Identification of Men with Low-Risk Biopsy-Confirmed Prostate Cancer as Candidates for Active Surveillance

Running Title: Detection of Men with Low-Risk Prostate Cancer

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Highlights

- A combined clinical cell-cycle risk (CCR) score has demonstrated in numerous retrospective studies to improve risk stratification compared to clinical variables alone.
- CCR score thresholds were developed to select men for active surveillance (AS).
- Owing to improved risk stratification, these thresholds should improve selection of AS candidates over clinical features alone.

ABSTRACT

Background: A combined clinical cell-cycle risk (CCR) score that incorporates prognostic molecular and clinical information has been recently developed and validated to improve prostate cancer mortality (PCM) risk stratification over clinical features alone. As clinical features are currently used to select men for active surveillance (AS), we developed and validated a CCR score threshold to improve the identification of men with low-risk disease who are appropriate for AS.

Methods: The score threshold was selected based on the 90th percentile of CCR scores among men who might typically be considered for AS based on NCCN low/favorable-intermediate risk criteria (CCR=0.8). The threshold was validated using 10-year PCM in an unselected, conservatively managed cohort and in the subset of the same cohort after excluding men with high-risk features. The clinical impact was evaluated in a contemporary clinical cohort.

Results: In the unselected validation cohort, men with CCR scores below the threshold had a predicted mean 10-year PCM of 2.7%, and the threshold significantly dichotomized low- and high-risk disease ($p=1.2 \times 10^{-5}$). After excluding high-risk men from the validation cohort, men with CCR scores below the threshold had a predicted mean 10-year PCM of 2.3%, and the threshold significantly dichotomized low- and high-risk disease (p=0.020). There were no prostate cancer-specific deaths in men with CCR scores below the threshold in either analysis. The proportion of men in the clinical testing cohort identified as candidates for AS was substantially higher using the threshold (68.8%) than using clinicopathologic features alone (42.6%), while mean 10-year predicted PCM risks remained essentially identical (1.9% vs. 2.0%, respectively).

Conclusions: CCR score thresholds appropriately dichotomize patients into low- and high-risk groups for 10-year PCM, and may enable more appropriate selection of patients for AS.

1 INTRODUCTION

Wide adoption of PSA screening has resulted in earlier prostate cancer diagnosis and is a likely factor in the reduction of disease-specific mortality [1,2]. However, this intensive population screening has also increased the identification of patients with indolent disease [3-5]. As a result, many men with screen-detected cancer are over-treated and needlessly suffer treatment-related side effects without a meaningful change in prognosis. Recent studies have shown that deferred treatment options, such as active surveillance (AS), are a safe way for men with newly diagnosed low-risk disease to minimize these adverse effects [6].

Traditionally, patients have been selected for AS based on prognostic clinicopathologic variables that are evaluable at disease diagnosis, including Gleason score, PSA, clinical stage, PSA density, and percent of needle cores that contain tumor. However, better stratification of patients with low-grade localized disease is needed. In addition, AS selection criteria from the American Urological Association (AUA) [7] and National Comprehensive Cancer Network (NCCN) [8] differ and there are numerous additional variations in the literature [9-11]. Collectively, these uncertainties can lead to misclassification of patient risk and increased anxiety in both patients and physicians when selecting AS.

A combined clinical cell-cycle risk (CCR) score has been recently developed to improve prostate cancer risk stratification. This score incorporates a prognostic molecular risk score based on the expression of 31 cell-cycle progression (CCP) genes [12,13] with clinicopathologic risk from the Cancer of the Prostate Risk Assessment (CAPRA) model [14]. This combined molecular and clinical model has been previously validated in a cohort of conservatively managed men and provides a superior discrimination of 10-year prostate cancer-specific mortality (PCM) risk relative to molecular or clinicopathologic parameters alone [15].

As clinicopathologic information is currently the standard for identifying men for AS, we hypothesized that the CCR score would improve the selection of men with low-risk prostate cancer who are appropriate for AS. To this end, we developed and validated a predefined CCR

score threshold to identify high- and low-risk disease in order to select suitable candidates for AS. The CCR score threshold was developed in men who might typically be considered for AS based on NCCN guidelines and validated in a cohort of conservatively managed men with long-term clinical outcomes. In addition, we evaluated the ability of the CCR threshold scores to alter the selection of patients for AS in a contemporary clinical cohort of men with localized disease.

2 MATERIALS AND METHODS

2.1 Patients

2.1.1 *Training Cohort*

CCR score threshold was developed in a training cohort of men who underwent clinical testing (Myriad Genetic Laboratories, Salt Lake City, UT) between August 2012 and September 2013 (N=1718). Samples were required to be from a post-2005 diagnostic biopsy and of good quality, as defined by having a mean C_t for housekeeper genes <22 (95th percentile of housekeeper C_t). All patients provided consent for clinical testing and all clinical information was obtained from the test request form (TRF).

