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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,