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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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Abstract #MP11

INTRODUCTION

- 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 evaluated 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.

METHODS

COHORT

- 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]

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 x CCP) + (0.39 x CAPRA).

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.

RESULTS

- In the combined cohort, 3.3% (35/1,062) of the patients progressed to metastatic disease by 10 years.
- Despite significant differences between the individual cohorts for all clinical and molecular variables except pre-biopsy PSA (Table 1), the differences between the cohorts were not significant in the multivariable analysis (p=0.37) (Table 2).
- There was no difference in the distribution of CCP scores between the cohorts (p=0.69).

Table 1. Clinical Characteristics and Outcomes by Cohort

	Ochsner Clinic		Bishoff et al.	
Clinical 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	6.0 (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)
Gleason Score (Diagnostic Biopsy)	**N**	**Frequency**	**N**	**Frequency**
< 7	333	51.5%	236	62.4%
3 + 4 = 7	156	24.1%	86	22.8%
4 + 3 = 7	61	9.4%	28	7.4%
> 7	96	14.9%	28	7.4%
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 Follow-Up Time (IQR)***	**event/N (%)**	**Median Follow-Up Time (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)

*Men who had not experienced event and were alive at the end of follow-up

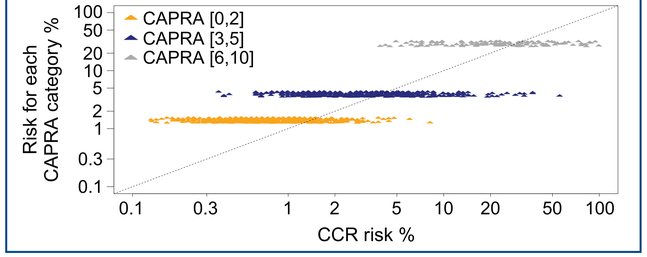
- The CCP score was strongly associated with a 10-year risk of metastatic disease in multivariable analysis (p=1.9x10^{-6}) after adjusting for CAPRA and treatment (Table 2).
- The amount of new prognostic information provided by the CCR score is illustrated by comparing the difference in predicted risk between CCR and CAPRA (Figure 1).
  - The C-index was 0.857 for CAPRA and improved to 0.894 for CCR, indicating that the new information is clinically relevant.

Table 2. Univariate and Multivariable Cox Models - Metastasis in Combined Ochsner and Bishoff Cohorts

Variable	Hazard Ratio* (95% Confidence Interval)	P-Value
Univariate		
CCR score	4.00 (2.97, 5.47)	6.3x10^{-21}
CCP score	2.93 (2.21, 3.90)	1.8x10^{-11}
CAPRA	1.75 (1.53, 2.00)	4.2x10^{-15}
Ancestry (AA/non-AA)	0.62 (0.27, 1.43)	0.24
Treatment (EBRT/RP)	5.14 (2.58, 10.23)	4.5x10^{-6}
Cohort	3.98 (1.64, 9.69)	6.1x10^{-4}
Multivariable		
CCP score	2.21 (1.64, 2.98)	1.9x10^{-6}
CAPRA	1.61 (1.37, 1.90)	1.3x10^{-8}
Treatment (EBRT/RP)	1.36 (0.58, 3.20)	0.48
Cohort	1.63 (0.55, 4.78)	0.37

*Hazard Ratio per unit score
AA, African American

Figure 1. Predicted Risk of Prostate Cancer Metastasis within 10 Years



- CCR accounts for variability in the clinical information (p-value of CAPRA after adjusting for CCR is 0.721) and molecular component (p-value of CCP after adjusting for CCR is 0.718).
- There was no evidence of interaction between CCR and ancestry (p=0.39), CCR and treatment (p=0.78), and CCR and cohort (p=0.86).
- Observed patient CCR-based predicted risks for metastatic disease by 10 years ranged from 0.1% to 99.4%, (IQR: 0.7%, 4.6%).

Figure 2. 7-year Risk in Ochsner and Bishoff (2014) Cohorts

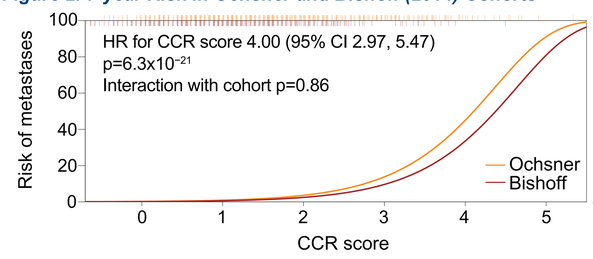
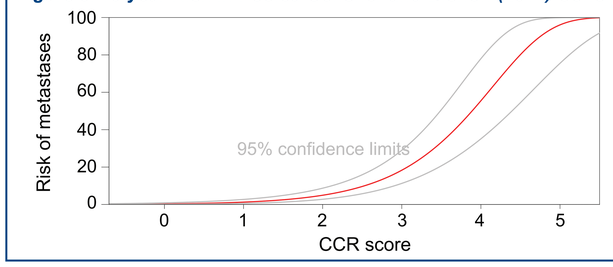


Figure 3. 10-year Risk in Pooled Ochsner and Bishoff (2014) Cohorts



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.

REFERENCES

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