Davide Maffei ORCID iD: 0000-0001-5012-7219

Paolo Casale ORCID iD: 0000-0002-7899-5736

Diagnostic performance of Micro-Ultrasound at MRI-guided confirmatory biopsy in patients under active surveillance for low-risk prostate cancer

Authors:

- Davide Maffei, MD [1,2] – davide.maffei@humanitas.it (ORCID ID: 0000-0001-5012-7219)
- Vittorio Fasulo, MD [1,2] - vittorio.fasulo@humanitas.it
- Pier Paolo Avolio, MD [1,2] - pierpaolo.avolio@humanitas.it
- Cesare Saitta, MD [1,2] - cesare.saitta@humanitas.it
- Marco Paciotti, MD [1,2] - marco.paciotti@humanitas.it
- Fabio De Carne, MD [1,2] - fabio.decarne@humanitas.it
- Piergiuseppe Colombo, MD [1,3] - piergiuseppe.colombo@hunimed.eu
- Luisa Pasini, MD [2] - luisa.pasini@humanitas.it
- Silvia Zandegiacomo De Zorzi, MD [2] - silvia.zandegiacomo_de_zorzi@humanitas.it
- Alberto Saita, MD [2] - alberto.saita@humanitas.it
- Rodolfo Hurle, MD [2] - rodolfo.hurle@humanitas.it
- Massimo Lazzeri, MD PhD [2] - massimo.lazzeri@humanitas.it
- Giorgio Ferruccio Guazzoni, MD [1,2] – giorgio.guazzoni@hunimed.eu
- Paolo Casale, MD [2] – paolo.casale@humanitas.it
- Nicolò Maria Buffi, MD [1,2] – nicolo.buffi@hunimed.eu
- Giovanni Lughezzani, MD [1,2] – giovanni.lughezzani@hunimed.eu

[1] Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, Pieve Emanuele, 20090 Milan - Italy

[2] IRCCS Humanitas Research Hospital, Department of Urology, via Manzoni 56, 20089 Rozzano (Mi) - Italy

[3] IRCCS Humanitas Research Hospital, Department of Pathology, via Manzoni 56, 20089 Rozzano (Mi) – Italy

Institution: IRCCS Humanitas Research Hospital, Department of Urology, via Manzoni 56, 20089 Rozzano (Mi) - Italy

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Corresponding author: Paolo Casale – paolo.casale@humanitas.it.

Via Manzoni 56, 20089 Rozzano (Mi) - Italy

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DM, VF, MP, GGF, NMB and GL were responsible for conception and design of the study. DM, PPA, CS and MP were responsible for data acquisition. DM, VF, PPA, CS, MP, LP, SZDZ, PGC, ML and GL were involved in the investigation. DM and VF analysed the data and GL supported in data interpretation. DM drafted the manuscript. AS, RH, ML, GGF, PC made critical revisions for important intellectual content. NMB and GL supervised the project. All authors have read and agreed to the published version of the manuscript.

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BACKGROUND:

Active surveillance (AS) represents a standard of care of low-risk prostate cancer (PCa). However, identification and monitoring of AS candidates remains challenging. Micro-ultrasound (microUS) is a novel high-resolution imaging modality for transrectal ultrasonography (TRUS). We explored the impact of microUS TRUS and targeted biopsies in mpMRI-guided confirmatory biopsies.

METHODS:

Between October 2017 and September 2021 we prospectively enrolled 100 patients scheduled for MRI-guided confirmatory biopsy at 1 year from diagnosis of ISUP 1 PCa. TRUS was performed using the ExactVu microUS system; PRI-MUS protocol was applied to identify suspicious lesions (i.e. PRIMUS score ≥3). All patients received targeted biopsies of any identified microUS and mpMRI lesions and complementary systematic biopsies. The proportion of patients upgraded to clinically significant PCa (defined as ISUP≥2 cancer; csPCa) at confirmatory biopsies was determined, and the diagnostic performance of microUS and mpMRI were compared.

RESULTS:

92 patients had a suspicious MRI lesion classified PI-RADS 3, 4 and 5 in respectively 28, 16 and 18 patients. MicroUS identified 82 patients with suspicious lesions, classified as PRI-MUS 3, 4 and 5 in respectively 20, 50 and 12 patients, while 18 individuals had no lesions. 34 patients were upgraded to ISUP≥2 cancer and excluded from AS.

MicroUS and mpMRI showed a sensitivity of 94.1% and 100% and a NPV of 88.9% and 100% respectively in detecting ISUP≥2 patients. A microUS-mandated

protocol would have avoided confirmatory biopsies in 18 patients with no PRI-MUS ≥3 lesions at the cost of missing 4 upgraded patients.

CONCLUSIONS:

MicroUS and mpMRI represent valuable imaging modalities showing high sensitivity and NPV in detecting csPCa, thus allowing their use for event-triggered confirmatory biopsies in AS patients. MicroUS offers an alternative imaging modality to mpMRI for the identification and real-time targeting of suspicious lesions in AS patients.

Key-words: MicroUltrasound; Multiparametric MRI; active surveillance; prostate cancer; confirmatory biopsy.

