THE CCP SCORE PROVIDES SIGNIFICANT PROGNOSTIC INFORMATION IN GLEASON SCORE ≤ 6 PATIENTS

Abstract MP02

Jay T. Bishoff[1], Stephen J. Freedland[2], Thorsten Schlomm[3], Julia E. Reid[4], Michael K. Brawer[5], Steven Stone[4], Jack Cuzick[6]

1. Intermountain Urological Institute, Murray, UT 2. Durham VA Medical Center, Durham, NC and Cedars-Sinai Medical Center, Los Angeles, CA 3. University Medical Center Hamburg-Eppendorf, Hamburg, Germany
4. Myriad Genetics, Inc., Salt Lake City 5. Myriad Genetic Laboratories, Inc., Salt Lake City 6. Wolfson Institute of Preventive Medicine, London, United Kingdom

INTRODUCTION

- The Cell Cycle Progression (CCP) score was developed and validated to provide prognostic information to prostate cancer patients in all risk groups [1-7].
- These previous studies of CCP focused on distant oncologic outcomes (e.g. BCR, metastases, and mortality). Each individual study lacked power to demonstrate prognostic utility of the score in low-risk patients, owing to low event rate.
- However, in no study (N=9) have we seen a significant interaction between CCP and clinico-pathologic variables, suggesting that the effect size is independent of clinical risk.
- Here we present a meta-analysis of 5 previous studies that evaluated the CCP score in men who had Gleason ≤ 6 disease diagnosed by needle biopsy and were either managed conservatively initially or treated by radical prostatectomy.

METHODS

Cohort

- This study assessed men with Gleason score ≤ 3+3 in a meta-analysis combining two conservatively managed cohorts, and three cohorts after radical prostatectomy (Table 1).

Gene Expression Testing

- Formalin-fixed paraffin-embedded biopsy samples were analyzed for the expression levels of 31 CCP genes and 15 house-keeping genes by quantitative RT-PCR.
- The CCP Score is an un-weighted average of the cell cycle genes normalized by the average of housekeeping genes [5].
- The CCR Score is a pre-specified prognostic model that combines the CCP score with the CAPRA score [2,5].
  - (0.57 × CCP score) + (0.39 × CAPRA score)

Statistical Methods

- The score was evaluated for association with adverse outcome. Outcome was either prostate cancer death (in conservatively managed cohorts) or biochemical recurrence (in post-RP cohorts).
- Association with outcomes was evaluated by Cox proportional hazards survival analysis and likelihood ratio tests. Survival times were censored at 10 years.
- PSA was divided into levels and integer-valued: 1=[0-6], 2=(6-10], 3=(10-20], 4=(20-30], 5=(30-100].
- Analyses were stratified by cohort (the two conservatively managed cohorts were pooled as there was minimal difference in prognosis). There was no evidence that CCP behaved differently for either outcome or cohort.
- Hazard ratios (HR) are given for a one-unit increase in score, which is the interquartile range (IQR) for CCP, CAPRA, and CCR. (In the CCP score, 1 unit is equivalent to a doubling of gene expression).

Table 1. List of cohorts for Gleason ≤ 6 with CCP and CAPRA scores

Cohort	Adverse Event	Number of Patients	Number of Adverse Events
Trans-Atlantic Prostate Group (TAPG-1) [4]	Death from prostate cancer	53	4 (8%)
Trans-Atlantic Prostate Group (TAPG-2) [5]	Death from prostate cancer	151	4 (3%)
Martini-Clinic, Prostate Cancer Center, University Medical Center, Hamburg-Eppendorf, Hamburg, Germany (MC) [1]	Biochemical recurrence	83	7 (8%)
Durham VA Medical Center, Department of Surgery (Urology), Duke University School of Medicine, Durham, NC (DVA) [1]	Biochemical recurrence	76	36 (47%)
Intermountain Healthcare, Salt Lake City, UT (IHC) [1]	Biochemical recurrence	77	13 (17%)
		440	64 (15%)

RESULTS

- The cell cycle progression signature was a significant predictor of outcome in the meta-analysis.
- In univariate analysis, both CCP and CCR scores were significant predictors of outcome (Table 2).
  - CCP: HR = 1.50, p= 0.0099CCR: HR =1.83, p = 0.0014
- CCP remained significant after adjusting for CAPRA (HR = 1.46, p = 0.019) (Table 2).
- CCP also remained significant in a de novo multivariable model adjusting for the components of CAPRA, including PSA, clinical stage, % positive cores and age of diagnosis (HR= 1.47, p = 0.017) (Table 3).

