APPLICATION OF ACTIVE SURVEILLANCE THRESHOLD TO SERIES OF SAMPLES SUBMITTED FOR COMMERCIAL TESTING

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INTRODUCTION

- Active surveillance (AS) is an increasingly popular treatment modality for men with localized prostate cancer.
- Recently, we developed a method to select men for AS based on a score that combines cell cycle progression (CCP) with CAPRA (combined clinical CCP risk (CCR) score).
- Here, we apply our validated AS CCR threshold to a series of samples submitted for commercial testing.

METHODS

Patients

- Samples from 11,665 patients were submitted by their physicians to Myriad Genetic Laboratories for CCP analysis with sufficient tissue for testing.
- Patient clinicopathological data were obtained from the test request form.

Gene Expression Testing

- Formalin-fixed paraffin-embedded surgical tumor samples were analyzed for the expression levels of 31 CCP genes and 15 house-keeping genes by quantitative RT-PCR.
- The CCP Score is an un-weighted average of the cell cycle genes normalized by the average of housekeeping genes.
- Scores ranged from -2.9 to 4.1.
- The CCR score is the proportional hazard model combination of CAPRA and CCP scores
  - (0.57 × CCP score) + (0.39 × CAPRA score)

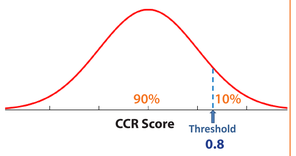
Statistical Methods

- The clinicopathological data of patients with a CCR score meeting the AS threshold (≤ 0.8) were analyzed focusing on their PSA, % positive cores, Gleason score, stage, AUA risk classification, and CAPRA score.

CCR THRESHOLD

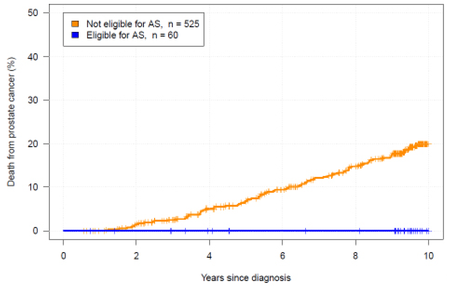
- A CCR threshold has been previously developed in a training cohort of men who might typically be considered for AS based on their clinical characteristics alone (N=505).
  - The training cohort consisted of men with: Gleason score ≤ 3+4, PSA < 10 ng/ml, < 25% cores positive, Clinical stage ≤ T2a.
- A threshold of 0.8 was selected such that 90% of the men in the training cohort had scores below the threshold (Figure 1).
- This threshold was validated in two independent cohorts of conservatively managed men with known outcomes (combined N=765).

Figure 1. CCR threshold in training cohort



- In the validation cohort, the average risk was 2.6% for men below the threshold (low risk) and 21.4% for men above the threshold (high risk) (Figure 2).
  - There were no prostate cancer deaths in patients below the threshold (survival data were censored at 10 years).

Figure 2. Disease specific risk for low and high risk groups in the combined validation cohort



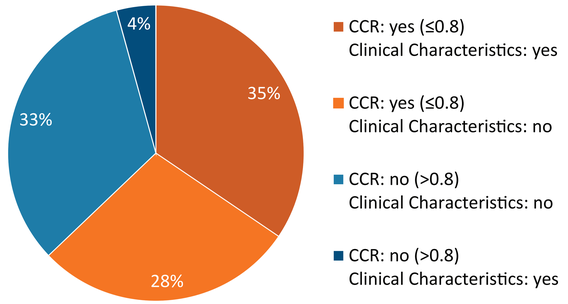
RESULTS

Table 1. Clinical Characteristics of Men with a CCR ≤ 0.8

Variable		All Patients with CCR Score ≤ 0.8 (N=7,325)	Qualifies for AS using Clinical Characteristics (N=4,019)	Does not Qualify for AS using Clinical Characteristics (N=3,306)
Age at Diagnosis (years)	N	7,325	4,019	3,306
	mean ± sd	64.6 ± 7.9	64.4 ± 7.7	64.8 ± 8.1
	min, max	27, 93	39, 91	27, 93
PSA (ng/ml)	0 – 4	1,715 (23.4%)	1,036 (25.8%)	679 (20.5%)
	4.01 – 10	5,318 (72.6%)	2,983 (74.2%)	2,335 (70.6%)
	> 10	292 (4.0%)	0	292 (8.8%)
Positive Cores (%)	N	7,325	4,019	3,306
	mean ± sd	22.4 ± 15.4	12.6 ± 4.6	34.3 ± 15.7
	min, max	0, 100	0, 24.1	2.1, 100
Gleason Score	4	1 (<0.1%)	1 (<0.1%)	0
	5	14 (0.2%)	12 (0.3%)	2 (0.1%)
	6	5,647 (77.1%)	3,290 (81.9%)	2,357 (71.3%)
	3+4=7	1,620 (22.1%)	716 (17.8%)	904 (27.3%)
	4+3=7	30 (0.4%)	0	30 (0.9%)
	5+2=7	0	0	0
	8	11 (0.2%)	0	11 (0.3%)
	9	2 (<0.1%)	0	2 (0.1%)
	10	0	0	0
Clinical Stage	T1a	216 (2.9%)	169 (4.2%)	47 (1.4%)
	T1b	60 (0.8%)	37 (0.9%)	23 (0.7%)
	T1c	5,896 (80.5%)	3,354 (83.5%)	2,542 (76.9%)
	T2a	796 (10.9%)	459 (11.4%)	337 (10.2%)
	T2b	222 (3.0%)	0	222 (6.7%)
	T2c	133 (1.8%)	0	133 (4.0%)
	T3a	2 (<0.1%)	0	2 (0.1%)
	T3b	0	0	0
AUA Risk Classification	Low Risk	5,183 (70.8%)	3,303 (82.2%)	1,880 (56.9%)
	Intermediate Risk	1,984 (27.1%)	716 (17.8%)	1,268 (38.4%)
	High Risk	158 (2.2%)	0	158 (4.8%)
CAPRA Score	Low (0–2)	6,244 (85.2%)	3,856 (95.9%)	2,388 (72.2%)
	Intermediate (3–5)	1,081 (14.8%)	163 (4.1%)	918 (27.8%)
	High (≥6)	0	0	0

- Of the 11,665 patients included in the analysis, 7,325 (62.8%) qualified for AS based on their CCR score.
- A summary of the patients' clinicopathological characteristics is shown in Table 1.
- A substantial number of these patients, 3,306 (45.1%), would not have qualified for AS based on their clinical characteristics alone (Figure 3).

Figure 3. Qualifying for AS Based on CCR and/or Clinical Characteristics



CONCLUSIONS

- A CCR threshold of 0.8 has been previously validated in a large cohort with known outcomes, with no deaths in low risk men.
- This analysis showed that 62.8% of commercially tested patients qualified for AS, nearly half of whom would not have qualified for AS based on their clinicopathological characteristics alone.
- For patients considering deferred treatment, the CCR score provides significant prognostic information at disease diagnosis.

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