Introduction

Active surveillance (AS) has established itself as standard of care for low-risk prostate cancer (PCa) patients [1,2]. Its implementation mitigates the burden of overtreatment that up to 20-50% newly diagnosed men may experience [3]. However, identification and monitoring strategies of patients who may benefit from AS remain challenging [4].

AS protocols require a multimodal assessment based on clinical parameters (digital rectal examination, DRE), laboratory testing (Prostate-Specific Antigen, PSA), imaging (multiparametric MRI, mpMRI), as well as patient willingness to continue surveillance [5]. Since mpMRI introduction in prostate examination, it has been shown to improve the detection of clinically significant prostate cancer (csPCa) and reduce the diagnosis of indolent disease [6]. MpMRI has henceforth

been implemented in AS protocols for monitoring of disease progression and to perform targeted sampling during surveillance biopsies [7].

Nevertheless, mpMRI may not be sufficient as a standalone test to entirely omit protocol-mandated biopsies in AS patients [8,9]. Furthermore, access to mpMRI examinations remains limited in many health care systems and the inter-reader variability outside of centers of excellence with dedicated urogenital-radiologists affects its universal adoption [10–12].

MicroUltrasound (microUS), a high-frequency transrectal ultrasound working at 29MHz, has recently emerged for the identification of PCa [13]. A stratification protocol for risk classification, the Prostate-Risk Identification Using Micro-Ultrasound (PRI-MUS), has been developed and validated to identify and grade suspicious areas within the prostate [14]. Potential lesions can be targeted for microUS-guided cognitive target biopsies. Our group has previously shown that MicroUS is able to improve the identification of patients harboring csPCa [15].

In our study, we evaluated the adoption of microUS in a contemporary cohort of patients with low-risk PCa undergoing confirmatory biopsies at 1 year from AS initiation. We aimed at determining the proportion of patients diagnosed with International Society of Uropathologist (ISUP) grade group 2 PCa after disease reclassification with microUS-guided targeted and systematic prostate biopsies, while comparing the diagnostic accuracy of microUS and mpMRI and estimating the number of potential biopsies avoided in patients if microUS showed no suspicious lesions.

Patients and methods

Patient Population

The current study, which represents a subgroup analysis of a previously published experience, was approved by our institution's ethical committee, and all participants provided informed consent for the clinical trial (ICH 003 v1.0 27/09/2017; study number 2004). A prospectively collected database of patients undergoing microUS-guided prostate biopsies was maintained since October 2017 [15]. Among 968 procedures performed up to September 2021, 149 patients undergoing confirmatory biopsies at 1yr from initial diagnosis of low-risk PCa and enrolment in the AS protocol were identified.

Inclusion criteria for enrollment in the AS program were diagnosis upon prostate biopsy of overall ISUP 1-2 PCa, ≤2 systematic positive cores, clinical stage ≤cT2b, PSA≤20ng/mL, PSA density ≤0.20ng/ml/ml at diagnosis and willingness to adhere to AS protocol. Before inclusion in AS protocol, all histological core biopsies were internally revised by a dedicated uro-pathologist(PGC).

Patients with prior diagnosis of ISUP 2, incidental finding upon resection of the prostate for benign pathology or without available MRI pre- confirmatory biopsy were excluded from this analysis. The number of positive cores on MRI-targeting samples was not considered an exclusion criterion, nor absence of MRI prior to diagnostic biopsies.

Biopsy protocol

Two independent urologists were involved at different steps of the biopsy procedure.

Prior to confirmatory biopsy, "urologist A" was responsible for planning the MRI-US fusion software procedure by acquiring the mpMRI data onto the Biojet fusion software and performing prostate and lesion contouring of all PI-RADS ≥3 regions of interest (ROIs) (Medical Targeting Technologies GmbH, Germany).

A second urologist ("Urologist B"), blinded to mpMRI results, was responsible for carrying out the microUS prostate exam and acquire the biopsy cores. All urologists involved in this step had completed the training module developed by ExactVu Imaging for microUS reading. Prostate sextant areas were scored against the PRI-MUS protocol and graded for the risk of malignancy. All suspicious lesions identified and graded PRI-MUS ≥3 were reported on a worksheet and received real-time targeting with a minimum of two cores using a transrectal approach.

At this stage, "urologist B" accessed Biojet software and was unblinded from mpMRI images. After MRI-US image software-fusion using a BK ultrasound probe, microUS and mpMRI identified lesions would be compared (BK Medical, London, UK). Urologist B acquired targeted biopsies with a minimum of 2 cores of all microUS-discordant mpMRI ROIs. When the MRI-contoured ROI was considered concordant with the already targeted microUS identified lesion, no separate target cores were taken to minimize the total number of biopsy cores. All patients received a 12-core systematic biopsy at the end of the procedure.

Patients were subjected to a mixed transrectal and transperineal biopsy according to target lesion locations. All microUS targeting was performed using a transrectal approach. MRI-targeting was performed with a transperineal approach in patients with anterior and apical lesions.

The histological samples were analyzed by a dedicated uro-pathologist using the ISUP grade groups.

