ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2016) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Predictive models and risk of biopsy progression in active surveillance patients

Viacheslav Iremashvili, M.D., Ph.D.*, Murugesan Manoharan, M.D., Bruce R. Kava, M.D., Dipen J. Parekh, M.D., Sanoj Punnen, M.D., M.P.H.

Department of Urology, Miller School of Medicine, University of Miami, Miami, FL

Received 11 June 2016; received in revised form 7 August 2016; accepted 23 August 2016

Abstract

Objective: To analyze the performance of different radical prostatectomy–based prognostic tools in predicting the biopsy progression in our active surveillance cohort.

Materials and methods: We analyzed 326 patients with biopsy Gleason grade ≤ 6, ≤ 2 positive biopsy cores, $\leq 20\%$ tumor present in any core, prostate-specific antigen <15 ng/dl, and clinical stages T1–T2a all of whom had at least single surveillance biopsy. Probabilities of pathologically relatively aggressive disease were estimated using Partin and Dinh risk tables and Kattan, Truong, and Kulkarni nomograms for each individual patient. Using these predictions, performance of these tools was quantified regarding discrimination, stratification at different cut-points, calibration, and the clinical net benefit.

Results: Predictions of Partin and Dinh tables were not associated with the biopsy progression. The predictive value of Kattan and Truong nomograms was higher when compared with the other tools, although it was significant only on the first and second surveillance biopsies. Both nomograms were able to identify low- and high-risk subgroups within the cohort. Kattan nomogram demonstrated better correlation with the observed rate of progression over the first 3 biopsies and higher clinical net benefit.

Conclusion: Kattan and Truong nomograms demonstrated the best performance in predicting biopsy progression, although their value was largely limited to the first 2 surveillance biopsies. Both tools were able to stratify patients into subgroups with different risks of progression. These nomograms have important differences, which suggest that a more effective predictive model combining the strong sides of both tools and possibly some other variables could be developed.

Keywords: Prostate cancer; Active surveillance; Nomogram; Prostate biopsy; Prostate-specific antigen

1. Introduction

Overdiagnosis and resulting overtreatment are among the most important current issues in the field of prostate cancer. Although it is clear that many contemporary men diagnosed with prostate cancer have indolent disease and do not benefit from any treatment, our ability to accurately identify such patients is severely limited. Active surveillance (AS), which includes close follow-up of patients with apparently low-risk disease with regular prostate-specific antigen (PSA) checks and repeat biopsies, has emerged as one of the solutions to the problem of overtreatment and is becoming increasingly popular. Currently, there are several thousand patients managed by AS in major academic centers and within international protocols worldwide and likely much more in other settings [1]; however, this management strategy is still grossly underused and most patients with low-risk disease are undergoing immediate treatment [2].

One of the problems limiting wider application of AS by the urological community is the concern that patients with clinically low-risk prostate cancer actually harbor more aggressive disease. Multiple studies consistently show that clinical predictions of the true biology of prostate cancer lack accuracy as evidenced by large proportions of men with low-risk disease who experience pathological upgrading and upstaging [3–5]. Delay in definitive treatment in

* Corresponding author. Tel.: +1-305-243-6591; fax: +1-305-243-6597.
E-mail address: viremashvili@med.miami.edu (V. Iremashvili).

http://dx.doi.org/10.1016/j.urolonc.2016.08.015
1078-1439/

some of these men may result in disease progression beyond a curable stage. In an attempt to address this problem, multiple prognostic models, which estimate the probability of certain pathological features in the prostatectomy specimens such as low-grade, low-volume, or organ confined disease, have been developed [4,6–9]. Although the practical value of these tools lies in the area of AS, they have been scarcely investigated in this setting. Furthermore, to our knowledge different types of instruments have never been directly compared. Thus, in this study we looked at the performance of different radical prostatectomy–based prognostic tools in predicting the biopsy progression in our AS cohort.

