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CLINICAL INVESTIGATION

The Clinical Cell-Cycle Risk (CCR) Score Is Associated With Metastasis After Radiation Therapy and Provides Guidance on When to Forgo Combined Androgen Deprivation Therapy With Dose-Escalated Radiation

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Purpose: The clinical cell-cycle risk (CCR) score, which combines the University of California, San Francisco's Cancer of the Prostate Risk Assessment (CAPRA) and the cell cycle progression (CCP) molecular score, has been validated to be prognostic of disease progression for men with prostate cancer. This study evaluated the ability of the CCR score to prognosticate the risk of metastasis in men receiving dose-escalated radiation therapy (RT) with or without androgen deprivation therapy (ADT).

Methods and Materials: This retrospective, multi-institutional cohort study included men with localized National Comprehensive Cancer Network (NCCN) intermediate-, high-, and very high-risk prostate cancer (N = 741). Patients were treated with dose-escalated RT with or without ADT. The primary outcome was time to metastasis.

Results: The CCR score prognosticated metastasis with a hazard ratio (HR) per unit score of 2.22 (95% confidence interval [CI], 1.71-2.89; $P < .001$). The CCR score better prognosticated metastasis than NCCN risk group (CCR, $P < .001$; NCCN, $P = .46$), CAPRA score (CCR, $P = .002$; CAPRA, $P = .59$), or CCP score (CCR, $P < .001$; CCP, $P = .59$) alone. In bivariable analyses, CCR score remained highly prognostic when accounting for ADT versus no ADT (HR, 2.18; 95% CI, 1.61-2.96; $P < .001$), ADT duration as a continuous variable (HR, 2.11; 95% CI, 1.59-2.79; $P < .001$), or ADT given at or below the recommended duration for each NCCN risk group (HR, 2.19; 95% CI, 1.69-2.86; $P < .001$). Men with CCR scores below or above the multimodality threshold (CCR score, 2.112) had a 10-year risk of metastasis of 3.7% and 21.24%, respectively. Men with below-threshold scores receiving RT alone had a 10-year risk of metastasis of 3.7%, and for men receiving RT plus ADT, the 10-year risk of metastasis was also 3.7%.

Conclusions: The CCR score accurately and precisely prognosticates metastasis and adds clinically actionable information relative to guideline-recommended therapies based on NCCN risk in men undergoing dose-escalated RT with or without ADT. For men with scores below the multimodality threshold, adding ADT may not significantly reduce their 10-year risk of metastasis.

Introduction

The Prolaris gene expression classifier test combines the University of California, San Francisco's Cancer of the Prostate Risk Assessment (CAPRA)[1] score with a cell cycle progression (CCP) score derived from a tumor RNA expression profile to produce a personalized metastasis risk score after definitive treatment for localized prostate cancer. This combined clinical cell-cycle risk (CCR) score can prognosticate an individual's risk of metastasis with single-modality or multimodality therapies.[2] A CCR score threshold has also been developed, under which using multimodality therapies in men with National Comprehensive Cancer Network (NCCN) intermediate- or high-risk prostate cancer may not be warranted, given that the absolute risk reduction for 10-year risk of metastasis would not exceed 5% compared with monotherapy.[2,3]

The CCR risk model is a precise and accurate estimator of adverse outcomes, as shown in studies of those who received conservative management, radical prostatectomy, and radiation therapy (RT).[2,4-7] However, to our knowledge, none of the prior RT validation studies accounted for the effect of RT dose escalation or the duration of androgen deprivation therapy (ADT) used. This study aimed to validate the CCR score as a prognosticator of metastasis, which would add additional prognostic value to the CAPRA score or NCCN risk stratification in men undergoing curative-intent RT when accounting for these and other important clinical details. We also sought to validate that the CCR score multimodality threshold may identify NCCN unfavorable intermediate- and high-risk men who might consider treatment with RT alone instead of the guideline-recommended ADT plus RT and thus potentially avoid the significant toxicities and quality-of-life impairment associated with ADT therapy.

Methods and Materials

Cohort

The study cohort pooled patients from 15 academic and private-practice clinics to validate a risk-based CCR score in men with NCCN intermediate-, high-, and very high-risk prostate cancer treated with dose-escalated external beam RT (EBRT) with or without ADT (Table E1). To our knowledge, none of these cohorts have been used previously for evaluating the prognostic ability of the CCP test. Oncologic outcomes and clinical demographics were gathered retrospectively for men treated consecutively between 2003 and 2017. After treatment was completed, CCP and CCR scores were derived from clinical archival biopsy pathology tissue but were not shared with the treating physicians. Scores were not used to inform patient selection, the treatment decision, or data abstraction. The deidentified outcome data were pooled and matched to the CCP and CCR scores before analysis. Treatment modality and ADT duration were based on physician-patient preference. Institutional review board approval was obtained for each data set and all prespecified analyses.

