In-parallel comparative evaluation between multiparametric magnetic resonance imaging, prostate cancer antigen 3 and the prostate health index in predicting pathologically confirmed significant prostate cancer in men eligible for active surveillance

IN PARALLEL COMPARATIVE EVALUATION BETWEEN MULTIPARAMETRIC MRI, PCA3 AND PHI IN PREDICTING PATHOLOGICALLY CONFIRMED SIGNIFICANT PROSTATE CANCER IN MEN ELIGIBLE FOR ACTIVE SURVEILLANCE

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Keywords:	multiparametric MRI, PHI, PCA3, Prostate Cancer, Prognostic Accuracy, Active Surveillance
Abstract:	Objective: To assess the performance capabilities of multiparametric Magnetic Resonance Imaging (mpMRI), Prostate Health Index (PHI) and Prostate Cancer Antigen 3 gene (PCA3) in predicting the presence of pathologically confirmed significant Prostate Cancer (PCSPCa), according to the European Randomized Study of Screening Prostate Cancer (ERSPC) definition, in a same cohort of patients who underwent Radical Prostatectomy (RP) but eligible for Active Surveillance (AS). Materials and Methods: An observational retrospective study was performed in 120 prostate cancer (PCa) patients treated with robot-assisted RP but eligible for AS according to Prostate Cancer Research International: Active Surveillance (PRIAS) criteria. Blood and urinary specimens were collected before initial prostate biopsy for PHI and PCA3 measurements, respectively. In addition, all patients underwent preoperatively and after 6-8 weeks from biopsy to mpMRI with a 1.5T scanner using a 4-5 channel phase array coil combined with an endorectal coin. mpMRI images were assessed and diagrams depicting prostate sextants were used to designate regions of abnormalities within the prostate. Findings in the prostate were assigned to one of five categories according Prostate Imaging-Reporting and Data System guidelines (PI-

	RADS) and considered positive for PCa if final PI-RADS was >3 and negative if ≤3. Results: A pathologically confirmed reclassification was observed in 55 patients (45.8%). mpMRI demonstrated a good specificity and negative predictive value (0.61 and 0.73, respectively) for ruling out a PCSPCa compared with PHI and PCA3. On multivariate analyses and after one thousand bootstrapping resampling, the inclusion of both PHI and mpMRI significantly increased the accuracy of the base model in predicting PCSPCa. Particularly, to predict PCSPCa, the base model had an AUC of 0.71 which significantly increased by 4% with the addition of PHI (AUC=0.75; p<0.01) and by 7% with the addition of mpMRI (AUC=0.78; p<0.01). Decision curve analysis revealed that the multivariable model with mpMRI had the highest net benefit. Conclusion: In a same cohort of patients underwent to RP but eligible to AS, mpMRI and, to a lesser extent, PHI showed an important role in discriminating the presence of a PCSPCa. Consequently, they could be useful in both the selection and monitoring of patients undergoing AS.

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ABSTRACT

Objective: To assess the performance capabilities of multiparametric Magnetic Resonance Imaging (mpMRI), Prostate Health Index (PHI) and Prostate Cancer Antigen 3 gene (PCA3) in predicting the presence of pathologically confirmed significant Prostate Cancer (PCSPCa), according to the European Randomized Study of Screening Prostate Cancer (ERSPC) definition, in a same cohort of patients who underwent Radical Prostatectomy (RP) but eligible for Active Surveillance (AS).

Materials and Methods: An observational retrospective study was performed in 120 prostate cancer (PCa) patients treated with robot-assisted RP but eligible for AS according to Prostate Cancer Research International: Active Surveillance (PRIAS) criteria. Blood and urinary specimens were collected before initial prostate biopsy for PHI and PCA3 measurements, respectively. In addition, all patients underwent preoperatively and after 6-8 weeks from biopsy to mpMRI with a 1.5T scanner using a 4-5 channel phase array coil combined with an endorectal coin. mpMRI images were assessed and diagrams depicting prostate sextants were used to designate regions of abnormalities within the prostate. Findings in the prostate were assigned to one of five categories according Prostate Imaging-Reporting and Data System guidelines (PI-RADS) and considered positive for PCa if final PI-RADS was >3 and negative if ≤3.

