The clinical cell-cycle risk score is associated with metastasis after radiation therapy and may identify men with prostate cancer who can forgo combined androgen deprivation therapy

Jonathan Tward, MD, PhD[1]; Lauren Lenz, MS[2]; Darl D. Flake II, PhD[2]; Saradha Rajamani, PhD[2]; Carl Olsson, MD[3]; Deepak A. Kapoor, MD[3]; Constantine Mantz, MD[4]; Stanley L. Liauw, MD[5]; Tatjana Antic, MD[5]; Neal Shore, MD[6]; Dan Albertson, MD[7]; Jonathan Henderson, MD[8]; Steve P. Lee, MD[9]; Hiram A. Gay, MD[10]; Jeff Michalski, MD[10]; Arthur Hung, MD[11]; David Raben, MD[12]; Isla Garraway, MD, PhD[13]; Michael S. Lewis, MD[13]; Paul L. Nguyen, MD[14]; David T. Marshall, MD, MS[15]; Steven Stone, PhD[2]; **Todd Cohen, MD[2]**

1. Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; **2.** Myriad Genetics, Inc., Salt Lake City, UT; **3.** Advanced Radiation Center of New York, New Hyde Park, NY, and Integrated Medical Professionals, North Hills, NY; **4.** 21st Century Oncology, Fort Meyers, FL; **5.** University of Chicago Medical Center, Chicago, IL; **6.** Carolina Urologic Research Center, Myrtle Beach, SC; **7.** University of Utah Department of Anatomic Pathology and Molecular Oncology, Salt Lake City UT; **8.** Regional Urology, LLC, Shreveport, LA; **9.** Long Beach VA Medical Center, Long Beach, CA; **10.** Department of Radiation Oncology, Washington University, St. Louis, MO; **11.** Oregon Health & Science University, Portland, OR; **12.** University of Colorado, Aurora, CO; **13.** Greater Los Angeles-VA Medical Center, Los Angeles, CA; **14.** Dana-Farber Cancer Institute, Boston, MA; **15.** Medical University of South Carolina, Charleston, SC

INTRODUCTION

- This study evaluated the ability of the combined clinical cell-cycle risk score (CCR) to prognosticate the risk of prostate cancer metastasis in men receiving dose-escalated radiation therapy (RT) with or without androgen deprivation therapy (ADT).
- **BASIC CLINICAL QUESTION:** Can we identify individuals with intermediate, high, or very-high risk localized prostate cancer who have a risk of metastasis that is so low after treatment with dose-escalated radiation therapy that the relative benefit of adding ADT no longer makes clinical sense?

METHODS

- The CCR score is a validated model that combines the cell cycle progression score (CCP) with the UCSF Cancer of the Prostate Risk Assessment score (CAPRA).
- **The CCR score and a CCR-based multimodality threshold score (2.112) were evaluated in a retrospective, multi-institutional cohort of men with National Comprehensive Cancer Center (NCCN) intermediate or high-risk localized disease (N=741) who received single (RT) or multimodality therapy (ADT with RT).**
- Effects of prognostic variables were analyzed using Kaplan-Meier and Cox regression methods.

RESULTS

Table 1. CCR is a more precise prognosticator of metastasis.

	Hazard Ratio	95% CI	p-value	Concordance (C-index)
Univariate Analyses				
CCP	2.04	1.48 – 2.79	2.2×10^{-5}	0.69
CAPRA	1.39	1.22 – 1.58	9.0×10^{-7}	0.71
CCR	2.21	1.70 – 2.87	5.6×10^{-9}	0.78
NCCN Risk Group				
Favorable Intermediate	reference	-		
Unfavorable Intermediate	2.08	0.70 – 6.13	1.7×10^{-5}	0.72
High	2.79	0.82 – 9.55		
Very High	8.89	3.00 – 26.27		
CCR Split by Modality				
RT alone	2.82	1.44 – 5.30	0.0029	0.78
RT + ADT	2.08	1.48 – 2.93	2.3×10^{-5}	0.74
Bivariate Analyses				
CCP + CAPRA				
CCP	1.72	1.24 – 2.38	0.0014	
CAPRA	1.33	1.16 – 1.52	5.4×10^{-5}	0.78
CCP + NCCN				
CCP	1.66	1.19 – 2.01	0.003	
NCCN Risk Group				0.79
Favorable Intermediate	Reference	-		
Unfavorable Intermediate	1.89	0.64 – 5.60		
High	2.14	0.62 – 7.41		
Very High	6.10	2.00 – 18.62	0.0014	
CCP + ISUP Grade				
CCP	1.78	1.27 – 2.49	9.9×10^{-4}	
ISUP Grade				
Grade 1, Gleason < 7	Reference	-		
Grade 2, Gleason = 3+4	1.31	0.17 – 10.26	0.024	0.76
Grade 3, Gleason = 4+3	2.91	0.38 – 22.01		
Grade 4, Gleason = 8	2.90	0.35 – 23.75		
Grade 5, Gleason ≥ 9	5.36	0.68 – 42.29		
CCR + ADT continuous duration (n = 733)				
CCR	2.11	1.59 – 2.79	3.0×10^{-7}	0.77
Months of ADT	1.01	0.99 – 1.03	0.45	
CCR + Sufficient ADT duration (n = 734)				
CCR	2.19	1.68 – 2.84	1.0×10^{-8}	
Insufficient ADT	Reference			0.77
Sufficient ADT	1.43	0.79 – 2.66	0.24	