Analysis

The primary endpoint was to assess the number of patients reclassified to ISUP≥2 PCa at confirmatory biopsy using microUS targeted and systematic biopsies.

Secondary endpoints were the following: to compare the diagnostic accuracy of microUS and mpMRI in identifying patients with ISUP≥2 PCa and the concordance between microUS and mpMRI lesion localization and risk stratification; to assess PRI-MUS and PI-RADS score as predictors of csPCa; to assess the number of potential biopsies avoided using imaging as screening tool; to compare the ability of microUS-targeted, mpMRI-targeted and randomized systematic approach, both individually and combined, to correctly identify patients excluded from AS. Targeted cores were classified according to the imaging methodology that identified the ROI. When the ROI was visible both at microUS and mpMRI, the target cores taken were analyzed as being performed by both targeting methods, independently of the actual biopsy technique applied in obtaining those cores.

Patient groups were compared with chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. A Cochran-Armitage test for trend was used to compare biopsy result (i.e. negative or ISUP1PCa vs csPCa) by PRI-MUS or PI-RADS scores. The sensitivity, specificity, positive predictive value(PPV), and negative predictive value (NPV) of microUS and mpMRI were calculated based on the underlying pathology results from any biopsy sample in

the per patient analysis. In the per lesion analysis, these were calculated according to the specific targeting modality that identified the lesion.

Statistical significance was set at $p < 0.05$. Statistical analysis was done with STATA®16.1 (*StataCorp, College Station, Texas*).

Results

1. Patient characteristics

We identified 100 patients for analysis. Descriptive statistics are presented in table 1 for overall population and stratified for outcome of confirmatory biopsy, i.e. patients with either negative biopsy or confirmation of ISUP 1 disease and for patients upgraded to ISUP≥2 disease.

2. Results of microUS and mpMRI imaging

Overall, 92% of patients had at least one PI-RADS ≥3 lesion, while microUS classified 82% patients as PRI-MUS≥3. Detailed patient stratification and concordance between PRI-MUS an PI-RADS scores is show in Suppl. Table 1. In 57% patients the index lesions, i.e. highest PI-RADS or PRI-MUS score lesions, were concordant in location, while 20% had discordant index lesions, 20% had lesions identified on one modality only and 3 patients had no lesions at all (Suppl Table 2). Among the patients with concordant lesions, 25/57 (43.9%) had equivalent PRI-MUS and PI-RADS scores.

3. Results of Confirmatory Biopsy

Overall, PCa detection rate was 65%. A confirmed ISUP 1 diagnosis was made in 31% individuals, while 35% had a negative biopsy and 34% patients were upgraded to ISUP≥2 disease and excluded from AS.

No significant differences were identified in population characteristics (DRE, family history, prostate volume, PSA density, number of microUS and MRI-identified lesions or rate of microUS and MRI lesion concordance) between those continuing on AS and those with reclassification to ISUP≥2 disease. A statistically significant difference among the two groups was found only in PRI-MUS scores (table 1; p=.010), while PI-RADS did not reach statistical difference (p=0.081)

3.1 Per patient analysis

MicroUS and mpMRI were able to each identify 94.1% and 100% out of 34 patients with ISUP≥2 disease, respectively. The NPV for microUS and mpMRI in excluding men with no upgrading was 88.9%(16/18) and 100%(8/8), respectively. A detailed comparison of diagnostic accuracy of microUS and mpMRI as imaging modalities is found in Table 2a.

Figure 1 shows overall and csPCa detection rates according to PRI-MUS and PI-RADS scores. Increasing PRI-MUS score was confirmed to be statistically significantly associated with csPCa identification(chi-square for trend: p< 0.01), while PI-RADS did not reach statistical significance(chi-square for trend: p=0.090). Supplementary Table 3 shows per patient csPCa detection rate according to patient's PRI-MUS and PIRADS scores.

Fig. 2 shows a microUS image of a PRI-MUS 5 lesion and the corresponding MRI lesion scored PI-RADS 4, classified as ISUP 3 PCa at pathology.

3.2 Per lesion analysis

ISUP≥2 disease was identified in 42(25.9%) of targeted lesions. MicroUS and mpMRI were able to identify 26(61.9%) and 24(57.1%) of 42 lesions with csPCa, respectively. The complete per lesion csPCa detection rate is shown in supplementary Fig. 1. Table 2b shows the per lesion analysis of the diagnostic accuracy of microUS and mpMRI in identifying lesions positive for csPCa on targeted and systematic biopsy.

3.3 Combined approach - Results of Targeted biopsies and mixed targeting modalities

Overall, 12(35.3%) csPCa individuals were missed by systematic sampling and detected only on targeted cores. Of these, 7 were detected by both microUS and MRI-targeted biopsies, 2 by microUS-targeted only and 3 by MRI-targets only. Conversely, systematic randomized biopsies detected csPCa in additional 6 patients: four with ISUP 2 disease (with ≥2 positive cores) and two with ISUP 3 disease.

