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

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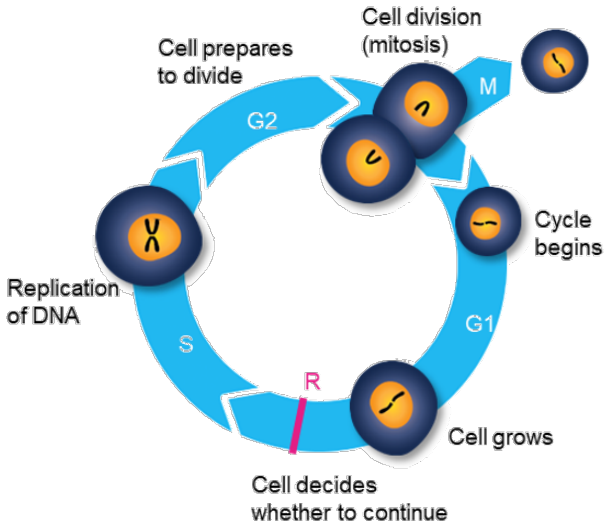
The Basic Clinical Question

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?

What Does the Prolaris™ Test Measure?

Cell Cycle Proliferation (CCP) Genes Control Cell Growth and Division



MYRIAD Prolaris® Prostate Cancer

Intended Use:

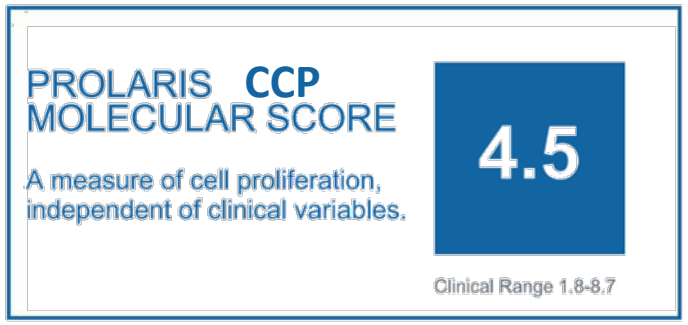
- Biopsy-confirmed, localized prostate cancer
- Treatment decision not yet made

Reports:

- Aggressiveness of tumor growth
- 10-year disease-specific mortality risk
- 10-year metastasis risk

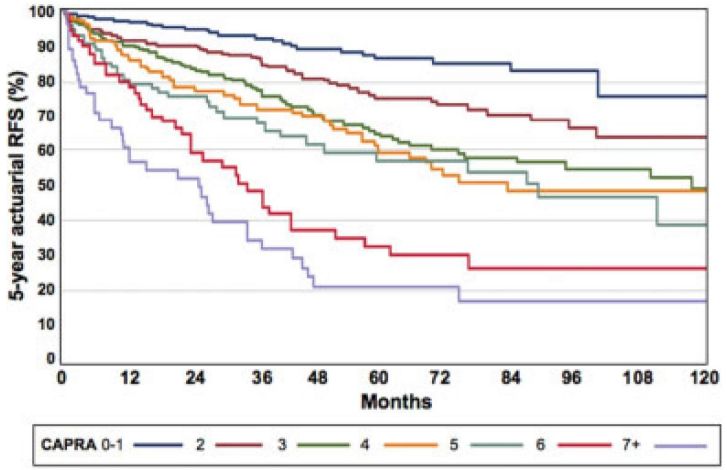
- **31 CCP genes**
- **15 housekeeper genes**
- **The CCP score is the average expression level of the CCP genes, normalized to the housekeepers**

The Risk of Metastasis is based on a **Combined** Clinical and Cell-Cycle Risk Score (**CCR**)



Cell Cycle Score:
4.0 is the Average
1.8 – 8.7 scale
IQR= 3-4

AND



UCSF CAPRA
0-10 scale
Clinical Factors:

- Age
- PSA
- Gleason
- T-Stage
- % cores +

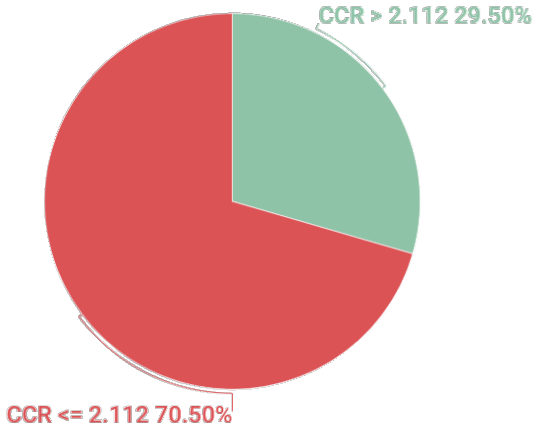
CCR = (0.39 * CAPRA Score) + (0.57 * (CCP Score – 4))

