Prognostic Value of a Cell Cycle Progression Score for Men with Prostate Cancer

Jack Cuzick

Abstract

A new prognostic score called the cell cycle progression or CCP score has been evaluated for predicting outcome in men with prostate cancer. The score is based on 31 cell cycle progression genes and 15 housekeeper control genes. Results on 5 cohorts have been reported. In all cases the CCP score was strongly predictive of outcome both in univariate models and in multvariate models incorporating standard factors such as Gleason grade, PSA levels and extent of disease. Two cohorts evaluated patients managed by active surveillance where the outcome was death from prostate cancer, two cohorts examined patients treated by radical prostatectomy where biochemical recurrence was the primary endpoint, and one smaller cohort looked at patients treated with radiotherapy where again biochemical recurrence was used as the endpoint. In all cases a unit change in CCP score was associated with an approximate doubling of risk of an event. These data provide strong event to support use of the CCP score to help guide clinical management.

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J. Cuzick (✉)
Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine,
Queen Mary University of London, London, EC1M 6BQ, UK
e-mail: j.cuzick@qmul.ac.uk

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Table 1 Summary of the five prostate cancer cohorts in which the cell cycle progression (CCP) score has been evaluated

Study	Sample type	Number of patients (events)	Endpoint	Reference
TURP conservatively managed	Biopsy	337 (76)	Death from prostate cancer	Cuzick et al. (2011)
Needle biopsy conservatively managed	Biopsy	349 (90)	Death from prostate cancer	Cuzick et al. (2012)
Radical prostatectomy 1	Surgical tumor	353 (132)	Biochemical recurrence	Cuzick et al. (2011)
Radical prostatectomy 2	Surgical tumor	413 (83)	Biochemical recurrence	Cooperberg et al. (2013)
External beam XRT	Biopsy	141 (19)	Biochemical recurrence	Freedland et al. (2013)

The natural history of prostate cancer is highly variable and accurately assessing a tumor's aggressiveness based on currently available clinical and pathologic features is challenging. Useful prognostic information is contained in Gleason score, PSA level, extent of disease (including clinical stage) (Cuzick et al. 2006; Kattan et al. 1998), and a minor gain is seen with some immunohistochemical markers such as Ki-67 and PTEN (Berney et al. 2009; Cuzick et al. 2013), but much room for improvement remains. Other expression profile and methylation markers show some promise (Vasiljević et al. 2011; Erho et al. 2013; Chao et al. 2013; Wu et al. 2013; Penney et al. 2011; Markert et al. 2011; Wang et al. 2012), but are still at an early stage of development.

Novel prognostic markers are needed to more precisely guide therapeutic decisions. The cell cycle progression (CCP) score measures the expression levels of 31 CCP genes in prostate cancer tissue and offers a new approach to dealing with this problem. To date, the CCP score has been evaluated in five independent cohorts. The study characteristics are summarized in Table 1.

All studies were retrospective and analyzed formalin-fixed paraffin imbedded prostate tissue from men diagnosed with adenocarcinoma. The CCP score was calculated by measuring the average RNA expression level of 31 CCP genes normalized by the average expression of 15 housekeeping genes as quantified by RT-PCR. The specific genes involved are given in Table 2 and further details are given elsewhere (Cuzick et al. 2011). Hazard ratios (HR) are given for a one-unit change in CCP score. The median size of the interquartile range (IQR) of the CCP score in these studies was 1.1, so a one-unit change is a good measure of the population variability and the extent to which the risk of progression or death in these populations that can be accounted for by the CCP score. A histogram of the spread of CCP score for the needle biopsy cohort is shown in Fig. 1 and is representative of that seen in the other cohorts.

