Presented at AUA - May 20, 2014

VALIDATION OF A 46-GENE CELL CYCLE PROGRESSION (CCP) RNA SIGNATURE FOR PREDICTING PROSTATE CANCER DEATH IN A CONSERVATIVELY MANAGED WATCHFUL WAITING NEEDLE BIOPSY COHORT

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INTRODUCTION

- Since the natural history of newly diagnosed prostate cancer is variable and difficult to predict, validated prognostic biomarkers could have a major impact on patient care.
- Previously, a 46 gene cell cycle progression score (CCP score, previously described)1 has proven to be a robust predictor of prostate cancer outcomes in various clinical settings, including in a conservatively managed cohort diagnosed by needle biopsy.1-5

Here, we present a validation study of both the CCP score and a pre-specified linear combination of the score with standard clinical variables (cell-cycle-cell-cycle-risk (CCR) score) for predicting disease specific mortality (DSM) in a cohort of conservatively managed patients diagnosed by needle biopsy.

METHODS

- CCP score was generated from mRNA extracted from FFPE needle biopsies from 761 UK men diagnosed with clinically localized prostate cancer between 1990 and 2004 (Figure 1). The median year of diagnosis was 2002.
- Watchful waiting was the primary therapy.
- CCP score was calculated as previously described.1
- Clinical variables were summarized by calculating a CAPRA score (a validated prediction score at disease diagnosis)2.
- Two other previously published risk scores, the Kattan nomogram and the Cuzick score7 were also calculated for each patient.
- The primary endpoint was DSM (17%), and the median clinical follow-up was 9.52 years.
- The molecular data were generated blinded to disease status, and all analyses were pre-specified.

RESULTS

- In univariate analysis, the CCP score hazard ratio (HR) for DSM was 2.08 (95% CI 1.76, 2.46; P < 0.001) for a unit change in the score (Figure 2).
- In a multivariate analysis (n = 585) including CAPRA, the CCP score HR was only marginally decreased (1.76, 95% CI 1.44, 2.14), and remained highly significant (P = 4 x 10^-10). The score performed similarly across different clinical risk groups (Figure 3).
- In a sub-analysis of conservatively managed cohort diagnosed by needle biopsy.2
- The Kattan nomogram and the Cuzick score were highly correlated with CAPRA (Kattan nomogram, p < 0.8, Cuzick score, p < 0.85) and the hazard ratio for adding the CCP score was similar regardless of which clinical score was used (CAPRA, HR = 1.76; Kattan, HR = 1.70; Cuzick, HR = 1.71).
- The CCR score was also highly predictive of DSM (P = 3.9 x 10^-5), and accounted for virtually all prognostic information (Figure 4).
- The 10-year risk of prostate cancer death as a function of CCR is shown in Figure 5, and is virtually identical to the 10-year risk curve derived from our previously published conservatively managed biopsy cohort.2

CONCLUSIONS

- For patients managed by deferred treatment regimens (i.e. watchful waiting or active surveillance), the CCP score provides significant pre-treatment prognostic information that cannot be provided by clinical variables.
- As such, the CCP score is a valuable addition for the informed management of newly diagnosed prostate cancer patients.

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