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Early Second Round Targeted Biopsy of PI-RADS Score 3 or 4 in 256 Men With Persistent Suspicion of Prostate Cancer

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Abstract. *Background/Aim: The aim of the study was to determine the rate of clinically significant prostate cancer (csPCa) cases in men submitted to early second round mpMRI/TRUS (multiparametric magnetic resonance imaging/transrectal ultrasound) fusion biopsy (TPBx). Materials and Methods: From January 2016 to December 2018, 256 men with a PI-RADS (Prostate Imaging-Reporting and Data System) score 3 (80 cases) or 4 (176 cases) and negative repeat transperineal saturation biopsy plus TPBx, underwent a new TPBx (four cores) for the persistent clinical suspicion of cancer. The accuracy of mpMRI ADC (apparent diffusion coefficient) values in the diagnosis of csPCa were evaluated. Results: Overall detection rate of csPCa was equal to 10.1% (26/256 cases): 2.5% (2/80) versus 13.6% (24/176) had a PI-RADS score equal to 3 versus 4, respectively. The presence of csPCa was significantly correlated with an ADC value of 0.747×10^{-3} mm^2/sec. Conclusion: A negative TBPx missed a csPCa in 13.6% of PI-RADS score 4 that was diagnosed by an early second round TBPx; the evaluation of ADC maps could select mpMRI lesions deserving a repeat TPBx.*

Multiparametric magnetic resonance imaging (mpMRI) is strongly recommended for the diagnosis of clinically significant prostate cancer (csPCa) (1-3) in order to reduce the risk of over-diagnosis and improve the cost-effectiveness of prostate biopsy (4). On the other hand, mpMRI is still associated with a significant percentage of false-negative results for csPCa and it is not clearly estabilished in the presence of negative mpMRI targeted biopsy which lesions need an early second round biopsy. In this respect, the diameter, shape and location of mpMRI index lesion have been highly considered as indexes for PCa; in particular, the ADC values maps of the apparent diffusion coefficient (ADC), computed from diffusion-weighted imaging (DWI), provide a quantitative parameter to evaluate prostate regions with suspicion of PCa. In neoplastic tissue, ADC values are lower compared to normal prostatic tissue and some studies have demonstrated a possible differentiation in PCa aggressiveness (5-9).

In this study, we report the detection rate for csPCa in men submitted to early second round mpMRI/TRUS fusion biopsy (TPBx) of index lesions with PI-RADS (Prostate Imaging-Reporting and Data System) score 3 or 4.

Patients and Methods

From January 2016 to December 2018, 256 men (median age 64 years; range=47-75 years) with negative digital rectal examination, PI-RADS score 3 (80 cases) or 4 (176 cases) and previous (range=6-9 months before) negative repeat transperineal saturation (SPBx: 24 or more cores) combined with TPBx underwent a third procedure for the persitent suspicion of cancer because of increasing PSA values. After institutional review board and ethical committee approval were granted the informed consent was obtained from all individual participants included in the study. All mpMRI examinations were previously 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, and axial diffusion weighted imaging, and axial dynamic contrast enhanced MRI were performed for each patient (10). All the mpMRI index lesions, characterized by a PI-RADS (version 2) equal to 3 or 4, and negative for Pca, underwent second round TPBx (four cores); the procedure was performed transperineally using a Tru-Cut 18-gauge needle (Bard; Covington, GA, USA) under local anesthesia and antibiotic prophylaxis (one tablet daily of 500 mg for 3 days) (11). The TBPx was done using an Hitachi 70 Arietta echograph, Chiba, Japan) supplied by a bi-planar trans-rectal probe (6). The data have been collected following the START criteria (12). Two radiologists with 10 years of experience, blinded to pre-imaging clinical parameters, evaluated the mpMRI data separately and independently. The accuracy of

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Key Words: Prostate cancer, MRI and prostate cancer, repeat MRI/TRUS targeted prostate biopsy, transperineal targeted biopsy.

Table I. *Quantitative biopsy histology, PI-RADS (Prostate Imaging-Reporting and Data System) score and ADC values in the 26 men with csPCa.*

csPCa: quantitative histology	PI-RADS 3	PI-RADS 4
Number of patients	2/80 (2.5%)	24/176 (13.6%)
Median PSA values (ng/ml)	11.3	12.9
Gleason score (ADC value)	7	6.9 (6-7)
3+3 (0.750±0.162)	-	1
3+4 (0.635±0.117)	1	8
4+3 (0.489±0.093)	-	3
Median number of positive cores	1.0	2.0
TPBx (range)	25% (1-4)	50% (2-4)
Median GPC (range)	50%	55% (40-70%)
Median prostate weight (grams)	50	45
Median mpMRI lesion index diameter (mm)	9	10

PSA: Prostate specific antigen; TPBx: targeted transperineal fusion biopsy; GPC: greatest percentage of cancer for single core; csPCa: clinically significant prostate cancer; ADC: apparent diffusion coefficient.; mpMRI: multiparametric magnetic resonance imaging.