Clinicopathologic data from the TRF was used to select a subset of men who might be considered for AS based on modified NCCN guidelines (**Figure 1**). Specifically, we selected a subset of men with low/favorable intermediate-risk disease based on a conservative interpretation of NCCN guidelines: Gleason score ≤3+4; PSA <10 ng/mL; <25% positive cores; T-stage ≤T2a (N=505) [8]. This subset was used to select a CCR score threshold in men with low/favorable-intermediate clinicopathologic AS based NCCN guidelines.

2.1.2 *Validation Cohort*

The ability of the CCR score threshold to separate patients with high- and low-risk disease was validated in a cohort of conservatively managed men with needle biopsy-detected disease and long-term outcomes. Cases of adenocarcinoma of the prostate (N=585) diagnosed between 1990 and 2003 (median diagnosis date May 2002; IQR January 2001, May 2003) were

identified from three cancer registries in Great Britain (**Figure 1**). This cohort has been previously described and was used to validate the CCR score model, but not the CCR score threshold [15]. The full cohort description is provided in the **Supplemental Materials**. We also validated the threshold in a modified validation cohort that more closely resembles the spectrum of clinicopathologic features among men who may be considering AS. This was done by evaluating the performance of the threshold after excluding men from the validation cohort with high-risk disease (PSA > 20 ng/ml or Gleason score ≥ 8 or clinical stage ≥ T2C). Unless otherwise specified, risk estimates for DSM presented in this paper are based on risk curves derived from the entire validation cohort. National ethics approval was obtained from the Northern Multicentre Research Ethics Committee, followed by local ethics committee approval at each collaborating hospital.

2.1.3 *Evaluation of AS Threshold in a Modern Clinical Cohort*

The potential clinical impact of selecting men for AS using the CCR threshold score was evaluated in a sequential, unselected set of 19,215 patients whose diagnostic biopsies were submitted for clinical testing (Myriad Genetic Laboratories) by their physician between October 2013 and December 2016 (**Figure 1**). Patients underwent consent for testing and clinical data obtained from the TRF was used to determine whether patients met NCCN criteria for AS based on clinicopathologic features alone. Clinical follow-up was not collected as part of clinical testing.

2.2 Molecular Testing

All samples were processed as previously described [16]. In brief, the expression of 31 CCP genes and 15 housekeeper genes was measured by quantitative RT-PCR. The CCP score was calculated as the un-weighted average of the CCP gene expression normalized by the average expression of the housekeeper genes [12,13]. The CCR score is the proportional hazard model combination of CAPRA (clinical variables) [14] and the molecular CCP score,

calculated as CCR=(0.39xCAPRA)+(0.57xCCP). This formula was optimized to predict adverse disease outcome in a study combining four previously published prostate cancer cohorts [17], and validated to predict 10-year PCM [15].

2.3 Statistics

The Firth penalized likelihood test was used to compare survival curves of patients in the validation cohort with CCR scores above and below the threshold score. Cox proportional hazards models were used to estimate the 10-year risk of PCM associated with the threshold score. The beta product confidence procedure for the Kaplan-Meier estimator was used to calculate a one-sided confidence interval (CI) for the negative predictive value (NPV) for patients with CCR scores below the threshold. Statistical analyses were conducted in R [18].

3 RESULTS

3.1 Development of CCR Threshold Scores

Table 1 describes the clinicopathologic features of men within the training cohort. There was a significant high-risk tail in the CCR score distributions within the subset of men with low/favorable-intermediate clinicopathologic features who might be considered for AS based on conservatively modified NCCN guidelines (Gleason score ≤3+4; PSA <10 ng/ml; <25% cores positive; clinical stage ≤T2a; **Figure 2**). This suggests that a proportion of men who present with low/favorable intermediate-risk clinical features may harbor higher risk disease and may not be good candidates for AS.

To accommodate this, the 90th percentile of the CCR score distribution was conservatively selected as a proposed threshold to select men who are appropriate for AS. Using this cut-off, the CCR threshold score was 0.8 (rounded from 0.8334). Men with CCR scores equal to or below the threshold are considered candidates for AS.

3.2 Validation of CCR Score Threshold

First, the CCR score threshold was validated in a cohort of 585 men who were conservatively managed, with the primary endpoint being PCM within the first 10 years of follow-up (**Table 1**). There were 60 men (10%) with CCR scores below the threshold. The threshold score was highly predictive of high (CCR >0.8) and low risk (CCR ≤0.8) of 10-year PCM (p=0.00080, **Figure 3A**) and there were no observed deaths in men with CCR scores at or below the threshold. The estimated 10-year PCM risk was 2.7% for men with CCR scores below the threshold and the risk at the threshold was 3.3% (95% CI 1.94, 5.70). The NPV for the CCR score threshold was 100% (95% lower CI 89.5%). 525 men had CCR scores above the threshold and 87 prostate cancer deaths occurred in this group.

Second, the threshold score was evaluated in modified validation cohort that excluded all men with high-risk clinicopathologic features (**Table 1**). The intent was to evaluate the performance of the AS threshold in a cohort that more closely matches the spectrum of risks in men who may be considering AS. The threshold score remained significantly predictive of high (CCR >0.8) and low risk (CCR ≤0.8) of 10-year PCM (p=0.02, **Figure 3A**). The estimated 10-year PCM risk was 2.3% for men with CCR scores below the threshold and the risk at the threshold was 2.9% (95% CI; 1.25, 6.74). As before, there were no observed deaths in men with CCR scores at or below the threshold so the calculation of NPV does not change, remaining at 100% NPV.

