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Prostate Mapping for cancer diagnosis: The Madrid protocol. Transperineal prostate biopsies using mpMRI fusion and micro-ultrasound guided biopsies

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Transperineal prostate biopsies combining mpMRI fusion and microultrasound guided biopsies

Abbreviations:

micro-US = micro-ultrasound

TBX= Ultrasound Fusion targeted biopsy

SBX = Systematic biopsies

TRUS-BX= Transrectal ultrasound biopsy

mpMRI = multiparametric MRI

PCa = Prostate Cancer

csPCa = clinically significant Prostate Cancer

PRI-MUS = Prostate Risk Identification Using Micro-Ultrasound

PI-RADS = Prostate Imaging-Reporting and Data System

Abstract

Purpose:

To assess the prostate cancer (PCa) detection accuracy of transperineal prostate biopsy using mpMRI/Ultrasound Fusion Targeted Biopsy (TBX) and Micro-Ultrasound (micro-US) during the same procedure. Micro-US is a new high-resolution imaging system that allows real-time targeted biopsy.

Methods:

194 consecutive patients underwent transperineal prostate biopsies using real-time targeted Micro-US (ExactVu™) and TBX (BiopSee®) in the same procedure, from February 2018 - September 2019. Biopsies were performed using a transperineal needle guide attached to the 29MHz High resolution Micro-US transducer.

Results:

The overall positive rate was 56% (108) for PCa and 42% (81) for csPCa (GG>1), adding Micro-US and MRI detected significantly more csPCa than systematic biopsy (SBX) ($p<0.001$). Micro-US found 12/108 (11%) PCa that were missed by all other techniques and 11 (92%) were csPCa. Both PI-RADS and PRI-MUS were strong predictors of csPCa in a Logistic Regression Model (AUC = 0.76). For PSA>4, PI-RADS>3 there was an improvement in detection rate between PRI-MUS 4 and PRI-MUS 5 (52% GG>1 to 92% GG>1). No fever or clinical infection was observed, 17 (8.7%) patients presented minor complications (Clavien Dindo I).

Conclusion:

This is the first study using a transperineal approach for Micro-ultrasound guided biopsy and mpMRI fusion biopsy. The results show a high accuracy for PCa and csPCA diagnosis, without infectious complications. The proposed method should be validated in large randomized clinical trials.

INTRODUCTION

Prostate cancer (PCa) is a significant health concern. It is the second most frequent cancer diagnosed in men[1]. The current standard for PCa diagnosis includes screening with PSA, digital rectal examination (DRE) and transrectal ultrasound biopsy (TRUS-BX)[1]. This approach has a low specificity and sensitivity, leading to a high rate of unnecessary biopsies, underdiagnosis of clinically significant prostate cancer (csPCa) as well as overdiagnosis and overtreatment of clinically insignificant prostate cancers (iPCa)[2,3]

Multiparametric magnetic resonance imaging (mpMRI) is a game-changer in the PCa diagnosis pathway; it allows image-based identification of suspicious areas in the prostate, which may improve diagnostic accuracy for intermediate/high-risk PCa. mpMRI and Ultrasound Fusion Targeted Biopsy (TBX) is increasingly used as an alternative to randomized biopsies and is a useful tool to improve accuracy of PCa detection[4–7]. However, mpMRI may miss some csPCa[8–11], there is heterogeneity between PIRADS scores and corresponding calibrations of biopsy yield. In addition, it cannot be used in certain patients with pacemakers, prostheses and severe claustrophobia[9,12,13].

Micro-ultrasound (ExactVu™) (micro-US) emerges as a promising new high-resolution imaging technology, which could be a potential alternative or complementary tool to MRI, to further improve csPCa yield[14]. The 29MHz micro-US transducer provides a 70µm resolution, which is a 300% improvement in resolution compared to conventional transrectal ultrasound (TRUS)[15,16]. Micro-US allows identification of suspicious lesions using the PRI-MUS™ scale (Prostate Risk Identification Using Micro-Ultrasound)[16] and performance of real-time targeted biopsies during the same procedure, with a short learning curve[14,17]. Moreover, It has been hypothesized that mpMRI and micro-US may be complementary in some patients as each technique may identify lesions missed by the other modality[14].