Results: A pathologically confirmed reclassification was observed in 55 patients (45.8%). mpMRI demonstrated a good specificity and negative predictive value (0.61 and 0.73, respectively) for ruling out a PCSPCa compared with PHI and PCA3. On multivariate analyses and after one thousand bootstrapping resampling, the inclusion of both PHI and mpMRI significantly increased the accuracy of the base model in predicting PCSPCa. Particularly, to predict PCSPCa, the base model had an AUC of 0.71 which significantly increased by 4% with the addition of PHI (AUC=0.75; $p<0.01$) and by 7%

with the addition of mpMRI (AUC=0.78; p<0.01). Decision curve analysis revealed that the multivariable model with mpMRI had the highest net benefit.

Conclusion: In a same cohort of patients underwent to RP but eligible to AS, mpMRI and, to a lesser extent, PHI showed an important role in discriminating the presence of a PCSPCa. Consequently, they could be useful in both the selection and monitoring of patients undergoing AS.

INTRODUCTION

In the era of opportunistic screening, the increasingly widespread use of Prostate Specific Antigen (PSA) test has led an increased incidence of low risk Prostate Cancers (PCa) that present a low likelihood of future progression during lifetime and could benefit of Active Surveillance (AS). AS aims to mitigate the overtreatment of indolent disease and potentially harmful side effects of active treatments, retaining the option of definitive therapy for patients who are reclassified over time as high risk [1]. The short and medium term safety for AS has been well demonstrated in multiple study cohort with only rare occurrence of PCa related death or metastasis reported. [2-5]. More recently, Klots et al confirmed the feasibility of AS in a large cohort study with a log-term follow-up, reporting a 10- and 15- year actuarial cancer-specific survival rates of 98.1 and 94.3%, respectively, with an active treatment free survival of 75.7, 63.5 and 55.0% at 5, 10 and 15 years, respectively [6].

However, the long term safety and effectiveness of AS depends on ability to select appropriate patients. At today, current stratification risk schemes are not perfect and the clinical and pathological parameters (total PSA, density PSA, biopsy Gleason Scores, number of positive cores, percentage of core involvement, clinical Stage) traditionally used to identify the presence of indolent PCa misclassify some patients, which are selected with apparent low risk disease and then harbor unfavorable disease. This is likely attributable to an initial misclassification instead of a true progression of indolent cancer, given the mutifocality of the disease and the well-known clonal heterogeneity of PCa. In fact, in the updated results from the Prostate Cancer Research International: Active Surveillance (PRIAS study), 28% of the cohort experienced disease reclassification (defined as Gleason score >6 and/or more than two positive cores) at the first repeated biopsy during follow-up [7]. Furthermore, 20-30% of men

eligible for AS but elect to primary radical prostatectomy (RP) are found to have unfavorable (Gleason≥ 7 or pT3) disease at RP [8]. On the other hand, we must not forget that current AS criteria may be too strict, thereby excluding some patients in whom expectant management would be appropriate and safe. In this context, GS 3+4 patients, with a very small volume of a secondary Gleason 4 and a PSA<10 ng/ml, have been shown to have a disease comparable to GS 3+3 patients [9,10].

For these reasons, there is an urgent need to better tools, including biomarkers and new imaging technique, that could be used to better select patients for AS and to monitor them during their subsequent course. Van der Bergh et al [11] recently published a systematic review of 30 studies on all clinical tools for AS patients selection and monitoring, including studies on magnetic resonance imaging (MRI), on serum biomarkers (-2proPSA, an isoform of PSA, and the Prostate Health Index, PHI) and on urinary markers (Prostate Cancer Antigen 3 gene, PCA3). The authors concluded that the use of high quality multiparametric MRI (mpMRI) showed particular promise because of the very high negative predictive value respect to significant PCa and a favorable mpMRI might obviate the need for repeat biopsy during AS. In addition, the use of PSA isoform data to current AS criteria might provide further added benefit.

Keeping this in mind, we evaluate the performance capabilities of PHI, PCA3 and mpMRI in predicting the presence of pathologically confirmed significant PCa (PCSPCa, updated ERSPC definition) in a same cohort of patients who underwent RP but eligible for AS.