As the clinical criteria for selecting AS candidates is highly variable [9,10], we also developed and validated AS thresholds based on either AUA [7] or CARPA [14] risk stratification (**Supporting Information**). The performance of these alternative thresholds was qualitatively similar to the threshold at 0.8 (**Supplemental Table 1**).

Finally, we evaluated the performance of all thresholds to dichotomize high and low risk of biochemical recurrence after 10 years in a contemporary cohort of men with screen-detected prostate cancer treated by radical prostatectomy (**Supporting Information**, **Supplemental**

Table 4). This suggests that the threshold scores can differentiate high- and low-risk disease among treated men.

3.3 Clinical Impact of the CCR Threshold Score in a Modern Clinical Cohort

The potential clinical impact of identifying men for AS using the CCR score thresholds was evaluated in a consecutive group of 19,215 men who had clinical testing (**Table 1**). Overall, 8,177 (42.6%) men in the clinical cohort met criteria for AS based on low/favorable intermediate-risk clinicopathologic features. However, 13,221 of 19,215 (68.8%) men had CCR scores below the threshold (**Table 2**), with a mean 10-year PCM risk of 1.9%. **Table 3** details of the cliniocopathologic features of the extended AS population defined by the threshold. Alternative thresholds based on either AUA or CAPRA risk stratification also dramatically increased the number of men who might be considered for AS compare to clinical features only (**Supplemental Table 2**).

4 DISCUSSION

Men with newly diagnosed prostate cancer are recommended for AS based on a low risk of having aggressive disease as defined by available clinical and pathologic information. An integrated assessment of risk that incorporates prognostic molecular (CCP score) and clinical variables (CAPRA) has been recently developed. This CCR score has been shown to improve risk stratification over clinical variables alone [15]. As men are traditionally selected for AS based only on clinicopathologic features, we developed CCR score thresholds to improve the identification of men with low-risk disease.

The CCR score threshold was developed in men who might typically be considered appropriate for AS based on having low or favorable intermediate-risk disease according to a conservative interpretation of NCCN guidelines [8]. When the clinical performance was validated in conservatively managed men, the CCR score threshold significantly dichotomized men with

high- and low-risk of 10-year PCM ($p=1.2x10^{-5}$ for the full validation cohort, or p=0.02 for the modified validation cohort). Depending on the patient composition of the validation cohort, men with CCR scores below the threshold had a predicted 10-year PCM risk of about 2.5%, while the NPV (probability of survival in patients with CCR scores equal to or below the threshold) was 100% (95% lower CI 89.5%). These analyses indicate that the threshold can be safely used to identify candidates for AS.

The clinical impact of selecting men for AS using the CCR score threshold as evaluated in a modern commercial cohort and is two-fold. First, the estimated PCM risk should decrease among men considered candidates for AS based on their CCR score relative to those selected by clinicopathologic criteria. The threshold was developed based on the 90^{th} percentile of men who fulfill the typical clinical criteria for AS. Patients in the top tenth percentile of CCR risk were excluded to minimize the potential of missing occult lethal disease. As such, men who had CCR scores below the threshold had an estimated 10-year PCM risk of less than 2%. In addition, the maximum estimated 10-year PCM risk was ~16% in men who qualify for AS based on low/favorable intermediate-risk clinicopatholgic criteria; however, this was reduced to ~3% when the CCR score threshold was applied. Second, application of the CCR score threshold should result in a substantial increase in the number of men identified as candidates for AS. Many men have low/favorable intermediate-risk disease, despite having some clinical features that would traditionally exclude them from AS. In this cohort, 42.6% of men were eligible for AS based on NCCN clinicopathologic criteria. However, 68.8% qualified for AS when the CCR score threshold was used to identify AS candidates. These data suggest that there is significant clinical utility in utilizing the CCR score thresholds to select men for AS.

There are some limitations of this study, mostly related to the validation cohort. The validation cohort was composed of men who deferred curative therapy, but it was not a 'true' AS cohort in that there was little to no scheduled surveillance in the absence of symptoms of clinical progression. The cohort was retrospectively collected in order to include patients with long-term

outcomes, which may introduce unknown biases in patient composition. However, it included patients from three independent cancer registries and employed disease population-based sample collection, both of which should reduce the potential for this bias. The validation cohort also contained relatively few low-risk men, which limits the precision of our estimate for NPV. And finally, the cohort contains higher risk men then typically consider AS which is a reflection of contemporaneous disease management in the UK. As a result, the estimated risks for DSM reported here may not be representative of what would be observed in a modern AS cohort and maybe overestimated.

5 CONCLUSIONS

Here we have shown that a CCR score threshold can be used to identify men with some higher-risk features that nevertheless have low-risk disease as well as men with low-risk features and occult aggressive disease who are not appropriate for AS. Because retrospective studies have demonstrated that CCR score improves risk stratification compared to standard clinicopathologic features, clinical adoption of the threshold should enable improved identification of men with newly diagnosed localized prostate cancer who are appropriate for AS.

