RESEARCH LETTER

Long-term Follow-up of a Randomized Trial of Radiation With or Without Androgen Deprivation Therapy for Localized Prostate Cancer

Six months of androgen deprivation therapy (ADT) and radiation therapy (RT) vs RT alone prolongs survival and is the standard treatment for unfavorable-risk prostate cancer. A post-randomization hypothesis-generating analysis suggested that men with moderate or severe comorbidity had no survival benefit from combined therapy.

In addition, ADT use in men with unfavorable-risk prostate cancer was not associated with increased cardiac mortality in a meta-analysis, but whether men with moderate or severe comorbidity experience increased cardiac mortality with ADT remains unknown. Using updated data from our randomized trial, we compared overall survival and mortality from prostate cancer, cardiac, or other causes in all men and those within comorbidity subgroups by randomized treatment group.

Methods | Between December 1, 1995, and April 15, 2001, 206 men with unfavorable-risk prostate cancer were randomized to receive RT alone or RT and 6 months of ADT at 3 academic and 3 community-based centers in Massachusetts. Using information collected before randomization, a comorbidity score was assigned using the Adult Comorbidity Evaluation 27. The patient’s oncologist determined the cause of death, which was updated through February 21, 2015. To assign prostate cancer as the cause of death, castration-resistant metastatic disease, prostate-specific antigen test results with increasing levels despite hormonal manipulation, and usually chemotherapy before death was required; a lethal myocardial infarction defined cardiac mortality. Men signed an informed consent form approved by the institutional review boards at St Anne’s Hospital and the Dana Farber Harvard Cancer Center, and a waiver of consent was obtained for long-term follow-up.

Kaplan-Meier survival and cumulative incidence cause-specific mortality estimates stratified by randomized treatment and comorbidity were compared using log-rank and k-sample P values. For the postrandomization analyses, Cox regression methods and the methods of Fine and Gray were used to evaluate whether a significant interaction existed between ADT and comorbidity regarding overall mortality and prostate cancer, cardiac, and other-cause mortality, adjusting for randomized treatment, age, comorbidity, and prostate cancer prognostic factors. R version 3.0.1 (R Foundation for Statistical Computing) was used for calculations pertaining to the k-sample test of Gray and the regression methods of Fine and Gray. SAS version 9.3 (SAS Institute Inc) was used for the remaining statistical analyses. A 2-sided P value <.05 was considered statistically significant.

Results | After a median follow-up of 16.62 years (interquartile range, 15.42-17.67 years), 156 men died (76%); 29 died of prostate cancer (19%), 39 of cardiac causes (25%), and 88 of other causes (56%). Of men with moderate or severe comorbidity, of 49 died (94%) vs 110 of 157 (70%) with none or minimal comorbidity. Survival did not differ in the RT alone group vs the RT and ADT group, but opposite effects of treatment on survival were observed in the comorbidity subgroups (Figure).

Figure. Overall Survival Stratified by Randomized Treatment Group

A. Entire study cohort (N = 206)
B. None or minimal comorbidity (n = 157)
C. Moderate or severe comorbidity (n = 49)

The 15-year survival estimates for panel A were 27.58 (95% CI, 19.16-36.64) for radiation therapy (RT) alone vs 35.47 (95% CI, 26.20-44.84) for RT and androgen deprivation therapy (ADT); panel B, 30.52 (95% CI, 20.52-41.09) for RT alone vs 43.77 (95% CI, 32.41-54.56) for RT and ADT; panel C, 20.00 (95% CI, 7.28-37.20) for RT alone vs 8.33 (95% CI, 1.44-23.30) for RT and ADT. The 2-sided log-rank P value comparing survival in men across the 2 treatment groups was .22 for panel A, .04 for panel B, and .07 for panel C.

* Description of comorbidity based on the 4 grades (grade 0, none; grade 1, minimal; grade 2, moderate; and grade 3, severe) of the Adult Comorbidity Evaluation 27; the grade corresponds to the severity of the individual organ system decompensation and prognostic effect.

