INTRODUCTION

- Standard clinical parameters can risk-stratify prostate cancers to aid treatment decision-making.
- However, in light of ongoing over-treatment of low-risk disease and undertreatment of occult high-risk disease, novel biomarkers are needed which can help predict tumor behavior with greater accuracy.
- We aimed to validate a previously described expression panel of cell-cycle progression (CCP) genes in predicting recurrence in a contemporary cohort of man undergoing radical prostatectomy (RP).

METHODS

- 413 men treated at UCSF with radical prostatectomy who had >5 years followup after surgery
- RNA extracted from FFPE RP specimens, expression levels of 46 genes determined in triplicate using TaqMan low-density arrays
- CCP score = average expression of 31 CCP genes, normalized to 15 housekeeper genes.
- Postoperative risk by standard variables determined via CAPRA-S score, based on preoperative PSA, pathologic Gleason grade, and pathologic staging variables (ECE, SVI, LN involvement, and SM status)
- Biochemical progression = PSA >0.2 with verification or any second treatment
- Based on a Cox regression model, a combined CAPRA-S + CCP score was defined as 0.38 * CAPRA-S + 0.57 * CCP.
- Discrimination and calibration assessed via c-index, prediction models, and decision curve analysis

RESULTS

- CAPRA-S scores ranged from 0 to 10, and CCP scores from -1.62 to 2.16 (figure 1).
- 67 / 28 / 6% of patients were low, intermediate, or high risk by the criterion of CAPRA-S score 0-2 / 3-5 / ≥6.
- 19.9% progressed at median 34 months; median followup for censored pts was 88 months.
- The CCP score effectively stratified the cohort in terms of recurrence risk, and sub-stratified both clinically low- and intermediate/high-risk groups as defined by CAPRA-S scores (figure 2, table 1).
- The CCP score was well-validated in this external RP cohort, and was demonstrated to offer independent prognostic information beyond PSA, Gleason grade, and pathologic staging variables.
- The CCP score is notably able to sub-stratify both the low- and intermediate/high-risk subgroups as defined by clinical criteria
- The CAPRA-S + CCP combined score demonstrates excellent discrimination and calibration, and performs better than either score alone in predicting outcomes after RP.
- These findings may help men make better-informed decisions regarding treatment after surgery; with further validation in biopsy tissue, the CCP score will likely facilitate initial treatment decision-making as well.

CONCLUSIONS

- The CCP score was well-validated in this external RP cohort, and was demonstrated to offer independent prognostic information beyond PSA, Gleason grade, and pathologic staging variables.
- The CCP score is notably able to sub-stratify both the low- and intermediate/high-risk subgroups as defined by clinical criteria
- The CCP score effectively stratified the cohort in terms of recurrence risk, and sub-stratified both clinically low- and intermediate/high-risk groups as defined by CAPRA-S scores (figure 2, table 1).
- The CCP score alone could predict risk of recurrence across the range of risk with the combined CAPRA-S + CCP score.

Figure 1: Panels A and B present histogram distributions for CAPRA-S and CCP scores. Panel C shows a scatter plot of CAPRA-S vs. CCP score, and panel D shows risk of recurrence as determined by CAPRA-S alone vs. CAPRA-S + CCP combined score.

Figure 2: Kaplan-Meier survival analysis by CCP score. Survival curves are presented for the overall cohort (panel A), for clinically low-risk (CAPRA-S 0-2) patients (panel B), and for clinically intermediate/high-risk (CAPRA-S ≥3) patients (panel C).

Figure 3: Based on a Weibull regression model, predicted 10-year recurrence was estimated across the cohort for the CCP score (panel A) and for the CAPRA-S + CCP combined score (panel B). The combined score in particular covered the full range of risk, and with narrow confidence intervals (dashed lines).

Figure 4: Decision curve analysis: the CCP score and CAPRA-S score provided actionable information across threshold probabilities ranging from 10% to 55%, but the greatest net benefit, indicative of discrimination and calibration, was gained across the range of risk with the combined CAPRA-S + CCP score.

Table 1: Cox regression results for CCP score alone, and with control for clinical variables. Adjusted model 1: CCP and the CAPRA-S score. Adjusted model 2: CCP, PSA, pGSI, age, year of treatment, ECE, SVI, LN involvement, and SM status.

<table>
<thead>
<tr>
<th>CCP score</th>
<th>Univariate</th>
<th>Adjusted model 1</th>
<th>Adjusted model 2</th>
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<tr>
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<td>HR p 95% CI</td>
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<td>3.1 - 70.3</td>
<td>9.4 0.005</td>
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Figure 3A: Kaplan-Meier survival analysis by CCP score. Survival curves are presented for the overall cohort (panel A), for clinically low-risk (CAPRA-S 0-2) patients (panel B), and for clinically intermediate/high-risk (CAPRA-S ≥3) patients (panel C).