Nomogram to Predict Prostate Cancer Diagnosis on Primary Transrectal Ultrasound-Guided Prostate Biopsy in a Contemporary Series

Christopher J. DiBlasio^{a,b} Ithaar H. Derweesh^a Michael M. Maddox^a Reza Mehrazin^a
Changhong Yu^c John B. Malcolm^a Michael A. Aleman^a Anthony L. Patterson^a
Robert W. Wake^a Michael W. Kattan^c

^aDepartment of Urology, University of Tennessee Health Sciences Center, Memphis, Tenn.; ^bDepartment of Urology, North Shore Medical Group of the Mount Sinai School of Medicine, Huntington, N.Y.; ^cDepartment of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio, USA

Key Words

Nomograms • Prostatic neoplasm • Risk factors • Outcomes assessment • Predictive factors • Prostate biopsy

Abstract

Objective: Transrectal ultrasound-guided biopsy (TRUSB) remains the mainstay for prostate cancer (CaP) diagnosis. Numerous variables have shown associations with development of CaP. We present a nomogram that predicts the probability of detecting CaP on TRUSB. **Methods:** After obtaining institutional review board approval, all patients undergoing primary TRUSB for CaP detection at a single center at our institution between 2/2000 and 9/2007 were reviewed. Patients undergoing repeat biopsies were excluded, and only the first biopsy was included in the analysis. Variables included age at biopsy, race, clinical stage, prostate specific antigen (PSA), number of cores removed, TRUS prostate volume (TRUSPV), body mass index, family history of CaP, and pathology results. S-PLUS 2000 statistical software was utilized with $p < 0.05$ considered significant. Cox proportional hazards regression models with restricted cubic splines were utilized to construct the nomogram. Validation utilized bootstrapping, and the concordance index was calculated based on these predictions. **Results:** A total of 1,542 consecutive

patients underwent primary TRUSB with a median age of 64.2 years (range 34.9–89.2 years), PSA of 5.7 ng/ml (range 0.3–3,900 ng/ml), number of cores removed of 8.0 (range 1–22) and TRUSPV of 36.4 cm³ (range 9.6–212.0 cm³). CaP was diagnosed in 561 (36.4%) patients. A nomogram was constructed incorporating age at biopsy, race, PSA, body mass index, clinical stage, TRUSPV, number of cores removed, and family history of CaP. The concordance index when validated internally was 0.802. **Conclusions:** We have developed and internally validated a model predicting cancer detection in men undergoing TRUSB in a contemporary series. This model may assist clinicians in risk-stratifying potential candidates for TRUSB, potentially avoiding unnecessary or low-probability TRUSB.

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Introduction

With an estimated 241,740 new cases and 28,170 deaths in 2012, prostate cancer (CaP) remains the most common malignancy in United States males [1]. Transrectal ultrasound-guided biopsy (TRUSB) remains the

mainstay for CaP diagnosis. Numerous variables have shown associations with the development of CaP [2–6]. A variety of predictive models have been developed to facilitate optimal CaP detection [7–10]. However, to date, no instrument has attained widespread applicability and acceptance in the clinical setting. Herein, we present a nomogram that predicts the probability of detecting CaP on TRUSB in a contemporary cohort of patients at an equal-access health care facility.

Materials and Methods

After receiving institutional review board approval, all patients undergoing primary TRUSB for CaP detection at a single center at our institution (Veterans Affairs Medical Center, Memphis) between Feb. 2000 and Sept. 2007 were reviewed. Patients undergoing repeat biopsies were excluded and only the first biopsy was included in the analysis. Variables included age at biopsy, race, clinical stage [11], prostate specific antigen (PSA), number of cores removed, number of positive cores, digital rectal exam (DRE) and TRUS prostate volume (TRUSPV), body mass index (BMI), family history of CaP, mortality events, and pathology results.

Using S-PLUS 2000 statistical software for analysis, Cox proportional hazards regression models with restricted cubic splines were utilized to construct a nomogram to predict the likelihood of obtaining a biopsy positive for adenocarcinoma based on the following variables: age at biopsy, pre-biopsy PSA, BMI at biopsy, race, clinical stage, TRUSPV, number of cores removed, and family history of CaP. Using bootstrapping [12, 13], internal validation was performed, and the concordance index (CI) was calculated based on these predictions.

Results

During the study period, a total of 1,977 TRUSB were performed at the study center. After exclusions, 1,542 consecutive patients were identified that underwent primary TRUSB which were included in the analysis. The mean age at biopsy was 64.4 years (median 64.2, range 34.9–89.2 years) and the mean PSA was 20.8 ng/ml (median 5.7, range 0.3–3,900 ng/ml). The mean number of cores removed was 9.7 (median 8.0, range 1.0–22.0) and mean TRUSPV was 42.6 cm³ (median 36.4, range 9.6–212.0 cm³). CaP was diagnosed in 561 (36.4%) patients. Demographic and clinical data are presented in table 1.

