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Original article

Prognostic accuracy of Prostate Health Index and urinary Prostate Cancer Antigen 3 in predicting pathologic features after radical prostatectomy

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Abstract

Objective: To compare the prognostic accuracy of Prostate Health Index (PHI) and Prostate Cancer Antigen 3 in predicting pathologic features in a cohort of patients who underwent radical prostatectomy (RP) for prostate cancer (PCa).

Methods and materials: We evaluated 156 patients with biopsy-proven, clinically localized PCa who underwent RP between January 2013 and December 2013 at 2 tertiary care institutions. Blood and urinary specimens were collected before initial prostate biopsy for [-2] pro–prostate-specific antigen (PSA), its derivates, and PCA3 measurements. Univariate and multivariate logistic regression analyses were carried out to determine the variables that were potentially predictive of tumor volume >0.5 ml, pathologic Gleason sum ≥ 7, pathologically confirmed significant PCa, extracapsular extension, and seminal vesicles invasions.

Results: On multivariate analyses and after bootstrapping with 1,000 resampled data, the inclusion of PHI significantly increased the accuracy of a baseline multivariate model, which included patient age, total PSA, free PSA, rate of positive cores, clinical stage, prostate volume, body mass index, and biopsy Gleason score (GS), in predicting the study outcomes. Particularly, to predict tumor volume >0.5, the addition of PHI to the baseline model significantly increased predictive accuracy by 7.9% (area under the receiver operating characteristics curve [AUC] $=$ 89.3 vs. 97.2, $P > 0.05$), whereas PCA3 did not lead to a significant increase.

Although both PHI and PCA3 significantly improved predictive accuracy to predict extracapsular extension compared with the baseline model, achieving independent predictor status (all P's < 0.01), only PHI led to a significant improvement in the prediction of seminal vesicles invasions (AUC $=$ 92.2, $P < 0.05$ with a gain of 3.6%).

In the subset of patients with GS ≤ 6, PHI significantly improved predictive accuracy by 7.6% compared with the baseline model (AUC $=$ 89.7 vs. 97.3) to predict pathologically confirmed significant PCa and by 5.9% compared with the baseline model (AUC $=$ 83.1 vs. 89.0) to predict pathologic GS ≥ 7. For these outcomes, PCA3 did not add incremental predictive value.

Conclusions: In a cohort of patients who underwent RP, PHI is significantly better than PCA3 in the ability to predict the presence of both more aggressive and extended PCa.

Keywords: PHI; PCA3; Radical prostatectomy; Prostate cancer; Prognostic accuracy; Active surveillance

1. Introduction

Most recent data from European Study of Screening for Prostate Cancer reported a 21% relative reduction in the risk of death due to prostate cancer (PCa) at 13 years of

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follow-up, with a 27% reduction after adjustment for non-participation [1] and the Goteborg study, one of the European Study of Screening for Prostate Cancer centers, showed a 44% relative reduction at 14 years of follow-up [2]; however, currently, population screening for PCa remains controversial. The most important reason for controversy is the high percentage of overdiagnosis, calculated as ranging from 1.7% to 67% according to the different designs of the studies (epidemiological, clinical, and autopsy studies) and the consequent overtreatment [3]. However, in the current clinical practice, the increasing use of prostate-specific antigen (PSA) for the detection of PCa, in an "opportunistic" screening scenario, has already led to an important increase in incidence of diagnosed low-risk PCa that may not clinically progress during lifetime [4]. The preoperative tools currently used in this clinical setting, such as PSA, digital rectal examination, and biopsy results fail to accurately predict PCa aggressiveness and distinguish between insignificant PCa, eligible for protocol of active surveillance (AS) or focal therapy, and clinically significant PCa, eligible for radical prostatectomy (RP) or radiation therapy.

Consequently, numerous predictive and prognostic tools have been recently introduced to assist the physicians in the clinical decision-making process. However, these available models are far from perfect in their predictive ability and new biomarkers are required to correctly stratify patient risk before treatment.

In this context, several studies have analyzed the capability of prostate cancer antigen 3 (PCA3) [5–11] and [-2] proPSA (p2PSA) and its derivative, %[-2] proPSA (%p2PSA), and Prostate Health Index (PHI) [12–15] in predicting PCa characteristics at final pathology in different and separate study cohorts.

Currently, no evidence is available on the prognostic and pathologic comparison of PCA3 and PHI in a same study cohort at the time of RP.