Study cases included men with biopsy-proven intermediate- or high-risk localized prostate adenocarcinoma as categorized by the 2012 NCCN guidelines (Gleason score ≥7, or prostate-specific antigen level >10 ng/mL, or ≥cT2b disease).[8] The treatment received was EBRT with curative intent via 3-dimensional (3D) conformal or intensity modulated RT techniques

using moderately hypofractionated to conventional fractionation schemes, with linear accelerators producing photon beam energies between 4 and 18 MeV. Doses to the prostate had to be radiobiologically ≥ an equivalent dose in 2 Gy fractions (EQD2) of 71.8 Gy (equivalent to at least 75.6 Gy at 1.8 Gy per fraction), calculated using the linear-quadratic model assuming an alpha/beta ratio of 2. The RT field had to encompass the prostate with or without the seminal vesicles with a ≥5 mm margin to the planning target volume. Alternatively, if the dose was prescribed to a block edge, the minimum allowable distance from the prostate to the block edge was 1 cm. Computerd tomography–based treatment planning was required. Men who received elective pelvic nodal RT in addition to RT of the prostate were allowed, regardless of pelvic field design or dose.

Men were excluded for any of the following reasons: progression to metastatic disease or loss to follow-up within 6 months of disease diagnosis, based on the date of the diagnostic biopsy; a daily fractionation dose exceeding 4 Gy/fraction; clinical node-positive or metastatic disease at the time of diagnosis; a known baseline total serum testosterone level of <100 ng/dL before RT; use of brachytherapy; other primary malignant neoplasms preceding the prostate cancer diagnosis, except epithelial skin cancers; prior pelvic RT for another malignancy; nonadenocarcinoma prostate cancer histology; or a CAPRA score that could not be calculated (Table E1).

CCP testing

All CCP testing was performed at Myriad Genetics, Inc (Salt Lake City, UT) and was blinded to patient outcome, as described previously.[7,9-11] The CCP molecular score was combined with the CAPRA score to produce the predefined CCR score ([0.39 × CAPRA] + [0.57 × CCP]).[7] The multimodality threshold (CCR score ≤2.112) was determined as previously described.[2]

Statistical analyses

This study followed the REMARK criteria for evaluating prognostic biomarkers, except for the predetermined sample size.[12,13] The primary endpoint, time to metastasis, was prespecified and defined as the time to the first occurrence of any nonregional nodal, bone, or visceral progression after completing initial therapy. Time to metastasis was calculated as the time from diagnosis to metastasis and was censored at the earliest of the following: date of last follow-up, date of death, or 10 years. This cohort acted as an additional validation of the CCR score and multimodality threshold and was not split into separate training and validation sets.

The current NCCN guidelines refined the intermediate- and high-risk categories into favorable, unfavorable, high, and very high risk after the initiation of this study. We used version 1.2020 of the NCCN guidelines to stratify patients into these risk groups.[8,14] To further explore the prognostic ability of the CCR score in the context of ADT use and duration, 3 separate variables for analysis were created: a binary indicator of ADT use, categorized ADT sufficiency, and ADT duration (months) as a continuous variable. The binary ADT-use indicator included patients receiving no ADT versus those receiving ADT (any duration) before or within 6 months of RT completion (RT alone versus RT plus ADT). Categorized ADT sufficiency was based on the NCCN guidelines, version 1.2020,[14] and was characterized as sufficient or insufficient based on the risk group. ADT was considered sufficient if the patient was at favorable intermediate risk with or without receiving ADT, at unfavorable intermediate risk with ≥4 months of ADT, or at high or very high risk with ≥18 months of ADT. Conversely, ADT was considered insufficient if the patient was at unfavorable intermediate risk with <4 months of ADT or at high or very high risk with <18 months of ADT. Seven patients categorized by NCCN guidelines as being at unfavorable intermediate, high, or very high risk were known to have received ADT but had unknown duration and were not categorized by this variable. Finally, for ADT duration in months (continuous), patients who received no ADT were recorded as 0 months. Eight patients known to have received ADT but with unknown duration were not described.

Univariable and multivariable cause-specific Cox proportional hazards regressions were used for the analyses.[15] Hazard ratios (HRs) were expressed based on a 1-unit score change and are reported with 95% profile likelihood-based confidence intervals (CIs) with P values determined from partial likelihood ratio tests. Cumulative-incidence functions accounting for competing risks were used to estimate the risk of metastasis over time. All risk-estimate CIs are based on the log-log transformation. The ability to predict metastasis risk was evaluated by the comparison of cause-specific Cox proportional hazard models using likelihood ratio tests. Prognostic ability is further described using the Harrell concordance statistic (C-index) adjusted for competing risks and the time-dependent areas under the receiver operating characteristic curve (AUCs).[16] All analyses were performed using STATA, version 15 (StataCorp LLC, College Station, TX), and R, version 3.5.0 or higher (R Core Team, Vienna, Austria).

Sensitivity analyses for institutional site differences were performed by comparing the results of cause-specific Cox proportional hazards models fit without accounting for site and fit with a strata term for the site or type of institution. Because there were no substantial differences in major conclusions, the site or institution type was not accounted for in the reported models (Supplement, *Sensitivity Analysis for the Effect of Site and Site Type*). A sensitivity analysis comparing the results of cause-specific and Fine-and-Gray method Cox proportional hazards models also showed no substantial difference (Supplement, *Sensitivity Analysis for the Effect of Site and Site Type*). An ad hoc sensitivity analysis was conducted to confirm the assumption of linearity for CCR. The linear effect of CCR was confirmed (P = .06; Supplement, *Sensitivity Analysis for Linear Effect of CCR*).