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## Table: All-Cause, Prostate Cancer, Cardiac, and Other-Cause Mortality Hazard Ratios by Patient, Prostate Cancer, and Treatment Factors

<table>
<thead>
<tr>
<th>Type of Mortality</th>
<th>No. of Men</th>
<th>No. of Deaths</th>
<th>Bivariable Analysis</th>
<th>Multivariable Analysis</th>
<th>No. of Deaths</th>
<th>Bivariable Analysis</th>
<th>Multivariable Analysis</th>
<th>No. of Deaths</th>
<th>Bivariable Analysis</th>
<th>Multivariable Analysis</th>
<th>No. of Deaths</th>
<th>Bivariable Analysis</th>
<th>Multivariable Analysis</th>
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<tbody>
<tr>
<td><strong>Overall</strong></td>
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<tr>
<td>Age at randomization, per year</td>
<td>206&lt;sup&gt;a&lt;/sup&gt;</td>
<td>156</td>
<td>1.08 (1.05-1.12)</td>
<td>&lt;.001</td>
<td>1.09 (1.05-1.12)</td>
<td>&lt;.001</td>
<td>29</td>
<td>1.01 (0.96-1.07)</td>
<td>.64</td>
<td>1.02 (0.96-1.08)</td>
<td>.58</td>
<td>39</td>
<td>1.02 (0.97-1.07)</td>
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<tr>
<td><strong>Prostate Cancer</strong></td>
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<td><strong>Cardiac</strong></td>
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<td><strong>Other Cause</strong></td>
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<td><strong>Interaction Terms</strong></td>
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<tr>
<td>None or minimal comorbidity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RT and ADT</td>
<td>78</td>
<td>0.59 (0.32-1.06)</td>
<td>.04</td>
<td>1.47 (1.01-2.15)</td>
<td>.04</td>
<td>5</td>
<td>4.52 (1.71-12.0)</td>
<td>.02</td>
<td>4.30 (1.60-11.50)</td>
<td>.27</td>
<td>7</td>
<td>1.69 (0.67-4.26)</td>
</tr>
<tr>
<td>Moderate or severe comorbidity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RT and ADT</td>
<td>24</td>
<td>0.59 (0.32-1.06)</td>
<td>.04</td>
<td>1.47 (1.01-2.15)</td>
<td>.04</td>
<td>5</td>
<td>4.52 (1.71-12.0)</td>
<td>.02</td>
<td>4.30 (1.60-11.50)</td>
<td>.27</td>
<td>7</td>
<td>1.69 (0.67-4.26)</td>
</tr>
<tr>
<td>ADT × comorbidity</td>
<td>206</td>
<td>156</td>
<td>0.35 (0.17-0.70)</td>
<td>.003</td>
<td>1.68 (0.73-3.85)</td>
<td>.01</td>
<td>29</td>
<td>1.30 (0.67-2.52)</td>
<td>.71</td>
<td>0.56 (0.47-0.66)</td>
<td>.01</td>
<td>39</td>
<td>1.05 (0.42-2.59)</td>
</tr>
</tbody>
</table>

### Prostate Cancer Prognostic Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Men</th>
<th>No. of Deaths</th>
<th>Bivariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
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<tbody>
<tr>
<td>PSA level, ng/mL</td>
<td>206</td>
<td>156</td>
<td>1.11 (0.87-1.40)</td>
<td>.41</td>
</tr>
<tr>
<td>AJCC clinical tumor category</td>
<td>T1</td>
<td>99</td>
<td>0.90 (0.59-1.37)</td>
<td>.63</td>
</tr>
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<td>T2a</td>
<td>46</td>
<td>31</td>
<td>1.90 (0.95-3.79)</td>
<td>.18</td>
</tr>
<tr>
<td>T2b</td>
<td>61</td>
<td>49</td>
<td>1.30 (0.75-2.66)</td>
<td>.66</td>
</tr>
</tbody>
</table>

### Highest Gleason score

<table>
<thead>
<tr>
<th>Score</th>
<th>No. of Men</th>
<th>No. of Deaths</th>
<th>Bivariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>s1 + 4&lt;sup&gt;g&lt;/sup&gt;</td>
<td>130</td>
<td>91</td>
<td>1.70 (1.16-2.48)</td>
<td>.066</td>
</tr>
<tr>
<td>4 + 3&lt;sup&gt;h&lt;/sup&gt;</td>
<td>46</td>
<td>39</td>
<td>1.30 (1.16-2.48)</td>
<td>.066</td>
</tr>
<tr>
<td>8-10</td>
<td>30</td>
<td>26</td>
<td>1.97 (1.27-3.06)</td>
<td>.002</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADT, androgen deprivation therapy; AHR, adjusted hazard ratio; AJCC, American Joint Commission on Cancer; HR, hazard ratio; PSA, prostate-specific antigen; RT, radiation therapy.

<sup>a</sup> There were 206 men randomized to ADT. The event rate was 76% for all-cause death, 14% for prostate cancer death, 19% for cardiac death, and 43% for other cause death.