TPBx in the diagnosis of csPCa (Gleason score>6 and/or greatest percentage of cancer for single core>50%) was evaluated (13); moreover, the Clavien-Dindo grading system for the classification of biopsy complications was used (14). Finally, the diameter of mpMRI lesion, the presence of PI-RADS score 3 *vs*. 4 and ADC values were evaluated in men with csPCa; in this respect, a receiver operating characteristic (ROC) curve was calculated in the peripheral mpMRI lesions to evaluate the diagnostic performance of ADC values as well as to determine the ADC cut-off level that provided the highest diagnostic performance. For statistical analysis the Student's *t*-test was used; a p-value <0.05 was considered statistically significant.

Results

The median total PSA and prostate weight were 11.6 ng/ml (range=6.7-29 ng/ml) and 51 g (range=20-120 g), respectively; median PSA levels increased by 2.3 ng/ml (range=1.8-4.2 ng/ml) from the values evaluated prior the last SPBx. None had significant complications (Clavien-Dindo grade I) from prostate biopsy that needed hospital admission. The detection rate for overall cancers *versus* csPCa was equal to 14% (36/256 cases) *versus* 10.1% (26/256 cases); a clinical T1c PCa was found in 6/80 (7.5%) *versus* 30/156 (17%) patients with a PI-RADS score equal to 3 *versus* 4, respectively. In detail, among the 26/36 (77.3 %) cancers classified as csPCa only 2/6 (33.3%) *versus* 24/30 (80%) had a PI-RADS score equal to 3 *versus* 4 (p=0.0001), respectively; 18 (64.3%) and 8 (35.7%) of the csPCa were located in the peripheral and anterior zone of the prostate. The biopsy quantitative histology (*i.e.*, number of positive cores, greatest percentage of cancer and Gleason score) is presented in Table I. A normal parenchyma was diagnosed in the remaining 220/256 (86%) men. The median prostate weight and PSA density were equal to 52 and 0.20 *vs*. 63 g and 0.15 in men with PCa *vs*. normal parenchyma, respectively; moreover, the median diameter of mpMRI lesions were similar in men with csPCa (10 mm) and in men with normal parenchyma (9 mm). Finally, the presence of csPCa was significantly correlated with an ADC value of 0.747×10^{-3} mm^2/sec, threshold obtained from ROC curve analysis (Figure 1).

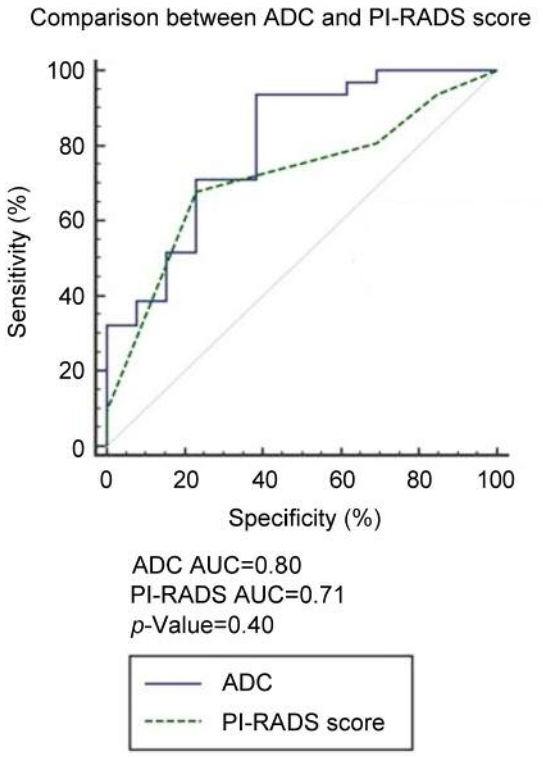

Figure 1. *ROC curve of ADC (cut-of $0.747\times10^{-3}mm^2$/sec) vs. PI-RADS score 3 and 4 in the diagnosis of csPCa. ADC: Apparent diffusion coefficient; PI-RADS: prostate imaging reporting and data system; AUC ROC: area under the curve receiver operating characteristic; csPCa: clinically significant prostate cancer.*