Results

There were 741 men evaluable, with a median follow-up time of 5.8 years. There were 351 men (47.4%) treated initially with RT and 390 (52.6%) treated initially with RT and ADT (Table 1). The median CCR score was 2.12 (range, −0.018 to 5.51), and the CCR score was treated as a linear predictor. Future work may explore a nonlinear term for CCR score. There were 572 men with unfavorable intermediate-, high-, or very high-risk prostate cancer; of those, 216 (37.8%) received RT alone. There were 95 patients treated with 3D conformal RT (12.8%), 643 with intensity modulated RT (86.8%), and 3 with volumetric modulated arc therapy (0.4%).

Table 1 Demographics of the study population

Characteristic	Median (IQR) or n (%)
CCP	0.5 (0.0-1.1)
CCR score	2.12 (1.46-2.86)
Below multimodality threshold (CCR ≤2.112)	370 (49.9)
Above multimodality threshold (CCR >2.112)	371 (50.1)
CAPRA	5 (3-6)
Low risk (score, 0-2)	87 (11.7)
Intermediate risk (score, 3-5)	395 (53.3)
High risk (score, 6-10)	259 (35.0)
2020 NCCN risk category	
Favorable intermediate	169 (22.8)
Unfavorable intermediate	351 (47.4)
High	128 (17.3)
Very high	93 (12.6)
Age at diagnosis, y	70 (65-75)
ISUP grade	
1, Gleason score <7	49 (6.6)
2, Gleason score = 3+4	318 (42.9)
3, Gleason score = 4+3	209 (28.2)
4, Gleason score = 8	92 (12.4)
5, Gleason score ≥9	73 (9.9)
PSA level (ng/mL)	7.9 (5.2-13.4)
<10	447 (60.3)
10-20	195 (26.3)
>20	99 (13.4)
Positive cores, %	41.7 (25.0-66.7)
<34%	313 (42.2)
34%-50%	191 (25.8)
>50%	237 (32.0)
Radiation technique	
3D	95 (12.8)
IMRT	643 (86.8)
VMAT	3 (0.4)
EQD2	76.95 (75.24-76.95)
ADT use	
RT only	351 (47.4)
RT + ADT	390 (52.6)
ADT sufficiency	
Insufficient	324 (43.7)
Sufficient	410 (55.3)
Unknown	7 (0.9)
Duration of ADT when used, mo	8 (6-20)
Metastasis (within 10 y)	47 (6.3)

Abbreivations: 3D = 3-dimensional; ADT = androgen deprivation therapy; CAPRA = Cancer of the Prostate Risk Assessment; CCP = cell cycle progression; CCR = clinical cell-cycle risk; EQD2 = equivalent dose in 2 Gray fractions; IMRT = intensity-modulated radiation therapy; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; RT = radiation therapy; VMAT = volumetric modulated arc therapy.

The median duration of ADT use for patients receiving any ADT before or within 6 months of radiation was 8 months (interquartile range [IQR], 6-20 months). Men with unfavorable intermediate-, high-, or very high-risk disease received a sufficient duration of ADT 41.3%, 34.7%, and 58.7% of the time, respectively. In men receiving an insufficient duration of ADT, the median duration of ADT used was 0 months (IQR, 0-0 months) for unfavorable intermediate-risk patients, 6 months (IQR, 0-6 months) for high-risk patients, and 8 months (IQR, 4-12 motnhs) for very high-risk patients.

CCR score prognostication of metastasis

The CCR score was highly prognostic for metastasis in the full cohort (HR, 2.22; 95% CI, 1.71-2.89; $P < .001$). In a bivariable analysis including continuous CAPRA and CCR scores, the CAPRA score was insignificant (HR, 0.92; 95% CI, 0.69-1.23; $P = .59$), whereas the CCR score remained significant (HR, 2.55; 95% CI, 1.43-4.49; $P = .0017$), indicating that the clinicopathologic features within the CCR score were properly weighted and the CCR score is a better prognosticator of risk than the CAPRA score alone. By the likelihood ratio test, the CCR score is also a better prognosticator of risk than the NCCN risk category alone (CCR, $P < .001$; NCCN, $P = .46$) or the CCP score alone (CCR, $P < .001$; CCP, $P = .59$). The C-indices from univariable cause-specific models support the results of the likelihood ratio tests, indicating that the CCR score is a robust prognosticator of metastasis (C-index, 0.72; 95% CI, 0.65-0.79), with point estimates outperforming the CAPRA score (C-index, 0.68; 95% CI, 0.60-0.76), the NCCN risk group (C-index, 0.63; 95% CI, 0.57-0.72), and the CCP score (C-index, 0.64; 95% CI, 0.57-0.72) alone (Table 2). Time-dependent AUCs are included in Table E2.

