Development and Validation of an Active Surveillance Threshold Based on the CCP score and CAPRA to Predict Risk of Aggressive Disease

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BACKGROUND

- Active surveillance (AS) is an appropriate and increasingly utilized treatment modality for men with localized prostate cancer.
- Better risk stratification is needed to appropriately select men for AS.
- The cell cycle progression (CCP) score is based on the expression of 31 genes involved in CCP.[1,2]
- CCP Score has proven to be a robust predictor of prostate cancer outcomes in various clinical settings including conservatively managed cohorts.[3]
- We developed and validated potential AS thresholds based on a combined CCP score with CAPRA (pre-defined as the combined clinical-cell-cycle risk (CCR) score[4]) for prediction of prostate cancer mortality in men considering deferred treatment.

METHODS

- A training cohort of men who underwent commercial CCP testing between August 2012 and October 2013 was used to develop two different CCR thresholds based on AUA[5] and NCCN[6] guidelines (Table 1).
  - Thresholds were selected such that 90% of the men in the training cohort had scores below the threshold.

Table 1. Clinical criteria for CCR threshold development

	AUA-based (N=385)	NCCN-based (N=505)
Gleason Score	≤ 3+3	≤ 3+4
PSA (ng/mL)	< 10	< 10
Positive Cores (%)	< 25%	< 25%
Clinical Stage	≤ T2a	≤ T2a
CCR Threshold	0.6	0.8

- The performance of both thresholds was evaluated in:
  - An independent validation cohort of men with prostate cancer who were initially conservatively managed (N=765) (survival data were censored at 10 years)
  - A consecutive series of 7,881 men who were submitted for commercial testing at Myriad Genetic Laboratories, Inc.

RESULTS

- Both thresholds dichotomized the validation cohort into high and low risk groups (p=0.012 and 0.00048, respectively) (Figure 1).
- There were no deaths in patients below either threshold, and the Cox proportional hazard estimates of 10-year prostate cancer mortality (PCM) associated with the CCR thresholds of 0.6 and 0.8 were 2.7% and 3.2%, respectively (Figure 2).

Figure 1. CCR score distribution in men within the training cohort who may be considered good candidates for AS based on clinical characteristics

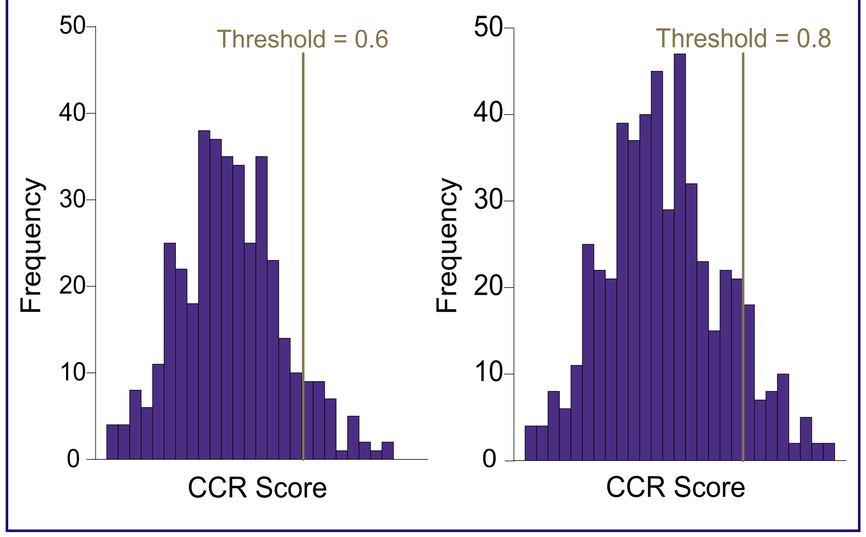
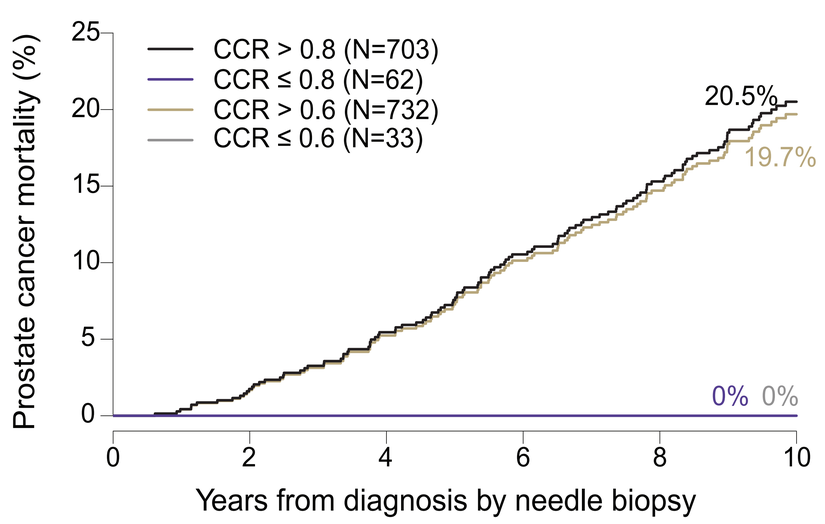


Figure 2. Kaplan-Meier plot showing prostate cancer mortality



- Using the more liberal NCCN criteria for AS to evaluate the commercial cohort, 36% of the patients qualified based on clinical parameters alone.
- When applying the threshold of 0.8 to this cohort, 60% had CCR scores below the AS threshold and, therefore, had estimated risks of aggressive disease that were consistent with typical AS patients (Table 2).

Table 2.Clinical summary of all patients in the commercial cohort and those who would qualify for AS based on the NCCN-based CCR score threshold

		All Patients*	All Patients with CCR Score ≤ 0.8 (N=4,758)
Age at Diagnosis (yr)	n	7881	4758
	mean ± sd	66.6 ± 8.3	64.9 ± 7.9
	IQR	(61 to 72)	(60 to 70)
PSA (ng/mL)	0 – 4	1436 (18.2%)	1151 (24.2%)
	4.01 – 10	5244 (66.5%)	3394 (71.3%)
	>10	1201 (15.2%)	213 (4.5%)
Positive Cores (%)	n	7867	4758
	mean ± sd	29.6 ± 21.6	22.7 ± 15.6
	IQR	(15.4 to 41.7)	(8.3 to 30.8)
Gleason Score	4	1 (<0.1%)	1 (<0.1%)
	5	11 (0.1%)	10 (0.2%)
	6	4068 (51.6%)	3543 (74.5%)
	3+4=7	2461 (31.2%)	1176 (24.7%)
	4+3=7	814 (10.3%)	20 (0.4%)
	5+2=7	1 (<0.1%)	0
	8	346 (4.4%)	6 (0.1%)
	9	158 (2.0%)	2 (<0.1%)
	10	21 (0.3%)	0
Clinical Stage	T1	6106 (77.5%)	3975 (83.6%)
	T2	1733 (22.0%)	783 (16.5%)
	T3	42 (0.5%)	0
AUA Risk Category	Low	3497 (44.4%)	3208 (67.4%)
	Intermediate	3428 (43.5%)	1442 (30.3%)
	High	956 (12.1%)	108 (2.3%)

*14 patients have missing information regarding qualification for active surveillance

CONCLUSIONS

- The thresholds presented here are based on an integrated risk assessment that combines both clinicopathologic and molecular features for a better prediction of disease outcome, and as such, could enable more appropriate selection of patients for AS.

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