Value of Prostate Specific Antigen Density and Percent Free Prostate Specific Antigen for Prostate Cancer Prognosis

Jonas Busch,* Kristin Hamborg, Hellmuth-Alexander Meyer, John Buckendahl, Ahmed Magheli, Michael Lein, Klaus Jung, Kurt Miller and Carsten Stephan

From the Department of Urology (JB, KH, HAM, JB, AM, KJ, KM, CS) and Institute of Physiology (HAM), Charité University Medicine, and Berlin Institute for Urologic Research (ML, KJ, CS), Berlin, and Department of Urology, University Teaching Hospital, Offenbach (ML), Germany

Purpose: Limited data exist on the relationship of percent free prostate specific antigen and prostate specific antigen density with prostate cancer prognosis. Therefore, we compared percent free prostate specific antigen and prostate specific antigen density with prostate specific antigen, Gleason sum and stage to predict prostate cancer prognosis in a large cohort using a single prostate specific antigen and free prostate specific antigen assay.

Materials and Methods: Between 1999 and 2007 a total of 1,656 patients with prostate cancer underwent laparoscopic radical prostatectomy at the Charité Berlin. There were 322 patients excluded from analysis for a variety of reasons. The final 1,334 patients had prostate specific antigen, free prostate specific antigen, prostate volume and complete pathological analysis available.

Results: Median followup was 60.3 months (range 0.2 to 135). Median age (63 years, range 43 to 75) did not differ between the 1,092 patients without and the 242 with biochemical recurrence ($p = 0.956$), but prostate volume, prostate specific antigen and percent free prostate specific antigen differed significantly ($p < 0.0001$). While prostate specific antigen and prostate specific antigen density increased significantly in patients with Gleason less than 7, 7 and greater than 7 tumors, percent free prostate specific antigen decreased significantly ($p < 0.0001$). Prostate specific antigen, percent free prostate specific antigen and prostate specific antigen density differed significantly between pT2 and pT3 tumors, and between patients with vs without positive surgical margins. On univariate analysis Gleason sum, pathological stage, positive surgical margin, total prostate specific antigen, percent free prostate specific antigen and prostate specific antigen density were predictors of biochemical recurrence-free survival. Multivariate Cox regression analysis identified Gleason sum, pathological stage, positive surgical margin and prostate specific antigen density as independent predictors of biochemical recurrence-free survival, while percent free prostate specific antigen and total prostate specific antigen failed to be significant.

Conclusions: Few models for prostate cancer prognosis include prostate specific antigen density. There is substantial value in prostate specific antigen density but not in percent free prostate specific antigen for improving prostate cancer prognosis and biochemical recurrence prediction.

Key Words: prostatic neoplasms, prognosis

Abbreviations and Acronyms

BCR = biochemical recurrence
BCR-FS = biochemical recurrence-free survival
fPSA = free prostate specific antigen
%fPSA = percent free prostate specific antigen
KLK2 = kallikrein 2
LRP = laparoscopic radical prostatectomy
NSM = negative surgical margin
PCa = prostate cancer
PSA = prostate specific antigen
PSAD = prostate specific antigen density
PSM = positive surgical margin
RFS = recurrence-free survival
tPSA = total prostate specific antigen
TRUS = transrectal ultrasound

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* Correspondence: Department of Urology, Charité University Medicine Berlin, Charitéplatz 1, D-10117 Berlin, Germany (telephone: ++49-30/450-515041/515250; FAX: ++49-30/450-515904; e-mail: jonas.busch@charite.de).

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Prognostic models for prostate cancer prediction incorporate clinical and pathological parameters such as pretreatment prostate specific antigen (tPSA), clinical stage, biopsy Gleason sum or pathological stage, Gleason sum and surgical margin status.[1–3]

In 2006 Steuber et al published their prediction model consisting of pretreatment total PSA, clinical stage and biopsy Gleason score combined with preoperative free PSA and human glandular kallikrein 2.[4] Adding those 2 parameters to the present model of 461 patients undergoing radical prostatectomy improved the preoperative accuracy of predicting biochemical recurrence in men with a moderately increased pretreatment tPSA of less than 10 ng/ml.[4] Similarly, Wenske et al investigated the additive effect of human glandular kallikrein 2 and fPSA to a common prediction model.[5] They detected a moderately improved accuracy for their model and concluded that further investigations concerning a possible role of fPSA in preoperative risk assessment of BCR should be performed.

