

Multiparametric MRI *Versus* SelectMDx Accuracy in the Diagnosis of Clinically Significant PCa in Men Enrolled in Active Surveillance

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Abstract. *Background/Aim:* To evaluate the diagnostic accuracy of the urinary SelectMDx test in the diagnosis of clinically significant prostate cancer (csPCa) in men enrolled in an active surveillance (AS) protocol. *Patients and Methods:* From July 2015 to July 2018, 125 men with very low-risk PCa were enrolled in the AS protocol; all patients underwent confirmatory transperineal saturation biopsy (SPBx). In the presence of PI-RADS score ≥ 3 , a targeted MRI/TRUS fusion-guided biopsy was added to SPBx. Post-digital rectal examination urine was collected in 45/125 (36%) patients before SPBx; the genetic urine analysis was performed using a biomarker-based risk score model, the SelectMDx, that measured mRNA levels of distal-less homeobox 1 (DLX1) and homeobox C6 (HOXC6). *Results:* A total of 9/45 (20%) patients were reclassified as csPCa (7 cases=Grade Group 2; 2 cases=Grade Group 3); sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of mpMRI vs. SelectMDx in the diagnosis of csPCa were equal to 66.6 vs. 55.6%, 87.7 vs. 65.8%, 54.5 vs. 27.8%, 92.3 vs. 87%, 84.9 vs. 70.3%, respectively. *Conclusion:* SPBx combined with MRI/TRUS fusion biopsy significantly outperformed the diagnostic accuracy of SelectMDx (70.3%) in the diagnosis of csPCa in men enrolled in AS.

Prostate cancer (PCa) is the second commonest tumor among men; PSA screening has been shown to reduce PCa mortality but, at the same time, it is known to lead to unnecessary prostate biopsies and overdiagnosis/overtreatment of indolent PCa (1). Therefore, the necessity to select candidate patients

for prostate biopsy using more clinical parameters (*i.e.*, risk calculator, prostate health index, 4Kscore, diagnostic imaging) to better separate men at risk for clinically significant prostate cancer (csPCa) (2-5), exists in clinical routine practice. In this respect, multiparametric magnetic resonance image (mpMRI) and novel urine-based molecular tests that combine mRNA biomarkers with clinical factors have improved the diagnosis for csPCA (6). Urine is a promising source for the development of new biomarkers because after digital rectal examination, it is enriched with DNA, RNA and proteins correlated with PCa. The urinary prostate cancer antigen 3 test (PCA3) was the first Food and Drug Administration-approved RNA-based urinary marker (7-9); recently, the SelectMDx test based on messenger RNA detection of DLX1 and HOXC6 in urine, after prostate massage, has been introduced in clinical practice to detect high-risk PCa (10-14). At the same time, novel biomarkers combined with mpMRI can help towards a better selection of patients who are candidates to Active Surveillance (AS) reducing the risk of undergrading; in fact, AS is an alternative to initial definitive treatment of low-risk PCa. Current criteria for selection and follow-up incorrectly exclude some patients eligible for AS and misclassify others who actually harbour significant disease; better prediction of cancer behaviour at diagnosis would allow less strict monitoring and may improve acceptance of AS (15-17). Nomograms, or risk calculators, have the advantage of incorporating easy to retrieve clinical variables such as age, family history, DRE, PSA density, mpMRI and biomarkers. In this study, the diagnostic accuracy of the urinary SelectMDx test in the evaluation of men enrolled in an AS protocol has been prospectively evaluated.

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Patients and Methods

From July 2015 to July 2018, a prospective study was conducted on 125 consecutive men aged between 60 and 73 years (median age: 66 years) with very low-risk PCa enrolled in an AS protocol. The presence of the following criteria defined eligibility: life expectancy greater than 10 years, clinical stage T1c, prostate-specific antigen

(PSA) below 10 ng/ml, prostate specific antigen density (PSAD) less than 0.20 ng/ml, two or fewer unilateral positive biopsy cores, Gleason score (GS) equal to 6 (ISUP Grade Group 1) and greatest percentage of cancer (GPC) $\leq 50\%$ (17, 18). The study was approved by the local ethics committee and informed written consent was obtained from each man before enrolment. Six months after PCa diagnosis, all patients underwent digital rectal examination, total PSA, PSAD, 3.0 T pelvic mpMRI and confirmatory transperineal saturation biopsy (SPBx: 30 cores; 24 in the periphery and six in the anterior zone). The procedure was performed with the use of a GE Logiq P6 ecograph (General Electric, Milwaukee, WI, USA) supplied with a biplanar transrectal probe (5-7.5 MHz) using a trucut 18 gauge needle (Bard, Covington, GA, USA) under sedation and antibiotic prophylaxis (19). All mpMRI examinations were performed using a 3.0 T scanner (ACHIEVA 3T; Philips Healthcare, Best, The Netherlands) equipped with a surface 16 channel phased-array coil placed around the pelvic area with the patient in the supine position. Multiplanar turbo spin-echo T2-weighted imaging, axial diffusion-weighted imaging, axial dynamic contrast-enhanced imaging were performed for each patient. mpMRI lesions characterized by a Prostate Imaging Reporting and Data System (PI-RADS) score ≥ 3 were considered suspicious for cancer; two radiologists blinded to pre-imaging clinical parameters evaluated the MRI data separately and independently. In the presence of mpMRI lesions suggestive of cancer, targeted MRI/TRUS fusion guided biopsies were added to SPBx using a Hitachi 70 Arietta ecograph (Chiba, Japan) supplied with a transrectal biplanar probe. All mpMRI procedures were performed 1 week before prostate biopsy by a radiologist experienced in the field of MRI in PCa. Post-digital rectal examination urine was collected in 45/125 (36%) patients before SPBx; the genetic urine analysis was performed using a commercially available biomarker-bases risk score model SelectMDx (MDx Health, Irvine, CA, USA) (10-14). The test measured mRNA levels of distal-less homeobox 1 (DLX1) and homeobox C6 (HOXC6) in a post-DRE urine specimen and combines these with serum PSA, PSA density, DRE status, age, and family history of PCa. Finally, the diagnostic accuracy in the diagnosis of csPCa of SelectMDx was compared with mpMRI results.