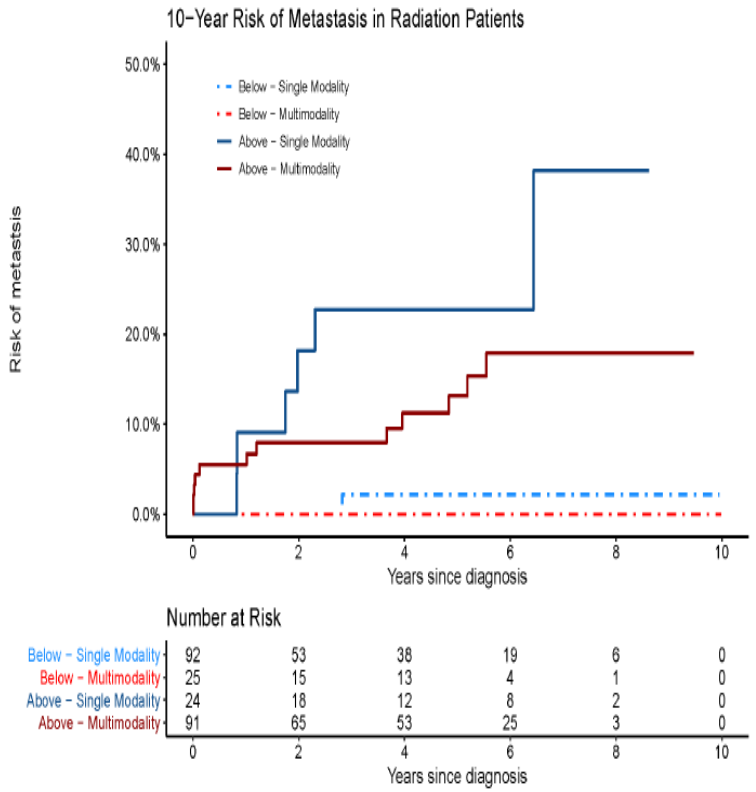
1. Cuzick, J., Stone, S., Fisher, G., Yang, Z. H., North, B. V., Berney, D. M., Beltran, L., Greenberg, D., Møller, H., Reid, J. E., Gutin, A., Lanchbury, J. S., Brawer, M., & Scardino, P. (2015). Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *British journal of cancer*, *113*(3), 382–389. https://doi.org/10.1038/bjc.2015.223
2. Cooperberg MR, Freedland SJ, Pasta DJ, et al: Multiinstitutional validation of the UCSF cancer of the prostate risk assessment for prediction of recurrence after radical prostatectomy. Cancer 107:2384-2391, 2006
3. Cooperberg, M.R., J.M. Broering, and P.R. Carroll, Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. J Natl Cancer Inst, 2009. 101(12): p. 878-87.

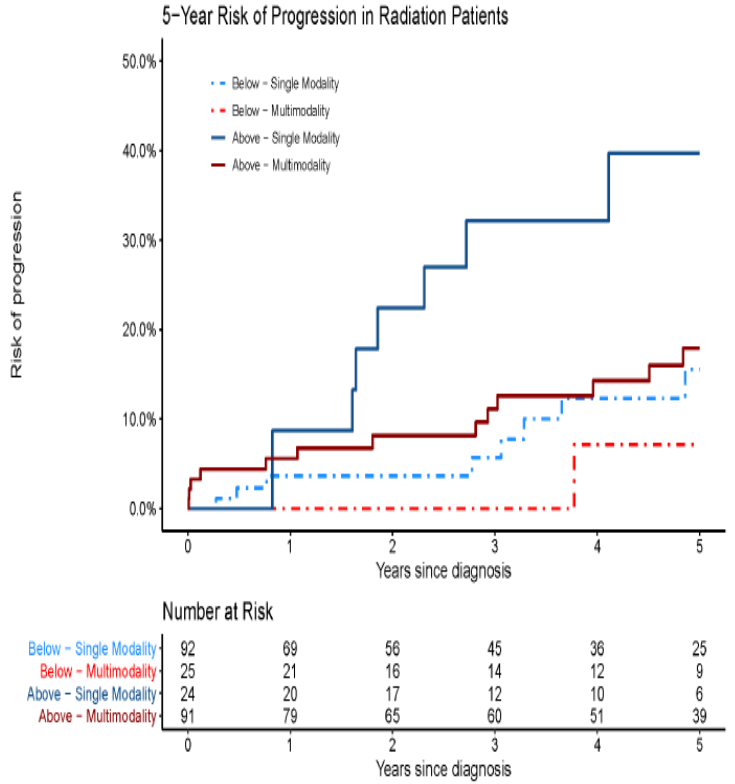
Prior **development study** of a CCR multimodality score threshold in radiated patients with or without ADT

In a **Prior Study** with both surgery and radiation patients, we PRE-SPECIFIED
A CCR score= 2.112 as a threshold
To evaluate if men below this threshold Could omit multimodality therapies

Distribution of CCR scores in 15,669 Intermediate or High Risk Patients from commercial testing







POSTER at GUCASYM 2020: Manuscript submitted and under editor requested revisions
Ability of the combined clinical cell-cycle risk score to identify patients that benefit from multi versus single modality therapy in NCCN intermediate and high-risk prostate cancer.
Tward JD, Schlomm T, Bardot S, Freedland SJ, Lenz L, Cohen T, Stone S, and Bishoff J. Journal of Clinical Oncology 2020 38:6_suppl, 346-346

Limitations of the Development Study in RT Patients Addressed by the Current Study

1. Dose of Radiation used was not accounted for
2. Heterogeneity of RT techniques used (beam, brachy, combos; 3D, IMRT, field design, margins not accounted for etc.)
3. Duration of ADT use not accounted for
4. Relatively small number of radiation subsets

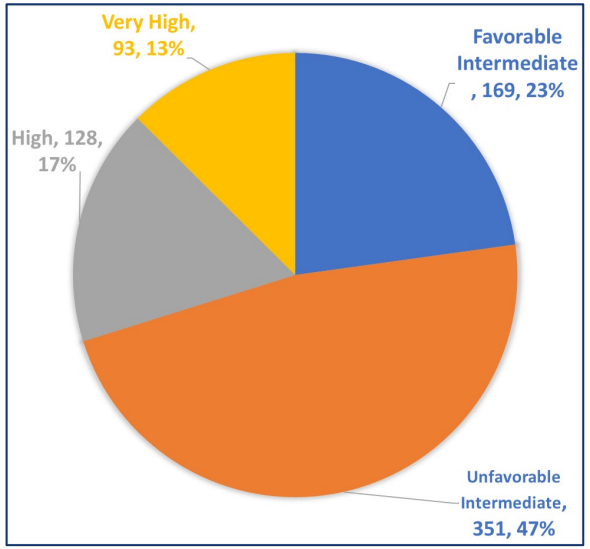
Validation Study: Inclusion Criteria:

- Biopsy proven NCCN intermediate or high/very high risk localized prostate cancer
- EBRT (no brachy) using 3D conformal, IMRT, VMAT, or DCA techniques using moderately hypofractionated to conventional fractionation on linear accelerators with energies between 4 and 18 MeV.
- EQD2 of >=71.8 Gy (**equivalent to at least 75.6Gy at 1.8Gy per fraction**), assuming a/b ratio =2
- Field: prostate ± seminal vesicles with no less than a 5mm margin to the Planning Target Volume (PTV).
- CT-based treatment planning was required.
- Subjects who received elective pelvic nodal radiotherapy in addition to radiotherapy of the prostate was allowed, regardless of pelvic field design or dose.
- **ADT use and duration known**

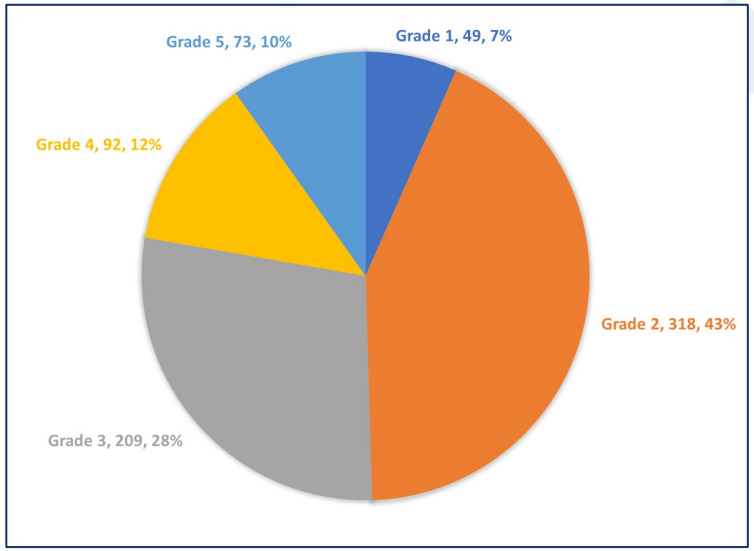
Demographics, N=741

	Median (IQR)
Age (yrs)	70 (65 -75)
CCP Score	4.5 (4 – 5.1)
CCR Score	2.1 (1.5 – 2.9)
CAPRA score	5 (3 – 6)
PSA	7.9 (5.2 – 13.4)