We compared the optimized exploratory risk models with the CCR scores. The CCP score remained a highly significant prognosticator of metastasis risk after accounting for CAPRA score (CCP HR, 1.71; 95% CI, 1.23-2.35; $P = .0017$), NCCN risk group (CCP HR, 1.65; 95% CI, 1.18-2.29; $P = .0037$), or International Society of Urological Pathology risk group (CCP HR, 1.77; 95% CI, 1.26-2.47; $P = .0012$). However, these exploratory alternative risk models did not improve prognostic accuracy compared with the CCR score alone, because no significant prognostic information was added to the CCR by the optimized combination of the CCP and CAPRA scores ($P = .59$), the optimized combination of the CCP score and the NCCN risk group

Table 2 Performance of CCR and bivariable cause-specific Cox regression models in prognosticating metastasis*

	Hazard ratio	95% CI	*P* value	Concordance (95% CI)
Univariable analyses				
CCP	2.03	1.47-2.78	<.001	0.64 (0.56-0.72)
CAPRA	1.39	1.22-1.58	<.001	0.68 (0.60-0.76)
CCR	2.22	1.71-2.89	<.001	0.72 (0.65-0.79)
NCCN risk group			<.001	0.63 (0.57-0.72)
Favorable intermediate	Reference	-		
Unfavorable intermediate	2.08	0.71-6.16		
High	2.76	0.81-9.43		
Very high	8.87	3.00-26.22		
CCR split by modality				
RT alone (n = 351)	2.77	1.41-5.22	.0036	0.70 (0.57-0.83)
RT + ADT (n = 390)	2.07	1.47-2.92	<.001	0.67 (0.56-0.77)
Bivariable analyses				
CCP + CAPRA				
CCP	1.71	1.23-2.35	.0017	0.72 (0.65-0.79)
CAPRA	1.33	1.16-1.52	<.001	
CCP + NCCN				
CCP	1.65	1.18-2.29	.0037	0.70 (0.63-0.78)
NCCN risk group			.0014	
Favorable intermediate	Reference	-		
Unfavorable intermediate	1.92	0.65-5.67		
High	2.15	0.62-7.44		
Very high	6.15	2.02-18.75		
CCP + ISUP grade				
CCP	1.77	1.26-2.47	.0012	0.68 (0.63-0.77)
ISUP grade			.025	
1, Gleason score < 7	Reference	-		
2, Gleason score = 3+4	1.28	0.16-10.04		
3, Gleason score = 4+3	2.87	0.38-21.74		
4, Gleason score = 8	2.85	0.35-23.31		
5, Gleason score ≥ 9	5.18	0.66-40.88		
CCR + ADT continuous duration (n = 733)				
CCR	2.11	1.59-2.79	<.001	0.72 (0.63-0.78)
ADT duration, mo	1.01	0.99-1.03	.42	
CCR + sufficiency of ADT duration (n = 734)				
CCR	2.19	1.69-2.86	<.001	0.74 (0.64-0.80)
Insufficient ADT	Reference		.20	
Sufficient ADT	1.47	0.82-2.73		

Abbreviations: ADT = androgen deprivation therapy; CAPRA = Cancer of the Prostate Risk Assessment; CCP = cell cycle progression; CCR = clinical cell-cycle risk; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; RT = radiation therapy.

* Results of univariable and bivariable cause-specific Cox regression analyses are shown; concordance is reported using the Harrell C-index adjusted for competing risks.

(*P* = .51), or the optimized combination of the CCP score and the International Society of Urological Pathology grade (*P* = .88).

In addition to discriminating the risk of metastasis in all patients, the CCR score is a well-calibrated prognosticator of 10-year metastasis risk in patients treated with single-mode therapy. The calibration plot shown in Figure 1 separates patients treated with single-modality therapy in this study population into event-based quintiles and compares the observed risk of 10-year metastasis with the mean predicted risk from the univariable CCR model fit in patients treated with single-mode therapy in a previous study.[2] The risk curves in Figure 2 compare the estimated 10-year risk of metastasis with single-mode therapy in this study with that of the prior threshold validation study for a continuum of CCR scores. The risks of metastasis for the majority of CCR scores are highly comparable, and the risk precisely at the threshold was 8.7% (95% CI, 4.8%-15.3%) in this study, which is concordant with the risk in the prior threshold development study, at 8.1% (95% CI, 4.0%-15.8%).[2]

CCR and the effect of ADT

The CCR score prognosticated the risk of metastasis for patients receiving either RT alone (HR, 2.77; 95% CI, 1.41-5.22; *P* = .0036) or RT and ADT (HR, 2.07; 95% CI, 1.47-2.92; *P* < .001). In bivariable analyses, the CCR score

