Lateral micro-ultrasound of the left lobe of the prostate. The ExactVu^{TM} *shows mottled tissue consistent with PRI-MUS grade 4 causing irregular prostate border (arrow).*



Statistical analysis

Patient's demographic and detection performance of *ExactVu*^{TM} were analysed descriptively. For generating metrics of accuracy, the risk strata from the biopsy report was dichotomized to a non-clinically significant PCa and a Clinically Significant PCa. The presence of a "*fusion biopsy proven CsPCa*" was set as the gold standard and then the *ExactVu*^{TM} detection rate was evaluated. PRI-MUS scoring system was considered as correct when the ExacVu findings matched with the location of the CsPCa at fusion biopsy. Sensitivity, specificity, *positive predictive value* (PPV), *negative predictive value* (NPV) and area under the receiver operator characteristic curve (AUC) were calculated. Chi square test was used to evaluate the correlation between PRI-MUS score and CsPCa.
Statistical analysis were performed using SPSS Statistics 20 (*IBM Corp, Armonk, NY, USA*).

RESULTS

The demographic and clinical characteristics of the 68 patients available for the final analysis are shown in Table 2. Mean age at diagnosis was 63 years (± 8.6) and mean PSA value was 9.6 ng/mL (± 2.8). Digital-rectal examination was suspicious for PCa in 17 men (25%).

Table 2.
Clinical characteristics of 68 patients in the study group.

Parameters	Value
Age	
Mean ± SD	63.4 ± 8.6
Median (IQR)	67.5 (56-71)
PSA ng/mL	
Mean ± SD	9.6 ± 2.8
Median (IQR)	9.0 (7-12)
DRE, n (%)	
Positive	17 (25)
Prostate volume, mL	
Mean ± SD	42 ± 16.4
Median (IQR)	37 (31-52)
Prior negative biopsy, n (%)	23 (34)
MpMRI score, n (%)	
PI-RADS 3	28 (41.2)
PI-RADS 4	36 (52.9)
PI-RADS 5	4 (5.9)
Transition/Anterior Lesions, n (%)	14 (20.6)
Targeted mpMRI/ultrasound fusion biopsy cores per patient	
Mean ± SD	4 ± 0.6
Median (IQR)	4 (4-4)
Total positive cores	
Mean ± SD	3 ± 1.1
Median (IQR)	3 (2-4)
PRI-MUS score, n (%)	
PRI-MUS 1	10 (14.7)
PRI-MUS 2	16 (23.5)
PRI-MUS 3	18 (26.5)
PRI-MUS 4	17 (25.0)
PRI-MUS 5	7 (10.3)

Table 3.
Pathological characteristics of 68 patients in the study group.

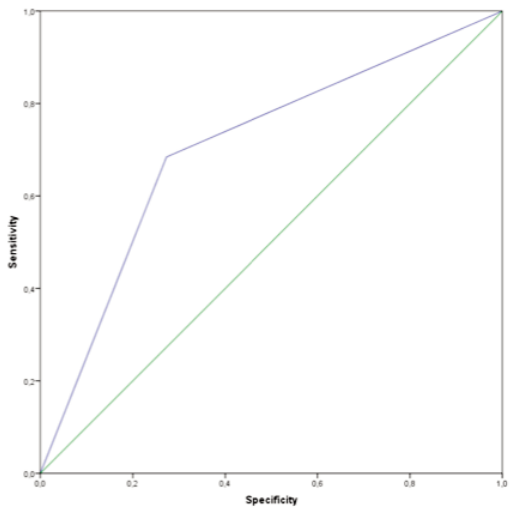
Parameters	Value
Biopsy Gleason score, n (%)	
6	11 (16.2)
7 (3+4)	44 (64.7)
7 (4+3)	6 (8.8)
8 or Greater	7 (10.3)

Table 4.
Performance characteristic of ExactVu™ ultrasound in the detection of prostate cancer in the overall population.

