CCP SCORE IS A STRONG PREDICTOR OF OUTCOME IN SEVERAL PROSTATE CANCER COHORTS

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BACKGROUND

- The natural history of newly diagnosed prostate cancer is highly variable and difficult to predict so improved tools are needed to more appropriately match treatment to a patient's risk of progression.
- Previous data has shown that a 46-gene cell cycle progression (CCP) RNA signature is a robust predictor of biochemical recurrence after radical prostatectomy, and of prostate cancer-specific death in a conservatively managed cohort diagnosed by transurethral resection of the prostate.[1]
- Here we report the prognostic utility of the CCP score obtained in 3 different clinical settings including needle biopsies in newly diagnosed men.

METHODS

- mRNA was extracted from formalin fixed and paraffin embedded (FFPE) tumor sections from 1) 366 U.S. patients after radical prostatectomy; 2) 337 conservatively managed (i.e. watchful waiting) UK patients diagnosed by TURP; and 3) 349 conservatively managed UK patients diagnosed by needle biopsy (Table 1).
- RNA levels of 31 CCP genes and 15 housekeeper genes were determined and a mean composite score calculated (CCP score).
- Clinical variables for multivariate analysis included Gleason score, baseline PSA, age, and stage.
- Primary endpoint was death from prostate cancer in the TURP and needle biopsy cohorts, and biochemical recurrence in the RP cohort.

RESULTS

1) CCP score was highly prognostic of outcome in all tested clinical settings (Table 2 and Table 3).
2) CCP score was highly predictive of biochemical recurrence after prostatectomy (p-value < 10^{-8}; HR = 1.89). After adjustment for clinical parameters including PSA, Gleason, pStage and margins CCP score remained highly significant (p-value <10^{-5}; HR = 1.77).
3) In the TURP cohort, the CCP score was highly predictive of disease-specific death (p-value < 10^{-21}; HR = 2.92). It remained a significant predictor of cancer death after adjustment for Gleason grade, PSA, Ki67 status, and cancer extent (p-value < 10^{-7}; HR = 2.56).
4) In the needle cohort, CCP score was the strongest univariate predictor of cancer death (p-value < 10^{-9}; HR = 2.02). It remained significant after adjustment for Gleason grade, PSA, Ki67, and extent of disease (p-value < 10^{-4}; HR = 1.65).

CONCLUSIONS

- An mRNA expression signature based on CCP gene expression is prognostic in prostate cancer patients at diagnosis and after prostatectomy.
- CCP score provides important prognostic information that is not provided by other clinical or pathological variables.
- The CCP signature should be a valuable addition to clinical variables for differentiating aggressive from indolent disease.

Table 1. Patient characteristics for all 3 cohorts.
Numbers are median (IQR) or n (%) as appropriate.

Cohort	Post-RP[1]	TURP[1]	Needle biopsy[2]
	N=366	N=337	N=349
Outcome	Time to biochemical recurrence	Death from prostate cancer	Death from prostate cancer
Events	138 (38)	75 (22)	90 (26)
Follow-up	9.5 (6.8, 11.0)	10.3 (5.9, 12.3)	10.3 (5.5, 11.6)
Age (years)	68 (63, 72)	71 (67, 73)	71 (66, 73)
Gleason Score			
<7	240 (66)	172 (51)	106 (30)
7	110 (30)	73 (22)	152 (44)
>7	16 (4)	92 (27)	91 (26)
PSA (ng/ml)	6.9 (4.5, 10.7)	8.3 (2.8, 21.0)	21.4 (11.9, 42.0)

Figure 1. Risk of 10-year prostate cancer mortality by Combined risk (CCP + Gleason + PSA) for patients in the needle biopsy cohort.

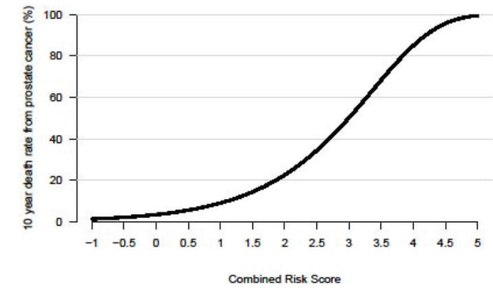

Figure 2. 10-year predicted risk in needle cohort for model with CCP score compared to model with PSA and Gleason.
Blue = Gleason 6; Black = Gleason 7; and Turquoise = Gleason 8-10.

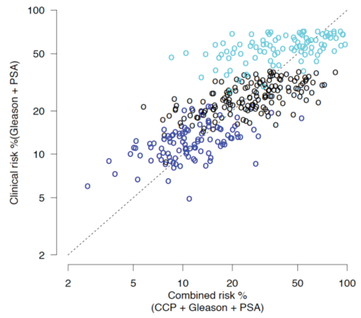

Table 2. Summary of Cox proportional hazards univariate analysis.
Numbers are hazard ratio (95% CI) Hazard ratio for CCP score is for an increase in one score unit.

Cohort	Post-RP[1]		TURP[1]		Needle biopsy	
Outcome	Time to biochemical recurrence		Death from prostate cancer		Death from prostate cancer	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
CCP score	1.89 (1.54, 2.31)	5.6×10^{-9}	2.92 (2.38, 3.57)	6.1×10^{-22}	2.02 (1.62, 2.53)	8.6×10^{-10}
Gleason score						
<7	1 (ref)	1.5×10^{-13}	1 (ref)	3.7×10^{-19}	1 (ref)	1.6×10^{-9}
7	2.81 (2.01, 3.94)		5.20 (2.40, 11.29)		2.17 (1.16, 4.07)	
>7	6.32 (3.65, 10.93)		13.67 (6.90, 27.11)		5.85 (3.11, 11.01)	
log(1 + PSA) ng/ml	3.07 (2.38, 3.97)	3.4×10^{-17}	2.30 (1.83, 2.88)	3.4×10^{-14}	1.70 (1.31, 2.20)	4.2×10^{-5}

Table 3. Summary of Cox proportional hazards multivariate analysis.
HRs are given per unit increase in CCP score.

Cohort	HR (95% CI)	p-value	Clinical variables included in model
Post-RP	1.74 (1.39 - 2.17)	3.3×10^{-6}	Gleason, PSA, stage, margins
TURP	2.56 (1.85 - 3.53)	1.3×10^{-8}	Gleason, PSA, Ki67, % positive chips
Needle biopsy	1.65 (1.31, 2.09)	3.0×10^{-5}	Gleason, PSA, stage, hormone use, age

REFERENCES

1. Cuzick et al. *Lancet Oncol* 2011; 12(3): 245-55.