The aim of this study is to compare the prognostic accuracy of PCA3 and PHI in predicting pathologic features in a cohort of patients who underwent RP for clinically localized PCa.

2. Material and methods

2.1. Study design

The current study is a prospective, observational cohort study, carried out between January 2013 and December 2013, of patients recruited at 2 tertiary care institutions: University of Catanzaro and National Institute of Cancer, Naples.

The study was designed according to the Standards for the Reporting of Diagnostic Accuracy Studies methodology to test the sensitivity, specificity, and accuracy of p2PSA, its derivates, and PCA3 in predicting pathologic features at the time of RP (http://www.stard-statement.org).

2.2. Study population and clinical evaluation

We included 156 patients with biopsy-proven, clinically localized PCa who underwent, within 3 months of diagnosis, laparoscopic or robot-assisted laparoscopic RP. None of the study patients received neoadjuvant hormonal therapy (antiandrogens or luteinizing hormone–releasing hormone analogues or antagonists) or other hormonal preparations (i.e., 5-α reductase inhibitors) that could alter their PSA values. We also excluded patients with bacterial acute prostatitis or previous prostate surgery in the 3 months before biopsy. In addition, subjects with chronic renal disease, marked alterations in blood protein levels (plasma normal range: 6–8 g/100 ml), hemophilia, or those previously multiply transfused were excluded from the study because these conditions could alter the concentration of free PSA (fPSA) and, consequently, of p2PSA, as the p2PSA is a molecular isoform of fPSA [13].

The local hospital ethics committee approved the study protocol and all participants signed written informed consents.

Blood specimens were collected before initial prostate biopsy. Whole blood was allowed to clot before the serum was separated by centrifugation. Serum aliquots were stored at −80°C until the samples were processed, as given by Semjonow et al. [16]. Specimens were analyzed in a blinded fashion for PSA, fPSA, and p2PSA by Access 2 Immunoassay System analyzer (Beckman Coulter, Brea, CA).

First-catch urine samples were also collected before prostate biopsy and following an attentive digital rectal examination (3 strokes per lobe) and stored in a Progensa urine specimen transport kit, as described by Groskopf et al. [17]. Urine samples were processed and tested to quantify messenger RNA (mRNA)-PCA3 and mRNA-PSA concentrations using the Progensa PCA3 assay (Gen-probe, San Diego, CA). The PCA3 score was calculated as mRNA-PCA3/mRNA-PSA × 1,000.

Both p2PSA and, consequently, its derivates and PCA3 score for each patient were determined in the same laboratory (NIC-Naples). RP specimens were evaluated using 3-mm serially sectioned whole-mount specimens according to the Stanford protocol [18] and primary and secondary Gleason scores (GSs) were assigned by an experienced uropathologist at each center, blinded to the biomarkers value, according to the 2005 consensus conference of the International Society of Urological Pathology definitions [19]. All tumor foci were identified, and cumulative tumor volume (TV) was assessed using computerized planimetry accounting for all of them [20].

2.3. Study end points

The primary end points of the study were to determine the accuracy of PHI and PCA3 in predicting the presence of TV > 0.5 ml, extracapsular extension (ECE), seminal vesicles invasions (SVI), pathologic GS sum ≥ 7,

pathologically confirmed significant PCa (PCSPCa) (we considered the Epstein criteria [organ confined disease, TV $\leq$ 0.5 ml, and no Gleason pattern 4/5] to exclude pathologically confirmed insignificant PCa) [21].

2.4. Statistical analysis

All statistical analyses were completed using *SPSS v. 19 software* (SPSS Inc, IBM Corp, Somers, NY). The qualitative data were tested using the Chi-square test or the Fisher exact test as appropriate and the continuous variables were tested using the Mann-Whitney *U* test or the Student *t* test according to their distribution (according to Kolmogorov-Smirnov test) and were presented as median (interquartile range) or mean ($\pm$ standard deviation), as appropriate. Univariate and multivariate logistic regression analyses were carried out to identify variables potentially predictive of TV $>$ 0.5 ml, pathologic GS sum $\geq$7, ECE, SVI, PCSPCa, from a model including age, body mass index, total PSA (tPSA) level, fPSA level, PHI, PCA3 level, prostate volume, biopsy GS, percentage of positive cores, and clinical stage. Pathologic GS sum $\geq$7 and PCSPCa were evaluated in a subcohort of patients with GS $\leq$ 6 on biopsy.

