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Original article

Preoperative prostate health index is an independent predictor of early biochemical recurrence after radical prostatectomy: Results from a prospective single-center study

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Abstract

Background: The aim of this study was to test the hypothesis that preoperative prostate health index (PHI) levels could help to predict early biochemical recurrence (BCR) in a contemporary population of patients with prostate cancer treated with robot-assisted radical prostatectomy (RARP).

Methods: The study population consisted of 313 patients treated with RARP for clinically localized prostate cancer at a single institution between 2010 and 2011. Patients subjected to neoadjuvant or adjuvant therapies and patients with a follow-up of <2 years were excluded. BCR was defined as a postoperative level of total prostate-specific antigen ≥ 0.2 ng/ml and elevating after RARP. The minimum *P*-value method was used to determine the most significant PHI cutoff value to discriminate between patients with and without BCR. The Kaplan-Meier method was used to determine BCR-free survival rates. Finally, Cox regression models were fitted to determine the predictors of BCR, and the predictive accuracy (area under the curve) of each predictor was determined with the Harrell concordance index.

Results: Mean total prostate-specific antigen and mean PHI levels were 5.76 ng/ml (interquartile range: 4.2–8.7) and 46.0 (35–62), respectively. Biopsy Gleason score was 6 in 173 (55.3%), 7 in 121 (38.7%), and ≥ 8 in 19 (6.1%) patients. At final pathology, extracapsular extension was observed in 59 (18.8%), seminal vesicle invasion in 24 (7.7%), and lymph node invasion in 11 (3.5%) patients, whereas 228 (72.8%) patients had organ-confined disease. The 2-year BCR-free survival rate was 92.5% in the overall population and was 96.7% in patients with organ-confined disease. The most significant PHI cutoff value to discriminate between patients with and without BCR was 82. Specifically, the 2-year BCR-free survival rate was 97.7% in patients with a preoperative PHI level <82 relative to 69.7% in patients with a PHI level ≥ 82 (log-rank test: $P < 0.001$). Finally, in multivariable Cox regression analyses, PHI level emerged as an independent predictor of BCR in both the preoperative and the postoperative settings and was more accurate than several established BCR predictors were.

Conclusions: Preoperative PHI levels may discriminate between patients who are at a high risk vs. low risk of BCR after RARP. External validation of our findings within a larger population with a longer follow-up time is needed.

Keywords: Prostate health index; Prostate cancer; Biochemical recurrence; Radical prostatectomy

1. Introduction

Despite definitive treatment, approximately 25% of patients experience biochemical recurrence (BCR) after radical prostatectomy (RP) for prostate cancer (PCa) [1–4]. Most of these patients have recurrence within the first 2 years after surgery, probably because of more aggressive disease [5]. Although disease recurrence may be expected in patients with locally advanced disease, recent studies have demonstrated that a nonnegligible proportion of patients with organ-confined disease at final

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pathology may have recurrence even after definitive treatment [6].

Several authors have investigated the potential predictors of BCR after RP in both the preoperative and the postoperative settings [7,8]. However, the predictive ability of these established predictors is limited, especially in patients with organ-confined disease. Consequently, more accurate biomarkers are urgently needed to better determine the prognosis of these patients, in both the preoperative and the postoperative settings.

Recent studies have demonstrated that a [−2]pro–prostate-specific antigen (PSA) derivative, namely the Beckman Coulter prostate health index (PHI), is related to PCa aggressiveness and could be used to predict tumor characteristics before RP [9,10]. Based on these findings, we investigated whether PHI level could be used as a predictor of early BCR in a prospectively collected cohort of patients subjected to robot-assisted RP (RARP) at a single tertiary care center. In addition, we investigated whether PHI level could predict BCR in patients with organ-confined disease at final pathology. Finally, we aimed to determine the most significant PHI cutoff value capable of discriminating between patients who are at a high risk vs. low risk of BCR.

2. Materials and methods

2.1. Study population

Our study cohort consisted of 313 consecutive patients with biopsy-proven clinically localized PCa who were prospectively recruited between June 2010 and June 2011, who underwent RARP and pelvic lymph node dissection at our tertiary department of urology. The minimum follow-up time for each noncensored patient was 2 years. For the scope of the current article, patients were subsequently categorized into 2 groups: the overall population, consisting of 313 patients with clinically localized PCa based on the preoperative evaluation, and the population of patients having organ-confined disease, consisting of 228 patients with pT2cR0pN0 disease at final pathology. No patient included in the current study received neoadjuvant androgen deprivation therapy or immediate adjuvant therapy after surgery. The hospital ethics committee approved the study, and all patients signed written informed consent before being enrolled.

2.2. Methods

A preoperative blood sample was collected before any manipulations that might cause a transient increase in the levels of biomarkers. Blood samples were processed by UniCel DxI800 Immunoassay System analyzer (Beckman Coulter, Brea, CA) and were managed according the criteria described by Semjonow et al. [11]. Total PSA (tPSA), free PSA (fPSA), free to tPSA ratio (%fPSA), p2PSA, and PHI ([p2PSA/fPSA × $\sqrt{t\,\mathrm{PSA}}$]) levels were determined using the Hybritech calibration in all patients. The specimens were processed and evaluated by an experienced genitourinary pathologist. PCa was graded according to the 2005 consensus conference of the International Society of Urological Pathology definitions [12]. Surgical specimens were processed and evaluated according to the Stanford Protocol, and PCa was staged according to the 2002 TNM staging system [13].

2.3. Follow-up

According to Institutional guidelines, tPSA level was measured 1, 3, 6, and 12 months after surgery, and every 6 months thereafter. BCR was defined as a postoperative level of tPSA $\geq$0.2 ng/ml and elevating after RARP [14,15]. Time to BCR was defined as the months intercurring between surgery and BCR development (first measurement of a tPSA level $\geq$0.2 ng/ml). On the contrary, patients without BCR were censored at the time of last follow-up.

2.4. Statistical analysis

Univariable and multivariable Cox regression models were fitted to test the predictors of BCR. In the preoperative setting, the following variables were available and tested: patient age, prostate volume, biopsy Gleason score, tPSA level, and PHI level (both continuously and categorically coded). We also developed 2 models to investigate BCR predictors in the postoperative setting, focusing on both the overall population and patients with organ-confined disease at final pathology. The following predictors were investigated: patient age, prostate volume, bioptic and pathological Gleason score, pathological T category, surgical margins, pathological N category, tumor volume, tPSA level, and PHI level (both continuously and categorically coded). The minimum *P*-value method was used to determine the most informative PHI cutoff value for BCR. The accuracy of single predictors and of multivariable models was quantified with receiver operating characteristics–derived area under the curve estimates. Predictive accuracy comparisons were performed using the DeLong method [16].

All statistical analysis were performed using SPSS version 16.0 or S-Plus professional. In all analyses, a 2-sided $P < 0.05$ was considered significant.

3. Results

3.1. Descriptive analyses

The characteristics of the study population are summarized in Table 1. Overall, 228 patients had organ-confined disease. Median patient age was 64.0 years (interquartile range [IQR]: 59–69) and median total PSA level was