6 ACKNOWLEDGMENTS

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Figure 1. Study flow and summary of patient cohorts.

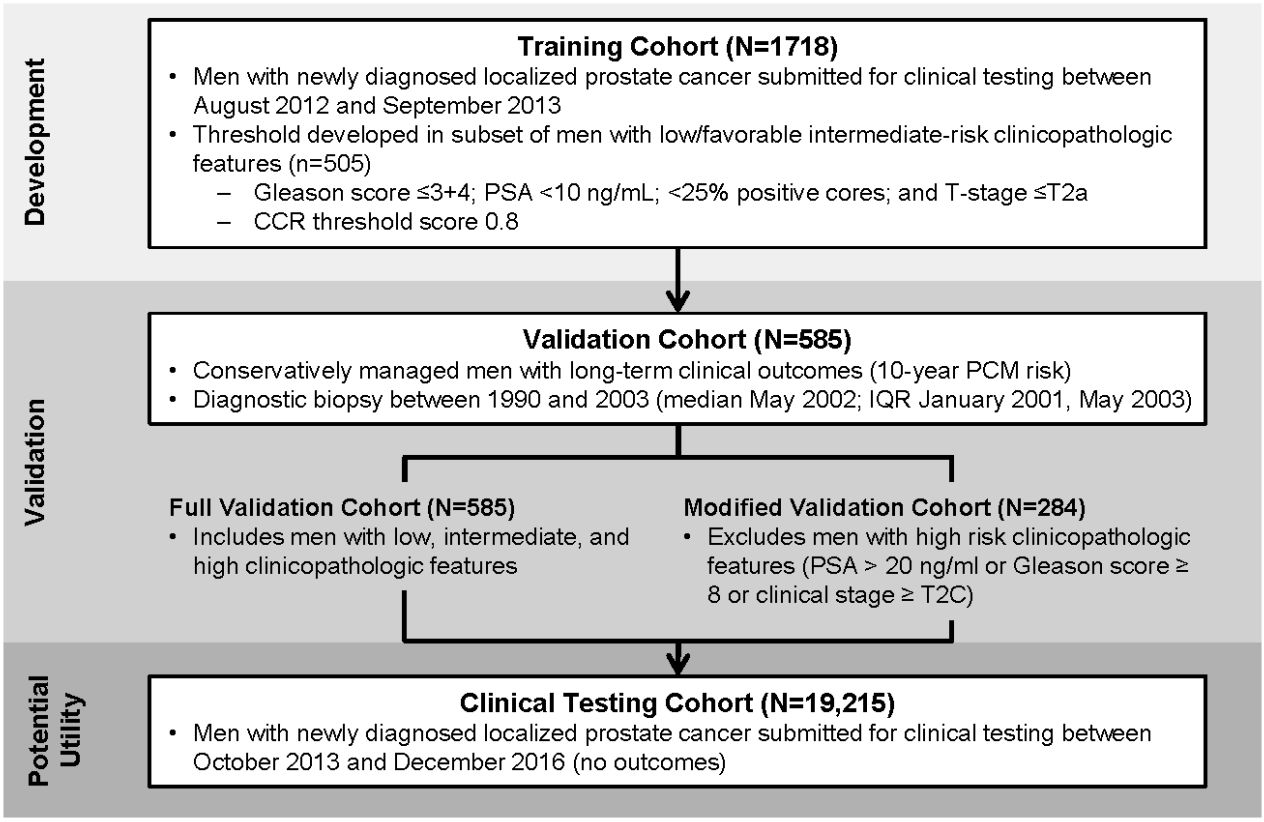


Figure 2. CCR score distribution in the training cohort (gray), with the NCCN-based subset (Gleason score ≤3+4; PSA <10 ng/ml; <25% positive cores; T-stage ≤T2a) in dark blue. The threshold score represents the 90th percentile for the low/favorable intermediate risk subset.

