

Pooled Analysis of the Prognostic Utility of the Cell Cycle Progression Score Generated from Needle Biopsy in Men Definitively Treated for Localized Prostate Cancer

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Introduction: CCP and CCR Scores

- The cell cycle progression (CCP) score is a validated prognostic molecular RNA signature that has proven utility in various clinical settings.¹
- The clinical cell-cycle risk (CCR) score is a validated prediction model that combines the CCP score and the cancer of the prostate risk assessment (CAPRA) score.²
- Here, we evaluate the ability of both scores to predict the 10-year risk of metastatic disease in a large pooled analysis of patients who received definitive therapy.

1. Sommariva S et al. Eur Urol. 2016;69:107-115. 2. Cuzick J et al. Br J Cancer. 2015;113:382-389.

Methods: Pooled Analysis of Two Cohorts

- A pooled analysis was performed using data from two completed studies of men treated for localized prostate cancer by either radical prostatectomy (RP) or external beam radiotherapy (EBRT).
- The combined patient cohort included 1,062 patients with complete clinical and molecular testing information:
 - Bishoff et al.: Martini Clinic, Hamburg, Germany; Durham VA Medical Center, Durham, NC; Intermountain Healthcare, Murray, UT (n=416)³
 - Ochsner Clinic, New Orleans, Louisiana (n=646)⁴

Methods: Molecular Testing

- Formalin–fixed paraffin embedded biopsy tissue was analyzed for the expression levels of 31 CCP genes and 15 housekeeper genes by quantitative RT-PCR.
- A CCP score was calculated as the normalized expression of the CCP genes.²
- A CAPRA score for each patient was generated based on available clinicopathologic variables.²
- We also evaluated the performance of a CCR score for predicting metastatic disease and derived a CCR-based metastatic risk curve: $CCR = (0.57 \times CCP) + (0.39 \times CAPRA)$.

Methods: Statistical Analysis

- The CCP score was evaluated for association with 10-year risk of metastatic disease following definitive therapy after adjusting for other clinical information.
- Patient data was censored at 10 years.
- The CCR score was used to generate risk curves using Cox proportional hazard methods.

Clinical Information by Cohort

- In the combined cohort, 3.3% (35/1,062) of the patients progressed to metastatic disease by 10 years.

	Ochsner Clinic		Bishoff et al.	
Characteristic	N	Median (IQR)	N	Median (IQR)
Age at diagnosis, years	646	64 (58, 70)	416	62 (58, 66)
Pre-biopsy PSA, ng/μl	646	5.8 (4.5, 8.3)	416	6.0 (4.6, 9.0)
Positive cores, %	646	42.9 (28.6, 66.7)	416	33.3 (20.0, 50.0)
CCP score	646	0.3 (-0.2, 0.9)	416	-0.1 (-0.6, 0.5)
Biopsy Gleason Score†	N	Frequency	N	Frequency
< 7	333	51.5%	159	54.3%
3 + 4 = 7	156	24.1%	86	29.4%
4 + 3 = 7	61	9.4%	28	9.6%
> 7	96	14.9%	28	6.8%
Clinical T Stage	N	Frequency	N	Frequency
T1	471	72.9%	261	62.7%
T2	151	23.4%	154	37.0%
T3	24	3.7%	1	0.2%
CAPRA Risk Category	N	Frequency	N	Frequency
Low (0–2)	288	44.6%	202	48.6%
Intermediate (3–5)	258	39.9%	187	45.0%
High (6–10)	100	15.5%	27	6.5%
Clinical Outcomes	event/N (%)	Median (IQR)*	event/N (%)	Median (IQR)*
Progression to Metastatic disease	28/646 (4.3%)	5.5 (4.0, 6.8)	7/416(1.7%)	7.1 (5.4, 10.0)

† - IHC cohort excluded from Bishoff cohort due to some patients missing secondary Gleason.

*Follow-up time for men who had not experienced an event and were alive at the end of follow-up

Results: CCP & CCR are Strongly Associated with Progression to Metastatic Disease

- Despite significant differences between the individual cohorts for all clinical and molecular variables except pre-biopsy PSA, the differences between the cohorts were not significant in the multivariable analysis (p=0.37).
- The CCP score was strongly associated with a 10-year risk of metastatic disease in multivariable analysis after adjusting for CAPRA and treatment (p=1.9x10⁻⁶).
- The CCR score was also strongly associated with metastatic disease (HR 3.63 95% CI 2.60, 5.05; p=2.1x10⁻¹⁶).