Detection rate	72%
Positive predictive value	94%

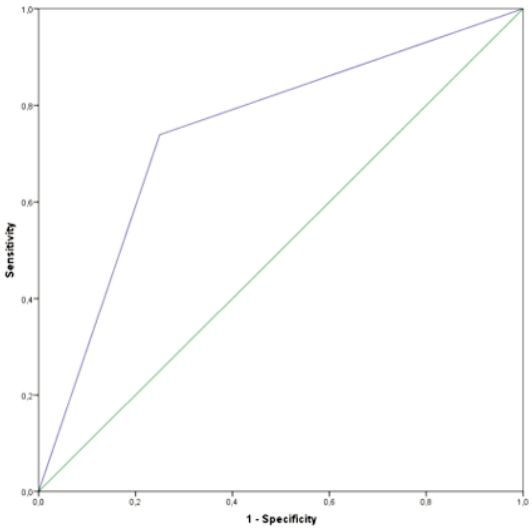
Twenty-three patients (34%) had a previous negative random biopsy. Mean prostate volume was 42 mL (± 16.4). Mean number of cores taken in the index lesion were 4 (± 0.6), mean number of positive cores was 3 (± 1.1), 20% of the index lesions were in the transition/anterior zone and PRI-MUS score ≥ 3 was found in 42 (62%) patients.
Table 3 depicts in detail the pathological features of the targeted mpMRI/ultrasound fusion biopsy: 57 patients out of 68 (84%) had a csPCa. Gleason score 3+3 was found in 11 patients (16.2%), Gleason score 3+4 was found in 44 patients (64.7%), Gleason score 4+3 was found in 6 patients (8.8%) and Gleason score ≥ 8 was found in 7 patients (10.3%).

Figure 5.
Receiver operating characteristic curve of ExactVu™ in the detection of clinically significant prostate cancer.



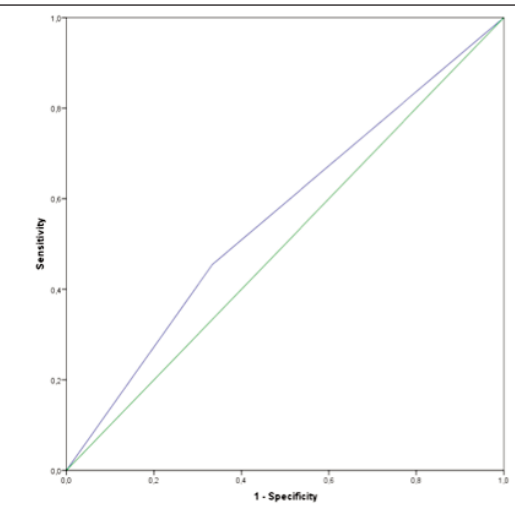
Performance characteristics of ExactVuTM e ultrasound in the detection of Clinically Significant Prostate Cancer	
Sensitivity	68 %
Specificity	73 %
Positive predictive value	93 %
Negative predictive value	31 %
AUC (95 % CI)	0.706 (0.5-0.8)

Figure 6.
Receiver operating characteristic curve of ExactVu™ in the detection of clinically significant prostate cancer located in the peripheral zone.

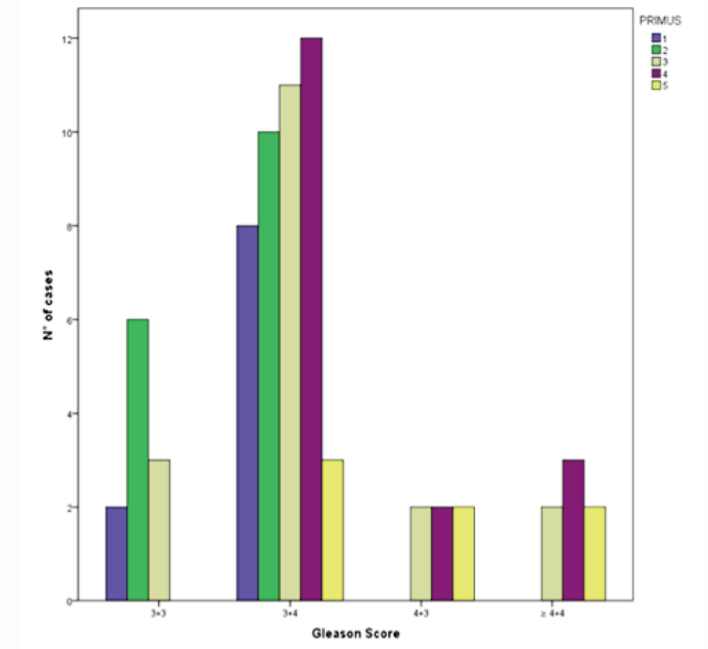


Performance characteristics of ExactVuTM e ultrasound in the detection of Clinically Significant Prostate Cancer in the peripheral zone	
Sensitivity	74 %
Specificity	75 %
Positive predictive value	94 %
Negative predictive value	33 %
AUC (95 % CI)	0.754 (0.5-0.9)

Figure 7.
Receiver operating characteristic curve of ExactVu™ in the detection of clinically significant prostate cancer located in the anterior/transition zone.