On the other hand, TRUS-BX carries a significant risk of severe infections and sepsis[18,19]. The alternative transperineal approach offers advantages such as better access to the whole prostate and a lower infection rate[20,21]. Transperineal prostate biopsy is recommended as an alternative to prevent infections and limit antibiotic use side effects[21,22]. It is foreseeable that an increase in transperineal prostate biopsy will be observed in the coming years.

This study aims to assess transperineal biopsy accuracy for PCa detection using both novel methods: Micro-US guided biopsy and TBX during the same procedure.

MATERIAL AND METHODS

Patients

From February 2018 to September 2019, 194 consecutive patients with suspicion of PCa, underwent transperineal prostate biopsy using Micro-US (ExactVu™, Exact Imaging, Markham, Canada), and TBX (Biopsee System) using the Ginsburg protocol. This was performed in a single centre (ICUA-Clínica CEMTRO, Madrid-Spain). All patients received informed consent and biopsies were performed by six urologists, who received training in transperineal biopsies using micro-US and TBX.

Criteria for suspicion of PCa and consequently for deciding to perform prostate biopsy included elevated PSA ($\geq$ 4 ng/ml) or suspicious DRE or visible lesion in mpMRI (PI-RADS ≥3). Both initial biopsy and repeat negative biopsy were permitted, however patients in whom either micro-US or mpMRI was not performed or with a known diagnosis of prostate cancer were excluded.

Parameters assessed included age, PSA, prostate volume, MRI lesions, PCa and csPCa in targeted and systematic biopsies (SBX), number of cores, and Gleason Grade Group (GG). CsPCa was defined as GG > 1, complications are reported according to Clavien-Dindo classification.

Biopsy protocol: **Prostate Mapping (Transperineal prostate biopsies using micro-ultrasound and TBX).**

Patients were positioned in a lithotomy position, prostate biopsy was performed under spinal short-term anesthesia with lidocaine. No Foley catheter was placed unless deemed necessary due to urethral bleeding and patients were discharged from the ambulatory centre the same day of the procedure after a few hours. Careful asepsis and shaving of the perineal area, as well as DRE were performed. All patients were initially submitted to real-time targeted transperineal prostate biopsies using micro-US while blinded to mpMRI findings. After that, patients with suspected mpMRI lesions (PIRADS $\geq$ 3) were additionally subjected to TBX using BiopSee® system (MedCom GmbH, Germany) and SBX according to the Ginsburg protocol or using the *"automatic placement"* tool from BiopSee® system. Patients without mpMRI suspicious lesions (PIRADS < 3) were submitted to real-time targeted biopsies using micro-US (ExactVu™) and SBX (BiopSee® system) by transperineal approach **(Figure 1).**

a. Micro-Ultrasound procedure

A transperineal guide was attached to the 29MHz micro-US High resolution transducer by ExactVu™ (Figure 2). The transducer with the attached transperineal guide was fixed on an articulated arm that allows stabilizing the transducer and moving it conveniently (Figure 2). When the transducer was positioned transrectally, urologists identified suspicious prostate lesions according to PRI-MUS™ (Prostate Risk Identification Using Micro-Ultrasound) classification, and targeted biopsies using micro-US were performed (Figure 2). The software includes a navigation system which allows targeting suspicious areas, according to the prostate zone and rotation angle with respect to the sagittal axis (Figure 2).

b. Fusion mpMRI targeted and systematic biopsies

After finishing the biopsies using micro-US, the high-resolution 29MHz transducer was removed, and the BiopSee® system for TBX was positioned, using a conventional biplanar transrectal ultrasound transducer. Lesions and prostate were marked on the MRI images and then the fusion process with a 3D ultrasound capture was carried out, using the BiopSee® software. If fusion was satisfactory the procedure followed, if it was not satisfactory, additional marking of the contour of the prostate was performed on the ultrasound images, and the elastic fusion feature was used. Subsequently TBX were first planned and then performed, taking up to 5 biopsies by lesion depending on the lesion's size and thereafter SBX according to Ginsburg protocol were taken. If the MRI was negative we used the *"automatic placement"* tool from the BiopSee® system to achieve a similar number of biopsies.

Histopathological analysis

Cores obtained from micro-US targeted biopsies and TBX transperineal biopsies, were collected into cassettes for histopathological analysis. A uropathologist performed core analysis according to ISUP classification, csPCa was defined as GG >1.