Targeted cores of microUS and mpMRI suspicious lesions were able to diagnose independently 25(73.5%) and 22(64.7%) of all csPCa, patients, compared to 22 patients at pathological evaluation of systematic samples.

A combined systematic and targeted approach of either microUS- or mpMRI-targets would have diagnosed 31(91.2%) and 32(94.1%) patients, therefore missing only 3 and 2 patients respectively.

Full results of single and mixed biopsy approaches are provided in Table 3; supplementary table 4 shows a McNemar table for confirmation of csPCa per lesion according to biopsy strategy.

Discussion

In this study we introduced high-resolution microUS as a new imaging modality in the monitoring of patients under PCa AS. We evaluated its use in the identification of patients suspected of disease progression and the targeting of suspicious lesions during confirmatory biopsies. We compared its diagnostic accuracy to that of systematic and MRI-targeted biopsies, showing comparable csPCa detection rates between microUS- and mpMRI-driven biopsy approaches. A microUS-driven AS program using event-triggered confirmatory biopsies would have spared 18% men from biopsy at the cost of missing csPCa in 4% of patients.

Despite the improvements in PCa diagnostics, urologists remain challenged with the management of low-risk PCa. Introduction of MRI in the biopsy-decision making step and in guiding biopsy has been shown to reduce the overdiagnosis of indolent disease, while AS has helped preventing overtreatment [16].

The adoption of imaging in AS protocols has gained increasing support [17,18]. Stavrinides et al. have proposed an MRI-guided surveillance protocol with event-triggered biopsy, shown to safely monitor patients while reducing the number of protocol-mandated biopsies [19]. A dedicated PRECISE score was developed to determine risk of disease progression of mpMRI lesions during AS [20]. Pre-bioptic MRI and ROI targeting is recommended to complement systematic sampling during any reclassification biopsy [21]. It allows for accurate disease localization without biopsy-related artifacts, and to guide treatment for focal and radical therapies [22,23].

mpMRI may nevertheless miss some csPCa, and the search for other imaging modalities has continued with investigations on PSMA-PET and multiparametric

US, even if less widely available than mpMRI [24–26]. The CADMUS trial showed that multiparametric US was non inferior to mpMRI in detecting csPCa defined as ISUP≥2 disease, with a non-statistically significant difference of 21.2% missed cancer by mpUS [27]. Furthermore, many health care systems struggle with the increased demand of prostate MRI for screening, monitoring and staging, pushing for the search of alternative imaging modalities with reduced costs and wider availability.

MicroUS has recently been evaluated as a targeted biopsy modality that compared favourably to conventional US based on highly accurate US features associated with PCa. It was shown to increase csPCa detection in patients undergoing systematic biopsy and have similar diagnostic accuracy to mpMRI-US targeted biopsies [28–30]. A feasibility study confirmed superior sensitivity for csPCa detection of both microUS and mpMRI compared to conventional US in a small AS series [31].

Our results confirmed that microUS-targeting has similar csPCa detection at confirmatory biopsies compared to mpMRI-targeting, with 31 and 32 patients identified out of 34, respectively. Moreover, we showed that the addition of microUS-targeted biopsies to mpMRI-targeted sampling can further help in the identification of patients who should exit AS. As confirmed in previous comparative studies in the primary setting, both imaging modalities achieved high sensitivity (94.1% vs 100%) and negative predictive value (88.9% vs 100%) in detecting csPCa. These results were less evident in the per lesion analysis, with microUS and mpMRI achieving similar sensitivity (61.9% and 57.1% respectively)

and positive predictive values (25.0% and 19.4%), suggesting that systematic biopsies are still required for PCa mapping for treatment planning.

MicroUS introduction in AS protocols allows for a "real-time" examination of the prostate during routine outpatient follow-up where patient may be offered immediate lesion targeting in case of suspicious features. MicroUS could be used as a further instrument to guide in the decision for reclassification biopsies and we showed that this approach would spare 18% of men from biopsy at 1 year at the cost of missing 4% of csPCa. Such approach may minimize the burden of repeat hospital attendance, limiting patients' exposure to diagnostic examinations and the potential to increase compliance with AS protocols [32].

We were able to evaluate a variety of biopsy modalities including all combinations of microUS-targeted, mpMRI-targeted and systematic biopsies. MicroUS- and mpMRI-targeted biopsies yielded a similar csPCa detection, whether combined with systematic sampling or not. Interestingly, the addition of systematic sampling did increase the csPCa with 11/34 patients missed by target cores. Future possibilities for microUS may see it as an alternative for MRI-targeted biopsies as well as an inclusion in an mpMRI-diagnostic protocol for mpMRI-target microUS-guided cognitive biopsies. This was not evaluated in our study as our MRI-targeted biopsy standard-of-care protocol was based on MRI-US software-assisted fusion biopsies. In addition, the commercialization of a transperineal needle guide for microUS, not available at the time of study initiation, would allow microUS targeted biopsy implementation following the recent guideline indication to perform transperineal biopsy.

The present study represents the largest effort to date to evaluate a new imaging modality with adequate blinding in a cohort of AS patients against the gold standard of mpMRI. Among the strengths of our work, the blinding of the urologist performing microUS from mpMRI results allows for a direct comparison between the diagnostic accuracy of the two techniques.