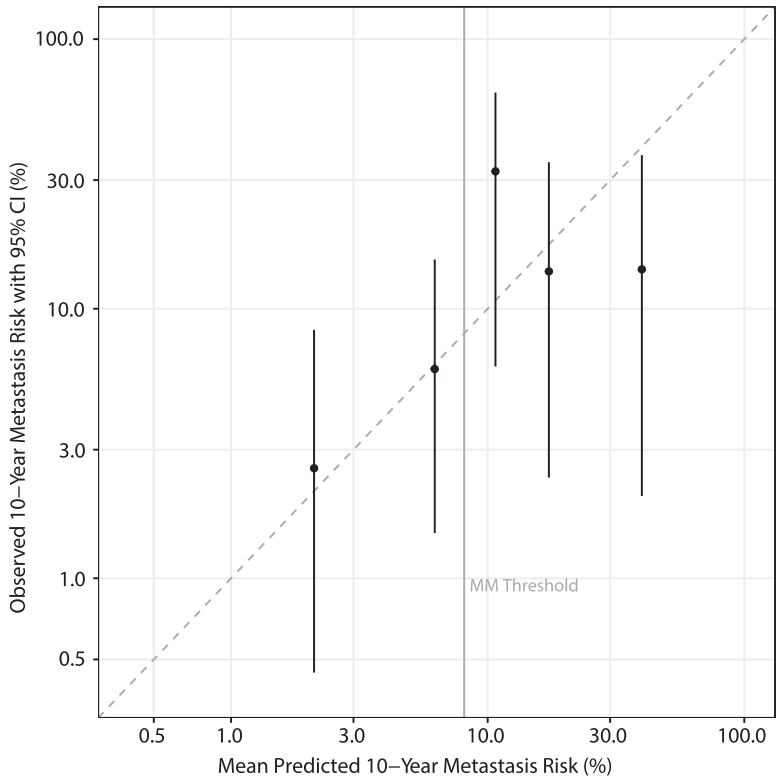

Fig. 1. Calibration plot comparing the mean predicted risk of 10-year metastasis with single-mode therapy and the observed risk for event-based quintiles among 351 patients.

remained highly prognostic for metastasis when accounting for the use of any ADT versus none (CCR HR, 2.18 [95% CI, 1.61-2.96; $P < .001$]; ADT HR, 1.08 [95% CI, 0.52-2.31] $P = .84$), ADT duration as a continuous variable in months (CCR HR, 2.11 [95% CI, 1.59-2.79; $P < .001$]; ADT duration HR, 1.01 [95% CI, 0.99, 1.03; $P = .42$]), or sufficiency of ADT use (CCR HR, 2.19 [95% CI, 1.69-2.86; $P < .001$; sufficiency of ADT HR, 1.47 [95% CI, 0.82-2.73; $P = .20$]).

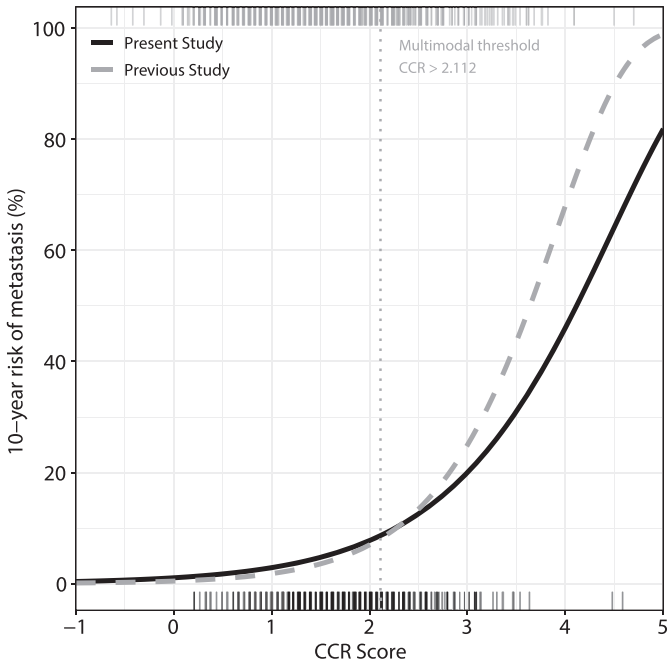

Fig. 2. Risk curves comparing the predicted 10-year risk of metastasis with single-mode therapy in this study of 351 patients and a previous validation study.

Performance of the CCR multimodality threshold

When dichotomized at the threshold (CCR score, 2.112; men with scores of 2.112 were grouped in the below-threshold group), the majority of NCCN favorable intermediate-risk men (161 of 169 [95.3%]) were at or below the threshold, whereas all but 1 man with an NCCN classification of very high risk were above the threshold (92 of 93 [98.9%]; Table E3). Approximately half of unfavorable intermediate-risk men were below the threshold (184 of 351 [52.4%]), whereas 24 of 128 (18.8%) high-risk men were below the threshold.

Figure 3 shows the cumulative incidence of metastases in men above or below the threshold in various ADT-use contexts (see also Table E4). Additional stratification by ADT use and NCCN risk group context for men below the threshold is shown in Figure E1, and the effect of ADT in men above the threshold is shown in Figure E2. Men in the above-threshold group who were treated with single-modality therapy had more than a 6-fold predicted risk of

