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ORIGINAL PAPER

MRI/TRUS FUSION guided biopsy as first approach in ambulatory setting: Feasibility and performance of a new fusion device

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Summary ***Purpose: To evaluate the detection rate of Magnetic Resonance Imaging/Transrectal Ultrasound (MRI/TRUS) Fusion Biopsy performed in a series of patients with suspicious prostate cancer in an ambulatory setting.***
Materials and methods: Between March 2018 and January 2019 a series of 155 patients undergoing MRI/TRUS fusion-guided biopsy were prospectively enrolled. All patients presented a suspected diagnosis for prostate cancer because of raised Prostate Specific Antigen (PSA) serum level and/or abnormal physical examination (digital rectal examination), and showed at least one suspicious area at the multiparametric Magnetic Resonance Imaging (mpMRI).
Results: Of 155 patients, 58 (37.4%) were biopsy-naïve, 97 (62.6%) had at least 1 previous negative TRUS-guided biopsy. The median age of the patient cohort was 66 years (IQR, 61-69); the median prebiopsy PSA value was 7.1 ng/ml (IQR, 5-8.9). Overall, the Fusion-TB findings were positive in 94 of 155 patients with a detection rate (DR) of 60%; a significantly high DR was obtained in terms of clinically significant prostate cancer (csPCa) by Fusion-TB (61 pts; 41.9%). The overall DR in the 121 biopsy-naive patients was 60.6%. In the subgroup of the 34 patients with at least 1 previous set of TRUS-GB, overall DR was 39.3% (35/50).
Conclusions: The targeted MRI/TRUS fusion-guided biopsy represents a safe and accurate approach for diagnosis of csPCa, especially in patient with previous TRUS guided biopsy negative and suspicious prostate cancer.

KEY WORDS: *Prostate cancer; Magnetic Resonance; Prostate biopsy.*

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INTRODUCTION

Prostate cancer (PCA) is the most frequent among solid tumors in the male sex, as emerges from the 2016 estimate of the *American Cancer Society* (1). Currently, diagnosis of PCA is one of the most debated topics in the urology literature (2) and is based on the serum dosage of *prostate specific antigen* (PSA) and digital rectal exploration. PSA levels can be elevated not only in the case of prostatic carcinoma but also in the case of other pathologies, such as benign prostatic hyperplasia and inflammatory states of different nature (3) with consequent risk of over-diagnosis and over-treatment. Although the introduction of PSA has radically changed the diagnosis of PCA, as amply highlighted by the literature, it is a test that has limits in terms of sensitivity and specificity; for example about 15% of men with PSA levels equal to or below 4.0 ng/ml are affected by prostatic carcinoma that in about 15% of cases is of high-grade (4). To date, the conventional diagnosis of prostatic carcinoma is performed by identifying histopathology on systematic ultrasound-guided biopsy specimens with a sensitivity of 45-70% for clinically significant PCA (5). The main disadvantages related to this method are the loss of identification of a substantial portion of patients with significant prostatic carcinoma (about 20%) linked to sampling errors, in particular at the level of the anterior prostate area (6) and the possibility of important complications following the procedure, above all related to sampling performed by trans-rectal ultrasound-guided biopsy (7). The actually limited detection rate represents an important concern and the management of patients with persistent suspected diagnosis of PCA and previous set of negative biopsies represents a continuing challenge. *Magnetic Resonance Imaging* (MRI) has shown a high sensitivity and specificity in diagnosing *clinically significant PCA (csPCa)* (5, 6) and, exploiting the use of functional studies, multiparametric MRI (mpMRI) improves the identification of PCA lesion within the gland (7, 8). A growing body of evidence suggests that mpMRI, improving the risk classification of lesions, could reduce false-negative rates and the necessity of repeat biopsies in presence of suspected PCA (8, 9); not surprisingly, a MRI targeted biopsy should be strongly applied for any patient with a prior negative set of prostate biopsy who has persistent clinical suspected diagnosis for PCA as reported by recent AUA Consensus Statement (9); more frequently MRI is used in the first diagnostic phase for PCA; for this reason the MRI-guided approach of prostatic biopsy is increasingly used. Approaches for targeted biopsy include visual estimation TRUS-GB (cognitive technique), software co-registered MRI-ultrasound fusion (fusion technique) and in-bore *MRI-guided biopsy* (MRI-GB). Studies from literature suggest that there was no significant advantage of MRI-GB compared with fusion technique concerning overall

