The CCP score provides significant prognostic information in Gleason score <7 patients

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OBJECTIVES

- The Cell Cycle Progression (CCP) score was developed and validated to provide prognostic information to prostate cancer patients in all risk groups.[1-4]
- As previous studies of CCP focused on the distant oncologic outcomes (e.g. biochemical recurrence, metastases, and mortality), each individual study lacked power to demonstrate prognostic utility of the score in low risk patients owing to low event rate.
- Here we present a meta-analysis of previous studies that evaluated the CCP score in men who had Gleason <7 disease diagnosed by needle biopsy and were either managed conservatively initially or treated by radical prostatectomy (RP).
- In addition, we evaluate AUA-defined risk in men who underwent clinical CCP testing and had Gleason <7.

METHODS

GENE EXPRESSION TESTING

- A CCP score was derived from the biopsy as the mean expression of 31 CCP genes normalized by 15 housekeeper genes.
- A clinical cell-cycle risk (CCR) score, which combines the CCP score with CAPRA to determine risk of prostate cancer mortality, was also calculated.[4]
  - (0.57 x CCP score) + (0.39 x CAPRA score)
- The CAPRA score is based on clinical characteristics, such as PSA levels, clinical stage, and Gleason score, but CAPRA has less granularity when the Gleason score range is restricted to <7.

COHORTS

- The CCP and CCR scores were evaluated for association with adverse outcome using Gleason <7 men in a meta-analysis combining two conservatively managed cohorts (N=204),[2,3] and three cohorts after R
- The range of clinical characteristics for men who underwent clinical CCP testing who had Gleason <7 (N=8,450) was also evaluated.

STATISTICAL ANALYSIS

- 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.
- Analyses were stratified by cohort, and there was no evidence that CCP behaved differently by outcome.
- Hazard ratios (HR) are given for one-unit increase in CCP score (equivalent to a doubling of gene expression).
- Clinical characteristics and AUA risk category were also evaluated for Gleason <7 men who underwent clinical CCP testing.

RESULTS

Table 1. Univariate, Bivariate, and Multivariable 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
Multivariable			
CCP	1.47	1.08, 2.00	0.017
PSA	2.15	1.29, 3.6	0.0045
Clinical Stage	-	-	0.012
>T1 vs T1	2.09	1.14, 3.8	-
Positive Cores (%)	0.94	0.60, 1.46	0.79
Age at Diag (yr)	1.44	0.95, 2.18	0.080

Figure 1. Predicted Prostate Cancer Mortality Risk by PSA Level and Clinical Stage Among Men with Gleason <7

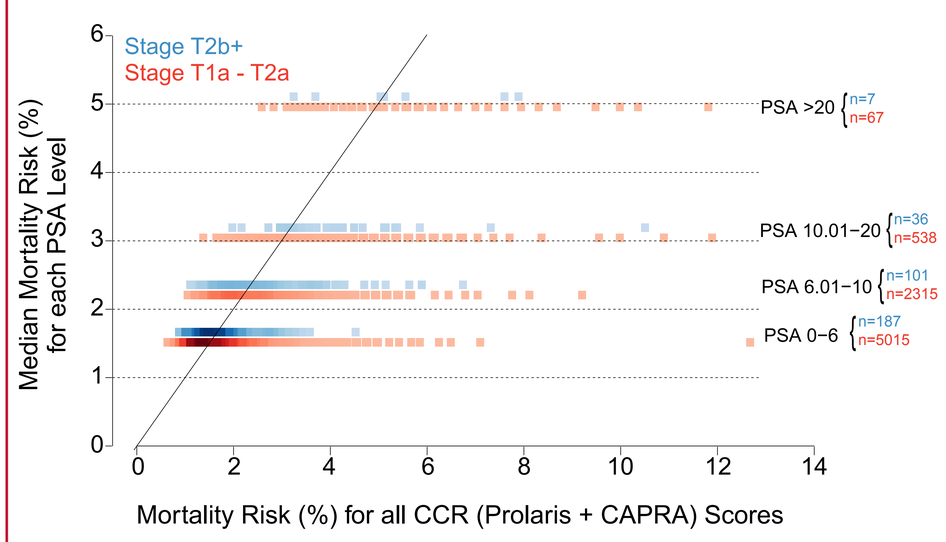

Table 2. Characteristics of Clinical CCP Testing in Patients with Gleason < 7

Variable		AUA High Risk (N=220)	AUA Int. Risk (N=736)	AUA Low Risk (N=7494)	Total (N=8450)
Age at Diag. (yr)	n	220	736	7494	8450
	mean ± sd	64.7 ± 9.06	65.7 ± 7.88	64.4 ± 7.68	64.6 ± 7.75
	min, max	39, 93	46, 87	27,93	27, 93
PSA (ng/mL)	0 - 6	88 (40.0%)	105 (14.3%)	5134 (68.5%)	5327 (63%)
	6.01 - 10	39 (17.7%)	64 (8.7%)	2360 (31.5%)	2463 (29.1%)
	10.01 - 20	13 (5.9%)	567 (77%)	0	580 (6.9%)
	>20	80 (36.4%)	0	0	80 (0.9%)
Positive Cores (%)	n	219	736	7486	8441
	mean ± sd	30.9 ± 22.07	25.4 ± 19.88	21.9 ± 15.63	22.5 ± 16.32
	min, max	2.1, 100	0, 100	0, 100	0, 100
Gleason Score	2	0	0	1 (<0.1%)	1 (<0.1%)
	4	0	0	1 (<0.1%)	1 (<0.1%)
	5	1 (0.5%)	0	19 (0.3%)	20 (0.2%)
	6	219 (99.5%)	736 (100%)	7473 (99.7%)	8428 (99.7%)
Clinical Stage	T1a-T2a	73 (30%)	544 (73.9%)	7494 (100%)	8111 (96.1%)
	T2b	4 (1.8%)	192 (26.1%)	0	196 (2.3%)
	T2c	138 (62.7%)	0	0	138 (1.6%)
	T3	5 (2.3%)	0	0	5 (<0.1%)

- In univariate analysis, both CCP and CCR were significant predictors of outcome in the conservatively managed and RP cohorts (Table 1).
- CCP remained significant in multivariable analysis after adjusting for clinical variables (Table 1).
- PSA and clinical stage were other clinical variables that remained significant in the multivariable model.
- A wide range of CCR risks were observed within the clinical testing cohort of men with Gleason <7 (Table 2).
- There was significant overlap in CCR risks, regardless of PSA and stage (Figure 1).

CONCLUSIONS

- The CCP score predicts oncologic outcomes (prostate cancer death or biochemical recurrence) in Gleason <7 prostate cancer patients (HR=1.50, p=0.0099), and remains significant when accounting for clinical variables (HR=1.47, p=0.017).
- The CCR disease-specific risk estimates ranged from 0.6–12.7% for Gleason <7 men who underwent clinical testing, regardless of PSA and stage.
- Together, these analyses add to the evidence that CCP score provides significant prognostic discrimination to patients with low-risk localized disease.

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