Performance characteristics of ExactVuTM e ultrasound in the detection of Clinically Significant Prostate Cancer in the anterior/transition zone	
Sensitivity	45 %
Specificity	66 %
Positive predictive value	83 %
Negative predictive value	25 %
AUC (95 % CI)	0.540 (0.2-0.9)



Gleason Score	PRI-MUS score		P value
	<3	≥3	
3+3	8 (73%)	3 (27%)	0.05
3+4	18 (40%)	26 (60%)	
4+3	-	6 (100%)	
≥ 4+4	-	7 (100%)	

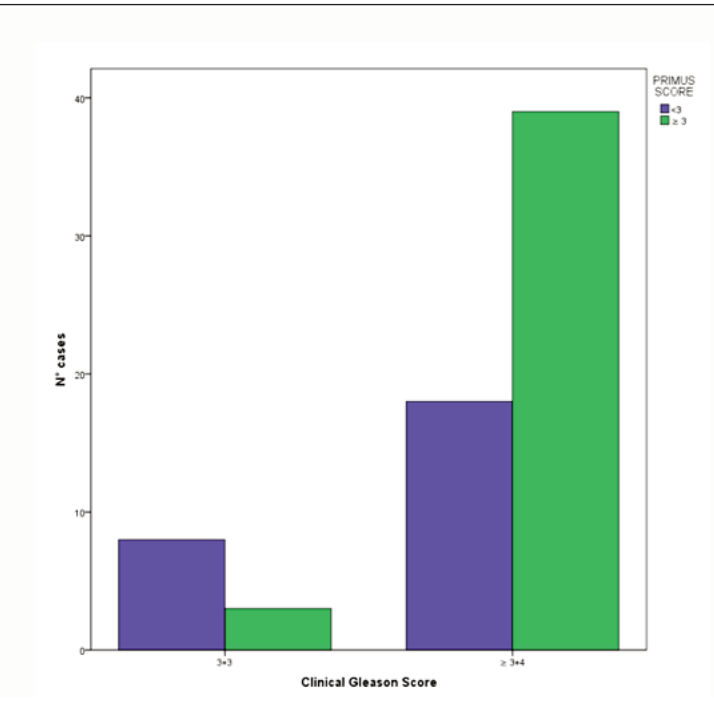
Figure 8.
Detailed report of the PRI-MUS score assignment in a cohort of 68 patients.

Diagnostic accuracy of the ExactVu™ e micro-ultrasound

Table 4 shows the pooled *detection rate* (DR) and PPV of *ExactVu™* e imaging for the diagnosis of PCa. Overall, *ExactVu™* micro ultrasound had DR and PPV of 72% and 94%, respectively. Considering exclusively the CsPCa (Figure 5), sensitivity, specificity, PPV, and NPV in the detection of CsPCa was 68%, 73%, 93%, and 31%, respectively and the AUC was 0.706 (95% CI 0.5-0-8). Accounting the anatomic distribution of the index lesions using the PIRADs-v2 scheme, the sensitivity, specificity, PPV, and NPV were 45%, 66%, 83%, 25% with AUC 0.540 (95% CI 0.2-0-9) for the detection of CsPCa in the transition/anterior zone, while for the CsPCa located in the peripheral zone the sensitivity, specificity, PPV, and NPV raised up to 74%, 75%, 94%, 33%, with AUC 0.754 (95% CI 0.5-0-9) (Figures 6, 7). Figure 8 shows the correlation between PRI-MUS score and presence of PCa: there were no cases of PRI-MUS 1-2 in Gs 3+3 PCa.

In Gleason score 3+4 PCa patients, PRI-MUS was false negative in 18 (40%; p = 0.05) cases (PRI-MUS grade 1-2).

However, for Gleason score 4+3 or higher, *ExactVu™* was always (100%; p = 0.05) reported as positive (PRIMUS ≥ 3). Figure 9 depicts graphically the correlations between PRI-MUS score and presence of CsPCa: among the 57 CsPCa, in 39 (68%) cases *ExactVu™* was considered as positive (PRIMUS ≥ 3; p = 0.01).



Gleason Score	PRI-MUS score		P value
	<3	≥3	
≤ 3+3	8 (73%)	3 (27%)	0.01
≥ 3+4	18 (32%)	39 (68%)	

Figure 9.
Correlation between PRI-MUS score and clinically significant Prostate cancer in 68 patients. Table shows the chi square analysis.

Discussion

The biggest issue linked to PCa workup is represented by the need to avoid overdiagnosis of low-grade tumours and the prominence of csPCa detection. Trans-rectal ultrasound (TRUS) has been widely used for the diagnosis and staging of PCa, showing poor sensitivity in identifying neoplastic lesion, often indistinguishable from normal tissue. Traditionally, men with a clinical suspicion of PCa underwent a random transrectal ultrasonography-guided biopsy, which has a rough overall detec-