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detection rate and clinical significant neoplasm detection rate (10) even if the main potential limitation of MRI-GB consist of impossibility to perform a simultaneous standard TRUS biopsy, especially in biopsy naive patients, since up to 16% of men with no suspicious mpMRI could reveal csCaP on systematic biopsy (11). Different software for MRI/TRUS fusion-guided biopsy systems are at the present time used: the aim of this study was to evaluate the detection rate of MRI TRUS Fusion Biopsy performed in a series of patients with suspicious PCA in ambulatory setting with a new fusion device.

Materials and methods

Patients cohort and methodology

Between March 2018 and January 2019 a series of 155 patients undergoing MRI/TRUS fusion-guided biopsy were prospectively enrolled. All patients had a suspected diagnosis for PCA because of elevated value of *Prostate Specific Antigen* (PSA) serum level and/or abnormal physical examination (digital rectal examination), and showed at least one suspicious area at the mpMRI. According to the *European Society of Urogenital Radiology* (ESUR) guidelines, the presence of csPCa at mpMRI was defined equivocal, likely or highly likely basing on the PIRADS-v2 (*Prostate Imaging Reporting and Data System-version 2*) score of 3/5, 4/5 or 5/5, respectively; the localization of index lesion are reported in Table 2 (12).

This study was conducted under the approval of local *Institutional Review Board* and in the accordance with good clinical practice guidelines and the ethical principles of the Declaration of Helsinki.

Primary endpoints of this study were overall detection rates of PCA (PCA DR), *csPCa Detection Rate* (csPCa DR). Secondary endpoints were correlations between mpMRI parameters biopsy results, comparison to definitive pathologic results of surgical specimens (when available) and complications rates.

Multiparametric Magnetic Resonance Imaging and analysis

MRI examination and analysis. All the MRI examinations were performed with a 32 channels 1.5 T whole body scanner (*Achieva XR; Philips Medical Systems, Best, Netherlands*) with a 32-channels phased-array surface coil without endorectal coil. After local three-plane acquisition, required for the correct positioning of the sequences, the morphological and functional studies were carried out. Morphological study of the prostate gland were obtained with *Turbo Spin Echo* (TSE) T2-weighted sequences (TE 100 msec, TR 4074 msec, Slice Thickness 3 mm, Slice Spacing 0.3 mm, Field of View - FOV 180 x 180 mm and matrix size 276 x 205) in the sagittal, axial and coronal planes, including seminal vesicles and the entire prostate gland. For the functional study, DWI, DCE-MRI and MRS acquisition were performed. The DWI acquisition was carried out in the axial plane, using a single-shot echo-planar imaging (SSEPI) sequence, with three b-values (0, 600 and 1500 s/mm^2), slice thickness of 3 mm, FOV 180 x 180 mm and matrix size 80 x 71. The DCE-MRI was obtained using three-dimensional (3D) *T1W High Resolution Isotropic Volume Examination* (THRIVE) sequence during the intravenous injection of a contrast bolus of 0.1 mmol per kilogram of body weight of *Meglumine gadobenate* (*Multihance, Bracco Diagnostics, Milan, Italy*), at flow rate of 3.5 ml/sec followed by 15 ml of saline solution.

Conduct of the biopsy

The biopsies were performed within three weeks from the first diagnostic mpMRI study by a single urologist with a consolidated experience in MRI Fusion-GB.