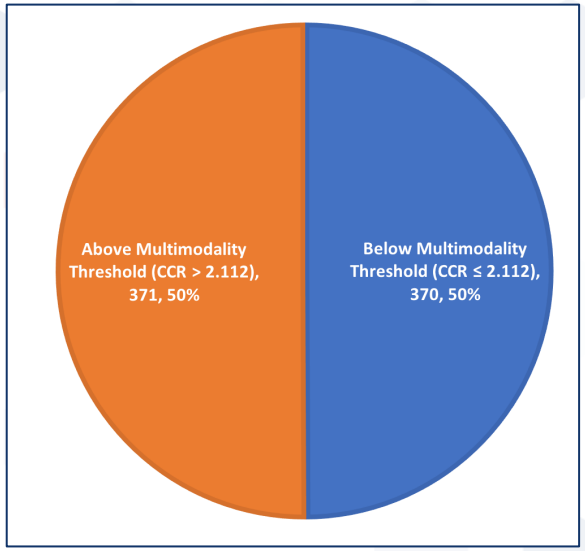
NCCN RISK GROUP

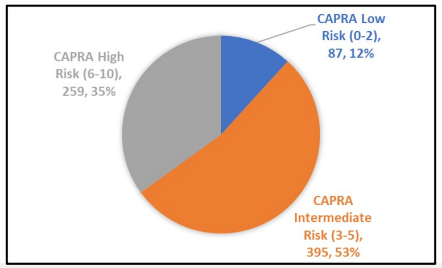


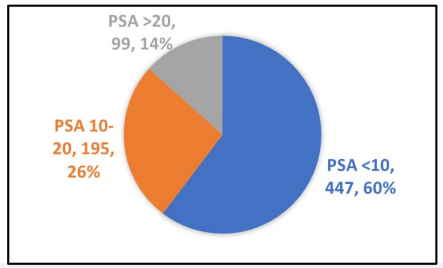
ISUP GRADE GROUP

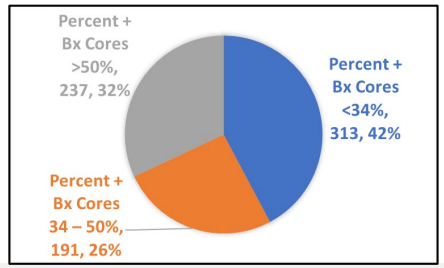


CCR Threshold Distribution



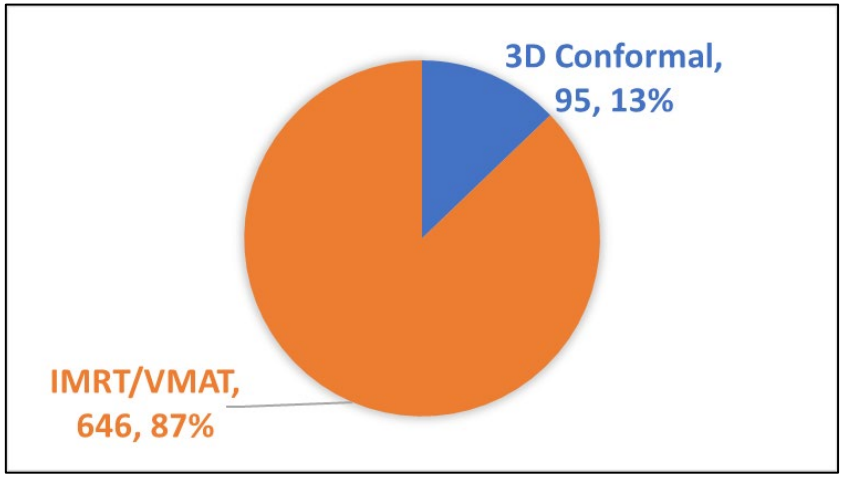




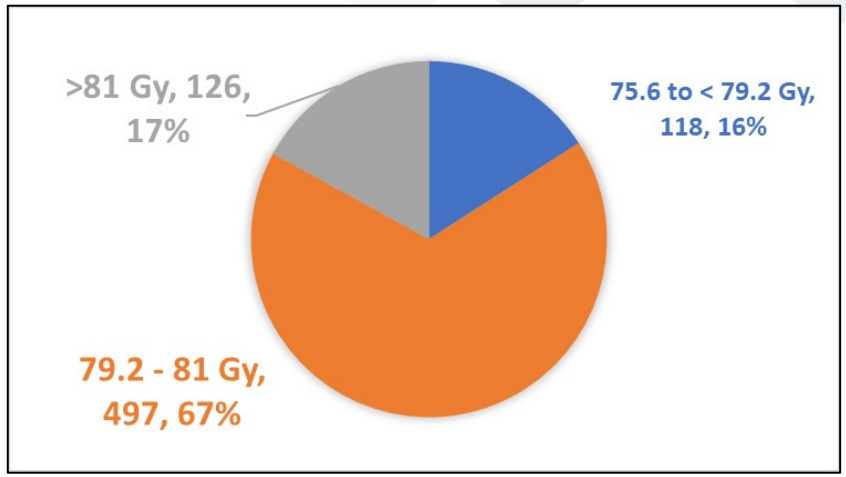


Radiation/ADT Details

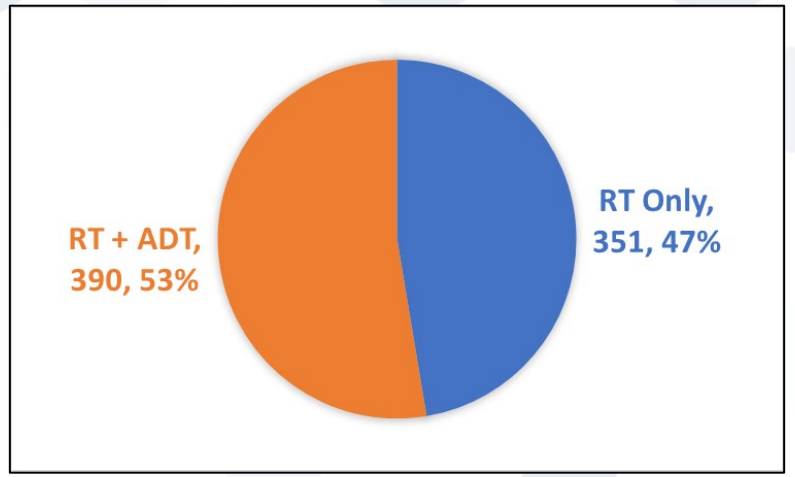
RT Technique

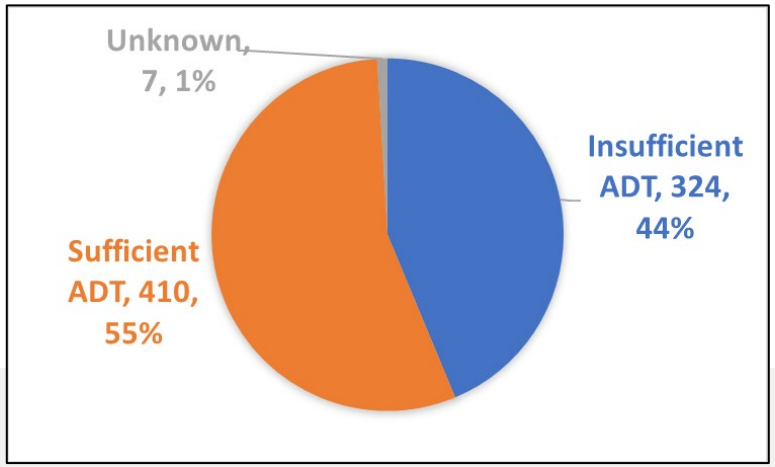


Dose in 1.8 Gy Equivalents



ADT use





ADT Sufficiency Definition:

- Fav Int patients: Any or No ADT
- Unfav Intermediate: 4 months minimum
- High/Vhigh: 18 months minimum

Risk Group	ADT Duration in months Mean (IQR)
Fav Int.	0.9 (0 – 0)
Unfav. Int.	4.0 (0 – 6)
High/Vhigh	14.6 (5 – 24)

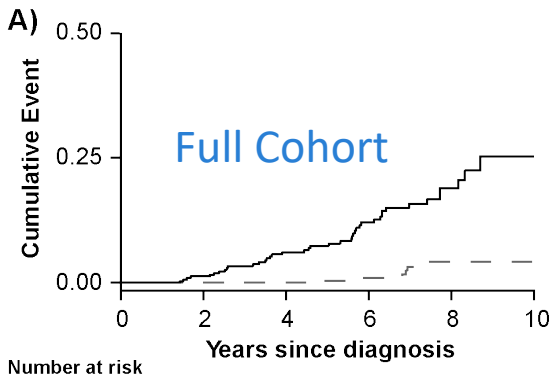
Results

	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				
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}	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		

