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

INTRODUCTION

- The cell cycle progression (CCP) score is a validated prognostic molecular RNA signature that has proven utility in various clinical settings.1,2
- 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
- In the combined cohort, 3.3% (35/1,062) of the patients progressed to metastatic disease after a median follow-up time of 56 months.2
- 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).2
- There was no difference in the distribution of CCP scores between the cohorts (p=0.69).

RESULTS

- The CCP score was strongly associated with a 10-year risk of metastatic disease in multivariable analysis (p=10-6) after adjusting for CAPRA and treatment (Table 2).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).2
- The C-index was 0.857 for CAPRA and improved to 0.894 for CCR, indicating that the new information is clinically relevant.

METHODS

- 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).2
- 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=1,062); Ochsner Clinic, New Orleans, Louisiana (n=646).2

MOLECULAR TESTING

- Formalin-fixed paraffin embedded biopsy tissue was analyzed for the expression levels of 31 CCP genes in 646 patients from the Ochsner Clinic cohort and 416 patients from the Bishoff et al. cohort.
- 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 clinical and molecular variables.2
- We also evaluated the performance of a CCR score for predicting metastatic disease and derived a CCR-based risk curve: CCR = (0.57 x CCP) + (0.39 x CAPRA).2

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.2
- We also performed a univariate and multivariable analysis of patients who received definitive therapy.
- 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
- CCR accounts for variability in the clinical information (p-value of CAPRA after adjusting for CCR is 0.718).2
- 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).
- Yes, the patient CCR-based predicted risks for metastatic disease by 10 years ranged from 0.1% to 99.4%, (IQR: 0.7%, 4.6%).2

CONCLUSIONS

- The CCP score derived from biopsy sample was strongly associated with adverse outcome after definitive therapy.2
- 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

1. Bishoff et al. (2014) Cohorts
2. Ochsner Clinic, Ochsner Clinic
3. Martini Clinic, Hamburg, Germany; Durham VA Medical Center, Durham, NC; Intermountain Healthcare, Murray, UT (n=1,062); Ochsner Clinic, New Orleans, Louisiana (n=646)
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13. Yes, the patient CCR-based predicted risks for metastatic disease by 10 years ranged from 0.1% to 99.4%, (IQR: 0.7%, 4.6%).

Table 1. Clinical Characteristics and Outcomes by Cohort

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Ochsner Clinic N</th>
<th>Bishoff et al. N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years</td>
<td>646</td>
<td>416</td>
</tr>
<tr>
<td>Pre-biopsy PSA, ng/ml</td>
<td>646</td>
<td>416</td>
</tr>
<tr>
<td>Positive cores, %</td>
<td>646</td>
<td>416</td>
</tr>
<tr>
<td>CCR score</td>
<td>646</td>
<td>416</td>
</tr>
<tr>
<td>Gleason Score (Diagnosis)</td>
<td>333</td>
<td>236</td>
</tr>
<tr>
<td>Clinical T Stage</td>
<td>71</td>
<td>76</td>
</tr>
<tr>
<td>CAPRA Risk Category</td>
<td>151</td>
<td>154</td>
</tr>
<tr>
<td>Intermediate (3–5)</td>
<td>289</td>
<td>202</td>
</tr>
<tr>
<td>High (6–10)</td>
<td>100</td>
<td>27</td>
</tr>
<tr>
<td>Clinical Outcomes</td>
<td>258</td>
<td>187</td>
</tr>
<tr>
<td>Progression to Metastatic disease</td>
<td>23/946</td>
<td>4.3% (4.0, 6.8)</td>
</tr>
</tbody>
</table>

The CCP score was strongly associated with a 10-year risk of metastatic disease in multivariable analysis (p=10-6) after adjusting for CAPRA and treatment (Table 2).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).2

The C-index was 0.857 for CAPRA and improved to 0.894 for CCR, indicating that the new information is clinically relevant.

The CCP score was strongly associated with a 10-year risk of metastatic disease after a median follow-up time of 56 months.2

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).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio* (95% Confidence Interval)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR score</td>
<td>4.00 (2.97, 5.47)</td>
<td>6.3x10^{-11}</td>
</tr>
<tr>
<td>CAPRA score</td>
<td>2.93 (2.21, 3.90)</td>
<td>1.8x10^{-9}</td>
</tr>
<tr>
<td>Anomaly (AA/non-AA)</td>
<td>0.62 (0.27, 1.43)</td>
<td>0.24</td>
</tr>
<tr>
<td>Treatment (EBRT/RP)</td>
<td>5.14 (2.89, 10.23)</td>
<td>4.5x10^{-3}</td>
</tr>
<tr>
<td>CCR cohort</td>
<td>3.98 (1.84, 9.89)</td>
<td>6.1x10^{-1}</td>
</tr>
<tr>
<td>Multivariable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCP score</td>
<td>2.21 (1.64, 2.98)</td>
<td>1.9x10^{-3}</td>
</tr>
<tr>
<td>CAPRA</td>
<td>1.61 (1.37, 1.90)</td>
<td>1.3x10^{-3}</td>
</tr>
<tr>
<td>Treatment (EBRT/RP)</td>
<td>1.36 (0.58, 3.20)</td>
<td>0.48</td>
</tr>
<tr>
<td>CCR cohort</td>
<td>1.63 (0.55, 4.78)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Hazard Ratio per unit score

AA, African American

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

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

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

0 1 2 3 4 5 6 7 8 9 10
0 1 2 3 4 5

Ochsner Bishoff

0 1 2 3 4 5 6 7 8 9 10
0 1 2 3 4 5

Risk of metastases

95% confidence limits

This study was funded by Myriad Genetics, Inc. Please email Daniel Canter (daniel.canter@ochsner.org) with any questions or comments.