Statistical analysis

Data were collected in a prospective database and processed using SPSS V21 (SPSS inc, IBM Corp). McNemar's test and a Logistic Regression Model were conducted, $p \leq 0.05$ was considered statistically significant.

Note that all sensitivities and specificities should be viewed as relative measures as no true reference standard was collected (i.e. prostatectomy specimens or template biopsy) to confirm that patients with benign Micro-US, MRI, and SBX were indeed benign.

Results:

Demographic characteristics of 194 patients are summarized in Table 1. Median patient age was 62 (IQR 58-68), PSA 6.5 (IQR 4.7 - 9.2), prostate volume by MRI 58.1 (IQR 36.6 - 81.5). In 34 patients mpMRI was not suggestive for PCa (PI-RADS v2 score, ≤2). 65 (33.9%) had a previous biopsy and in 19 (9.5%) some additional test like SelectMDx, PCA3, or 4k score were available. Transperineal (TP) - guide and stepper were used in 141 (73%) patients, the remaining biopsies were performed freehand without the stabilization of stepper or needle guide.

The overall positive rate was 56% (108) for PCa and 42% (81) for csPCa (Table 2), adding Micro-US and TBX detected significantly more PCa than SBX alone ($p<0.001$), and significantly more csPCa ($p<0.001$). TBX compared with micro-US targeted biopsies did not reach statistical difference for PCa or csPCa diagnosis ($p=0.24$ and 0.15, McNemar test) (Table 2). Both PI-RADS and PRI-MUS were strong predictors of csPCa in a Logistic Regression Model (AUC for model with leave-one-out validation = 0.76). For PSA >4, PIRADS>3 there was an improvement in csPCa detection rate between PRI-MUS 4 and PRI-MUS 5 of 51% to 92% (figure 3).

PCa and csPCa findings according to PRI-MUS scale and PI-RADS classification using micro-US, TBX, SBX, and combining all techniques ("Mapping") are shown in Table 3. In 35 cases mpMRI was not suggestive of PCa (PI-RADS v2 score, ≤2), but with clinical suspicion or some additional positive test like SelectMDx, PCA3, or 4k, underwent micro-US biopsies + SBX, we found 15 (43%) PCa and 12 (34%) csPCa (Figure 1; Table 3).

Micro-US found 12/108 (11%) PCa that were missed by all other techniques and 11 (92%) were csPCa. In the other hand, SBX found 8 (4%) csPCa missed by TBX and micro-US; while TBX found just 1 (0.5%) csPCa missed by micro-US and SBX.

9 of 13 patients with previous prostatic surgery were positive for csPCa with no additional PCa. Interestingly, in these 9/13 csPCa the PRI-MUS score was 4-5, while the PRI-MUS score for the remaining 4/13 negative cases was $\leq$ 3.

Micro-US sensitivity, specificity, PPV and NPV to predict csPCa at the patient level were uniformly higher than mpMRI (Table 4). Both sensitivity and NPV achieved statistical significance with

p<0.001, however the implication of this is unclear given the clear patient selection and small number of mpMRI negative cases.

Performance of micro-ultrasound differed with prostate volume, finding more csPCa than mpMRI in smaller glands (<=50cc, 34 vs. 33) and less in larger glands (>50cc, 9 vs 19).

No fever or clinical infection were observed, nor any Clavien-Dindo > II complications. 17 (8.5%) patients presented minor complications (Clavien Dindo I-II), mainly acute urinary retention (Table 5 supplementary material).

Discussion:

PCa is classically suspected based on a suspicious DRE or high PSA levels or both. Definitive diagnosis depends on pathological verification in prostate biopsy cores with ultrasound-guided biopsy still standard of care[1]. A prostate biopsy can be performed by either the transrectal or the transperineal approach[20,21]. The conventional TRUS-BX approach based on a patient's selection with PSA/DRE and blind targeting has proven to be an inadequate diagnostic procedure due to a high rate of false negatives, miss-grading, and over-diagnosis of low risk disease[3].

Our study recommends a change in the clinical pathway of PCa diagnosis. The detection rate of prostate mapping by transperineal approach, was 56% for all PCa and 42% for csPCa. Adding Micro-US and TBX detected significantly more csPCa than SBX. Interestingly, micro-US found 11% PCa missed by all other techniques, a high percentage of those (92%) were csPCa.