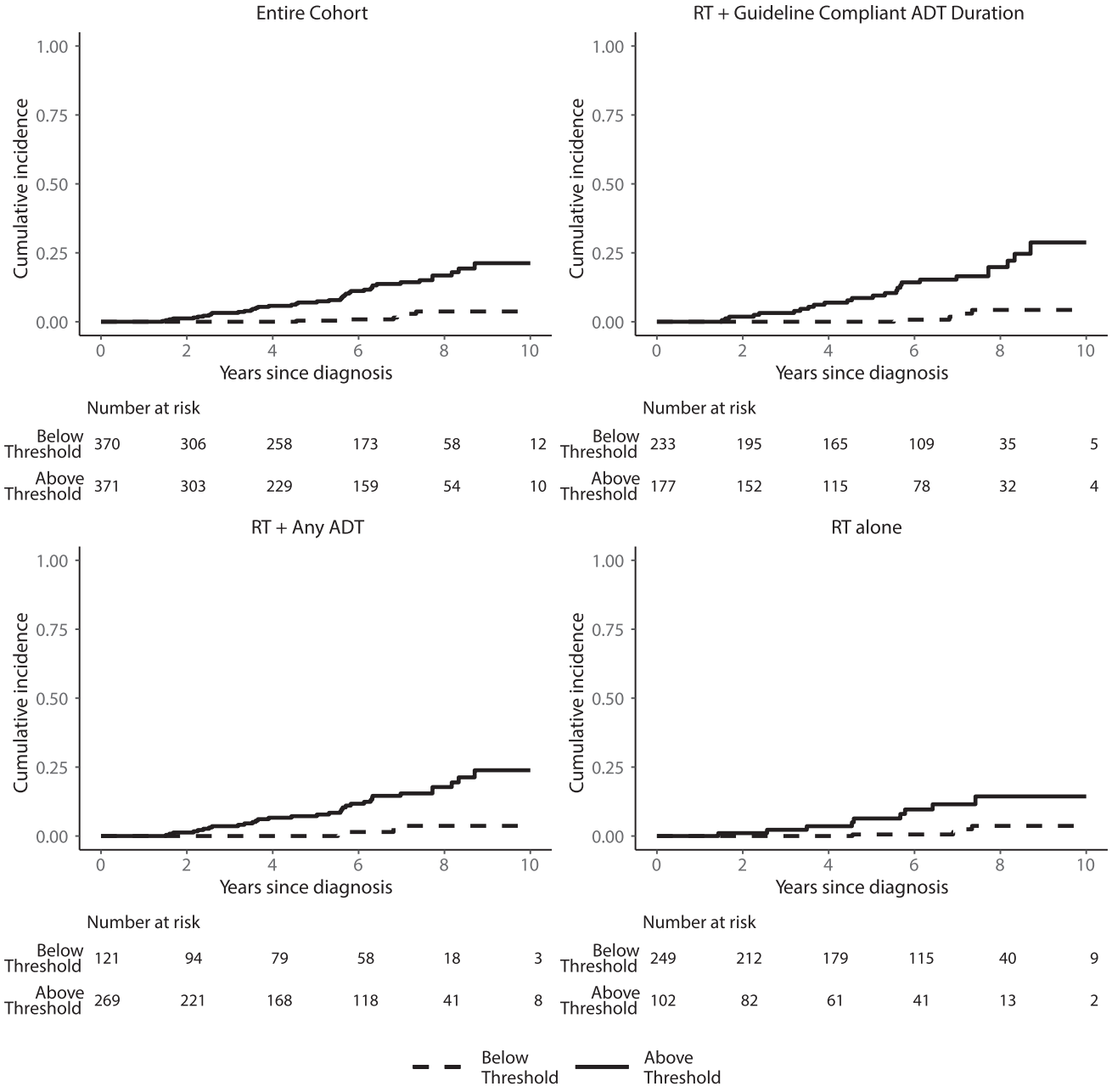

Fig. 3. Risk of metastasis during years 0 to 10 for men above or below the multimodality threshold (clinical cell-cycle risk score ≤ 2.112) stratified by treatment type. (A) Full cohort (741 patients). (B) Radiation therapy plus duration of guideline-compliant androgen deprivation therapy (ADT) (410 patients). (C) Radiation therapy plus any ADT (390 patients). (D) Radiation therapy only (351 patients).

developing metastasis compared with those in the below-threshold group (HR, 6.36; 95% CI, 2.07-23.46; P = .0012). Men with CCR scores below or above the threshold had an observed 10-year risk of metastasis of 3.7% (95% CI, 1.1%-8.7%; n = 249) and 14.4% (95% CI, 6.6%-25.0%; n = 102), respectively, when treated with RT alone (Fig. 1D). For men below the threshold, ADT of any duration did not significantly reduce the risk of 10-year metastasis (risk with RT alone, 3.7% [95% CI, 1.1%-8.7%; n = 249; Fig. 1D]; risk with RT plus ADT, 3.7% [95% CI, 0.6%-11.6%; n = 121; Fig. 1C]; P = .86). Receiving sufficient ADT versus insufficient ADT also did not significantly affect the 10-year risk of metastasis for patients below the threshold (risk with insufficient ADT, 2.8% [95% CI, 0.5%-8.9%; n = 136]; risk with sufficient ADT, 4.3% [95% CI, 1.3%-10.0%; n = 233; Fig. 1B]; P = .83).

The risk of developing metastasis by NCCN risk group stratified by the threshold is shown in Figure 4. The overall risk of metastasis by NCCN risk group is included in Table E5. The risk of metastasis below the threshold was low, regardless of NCCN category (favorable intermediate, 3.5%; 95% CI, 0.6%-10.8% [Fig. 4A]; unfavorable intermediate, 4.1%; 95% CI, 1.3%-9.7% [Fig. 4B]; high and very high, 0%; no events [Fig. 4C]).