MATERIAL AND METHODS

We retrospectively reviewed our RP database from January 2012- December 2014, consisting of patients with biopsy-proven, clinically localized PCa who underwent to robot-assisted RP at a surgical

high volume center (San Luigi Hospital, Orbassano, University of Turin) and to mpMRI at two important and proved expertise centers in mpMRI (San Luigi Hospital,Orbassano, University of Turin and Cancer Institute of Candiolo, Turin). From this database, we identified patients eligible for AS based on PRIAS criteria (clinical stage T1c or T2 disease, PSA level of ≤ 10 ng/ml, Gleason score ≤ 6, PSA-D of <0.2 ng/ml and one or two positive biopsy cores) [7]. These patients had been proposed AS but they had refused opting for surgery. We excluded patients who received neo-adjuvant hormonal therapy (anti-androgens or luteinizing hormone-releasing hormone analogues or antagonists) or/and other hormonal preparations (ie, 5-alpha reductase inhibitors), patients with bacterial acute prostatitis or previous prostate surgery in the 3 months prior to biopsy, subjects with chronic renal disease , marked blood protein alterations (plasma normal range: 6-8 g/100 ml), hemophilia, or those previously multiply transfused in order to not alter fPSA concentrations and consequently of -2proPSA[12]. A final cohort of 120 patients was identified.

All patients underwent serum measurements of tPSA, %fPSA and PHI before biopsy. The PHI analyses were performed using Hybritech Calibrated Access_assays (Beckman Coulter, Brea, California) after processing with a Unicel_ DxI 800 Immunoassay System analyzer (Beckman Coulter). In addition, all patients underwent PCA3 testing before prostate biopsy via a Progensa_PCA3 assay (Gen-Probe Inc, San Diego, California) according to the manufacturer's specific instructions. All examinations were carried out at Laboratory Medicine of San Luigi Hospital, Orbassano, Turin for PCA3 and at Cancer Institute of Candiolo, Turin for PHI.

Finally, all patients underwent preoperatively and after 6-8 weeks from biopsy (to minimize post-biopsy artifact) to mpMRI with a 1.5T scanner (SIgna Excite HD, GE Healthcare,) using a 4-channel phase array coil combined with an endorectal coil (Medrad, Warrendale) or with a 1.5T scanner (Achieva HD, Philips Healthcare) using a 5-channel phase array coil combined with an endorectal coil (Medrad, Warrendale). The prostate and seminal vesicle anatomy was assessed on T2-weighted images

in the axial, coronal and sagittal planes. T1 fast spin echo axial images were generated to identify areas of intraprostatic hemorrhage and to evaluate the pelvic lymph nodes and bones. Functional information was obtained by Diffusion Weight Imaging (DWI) and Dynamic Contrast Enhanced (DCE) MRI. DWI was performed using axial echo planar imaging sequences at different b-values. The sequences parameters satisfied the recommendations from an European consensus meeting on MRI imaging for the detection, localization and characterization of PCa [13].

All images were sent to two workstations and post processed (Functool v. 9.4.05a, GE Healthcare and Intellispace Portal v. 6.0.3.12200, Philips Healthcare). Two single experienced uro-radiologists analyzed the mpMRI findings. The uro-radiologists were blinded to the biomarkers results and to the pathologist biopsy reports. Diagnostic features for malignancy were a low T2 signal in the peripheral zone, a relatively low Apparent Diffusion Coefficient (ADC) calculated from DWI, early enhancement and washout on DCE MRI. For the transitional zone a poorly defined nodule that distorted the normal architecture and had concordant abnormalies on DWI and DCE was considered suspicious for malignancy. mpMRI images were assessed and diagrams depicting prostate sextants were used to designate regions of abnormalities within the prostate. Findings in the prostate were assigned to one of five categories according Prostate Imaging-Reporting and Data System guidelines, developed by the European Society of Urogenital Radiology (ESUR) in order to standardize the evaluation and reporting of prostate mpMRI [14]. A recent meta-analysis on the use of PI-RADS for PCA detection with mpMRI showed a good diagnostic accuracy with a sensitivity of 0.78 and a specificity of 0.79 [15]. Particularly, we assigned a 0-5 score to each of the three MRI sequences (T2-weighted, DWI and dynamic contrast enhanced MRI) and a final PI-RADS score was obtained by adding the single scores and dividing by three (rounding down or up depending on the case). Overall, the mpMRI finding was considered positive if final PI-RADS was > 3 and negative if ≤ 3.

