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Original article

Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance

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Abstract

Background: A combined clinical cell-cycle risk (CCR) score that incorporates prognostic molecular and clinical information has been recently developed and validated to improve prostate cancer mortality (PCM) risk stratification over clinical features alone. As clinical features are currently used to select men for active surveillance (AS), we developed and validated a CCR score threshold to improve the identification of men with low-risk disease who are appropriate for AS.

Methods: The score threshold was selected based on the 90th percentile of CCR scores among men who might typically be considered for AS based on NCCN low/favorable-intermediate risk criteria (CCR = 0.8). The threshold was validated using 10-year PCM in an unselected, conservatively managed cohort and in the subset of the same cohort after excluding men with high-risk features. The clinical effect was evaluated in a contemporary clinical cohort.

Results: In the unselected validation cohort, men with CCR scores below the threshold had a predicted mean 10-year PCM of 2.7%, and the threshold significantly dichotomized low- and high-risk disease ($P = 1.2 \times 10^{-5}$). After excluding high-risk men from the validation cohort, men with CCR scores below the threshold had a predicted mean 10-year PCM of 2.3%, and the threshold significantly dichotomized low- and high-risk disease ($P = 0.020$). There were no prostate cancer-specific deaths in men with CCR scores below the threshold in either analysis. The proportion of men in the clinical testing cohort identified as candidates for AS was substantially higher using the threshold (68.8%) compared to clinicopathologic features alone (42.6%), while mean 10-year predicted PCM risks remained essentially identical (1.9% vs. 2.0%, respectively).

Conclusions: The CCR score threshold appropriately dichotomized patients into low- and high-risk groups for 10-year PCM, and may enable more appropriate selection of patients for AS.

1. Introduction

Wide adoption of prostate specific antigen (PSA) screening has resulted in earlier prostate cancer diagnosis and is a likely factor in the reduction of disease-specific mortality [1,2]. However, this intensive population screening has also increased the identification of patients with indolent disease [3–5]. As a result, many men with screen-detected cancer are over-treated and needlessly suffer treatment-related side effects without a meaningful change in prognosis. Recent studies have shown that deferred treatment options, such as active surveillance (AS), are a safe way for men with newly

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diagnosed low-risk disease to minimize these adverse effects [6].

Traditionally, patients have been selected for AS based on prognostic clinicopathologic variables that are evaluable at disease diagnosis, including Gleason score, PSA, clinical stage, PSA density, and percent of needle cores that contain tumor. However, better stratification of patients with low-grade localized disease is needed. In addition, AS selection criteria from the American Urological Association (AUA) [7] and National Comprehensive Cancer Network (NCCN) [8] differ and there are numerous additional variations in the literature [9–11]. Collectively, these uncertainties can lead to misclassification of patient risk and increased anxiety in both patients and physicians when selecting AS.

A combined clinical cell-cycle risk (CCR) score has been recently developed to improve prostate cancer risk stratification. This score incorporates a prognostic molecular risk score based on the expression of 31 cell-cycle progression (CCP) genes [12,13] with clinicopathologic risk from the Cancer of the Prostate Risk Assessment (CAPRA) model [14]. This combined molecular and clinical model has been previously validated in a cohort of conservatively managed men and provides a superior discrimination of 10-year prostate cancer-specific mortality (PCM) risk relative to molecular or clinicopathologic parameters alone [15].

As clinicopathologic information is currently the standard for identifying men for AS, we hypothesized that the CCR score would improve the selection of men with low-risk prostate cancer who are appropriate for AS. To this end, we developed and validated a predefined CCR score threshold to identify high- and low-risk disease in order to select suitable candidates for AS. The CCR score threshold was developed in men who might typically be considered for AS based on NCCN guidelines and validated in a cohort of conservatively managed men with long-term clinical outcomes. In addition, we evaluated the ability of the CCR threshold score to alter the selection of patients for AS in a contemporary clinical cohort of men with localized disease.

2. Materials and methods

2.1. Patients

2.1.1. Training cohort

The CCR score threshold was developed in a training cohort of men who underwent clinical testing (Myriad Genetic Laboratories, Salt Lake City, UT) between August 2012 and September 2013 ($N = 1{,}718$). Samples were required to be from a post-2005 diagnostic biopsy and of good quality, as defined by having a mean C_t for housekeeper genes <22 (95th percentile of housekeeper C_t). All patients provided consent for clinical testing and all clinical information was obtained from the test request form (TRF).

Clinicopathologic data from the TRF were used to select a subset of men who might be considered for AS based on modified NCCN guidelines (Fig. 1). Specifically, we selected a subset of men with low/favorable intermediate-risk disease based on a conservative interpretation of NCCN guidelines: Gleason score $\leq 3+4$; PSA <10 ng/ml; $<25\%$ positive cores; and T-stage $\leq$T2a ($N = 505$) [8]. This subset was used to select a CCR score threshold in men who would be candidates for AS based NCCN guidelines.

2.1.2. Validation cohort

The ability of the CCR score threshold to separate patients with high- and low-risk disease was validated in a cohort of conservatively managed men with needle

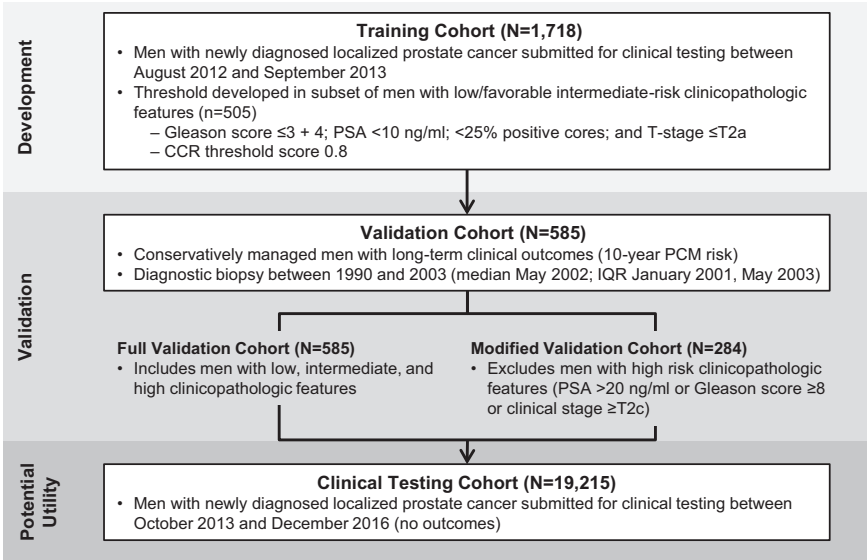

Fig. 1. Study flow and summary of patient cohorts.