PCa detection rates with either transperineal or TRUS-BX approach were comparable before the MRI era[20]. However, transperineal biopsies are recommended as an alternative to TRUS biopsies to avoid serious infections[18,22]. In our series, no infection was observed in any of the 194 patients as a result of the biopsy.

The need for a more accurate diagnosis pathway for PCa has involved imaging tools such as mpMRI and micro-US. Micro-US has emerged as a relatively inexpensive technique to capture images at higher frequencies[15] and is used in various applications in cancer, developmental biology, and cardiovascular disease. In urology, this technology has been applied to prostate and more recently in bladder cancer[16,17,23–26]. Lughezzani et al.[17], compared the diagnostic accuracy of micro-US targeted biopsies and TBX in detecting csPCa, in a cohort of 104 patients where Micro-US's relative sensitivity for csPC detection was 94%. Of note, the technique used in Lughezzani et al [17] study, was a TRUS-BX approach; our study is the first one describing a transperineal approach, with the benefit of a very low rate of infection.

Another application of Micro-US that has been is studied is the active surveillance of PCa[24,27,28]. Eure et al.[24], enrolled 9 patients on active surveillance; mpMRI and micro-ultrasound both demonstrated superior sensitivity to Gleason 7 or higher cancer compared to TRUS.

Level 1 evidence leading to changes in the PCa diagnostic paradigm with mpMRI has emerged in the last decade, including PRECISION[4], MRI 1st [6], 4M [7], BIDOC and systematic reviews[5]. While mpMRI is not a perfect solution, due to a percentage of MRI-invisible csPCa, and other limitations like reader variability, and the imprecision of current targeting methods20/04/2020 11:45:00, TBX substantially improves the detection of csPCa. Therefore, there is a need to standardize both MRI interpretation and prostate biopsy technique.

29 MHz Micro-US can be complementary to mpMRI in the same way as conventional US, with the advantage that Micro-US also identifies targets, especially in those cases of negative MRI with high suspicion of PCa or indeterminate (PI-RADS 3) lesions[4–7,29]. In our study, both PI-RADS and PRI-MUS were strong predictors of csPCa. mpMRI appears to perform better in larger prostates, perhaps due to limited penetration of micro-US. Imaging enhancements to improve image quality in the anterior prostate and a modified PRI-MUS scale addressing regions outside the peripheral zone should address this discrepancy and provide further improvement to micro-US performance.

The limitations of our study are similar to previous single-center studies. We did not complete a proper learning curve, and had no prior experience with micro-US other than the training received before the study. The lack of randomization and a control arm may have caused bias due to knowledge of mpMRI results and target location despite the Micro-US sampling occurring first before MRI review. Further, micro-US systematic sampling was not performed, the BiopSee automated placement system was used for systematic spacing. It is not certain that SBX taken using Micro-US would behave the same way. The sample size is small; however, this is the first study using the transperineal approach. The reported NPV for MRI was lower here than in other studies, however this may be due to the effect of additional cancers detected by Micro-US[30]. An analysis of the data with micro-US cores removed shows an MRI NPV of 80.2% [95% CI 66.6%-90.4%], which is much closer to values from the literature for this definition of csPCa[4,5].

Conclusion:

This is the first study using Micro-ultrasound guided biopsy and mpMRI fusion biopsy for PCa detection by transperineal approach. The results show a high accuracy for PCa and csPCA

diagnosis, avoiding infectious complications due to biopsy. The proposed method should be validated in large randomized clinical trials.

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Table 1. *Demographics n= 194 patients underwent Tranperineal prostate biopsies using micro-US and mpMRI*

Age (years), mean [IQR]	62.0 [58.0 - 68.0]
PSA, ng/ml mean IQR]	6.5 [4.7 - 9.2]
US Prostate Vol (cc), mean [IQR]	47.0 [32.0 - 67.0]
MRI prostate Vol (cc), mean [IQR]	58.1 [36.6 - 81.5]
Positive DRE, n (%)	31 (16.5%)
Previous biopsy	65 (33.9%)
Other test (Select MDx, PCA3, 4k score), n (%)	19 (9.5%)
mpMRI Lesions, n; mode(range)	258; 1 [0 - 4]
Anticoagulant therapy, n (%)	19 (9.8%)
Previous prostate surgery, n (%)	13 (6.7%)

micro-US = micro-ultrasound; PSA = Prostate Specific Antigen; US = Ultrasounds; MRI = Magnetic Resonance Imaging, mpMRI = multiparametric MRI; DRE = Digital Rectal Examination.