RP specimens were evaluated using serially 3 mm sectioned whole-mount specimens according to the Stanford protocol [16] and primary and secondary Gleason Score (GS) were assigned by an experienced uropathologist, blinded to the biomarkers value and mpMRI results, according to the 2005 consensus conference of the International Society of Urological Pathology definitions [17]

For study purposes, all tumor foci were identified. Specifically, we evaluated the largest tumor focus of the prostate - index tumor lesion (approximately a lesion of 1 cm corresponds to a spherical volume of 0.5 ml) and cumulative tumor volume was assessed using computerized planimetry accounting for all tumor foci [18].

The primary end points of the study were to determine the performance capabilities of PHI, PCA3 and mpMRI in parallel in predicting the presence of PCSPCa using the ERSPC definition (insignificant PCa at RP: organ-confined Gleason 3+3 tumours, with no Gleason grade 4 or 5, index tumour volume ≤ 1.3 cm^3 and a total tumour volume of ≤ 2.5 cm^3) [19]. In according with other authors [20] we used these criteria because we consider the well-established 0.5 cm^3 PCa volume threshold for the index tumor in the classic histopathologic Epstein definition of insignificant PCa (absence of GS pattern 4 or 5, extra capsular disease and a lesion >0.5 cm^3) too much restrictive. Indeed, against the small (approximately 5%) increased risk of underestimation of significant PCa, a much larger proportion of men would have the chance to enter and participate in AS programs and forgo definitive treatments. This situation would be beneficial of both quality of life and costs.

The study was designed according to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) methodology to test the sensitivity, specificity, and accuracy of -2proPSA, its derivates, PCA3 and mpMRI (http://www.stard-statement.org).

Statistical analysis

The qualitative data were tested using the chi-square test or Fisher's exact test as appropriate and the continuous variables were tested by Mann-Whitney U-Test or T-Student Test according to their distribution (according to Kolmogorov-Smirnov test) and presented as median (IQR) or mean (± standard deviation), as appropriate. Univariate and multivariate logistic regression analyses were carried out to identify variables potentially predictive of PCSPCa.

We preferred to exclusively consider PHI and exclude from the univariate and multivariate analysis both the -2proPSA and its derivative -2proPSA over fPSA (%-2proPSA) because the variable PHI could be more easy to interpret and understand by the reader since it is generally evaluated in a clinical setting and because statistically speaking, PHI could capture much of the effects and obscure results when it is evaluated in same multivariate analysis together with its components (-2proPSA), as previously described [21].

Predictive accuracy of the model was assessed in term of the area under the receiver operating characteristics curve (AUC) value. One thousand bootstrap resamples were used for all accuracy estimates and to reduce overfit bias. The areas under the curve were compared via the Mantel-Haenszel test.

We performed decision curve analysis (DCA) to evaluate the potential clinical usefulness of making decisions based on the models including the markers [22].

We estimated net benefit (NB) for prediction models by summing the benefits (true-positive PCSPCa) and subtracting the harms,(false-positive PCSPCa). The threshold probability of each model were estimated. The interpretation of DCA is straightforward; a model with the highest NB at a particular threshold should be chosen over alternative models. For all statistical comparisons significance was considered as $p < 0.05$. Standard statistical software was used (SPSS v.18.0,IBMCorp,Armonk, NY, USA; R version 2.15.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

After pathological specimens examination of all included subjects, we observed pathologically confirmed reclassification in 55 patients (45.8%). Table 1 summarizes the characteristics of patients according to the presence or not of PCSPCa. A positive mpMRI (PI-RADS ≥4) was found in 72.7% of PCSPCa and a negative mpMRI (PI-RADS ≤3) in 61% of PCIPCa. The sensitivity of mpMRI (PI-RADS ≥ 4) was 73%, the specificity (PI-RADS ≤3) was 61%, the negative predictive value (NPV) was 73% and the positive predictive value (PPV) was 61.5%. At the best balance value between sensibility and specificity (PHI ≥32.47), the sensitivity of PHI was 75%, the specificity was 54%, the NPV was 66% and the PPV was 67%. At the best balance value between sensibility and specificity (PCA3 ≥ 52.50), the sensitivity of PCA3 was 73%, the specificity was 64%, the NPV was 37% and the PPV was 76%.

On multivariate analyses and after one thousand bootstrapping resampling, the inclusion of both PHI and mpMRI significantly increased the accuracy of the base model in predicting PCSPCa, that included patient age, total PSA, free/total PSA ratio, PSA density, clinical stage, biopsy GS, number of positive cores (2 vs. 1). To predict PCSPCa, the base model had an AUC of 0.71 which significantly increased by 4% with the addition of PHI (AUC=0.75; $p<0.01$) and by 7% with the addition of mpMRI (AUC=0.78; $p<0.01$) (Table 2).

