Predicting Absolute Benefit in Risk of Metastasis of Androgen Deprivation Therapy added to Radiation Therapy in Patients with Newly Diagnosed Prostate Cancer

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The CCR score can accurately predict an individual's absolute risk reduction for metastasis by using multimodality ADT+RT over RT alone, regardless of NCCN risk group.

The Multimodality Treatment Threshold is consistent with patient attitudes about when to use or omit ADT and can be a useful guideline for treatment intensification discussions.

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BACKGROUND/METHODS

Most patients would defer using androgen deprivation therapy (ADT) with radiation therapy (RT) when the number-needed-to-treat (NNT) exceeds 25 persons to prevent 1 from developing metastasis, corresponding to an absolute benefit (AB) of 4%.[1] However, no tools for estimating personalized NNT or AB from ADT exist. We aimed to quantify personalized AB and NNT for persons receiving ADT added to single modality RT.

The clinical cell-cycle risk (CCR) score combines the University of California, San Francisco's Cancer of the Prostate Risk Assessment and the cell cycle progression molecular score to accurately assess prostate cancer aggressiveness. The effect of ADT added to RT was modeled using a 10-year risk of metastasis as a function of continuous CCR score for patients treated with RT alone (Table 1). The relative benefit of ADT added to RT to reduce distant metastasis was modeled using published data from The Meta-Analysis of Randomized Trials in Cancer of the Prostate (MARCAP) which utilized several prospectively randomized RT±ADT trials.[2] Methods for calculating absolute benefit from risk and relative benefit are shown in Figure 1. The average absolute benefit was calculated for patients with CCR scores above and below a prespecified multimodality treatment threshold (MMT; CCR = 2.112) using the distribution of scores in a cohort of patients commercially tested by Myriad Genetics.

1. Spratt DE, Tward JD: IJROBP 108:899-902, 2020   2. Kishan AU, Sun Y, Hartman H, et al. Lancet Oncol 23:304-316, 2022

This study is funded by: Myriad genetics

A. Risk of 10-year metastasis with single-mode therapy

Ten-year risk of metastasis with single-mode RT was estimated from the Single-Mode Radiation Therapy Cohort. Risks were predicted using a cause-specific Cox proportional hazards model with continuous CCR score predicting time to metastasis, censored at 10-years.

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B. Model risk of 10-year metastasis with multimodal therapy (RT + ADT)

$$r_{RT+ADT} = 1 - (1 - r_{RT})^{HR_{ADT}}$$

r_{RT}	Risk of 10-year metastasis in patients treated with single-mode RT from part A
r_{RT+ADT}	Risk of 10-year metastasis in patients treated with RT+ADT
HR_{ADT}	Hazard ratio for relative benefit of ADT in the population, HR = 0.59, 95% CI 0.52 – 0.68[2]

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C. Calculate absolute benefit from ADT

$$AB = r_{RT} - r_{RT+ADT}$$

Figure 1: Overview of statistical methods to model ADT benefit as a function of CCR score.

	Single-Mode RT Cohort N=467 N (%) or Median (IQR)	Commercial Cohort N=56,485 N (%) or Median (IQR)
Patient age at diagnosis	70 (64, 76)	67 (62, 72)
Gleason Score		
<7	68 (14.6%)	22216 (39.3%)
3+4	263 (56.3%)	21962 (38.9%)
4+3	110 (23.6%)	7797 (13.8%)
>7	26 (5.6%)	4510 (8.0%)
Percent positive cores	33.3% (21.4%, 50.0%)	25.0% (13.0%, 41.0%)
Diagnostic PSA	7.0 (5.0, 11.1)	6.2 (4.8, 8.2)
CAPRA	4 (3, 5)	3 (2, 4)
NCCN		
Very Low/Low Risk	0 (0%)	19013 (33.7%)
Favorable Intermediate Risk	172 (36.8%)	16812 (29.8%)
Unfavorable Intermediate Risk	254 (54.4%)	14453 (25.6%)
High/Very High Risk	41 (8.8%)	6207 (11.0%)
CCP Score	0.3 (-0.2, 0.8)	-0.5 (-1.0, 0.0)
CCR Score	1.617 (1.122, 2.178)	0.771 (0.258, 1.503)
Below AS Threshold	56 (12.0%)	28859 (51.1%)
Between Thresholds	285 (61.0%)	20435 (36.2%)
Above MM Threshold	126 (27.0%)	7191 (12.7%)