All patients received oral antibiotic prophylaxis with quinolones (*Ciprofloxacin 500 mg*) twice a day, started the day before the procedure and prolonged for at least 2 days thereafter. Prostate biopsy procedures were conducted in an ambulatory setting with patient in lithotomic position. Peri-prostatic nerve blockade local anesthesia with lidocaine 2% was administered immediately before biopsy to each patient. Biopsies were conducted using a disposable biopsy gun with a 18-gauge needle and an Ultrasound Platform (*BK ultrasound 5000*) with a biplanar probe. Using the BK Ultrasound 5000 MRI-TRUS Fusion platform, Fusion-TB was performed on the previously identified suspicious area at the mpMRI using a real time alignment of the T2-weighted sequence to the TRUS image. MRI-TRUS images alignment was possible due to a tracking device consisted in a sensor coil on the TRUS probe paired with a magnetic field generator in order to register the location of the tracking device in the 3D space. At least 3 cores were taken for each lesion and the number of additional cores were based on the diameter of the lesion. The number of cores taken was related to the size of the lesions; the cores were carried out along the long axis of the lesion with a maximum of two biopsies taken for each needle. TRUS Standard Biopsy was a typical 12 cores double sextant template from lateral to medial of base, mid and apex. Only the TRUS images, with no mp-MRI target data available, were used for the standard biopsy portion of the case. After the procedure, patients were observed for 1 hour and were re-evaluated by outpatient visit after 7-10 days in order to record any potential complication.

Statistical analysis

Continuous variables were reported as medians with *interquartile ranges* (IQR) whereas categorical variables were described as frequencies with percentages.

The Mann-Whitney and Pearson Chi-square test were used to compare medians and frequencies among patients with positive and negative biopsies, respectively. Uni- and multivariate logistic regression models with enter method were used to identify which covariates could predict PCA, csPCa and concordance between mpMRI index lesion and bioptic index lesion. An alpha value of 5% was set to be the threshold to determine statistical significance.

Statistical analyses were conducted using *SPSS®* v21 (*IBM Corp, Armonk, NY*) for *Macintosh®*.

Results

The clinical, radiologic, and pathologic characteristics of the entire population are listed in Table 1. Of 155 patients, 58 (37.4%) were biopsy-naïve, 97 (62.6%) had

at least 1 previous negative set of random TRUS-GB. The median age of the patient population was 66 years (IQR, 61-69) and median prebiopsy PSA level was 7.1 ng/ml (IQR, 5-8.9). The median number of targeted biopsies per patient was 4 (IQR, 3-4), and, accordingly, the median total number of biopsies including the standard 12-cores was 14 (IQR,12-15). At the prebiopsy mpMRI study, a total of 155 suspected lesions were identified and were scheduled for Fusion-TB. The median diameter of the index lesion was 13 mm (IQR, 9-18.1 mm). The univariate logistic regression model showed a crucial role of V2-PIRADS score of index lesion in the prediction of PCA and csPCA (Tables 3, 4). Overall, the FUSION-TB findings were positive in 94 of 155 patients with a DR of 60%; a significantly high DR was obtained in terms of clinically significant PCA (csPCa) of Fusion-TB (61 pts; 41.9%). The overall DR in the 121 biopsy-naive patients was 60.6%. In the subgroup of the 34 patients with at least 1 previous set of TRUS-GB, overall DR was 39.3% (35/50). In the series of biopsy naïve patients whose clinically significant PCA (csPCa) was found, the location of index lesion was anterior in 26.3% (15/57 cases) while we observed a posterior lesion in 73.7% (42/57 cases).
In patients with previous negative TRUS-GB whose csPCa was diagnosed the location of index lesion was anterior in 32.4% (12/37 cases) and posterior in 67.5% (25/37 cases). Overall, in the patients with a PI-RADS-v2 score of 3 of 5, 4 of 5, and 5 of 5, DR for PCAa were 40.2% (29/72), 77.0% (41/53) and 80.0% (24/30), respectively ($p < 0.001$). In Table 5 are reported univariate logistic regres-