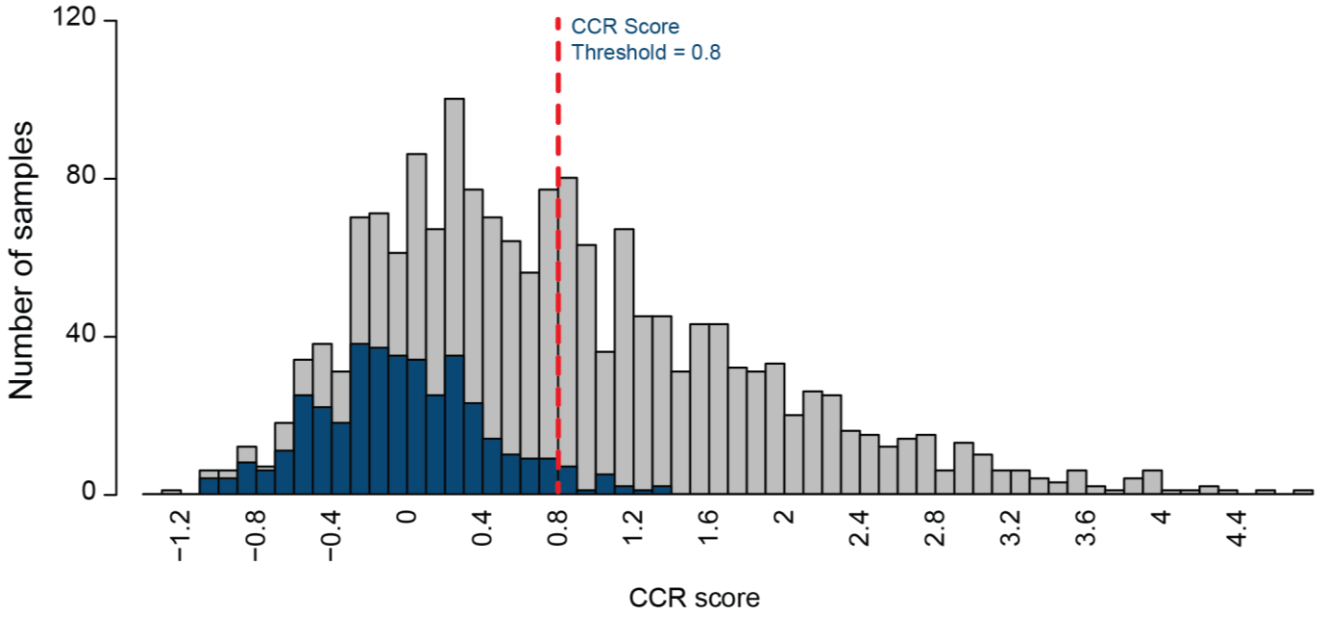
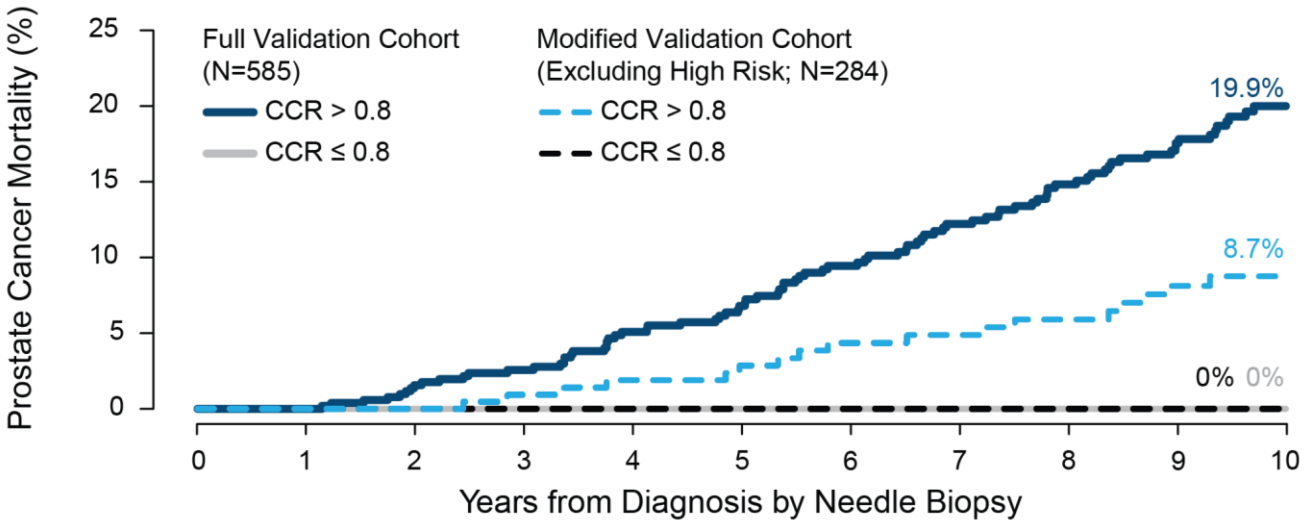


Figure 3. Kaplan-Meier plots showing prostate cancer mortality for patients in the validation cohort separated by CCR score threshold. The solid lines are for the full validation cohort (N=585) and dashed lines are for the modified validation cohort excluding men with high risk clinicopathologic features (N=284).



Full Validation Cohort (N=585)

CCR > 0.8	525	520	503	479	451	431	404	378	356	328	189
CCR ≤ 0.8	60	59	58	56	54	52	52	51	51	50	27

Modified Validation Cohort (Excluding High Risk; N=284)

CCR > 0.8	225	224	222	213	207	201	190	186	178	165	96
CCR ≤ 0.8	59	58	57	55	53	52	52	51	51	50	27

Table 1. Clinicopathologic features of patient cohorts.