Figure 1. CCR Multimodality Threshold Performance (Metastasis).

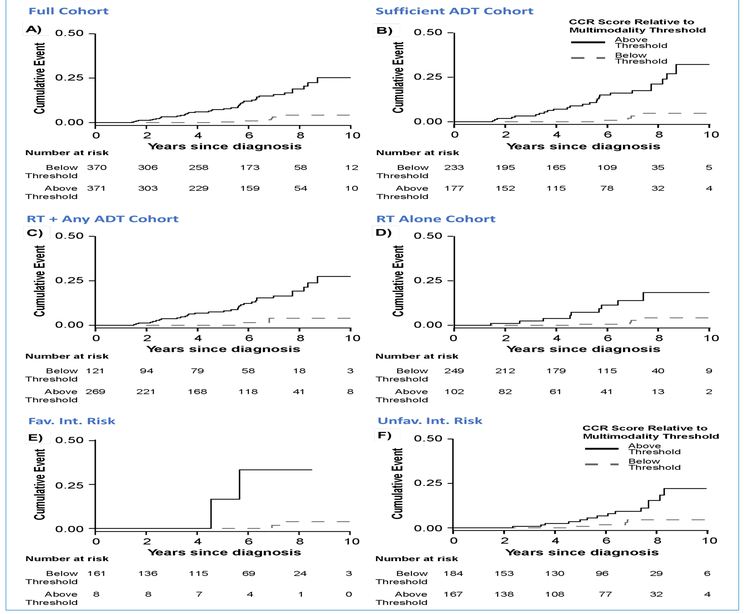
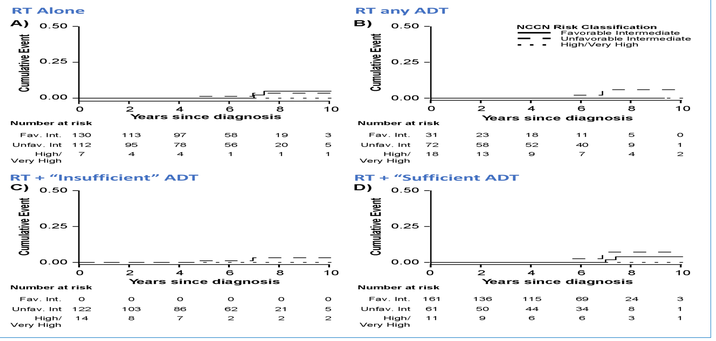


Figure 2. Performance below the threshold by NCCN Risk and ADT use.



- Median follow-up was 5.6 years. CCR predicted metastasis (Table 1).
- **The CCR score was a better prognosticator of metastasis than either NCCN-risk group, CAPRA score, or CCP score alone (Table 1).**
- **In bivariate analyses, the CCR score remained highly prognostic for metastasis when comparing any ADT vs none, ADT duration as a continuous variable, or ADT use given as less than or at the recommended duration for each NCCN risk group (Table 1).**
- Men with CCR scores either below or above the threshold (2.112) had a 10-year risk of metastasis of 4.1 % and 25.3%, respectively (Figure 1).
- For men below the threshold receiving RT alone versus RT+ADT, the 10-year risk of metastasis was 4.2% and 3.9%, respectively (Figure 2).