We preferred to exclusively consider PHI and exclude from the univariate and multivariate analysis both the p2PSA and %p2PSA because the variable PHI could be more easy to interpret and understand by the reader, as it is generally evaluated in a clinical setting and because statistically speaking, PHI could capture much of the effects and obscure results when evaluated in same multivariate analysis together with its components (p2PSA).

The predictive accuracy of the model was assessed in terms of the area under the receiver operating characteristics curve (AUC) value, incorporating all independent predictors. For bootstrapping, 1,000 resamples were used for all accuracy estimates and to reduce overfit bias. The Harrell concordance index was used to assess discrimination and was expressed as a value between 0.5 and 1.0, where 1.0 indicates perfect prediction.

The areas under the curve were compared via the Mantel-Haenszel test. For all statistical comparisons, significance was considered as $P < 0.05$.

3. Results

Table 1 summarizes the characteristics of patients included in the analysis. Pathologic T2- and T3-category disease was found in 102 (65.4%) and 54 patients (34.6%), respectively. TV $>$ 0.5 ml was found in 128 patients (82.1%), PCSPCa in 132 patients (84.6%), pathologic Gleason sum $\geq$7 in 104 patients (66.7%), ECE in 34 patients (21.8%), and SVI in 20 patients (12.8%). Table 2 lists the comparison of PSA derivatives according to study end points. In detail, p2PSA, %p2PSA, PHI, and PCA3 were significantly increased in subjects with TV $>$ 0.5 ml, PCSPCa, pathologic GS $\geq$ 7, ECE, and SVI. On univariate logistic regression analysis, PHI and PCA3 were accurate predictors of the presence of TV $>$ 0.5 ml, PCSPCa, and ECE, whereas only PHI predicted pathologic Gleason sum $\geq$7 and SVI (Supplementary Tables S1–S5).

Predictive accuracy was quantified as the AUC for each outcome of interest and different cut-offs at different levels of sensitivity and specificity were reported (Supplementary Tables S6–S10).

On multivariate analyses and after bootstrapping with 1,000 resamples, the inclusion of PHI significantly increased the accuracy of a baseline multivariate model, which included patient age, tPSA, fPSA, percentage of positive cores, clinical stage (cT1c vs. cT2), prostate volume, body mass index, and biopsy GS, in predicting the study outcomes. Particularly, to predict TV $>$ 0.5 ml, the baseline model had an AUC of 89.3, which significantly increased by 7.9% with the addition of PHI (AUC = 97.2, $P > 0.05$), whereas PCA3 did not lead to a significant increase (AUC = 92.1).

Although both PHI and PCA3 significantly improved predictive accuracy to predict ECE compared with the baseline model achieving independent predictor status (all *P*'s < 0.01), only PHI led to a significant improvement in the prediction of SVI (AUC = 92.2, $P < 0.05$ with a gain of 3.6%).

In the subset with GS $\leq$ 6, PHI significantly improved predictive accuracy by 7.6% compared with the baseline model (AUC = 89.7 vs. 97.3) to predict PCSPCa and by 5.9% compared with the baseline model (AUC = 83.1 vs. 89.0) to predict pathologic GS $\geq$ 7. For these outcomes, PCA3 did not add incremental predictive value (Tables 3–7).

4. Discussion

In the current study, we investigated the accuracy of PHI and PCA3 in predicting PCa characteristics at final pathology in a cohort of patients who underwent RP.

Although previous studies have separately determined the accuracy of these markers in predicting the pathologic features of PCa at the time of RP, to the best of our knowledge, this is the first study investigating these relationships in the same cohort of patients.

On univariate analysis, we demonstrated that both PHI and PCA3 were independent predictors of TV $>$ 0.5 cm^3, PCSPCa, and ECE, whereas PHI but not PCA3 achieved independent predictor status of more aggressive PCa (pathologic Gleason sum $\geq$7) and of SVI status. Multivariate analyses showed that the inclusion of PHI in multivariate models significantly increased the accuracy of a baseline model in predicting the 5 pathologic outcomes. The inclusion of PCA3 in multivariate models surprisingly increased the accuracy of only ECE with statistical significance. Therefore, our current RP specimens–based results