Key Points:

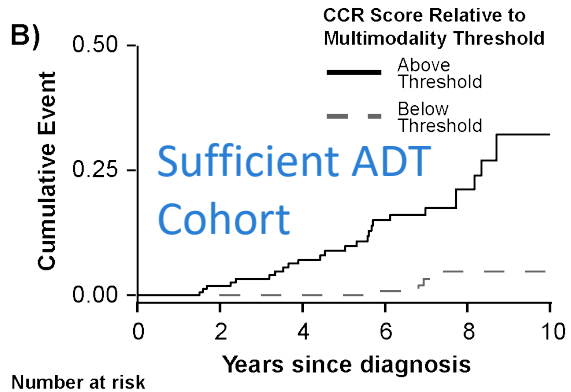
- CCR is Prognostic for Metastases in both RT alone and RT+ADT contexts
- CCR is prognostic for metastases no matter how you account for how ADT was given
- CCR is a more precise and accurate prognosticator of metastasis than NCCN Risk, CAPRA, or CCP Score alone.
- **The CCP Score adds additional useful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

CCR Multimodality Threshold Performance (Metastasis)



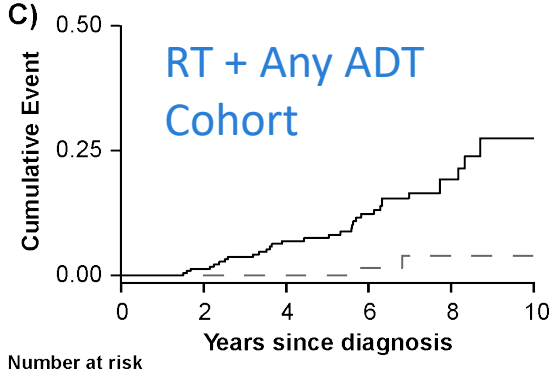
Number at risk

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



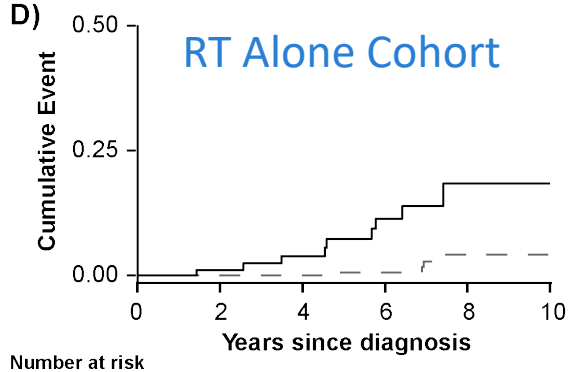
Number at risk

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



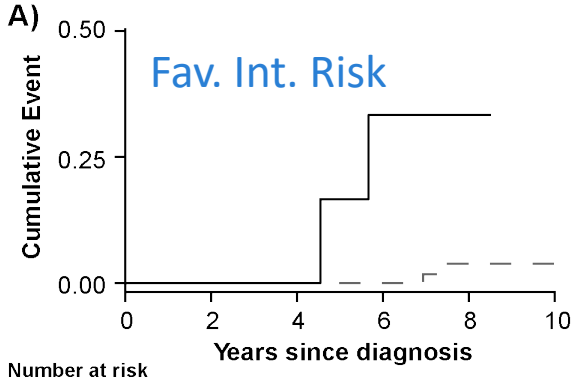
Number at risk

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



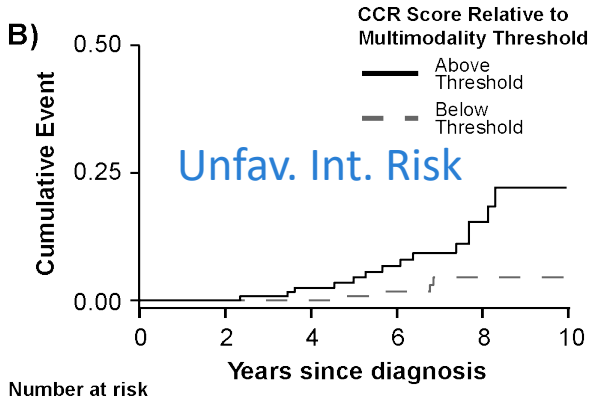