In another study from a high volume tertiary referral center Magheli et al found that PSAD was strongly associated with pathological stage and biochemical RFS after radical prostatectomy.[6] In patients with lower grade prostate cancer PSAD was significantly more accurate in predicting extraprostatic extension and BCR compared to tPSA. The role of pretreatment PSAD in the prediction of postoperative Gleason upgrading was recently reported by Magheli et al.[7] In their cohort of 1,061 consecutive patients PSAD was a significant independent predictor of Gleason upgrading even when considering tPSA.

The role of percent free PSA in the detection of postoperative pathological outcome was reported in 1999 by Southwick et al.[8] In their multivariate adjusted analysis %fPSA proved to be the strongest preoperative independent predictor of pathological stage.[8] Higher %fPSA and lower PSAD were both associated with less aggressive PCa. The %fPSA could be used in parallel or even instead of PSAD.[9] Recently %fPSA was also shown to be a strong predictor of later PCa detection, especially in men with low tPSA.[10] Lower %fPSA values further predict higher stage and higher Gleason sums after radical prostatectomy.[8,11]

However, data on fPSA and %fPSA and their value in PCa prognosis are rare.[4,5] In a small cohort with 90 cases of BCR including 28 with a pretreatment tPSA less than 10 ng/ml, the additional use of fPSA and KLK2 improved the accuracy of BCR prediction.[4] An update from the same group now including 146 BCR cases showed only a small benefit from fPSA and KLK2 when added to the model (with an AUC increase from 0.72 to 0.726, $p = 0.2$).[5] Both studies were performed with retrospective tPSA, fPSA and KLK2 measurements. In an earlier study %fPSA was shown not to be an independent predictor of BCR.[12] In this study we investigated the role of tPSA, PSAD and %fPSA for the prediction of BCR in a large PCa cohort on the basis of an extended followup using a single test assay system.

PATIENTS AND METHODS

From May 1999 to January 2007 a total of 1,656 patients with prostate cancer underwent LRP at the Charité Berlin. A total of 322 patients were excluded from the analysis due to loss to followup, neoadjuvant hormonal or other treatment, or missing values. The final 1,334 patients had tPSA and %fPSA (exclusively measured by Immulite® 2000 assays), prostate volume measured by TRUS (Combison 330, Kretz Technik, Zipf, Austria) using the prolate ellipse formula (height $\times$ width $\times$ length $\times$ 0.52) and complete pathological analysis available. Preoperative PSA specimens were drawn from the patients during admission to our hospital within a week before surgery. Followup data were obtained by telephone interview. Data on BCR were available for all patients. BCR was defined as an increasing tPSA of 0.1 ng/ml or greater after a postoperative decrease below the detection level as confirmed by another test. All data were collected under an internal review board approved protocol. All patients provided written informed consent to participate in this study before surgery.

Procession and histological evaluation were performed as previously described. PSAD was calculated as the ratio of tPSA-to-prostate volume measured by TRUS.[13] Patient age and prostate size were considered continuous variables. Gleason sum, pathological stage, tPSA, %fPSA, PSAD and surgical margin status were evaluated as categorical variables with the strata tPSA less than 10 and 10 ng/ml or greater, %fPSA less than 9% and 9% or greater, PSAD 0.22 ng/ml/cm^3 or less and greater than 0.22 ng/ml/cm^3, and Gleason sum less than 7, 7 and greater than 7. Pathological stage was stratified as pT2 or less and greater than pT2, and positive and negative surgical margins. PSAD and %fPSA were stratified according to the median value, whereas tPSA was initially stratified according to the tPSA risk strata proposed by D'Amico et al.[14] Due to a small number of patients with tPSA values greater than 20 ng/ml, this group was added to the intermediate risk group with tPSA values between 10 and 20 ng/ml.

Oncologic outcome represented by BCR was assessed using Kaplan-Meier analysis with the log rank test. Univariate and multivariate Cox regression analyses were performed. Differences between categorical variables were assessed using the chi-square test, whereas differences in continuous variables were calculated with the Mann-Whitney U test. All statistical analyses were 2-tailed and differences were considered significant if $p < 0.05$. The statistical analysis was conducted with IBM® SPSS® version 19.0.