Table 1
Patient characteristics and descriptive statistics

Patients characteristics ($n = 156$)	Mean
Age, mean (median) ± SD (IQR)	64.0 (65.0) ± 5.2 (61.0–67.0)
BMI, mean (median) ± SD (IQR)	27.2 (27.0) ± 4.4 (23.8–31.0)
tPSA, mean (median) ± SD (IQR)	6.70 (6.1) ± 2.9 (4.5–8.3)
fPSA, mean (median) ± SD (IQR)	1.00 (0.9) ± 0.5 (0.3–3.3)
%fPSA, mean (median) ± SD (IQR)	0.30 (0.17) ± 1.5 (0.0–13.2)
p2PSA, mean (median) ± SD (IQR)	26.8 (20.4) ± 19.4 (14.5–33.3)
%p2PSA, mean (median) ± SD (IQR)	4.2 (2.3) ± 12.3 (1.8–2.9)
PHI, mean (median) ± SD (IQR)	69.7 (54.2) ± 45.2 (40.0–84.3)
PCA3, mean (median) ± SD (IQR)	79.5 (73.5) ± 50.6 (35.0–110.7)
PV, mean (median) ± SD (IQR)	38.6 (49.0) ± 10.3 (30.0–69.0)
Percentage of positive cores, mean (median) ± SD (IQR)	18.95 (16.0) ± 11.25 (11.0–27.0)
Digital rectal examination, *n* (%)	
Negative	142 (91.0)
Positive	14 (9.0)
Clinical stage, *n* (%)	
T1c	142 (91.0)
T2	14 (9.0)
Biopsy Gleason score, *n* (%)	
≤6	106 (67.9)
7	30 (19.2)
≥8	20 (12.8)
Tumor volume, ml, *n* (%)	
≤0.5	28 (17.9)
>0.5	128 (82.1)
Insignificant PCa, *n* (%)	
No	132 (84.6)
Yes	24 (15.4)
PRIAS criteria compatibility, *n* (%)	
Yes	50 (32)
No	106 (68)
Epstein criteria compatibility, *n* (%)	
Yes	62 (40)
No	94 (60)
Pathologic Gleason score, *n* (%)	
≤6	52 (33.3)
7	74 (47.4)
≥8	30 (19.2)
Pathologic category, *n* (%)	
T2	102 (65.4)
T3a	34 (21.8)
T3b	20 (12.8)
Surgical margin, *n* (%)	
R0	120 (77)
R1	36 (23)
Lymph nodal category, *n* (%)	
N0	126 (81)
N+	30 (19)

BMI = body mass index; IQR = interquartile range; PRIAS = Prostate Cancer Research International: Active Surveillance; PV = prostate volume.

suggest that PHI significantly discriminates better than PCA3 the presence of both TV $> 0.5\,cm^3$ and PCSPCa and also of more aggressive and extended PCa (pathologic Gleason sum ≥7, ECE and SVI), and it could be used to stratify the risk of clinically insignificant or significant PCa at final pathology and be adopted in preoperative counseling to set clinical decision-making processes.

Several studies have aimed to clarify, in separate study cohorts, the potential role of these new biomarkers in predicting pathologic features of PCa at final pathology.

Table 2
Head-to-head comparison of variables according to tumor volume >0.5 cm^3, significant PCa, pathologic Gleason score ≥7, pathologic category ≥T3, and seminal vesicle invasion

