PROGNOSTIC UTILITY OF THE CELL CYCLE PROGRESSION (CCP) SCORE GENERATED FROM NEEDLE BIOPSY IN MEN TREATED WITH PROSTATECTOMY

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BACKGROUND

- The cell cycle progression (CCP) score has proven to have prognostic utility in predicting disease progression in various clinical settings utilizing biopsy, TURP and post prostatectomy specimens.
- Previous studies evaluating post–surgical outcomes were conducted using CCP gene expression measured in the prostatectomy specimen.
- Here, we demonstrate the ability of the CCP score to predict cancer progression, as measured by both BCR and metastatic disease after radical prostatectomy, using needle biopsy tissue.

METHODS

- We evaluated the CCP score in three patient cohorts:
  - Martini Clinic (MC) in Hamburg, Germany (N=283)
    - Diagnosed from 2005 and 2006
    - Simulated biopsy from FFPE tumor block
  - Durham VA Medical Center (DVA, N=176)
    - Diagnosed from 1992 to 2007
    - 60% patients had positive surgical margins and 47% had BCR (compared to 17% for MC)
  - Intermountain Healthcare (IHC, N=123)
    - Diagnosed from 1999 to 2002
    - Selected cohort (36 with BCR, 87 with no recurrence)
- The CCP score was derived from a simulated biopsy (MC) or diagnostic biopsy (DVA and IHC) and evaluated for association with biochemical recurrence (BCR) and metastatic disease in univariable analysis and after adjusting for other clinical information.

RESULTS

- In all three cohorts, the CCP score was associated with BCR and metastatic disease.
  - The association with BCR remained significant after adjusting for other prognostic clinical variables.
- In a combined analysis of all three cohorts (N=582), the CCP score was a strong predictor of BCR in both univariable (HR per Interquartile Range (IQR)=1.68 (95%CI: 1.41, 1.99), p–value < 10^{-6})) and multivariable analyses (HR per IQR=1.53 (95%CI: 1.28, 1.84), p–value < 10^{-4})).
- CCP score was the strongest predictor of metastatic disease in both univariable analysis (HR per IQR=6.32 (95% CI: 3.41, 11.71, p–value < 10^{-7})), and after adjusting for clinical variables (HR per IQR=4.83 (95% CI: 2.40, 9.74, p–value < 10^{-5})).

TABLE 1 • Clinical Characteristics

Variable	Statistic	MC	DVA	IHC
CCP score from RP	Median (IQR)	-0.4 (-0.9, 0.2)	0.0 (-0.4, 0.6)	0.3 (-0.3, 0.9)
Age at surgery (yrs)	Median (IQR)	63 (58, 66)	62 (58,67)	62 (57,67)
PSA (ng/ml)	Median (IQR)	6.4 (4.6, 9.2)	7.2 (5.1, 11.0)	5.5 (4.4, 7.6)
Gleason score				
<7	Number	159 (56%)	102 (58%)	77 (63%)
7	Number	107 (38%)	59 (34%)	38 (31%)
>7	Number	17 (6%)	15 (9%)	8 (6%)
Clinical stage				
T1	Number	216 (77%)	88 (62%)	52 (42%)
T2	Number	63 (21%)	53 (38%)	71 (58%)
T3	Number	4 (1%)	0 (0%)	0 (0%)
% Positive cores	Median (IQR)	33 (20, 50)	33 (20, 50)	36 (25,50)
Adjuvant therapy				
No	Counts	275 (97%)	142 (81%)	110 (89%)
Yes	Counts	8 (3%)	34 (19%)	13 (11%)
Time from last surgery to last follow-up (months)	Median (IQR)	61 (60,73)	88 (69, 119)	132 (123, 143)
Biochemical recurrence events (10-year censoring)	Events/Total	48/283 (17%)	83 /176 (47%)	35 /123 (28%)

FIGURE 1 • Kaplan-Meier plots of A) Biochemical recurrence and B) Metastasis-free survival (N=582).