Number at risk

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



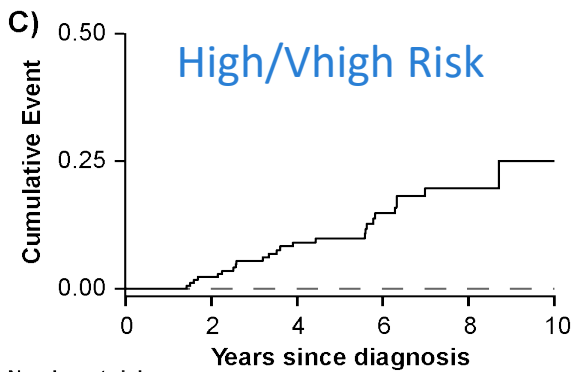
Number at risk

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



Number at risk

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



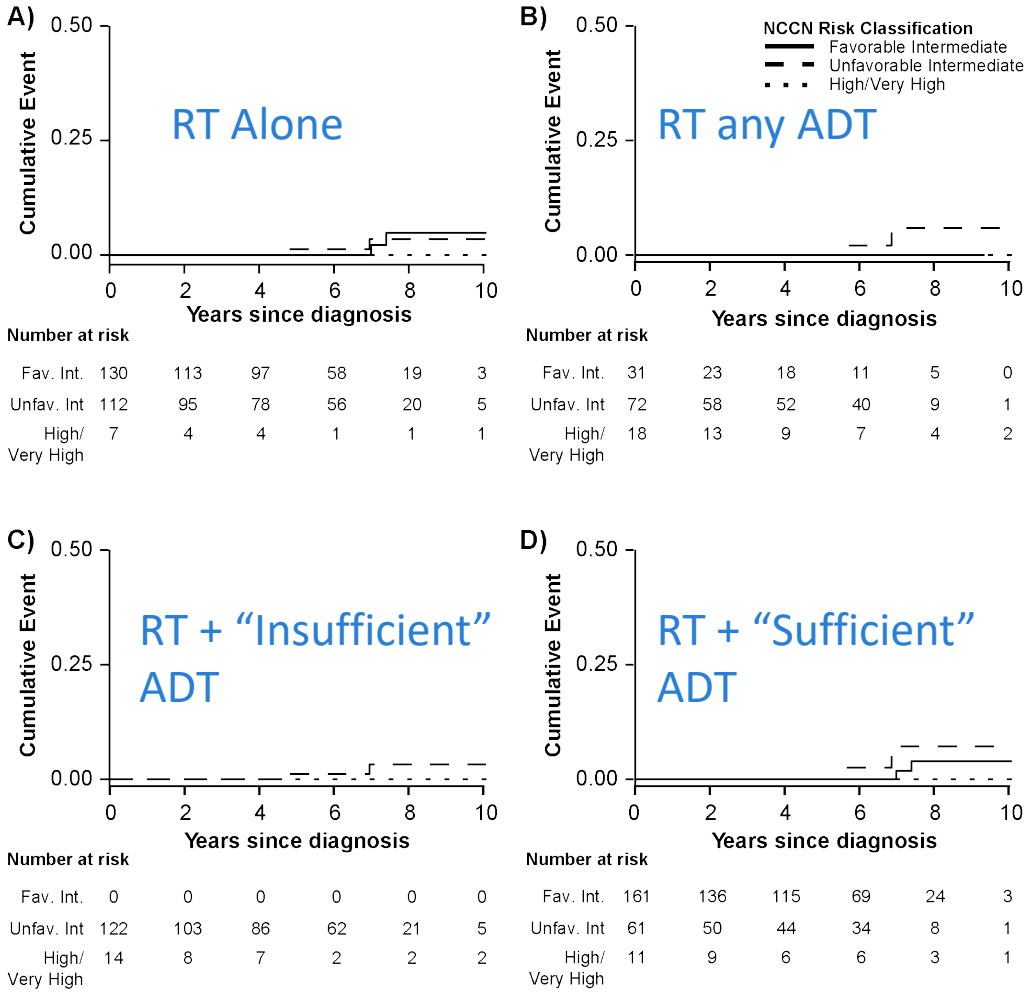
Number at risk

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

Key Point:

- 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



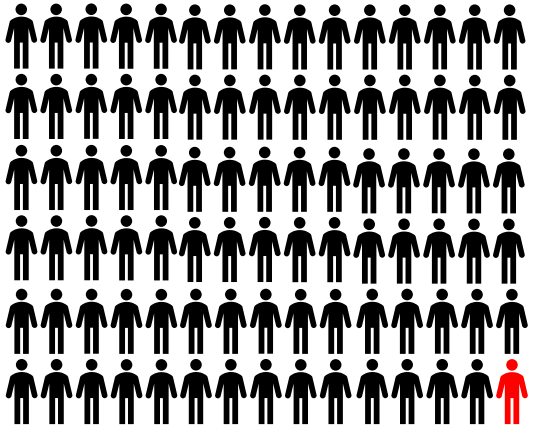
Key Points:

- 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

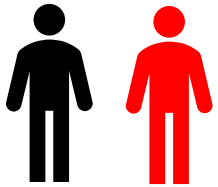
What proportion of men in each NCCN Risk Group could consider omitting ADT when undergoing dose-escalated RT?

About one of every two men with unfavorable intermediate-risk and one of every five with high-risk prostate cancer are below the multimodality threshold