	Tumor volume		Significant PCa		Pathologic Gleason score		Pathologic category ≥T3		Seminal vesicle invasion	
	≤0.5	>0.5	Yes	No	<7	≥7	No	Yes	No	Yes
Age (y), median (IQR)*	65.0 (62.0–67.75)	65.0 (61.0–66.0)	65.0 (62.0–67.0)	65.0 (61.0–67.5)	64.0 (21.0–68.0)	65.0 (61.25–67.0)	65.0 (61.0–68.0)	66.0 (63.5–69.0)	65.0 (61.0–67.0)	64.0 (61.0–68.0)
P value	0.97		0.98		0.59		0.70		0.61	
BMI (kg/m^2), median (IQR)*	28.2 (23.0–32.0)	26.1 (23.9–29.0)	26.5 (24.0–29.4)	27.0 (22.5–31.9)	26.2 (24.0–31.0)	27.0 (24.0–31.0)	27.0 (24.0–31.0)	24.9 (24.0–28.2)	27.0 (23.9–31.0)	26.9 (23.2–31.6)
P value	0.59		0.99		0.33		0.52		0.91	
tPSA (ng/ml), median (IQR)*	4.1 (3.2–4.8)	6.9 (5.0–8.6)	6.9 (4.9–8.5)	4.1 (3.2–4.8)	4.6 (3.9–6.3)	7.2 (5.1–8.9)	6.1 (4.5–7.9)	8.2 (5.1–9.4)	5.6 (4.9–8.2)	7.4 (6.1–9.0)
P value	<0.01		<0.01		<0.01		<0.01		0.31	
fPSA (ng/ml), median (IQR)*	0.82 (0.66–0.94)	0.91 (0.69–1.30)	0.91 (0.69–1.30)	0.82 (0.65–0.93)	0.90 (0.69–1.23)	0.85 (0.77–1.16)	0.86 (0.69–1.16)	1.15 (0.77–1.30)	0.87 (0.66–1.28)	0.89 (0.71–1.16)
P value	0.19		0.18		0.90		0.49		0.75	
% Free PSA, median (IQR)*	0.19 (0.16–0.26)	0.12 (0.11–0.20)	0.16 (0.11–0.20)	0.19 (0.14–0.26)	0.19 (0.16–0.26)	0.15 (0.10–0.19)	0.317 (0.12–0.22)	0.14 (0.10–0.18)	0.17 (0.12–0.22)	0.12 (0.10–0.16)
P value	0.66		0.69		<0.01		0.59		<0.05	
p2PSA (pg/ml), median (IQR)*	12.7 (8.8–15.7)	23.2 (16.3–35.5)	23.2 (16.1–34.7)	12.7 (7.8–15.5)	16.2 (12.3–22.8)	23.4 (15.8–35.5)	19.9 (13.9–25.8)	30.6 (19.7–43.8)	19.8 (14.1–30.2)	36.5 (23.2–51.2)
P value	<0.01		<0.01		0.02		0.03		<0.01	
%p2PSA, median (IQR)*	1.7 (1.1–1.9)	2.5 (1.9–3.3)	2.5 (1.8–3.2)	1.7 (1.1–1.9)	1.8 (1.5–2.2)	2.6 (2.0–3.5)	2.1 (1.7–2.8)	2.9 (2.1–3.6)	2.1 (1.8–2.9)	4.3 (2.8–7.4)
P value	<0.01		<0.01		<0.01		<0.01		<0.01	
PHI, median (IQR)*	34.4 (23.7–38.2)	62.3 (47.3–93.9)	61.3 (46.2–93.8)	34.4 (25.4–37.6)	38.2 (32.6–49.9)	65.4 (50.8–98.9)	49.9 (38.2–71.6)	81.7 (56.6–106.9)	52.1 (39.2–77.9)	107.1 (69.1–147.4)
P value	<0.01		<0.01		<0.01		<0.01		<0.01	
PCA3, median (IQR)*	29.0 (22.0–35.0)	81.0 (53.5–123.0)	61.3 (52.0–123.0)	25.0 (22.0–34.0)	33.0 (24.0–78.0)	85.5 (58.5–124.0)	66.0 (33.0–93.0)	98.0 (81.0–123.0)	70.0 (33.0–98.0)	125.0 (80.0–134.0)
P value	<0.01		<0.01		<0.01		<0.01		0.02	
Prostate volume (cc), median (IQR)*	39.45 (33.5–45.0)	33.0 (25.0–43.0)	39.0 (33.0–45.0)	36.6 (28.5–43.0)	39.5 (30.0–50.0)	39.0 (33.0–45.0)	39.0 (30.0–45.0)	39.9 (34.5–40.0)	39.9 (30.0–45.)	35.0 (33.0–45.)
P value	0.111		0.48		0.65		0.90		0.36	
Percentage of positive cores, median (IQR)*	22.0 (11.0–27.0)	8.0 (5.0–11.0)	19.0 (11.0–27.0)	8.0 (5.0–11.)	11.0 (5.0–16.0)	27.0 (11.0–27.0)	16.0 (11.0–27.0)	22.0 (11.0–27.0)	16.0 (11.0–27.0)	27.0 (27.0–38.0)
P value	<0.01		<0.01		<0.01		<0.01		<0.01	

BMI = body mass index; IQR = interquartile range.
*Mann-Whitney test.