Table 1.
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	Overall population (n = 155)	Biopsy+patients (n = 94)	Biopsy-patients (n = 61)	p-value
Age				
Median	66	66	65	0.5
IQR	61-69	61-70	61-69	
PSA (ng/ml)				
Median	7.1	7.2	7	0.9
IQR	5-8.9	5.4-9.3	4.6-8.8	
PSA density (ng/ml/cm^3)				
Median	0.12	0.13	0.11	0.03
IQR	0.09-0.16	0.1-0.17	0.08-0.13	
Prostate Volume (cm^3)				
Median	55	50	58	0.2
IQR	43-75	40-60	46-80	
Previous TRUS-GB (%)				
No	121 (78.1)	57 (60.6)	40 (65.6)	0.6
Yes	34 (21.9)	37 (39.3)	21 (34.4)	
Index lesion diameter (mm)				
Median	13	11	13	0.9
IQR	9-18.1	8-16	9-16.5	
Index lesion location (%)				
Anterior	44 (28.4)	27 (28.7)	17 (27.9)	0.7
Posterior	111 (71.6)	67 (71.3)	44 (72.1)	
Index lesion site (%)				
Peripheral	107 (69)	65 (69.1)	42 (68.9)	0.1
Central	48 (31)	29 (28.7)	19 (31.1)	
Index lesion PIRADS V2 score (%)				
3	72 (46.5)	29 (38.5)	43 (70.5)	< 0.001
4	53 (34.2)	41 (38.5)	12 (19.7)	
5	30 (19.4)	24 (23.1)	6 (9.8)	
Total cores taken per patient				
Median	14	14	13	0.96
IQR	12-15	12-15	12-15	
Target biopsy cores taken per patient				
Median	4	4	4	0.9
IQR	3-4	3-5	3-4	
ISUP grade group (%)				
Negative	61 (39.4)	0 (0)	61 (100)	-
1	29 (18.7)	29 (18.7)	0 (0)	
2	26 (16.8)	26 (16.8)	0 (0)	
3	28 (18.1)	28 (18.1)	0 (0)	
4	11 (7.1)	11 (7.1)	0 (0)	
5	0 (0)	0 (0)	0 (0)	

DRE: digito-rectal examination; IQR: interquartile range; PSA: prostate specific antigen; TRUS-GB: trans-rectal ultrasound-guided biopsy; MRI-GB: magnetic resonance imaging-guided biopsy.

Table 2.
Localization of Index lesion at mpMRI and bioptic results stratified according to previous biopsy status and bioptic findings.

	Biopsy+patients (n = 94)	Biopsy-patients (n = 61)	p-value
Biopsy näive patients (n = 97)			
Index Lesion Location (%)			
Anterior	15 (26.3)	13 (32.5)	0.7
Posterior	42 (73.7)	27 (67.5)	
Index lesion site (%)			
Central	17 (29.8)	15 (37.5)	0.3
Peripheral	40 (70.2)	32 (62.5)	
Previous negative biopsies (n = 58)			
Index Lesion Location (%)			
Anterior	12 (32.4)	4 (19)	0.4
Posterior	25 (67.6)	17 (81)	
Index lesion site (%)			
Central	12 (32.4)	4 (19)	0.4
Peripheral	25 (67.6)	17 (81)	

Table 3.
Uni-variate logistic regression model predicting PCa (n = 94) at Fusion biopsy.