2. Materials and methods

All patients managed by AS at our institution were entered in a prospectively maintained institutional review board–approved database. Our inclusion criteria for AS are biopsy Gleason grade ≤ 6, ≤ 2 positive biopsy cores, $\leq 20\%$ tumor present in any core, PSA < 15 ng/dl, and clinical stages T1–T2a. The outside biopsy slides are reviewed by an institutional genitourinary pathologist. Clinical stage is assigned by the attending urologist.

Each patient is followed every 3 to 4 months with a PSA and rectal examination. The first surveillance biopsy is performed within 1 year of the diagnosis. Furthermore surveillance biopsies took place every 1 to 2 years. The same template was used for the diagnostic and surveillance biopsies. None of the patients had magnetic resonance imaging–guided biopsies. Progression on the surveillance biopsy is defined as the presence of high-grade cancer, more than 2 positive cores or greater than 20% involvement of any core.

From October 1994 through December 2013, 366 men with prostate cancer enrolled in our AS program. Of these patients, 40 patients have not yet had their first surveillance biopsy. Exclusion of these patients resulted in a study population of 326 patients.

2.1. Statistical analysis

We tried to test a wide range of different prognostic tools and used 5 instruments (Table 1). Two of them (Kattan and Kulkarni nomograms) previously demonstrated superior performance in predicting their respective outcomes (pathologically nonindolent disease and pathological clinically significant upgrade) when compared with similar instruments in a head-to-head comparisons [10,11]. We also included a recently published nomogram of Truong et al. as well as 2 risk tables developed in large groups of patients undergoing radical prostatectomy. Probabilities of pathologically relatively aggressive disease (defined as nonindolent disease for Kattan nomogram, presence of high-grade Gleason pattern for Kulkarni and Truong nomograms and Dinh risk table, and nonorgan confined prostate cancer for Partin risk table) were estimated for each individual patient. As mentioned earlier, although all these tools were developed to predict pathological outcomes in prostatectomy specimens, their clinical value lies in predicting the risk of unfavorable disease characteristics in AS candidates. Using these predictions the performance of each nomogram was quantified regarding discrimination, stratification at different cut-points, calibration, and the clinical net benefit.

Discrimination was quantified using 2 different techniques. Firstly, we used Cox proportional hazards regression analysis to examine the relationship between the estimated risks and biopsy progression. Number of surveillance biopsies was used as a time variable. Harrell's C-index was used to quantify the predictive accuracy of each tool. Secondly, we used logistic regression to study the association between the estimated risks and progression on individual surveillance biopsies 1 through 4. For this analysis, we used area under the receiver operative characteristic curve to quantify the discriminative performance of the predictions.

All further analyses were done only for the tools that demonstrated the best discriminative properties. To assess the ability of these tools to stratify patients, we calculated the predictive accuracy of different cut-points at the first surveillance biopsy. We selected optimal cut-points for relatively high- and low-risk subgroups using the likelihood ratios for progression on the first surveillance biopsy as suggested by Choi [12]. The cumulative incidence of biopsy progression in these subgroups was estimated using the Kaplan-Meier method. Calibration was assessed by a plot of the predicted risk of aggressive pathology compared with the Kaplan-Meier estimates of progression during the first 3 surveillance biopsies calculated for each decile of predicted unfavorable pathological outcome. We used decision curve analysis (DCA) to compare the best performing tools based on the probability of biopsy progression over the first 3 surveillance biopsies. This method estimates potential clinical benefit resulting from altering clinical management (i.e., proceeding with treatment with curative intent) in patients with different threshold probabilities. Finally, we used Cox proportional hazards regression analysis and Harrell's C-index to quantify the predictive value of different variables included the in the best performing tools.

All *P*-values resulted from the use of 2-sided statistical tests, and the significance level was set at 0.05. All analyses were performed using STATA version 11.0 software (College Station, TX).

3. Results

Characteristics of the patients included in the study are presented in Table 2. Most men in our cohort are whites with mildly elevated PSA, low-PSA density (PSAD), single positive core in the diagnostic biopsy, and clinical stage