At the threshold > 20% the prediction models including mpMRI added value over base model. At the threshold > 60% the prediction models including PHI added Net Benefit over base model. The model including PCA3 did not added value (Figure 1).

DISCUSSION

A lot of published studies evaluated the utility of PCA3 and PSA isoforms, in addition to clinical and pathological parameters, to determine initial eligibility for AS and to monitor disease progression [11]. Recently, it has been published a direct comparison between PHI and PCA3 in a same cohort of patients underwent RP in predicting final pathologic features, demonstrating that PHI was significantly better than PCA3 in discriminating the presence of PCSPCa according to Epstein criteria [21]. Based on these results, the same authors also demonstrated that Epstein and PRIAS protocols could be improved by the addition of PCA3 or PHI resulting in greater NB in predicting insignificant prostate cancer in men eligible for AS. Particularly, PHI outperformed PCA3 demonstrating a better discriminative performance [21].

However, recent evidences also suggest a particular and prominent role played by mpMRI in this clinical scenario [23,24,25] For these reasons, in the current study, using histology at RP time as the reference standard, we evaluated the performance of mpMRI and urinary and serum biomarkers in parallel, demonstrating a higher capability of mpMRI than biomarkers in detecting pathologically confirmed significant disease according to the ERSPC definition. At our acknowledge, this is the first study the evaluates the prognostic performance of these three new tools in the same dataset of patients. In our cohort, mpMRI showed the highest gain in predictive accuracy of PCSPCa than both PCA3 and PHI (AUC=0.78; $p<0.01$). A negative prostate mpMRI has been shown to have a NPV for ruling out PCSPCa of 73%. Consequently, we can hypothesize that patients with a negative mpMRI and low-risk disease should be encouraged to pursue AS and a favourable mpMRI might obviate the need for repeat biopsy during AS follow up in two third of cases. On the other hand, we observed a lower PPV of 61% for a high risk disease. This suggests that lesions seen on mpMRI (or modification in mpMRI findings during AS program) not necessary correspond to not favorable PCa and it should ideally be confirmed

on prostate biopsy rather than being an indicator for RP. Herein, after performing DCA we demonstrated that adding mpMRI and PHI added net benefit over base model when the threshold probabilities was greater than 20% for mpMRI and greater than 60% for PHI. To reduce the ever-increasing number of patients suitable for AS, we applied this new statistical evaluation to help us to better understand the clinical benefit of adding mpMRI, PCA3 or PHI to a base model in order to improve the clinical decision-making and better choose patients candidate to AS.

However, with regard to this clinical scenario there are two important problem. No accepted definition of "radiological" progression in MRI in patients underwent AS has been formulated. This definition can be based both on morphological parameters (volume measured on T2W or contrast-enhanced images) and functional parameters (changes during time in qualitative and quantitative findings derived most of all from DWI sequences, using a specific standardized reporting system). For this reason, at today, a mpMRI alone is not able to really identify the disease progression and a combination of radiological and biopsy findings is still necessary. Second, whether MRI-target biopsies, or MRI/TRUS fusion biopsies, should be always completed by systematic TRUS-guided biopsies during first or repeat prostate biopsy in AS program remains unknown [26]. In addition, when transperineal saturation biopsy is set as the reference standard, approximately 10% of men with negative MRI and, for this reason, not underwent to transrectal ultrasound guided transperineal fusion biopsy still harbor intermediate risk disease [27]. It is plausible that with increasing precision in MRI target biopsy technologies, systematic biopsy will lose value. Moreover, histology parameters available at MRI target biopsy may not necessarily have the same value of those available at systematic TRUS guided biopsy. Typically, there is an upgrade in GS and higher percentage of cancer per core with MRI target biopsy. Consequently, a new definition of pathological significant PCa with MRI target biopsy should be necessary, most of all whether we perform MRI target biopsy alone.[26]