Table 2 CCP gene list

FOXM1	ASPM	TK1	PRC1
CDC20	BUB1B	PBK	DTL
CDKN3	RRM2	ASF1B	CEP55
CDC2	DLGAP5	C18orf24	RAD51
KIF11	BIRC5	RAD54L	CENPM
KIAA0101	KIF20A	PTTG1	CDCA8
NUSAP1	PLK1	CDCA3	ORC6L
CENPF	TOP2A	MCM10	

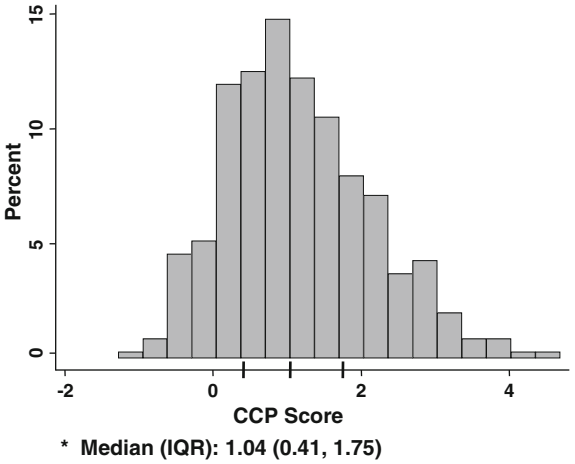

Fig. 1 Histogram for CCP scores in the needle biopsy cohort (Cuzick et al. 2012)

Two cohorts (Cuzick et al. 2011, 2012) examined conservatively managed patients with clinically localized disease—one consisted of patients diagnosed by TURP ($n = 337$), and in the other they were diagnosed by needle biopsy ($n = 349$). In both cohorts the outcome was death from prostate cancer. Both were from the United Kingdom and were cancer registry based. Cancers were diagnosed between 1990 and 1996 and median follow-up exceeded 10 years.

Two additional studies from the United States looked at patients treated by radical prostatectomy, where biochemical recurrence was the primary endpoint (Cuzick et al. 2011; Cooperberg et al. 2013). Here, the CCP score was performed on material taken from the prostatectomy specimen. Median follow-up for these studies is 9.4 and 7.1 year, respectively. A fifth cohort examined 141 men treated by external beam radiotherapy. The CCP score was assayed from the diagnostic needle biopsy and outcome was biochemical recurrence (Freedland et al. 2013). Follow-up was censored at 5 years in this study.

Table 3 Prognostic value of the CCP score in univariate and multivariate PH models for multivariate model, P-values are from the addition of specified variable in a model where the other variables are included

Study	Endpoint		CCP score		PSA	Gleason score
			Hazard ratio (95 % CI)	p-value	p-value	p-value
TURP conservatively managed (Cuzick et al. 2011)	CaP death	Univariate	2.9 (2.4, 3.6)	$<10^{-21}$	$<10^{-13}$	$<10^{-18}$
		Multivariate	2.6 (1.9, 3.4)	$<10^{-10}$	$<10^{-7}$	0.028
Needle biopsy conservatively managed (Cuzick et al. 2012)	CaP death	Univariate	2.0 (1.6, 2.5)	$<10^{-9}$	$<10^{-4}$	$<10^{-7}$
		Multivariate	1.7 (1.3, 2.1)	$<10^{-4}$	0.017	0.0022
Radical prostatectomy A (Cuzick et al. 2011)	BCR	Univariate	2.0 (1.6, 2.4)	$<10^{-8}$	$<10^{-17}$	$<10^{-9}$
		Multivariate	1.7 (1.4, 2.2)	$<10^{-5}$	$<10^{-8}$	0.015
Rad prostatectomy B (Cooperberg et al. 2013)	BCR	Univariate	2.1 (1.6, 2.9)	$<10^{-5}$	0.0035	$<10^{-5}$
		Multivariate	2.0 (1.4, 2.8)	$<10^{-4}$	0.12	0.17
External beam XRT (Freedland et al. 2013)	BCR	Univariate	2.6 (1.4, 4.6)	0.0017	$<10^{-3}$	0.051
		Multivariate	2.1 (1.0, 4.2)	0.035	0.054	0.20

The main results are summarized both for univariate and multivariate proportional hazard models in Table 3. In all cases except for one radical prostatectomy cohort the CCP score was the strongest predictor of failure, and in all cases significant prognostic information was obtained from the CCP score.