Table 3
Multivariate analysis predicting the probability of tumor volume >0.5 ml

Predictors	Baseline model[a] OR (95% CI)	*P* value	Baseline model with PHI[a] OR (95% CI)	*P* value	Baseline model with PCA3[a] OR (95% CI)	*P* value
Age	1.00 (0.91–1.10)	0.77	1.33 (1.01–1.75)	0.04	0.96 (0.84–1.09)	0.72
fPSA	0.21 (0.00–39.35)	0.5	0.34 (0.12–0.67)	0.47	0.38 (0.00–57.52)	0.71
tPSA	4.51 (1.16–17.61)	0.03	7.36 (2.17–25.10)	<0.01	3.03 (1.69–53.48)	<0.01
%PC	1.25 (1.10–1.42)	<0.01	1.40 (1.14–1.71)	<0.01	1.22 (1.05–1.41)	<0.01
PHI	–	–	1.36 (1.11–1.67)	<0.01	–	–
PCA3	–	–	–		1.04 (1.00–1.07)	0.02
AUC of multivariate models, %	89.3	–	97.2[b]		92.1	
Gain in predictive accuracy, %			7.9[b]		2.8	

%PC = percentage of positive cores; AUC = area under the curve; OR = odds ratio.
[a]Adjusted for clinical stage (T1c vs. T2), prostate volume, body mass index (BMI), and biopsy Gleason score (≤6 vs. ≥7).
[b]$P < 0.05$ vs. baseline model on Mantel-Haenszel test.

With regard to PCA3, most studies supported the hypothesis that PCA3 score was a significant predictor of low-volume disease [5–9] and PCSPCa [7–9]. Hessels et al. [10] did not confirm these correlations, but the number of RP specimens included in their study was small and the patient cohort was also different, including few men with favorable features. In addition, van Gils et al. [11] in their study did not prove the prognostic value of PCA3 but the study cohort was based on only 62 RP specimens, emphasizing the need of further research with larger number of patients. As in our study, Whitman et al. found a statistically significant association between PCA3 and ECE; whereas, regarding the association between PCA3 and aggressive disease, defined as GS sum ≥7, several studies demonstrated limited predictive capability, showing that PCA3 did not emerge, at multivariate logistic regression analysis, as an independent risk factor of more aggressive PCa [7–9].

Similarly, some studies have analyzed the predictive role of p2PSA, %p2PSA, and PHI on RP findings, confirming the predictive capability for aggressive cancer already seen during the time of biopsy [12,13,15]. For instance, Guazzoni et al. [14] have found that %p2PSA and PHI were accurate predictors of several PCa characteristics at final pathology, showing as, in a multivariate analysis, that their inclusion in a baseline model (including age, tPSA, fPSA, free/total PSA, clinical stage, and biopsy GS) significantly increased the accuracy in the prediction of high pathologic category and grade.

The capability to discriminate between insignificant or significant PCa at final pathology of these new biomarkers should be considered relevant because approximately one-third of new diagnosed tumors have features of insignificant PCa [22], and these patients may be candidates for AS. AS aims to delay or avoid radical treatment (RP or radiation therapy) and its related morbidity without compromising survival [23]. However, even with the most rigid selection criteria, several patients with apparently low-risk PCa might harbor unfavorable disease owing to inaccuracies in currently used tools, also in biopsy protocols that, in addition, are invasive and might alter the quality of care for these patients. Conversely, the current AS criteria might also be too strict, thereby excluding some patients in whom expectant management would be appropriate and safe. For these reasons, several studies have also analyzed the role of p2PSA, its derivates, and PCA3 in predicting RP findings in this clinical setting. Tosoian et al. [24] found that baseline

Table 4
Multivariate analysis predicting the probability of pathologically confirmed significant PCa[a]

Predictors	Baseline model[b] OR (95% CI)	*P* value	Baseline model with PHI[b] OR (95% CI)	*P* value	Baseline model with PCA3[b] OR (95% CI)	*P* value
Age	0.99 (0.87–1.13)	0.94	1.15 (0.93–1.41)	0.18	0.91 (0.78–1.06)	0.23
fPSA	0.86 (0.11–6.56)	0.88	0.56 (0.05–6.94)	0.65	0.27 (0.07–27.28)	0.39
tPSA	2.71 (1.54–4.74)	<0.01	4.49 (1.84–10.93)	<0.01	2.79 (1.26–6.21)	<0.01
%PC	1.22 (1.08–1.38)	<0.01	1.25 (1.09–1.43)	<0.01	1.16 (0.99–1.37)	0.06
PHI	–	–	1.22 (1.09–1.37)	<0.01	–	–
PCA3	–	–	–	–	1.09 (1.02–1.16)	<0.01
AUC of multivariate models, %	89.7	–	97.3		93.0	
Gain in predictive accuracy, %	–	–	7.6[c]		3.3	

%PC = percentage of positive cores; AUC = area under the curve; OR = odds ratio.
[a]Cohort included 106 patients (67.9%) with biopsy Gleason score ≤6.
[b]Adjusted for clinical stage (T1c vs. T2), prostate volume, and body mass index (BMI).
[c]$P < 0.05$ vs. baseline model on Mantel-Haenszel test.