There are several studies evaluating the performance of mpMRI in AS cohorts, using both RP histology and repeat biopsy data, and a systematic review has been also recently published [28]. However, it is necessary to emphasize that the evidence and the strength of this review are limited by the small number of studies and by the lack of standardization within these studies in terms of population study (age, prostate volume), selection criteria (Epstein, PRIAS), standardization in reporting MRI findings, detection and definition of clinically significant disease and type of follow up. In this review, data synthesis from RP histology (patients eligible for AS but undergone to RP with preoperatively MRI) showed that the likelihood of a positive MRI preoperatively was 73% and upgrading occurred in 43% of patients with positive MRI than 27% of patients with negative MRI, whereas no difference occurred in terms of upstaging between two groups. Data synthesis from men undergoing MRI and repeat standard biopsy on AS,confirmed that MRI is positive in roughly two-thirds of men: following positive MRI, reclassification occurred in 39% than 17% in patients with negative MRI. Focusing on positive MRI and MRI-target biopsy only, reclassification as significant PCa occurred in 47% of cases, confirming a strong correlation between a positive MRI and upgrading during AS follow up and the potential possibility to avoid biopsy in men with stable PSA and negative MRI.

There are also other studies, available in literature, that have not been included in this review [29,30,31]. However, these studies confirmed a very high NPV and specificity for disease upgrading (significant disease) in case of low suspicious scores, confirming that a favorable MRI may be used for selection and follow up of patients during AS and might obviate the need for repeat biopsies. Contextually, the PPV of MRI for higher risk disease seems to be lower in the selected population of patients with low-risk cancers, suggesting that lesion seen on MRI in patients on AS should be necessarily confirmed on guided biopsy. Stamakis et al [30] showed, in their multivariate analysis, that a model incorporating three MRI variables, number of lesion, rate of suspicious and density of lesion (lesion volume divided by prostate volume) presented a reasonable AUC of 0.72 for predicting

suitability for continued AS at repeat biopsy. Most recently Diaz et al [32] confirmed that mpMRI associated a MRI/TRUS fusion biopsy substantially increased the number of pathological progression that would not have been detected by standard biopsy alone. In addition, stable findings on mpMRI were strongly associated with GS stability in patients with GS 6 PCa on AS and could potentially reduce the number of unnecessary biopsies in men undergoing AS (NPV and specificity of 80%).

MRI characteristics have been also incorporated into established predictive preoperative nomograms of pathologically significant PCa. Shukla-Dave et al [33] demonstrated that MRI increased the accuracy of base models (including clinical an pathologic factor) in predicting insignificant disease.

Regarding the sequences of mpMRI, several studies showed the primary importance of DWI during MRI in holding additional information in selection of patients on AS and during follow up. The Apparent Diffusion Coefficient (ADC) of DWI provide information on tumor characteristics such as on tumor aggressiveness. Recently, it has been documentated that ADC values are inversely correlated with GS in PCa and may be help in differentiation of low, intermediate and high risk cancer [34]. Furthermore, ADC of DWI may be a useful marker for predicting insignificant PCa in candidates for AS as well as for predicting PCa progression during the monitoring of these patients [35]

Our study is not devoid of limitations. First, the study was limited by the relatively small number of cases examined and further studies with a larger number should be performed to confirm our findings. Second, the inclusion of only two expert uro-radiologists who interpreted all of the mpMR images may affect the reproducibility of our results in clinical practice. In this context, mpMRI should be standardized not only with regard to image reporting systems, but also with regard to technical equipment and examination protocols, image acquisition, processing and post-processing. Third, the study does not include any discussion of costs and logistics. Given the current health care crisis, these issues are of key importance and further studies should be advised.

Notwithstanding these limitations, we believe that our results are noteworthy and could be transferable to the urological community. mpMRI should be considered a promising tool in order to obtain important information for the best selection of patients to AS program and also during follow up to reduce the number of repeat prostate biopsy. Among biomarkers, PHI appears to add further information in this clinical setting, suggesting a possible combination of these tools.

CONCLUSION

Diverse novel tools are available that may further improve current AS protocols. We showed an important role of PHI and, most of all, of mpMRI in discriminating the presence of a PCSPCa in a cohort of patients underwent to RP but eligible to AS. Consequently, their use could improve the risk assessment in patients candidate to AS and also reduce the burden of monitoring during AS. However, the added value of mpMRI and PSA isoforms should be further assessed in prospective studies.

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Nothing to declare

CONFLICT OF INTEREST STATEMENT

Each author declares no conflict of interest.