	Statistic or Category	Training Cohort N=1,718	Validation Cohort N=585	Modified Validation Cohort N=284	Clinical Testing Cohort N=19,215
Age at Diagnosis (yr)	mean (sd)	68.3 (8.2)	69.5 (5.2)	68.7 (5.6)	64.5 (7.9)
	IQR	64.0 to 74.0	66.5 to 73.6	65.4 to 73.4	59.0 to 70.0
PSA (ng/mL)	0 – 4	294 (17.1%)	15 (2.6%)	14 (4.9%)	3442 (17.9%)
	4.01 – 10	1120 (65.2%)	175 (29.9%)	149 (52.5%)	13,568 (70.6%)
	10.01 - 20	223 (13.0%)	163 (27.9%)	121 (42.6%)	1737 (9.0%)
	20.01 - 100	81 (4.7%)	232 (39.7%)	0 (0%)	468 (2.4%)
	median	5.9	16.0	9.2	5.6
	IQR	4.5 to 8.5	8.4 to 33.0	6.9 to 14.0	4.4 to 7.6
Positive Cores (%)	n	1718	585	284	19,215
	median	25.0	57.1	33.3	23.1
	IQR	16.0 to 42.0	33.3 to 87.5	22.9 to 60.6	12.5 to 35.7
Gleason Score	≤4	1 (0.1%)	0 (0%)	0 (0%)	3 (<0.1%)
	5	3 (0.2%)	0 (0%)	0 (0%)	18 (0.1%)
	6	789 (45.9%)	151 (25.8%)	126 (44.4%)	12,004 (62.5%)
	3+4=7	597 (34.7%)	200 (34.2%)	158 (55.6%)	4716 (24.5%)
	4+3=7	191* (11.1%)	126 (21.5%)	0 (0%)	1555 (8.1%)
	8	86 (5.0%)	35 (6.0%)	0 (0%)	608 (3.2%)
	9	47 (2.7%)	66 (11.3%)	0 (0%)	286 (1.5%)
	10	4 (0.2%)	7 (1.2%)	0 (0%)	25 (0.1%)
Clinical Stage	T1a	33 (1.9%)	87 (14.9%)	65 (22.9%)	596 (3.1%)
	T1b	17 (1.0%)			174 (0.9%)
	T1c	1146 (66.7%)			14,993 (78.0%)
	T2a	221 (12.9%)	371 (63.4%)	219 (77.1%)	2225 (11.6%)
	T2b	179 (10.4%)			629 (3.3%)
	T2c	110 (6.4%)			529 (2.8%)
	T3a	9 (0.5%)	127† (21.7%)	0 (0%)	58 (0.3%)
	T3b	3 (0.2%)			11‡ (0.1%)
AUA Risk Classification	Low	648 (37.7%)	86 (14.7%)	86 (30.3%)	10,917 (56.8%)
	Intermediate	789 (45.9%)	198 (33.8%)	198 (69.7%)	6618 (34.4%)
	High	281 (16.4%)	301 (51.5%)	0 (0%)	1680 (8.7%)
NCCN Risk Classification**	Low	904 (52.6%)	22 (3.8%)	22 (7.7%)	10896 (56.7%)
	Favorable Intermediate	398 (23.2%)	262 (44.8%)	262 (92.3%)	3789 (19.7%)
	Intermediate	313 (18.2%)			3255 (16.9%)
	High	103 (6.0%)	301 (51.5%)	0 (0%)	1275 (6.6%)
CAPRA Score	Low (0 – 2)	848 (49.4%)	80 (13.7%)	80 (28.2%)	12,416 (64.6%)
	Intermediate (3 – 5)	687 (40.0%)	207 (35.4%)	174 (61.3%)	5543 (28.8%)
	High (≥6)	183 (10.7%)	298 (50.9%)	30 (10.6%)	1256 (6.5%)

∗Includes one 5+2=7

†Includes two T4

‡Includes one T4

** T stage subclassification was missing for some patients in validation cohort

Table 2. Eligibility for AS according to clinicopathologic criteria and CCR score threshold in the clinical testing cohort (N=19,215).

	CCR Score ≤ Threshold	**CCR Score > Threshold**
Meet NCCN Criteria for AS (N=8177, 42.6%)	7463 (91.3%)	714 (8.7%)
Do Not Meet NCCN Criteria for AS (N=11,038, 57.4%)	5758 (52.2%)	5280 (47.8%)
Total	13,221 (68.8%)	5,994 (31.2%)

Table 3. Clinicopathologic features of patients in the clinical testing cohort who qualify for AS based on the NCCN score threshold.