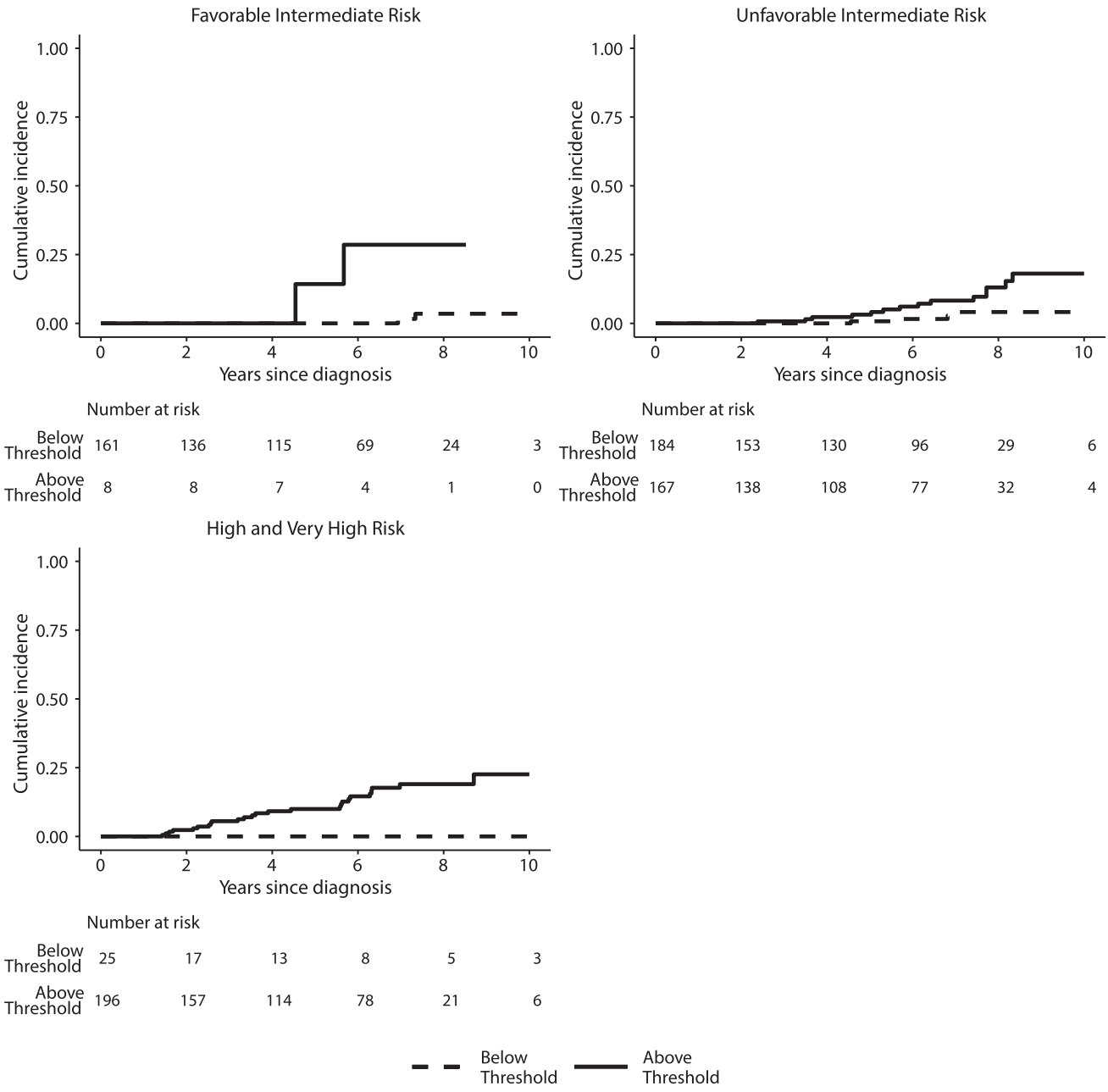

Fig. 4. Risk of metastasis during years 0 to 10 for men above or below the multimodality threshold (clinical cell-cycle risk score ≤ 2.112) stratified by National Comprehensive Cancer Network risk group. (A) Favorable intermediate risk (169 patients). (B) Unfavorable intermediate risk (351 patients). (C) High and very high risk (221 patients).

Discussion

Metastasis is one of the most clinically significant events that could occur in a man diagnosed with localized prostate cancer. The consequences include initiating systemic therapies, an increased risk of ongoing physical and emotional discomfort, financial toxicity, and decrement of quality of life. Prostate cancer metastasis is also a robust surrogate endpoint for the risk of death.[17,18] Landmark randomized controlled trials (RCTs) have shown that RT plus ADT decreases metastasis risk. The HRs for RT plus ADT versus RT alone to prevent metastases in these trials ranged from 0.37 to 0.69.[19-23] These trials included a spectrum of men who are now classified into NCCN risk groups ranging from low to very high risk. Subset analyses within each of these trials demonstrated that multimodality therapy's absolute benefit is mostly restricted to those with intermediate- or higher-risk disease.