CONCLUSIONS

- CCR is a highly precise and accurate predictor of metastasis in men undergoing dose-escalated RT, with or without ADT.
- **CCR adds clinically actionable information relative to guideline recommended therapies that are based on NCCN risk groups or CAPRA alone.**
- **Men with scores below the multimodality threshold may not significantly reduce their 10-year risk of metastasis with the addition of ADT.**

The Basic Clinical Question:

- *Can we identify individuals with intermediate, high, or very-high risk localized prostate cancer who have a risk of metastasis that is so low after treatment with dose-escalated radiation therapy that the relative benefit of adding ADT no longer makes clinical sense?*

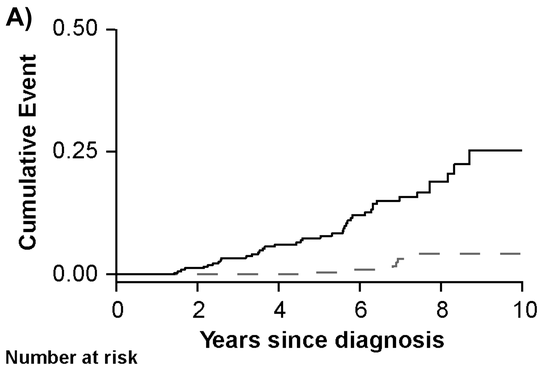
Key Points:

- CCR is Prognostic for Metastases in both RT alone and RT+ADT contexts.
- CCR is prognostic for metastases no matter how you account for how ADT was given.
- CCR is a more precise and accurate prognosticator of metastasis than NCCN Risk, CAPRA, or CCP Score alone.
- **The CCP Score adds additional useful prognostic information even when accounting for NCCN Risk, CAPRA, or ISUP Grade Group.**

	Hazard Ratio	95% CI	p-value	Concordance (C-index)
Univariate Analyses				
CCP	2.04	1.48 – 2.79	2.2×10^{-5}	0.69
CAPRA	1.39	1.22 – 1.58	9.0×10^{-7}	0.71
CCR	2.21	1.70 – 2.87	5.6×10^{-9}	0.78
NCCN Risk Group			1.7×10^{-5}	0.72
Favorable Intermediate	reference	-		
Unfavorable Intermediate	2.08	0.70 – 6.13		
High	2.79	0.82 – 9.55		
Very High	8.89	3.00 – 26.27		
CCR Split by Modality				
RT alone	2.82	1.44 – 5.30	0.0029	0.78
RT + ADT	2.08	1.48 – 2.93	2.3×10^{-5}	0.74
Bivariate Analyses				
CCP + CAPRA				
CCP	1.72	1.24 – 2.38	0.0014	0.78
CAPRA	1.33	1.16 – 1.52	5.4×10^{-5}	
CCP + NCCN				
CCP	1.66	1.19 – 2.01	0.003	0.79
NCCN Risk Group			0.0014	
Favorable Intermediate	Reference	-		
Unfavorable Intermediate	1.89	0.64 – 5.60		
High	2.14	0.62 – 7.41		
Very High	6.10	2.00 – 18.62		
CCP + ISUP Grade				
CCP	1.78	1.27 – 2.49	9.9×10^{-4}	0.76
ISUP Grade			0.024	
Grade 1, Gleason < 7	Reference	-		
Grade 2, Gleason = 3+4	1.31	0.17 – 10.26		
Grade 3, Gleason = 4+3	2.91	0.38 – 22.01		
Grade 4, Gleason = 8	2.90	0.35 – 23.75		
Grade 5, Gleason ≥ 9	5.36	0.68 – 42.29		
CCR + ADT continuous duration (n = 733)				
CCR	2.11	1.59 – 2.79	3.0×10^{-7}	0.77
Months of ADT	1.01	0.99 – 1.03	0.45	
CCR + Sufficient ADT duration (n = 734)				
CCR	2.19	1.68 – 2.84	1.0×10^{-8}	0.77
Insufficient ADT	Reference		0.24	
Sufficient ADT	1.43	0.79 – 2.66		

CCR Multimodality Threshold Performance (Metastasis)