	Statistic or Category	All Patients with CCR Score ≤ 0.8	Meet NCCN Criteria for AS	Do Not Meet NCCN Criteria for AS
Total	N (%)	13,221 (100%)	7463 (56.4%)	5758 (43.6%)
Age at Diagnosis (yr)	mean (sd)	64.0 (7.7)	64.2 (7.6)	63.7 (7.9)
	IQR	59.0 to 69.0	59.0 to 69.0	58.0 to 69.0
PSA (ng/mL)	0 – 4	2912 (22.0%)	1790 (24.0%)	1122 (19.5%)
	4.01 – 10	9895 (74.8%)	5673 (76.0%)	4222 (73.3%)
	> 10	414 (3.1%)	*NA*	414 (7.2%)
Positive Cores (%)	mean (sd)	22.4 (15.8)	12.5 (4.6)	35.1 (16.0)
	IQR	8.3 to 29.2	8.3 to 16.7	25.0 to 41.7
Gleason Score	≤4	3 (<0.1%)	3 (4.0%)	0 (0%)
	5	14 (0.1%)	12 (16.1%)	2 (<0.1%)
	6	10,788 (81.6%)	6404 (85.8%)	4384 (76.1%)
	3+4=7	2359 (17.8%)	1044 (14.0%)	1315 (22.8%)
	4+3=7	38 (0.3%)	*NA*	38 (0.7%)
	8	16 (0.1%)	*NA*	16 (0.3%)
	9	3 (<0.1%)	*NA*	3 (0.1%)
	10	0 (0%)	*NA*	0 (0%)
Clinical Stage	T1a	474 (3.6%)	352 (4.7%)	122 (2.1%)
	T1b	129 (1.0%)	78 (1.0%)	51 (0.9%)
	T1c	10,765 (81.4%)	6233 (83.5%)	4532 (78.7%)
	T2a	1384 (10.5%)	800 (10.7%)	584 (10.1%)
	T2b	261 (2.0%)	*NA*	261 (4.5%)
	T2c	199 (1.5%)	*NA*	199 (3.5%)
	T3a	9 (0.1%)	*NA*	9 (0.2%)
	T3b	0 (0%)	*NA*	0 (0%)
AUA Risk Classification	Low	10,141 (76.7%)	6419 (86.0%)	3722 (64.6%)
	Intermediate	2844 (21.5%)	1044 (14.0%)	1800 (31.3%)
	High	236 (1.8%)	*NA*	236 (4.1%)
CAPRA Score	Low (0 – 2)	11,552 (87.4%)	7228 (96.9%)	4324 (75.1%)
	Intermediate (3 – 5)	1669 (12.6%)	235 (3.1%)	1434 (24.9%)
	High (≥6)	0 (0%)	0 (0%)	0 (0%)

Supporting Information

Identification of Men with Low-Risk Biopsy-Confirmed Prostate Cancer as Candidates for Active Surveillance

Evaluating Additional Thresholds

There are numerous criteria used in the clinic to select patients for AS. [1-5] As such, we have developed and evaluated two additional AS thresholds based on AUA and CAPRA risk stratification.

Cohorts

CCR score thresholds based on AUA and CAPRA risk stratification were developed in the same training cohort described in the main text (N=1718). A subset of men with low-risk disease who may be considered for AS was selected based on a conservative interpretation of AUA guidelines: Gleason score ≤3+3; PSA <10 ng/mL; <25% positive cores; T-stage ≤T2a (N=385) [2,5,6]. This subset of the training cohort was used to select a CCR score threshold in men with low-risk clinicopathologic who would be considered for AS according to AUA guidelines (AUA score threshold). Second, a subset of men was selected from the training cohort based on having low-risk CARPA scores (0-2) [7]. This subset of the training cohort was used to select a CCR score threshold in men with low-risk clinicopathologic who would be considered for AS according to CAPRA (CAPRA threshold).

The ability of the CCR score thresholds to separate patients with high- and low-risk disease was validated in the same cohort of conservatively managed men with long-term outcomes described in the main text [8]. Both the full validation cohort (N=585) and modified validation cohort that excluded men with high-risk clinicopathologic features (N=284) were evaluated with the additional AUA and CAPRA-based thresholds.

Results

CCR-based risk distributions were calculated for men who may qualify for AS based on AUA guidelines (Gleason score ≤3+3; PSA <10 ng/ml; <25% cores positive; clinical stage ≤T2a) and for men who may qualify for AS based on CAPRA scores 0-2. The 90th percentile of the CCR score distribution in each subset was conservatively selected as a proposed threshold to select men who are appropriate for AS. Using this cut-off, the CCR threshold score was 0.6 (rounded from 0.552) in men would be considered for AS based on AUA criteria (AUA score threshold) and 0.7 (rounded from 0.723) in men who would be considered for AS based on CAPRA scores 0-2. The performance of these thresholds in

the entire validation cohort and in the modified validation cohort is summarized in **Supplemental Table 1.**

The potential clinical impact of identifying men for AS using these alternative CCR score thresholds was evaluated in a consecutive group of 19,215 men who had clinical testing (Clinical Testing Cohort). A comparison of men above and below the thresholds to men who would and would have not qualified for AS based on clinicopathologic criteria alone is shown in **Supplemental Table 2**.

Evaluation of CCR Score Thresholds in RP Treated Cohort

In addition to selecting men for active surveillance, stratifying risk is also of value in men with localized prostate cancer who have been treated and may improve identification of men who will benefit from treatment. To explore the utility of the CCR score thresholds to dichotomize high- and low-risk disease, we evaluated the score thresholds in men with screen-detected disease who were treated for localized prostate cancer by radical prostatectomy (RP). This cohort has been previously described and includes men who were diagnosed at three different clinics/hospitals between 1994 and 2006 (N=581).[9] Of these, 416 had complete data for calculating CAPRA score. IRB approval was obtained for all study sites. Follow-up included biochemical recurrence (BCR) data, which were censored at 10 years.