Our study presents some limitations. Firstly, the csPCa definition of any ISUP≥2 disease does not consider disease volume. While AS indications are expanding to include some low-to-intermediate grade disease, upgrading from ISUP 1 to 2 disease remains a commonly accepted criteria for exiting AS [33].

Secondly, both urologists and radiologists were aware of AS enrolment, potentially lowering the threshold for equivocal PRI-MUS 3 and PI-RADS 3 lesion identification. This may explain the low number of negative mpMRI exams and the low specificity of both modalities in excluding men with no or low-grade disease.

Thirdly, mpMRI images did not undergo internal revision by a dedicated uro-radiologist, introducing variability of expertise levels in reporting. Furthermore, not all patients undergone MRI prior to diagnostic biopsies. Concomitantly, the study included the urologists' microUS learning curve. These biases are expected to lower the overall diagnostic accuracy of both modalities with limited impact on the overall study results.

Fourthly, PRI-MUS is a novel risk identification tool that is being compared to a revised version of PI-RADS score (v2 or v2.1 depending on time of MRI reporting). While statistically significant association between higher PRI-MUS scores and csPCa was confirmed, no difference was noted between PRI-MUS 3 and 4

lesions. This suggests that further revision with a PRI-MUS version 2 may help to differentiate between suspicious and equivocal lesions. Longitudinal data obtained from monitoring AS patients may help in identifying new US features on microUS that are associated with csPCa and further improve the characterization of prostatic tissue with PRI-MUS score.

Lastly, no comparison with wholemount prostatectomy specimen was feasible. The specificity and negative predictive value may have been limited by a 2-core targeted and 12-core standard systematic sampling due to imaging-invisible disease and targeting failure. Nevertheless, MRI-invisible disease has been shown to correlate with lower risk disease and lower rates of failure during AS and after radical treatment. Long term-follow up of our population will be needed to evaluate whether this applies to microUS.

Conclusion

MicroUS represents a valid imaging modality for monitoring during AS programs for low grade prostate cancer with comparable metrics in terms of sensitivity, specificity, NPV and PPV compared to mpMRI for csPCa reclassification. The adoption of microUS in AS programs may allow for a ready-to-use and cost-effective alternative imaging modality to mpMRI for patient monitoring and target biopsy sampling.

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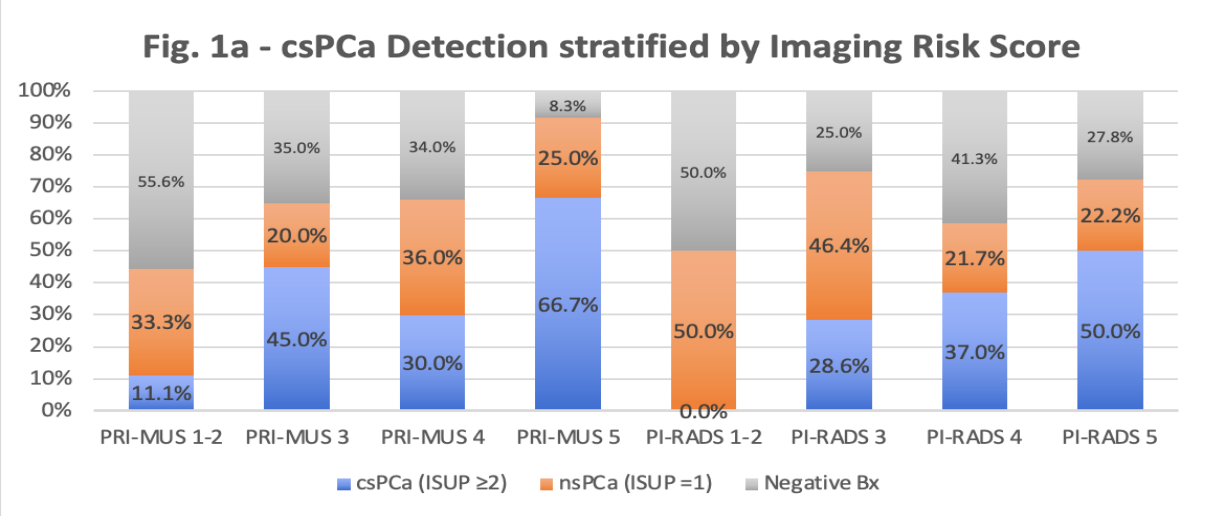
Figures



