

# Can multiparametric ultrasound improve cognitive MRI/TRUS fusion prostate biopsy

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**Summary** *Objective: To evaluate the accuracy of multiparametric transrectal ultrasound (contrast-enhanced ultrasound plus elastosonography) in the detection of the suspicious area diagnosed by multiparametric magnetic resonance (mpMRI).*

*Materials and methods: From June 2018 to June 2019 60 men (median age 63 years) with persistent suspicion of cancer underwent repeat saturation biopsy following pelvic mpMRI and the lesions characterized by a PI-RADS (Prostate Imaging Reporting and Data System) score  $\geq 3$  were submitted to 4 additional cores by transperineal cognitive fusion biopsy (TPBx). All patients, before prostate biopsy, underwent contrast-enhanced ultrasound (CEUS) following intravenous administration of a bolus of Sonovue® (2.4 mg of nonpyrogenic suspension of phospholipid/sulphur hexaphloride); in addition, a transrectal elastosonography (TRES) was done to evaluate prostate tissue elasticity. The accuracy of multiparametric ultrasound to detect the mpMRI lesions was evaluated.*

*Results: In 27/60 (45%) of men a T1c prostate cancer (PCa) was diagnosed by TPBx and 21 (77.8%) of them were classified as clinically significant cancer (csPCa); in detail, 16/21 (76.2%) vs. 5/21 (23.8%) csPCa were located in the peripheric and anterior zone of the gland, respectively. Median total PSA was 10.3 ng/ml (range: 4.9-51 ng/ml). TRES and CEUS were positive for csPCa only in 6/21 (28.5%) and 13/21 (62%) of TPBx showing an increased accuracy directly related with the PI-RADS scores*

*Conclusions: Multiparametric ultrasound using TRES and CEUS after Sonovue® administration did not improve the accuracy of TPBx in diagnosing csPCa.*

**KEY WORDS:** Prostate cancer; Contrast-enhanced ultrasound; Multiparametric ultrasound; Fusion prostate biopsy.

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## INTRODUCTION

Multiparametric magnetic resonance imaging (mpMRI) combined with transrectal ultrasound (TRUS) fusion targeted biopsy has improved the accuracy of standard biopsy schemes in detecting clinically significant prostate cancer (csPCa) (1-4). A lot of papers refer about the accuracy of mpMRI/TRUS targeted biopsy in the diagnosis of cancer but there are few data about the standardization of the procedure and/or the optimal technique of targeted biopsy (5-7). Although, the in-bore procedure seems to be more accurate to diagnose csPCa in comparison with MRI/TRUS fusion biopsy (61 vs. 47%) (8) no clinically significant difference has been reported in mul-

ticentric clinical trials comparing cognitive vs. fusion vs. in-bore targeted biopsy (5). In the last years, TRUS has been enriched by the introduction of tridimensional and computerized images and by the use of contrast media and transrectal elastosonography (TRES) (9, 10), which allow better characterization of intraparenchymal microvasculature. The use of microbubble ultrasound contrast agents (UCA: Sonovue®, Definity®, Imagent®) improve flow detection in small vessels distinguish the normal from pathological tissue (11-15).

In addition, the elastosonography measures the degree of distortion of ultrasound beam under the application of an external force that is displayed and scored over the B-mode image in a colour scale that corresponds to tissue elasticity (16-19).

In our series, the accuracy of multiparametric transrectal ultrasound (20) (CEUS plus TRES) in the detection of the suspicious area diagnosed by mpMRI and suitable of targeted transperineal prostate biopsy (TPBx) has been evaluated.

## MATERIAL AND METHODS

From June 2018 to June 2019 60 Caucasians men (median age 63 years; range: 47-75 years) with negative digital rectal examination and previous negative extended biopsy underwent repeat transperineal saturation biopsy (SPBx) for the suspicion of cancer (increasing or persistently elevated PSA values) (21).

After institutional review board and ethical committee approval were granted the informed consent was obtained from all individual participants included in the study. Ten days before SPBx, all the patients underwent pelvic mpMRI. All mpMRI examinations were performed using a 3.0 Tesla scanner, (ACHIEVA 3T; Philips Healthcare Best, the Netherlands) equipped with surface 16 channels phased-array coil placed around the pelvic area with the patient in the supine position; multi-planar turbo spin-echo T2-weighted, axial diffusion weighted imaging, axial dynamic contrast enhanced MRI were performed for each patient. The mpMRI lesions characterized by a PI-RADS (Prostate Imaging Reporting and Data System) version 2 score  $\geq 3$  were considered suspicious for cancer. Two radiologists blinded to pre-imaging clinical parameters evaluated the mpMRI data separately and independently.