Table 2. Univariate and Bivariate Models

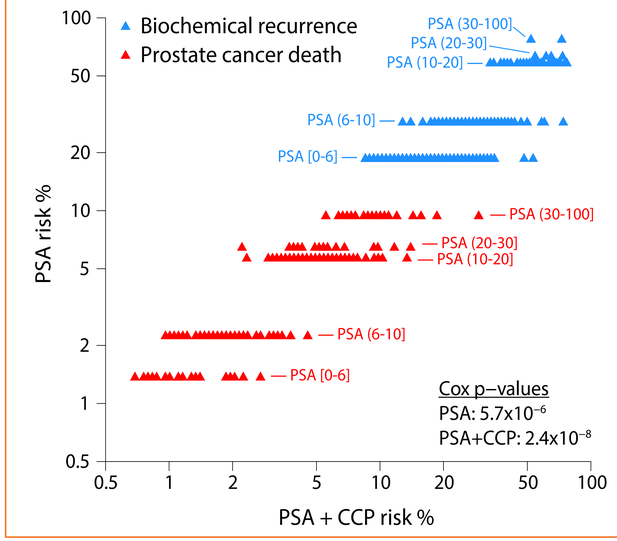
Variable	HR	95% CI	p-value
Univariate			
CCP	1.50	1.11, 2.03	0.0099
CAPRA	1.27	1.03, 1.56	0.030
CCR	1.83	1.27, 2.63	0.0014
Bivariate			
CCP	1.46	1.08, 1.98	0.019
CAPRA	1.23	1.00, 1.53	0.058

Table 3. Univariate and Multivariable Models with CAPRA Components

Covariate	IQR	HR	95% CI	p-value
Univariate				
CCP	1.0	1.50	1.11, 2.03	0.0099
PSA levels	2.0	2.12	1.31, 3.45	0.0033
Clinical stage				0.035
>T1 vs T1	1.0	1.86	1.02, 3.40	
% Positive Cores	33.3	1.05	0.70, 1.58	0.80
Age at Diagnosis (yrs)	10.0	1.55	1.02, 2.35	0.037
Multivariable				
CCP	1.0	1.47	1.08, 2.00	0.017
PSA levels	2.0	2.15	1.29, 3.60	0.0045
Clinical stage				0.012
>T1 vs T1	1.0	2.09	1.14, 3.80	
% Positive Cores	33.3	0.94	0.60, 1.46	0.79
Age at Diagnosis (yrs)	10.0	1.44	0.95, 2.18	0.080

- CCP and PSA were the most significant variables in the multivariable model. Figure 1 illustrates how CCP further discriminates within each level of risk predicted by PSA.

Figure 1. Predicted 10-Year Risk from Biopsy Diagnostic Gleason Score 6



CONCLUSIONS

- The CCP score predicts oncologic outcomes in Gleason 6 or less prostate cancer patients.
- This meta-analysis adds to the evidence that CCP score provides significant prognostic discrimination to patients with low-risk localized disease.

REFERENCES

1. Bishoff JT, et al. J Urol. 2014;192(2):409-414.
2. Brawer MK, et al. ASCO Meeting Abstracts. 2013; 31(6_suppl):67.
3. Cooperberg MR, et al. J Clin Oncol. 2013;31(11):1428-1434.
4. Cuzick J, et al. Br J Cancer. 2012;106(6):1095-1099.
5. Cuzick J, et al. Br J Cancer. 2015;113(3):382-389.
6. Cuzick J, et al. Lancet Oncol. 2011;12(3):245-255.
7. Freedland SJ, et al. Int J Rad Oncol Biol Phys. 2013;86(5):848-853.