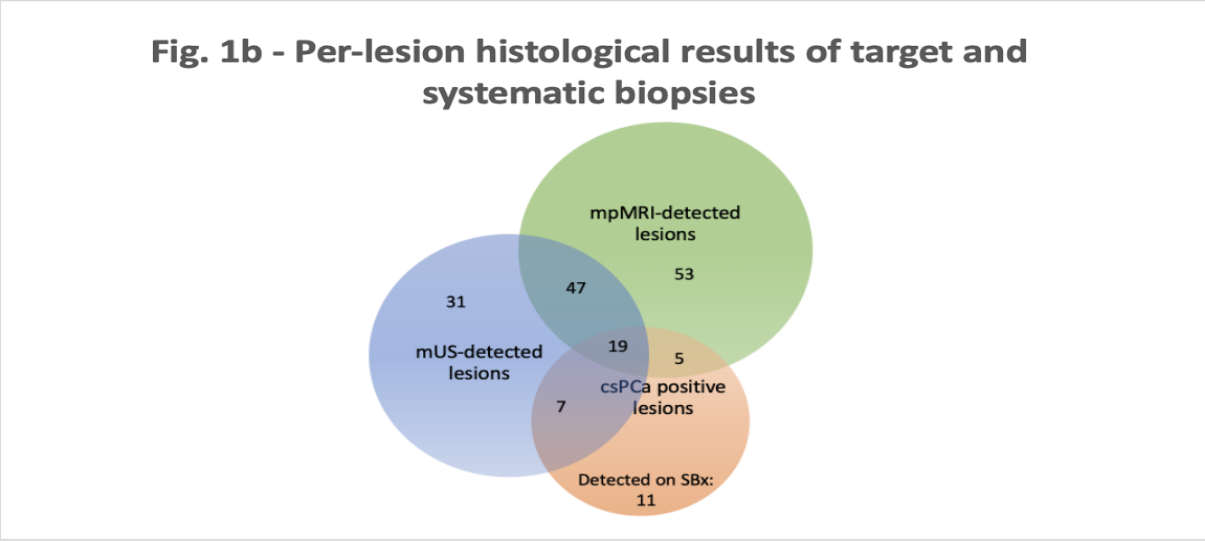
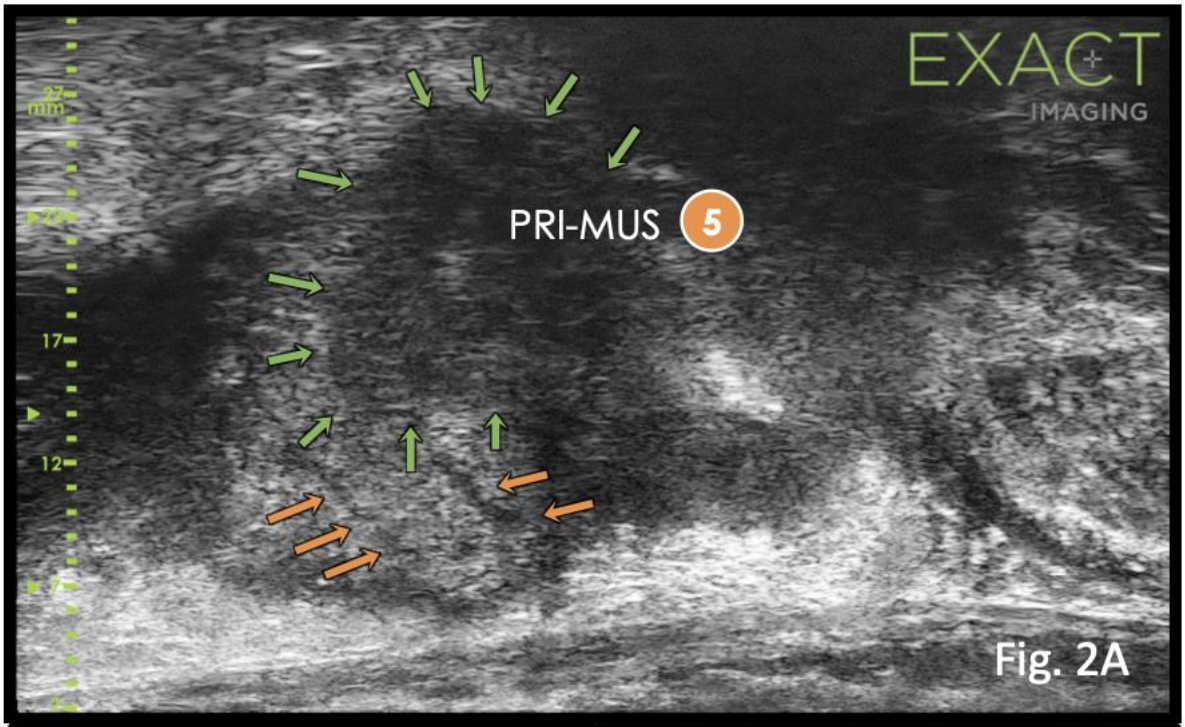
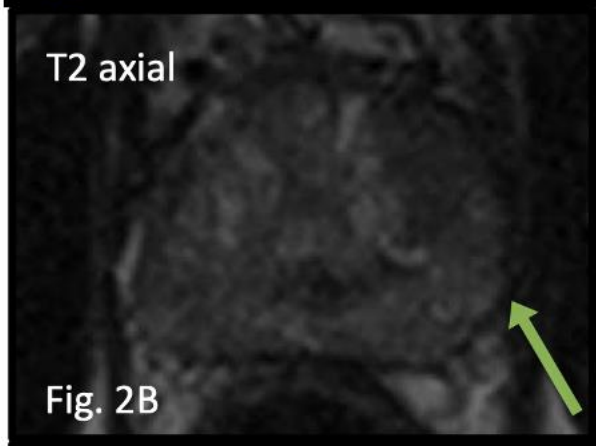
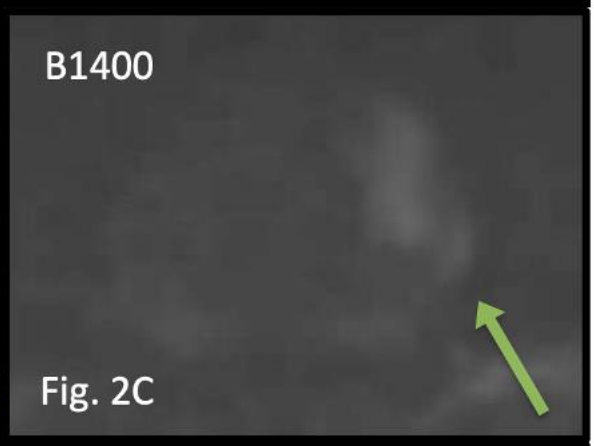


