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Prostate Cancer

Combined Value of Validated Clinical and Genomic Risk Stratification Tools for Predicting Prostate Cancer Mortality in a High-risk Prostatectomy Cohort

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Abstract

Background: Risk prediction models that incorporate biomarkers and clinicopathologic variables may be used to improve decision making after radical prostatectomy (RP). We compared two previously validated post-RP classifiers—the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) and the Decipher genomic classifier (GC)—to predict prostate cancer–specific mortality (CSM) in a contemporary cohort of RP patients.
Objective: To evaluate the combined prognostic ability of CAPRA-S and GC to predict CSM.
Design, setting, and participants: A cohort of 1010 patients at high risk of recurrence after RP were treated at the Mayo Clinic between 2000 and 2006. *High risk* was defined by any of the following: preoperative prostate-specific antigen >20 ng/ml, pathologic Gleason score ≥8, or stage pT3b. A case-cohort random sample identified 225 patients (with *cases* defined as patients who experienced CSM), among whom CAPRA-S and GC could be determined for 185 patients.
Outcome measurements and statistical analysis: The scores were evaluated individually and in combination using concordance index (c-index), decision curve analysis, reclassification, cumulative incidence, and Cox regression for the prediction of CSM.
Results and limitations: Among 185 men, 28 experienced CSM. The c-indices for CAPRA-S and GC were 0.75 (95% confidence interval [CI], 0.55–0.84) and 0.78 (95% CI, 0.68–0.87), respectively. GC showed higher net benefit on decision curve analysis, but a score combining CAPRA-S and GC did not improve the area under the receiver-operating characteristic curve after optimism-adjusted bootstrapping. In 82 patients stratified to high risk based on CAPRA-S score ≥6, GC scores were likewise high risk for 33 patients, among whom 17 had CSM events. GC reclassified the remaining 49 men as low to intermediate risk; among these men, three CSM events were observed. In multivariable analysis, GC and CAPRA-S as continuous variables were independently prognostic of CSM, with hazard ratios (HRs) of 1.81 ($p < 0.001$ per 0.1-unit change in score) and 1.36 ($p = 0.01$ per 1-unit change in score). When categorized into risk groups, the multivariable HR for high CAPRA-S scores (≥6) was 2.36 ($p = 0.04$) and was 11.26 ($p < 0.001$) for high GC scores (≥0.6). For patients with both high GC and high CAPRA-S scores, the cumulative incidence of CSM was 45% at 10 yr. The study is limited by its retrospective design.

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Conclusions: Both GC and CAPRA-S were significant independent predictors of CSM. GC was shown to reclassify many men stratified to high risk based on CAPRA-S ≥6 alone. Patients with both high GC and high CAPRA-S risk scores were at markedly elevated post-RP risk for lethal prostate cancer. If validated prospectively, these findings suggest that integration of a genomic-clinical classifier may enable better identification of those post-RP patients who should be considered for more aggressive secondary therapies and clinical trials.

Patient summary: The Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) and the Decipher genomic classifier (GC) were significant independent predictors of prostate cancer–specific mortality. These findings suggest that integration of a genomic-clinical classifier may enable better identification of those post–radical prostatectomy patients who should be considered for more aggressive secondary therapies and clinical trials.

1. Introduction

Accurate risk stratification of prostate cancer (PCa), both at time of diagnosis and at other decision points, is essential to identify those patients at high risk of PCa-specific mortality (CSM). These patients are most likely to benefit from aggressive multimodal therapy, and it is important to distinguish them from the larger majority of patients who are cured by surgery or are otherwise at low risk of CSM, who may be spared the potential impact of additive treatments. The Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score was developed in a multi-institutional, community-based cohort to predict biochemical recurrence (BCR) and CSM following radical prostatectomy (RP) by incorporating preoperative prostate-specific antigen (PSA) levels and pathologic information into a straightforward, easy-to-use calculation of postoperative patient risk [1]. CAPRA-S has also been validated in another multi-institutional, sociodemographically and clinically diverse cohort, which confirmed its ability to predict both recurrence and CSM [2].

Over the last decade, many studies have tried to address the unmet clinical need for predicting aggressive PCa using genomic information [3–7]. The Decipher PCa genomic classifier (GC) risk prediction model was developed by investigators at the Mayo Clinic and GenomeDx Biosciences to predict, with high specificity, early metastasis after RP [4]. Using oligonucleotide-microarray expression profiling of approximately 1.4 million markers in 545 tumors, machine learning algorithms were used to discover and validate a 22-marker gene expression signature of metastasis. The GC model measures the activity of genes implicated in proliferation, cell migration and adhesion, tumor motility, androgen-signaling, and immune system evasion [8]. In blinded validation studies in prospectively accrued cohorts [9], the GC model demonstrated improved performance over any individual clinicopathologic variable or clinical prediction model for clinical metastasis (confirmed by radiographic bone and computed tomography [CT] imaging) in post-RP [10] and post-BCR [11] patient cohorts.

In this study, we further examined the relationship between the CAPRA-S and GC scores for predicting CSM from the time of RP. We aimed to determine whether integrated genomic and clinical risk prediction models may further improve risk prediction compared with either model alone.

2. Materials and methods

2.1. Patient population

Subjects were identified from a population of 1010 men prospectively enrolled in the Mayo Clinic Department of Urology RP registry for PCa from 2000 to 2006. This population was clinically high risk, as defined by preoperative PSA level >20 ng/ml, pathologic Gleason score ≥8, or stage pT3b. Patients who received neoadjuvant therapy or who were diagnosed with metastatic disease or failed to achieve PSA nadir after surgery were excluded. Clinical staging for patients with D'Amico high-risk disease or preoperative PSA ≥10 ng/ml underwent cross-sectional imaging with either CT or magnetic resonance imaging and bone scan to rule out the presence of metastatic disease before surgery. Data were collected from patients selected using a case-cohort approach, as this design allows inference measures (eg, survival estimates, hazards) about the whole cohort without requiring assessment of all 1010 patients [12,13]. The case-cohort design is most useful in analyzing time to failure in a large cohort in which the failure event is rare. The case-cohort design included all CSM events and a random sample of the full cohort. Of the 1010 men, 28 (3.0%) were documented to have died from PCa (at median follow-up of 6.9 yr). A 20% random sample of the entire cohort was selected for the analysis, including 11 patients with CSM (cases). The remaining 17 cases, who were not selected by random sampling, were also included for analyses (Supplemental Fig. 1).

2.2. Tissue and RNA processing

Following histopathologic review, total RNA was extracted and amplified from four to six 4-μm formalin-fixed, paraffin-embedded primary prostatic adenocarcinoma tissue sections from the nodule with the highest Gleason score. Macrodissection was used to enrich for tumor cells. RNA was extracted and hybridized to Human Exon 1.0 ST GeneChips (Affymetrix, Santa Clara, CA, USA), which profile coding and noncoding regions of the transcriptome, as described previously [10]. Following exclusion for tissue unavailability and microarray quality control ($n = 38$), 187 of the 225 patients sampled from the cohort remained with GC scores, of whom 185 had complete clinicopathologic data for estimating CAPRA-S scores.

2.3. Classifier assessment

We compared and integrated two previously validated post-RP classifiers: CAPRA-S and GC. CAPRA-S was developed using the Cancer of the Prostate Strategic Urologic Research Endeavor registry and was validated in the Shared Equal Access Regional Cancer Hospital database. CAPRA-S scores may be grouped into three validated groups: 0–2, 3–5, and ≥6 [14,15]. GC is a 0–1 score developed using clinical metastasis