In univariate analyses (Table 3) the risk of an event was increased more than two-fold for every unit increase in CCP score (range 2.0–2.9). Kaplan–Meier survival curves for different CCP values in the cohorts are shown in Fig. 2a–e. In all cases there is a clear gradient of increased risk for each unit change in CCP score, across a wide spectrum of values. A unit change in score is equivalent to a doubling in normalized expression level. Multivariate models, adjusted for Gleason score, PSA level, and other clinical variables gave only slightly attenuated HR for the CCP score, ranging from 1.7 to 2.6 (Table 3). This was due to the weak positive correlation between the CCP score and other variables such as Gleason grade and PSA level. This is given in Table 4, where correlations were typically in the 0.10–0.40 range; the one exception being the TURP cohort where the correlation with Gleason score was 0.57.

The added value of CCP score to Gleason score and PSA level is shown in Fig. 3 for the conservatively managed needle biopsy cohort. Here, the prognostic value of Gleason score and PSA was determined by a model developed in the same cohort. Similar discrimination is seen when the CAPRA score (Cooperberg et al. 2011)

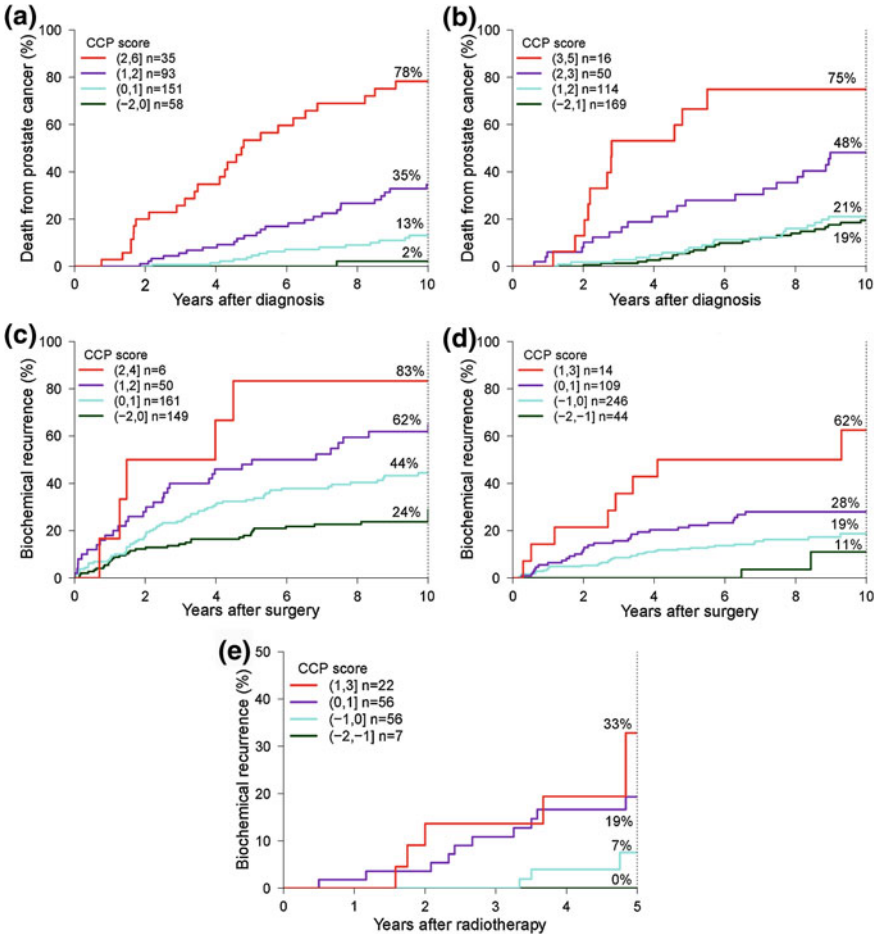

Fig. 2 Time to event curves for 5 cohorts examining the CCP score: **a** Conservatively managed TURP cohort, **b** conservatively managed needle biopsy cohort, **c** radical prostatectomy cohort A, **d** radical prostatectomy cohort B, and **e** radiotherapy cohort

is used to estimate the contribution from clinical variables, but this was available from only 60 % of the needle biopsy cohort.