Favorable Intermediate

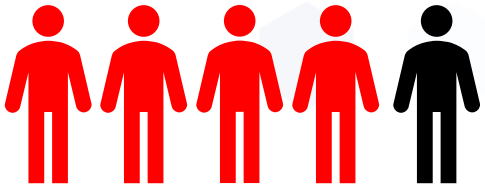


Unfavorable Intermediate



½ could avoid ADT

High/Very-High Risk



1/5 could avoid ADT

Below the Multimodality Threshold

Above the Multimodality Threshold

Discussion: the **RELATIVE** benefit of adding ADT to RT is Proven

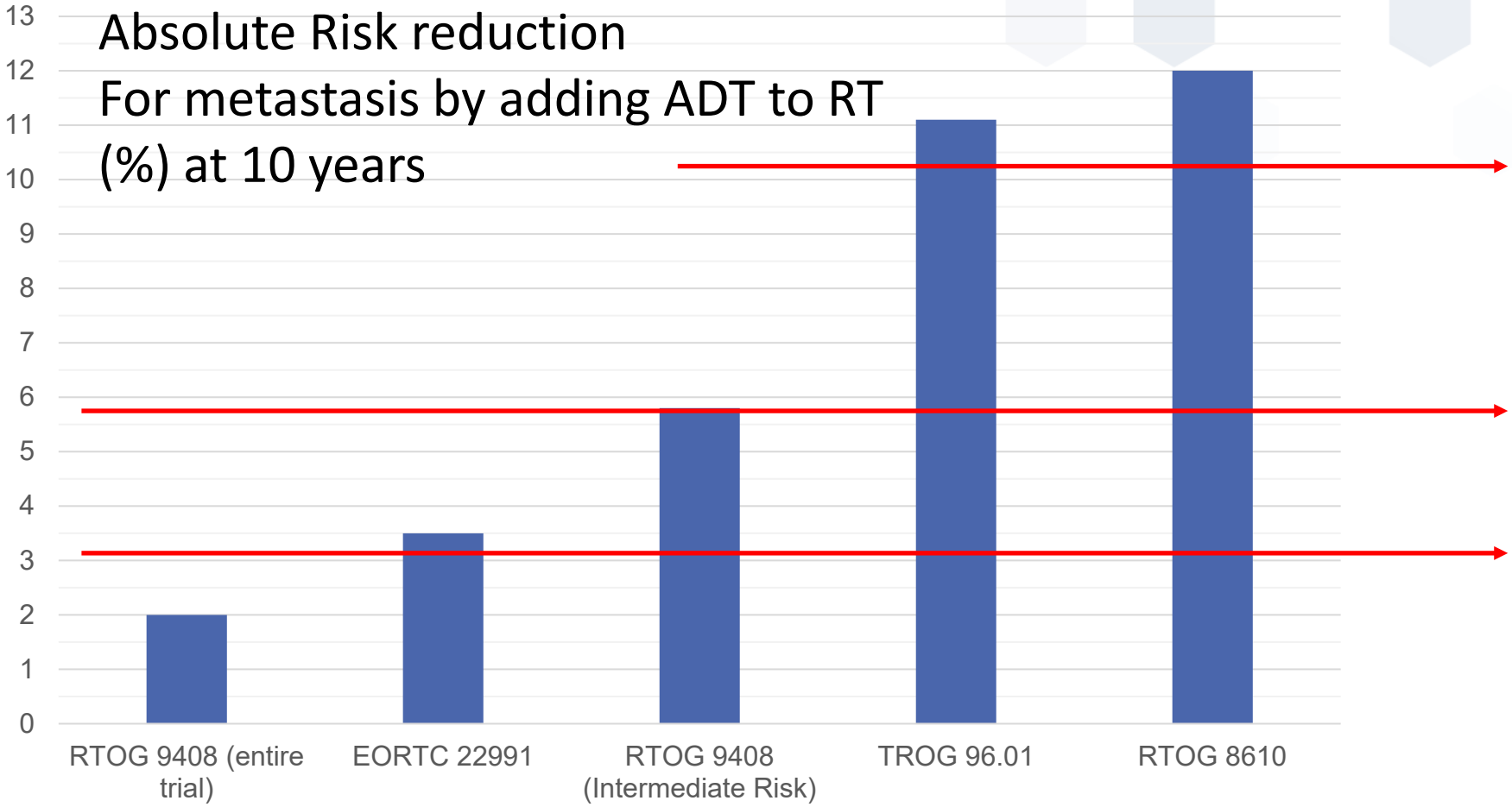
Trials of ADT+RT vs RT alone

Metastasis free survival hazard ratios supporting ADT

RTOG 8610, HR= 0.67 [1] – (generally bulky, high Gleason, high PSA, ± nodes)
RTOG 8531, HR=0.53[2] – (bulky T3, ± nodes)
RTOG 9408, HR 0.69[3] – (T1-T2, PSA<20, N0)
TROG 9601, HR 0.49[4] – (bulky T2b-T4, N0)
EORTC 22991, HR 0.63[5] – (basically intermediate and high-risk patients, non-bulky)

1. Roach M, Bae K, Speight J, et al: Short-Term Neoadjuvant Androgen Deprivation Therapy and External-Beam Radiotherapy for Locally Advanced Prostate Cancer: Long-Term Results of RTOG 8610. Journal of Clinical Oncology 26:585-591, 2008
2. Pilepich MV, Winter K, Lawton CA, et al: Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 61:1285-90, 2005
3. Jones CU, Hunt D, McGowan DG, et al: Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 365:107-18, 2011
4. Denham JW, Steigler A, Lamb DS, et al: Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol 12:451-9, 2011
5. Bolla M, Maingon P, Carrie C, et al: Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991. Journal of Clinical Oncology 34:1748-1756, 2016

But the **ABSOLUTE** benefit depends on the underlying risk of the populations



Number needed to treat
For 1 to benefit

Spratt D, Tward JD. *Absolute versus Relative Benefit of Androgen Deprivation Therapy for Prostate Cancer: Moving Beyond the Hazard Ratio to Personalize Therapy*. International Journal of Radiation Oncology, Biology, Physics, Volume 108, Issue 4, 899 - 902

Why is Metastasis a Good Endpoint?

VOLUME 35 · NUMBER 27 · SEPTEMBER 20, 2017

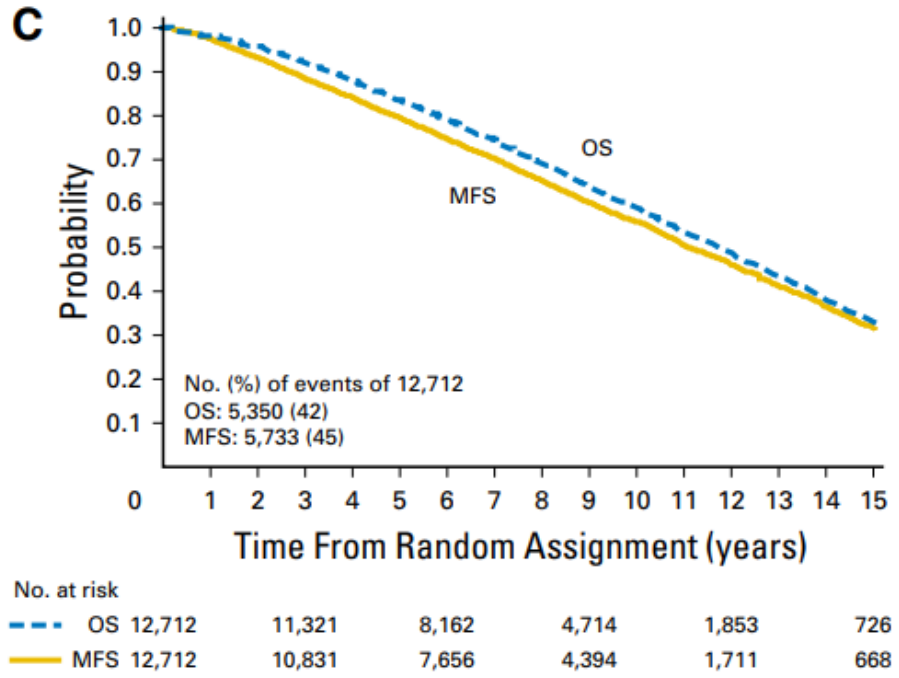
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy R. Paruleker, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher J. Sweeney, on behalf of the ICECaP Working Group

