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Outcomes for Favorable and Unfavorable Intermediate Risk Prostate Cancer Patients Receiving Radiation Therapy With or Without Short-term Androgen Deprivation Therapy

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In an editorial [¹] accompanying our report on cardiovascular mortality in patients treated with radiation therapy (RT) with or without short-term androgen deprivation therapy (ADT) enrolled on Radiation Therapy Oncology Group (RTOG) trial 94-08 [²], Dr. Chen highlighted a dilemma often faced in the prostate cancer clinic: how do results from randomized trials derived from a prior era (eg, with lower RT doses) best inform contemporary management recommendations, and to which patients do they exactly apply?

Owing in part to the decades-long data maturation in prostate cancer trials and diagnostic advances that may more precisely define patient populations and subpopulations, the answer is unclear for patients with intermediate-risk prostate cancer.

To this end, we agree with Dr. Chen that the decision to use ADT in intermediate-risk disease must be interpreted in the context of today's standard dose-escalated RT, which may or may not mitigate any survival benefit observed with ADT.

Patients with intermediate-risk prostate cancer (defined as Gleason score 7 and/or prostate-specific antigen of 10–20 ng/ml, and/or clinical stage cT2b–c) represent a heterogeneous population with a suspected spectrum of outcomes in response to treatment [^{3,4}]. Risk stratification of intermediate-risk patients into favorable and unfavorable subsets according to primary Gleason score, percentage of positive biopsy cores, and the number of intermediate risk factors has been proposed [⁵].

We performed additional analyses to determine if a survival benefit remains in intermediate-risk patients according to favorable/unfavorable status and the number of intermediate risk factors following receipt of RT with or without ADT in RTOG 94-08. These analyses confirmed an overall survival (OS) and disease-specific survival (DSS) benefit for treatment

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that included ADT (Table 1). Interaction tests showed no significant interaction between treatment arm and intermediate risk according to favorable/unfavorable status or the number of risk factors. These results suggest that addition of short-term ADT to (lower dose) RT provides both OS and DSS benefits in both favorable and unfavorable intermediate-risk patients and for patients with one or more risk factors.

In the setting of dose-escalated RT and short-term ADT, retrospective analyses provide conflicting results regarding any DSS advantage in intermediate-risk patients [6,7]. The prospective randomized trial RTOG 08-15 will provide further insight into the role of ADT with escalated RT doses in patients with intermediate-risk disease stratified by prostate cancer risk factors and baseline comorbidity status. Until mature results become available from this randomized trial, we believe that ADT should only be considered in scenarios of proven survival benefit (including intermediate-risk disease) and after informed patient-centered discussions regarding the risks, benefits, and potential side effects of treatment.

With a presidential call towards individualized treatments for disease, the field of oncology is at the forefront of the Precision Medicine Initiative to implement treatment strategies for patients based on disease traits and baseline patient characteristics [8]. Thus, the management of intermediate-risk prostate cancer highlights the challenges involved in the application of evidence-based practice and patient populations that are best defined as *not yet identified*, or more precisely as *a subset of one*.

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Table 1

Analysis for the intermediate-risk group

	Overall survival	<i>p</i> value	DSS	<i>p</i> value
Favorable/unfavorable group (<i>n</i> = 1064)	HR (95% CI)		HR (95% CI)	
Treatment arm (ADT + RT vs RT alone)	1.33 (1.03–1.70)	0.03	2.15 (1.06–4.36)	0.03
Group (favorable vs unfavorable) ^a	1.64 (0.89–3.03)	0.12	1.04 (0.17–6.26)	0.96
Treatment × group interaction	0.81 (0.56–1.19)	0.28	1.32 (0.48–3.64)	0.59
Risk factors, binary (<i>n</i> = 1069)				
Treatment arm (ADT + RT vs RT alone)	1.21 (1.02–1.64)	0.03	1.95 (1.01–3.78)	0.048
Number of risk factors (1 vs >1) ^b	1.70 (0.91–3.19)	0.10	0.74 (0.12–4.76)	0.75
Treatment × risk factor interaction	0.84 (0.57–1.24)	0.37	1.73 (0.61–4.93)	0.30

DSS = disease-specific survival; HR = hazard ratio; CI = confidence interval; ADT = androgen deprivation therapy; RT = radiation therapy.

^aUnfavorable defined as primary Gleason 4 or more than one intermediate-risk factor (Gleason 7, prostate-specific antigen 10–20 ng/ml, cT2b–c); percentage positive biopsy data not available in trial RTOG 94-08.

^bRisk factors defined as Gleason 7, prostate-specific antigen 10–20 ng/ml, stage cT2b–c.