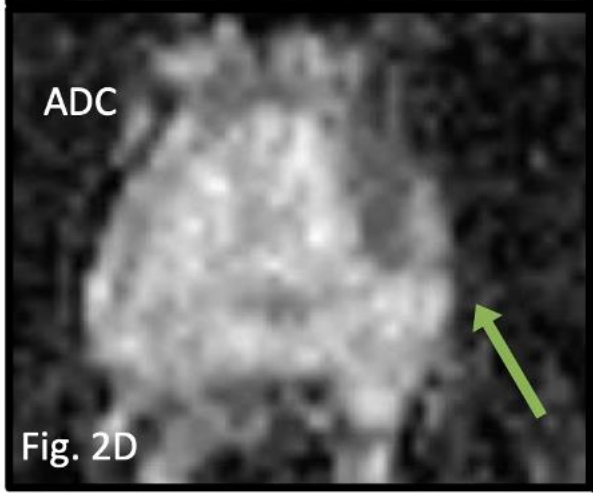
Fig. 1a – PCa detection rate stratified according to PRI-MUS and PI-RADS scores of index lesion. csPCA=ISUP≥2 PCa. nsPCA= ISUP 1 PCa. Negative Bx= No PCa found on prostate biopsy.

Fig. 1b - Venn diagram showing the histological results of all the microUS and mpMRI lesions and csPCa detection on systematic biopsy. Blue circle represents lesions identified on microUS; Green circle represents ROIs identified on mpMRI; Orange circle represents all csPCa positive areas identified by mUS-targeted only cores(n=7), MRI-targeted only cores (n=5), both MRI- and micro-US targeted cores (n=19) and at systematic Biopsy (1 patient with unilateral disease and 5 patients with bilateral disease).









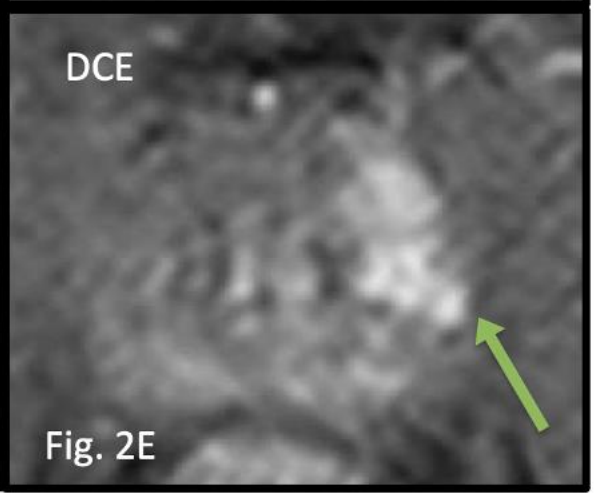


Fig. 2 - Small left middle-to-apical lesion seen on microUS as PRI-MUS 5 (A) and on mpMRI (2B - T2 axial; 2C - DWI b1400 values; 2D – DWI ADC map; 2E – DCE) classified as PI-RADS 4, highlighted by green arrows. Pathology evaluation of biopsy cores confirmed ISUP 3 disease with 75% pattern 4 and 6mm of maximal cancer core length. Orange arrows in fig. 2A show needle tracks of original diagnostic biopsy at initiation of AS, only tangentially approaching the lesion, likely resulting in ISUP 1 misclassification.

Tables

Table. 1 – Descriptive characteristics of population, classified according to reclassification biopsy in group continuing AS (confirmed ISUP=1 disease or negative biopsy) and group exiting AS (reclassification to ISUP≥2 disease); continuous variables are expressed in median and interquartile range (IQR).