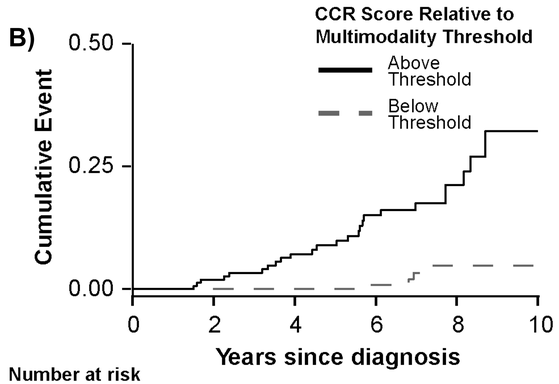
Full Cohort



Number at risk

Below Threshold	370	306	258	173	58	12
Above Threshold	371	303	229	159	54	10

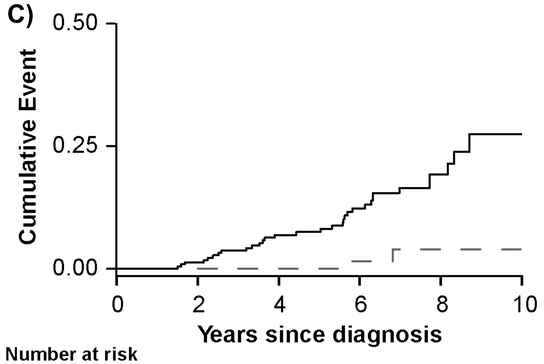
Sufficient ADT Cohort



Number at risk

Below Threshold	233	195	165	109	35	5
Above Threshold	177	152	115	78	32	4

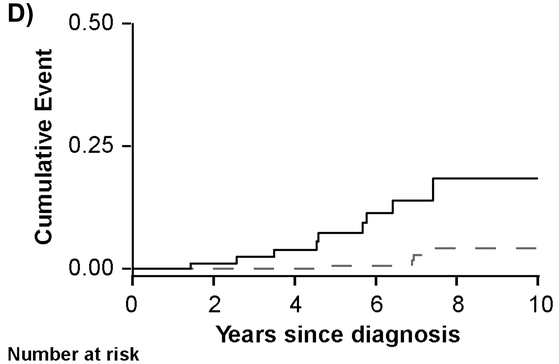
RT + Any ADT Cohort



Number at risk

Below Threshold	121	94	79	58	18	3
Above Threshold	269	221	168	118	41	8

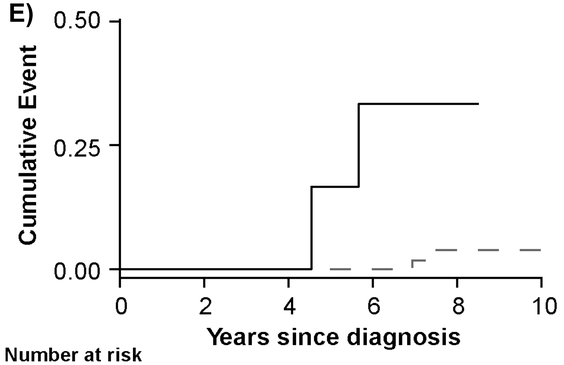
RT Alone Cohort



Number at risk

Below Threshold	249	212	179	115	40	9
Above Threshold	102	82	61	41	13	2

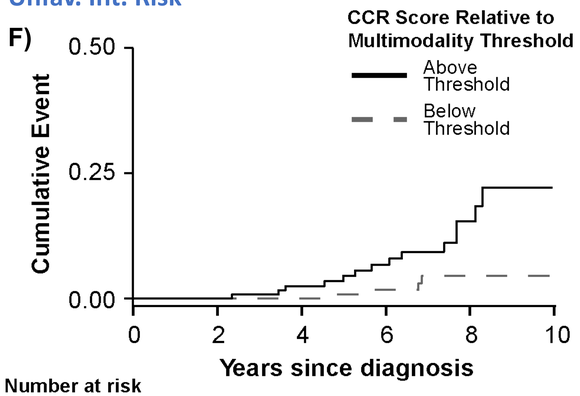
Fav. Int. Risk



Number at risk

Below Threshold	161	136	115	69	24	3
Above Threshold	8	8	7	4	1	0

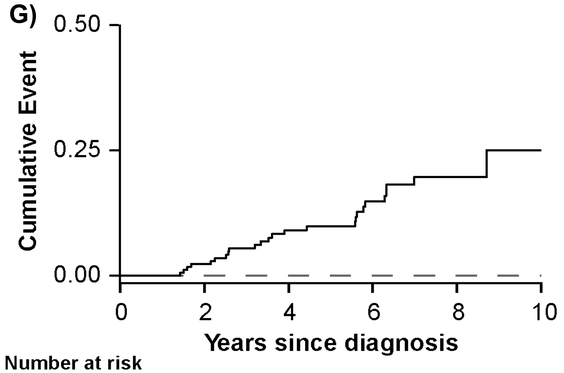
Unfav. Int. Risk



Number at risk

Below Threshold	184	153	130	96	29	6
Above Threshold	167	138	108	77	32	4

High/Vhigh Risk



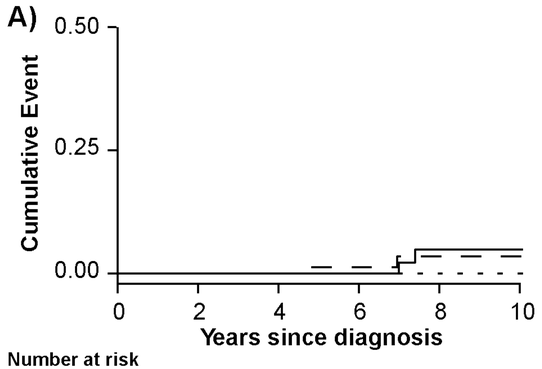
Number at risk

Below Threshold	25	17	13	8	5	3
Above Threshold	196	157	114	78	21	6

- **Below the threshold the risk of metastasis is less than 5% at ten years in any context.**

Performance below the threshold by NCCN Risk and ADT use

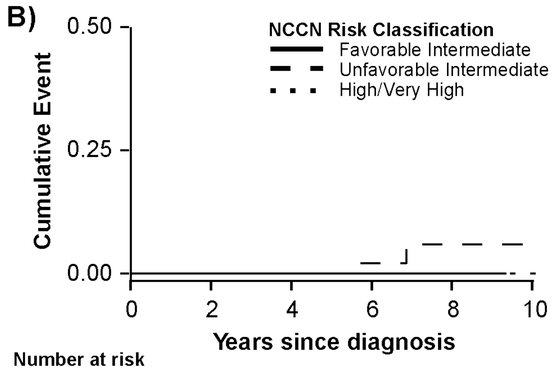
RT Alone



Number at risk

Fav. Int.	130	113	97	58	19	3
