Ability of the Combined Clinical-Cell Cycle Risk Score to Identify Patients who Benefit from Multi versus Single Modality Therapy in NCCN Intermediate and High Risk Prostate Cancer

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BACKGROUND

- Although multimodality therapies for prostate cancer can reduce the risk of recurrence and metastasis and can increase overall survival, they also substantially increase the risk of morbidity, and in some cases mortality.
- To reduce that risk, we need accurate methods to identify men with high risk of metastasis who may be candidates for these more aggressive treatments.
- We evaluated the ability of the Prolaris® clinical cell-cycle risk score (CCR) to identify men with NCCN intermediate- or high-risk localized prostate cancer who have increased risk of metastasis and who would or would not benefit from multimodality treatment.

METHODS

- Study cohort: Multi-institutional database of Prolaris-tested men with intermediate- or high-risk prostate cancer (N=718) (Table 1).
- The clinically validated CCR score combines RNA expression analysis of cell cycle progression (CCP) genes with the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score (0.39 × CAPRA + 0.57 × CCP).
  - A CCR "multimodality threshold" score of >2.112 was defined using a cohort of men with NCCN unfavorable intermediate- or high-risk disease and known CCR scores.
- Multimodality was defined as combined use of androgen deprivation therapy with radiation (RT) or surgery, or surgery with adjuvant RT.
- Kaplan-Meier and Cox regression analyses were used to estimate the effects of prognostic covariates on metastasis risk: CCR, CCP, NCCN risk group, CAPRA, and single versus multimodality therapy.

RESULTS

- 33.3% (239/718) of men had CCR scores above the multimodality threshold (>2.112) (Table 1).
- CCR predicted metastasis (HR=3.75 95% CI [2.7, 5.2], P=1.6x10^{-16}) and remained highly predictive after adjusting for the effect of CAPRA (HR=4.30 [2.65, 6.96], P=4.4x10^{-8}) (Table 2).
- CCR also was a significant predictor of metastasis in the subset of patients who received single modality treatment, as a continuous predictor (HR=3.97 [2.61, 6.06], P=1.6x10^{-10}) and when dichotomized at the multimodality threshold (HR=15.90 [5.43, 46.52], P=8.1x10^{-10}) (Table 2).

Table 1. Demographics of the study population.

Below-Threshold includes men with CCR scores ≤2.112; Above-Threshold includes men with CCR scores >2.112.

	Full Cohort N=718 Median (IQR) or N (%)	Below-Threshold n=479 Median (IQR) or n (%)	Above-Threshold n=239 Median (IQR) or n (%)
NCCN Risk Category			
Favorable Intermediate	171 (23.8%)	167 (34.9%)	4 (1.7%)
Unfavorable Intermediate	354 (49.3%)	259 (54.1%)	95 (39.8%)
High	193 (26.9%)	53 (11.1%)	140 (58.6%)
CAPRA	**4 (3, 5)**	**3 (3, 4)**	**6 (5, 7)**
<3	94 (13.1%)	94 (19.6%)	0 (0%)
3-7	592 (82.5%)	385 (80.4%)	207 (86.6%)
>7	32 (4.5%)	0 (0%)	32 (13.4%)
Treatment			
Single modality RT	116 (16.2%)	92 (19.2%)	24 (10.0%)
Multimodal RT	116 (16.2%)	25 (5.2%)	91 (38.1%)
Single modality RP	445 (62.0%)	339 (70.8%)	106 (44.4%)
Multimodal RP	41 (5.7%)	23 (4.8%)	18 (7.5%)
Ancestry			
African American	183 (25.5%)	107 (22.3%)	76 (31.8%)
Caucasian	530 (73.8%)	368 (76.8%)	162 (67.8%)
Other	5 (0.7%)	4 (0.8%)	1 (0.4%)

CAPRA, UCSF Cancer of the Prostate Risk Assessment; NCCN, National Comprehensive Cancer Network; RP, radical prostatectomy; RT, radiation therapy.