		Total	Confirmed ISUP 1 PCa or negative	Upgraded to ISUP ≥2 PCa	p-value
		N=100	N=66	N=34	
Age	years	64 (60-71)	63 (59-69)	66 (62-72)	0.060
Total PSA	ng/mL	7 (4.81-9.36)	7 (4.81-9.16)	7.78 (5.25-9.4)	0.70
DRE	No Nodule	86 (86%)	59 (89.39%)	27 (79.41%)	0.17
	Nodule	14 (14%)	7 (10.61%)	7 (20.59%)	
Prostate Volume	mL	49.13 (37-67)	49.5 (36.5-68.5)	48.13 (37.9-60)	0.99
PSA density	ng/mL/mL	.132 (.094-.189)	.127 (.087-.189)	.144 (.103-.202)	0.28
PSAD tri	<0.12ng/mL/mL	34 (34%)	24 (36.36%)	10 (29.41%)	0.53
	0.12<PSAd<0.15	18 (18%)	12 (18.18%)	6 (17.65%)	
	>=0.15 ng/mL/mL	33 (33%)	19 (28.79%)	14 (41.18%)	
	Missing	15 (15%)	11 (16.67%)	4 (11.76%)	
Family history	No	75 (75%)	48 (72.73%)	27 (79.41%)	0.82
	Yes	21 (21%)	14 (21.21%)	7 (20.59%)	
	Missing	4 (4%)	4 (6.061%)	0 (0%)	
Tot #mpMRI lesions		123	83	40	NA

MRI_#Lesions/patient		1 (1-2)	1 (1-2)	1 (1-1)	0.59
MRI PIRADS index lesion	1-2	8 (8%)	8 (12.12%)	0 (0%)	0.081
	3	28 (28%)	20 (30.3%)	8 (23.53%)	
	4	46 (46%)	29 (43.94%)	17 (50%)	
	5	18 (18%)	9 (13.64%)	9 (26.47%)	
Tot # microUS lesions		105	63	42	NA
US_#lesions/patient		1 (1-1)	1 (1-1)	1 (1-1)	0.068
US_PRIMUS_overall	1-2	18 (18%)	16 (24.24%)	2 (5.882%)	**0.010**
	3	20 (20%)	11 (16.67%)	9 (26.47%)	
	4	50 (50%)	35 (53.03%)	15 (44.12%)	
	5	12 (12%)	4 (6.061%)	8 (23.53%)	
microUS/MRI agreement on suspicious lesion presence/absence	Discordance	20 (20%)	18 (27.27%)	2 (6.25%)	0.16
	Concordance	80 (80%)	48 (72.73%)	32 (93.75%)	
ISUP Grade Group Overall	1	31 (31%)	31 (46.97%)	0 (0%)	NA
	2	25 (25%)	0 (0%)	25 (73.53%)	
	3	8 (8%)	0 (0%)	8 (23.53%)	
	4	1 (1%)	0 (0%)	1 (2.941%)	
	Missing	35 (35%)	35 (53.03%)	0 (0%)	
Max %PCa Target OVERALL Cores		50 (10-80)	12.5 (5-45)	70 (40-80)	**0.003**

Table 2 – Diagnostic accuracy of microUS and mpMRI in predicting csPCa. Table 2a shows the per patient analysis based on risk stratification score of index lesion (lesion with highest PI-RADS and PRI-MUS score). Table 2b shows the per lesions analysis for identification of each csPCa focus detected at microUS-targeted, mpMRI-targeted and systematic biopsy. MicroUS=MicroUltrasond; TRUS=Transrectal Utrasonography; mpMRI= Multiparametric Magnetic Resonance Imaging; Bx = Biopsy; PPV= Positive Predictive Value; NPV=Negative Predictive Value.

Table 2a - Per Patient analysis

	Sensitivity	Specificity	PPV	NPV
microUS TRUS	94.1% (32/34)	24.2% (16/66)	39.0% (32/82)	88.9% (16/18)
mpMRI imaging	100.0% (34/34)	12.1%(8/66)	37.0%(34/92)	100.0% (8/8)

Table 2b -Per Lesion analysis

	Sensitivity	Specificity	PPV	NPV
microUS Target Bx	61.9% (26/42)	40.5%(53/131)	25.0% (26/104)	76.8% (53/69)
mpMRI Target Bx	57.1%(24/42)	23.7%(31/131)	19.4%(24/124)	63.3%(31/49)

Table 3 – CsPCa detection according to different biopsy strategies. Table 3 shows the number of csPCa that would have been diagnosed and percentage over all csPCa if a specific biopsy strategy would have been applied. The results of single (systematic only, microUS-targeted only and MRI-Targeted only) are shown, as well as the possible combinations of all 3 biopsy approaches. csPCa= Clinically significant Prostate cancer; Bx= biopsy; microUS=MicroUltrasound; MRI=Magnetic Resonance Imaging.

Table 3 – Number of csPCa patients identified according to biopsy strategy	**CsPCa (n=34)**
Targeted + Systematic bx	
- **microUS-targeted + MRI-Targeted and Systematic**	34 (100%)
- **microUS-Targeted and Systematic**	31(91.2%)
- **MRI targeted and Systematic**	32 (94.1%)
Targeted only bx	
- **microUS-targeted + MRI-Targeted**	28 (82.4%)
- **microUS Targeted**	25 (73.5%)
- **MRI targeted**	22 (64.7%)
Systematic only Bx	22 (64.7%)