Table 1. Demographics n= 194 patients underwent Tranperineal prostate biopsies using micro-US and mpMRI

Table 2. findings n=194 underwent Transperineal prostate biopsies using micro-US Real Time Targeted, mpMRI targeted and systematic biopsies (Mapping).

	micro-US	mpMRI Targeted†	Systematic	Mapping (micro-US + mpMRI-T + Systematic)	*p* value
Benign, n (%)	121 (63%)	90 (45%)	82 (42%)	67 (34%)	
PIN, n (%)	8 (4%)	5 (2.5%)	7 (3.6%)	10 (5%)	
ASAP, n (%)	7 (3.6%)	2 (1%)	12 (6%)	12 (6%)	
PCa, n (%)	60 (31%)[a]	67 (35%)[a]	97 (50%)**	108 (56%)**	[a]p= 0.24, ** p<0.001
csPCa, n (%)	47 (24%)[b]	55 (28%)[b]	64 (33%)**	81 (42%)**	[b]p= 0.15, ** p<0.001
Number of lesions n; median [IQR]	407; 2 [1-5]¶	258; 1 [0 – 4] §	-	-	
Biopsy cores, n; mean [IQR]	911; 5 [3 - 6]	1269; 6 [5 - 9]	6340; 32 [30 – 37]	8520; 44 [38 - 48]	
Cores involved, mean [IQR]	2 [1 - 3]	2 [1 - 4]	3 [1 - 5]	5 [1 – 8]	

¶ PRIMUS ≥ 3; § PIRADS ≥ 3. †40 patients Negative mpMRI PIRADS 2 (no lesions)= 34 (17%),
micro-US = micro-ultrasounds (micro-US); mpMRI-T= multiparametric MRI Targeted biopsies; PIN = Prostatic intraepithelial neoplasia; ASAP= atypical small acinar proliferation: Pca = Prostate Cancer; csPCa= clinical significant Prostate Cancer.

Table 2. findings n=194 underwent Transperineal prostate biopsies using micro-US Real Time Targeted, mpMRI targeted and systematic biopsies (Mapping).

Table 3. PCa and csPCa findings according to PRI-MUS and PIRADS classification. n=194 patients under Transperineal Prostate biopsies using micro-US, mpMRI targeted (TBX), systematic biopsies (SBX) and combining all modalities (Mapping).

		Maximum PRI-MUS for Patient					Maximum PI-RADS for Patient				
PCa		**2** n=27 (14%)	**3** n=31 (16%)	**4** n=118 (61%)	**5** n= 18 (9%)	**Overall** n=194 (100%)	**2** n=35 (18%)	**3** n=44 (23%)	**4** n=88 (45%)	**5** n=27 (14%)	**Overall** n=194 (100%)
	micro-US	-	3 (1.5%)	46 (24%)	11 (5.7%)	60 (31%)	9 (4.6%)	7 (3.6%)	25 (13%)	19 (9.8%)	60 (31%)
	mpMRI targeted	0	5 (2.6%)	49 (25%)	14 (7.2%)	68 (35%)	-	8 (4.1%)	37 (19%)	23 (12%)	68 (35%)
	Systematic	1 (0.5%)	9 (4.6%)	72 (37%)	15 (7.7%)	97 (50%)	13 (6.7%)	13 (6.7%)	48 (25%)	23 (12%)	97 (50%)
	Mapping (micro-US + mpMRI targeted + Systematic)	1 (0.5%)	11 (5.7%)	80 (41%)	16 (8.2%)	108 (56%)	15 (7.7%)	16 (8.2%)	52 (27%)	25 (13%)	108 (56%)
csPCa (ISUP $\geq$ 2; Gleason $\geq$ 7)	micro-US	-	3 (1.5%)	33 (17%)	9 (5.2%)	46 (24%)	9 (4.6%)	4 (2.1%)	17 (8.8%)	16 (8.2%)	46 (24%)
	mpMRI targeted	0	4 (2.1%)	38 (20%)	12 (6.7%)	55 (28%)	-	4 (2.1%)	30 (16%)	21 (11%)	55 (28%)
	Systematic	0	2 (1%)	51 (26%)	10 (5.7%)	64 (33%)	8 (4.1%)	7 (3.6%)	28 (14%)	21 (11%)	64 (33%)
	Mapping (micro-US + mpMRI targeted + Systematic)	0	6 (3.1%)	60 (31%)	14 (7.7%)	81 (42%)	12 (6.2%)	9 (4.6%)	36 (19%)	24 (12%)	81 (42%)