	Univariate analysis	
	HR (95% CI)	p-value
Age (yrs)	1.01 (0.97 -1.07)	0.5
PSA (ng/ml)	1.08 (0.97-1.19)	0.2
PSA density (ng/ml/cm^3)		
< 0.15	Ref.	0.9
0.15	0.94 (0.47-1.87)	
Previous TRUS-GB		
No	Ref.	0.5
Yes	1.24 (0.63-2.42)	
Index Lesion Site		
Peripheral	Ref.	0.97
Central	0.99 (0.49-1.98)	
Lesion Location		
Posterior	Ref.	0.9
Anterior	0.98 (0.47-1.96)	
Index lesion PiRADS V2 score		
3	Ref.	
4	5.07 (2.28-11.24)	**< 0.001**
5	5.93 (2.16-16.3)	**0.001**
Index lesion diameter (mm)	1.01 (0.96-1.07)	0.7
N of cores taken	1 (0.86-1.16)	0.99
N of target cores taken	1.07 (0.72-1.58)	0.8

PCa: Prostate Cancer; HR: hazard ratio; CI: confidence interval; PSA: prostate specific antigen; TRUS-GB: trans-rectal ultrasound-guided biopsy.

Table 4.
Univariate logistic regression model predicting csPCa (n = 54) at fusion biopsy.

	Univariate analysis	
	HR (95% CI)	**p-value**
Age (yrs)	1.02 (0.97-1.07)	0.2
PSA (ng/ml)	1.03 (0.96-1.1)	0.4
PSA density (ng/ml/cm^3)		
< 0.15	Ref.	0.8
≥ 0.15	1.08 (0.55-2.12)	
Previous TRUS-GB		
No	Ref.	0.2
Yes	1.57 (0.82-3.02)	
Index Lesion Site		
Peripheral	Ref.	0.3
Central	0.67 (0.33-1.33)	
Index lesion PiRADS V2 score		
3	Ref.	
4	3.42 (1.63-7.22)	**0.001**
5	4.86 (1.95-12.11)	**0.001**
Index lesion diameter (mm)	1.01 (0.96-1.07)	0.6
N of cores taken	1.03 (0.89-1.19)	0.7
N of target cores taken	1.09 (0.74-1.6)	0.7

csPCa: Clinically significant Prostate Cancer; DRE: Digito-rectal examination; HR: Hazard ratio; CI: Confidence interval; PSA: Prostate specific antigen; TRUS-GB: Trans-rectal ultrasound-guided biopsy.

Table 5.
Univariate logistic regression model predicting concordance between Index lesion at mpMRI and highest cGS in the bioptic cores.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (yrs)	1.03 (0.96-1.1)	0.5	-	-
PSA (ng/ml)	1.05 (0.92-1.2)	0.4	-	-
PSA density (ng/ml/cm^3)				
< 0.15	Ref.	0.5	-	-
0.15	1.45 (0.51-4.15)			
Previous TRUS-GB				
No	Ref	0.1	-	-
Yes	2.2 (0.77-6.23)			
Index lesion site				
Peripheral	Ref.	0.01	Ref.	0.02
Central	0.29 (0.11-0.77)		0.3 (0.1-0.82)	
Index lesion location				
Posterior	Ref.	0.8	-	-
Anterior	0.84 (0.29-2.43)			
Index lesion PiRADS V2 score				
3	Ref.		Ref.	
4	0.74 (0.26-2.08)	0.6	0.75 (0.25-2.2)	0.6
5	8.76 (1.01-76.08)	0.05	8.83 (0.99-78.93)	0.05
Index lesion diameter (mm)	1.02 (0.95-1.1)	0.6	-	-
N of cores taken	1.07 (0.87-1.31)	0.5	-	-
N of target cores taken	0.89 (0.49-1.64)	0.7	-	-

mpMRI: Multi-parametric magnetic resonance imaging; cGS: Clinical Gleason Score; HR: Hazard ratio; CI: Confidence interval; PSA: Prostate specific antigen; TRUS-GB: Trans-rectal ultrasound-guided biopsy.

sion model predicting concordance between Index lesion at mpMRI and highest Gleason score in the bioptic cores.

Discussion

Several major changes have taken place in the last decade regarding the diagnosis of PCA; the introduction of new imaging techniques (traditional radiology, nuclear medicine, etc.) is radically changing the approach to the patient with PCA (13-17). In particular the most important innovation was represented by the introduction of *multiparametric magnetic resonance imaging* (mpMRI) in the diagnosis and management of PCA (active surveillance, surgery, radiotherapy, etc.) (18, 19).