SPBx (median of 28 cores; range: 26-30 cores) was per-

formed transperineally by a Hitachi 70 Arietta ecograph (Chiba, Japan) supplied with a bi-planar transrectal probe (5-7.5 MHz) and using a tru-cut 18 gauge needle (Bard; Covington, GA, USA) under sedation and antibiotic prophylaxis (intravenous administration of 1 gram of Cefazolin before prostate biopsy). One urologist with more than 8 years of experience regarding MRI/TRUS fusion targeted biopsy performed the procedure. In the presence of mpMRI lesions suggestive of cancer a TPBx (four cores) was added to SPBx using the Hitachi 70 Arietta ecograph (10). The data have been collected following the START criteria (22).

All patients, before prostate biopsy, underwent standard TRUS combined with administration of a bolus of Sonovue® (nonpyrogenic suspension of phospholipid/sulphur hexaphloride) equal to 2.4 mg into a large peripheral vein followed by a flush of saline (10 ml). Before scanning with contrast-enhanced ultrasound (CEUS), an appropriate setup that included low mechanical index (MI) and a split-screen view to display the contrast and B-Mode images at the same time was selected on the Logiq E9 echograph (General Electric; Milwaukee, WI USA) provided of an end-fire transrectal probe.

A timer was activated after UCA injection and the investigation was performed for 200 seconds (median; range 180-240); at the end of the procedure microbubbles were bursted.

Post-contrast imaging began as soon as contrast medium was visible on gray scale continuous harmonic imaging (HI); the microbubbles normally were distributed throughout the prostate, that appeared contrast-enhanced, and only areas characterized by the Sonovue® enhancement (15) were considered suspicious for PCa. The TRES evaluation was done before the execution of the targeted cognitive biopsy performing a real-time tissue elastosonography of the gland by the Shear Wave Measurement (SWM) analysis of the prostate (Hitachi 70 Arietta ecograph (Chiba, Japan)). After multiparametric ultrasound evaluation the patients were submitted to TPBx plus SPBx (1). The Clavien-Dindo grading system for the classification of biopsy complications was used (23).

The detection rate of TPBx in the diagnosis of csPCa (Gleason score > 6 and/or greatest percentage of cancer > 50% and/or more than two positive cores) was evaluated (24); in addition, the accuracy of multiparametric ultrasound (elastosonography and/or Sonovue®) to detect the MRI lesions was evaluated.

## RESULTS

The overall diagnosis of PCa vs. csPCa performing SPBx was equal to 32/60 (56.7%) vs. 25/60 (41.7%) cases, but the data will refer only to the TPBx detection rate for PCa. In 27/60 (45%) of men a T1c PCa was

**Table 1.**

Clinical and histological parameters in 21 patients with clinically significant prostate cancer (csPCa) diagnosed by cognitive targeted fusion biopsy.

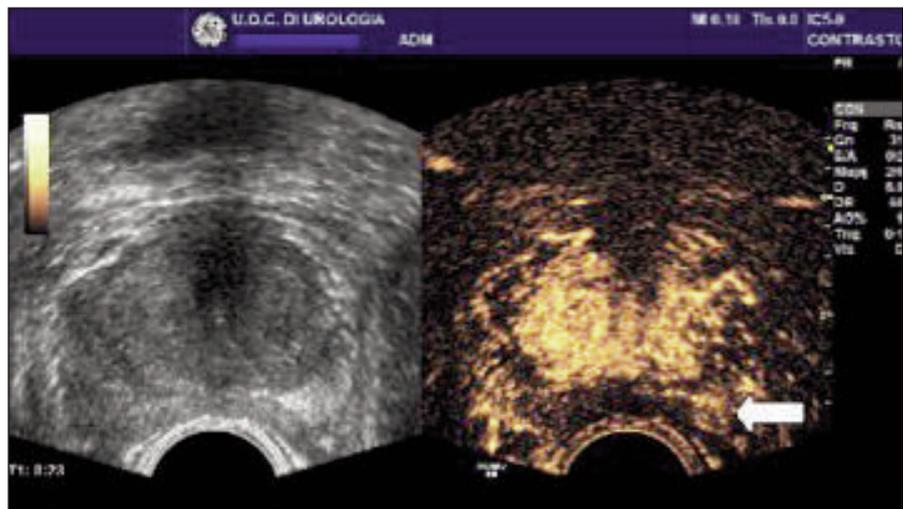
Biopsy histology and clinical parameters	Number of cases
<b>Gleason score 3 + 4 (GG2)</b>	<b>10 cases</b>
PIRAD-S score (3 vs. 4 vs. 5)*	3 7 0
Suspicious TRES	1 2 0
Suspicious CEUS	2 4 0
<b>Gleason score 4 + 3 (GG3)</b>	<b>7 cases</b>
PIRAD-S score*	3 3 1
Suspicious TRES	1 0 1
Suspicious CEUS	1 2 1
<b>Gleason score 4 + 4 (GG4)</b>	<b>3 cases</b>
PIRAD-S score*	0 2 1
Suspicious TRES	0 0 1
Suspicious CEUS	0 1 1
<b>Gleason score 4 + 5 (GG5)</b>	<b>1 case</b>
PIRAD-S score*	0 0 1
Suspicious TRES	0 0 0
Suspicious CEUS	0 0 1