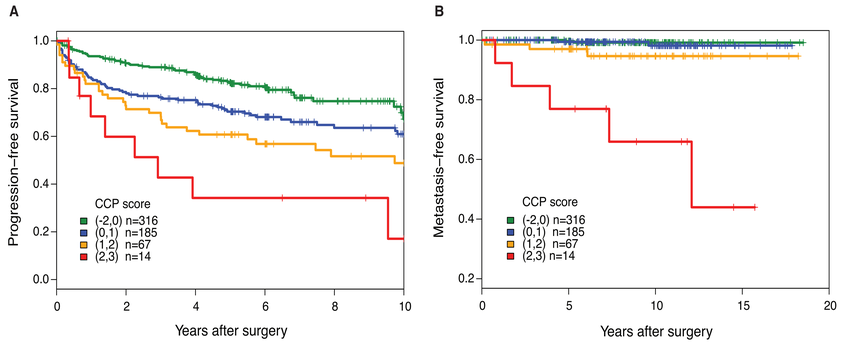

TABLE 2 • Cox PH models of time to BCR (N = 582 with 166 events).

Variable	Number of Patients	Hazard Ratio	95% CI	p-value	Variable	Hazard Ratio	95% CI	p-value
Univariable Analysis					Multivariable Analysis			
CCP score	582	1.60	1.35, 1.90	$<10^{-6}$	CCP score	1.47	1.23, 1.76	$<10^{-4}$
Ln (1+PSA ng/ml)	582	2.21	1.73, 2.84	$<10^{-8}$	Ln (1+PSA ng/ml)	1.89	1.47, 2.42	$<10^{-5}$
Gleason score					Gleason score			
<7	338	Ref	Ref		<7	Ref	Ref	
7	204	1.85	1.33, 2.56	$<10^{-4}$	7	1.48	1.06, 2.07	0.021
>7	40	2.87	1.75, 4.70		>7	1.85	1.10, 3.10	
Clinical stage					Adjuvant treatment			
I	356	Ref	Ref	0.66	No	Ref	Ref	0.19
II or III	191	1.08	0.77, 1.52		Yes	1.32	0.88, 1.98	
% Positive cores	437	1.00	1.00, 1.01	0.22				
Adjuvant treatment								
No	527	Ref	Ref	0.0052				
Yes	55	1.83	1.22, 2.73					
Age at diagnosis (yrs)	546	1.01	0.98, 1.03	0.75				

TABLE 3 • Cox PH models of time from surgery to metastatic disease (N = 582 with 12 events).

Variable	Number of Patients	Hazard Ratio	95% CI	p-value	Variable	Hazard Ratio	95% CI	p-value
Univariable Analysis					Multivariable Analysis			
CCP score	582	5.35	2.89, 9.92	$<10^{-7}$	CCP score	4.19	2.08, 8.45	$<10^{-5}$
Ln (1+PSA ng/ml)	582	1.57	0.64, 3.86	0.35	Ln (1+PSA ng/ml)	1.23	0.57, 2.68	0.60
Gleason score					Gleason score			
<7	338	Ref	Ref		<7	Ref	Ref	
7	204	4.82	0.93, 24.9	$<10^{-3}$	7	3.09	0.57, 16.7	0.15
<7	40	23.4	4.49, 122		>7	5.12	0.84, 31.2	
Clinical stage								
I	356	Ref	Ref	0.11				
II or III	191	2.77	0.76, 10.1					
% Positive cores	437	1.02	1.00, 1.05	0.089				
Adjuvant treatment								
No	527	Ref	Ref	0.61				
Yes	55	1.54	0.32, 7.42					
Age at diagnosis (yrs)	582	1.01	0.92, 1.11	0.88				

CONCLUSIONS

- The CCP score derived from a biopsy sample was strongly associated with adverse outcome after surgery.
- It was the strongest predictor of eventual metastatic disease of the tested variables including Gleason and PSA.
- These results indicate that the CCP score can be used at disease diagnosis to better define patient prognosis and appropriate clinical care.

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