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Original article

Creation and internal validation of a biopsy avoidance prediction tool to aid in the choice of diagnostic approach in patients with prostate cancer suspicion

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Abstract

Introduction: To reduce unnecessary prostate biopsies while using novel tests judiciously, we created a tool to predict the probability of clinically significant prostate cancer (CSPC) vs. low-risk prostate cancer or negative biopsy (i.e., when intervention is likely not needed) among men undergoing initial or repeat biopsy.

Methods: Separate models were created for men undergoing initial and repeat biopsy, identified from our institutional biopsy database and the placebo arm of the REDUCE trial, respectively, to predict the presence of CSPC (Gleason ≥ 7 or $>33\%$ of cores involved). Predictors considered included age, race, body mass index, family history of prostate cancer, digital rectal examination, prostate volume, prostate-specific antigen (PSA), free-to-total PSA, presence of high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation on prior biopsy, number of prior biopsies, and number of cores previously taken. Multivariable logistic regression models that minimized the Akaike Information Criterion and maximized out-of-sample area under the receiver operating characteristics curve (AUC) were selected.

Results: Of 7,963 biopsies (initial = 2,042; repeat = 5,921), 1,138 had CSPC (initial = 870 [42.6%]; repeat = 268 [4.5%]). Age, race, body mass index, family history, digital rectal examination, and PSA were included in the initial biopsy model (out-of-sample AUC = 0.74). Age, prostate volume, PSA, free-to-total PSA, prior high-grade prostatic intraepithelial neoplasia, and number of prior biopsies were included in the repeat biopsy model (out-of-sample AUC = 0.81).

Conclusion: These prediction models may help guide clinicians in avoiding unnecessary initial and repeat biopsies in men unlikely to harbor CSPC. This tool may also allow for the more judicious use of novel tests only in patients in need of further risk stratification before deciding whether to biopsy.

Keywords: Early detection of cancer; Prostate biopsy; Prostatic neoplasms

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1. Introduction

Prostate biopsy is considered standard-of-care in the evaluation of abnormal prostate cancer (PC) screening results. Unfortunately, it carries the risks of psychological distress, biopsy-related morbidity (e.g., pain, bleeding, and infection), and rarely even mortality [1,2]. Although the intent is to detect clinically significant prostate cancer (CSPC), nonlethal cancer can also be detected, leading to the unintended consequence of overdiagnosis and overtreatment. Although active surveillance has reduced PC overtreatment, additional invasive tests are still needed, including repeated prostate biopsies, and the anxiety of a cancer diagnosis remains [3]. Moreover, once labeled with a cancer diagnosis, many men still wish to have radical therapy [4,5] and may experience potential treatment-related adverse effects that impair quality of life [6,7].

To minimize the harms of PC screening, it would be helpful if biopsy could be avoided or deferred in patients unlikely to harbor CSPC. Although the 2 most popular biopsy risk calculators (RCs), the European Randomized Study for Prostate Cancer (ERSPC) RC [8] and the Prostate Cancer Prevention Trial (PCPT)-RC v2.0 [9] predict low (Gleason 6) and intermediate-to-high (Gleason $\geq$ 7) grade PC; this does not always equate to the necessity of treatment. Although multiparametric magnetic resonance imaging (mpMRI) [10–13] and novel biomarkers [14,15] may aid in decision-making, it may not be cost-effective to use them in every patient.

Thus, our objective was to use 2 large cohorts being considered for initial and repeat biopsy to create a biopsy avoidance tool that can predict the probability of CSPC vs. low-risk PC or negative biopsy (i.e., when intervention is likely not needed), with the intent of sparing this invasive diagnostic technique in select men where intervention is not usually pursued, while permitting the selective use of novel tests when further risk stratification is needed before consideration of biopsy.

2. Methods

2.1. Patients and data collection

Patients undergoing *initial biopsy* using transrectal ultrasound (TRUS) guidance at our institution between August 1, 2008 and June 30, 2013 were identified using the Genitourinary (GU) BioBank biopsy database at the Princess Margaret Cancer Centre. Biopsies were taken using 10 to 12 cores using a standardized template, with additional cores taken from any suspicious lesions. Those with missing prebiopsy serum prostate-specific antigen (PSA) values (n = 50) or unavailable pathology results (n = 2) were excluded.

Patients undergoing a *repeat biopsy* (i.e., at least 1 prior negative biopsy) were identified from the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, which mandated a negative biopsy before trial inclusion [16]. Both protocol-mandated and for-cause biopsies were included to take into account a broad scope of risk factor combinations. Each biopsy for each patient was analyzed separately.

The data collection methods for our institutional database [17–19] and for the REDUCE trial [16] have been previously described. Institutional research ethics board approval was obtained.

2.2. Outcomes and predictors

The primary outcome was the presence of CSPC, or in other words non–low-risk PC. The University of California – San Francisco (UCSF) definition for low-risk PC was used (Gleason $\leq$ 6, $\leq$33% of cores positive) [20]. The secondary outcome was defined as the presence of any PC on biopsy.

Patient age, race (white, African descent, or other), body mass index (BMI), family history of PC, digital rectal examination (DRE) findings (normal vs. abnormal), and serum PSA were considered for model inclusion. For repeat biopsies, we additionally considered TRUS-measured prostate volume (PV), free-to-total PSA, history of prior high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP), number of prior biopsies, and number of cores on prior biopsy for model inclusion. Furthermore, DRE findings were categorized as normal, abnormal and unchanged, and newly abnormal. TRUS-measured PV was not considered for inclusion in the main model for initial biopsy as this information is not conventionally available until after initial TRUS-guided biopsy. However, a supplementary analysis was performed in the initial biopsy setting to determine whether adding PV strengthened the final models, with the intent that it could be included as an optional predictor.

2.3. Statistical analysis

Cohort characteristics were summarized using descriptive statistics. Associations between predictors and outcomes were evaluated using univariate logistic regression. PSA, free-to-total PSA, number of prior biopsies, and PV were log-transformed to improve model fit.

Multivariable logistic regression models were created considering all possible combinations of parameters. The out-of-sample area under the receiver operating characteristics curve (AUC) for each model was determined using 4-fold cross-validation. Each cohort was randomly divided into 4 approximately equal subsets. Every model was fit on each three-quarter subset and then tested on the remaining subset. The mean of the 4 AUCs calculated in this manner was defined as the out-of-sample AUC [9]. We sought to identify models that minimized the number of predictors,