Table 5
Multivariate analysis predicting the probability of pathologic Gleason score ≥7[a]

Predictors	Baseline model[b] OR (95% CI)	*P* value	Baseline model with PHI[b] OR (95% CI)	*P* value	Baseline model with PCA3[b] OR (95% CI)	*P* value
Age	0.89 (0.80–0.99)	0.04	0.90 (0.80–1.01)	0.08	0.89 (0.80–0.99)	0.04
fPSA	0.80 (0.36–3.92)	0.76	1.24 (0.38–4.02)	0.72	0.74 (0.26–2.08)	0.57
tPSA	1.66 (1.25–2.20)	<0.01	1.56 (1.14–2.15)	<0.01	1.66 (1.25–2.20)	<0.01
%PC	1.13 (1.06–1.20)	<0.01	1.13 (1.06–1.20)	<0.01	1.13 (1.06–1.20)	<0.01
PHI	–	–	1.02 (0.990–1.02)	<0.01	–	–
PCA3	–	–	–	–	1.01 (0.99–1.01)	0.64
AUC of multivariate models, %	83.1	–	89.0	–	84.5	–
Gain in predictive accuracy, %		–	5.9[c]	–	1.4	–

%PC = percentage of positive cores; AUC = area under the curve; OR = odds ratio.
[a]Cohort included 106 patients (67.9%) with biopsy Gleason score ≤6.
[b]Adjusted for clinical stage (T1c vs. T2), prostate volume, and body mass index (BMI).
[c]$P < 0.05$ vs. baseline model on Mantel-Haenszel test.

and longitudinal measures of p2PSA, %p2PSA, ratio of p2PSA to free/total PSA ratio (%fPSA), and PHI were predictive of reclassification at repeat biopsy during a long-term follow-up (median = 4.3 y) in low-risk patients who underwent to AS. These results were comparable to those recently obtained in an Asians cohort by Hirama et al. [25] showing that %p2PSA and PHI were independent predictive factors for pathologic upgrade at 1 year after AS commencement. Finally, another study showed that the ratio of p2PSA to %fPSA in the serum at diagnosis was higher in men developing unfavorable findings on repeat biopsy and recently the same study group also showed that, in multivariate analysis, PHI and p2PSA to %fPSA, combined with biopsy tissue DNA content in benign and cancer areas, improved its accuracy in the prediction of unfavorable conversion biopsy findings at the annual surveillance biopsy examination [26].

With regard to PCA3, Tosoian et al. [27] also studied PCA3 within the Johns Hopkins surveillance program showing that, in patients with low-risk PCa who were carefully selected for AS, the PCA3 score was not significantly associated with short-term biopsy upgrading, failing to predict biological and clinical progression. In contrast, Ploussard et al. [9] and Nakanishi et al. [5] supported the hypothesis that PCA3 score may apply in selecting men who have low-volume/low-grade PCa and are eligible for AS, showing a direct correlation between PCA3 scores with GS and PCa volume at final pathology.

Our study has some strength. It is a prospective observational cohort study in which, for the first time, the prognostic performances of PCA3 and PHI are contextually evaluated on the histological findings on RP. In addition, all blood samples and urine samples were evaluated in the same laboratory to overcome the potential interlaboratory variability. Despite its strengths, our study is not devoid of limitations. This study is limited by its relatively small sample size of a single cohort of white patients and therefore its clinical findings should be further externally confirmed. We did not adopt a standardized and centralized pathologic evaluation and, consequently, pathologic examinations were performed by different pathologists. In this context, we did not have a second reference pathologist to confirm our findings. In addition, we did not evaluate the inclusion of PHI or PCA3 in predictive nomograms, which are often used for PCa prognosis, and we did not compare PHI and PCA3 with PSA density and PSA velocity. However, several studies have shown that PSA density and PSA velocity did not enhance the predictive accuracy