Results

Nine out 45 (20%) patients submitted to repeat SPBx were reclassified (Table I) based on upgraded Grade Group (7 cases had GS 3+4/Grade Group 2 and 2 cases had GS 4+3/Grade Group 3); in addition, the median number of positive cores was 5 (range=3-8) and median GPC was equal to 70% (range=40-100%). In detail, csPCa were located only in the anterior vs. the periphery zone of the gland in 3/9 (33.3%) vs. 6/9 (66.7%) cases, respectively.

Of the remaining 36 (80%) patients, 29 were found to have very low-risk PCa and in 7 cancer was absent. Multiparametric MRI and SelectMDx results are listed in Table I; in the presence of csPCa, mpMRI demonstrated a PI-RADS score of 3 and 4 in 4/9 (44.4%) and in 2/9 (22.2%) patients, and median SelectMDX value was 26% (range=12-40%). In one case of csPCa, only SelectMDx resulted abnormal, on the contrary, in three cases only mpMRI was

suspicious. No one suffered significant complication from prostate biopsy requiring admission to Hospital.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of mpMRI vs. SelectMDx in the diagnosis of csPCa were equal to 66.6 vs. 55.6%, 87.7 vs. 65.8%, 54.5 vs. 27.8%, 92.3 vs. 87%, 84.9 vs. 70.3%, respectively.

Discussion

Recent advances in genomic sequencing and molecular classification led to development of a plethora of assays for PCa diagnosis; therefore, considerable effort has been given to identify novel tissue, serum, and urine-based biomarkers to better stratify at-risk patients (20, 21). For the diagnosis of PCa, biomarkers should ideally be detectable in body fluids that can be obtained non-invasively and therefore urine has emerged as the substrate for the non-invasive detection of PCa. The first fully translated RNA-based molecular diagnostic test for the detection of prostate cancer in urine was the PCA3 test (9); although, the combined use of the ProgenSA PCA3 test and TMPRSS2-ERG could significantly improve the sensitivity for prostate cancer diagnosis (22, 23), the value of this combination for predicting biopsy csPCa in urine is controversial (24). A novel urinary assay-based risk score called SelectMDx combines serum PSA, PSAD and clinical factors such as age and prior negative biopsy with two mRNA signatures: urinary homeobox C6 and distal-less homeobox 1 (10-14). The test measures the amount of two genes that are associated with aggressive prostate cancer with a high NPV for Grade Group ≥ 2 (Gleason score ≥ 7). In definitive, SelectMDx combined with mpMRI could better select men candidates to AS ruling out patients who do not have csPCa improving the cost-effectiveness (25-27). In a multicenter study including 916 men submitted to initial prostate biopsy, Haese *et al.* (28) reported a sensitivity, specificity and NPV of SelectMDx in the diagnosis of csPCa equal to 93, 47 and 95%, respectively.

In our series, 9/45 (20%) patients were reclassified based on upgraded Grade Group (7 cases=GS 3+4; 2 cases=GS 4+3). Multiparametric MRI and SelectMDx missed 3/9 (33.3%) and 4/9 (44.5%) csPCa respectively; moreover, mpMRI combined with SelectMDx diagnosed 7/9 (77.8%) csPCa. SPBx combined with MRI/TRUS fusion biopsy outperformed significantly the diagnostic accuracy of mpMRI (84.5%) and SelectMDx (70.3%) in the diagnosis of csPCa. Therefore, SelectMDx should be considered as one piece of the puzzle assisting the physicians and patients in the re-evaluation of men enrolled in AS protocols (29) in order to select for upgrading men at risk in need of early repeat prostate biopsy; mpMRI improves prostate biopsy strategies to detect csPCa (30), but still today, systematic prostate biopsy should be anyway performed (31).

Table I. Multiparametric magnetic resonance imaging (mpMRI), PSA and SelectMDx findings in 9/45 men re-classified at confirmatory prostate biopsy.

Number of patients	mpMRI PI-RADS score ≤ 2	mpMRI PI-RADS score ≥ 3	SelectMDx test suspicious*
45 (overall)	34 (75.6%)	11 (24.4%)	18 (40%)
Indolent PCa/normal parenchyma 36/45 (80%)	31	5	14
csPCa 9/45 (20%)	3	6	5
False positive for csPCa	0	5	14
False negative for csPCa	3	0	4

csPCa: Clinically significant prostate cancer; PI-RADS: Prostate Imaging Reporting and Data System; *SelectMDX value: estimated risk for csPCa=26% (range=12-40%).

Regarding our results, some considerations should be addressed. Firstly, the results were evaluated on biopsy specimens and not on the entire prostate gland or performing a template mapping biopsy. Secondly, the diagnostic accuracy of SelectMDx equal to 70.3% in diagnosing csPCa has been obtained in patients AS with very low-risk PCA but it might improve in case of initial or repeat prostate biopsy. Finally, a greater number of patients should be evaluated.

In conclusion, SPBx combined with MRI/TRUS fusion biopsy significantly outperformed the diagnostic accuracy of SelectMDx (70.3%) in the diagnosis of csPCa in men enrolled in an AS protocol.

Conflicts of Interest

The Authors declare that no conflicts of interest exist in regard to this study.

Authors' Contributions

The Authors equally contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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