From: the international Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group

12,712 patients from 19 trials had documented data on MFS, **90% of these patients were enrolled on RT trials**

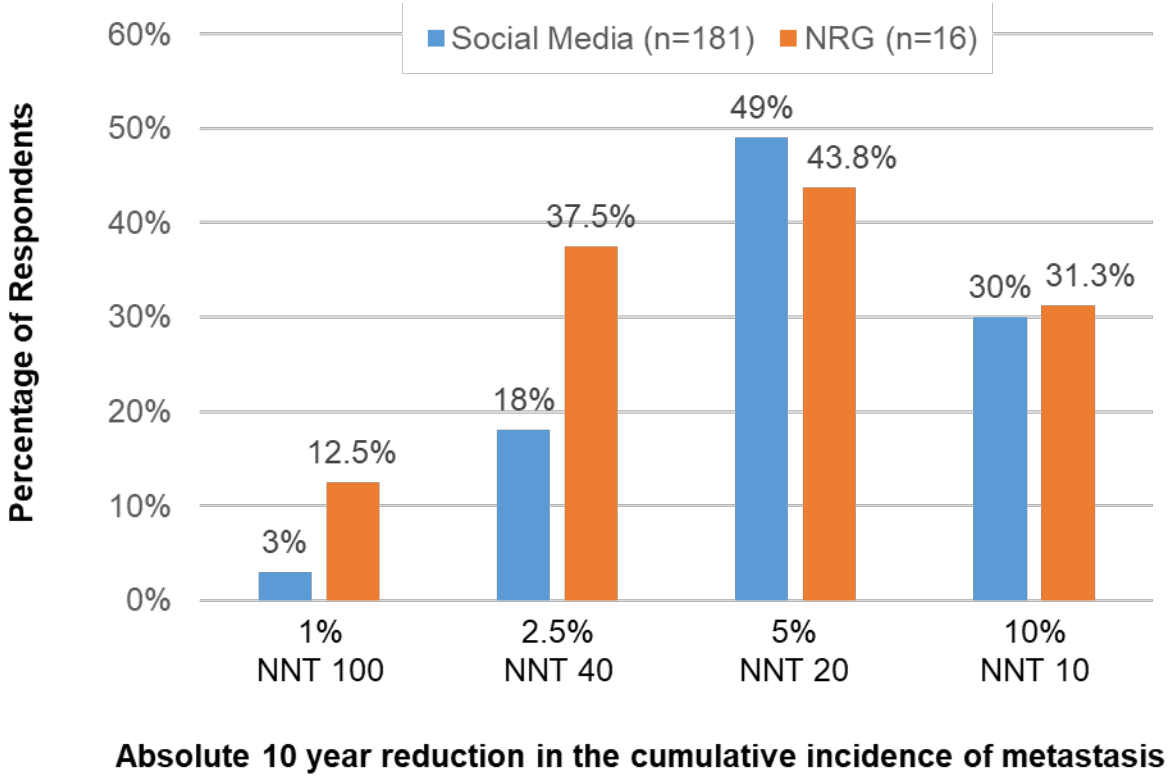


Conclusion

MFS is a strong surrogate for OS for localized prostate cancer that is associated with a significant risk of death from prostate cancer.

What absolute risk reduction of using ADT with RT to prevent metastasis is clinically significant?

Poll: At what absolute risk reduction threshold would you personally accept ADT with RT if you were the patient?



Key Points:

- No correct answer. Highly personal decision
- Both GU physician experts and physicians in general have different thresholds for when they would consider using ADT on themselves if they were the patient
- The CCR score provides a highly precise and personalized risk estimate that informs the discussion

Spratt D, Tward JD. *Absolute versus Relative Benefit of Androgen Deprivation Therapy for Prostate Cancer: Moving Beyond the Hazard Ratio to Personalize Therapy.* International Journal of Radiation Oncology, Biology, Physics, Volume 108, Issue 4, 899 - 902

Conclusion: The Prolaris ™ test provides useful and actionable information for shared-decision making between the patient and radiation oncologist

PROLARIS MOLECULAR SCORE

A measure of cell proliferation, independent of clinical variables.

2.3

Clinical Range 1.8-8.7

VARIABLES USED FOR RISK ASSESSMENT

Prolaris Molecular Score:	**2.3**
Patient Age at Biopsy:	**68**
PSA Prior to This Biopsy:	**7.0**
Clinical T Stage:	**T1c**
% Positive Cores:	**< 34%**
Gleason Score:	**4+3=7 (Group 3 ISUP[1])**
NCCN Risk[2]:	**Unfavorable Intermediate**

PROLARIS TEST RESULT SUMMARY

Based on a 10-year Metastasis (METs) risk of 1.8% with active treatment, this patient is a candidate for single-modal treatment.