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Table 1. Baseline characteristics of patients (n= 120)

	Pathologically Confirmed Significant PCa	Pathologically Confirmed Insignificant PCa	p-value
Patients, n (%)	55	65	
Median (IQR) age, years	65.0 (57.0-70.0)	66.0 (64.00-69.00)	0.55
Median (IQR) PSA, ng/ml	7.0 (6.39-10.10)	5.75 (4.88-9.22)	<0.01
Median (IQR) %fPSA	16.21 (13.00-10.00)	17.66 (15.00-19.00)	0.35
Median (IQR) PSA-D, ng/ml^2	0.16 (0.15-0.24)	0.13 (0.11-0.21)	0.08
Median (IQR) Prostate Volume, ml	42.76 (42.16-43.77)	43.39 (42.75-44.15)	0.09
Median (IQR) PHI	50.89 (28.44-61.33)	32.83 (29.08-45.29)	0.02
Median (IQR) PCA3	47.0 (13.0-58.00)	49.0 (28.0-65.0)	0.08
Clinical stage, n (%) T1c T2	 40 (72.7) 15 (27.3)	 60 (92.3) 5 (7.7)	<0.01
Median (IQR) number of positive cores	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.44
Pathological Index Tumoral Lesion Volume, n.(%) <1.3ml >1.3ml	 7(12.7) 48 (87.3)	 65 (100)	<0.01
Pathological T stage, n.(%) pT2 ≥pT3	 50 (90.9) 5 (9.1)	 65 (100)	<0.01
Extracapsular invasion, n.(%) Yes Not	 5 (9.1) 50 (90.9)	 65(100)	<0.01
Seminal Vesicles invasion, n.(%) Yes Not	 55(100)	 65(100)	--
Pathological Gleason score,n(%) ≤6 7 ≥8	 20 (36.4) 30 (54.5) 5 (9.1)	 60 (92.3) 5(7.7)	<0.01
mpMRI, n.(%) Pos Neg	 40 (72.7) 15 (27.3)	 25 (38.5) 40 (61.5)	<0.01

Table 2: Multivariate analysis predicting the probability of Pathologically Confirmed Significant Prostate Cancer

Predictors	Base Model† OR (95% CI)	p-value	Base Model with PHI† OR (95% CI)	p-value	Base Model with PCA3† OR (95% CI)	p-value	Base Model with mpMRI† OR (95% CI)	p-value
tPSA	1.082 (0.945-1.239)	0.25	1.110 (0.965-1.275)	0.14	1.072 (0.934-1.222)	0.32	1.199 (1.020-1.409)	0.02
f/tPSA	1.061 (0.982-1.147)	0.13	1.097 (1.008-1.195)	0.03	1.063 (0.978-1.149)	0.11	1.135 (1.134-1.241)	<0.01
Clinical stage, T2 vs. T1	4.211 (1.365-12.993)	0.12	1.926 (0.562-6.592)	0.29	9.317 (2.441-35.562)	0.01	2.348 (0.706-7.805)	0.16
N Pos Cores	1.232 (0.558-2.772)	0.02	1.060 (0.451-2.473)	0.08	3.078 (1.080-8.766)	0.03	1.449 (0.615-3.413)	0.39
PHI	-	-	1.044 (1.014-1.076)	<0.01	-	-	-	-
PCA3	-	-	-	-	1.02 (0.942-1.064)	<0.01	-	-
mpMRI	-	-	-	-	-	-	7.532 (2.812-20.173)	<0.01
AUC of Multivariate models %	0.71	-	0.75	-	0.72	-	0.78	-
Gain in predictive accuracy %	-	-	0.04	<0.01	0.01	<0.01	0.07	<0.01

OR= odds ratio; CI= confidence interval; tPSA =total PSA; f/tPSA=free/total PSA; N.Pos.Cores= number of positive cores; DRE= digital rectal exploration; PHI=prostate health index;PCA3=prostate cancer antigen 3; mpMRI=multiparametric magnetic resonance imaging; AUC= area under the curve

*p<0.05 vs. Base model at Mantel-Haenszel test

† adjusted for age, prostate volume and biopsy gleason score

Figure 1. Decision curve analysis of the effect of prediction models on the detection of significant PCa. The net benefit is plotted against various threshold probabilities. Model 1 includes PSA, PSA f/t, DRE, age, positive cores and biopsy gleason. Model 2 includes all the factors in Model 1 plus PHI. Model 3 includes all the factors in Model 1 plus PCA3. Model 4 includes all the factors in Model 1 plus mpMRI.