- There was no benefit to multimodality therapy in men CCR scores ≤2.112 (HR=1.13 [0.12, 10.68], P=0.91), whereas those with scores >2.112 had a significant benefit (HR=0.43 [0.20, 0.92], P=0.03) (Figure 1).
- When accounting for CCR and treatment modality in the full cohort, Multimodality treatment reduced patients' risk of metastasis (HR=0.46 [0.22,0.97], P=0.039) (Figure 2).

Table 2. Cox regression and concordance (Harrell's C-index) analyses.

Univariate and bivariate analyses.

	Hazard Ratio	95% CI	P	Concordance (C-index)
Univariable Analyses				
CCP	2.63	2.01, 3.43	1.1 x 10^{-10}	0.79
CAPRA	1.65	1.42, 1.93	5.4 x 10^{-11}	0.80
CCR	3.75	2.71, 5.20	1.6 x 10^{-16}	0.87
NCCN Risk Group				
Favorable Intermediate	reference	—	8.6 x 10^{-7}	0.76
Unfavorable Intermediate	6.13	0.80, 47.12		
High	21.82	2.95, 161.31		
CCR Split by Modality				
Single Modality Only	3.97	2.61, 6.06	1.6 x 10^{-10}	0.87
Multimodality Only	5.53	2.66, 11.51	1.2 x 10^{-7}	0.90
Bivariable Analyses				
CCR + CAPRA				
CCR	4.30	2.65, 6.96	4.4 x 10^{-8}	0.87
CAPRA	0.91	0.7, 1.18	0.47	
CCR + NCCN Risk Group				
CCR	3.74	2.46, 5.68	2.0 x 10^{-10}	0.87
Favorable Intermediate	reference	—	0.80	
Unfavorable Intermediate	1.84	0.23, 14.93		
High	1.61	0.18, 14.60		

CAPRA, UCSF Cancer of the Prostate Risk Assessment; CCP, cell cycle progression; CCR, clinical cell-cycle risk; NCCN, National Comprehensive Cancer network.

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Figure 1. Kaplan-Meier risk estimates for (A) metastasis and (B) progression, stratified by CCR above and below the threshold, and by single or multimodality therapy.

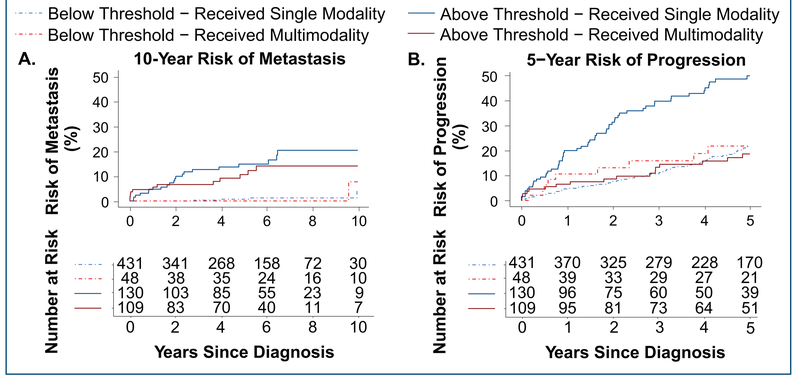
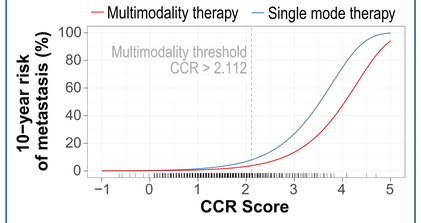
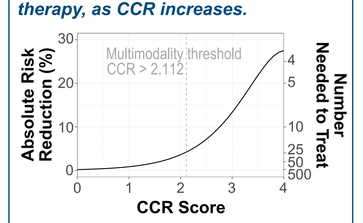


Figure 2. Risk prediction for metastasis at 10 years, stratified by single or multimodality therapy and by CCR.



CCR, clinical cell-cycle risk

Figure 3. Absolute risk reduction and number needed to treat using multimodality versus single modality therapy, as CCR increases.



CCR, clinical cell-cycle risk

- 10-year risk can be used to determine a continuum of the number needed to treat (NNT) with multimodality versus single modality therapy at any CCR score to prevent a metastasis (Figure 3).

CONCLUSIONS

- The CCR multimodality threshold score prognosticates a clinically meaningful benefit for those who receive multimodality versus single-modality treatment.