PRIMUS= Prostate Risk Identification Using Micro-Ultrasound; micro-US = micro-ultrasounds (micro-US); PI-RADS = Prostate Imaging-Reporting and Data System; mpMRI = multipatametric MRI; Pca = Prostate Cancer; csPCa= clinical significant Prostate Cancer.

Table 3. PCa and csPCa findings according to PRI-MUS classification. n=194 patients under Transperineal Prostate biopsies using micro-US, mpMRI targeted, systematic biospsies and combining all modalities (Mapping).

Table 4. *Relative Sensitivity, Specificity, PPV and NPV for PRI-MUS and PI-RADS scale, n =194 patients under Transperineal Prostate biopsies using micro-US and mpMRI. Note that no reference standard was available to distinguish false negative cases, although these may exist due to incomplete sampling of the prostate despite all 3 approaches. For this reason all values here should be considered relative to the other methods employed rather than absolute for the population.*

	PRI-MUS		**PI-RADS**		
	PCa	csPCa	PCa	csPCa	p-value for csPCa comparison
Sensitivity	98.9% [95.5%-99.9%]	99.7% [96.8%-100.0%]	85.5% [77.9%-91.3%]	84.3% [75.2%-91.1%]	<0.001
Specificity	29.3% [20.5%-39.2%]	23.1% [16.2%-31.4%]	21.4% [13.8%-30.6%]	18.8% [12.7%-26.8%]	0.21
PPV	62.3% [54.7%-69.2%]	46.0% [38.7%-53.7%]	56.3% [48.5%-63.8%]	40.7% [33.3%-48.4%]	0.16
NPV	95.6% [83.7%-99.6%]	99.2% [91.4%-100.0%]	55.8% [38.9%-71.6%]	64.5% [47.7%-79.0%]	<0.001

PRIMUS= Prostate Risk Identification Using Micro-Ultrasound; PI-RADS = Prostate Imaging-Reporting and Data System; mpMRI = multipatametric MRI; Pca = Prostate Cancer; csPCa= clinical significant Prostate Cancer.

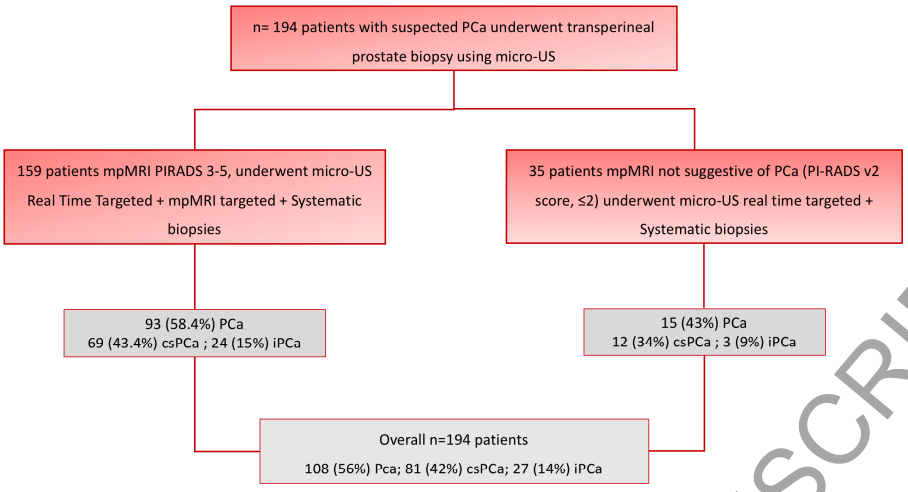


Figure 1. Diagnostic of Prostate Cancer (Pca), insignificant Prostate Cancer (iPCa) and clinical significant Prostate Cancer (csPCa) using micro-ultrasounds (micro-US) Real Time targeted biopsies and multiparametric MRI (mpMRI) targeted Biopsies combined with systematic biopsies; by transperineal approach, n=194 patients

