MP 79-17

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, based on measuring the expression levels of CCP genes) 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 (clinical-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).
  - Two other previously published risk scores, the Kattan score[6] and the Cuzick score[7] 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 outcome, and all analyses were pre-specified.

Figure 1. Cohort Assembly

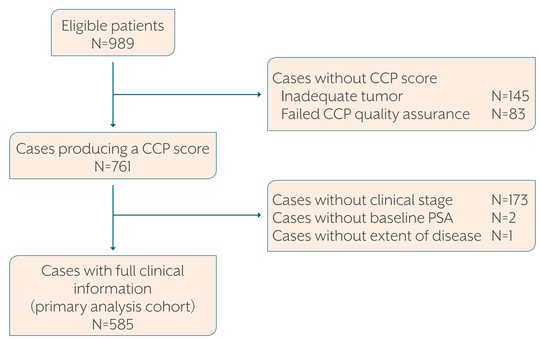
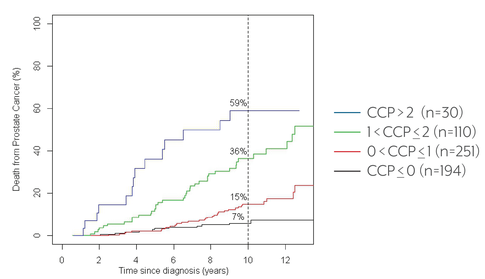


Figure 2. Kaplan Meier estimates of prostate cancer death according to CCP score (n=585)

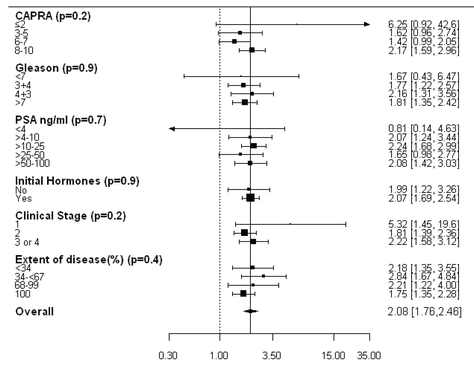


Estimated 10 year risks and 95% confidence interval are also shown.

RESULTS

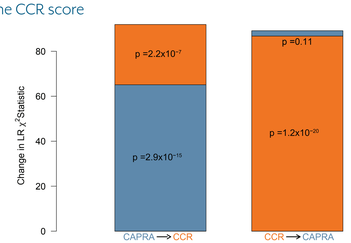
- In univariate analysis, the CCP score hazard ratio (HR) for DSM was 2.08 (95% CI 1.76, 2.46, $P = 6.0 \times 10^{-14}$) for a unit change in the score (Figure 2).
- In a multivariate analysis (n = 585) including CAPRA, the CCP score HR was only marginally decreased (1.76, 95% CI 1.44, 2.14), and remained highly significant ($P = 4.2 \times 10^{-7}$). The score performed similarly across clinical risk groups (Figure 3).
- The Kattan nomogram and the Cuzick score were highly correlated with CAPRA (Kattan nomogram, $\rho = 0.8$, Cuzick score, $\rho = 0.85$) 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).

Figure 3. Hazard ratio for prostate cancer death for a one unit change in CCP score for different clinical subgroups and CAPRA risk groups



The area of the box is proportional to the amount of information available, and the horizontal bars represent 95% confidence intervals. *P*-values after each variable indicate significance of a test for heterogeneity.

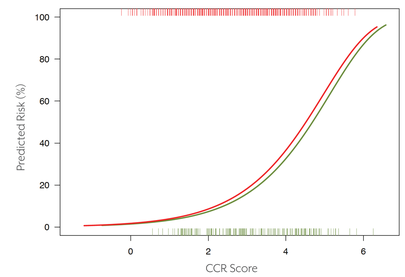
Figure 4. Likelihood ratio bar plots showing the relative contribution of information of CAPRA and the CCR score



Likelihood ratio bar plot shows the relative contribution of information by CAPRA and the CCR scores. Blue area on left bar is what CAPRA explains by itself, and the orange area is the additional information contributed by CCR. On the right bar, the orange area is what CCR explains by itself, and the blue area is additional information contributed by CAPRA. The p-value for the variable considered first is equivalent to the p-value for the univariate model; the p-values in the upper area of the graph are for additional information.

- The CCR score was also highly predictive of DSM ($P = 3.9 \times 10^{-21}$), 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]

Figure 5. 10-year predicted risk of prostate cancer death according to combined clinical-cell-cycle-risk (CCR) score



Red line based on this cohort; green line on previous needle biopsy cohort.
Ticks represent observed CCR scores.

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.

REFERENCES

1. Cuzick J et al. *Lancet Oncol*. 2011;12(3):245-255.
2. Cuzick J et al. *Br J Cancer*. 2012;106:1095-1099.
3. Cooperberg MR et al. *J Clin Oncol*. 2013;31(11):1428-1434
4. Freedland SJ et al. *Int J Radiat Oncol Biol Phys*. 2013;86(5):848-853.
5. Bishoff JT et al. *J Urol*. 2014 Feb 6. pii: S0022-5347(14)00248-1. doi: 10.1016/j.juro.2014.02.003. [Epub ahead of print].
6. Kattan M et al. *Cancer*. 2008;112(1):69-74.
7. Cuzick J et al. *Br J Cancer*. 2006;95:1186-1194.

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