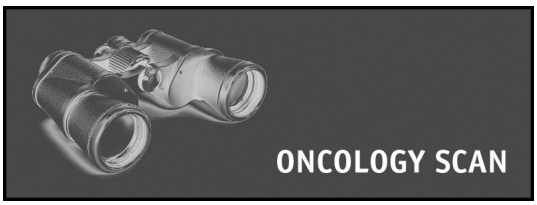

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Rethinking the Balance of Risk and Benefit of Androgen Deprivation Therapy for Intermediate-Risk Prostate Cancer

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In this month's Oncology Scan, we review 1 article from the *Journal of the American Medical Association* and 2 from the *Journal of Clinical Oncology* that help inform judgments about the relative value and harm of androgen deprivation therapy (ADT), particularly for men with intermediate-risk disease. The first is the long-term update of the Dana-Farber Cancer Institute (DFCI)/D'Amico randomized trial of radiation with or without 6 months of ADT, and the final 2 are studies evaluating the relationship between ADT and cognitive dysfunction. This review is a continuation of our coverage of recent developments in the literature on the treatment of genitourinary cancer (1-4).

D'Amico AV, et al. Long-term follow-up of a randomized trial of radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA* 2015. (5)

Summary: This is the long-term update of the DFCI 95-096 randomized trial of 206 men with mainly intermediate- (n = 153) or high-risk (n = 53) disease randomized to 70 Gy of radiation with or without 6 months of ADT. Eligibility required cT1b-T2b disease with at least 1 unfavorable factor, including Gleason $\geq$7, a prostate-specific antigen level of 10-40 ng/mL, or magnetic resonance imaging evidence of T3 disease. With its initial publication in 2004, this was the first randomized trial to demonstrate an overall survival benefit to short-course ADT in localized disease (88% vs 78% at 5 years, $P = .04$). In 2008 the update of this trial confirmed the overall survival benefit (74% vs 61% at 8 years, hazard ratio [HR] for death among radiation therapy [RT] vs RT+ADT 1.8 [95% confidence interval 1.1-2.9], $P = .01$) but speculated that the benefit may have been limited to healthy men. In a post hoc hypothesis-generating subgroup analysis, it was found that patients with no or minimal comorbidity on the ACE-27 scale had a large survival benefit with ADT (HR for death among RT vs RT+ADT 4.2 [2.1-8.5], $P < .001$), whereas those with moderate to severe comorbidity had a near-significant decrement in survival with ADT (HR for death among RT vs RT+ADT 0.54 [0.27-1.10], $P = .08$).

In this 2015 update with a median follow-up of nearly 17 years, there was no longer a significant overall survival benefit to the use of 6 months of ADT (HR for death among RT vs RT+ADT 1.22 [0.89-1.67], $P = .22$), although the 15-year estimate of overall survival still numerically favored the ADT patients (35.5% vs 27.5%). Once again, those with minimal to no comorbidity seemed to significantly benefit from ADT (HR 1.51 [1.03-2.21], $P = .04$), but the new information is that for those with moderate to severe comorbidity, overall survival was significantly better if they were randomized to RT alone instead of RT+ADT (HR 0.36 [0.19-0.67], $P = .001$), and cardiac deaths were also significantly lower for men with moderate to severe comorbidity randomized to the RT-alone arm (HR 0.17 [0.06-0.46], $P < .001$).

Comments: In this long-term update of the D'Amico/DFCI 95-096 trial of mainly intermediate-risk patients, the magnitude of the overall survival difference in the RT versus RT+ADT arms is smaller than was previously reported (HR for death 1.8 previously vs 1.22 now), leading to a loss of statistical significance. However, at 206 patients, the trial is relatively small, so it is less likely to demonstrate significance with a smaller effect size, and it should be noted that the new HR is nearly identical to the statistically significant HR of 1.23 for RT versus RT+ADT reported among intermediate-risk patients in the much larger Radiation Therapy Oncology Group 94-08 trial (n = 1979), which is the other major trial that has shown an overall survival benefit to the addition of short-term (4 months) of ADT to "conventional dose" radiation

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