The CCP score appears to give good added discrimination across all Gleason grades and PSA levels. In particular, this was seen for patients with low-risk cancers as judged by Gleason score 6, PSA <10 ng/ml, or low CAPRA score.

Table 4 Pearson correlation coefficient between the CCP score and Gleason score or PSA in the five cohorts

Study	CCP score versus Gleason score	CCP score versus PSA
TURP conservatively managed (Cuzick et al. 2011)	0.57	0.27
Needle biopsy conservatively managed (Cuzick et al. 2012)	0.37	0.14
Radical prostatectomy A (Cuzick et al. 2011)	0.22	0.21
Radical prostatectomy B (Cooperberg et al. 2013)	0.18	0.11
External beam XRT (Freedland et al. 2013)	0.23	0.31

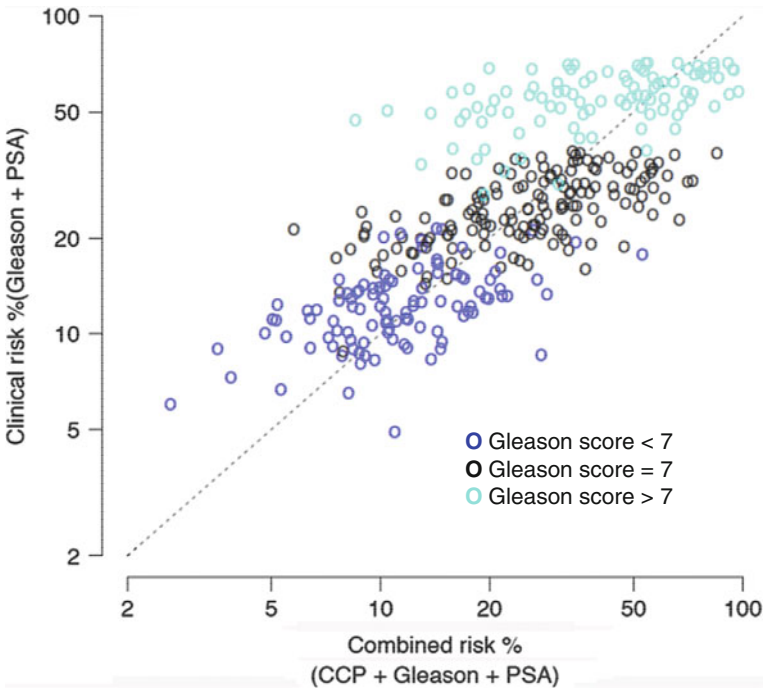

Fig. 3 Ten year predicted risk of death from prostate cancer in the needle biopsy cohort (cuzick et al. 2012) for combined CCPscore with Gleason and PSA (*horizontal axis*) vs Gleason and PSA alone (*vertical axis*). Each circle represents a person is the study and the colour of the circle indicates predicted risk using Gleason only

1 Conclusions

In conclusion, the CCP score predicts prostate cancer outcome in multiple patient cohorts and in diverse clinical settings. The CCP score provides independent information beyond that available from clinicopathologic variables such as Gleason score, PSA level, and extent of disease, and helps to further differentiate aggressive prostate cancer from indolent cancer.

There are several potential roles for this test which remain to be fully elucidated. The most obvious and potentially largest role is to help with the decision as to whether apparently low-risk patients can be safely managed by active surveillance, or whether radical prostatectomy or radiotherapy is needed. This is an important question especially in places where PSA testing is common. In the USA, for example, incidence is about eight times higher than mortality, and many patients are overtreated. Identifying a larger and more accurately assessed cohort which could be safely watched after diagnosis is an important goal. In such patients, the role of the CCP score in repeat biopsies is also an important question and studies in this area are needed to see if the CCP score can more rapidly anticipate the need for radical surgery before metastases have occurred. Other roles include determining the need for adjuvant hormonal treatment or chemotherapy in men who have been treated by radical prostatectomy or radiation.

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