Table 1: Characteristics of men with prostate cancer from Single-Mode RT Cohort (N=467) and Commercial Cohort (N=56,485).
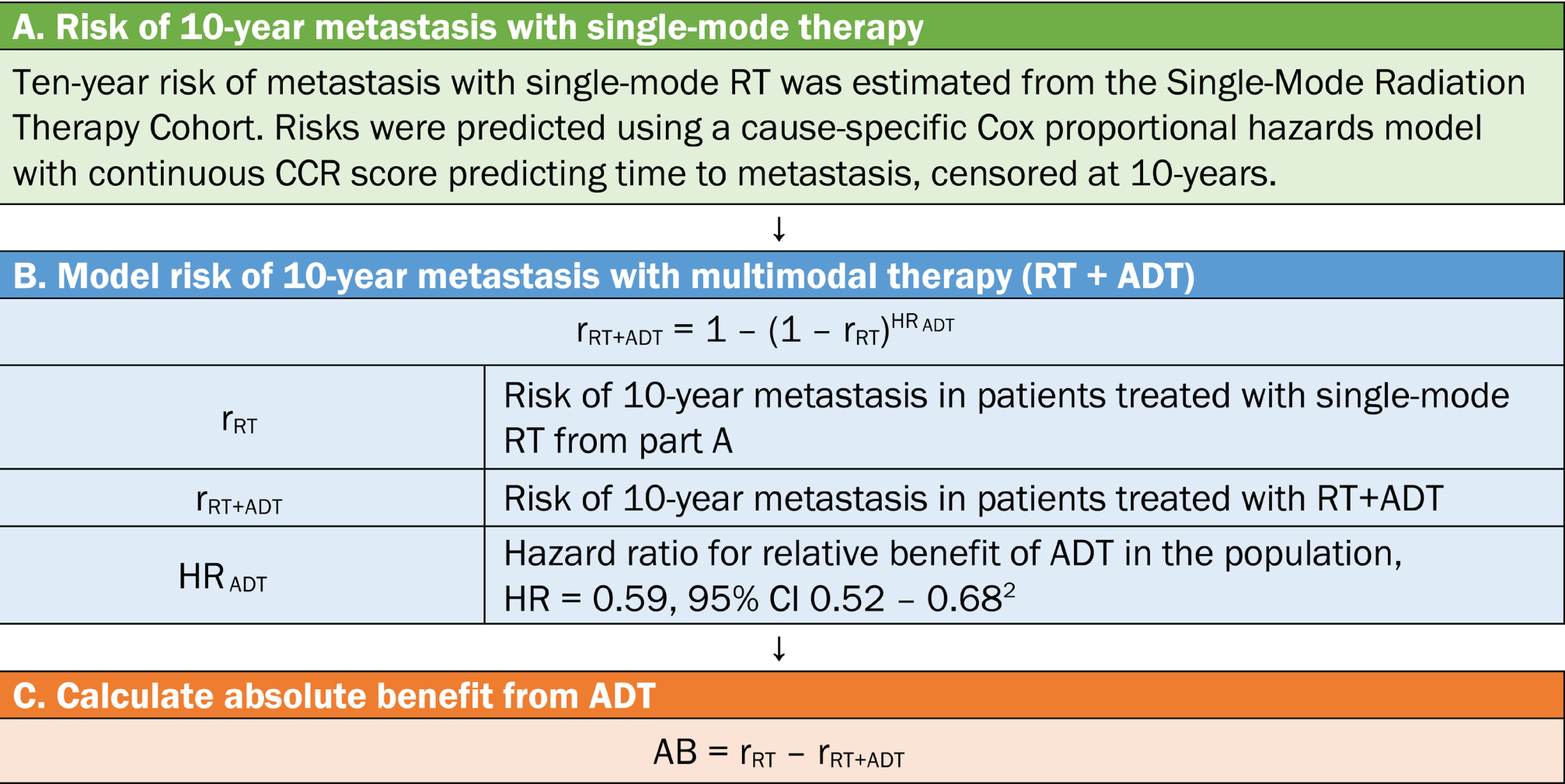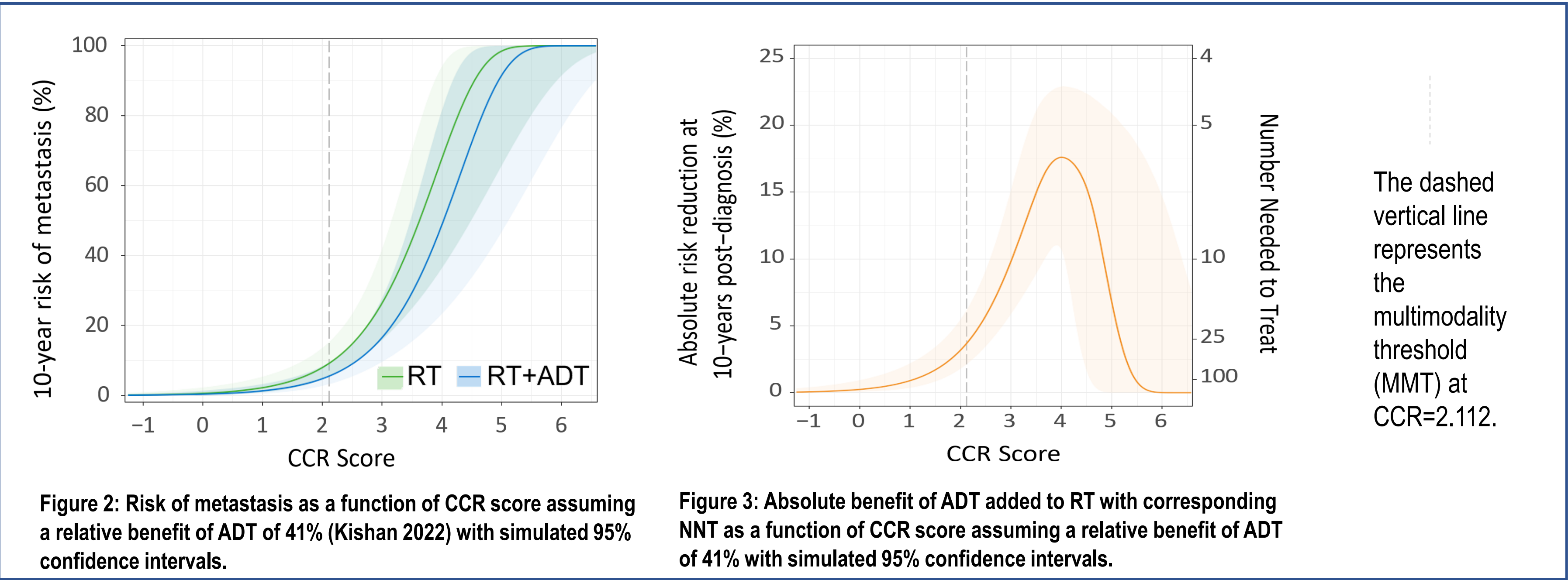

Figure 2: Risk of metastasis as a function of CCR score assuming a relative benefit of ADT of 41% (Kishan 2022) with simulated 95% confidence intervals.

Figure 3: Absolute benefit of ADT added to RT with corresponding NNT as a function of CCR score assuming a relative benefit of ADT of 41% with simulated 95% confidence intervals.

The dashed vertical line represents the multimodality threshold (MMT) at CCR=2.112.

RESULTS

- The *average* absolute benefit of adding ADT to RT in the commercially tested cohort was 0.86% (NNT=116) in patients below the multimodality treatment threshold (MMT), and 8.2% (NNT=12) for patients with CCR scores above the MMT.

- Patients with CCR scores precisely at the MMT had a predicted absolute benefit of 3.7% (NNT=27).

- The individualized risk of metastasis for each CCR score for patients treated with RT alone and with RT+ADT is shown in Figure 2. Figure 3 shows the absolute risk reduction and number needed-to-treat for ADT added to RT for each CCR score.