Discussion

The improvement of diagnostic imaging by mpMRI has allowed targeted biopsies of the suspicious area, increasing the diagnosis of csPCa (1) and reducing the number of unnecessary systematic biopsies. Although mpMRI is strongly recommended in men candidate for a repeat biopsy (3) or men enrolled in active surveillance protocols (15, 16), still today, systematic biopsy should be always combined with mpMRI/TRUS fusion biopsy due to the increased false negative rate (1, 17) of mpMRI (about 20% of the cases) (11, 18, 19) and the variable diagnostic accuracy of the different

Table II. *Detection rate of clinically significant prostate cancer (csPCa) vs. PI-RADS score*

Population/Group (reference)	Number of patients overall	PI-RADS<3 csPCa	PI-RADS 3 csPCa	PI-RADS 4 csPCa	PI-RADS 5 csPCa
Sathianathen NJ (24)	255	0%	21.4%	62.7%*	62.7%*
John S (27)	131	NR	11.0%	42.9%	35.6%
Bastian-Jordan M (26)	343	NR	12.0%	51.0%	80.0%
Shoots IG *et al*. (30)	8,252	NR	21.0%	39.0%	73.0%
Wenderink W (28)	1,057	NR	17.0%	34.0%	67.0%
Pepe P (11)	1,032	8.7%	25.4%	50%	100%
Hansen NL (25)	143	NR	21%	NR	NR

PI-RADS: Prostate Imaging-Reporting and Data System; *PI-RADS 4 and 5; NR: not reported; csPCa: Gleason score >6 and/or greatest percentage of cancer >50%.

mpMRI/TRUS fusion biopsy platforms (20). On the other hand, an alternative clinical approach is to begin with mpMRI to determine which patients need a targeted biopsy (21, 22).

The detection rate of csPCa is directly related to the PI-RADS score (Table II) (11, 23-30) and the results depend on clinical parameters, the number of previous negative biopsies and the quality of TPBx procedures; in a previous series, we reported a percentage of missed csPCa equal to 8.7 *versus* 23.5 *versus* 16.2 *versus* 0% in the presence of a PI-RAS score <3 *versus* 3 *versus* 4 *versus* 5 in patients that were diagnosed by transperineal SPBx (11). In addition, it is still unclear when and which mpMRI lesions negative for cancer should be submitted early to repeat TPBx; in this respect, about 15-20% of PI-RADS 3 could harbour a csPCa resulting in reclassification to PIRADS score 4 in a year (24, 25). On the other hand, the detection rate of csPCa in the presence of PI-RADS score 5 *versus* 4 is extremely variable ranging from 35.6-100% (11, 26) to 34-62.7% (23-27) of the cases, respectively.

To identify the PI-RADS score at high risk for csPCa irrespective of clinical findings many parameters have been reported: index lesion diameter, shape and location of the lesion (25) and the ADC values (4, 7, 9). Wu *et al*. (9) showed that higher ADC values (0.830×10^{-3} mm^2/sec) were significantly associated with low-risk prostate cancer; on the contrary, Kim *et al*. (6) reported a mean ADC value for csPCa equal to (0.741 ± 0.164) $\times10^{-3}$ mm^2/sec.

In our series, the majority of the csPCa diagnosed at a repeat TBPx had a PI-RADS score of 4 (24/26 equal to 92.3% of the cases) and only in two cases (7.7%) a PI-RADS score of 3 (p=0.0001) was found; an early second round TBPx (6 months later) of the same index lesions of PI-RADS score 3 or 4 diagnosed a csPCa in 2.5% (2/80) *vs*. 13.6% (24/176) of the cases, respectively. Finally, the presence of csPCa was significantly related with an ADC value of 0.747×10^{-3} mm^2/sec, threshold obtained from ROC curve analysis.

Regarding our results some considerations should be made. Firstly, the results were evaluated on biopsy specimens and not on the entire prostate gland or by performing a template mapping biopsy; secondly, the use of an in-bore mpMRI targeted biopsy, probably, would have improved the diagnosis of csPCa. Finally, a greater number of patients and a centralized evaluation of mpMRI results should be performed.

In conclusion, a negative TBPx performed for index lesions of PI-RADS score 3 or 4 missed a csPCa in 2.5% (2/80) *versus* 13.6% (24/156) of the cases that were diagnosed by an early second round TBPx; the evaluation of ADC maps could select mpMRI lesions deserving a repeat TPBx.

Conflicts of Interest

The Authors declare no conflicts of Interest regarding this study.

Authors' Contributions

The Authors contributed equally to this article.

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