TRES: transrectal elastosonography; PI-RADS: Prostate Imaging Reporting and Data System; CEUS: contrast-enhanced ultrasound; GG: Grade Groups ISUP (International Society of Urological Pathology).

diagnosed by targeted fusion biopsy and 21 (77.8%) of them were classified as csPCa (Table 1); in detail, 16/21 (76.2%) vs. 5/21 (23.8%) csPCa were located in the peripheric (Figure 1) and anterior zone (Figure 2) of the gland, respectively. Median total PSA was 10.3 ng/ml (range: 4.9-51 ng/ml); the PI-RADS scores, Sonovue® and TRES results are listed in Table 1. No side-effects were reported after Sonovue® administration; none had significant complications (Clavien-Dindo grade I) from prostate biopsy that needed hospital admission biopsy-related; moreover, the mpMRI procedure was well tolerated and successfully performed in all cases (men with claustrophobia, cardiac pacemaker and hip replacement were not included in the study).

**Figure 1.**

Sonovue® enhancement in correspondence of the left peripheric zone of the prostate (white arrow).



In detail, TRES and CEUS were positive for csPCa only in 6/21 (28.5%) and 13/21 (62%) of cognitive fusion biopsies showing an increased accuracy directly correlated with the PI-RADS scores (Table 1); in addition, TRES analysis did not improve the CEUS accuracy.

## DISCUSSION

The improvement of diagnostic imaging by mpMRI has allowed targeted biopsies of the suspicious area, increasing the diagnosis of csPCa (1, 2) and reducing the number of unnecessary systematic biopsies. Although mpMRI is strongly recommended in men candidate to prostate biopsy (3), still today, systematic biopsy should be always combined with mpMRI/TRUS fusion biopsy due to false negative rate of mpMRI (about 20% of the cases) (1) and the variable diagnostic accuracy of the different mpMRI/TRUS fusion biopsy platforms (25). On the other hand, an alternative clinical approach is to begin with mpMRI to determine which patients need a targeted biopsy (26). The detection rate of csPCa is directly related to the PI-RADS score (1, 2) and the results depend on clinical parameters, the number of previous negative biopsies and the quality of TPBx procedures. In the next future it would be good that the artificial intelligence for automatic delineation of the prostate on ultrasound could become reliable and applicable to different scanners to improve, guided prostate biopsies using magnetic resonance imaging-transrectal ultrasound fusion (27). Alternatively, the ideal approach to the diagnosis of PCa should be to detect significant disease performing a limited number of targeted biopsy cores improving the accuracy of standard TRUS by multiparametric ultrasound (28); in this respect, a lot of papers have been published on the use of UCA as an additional diagnostic tool for improving PCa diagnosis (2-4) showing a low detection rate included between 15.5 and 32% (14-20, 29). In addition, in recent years, elastosonography has improved by the introduction of *Shear Wave Elastosonography* (SWE) that is a quantitative method that evaluate local tissue elasticity resulting much less operator dependent; the sensitivity vs. specificity of TRES range from 71-82% vs. 60-95% (9) in definitive specimen of men who underwent radical prostatectomy. Recently, Micro-ultrasound (30) in preliminary studies has demonstrated similar sensitivity to clinically significant prostate cancer as mpMRI; unlike mpMRI, micro-ultrasound is performed in the office, in real-time during the biopsy procedure, and so is expected to maintain the cost-effectiveness of conventional ultrasound, but larger studies are needed before these results may be applied in a clinical setting.

In our series, TRES and CEUS were positive for csPCa only in 6/21 (28.5%) and 13/21 (62%) of cognitive fusion biopsies showing an increased positive results directly related with the PI-RADS scores (Table 1); in addition, TRES analysis did not increased the CEUS accuracy. In definitive, the additional use of multiparametric ultrasound did not improve the accuracy of cognitive fusion biopsy in the diagnosis of csPCa resulting only in an increased cost of the procedure.

Regarding our results some consideration should be

done. Firstly, non-targeted biopsies were performed in CEUS or TRES suspicious areas, therefore, it is unknown if multiparametric TRUS would have diagnosed csPCa missed by TPBx; secondly, CEUS was not performed during the execution of TPBx. Third, the false negative rate of mpMRI for csPCa (4/21 equal to 19% of the cases) has not been correlated to CEUS and TRES findings.

Finally, a greater number of cases is needed to confirm the results.

## CONCLUSIONS

Multiparametric ultrasound using TRES plus CEUS did not improved the accuracy of TPBx in diagnosing csPCa.

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