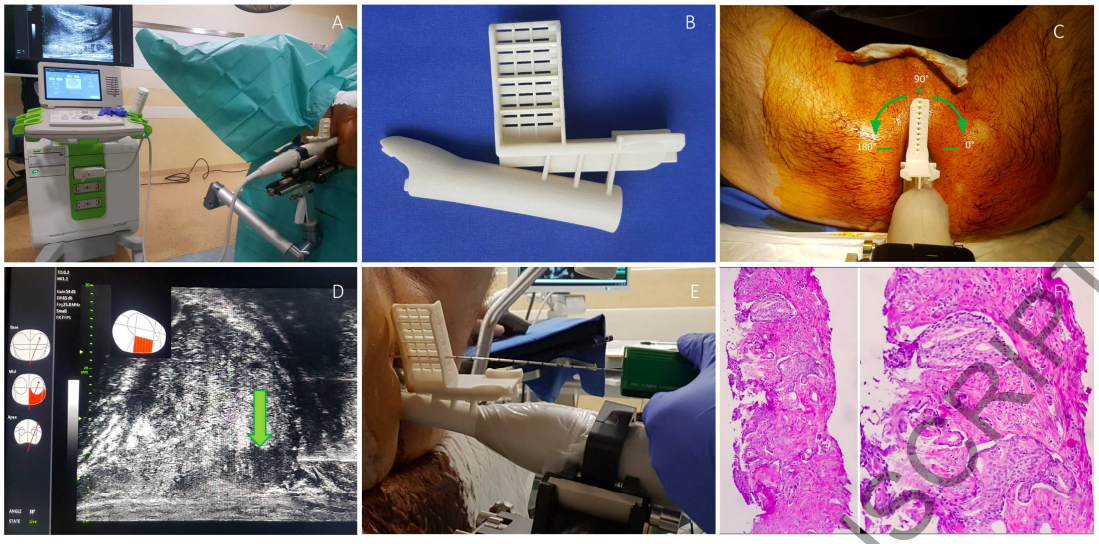
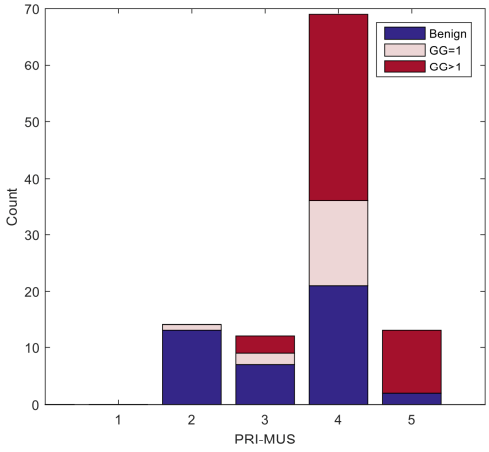


Figure 2: **Transperineal prostate biopsies using micro-US. A =** High resolution 29 MHz micro-US transducer, transperineal guide, stepper and console **B =** Transperineal guide; **C =** schema of movements & degrees in transperineal approach; **D - E =** Suspect area according to PRIMUS scale, identified and biopsied in real time, using micro-US and navigation system; **F =** csPCa findings in cores obtained from transperineal micro-US guided biopsy.



Factor	OR	p-value	VIF
Log10(PSA)	2.49 [10.26 - 0.61]	0.21	1.05
Age/10	1.42 [2.20 - 0.92]	0.11	1.13
DRE	1.42 [3.65 - 0.55]	0.47	1.03
Previous biopsy	0.67 [1.40 - 0.32]	0.28	1.06
PI-RADS 2	3.17 [9.59 - 1.05]	0.04	1.42
PI-RADS 3	Reference	-	-
PI-RADS 4	2.04 [5.00 - 0.84]	0.12	1.63
PI-RADS 5	6.37 [23.26 - 1.75]	0.01	1.65
PRI-MUS 2	0.00 [Inf - 0.00]	1	1.58
PRI-MUS 3	Reference	-	-
PRI-MUS 4	3.10 [8.40 - 1.14]	0.03	1.93
PRI-MUS 5	8.60 [41.39 - 1.79]	0.01	1.7

Figure 3. Logistic Regression Model (AUC for model with leave-one-out validation = 0.76) n=194 patients .