The clinicopathologic features of this cohort are given in **Supplemental Table 3**. All three thresholds (AUA, CAPRA, and NCCN) were highly predictive (log-rank test), dichotomizing the cohort into high and low risk of BCR. The hazard ratio (HR) for men with CCR scores below the AUA threshold was 0.45 (95% CI: 0.28, 0.73, $p= 8.8 \times 10^{-4}$). The hazard ratio (HR) for men with CCR scores below the CAPRA threshold was 0.47 (95% CI: 0.30, 0.74, $p=9.2 \times 10^{-4}$). And finally, hazard ratio (HR) for men with CCR scores below the NCCN threshold was 0.45 (95%CI: 0.30, 0.69, $p=1.7 \times 10^{-4}$). The number of observed events among men with CCR scores above and below the thresholds is given in **Supplemental Table 4**. For example, only 12% of men with CCR scores below the NCCN threshold had BCR within 5 years of RP compared to 31% of men with scores above the NCCN threshold. This provides preliminary evidence that the CCR score thresholds are also able to dichotomize disease risk in treated men

Supplemental Table 1. Validation of the AUA- and CAPRA-based CCR threshold scores. The validation of the original CCR threshold developed based on NCCN criteria is provided for comparison.

CCR Threshold Score	CCR Score = Threshold	CCR Score < Threshold				p-value*
	Mean Risk of 10-year DSM (95% CI)	Mean Risk of 10-year DSM	Events	Patients	NPV	
Full Validation Cohort (N=585)						
AUA (Threshold = 0.6)	2.8% (1.60, 5.03)	2.30%	0	32	100%	0.0027
CAPRA (Threshold = 0.7)	3.1% (1.80, 5.44)	2.50%	0	46	100%	$1.6x10^{-4}$
NCCN (Threshold = 0.8)	3.3% (1.94, 5.70)	2.70%	0	60	100%	$1.2x10^{-5}$
Modified Validation Cohort (Excluding men with high risk clinicopathologic features; N=284)						
AUA (Threshold = 0.6)	2.4% (0.95,6.19)	1.90%	0	28	100%	0.16
CAPRA (Threshold = 0.7)	2.7% (1.09, 6.45)	2.10%	0	45	100%	0.052
NCCN (Threshold = 0.8)	2.9% (1.25, 6.74)	2.30%	0	59	100%	0.020

*Comparing risk of 10-year disease specific mortality for men with CCR scores above versus below the threshold score

Supplemental Table 2. Eligibility for AS according to clinicopathologic criteria and CCR score threshold in the clinical testing cohort (N=19,215).

	CCR Score ≤ Threshold	CCR Score > Threshold
AUA Threshold (CCR score 0.6)		
Meet AUA Criteria for AS	89.5%	10.5%
Do Not Meet AUA Criteria for AS	44.7%	55.3%
Total	60.3%	39.7%
CAPRA Threshold (CCR score 0.7)		
Meet CAPRA score 0-2 for AS	89.4%	10.6%
Do Not Meet CAPRA score 0-2 for AS	18.4%	81.6%
Total	64.3%	35.7%

Supplemental Table 3. Clinicopathologic features of RP Treated Cohort.

	Statistic or Category	RP Cohort N=581
Age at Diagnosis (yr)	mean (sd)	62.0 (6.5)
	IQR	(57.9 to 66.6)
PSA (ng/mL)	0 – 4	84 (14.5%)
	4.01 – 10	363 (62.5%)
	10.01 - 20	109 (18.8%)
	20.01 - 100	25 (4.3%)
	median	6.4
	IQR	(4.7 to 9.5)
Positive Cores (%)	n	437
	median	33.3
	IQR	(20.0 to 50.0)
Gleason Score	≤4	6 (1.0%)
	5	44(7.6%)
	6	288 (49.6%)
	3+4=7	124 (21.3%)
	4+3=7	41 (7.1%)
	7	38 (6.5%)
	8	29 (5.0%)
	9	8 (1.4%)
	10	3 (0.5%)
Clinical Stage	T1a	0 (0%)
	T1b	0 (0%)
	T1c	356 (65.2%)
	T2a	153 (28.0%)
	T2b	24 (4.4%)
	T2c	9 (1.6%)
	T3a	4 (0.7%)
	T3b	0 (0%)
AUA Risk Classification	Low	63 (16.8%)
	Intermediate	241 (64.3%)
	High	71 (18.9%)
CAPRA Score	Low (0 – 2)	202 (48.6%)
	Intermediate (3 – 5)	187 (45.0%)
	High (≥6)	27 (6.5%)

Supplemental Table 4. BCR within 5 years of RP according to AS eligibility (CCR ≤ threshold).

CCR Score	No BCR within 5 years of RP N	BCR within 5 years of RP N (%)
AUA Threshold (CCR score 0.6)		
CCR Score ≤ Threshold	119	14 (11%)
CCR Score > Threshold	200	83 (29%)
CAPRA Threshold (CCR score 0.7)		
CCR Score ≤ Threshold	130	15 (10%)
CCR Score > Threshold	189	82 (30%)
NCCN Threshold (CCR score 0.8)		
CCR Score ≤ Threshold	145	19 (12%)
CCR Score > Threshold	174	78 (31%)

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