tion rate of 30-50% (19-21). Nowadays, mpMRI seems to be the best imaging technique for the prostate, with a negative predictive value of 90% and an accuracy of 98% in diagnosing significant cancers (22, 23). Indeed mpMRI is increasingly performed before prostate biopsy, leading to fewer men who underwent biopsy, higher detection rate of csPCa and reducing the overdetection of clinically insignificant cancer (8). However, to date, mpMRI is burdened by some contraindications such as claustrophobia and pacemakers ant its widespread diffusion is limited by high costs, steep learning curve reporting the MRI findings and it is also a time consuming test.
Since conventional TRUS have shown an overall detection rate of 30-50%, in the last two decades, a multitude of enhanced ultrasound devices have been proposed with the aim to improve the accuracy of ultrasonography (19-21). *Contrast-enhanced TRUS* (CE-TRUS) was first described in 1968, it's based on air bubbles that remains inside the blood vessels showing the increased tumour vascularity (23). CE-TRUS have shown a detection rate of 30-60% and nowadays is mainly used in other medical specialities such as detection of liver malignancies (24). Colour Doppler is another tool that have been proposed to improve the ultrasound performance, showing an overall detection rate of 20% (25).
Recently, the *ExactVu™* system has been introduced in the market as a real-time micro-ultrasound system capable of providing 300% higher resolution (down to 70 µm) compared to conventional TRUS (26). *Ghai et al.*, in a recent publication, developed the PRI-MUS protocol, based on the *ExactVu™* findings, demonstrating promising levels of accuracy for the detection of CsPCa (12).
Some results of our study are noteworthy: first, to our knowledge this represents one of the few prospective series of patients investigating the accuracy of *ExactVu™* imaging in the detection of CsPCa. Second, our study demonstrated that the improved visualization of prostatic parenchyma lead to an improved detection of CsPCa. *ExactVu™* ultrasound shows an overall sensitivity and specificity of 68% and 73%, respectively with an AUC of 0.7. These results are consistent with those previously described by *Ghai et al.* who have showed an AUC of 74% for csPCa. Similarly, *Pavolvich et al.* using a different high frequency probe (21MHz) found improved accuracy in the detection of high grade PCa compared to conventional TRUS (84% *vs* 60%) (10). Third, since PRIMUS protocol was developed for peripheral zone lesions, we found differences in the *ExactVu™* 's accuracy basing on their location. Indeed, as expected, we found some false-negative and false-positive results, particularly when the index lesions were in the transition/anterior zone. It is well known that TRUS has lower detection rate for the anterior zone, and TRUS-guided biopsy miss the 80% of anterior PCa (27). In our series, the sensitivity for transition/anterior lesions was 45%, but it raises up to 74% for the peripheral lesions.
Similarly, to PIRADS score, PRI-MUS score has been developed to ease the characterization of prostatic lesions, to standardize the imaging methodology and to provide a scoring system to differentiate the risk of carcinoma in each zone of the prostate. As PIRADS, PRI-MUS score evaluation requires experience and can be burdened by interobserver discrepancy. In our series, PRI-MUS was correctly assessed in 68% of cases.
As expected, the widest rates of misinterpretations were for low-intermediate (PCa Gleason Score ≤ 3+4), in higher Gleason Score no misinterpretations were observed.
Despite our limited experience, we gained surprisingly high sensitivity and specificity. These promising results, suggests a potential use of *ExactVu™* both as a triage tool, discerning the best patients candidates to underwent mpMRI and as well as an alternative to mpMRI in centers where this technology is not yet available. The low value of NPV can be explained by our limited practice with this new technology and by the small sample size.
Further studies with larger cohorts are needed to clarify the true potential of micro-ultrasound devices.
Unfortunately, the lack of similar studies using *ExactVu™* probe, made comparison more challenging.
Our study has some limitations: first all the investigators were naïve to micro-ultrasound devices and to PRI-MUS protocol. Second, even though investigators were blinded to the previous clinicopathological findings, all patients underwent a previous fusion biopsy, which scars can be detected by *ExactVu™* ultrasound, affecting the index lesion detection rate. Third, the number of the patient's cohort is quite limited, but it inevitably depends on the novelty of this diagnostic tool and the prospective design of the study. Fourth, we used the mpMRI-targeted fusion biopsy as a reference standard, even if the ideal gold standard for assessing the true diagnostic performance of an imaging tool actually remains the final pathology in radical prostatectomy specimens. Moreover, our study shows the accuracy of ExactVu in the detection of CsPCa, since all patients included in analysis already had a previous diagnosis of PCa.
In Conclusion, *ExactVu™* showed a promising and quite high accuracy in the detection of CsPCa as assessed by targeted mpMRI/fusion biopsy. *ExactVu™* provides high resolution of the prostatic peripheral zone and represents a step forward in the detection of CsPCa. These results encourage the use of *ExactVu™* as a triage test and can help clinicians in the selection of borderline patients candidate to mpMRI. Further studies with larger cohort taking in account as reference the pathologic specimen of radical prostatectomy are needed to confirm these promising results.

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