In fact, this examination showed an elevate detection and localization rate of csPCa thus making it possible to perform selected targeted biopsies instead of systematic ultrasound guided biopsies. In any case, TRUS-GB represents the "*gold-standard*" technique of histological diagnosis of PCA although MRI-targeted biopsies (cognitive, fusion and "*in bore*" technique) significantly increased the detection of high risk PCA while decreasing the detection of low risk PCA compared with standard biopsy; moreover a lower number of cores could be required in men with suspicious MRI findings reducing also potential complications related to the procedure and all the consequence on quality of life (20-22). In our experience we have analyzed the impact of one of the targeted biopsy techniques, the MRI-US "*fusion*" prostate biopsy, in the diagnosis of clinically significant PCA; in particular the MRI-US "*fusion*" biopsy is simply described as a way to align a pre-registered MRI to an intra-procedure US in order to identify and target suspected lesions within the gland through a dedicated hardware platforms targeting areas found during mpMRI and not clearly visible during US scan. Based on our experience we can affirm that this technique had high sensitivity, accuracy and specificity than TRUS-GB and no significant difference for treatment zone between combined biopsies and targeted.

The advantages are the high reproducibility and the real time feedback though counterbalanced by the high upfront cost of the device; another advantage of the fusion technique is the ability to perform a systematic biopsy during the same session. In our series of patients the MRI-US fusion biopsy showed an elevate accuracy for diagnosis of csPCa; in particular the overall DR of csPCa was 69.1% (65/94 cases); in particular we observed a statistically significant correlation between the PiRads V2 score and the presence of csPCa ($p < 0.001$).

These results were in line with available studies in literature (23). Evaluating the detection rate of different techniques of targeted biopsy, *Arsov et al.* (24) compared the DR between an "*in-bore*" approach and a fusion approach: in particular they not observed important improvement in DR by fusion approach. In our previous experience we evaluated the role of "*in-bore*" MRI guided biopsy in a series of 70 patients (25); we observed an overall DR of 45.7% and in particular > 75% in csPCa. Examining this series we observed an important correlation between the location of index lesion and the finding of PCA in the sample of biopsy. *Venderlink et al.* highlighted that there are no significant differences between magnetic resonance and fusion-guided biopsy; the only differences were related with an increasing lesion size (26). Considering the overall DR, in a NIH study of men with previous negative biopsy, a global DR of 37.4% using MRI fision biopsy was reported by *Vourganti et al.* (27). Other studies highlighted as performing 12 cores

random biopsies the DR for csPCa is increasing respect to MRI fusion biopsy (28-30); in particular *Radtke et al.* reported that systematic transperineal prostate biopsy was more likely to miss Gleason > 7 PCA compared with MRI targeted biopsy (20.9% *vs* 12.8%) (30).
This dates are apparently in contrast with the results of our study; in fact the elevate DR for clinically significant disease depends on the fact that in addition to perform a standard 12-core biopsy we have added cores in areas normally not considered (lesions of the anterior and transitional); these data support the thesis about the essential role of mpMRI and MRI guided biopsy of suspicious lesions in the algorithm for evaluating men with previous negative TRUS-GB but with ongoing suspicion for PCA. Our study has some limitations: the number of patients, exclusive inclusion of patients with positive findings at mpMRI, no follow-up data and the lack of control group.

Conclusions

In conclusion, the results from our present study confirm that the mpMRI and MRI fusion guided biopsy have the purpose to improve detection of clinically significant PCA.
In particular the targeted MRI/TRUS fusion-guided biopsy represent a safe and accurate approach for diagnosis of csPCa, especially in patient with previous TRUS guided biopsy negative and suspicious PCA. Given that the experience of radiologist for mpMRI and of urologist for MRI/TRUS fusion-guided biopsy are critical, further studies are necessary to confirm these promising results.

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