Unfav. Int	112	95	78	56	20	5
High/ Very High	7	4	4	1	1	1

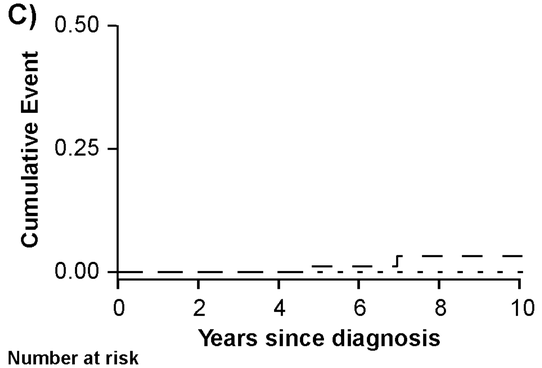
RT any ADT



Number at risk

Fav. Int.	31	23	18	11	5	0
Unfav. Int	72	58	52	40	9	1
High/ Very High	18	13	9	7	4	2

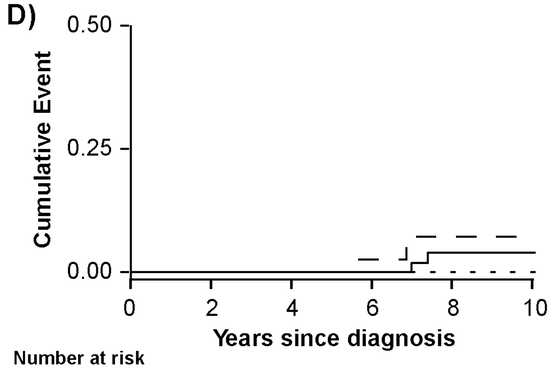
RT + "Insufficient" ADT



Number at risk

Fav. Int.	0	0	0	0	0	0
Unfav. Int	122	103	86	62	21	5
High/ Very High	14	8	7	2	2	2

RT + "Sufficient ADT



Number at risk

Fav. Int.	161	136	115	69	24	3
Unfav. Int	61	50	44	34	8	1
High/ Very High	11	9	6	6	3	1

- Men with a CCR score ≤2.112 (below or at the threshold) receiving dose-escalated EBRT have a 10-year risk of metastasis of only 4.1% overall. (RT alone 4.2%, RT+ADT 3.9%).
- The relative risk reduction ADT provides translates to a minimal absolute difference.
- NCCN Risk Groups are no longer metastasis "risk" prognosticators below the multimodality threshold.

CONCLUSIONS:

- **CCR is a highly precise and accurate predictor of metastasis in men undergoing dose-escalated RT, with or without ADT.**
- **CCR adds clinically actionable information relative to guideline recommended therapies that are based on NCCN risk groups or CAPRA alone.**
- **Men with scores below the multimodality threshold may not significantly reduce their 10-year risk of metastasis with the addition of ADT.**