Based on Cox proportional hazards regression analysis, a nomogram was constructed based on the aforementioned variables (fig. 1). Using bootstrapping techniques, the model was internally validated, with a CI of 0.802 (fig. 2). In this model, multivariable analysis demonstrat-

Table 1. Demographic and clinicopathologic variables for cohort of patients used to construct nomogram predicting prostate cancer on TRUS biopsy

Parameter	Mean (median; range)
Number of patients	1,542
Age at biopsy (years)	64.4 (64.2; 34.9–89.2)
PSA at biopsy (ng/ml)	20.8 (5.7; 0.03–3,900.0)
Biopsy Gleason grade sum	7.02 (7.0; 5.0–10.0)
Primary	3.5 (3.0; 2.0–5.0)
Secondary	3.6 (4.0; 2.0–5.0)
Clinical stage (%)	
T1c	1,047 (67.9)
T2a	354 (22.9)
T2b/c	120 (7.8)
Unknown	21 (1.4)
Race (N/%)	
Caucasian/other	861 (55.8)
African-American	681 (44.2)
BMI (kg/m ²)	28.1 (27.7; 13.9–58.4)
TRUS prostate volume (cm ³)	42.6 (36.4; 9.6–212.0)
DRE prostate volume (cm ³)	32.8 (30.0; 10.0–100.0)
Family history (%)	
Yes	187 (12.1)
No	1,355 (87.9)
Number of cores removed	
Overall	9.7 (8.0; 1.0–22.0)
Right	4.8 (4.0; 0.0–11.0)
Left	4.8 (4.0; 1.0–11.0)
Number of cores positive	4.0 (3.0; 1.0–15.0)
Pathology results (%)	
Adenocarcinoma	561 (36.4)
Benign	892 (57.9)
Atypical/HGPIN	89 (5.7)
Mortality event (%)	135 (8.8)
Death from CaP	13 (0.8)
Death from unknown cause	64 (4.2)
Death from non-CaP cause	58 (3.8)
Follow-up time (months)	42.6 (42.6; 0.09–90.6)

Table 2. Multivariate analysis of variables incorporated into nomogram for predicting prostate cancer on TRUS biopsy

Variable	p
Age at biopsy	0.0001
Race	0.0008
Clinical Stage	< 0.0001
BMI	0.0021
TRUS prostate volume	< 0.0001
Number of cores removed	< 0.0001
Family history of prostate cancer	0.158
PSA	< 0.0001

Fig. 1. Nomogram predicting probability of prostate cancer on TRUS biopsy.

Fig. 2. Calibration plot for nomogram predicting probability of prostate cancer on biopsy.

ed all variables except family history of CaP to remain significant, after adjusting for the remaining variables (table 2).

Discussion

With the increasing use of PSA testing over recent decades, a stage migration of contemporary CaP's has been recognized, with more cancers being detected at earlier clinical stages [14]. While PSA testing has been useful in this regard, the association between serum PSA levels and cancer-risk do not always correlate directly [15, 16]. Additional clinical variables have been identified as predictive for the development of CaP [2–6]. Subsequently, several prognostic models have been constructed in aims of providing improved CaP-detection [8–10]. Yet, despite these efforts, there remains a lack of a user-friendly, office-based instrument that has attained widespread use and applicability to the CaP-screening population. Schroder et al. [9] recently published an analysis of available models predictive of this particular endpoint, comparing their predictions to those of PSA alone. In their analysis, the authors identified an average increase in the area under the receiver-operating characteristic curve (AUC) of approximately 0.10 (range 0.02–0.26) when compared to PSA alone. Interestingly, the model demonstrating the smallest improvement in AUC was found to be one of the most systematic series, with over 5,500 men undergoing biopsy [17]. The authors contributed varying AUC results to such potential factors as the type of statistical analysis, variables incorporated, population differences, and the potential inter-dependence of clinical variables [9]. For this reason, we sought to develop a nomogram that would incorporate easily attainable variables and one constructed based on a patient population from an equal-access health care facility. Importantly, age and CaP characteristics in our cohort appear to be similar to the general United States CaP population, while race, lifestyle, and comorbid illnesses may be dependent on regional demographics [18]. Based on these premises, we constructed an instrument based on eight commonly-utilized clinical variables that predicted CaP detection with a CI of 0.802 (fig. 1, 2).

While we hope this instrument will be a useful adjunct to clinical decision-making and patient counseling and stratification, it is not without limitations. Firstly, we present a model based on a retrospective review of our findings at a single center and thus, our observations are subject to the inherent biases of this type of analysis.

Further, while multicenter external validation is planned, our instrument has only been validated internally thus far. While external validation remains optimal, internal validation utilizing bootstrapping is an accepted method for assessing the predictive accuracy of a model [12, 13]. Lastly, the use of a TRUS-derived prostate volume limits the ease of which this model can be used. However, since DRE findings have been noted to vary between examiners [19, 20], it is our feeling that TRUSPV provides a more accurate and reproducible assessment of gland size than DRE, and with the advent of smaller TRUS probes, remains a minimally-invasive method for obtaining this information.

Conclusions

We have developed and internally validated models that predict probability of detecting CaP on TRUS-directed prostate in a contemporary series of patients. This model incorporates easily attainable variables for prediction calculations, with robust predictive accuracy. Using this model, clinicians may be able to reduce the occurrence of potentially unnecessary or low-probability biopsies based on nomogram predictions, assisting in stratifying patients most appropriate to proceed with TRUSB. This may be of most great clinical potential when considering TRUSB in patients with multiple comorbidities, those with poor performance status, and those taking anticoagulation medications which would need to be ceased in order to perform TRUSB.

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