Table 6
Multivariate analysis predicting the probability of ECE

Predictors	Baseline model[a] OR (95% CI)	*P* value	Baseline model with PHI[a] OR (95% CI)	*P* value	Baseline model with PCA3[a] OR (95% CI)	*P* value
Age	1.03 (0.949–1.123)	0.46	1.04 (0.96–1.14)	0.34	1.01 (0.92–1.11)	0.82
fPSA	0.80 (0.302–2.145)	0.66	0.78 (0.28–2.21)	0.64	1.00 (0.32–3.08)	0.99
tPSA	1.21 (1.047–1.407)	<0.01	1.26 (1.10–1.46)	<0.01	1.08 (0.90–1.30)	0.41
%PC	0.98 (0.94–1.02)	0.34	0.97 (0.92–1.02)	0.19	0.96 (0.92–1.01)	0.10
PHI	–	–	1.01 (1.00–1.02)	<0.01	–	–
PCA3	–	–			1.07 (1.01–1.03)	<0.01
AUC of multivariate models, %	70.4	–	78.4		77.4	
Gain in predictive accuracy, %	–	–	8.0[b]		7.0[b]	

%PC = percentage of positive cores; AUC = area under the curve; OR = odds ratio.
[a]Adjusted for clinical stage (T1c vs. T2), prostate volume, body mass index (BMI), and biopsy Gleason score (≤6 vs. ≥7).
[b]$P < 0.05$ vs. baseline model at Mantel-Haenszel test.

Table 7
Multivariate analysis predicting the probability of seminal vesicle invasion

Predictors	Baseline model[a] OR (95% CI)	*P* value	Baseline model with PHI[a] OR (95% CI)	*P* value	Baseline model with PCA3[a] OR (95% CI)	*P* value
Age	0.90 (0.80–1.02)	0.07	0.91 (0.81–1.03)	0.13	0.88 (0.78–1.00)	0.06
fPSA	3.17 (0.78–12.93)	0.19	2.86 (0.63–12.89)	0.17	4.34 (0.86–21.91)	0.07
tPSA	0.96 (0.76–1.21)	0.74	0.96 (0.77–1.20)	0.71	0.89 (0.69–1.15)	0.37
%PC	1.16 (1.09–1.24)	<0.01	1.15 (1.08–1.22)	<0.01	1.16 (1.09–1.24)	<0.01
PHI	–	–	1.01 (1.00–1.02)	0.02	–	–
PCA3	–	–			1.01 (1.00–1.038)	0.15
AUC of multivariate models, %	88.6	–	92.2		89.6	–
Gain in predictive accuracy, %	–	–	3.6[b]		1.0	–

%PC = percentage of positive cores; AUC = area under the curve; OR = odds ratio.
[a]Adjusted for clinical stage (T1c vs. T2), prostate volume, body mass index (BMI), and biopsy Gleason score (≤6 vs. ≥7).
[b]$P < 0.05$ vs. baseline model on Mantel-Haenszel test.

of tPSA of pathologic outcomes in men undergoing RP [28,29].

In summary, we strongly believe that a *one-size-fits-all* approach to the PCa treatment is far from optimal and should be abandoned in favor of an individualized risk-stratified approach to choose the best treatment option for every patient. In this context, the use of a blood test to evaluate PHI may be cheaper and more practical than other more sophisticated tests (i.e., genomic tests), and it does not require vigorous rectal examination (i.e., PCA3). Certainly, the overall cost of these new biomarkers could limit their widespread use. However, PHI is less expensive than other available tests, and this should be considered when making a choice of the best biomarker, together with its clinical validity [30]. Furthermore, being able to estimate the risk of adverse pathologic characteristics could help in selecting preoperative candidates for new imaging methods such as multiparametric magnetic resonance imaging staging. We believe that the association with magnetic resonance imaging could represent a promising combination that would change preoperative therapeutic decision in selective patients with PCa. Unfortunately, no studies are actually available on this potential association with prognostic purposes. Therefore, we are aware that this will require ongoing commitment from researchers and physicians and further studies are still needed to develop the optimal tools in this setting of patients.

5. Conclusion

In this study, we showed that, in a cohort of patients underwent RP, PHI is significantly better than PCA3 in discriminating both the presence of more aggressive (pathologic Gleason sum ≥7,) and extended PCa (ECE and SVI), but further and larger studies are required to externally validate our findings. In our clinical practice, we should begin to consider these new biomarkers as part of the urologic armamentarium during the risk stratification and treatment selection in patients with PCa.

Appendix A. Supporting Information

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.urolonc.2014.12.002.

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