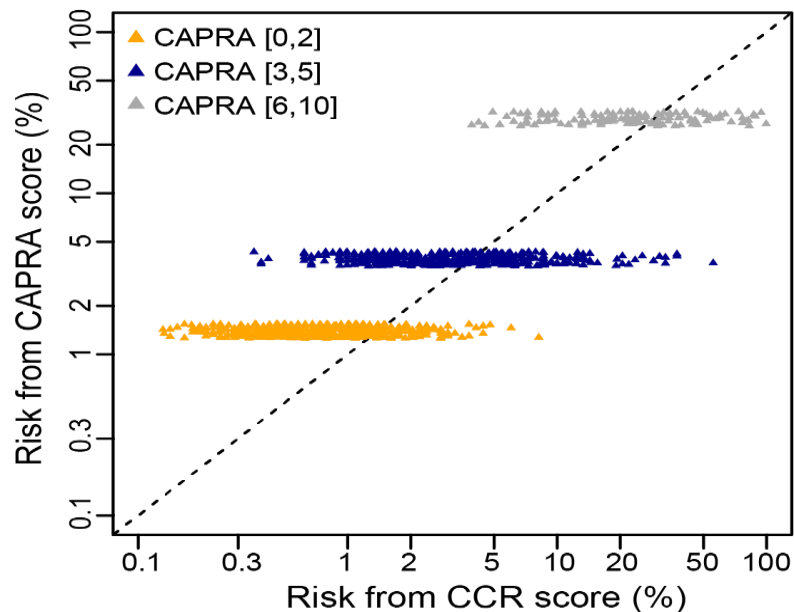
Variable	Hazard Ratio* (95% Confidence Interval)	P-Value
Univariate Analysis		
CCR score	4.00 (2.95, 5.42)	6.3×10 ⁻²¹
CCP score	2.93 (2.21, 3.90)	1.8×10 ⁻¹¹
CAPRA	1.75 (1.53, 2.00)	4.2×10 ⁻¹⁵
Ancestry (AA/Non-AA)	0.62 (0.27, 1.43)	0.24
Treatment (Radiation/RP)	5.14 (2.58, 10.23)	4.5×10 ⁻⁶
Cohort	3.98 (1.64, 9.69)	6.1×10 ⁻⁴
Multivariable Analysis for CCP**		
CCP score	2.21 (1.64, 2.98)	1.9×10 ⁻⁶
CAPRA	1.61 (1.37, 1.90)	1.3×10 ⁻⁸
Treatment (Radiation/RP)	1.36 (0.58, 3.20)	0.48
Cohort	1.63 (0.55, 4.78)	0.37
Multivariable Analysis for CCR**		
CCR Score	3.63 (2.60, 5.05)	2.1x10 ⁻¹⁶
Treatment (Radiation/RP)	1.33 (0.57, 3.11)	0.51
Cohort	1.64 (0.56, 4.83)	0.36

*Hazard ratio per unit score for continuous variables

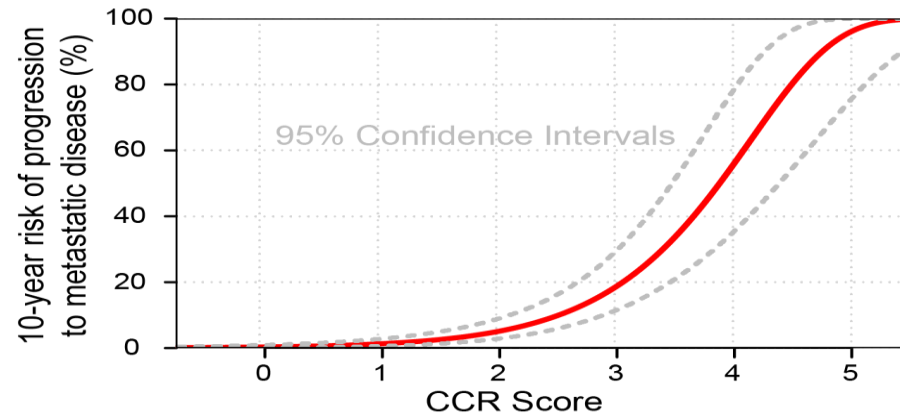
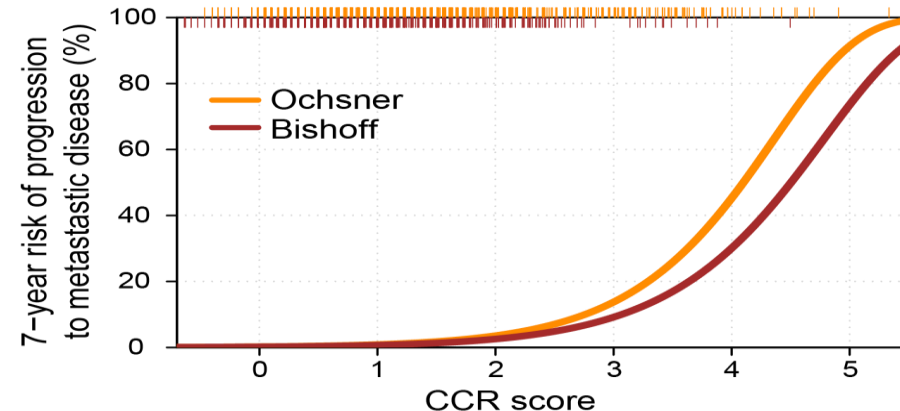
**Multivariable analysis performed separately for CCP and CCR scores because the CCR score is a linear combination of CCP and CAPRA.

Results: CCR is Highly Prognostic

- The amount of new prognostic information provided by the CCR score is illustrated by comparing the difference in predicted risk between CCR and CAPRA.
 - The C-index was 0.857 for CAPRA and improved to 0.894 for CCR, indicating that the new information is clinically relevant.



- The comparison of CCR and CAPRA risk estimates show the ability of CCR to further discriminate the metastasis risk within each CAPRA category.



Conclusions

- The CCP score derived from biopsy sample was strongly associated with adverse outcome after definitive therapy.
- The CCR score provides additive diagnostic and therapeutic data which can be used to guide intensity of therapeutic intervention in patients who need treatment.