When these trials were performed and when the current study was initiated, the NCCN had not yet further stratified intermediate-risk patients, and the recommendation for ADT use with RT was simply "plus or minus." The NCCN guidelines first stratified ADT' use with RT into those with favorable intermediate risk (not recommended) or unfavorable intermediate risk (4-6 months) in 2018. This division was based on retrospective evidence from a single center's retrospective study using dose-escalated RT. Other retrospective studies later supported this division.[24,25]

Other trials have shown that RT dose escalation (in the absence of ADT) beyond the doses used in the RCTs for RT plus ADT (≤70 Gy EQD2) could also significantly reduce the risk of metastasis in men with intermediate- or high-risk disease.[26,27] Likewise, numerous RCTs have established that longer-term ADT (≥18 months), compared with ADT of shorter duration (4-6 months), is appropriate in men with high-risk features.[28-33]

Recently, the question of whether ADT and dose-escalation combined were necessary to prevent recurrences in men with intermediate- or high-risk prostate cancer was addressed by a multicenter RCT that randomly assigned men with NCCN intermediate- and high-risk prostate cancer to receive either 4 months of neoadjuvant and concurrent ADT or an additional 24 months of ADT.[32] Those receiving long-term versus short-term ADT had a 5-year risk of metastasis of 6% versus 17% (P = .01), respectively, and the dose of RT used was ≥76 Gy EQD2. This trial validated the idea that appropriate ADT use and duration still matter in the dose-escalated RT era. It also illustrated a fundamental statistical point based on its planned subset analysis of the intermediate- versus high-risk men: The HRs for the benefit of long-term ADT were basically the same (intermediate-risk HR, 0.44; high-risk HR, 0.47), but the absolute excess risk reduction of metastasis at 5 years was quite different (5% vs 15%, respectively). This observation may be explained by the fact that the absolute baseline risk for developing metastasis differs for the intermediate- and high-risk populations, even though the relative benefit of using long-term ADT was the same in both risk groups.

The precision of time-to-event oncologic risk models is based on how well they can categorize any individual. The NCCN risk groups can categorize the men in the current study into only 4 categories (favorable and unfavorable intermediate, high, and very high risk), whereas the CAPRA system does so in 10 categories, which limits their precision. The CCR score effectively categorizes men into a continuum of risk, making it highly personalized and accurate. For both the CAPRA and the NCCN risk models, adding the information captured by the molecularly derived CCP score significantly improved prognostic performance as measured by Cox proportional hazards analysis. In addition, neither the CAPRA score nor the NCCN category added any significant prognostic information to the CCR score, but the CCR score added significant information to both the CAPRA score and the NCCN category. This indicates that the predefined CCR score fits the data well and is a better prognosticator than either the CAPRA score or the NCCN category.

Previously, a CCR multimodality threshold score was developed in men choosing surgery or RT when ADT durations and RT doses used were unknown.[2] Regardless of primary treatment (surgery or RT), men under the threshold had less than a 5% risk of progression to metastasis. For below-threshold men choosing RT, the use of ADT plus RT versus RT alone translated to an absolute risk reduction of approximately 2%. Some patients might judge the therapeutic ratio of such a small absolute benefit as clinically insignificant at the individual level, despite the proven benefit of using ADT in this population. The judgment that this modest benefit might warrant omission of ADT is shared by more than 90% of expert genitourinary radiation oncologists and 97% of other health care providers who routinely prescribe ADT.[3]

In this study population of men below the CCR score multimodality threshold, the 10-year metastasis probability was 3.7%. The observed difference in risk for metastasis in men receiving guideline-recommended durations of ADT versus an insufficient duration of ADT is <2%, with slightly but not significantly worse outcomes in men receiving the sufficient duration of ADT. This observation may represent some unaccounted-for selection bias but does not alter the fact that the baseline risk of metastasis in this population is low enough that some individuals might still consider omitting ADT when weighing the proven benefit of ADT against its potential for toxicities. This means that about 1 of every 2 men with unfavorable intermediate-risk prostate cancer and 1 of every 5 with high-risk prostate cancer might consider RT without ADT. Conversely, only 1 in 90 patients with very high-risk prostate cancer would fall below this threshold, indicating that testing in the very-high risk population is unlikely to alter management discussions with the patient. Additionally, in favorable intermediate-risk patients in whom ADT is not currently recommended with RT and genetic testing is often done to separate candidates for active

surveillance from those who should receive definitive therapy, about 1 in 20 men may benefit from the addition of ADT to RT.

The relative benefit of adding ADT of sufficient duration to RT has been proven repeatedly by large, well-powered RCTs designed to show even small differences in outcomes and is unquestioned.[19-23] However, as a prognostic biomarker in all the tested ADT-use contexts in the current study, we have shown that the CCR score is an accurate prognosticator of the absolute risk of metastasis, and exploiting this relative benefit would yield diminishing returns for most men below the threshold. The CCR score may identify patients who may derive less benefit from adding ADT to RT. Although the results showed that the CCR score is a prognostic biomarker, we do not know if it is predictive. A randomized trial would be required to prove whether omitting ADT with RT in men below the threshold identifies men who do not derive any clear benefit from multimodality therapy.

Conclusion

CCR testing is currently supported by NCCN guidelines and is a highly precise and accurate prognosticator of metastasis in men undergoing dose-escalated RT plus ADT. The CCR score adds clinically actionable information relative to guideline-recommended therapies based on NCCN risk groups. Men below the CCR multimodality threshold could be counseled about the modest absolute risk reduction of using ADT with contemporary RT doses. The ability to more accurately determine who would be less likely to derive clinically significant benefit from the addition of ADT to RT treatment would allow health care providers the opportunity to discuss mitigating ADT-related toxicities and improve quality of life in a large group of men. Patients and physicians can then decide if the relative risk-reduction, as proven by RCTs, of adding ADT to RT meets their overall treatment goals.

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