<sup>b</sup> Description of comorbidity based on the 4 grades (grade 0, none; grade 1, minimal; grade 2, moderate; and grade 3, severe) of the Adult Comorbidity Evaluation 27; the grade corresponds to the severity of the individual organ system decompensation and prognostic effect.

<sup>c</sup> The effect size was 0.24 and the power of detecting the observed interaction was 96.7%.

<sup>d</sup> The effect size was 0.56 and the power of detecting the observed interaction was 8.98%.

<sup>e</sup> The effect size was 0.10 and the power of detecting the observed interaction was 86.5%.

<sup>f</sup> The effect size was 4.67 and the power of detecting the observed interaction was 86.8%.

<sup>g</sup> The possible scores are 3 plus 3 or 3 plus 4.

<sup>h</sup> The only possible score is 4 plus 3.
Treatment with RT alone did not increase mortality (80 vs 76 deaths; hazard ratio [HR], 1.22 [95% CI, 0.89-1.67]; P = .22) as previously reported (HR, 1.8 [95% CI, 1.1-2.9])\(^1\) and it did not significantly affect cardiac mortality (HR, 0.74 [95% CI, 0.40-1.39]; P = .36).

In multivariable analyses, RT alone vs RT and ADT in men with none or minimal comorbidity was associated with significantly increased overall mortality (HR, 1.51 [95% CI, 1.03-2.21]; P = .04) and prostate cancer mortality (HR, 4.30 [95% CI, 1.60-11.50]; P = .004), no difference in cardiac mortality (HR, 1.72 [95% CI, 0.64-4.58]; P = .28), and decreased other cause mortality (HR, 0.60 [95% CI, 0.36-0.99]; P = .04) (Table). Conversely, in men with moderate or severe comorbidity, RT alone vs RT and ADT was associated with significantly decreased overall mortality (HR, 0.36 [95% CI, 0.19-0.67]; P = .001) and cardiac mortality (HR, 0.17 [95% CI, 0.06-0.46]; P < .001), no difference in prostate cancer mortality (HR, 2.41 [95% CI, 0.23-25.21]; P = .46), and increased other cause mortality (HR, 2.79 [95% CI, 1.02-7.60]; P = .05).

**Discussion** | At a median follow-up of 16.62 years, RT alone vs RT and ADT was associated with significantly decreased overall and cardiac mortality in men with moderate or severe comorbidity, in contrast to no association with overall mortality at a median follow-up of 7.6 years (HR, 0.54 [95% CI, 0.27-1.10]; P = .08).\(^1\) Although RT alone vs RT and ADT was associated with increased mortality in men with none or minimal comorbidity, mortality among all men randomized to RT alone was not significantly increased.

Limitations include that the results from postrandomization analyses are hypothesis-generating and in some cases based on low event rates and therefore require validation. Nevertheless, the association of treatment with RT alone with decreased cardiac and overall mortality in men with moderate or severe comorbidity suggests that administering ADT to treat unfavorable-risk prostate cancer in these men should be carefully considered.

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**Author Contributions:** Dr D’Amico had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** D’Amico, Kantoff.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** D’Amico, Chen.

**Critical revision of the manuscript for important intellectual content:** D’Amico, Chen, Renshaw, Loffredo.

**Statistical analysis:** Chen.

**Administrative, technical, or material support:** D’Amico, Loffredo.

**Study supervision:** D’Amico, Kantoff.

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00166220


**COMMENT & RESPONSE**

**Maternal Antidepressant Use and Persistent Pulmonary Hypertension of the Newborn**

**To the Editor** In a cohort study, Dr Huybrechts and colleagues\(^1\) found that maternal use of selective serotonin reuptake inhibitors (SSRIs) in late pregnancy was associated with a potential increased risk of persistent pulmonary hypertension of the newborn (PPHN). The source cohort was restricted to women with a depression diagnosis, and a logistic regression analysis was used to estimate the odds ratios for PPHN associated with antidepressant exposure. However, the authors decided not to adjust for cesarean delivery because it has been shown that conditioning on such an intermediate perinatal factor is susceptible to overadjustment bias.

Schisterman et al\(^2\) define overadjustment bias as “control for an intermediate variable ... on a causal path from exposure to outcome.” According to this definition, if one adjusts for cesarean delivery (intermediate variable), assuming it is on a casual pathway between maternal use of SSRIs in late pregnancy (exposure) and PPHN (outcome), the total causal effect of the use of SSRIs on PPHN cannot be consistently estimated. In fact, with adjustment for cesarean delivery, the observed association between maternal use of SSRIs in late pregnancy and PPHN will typically be a null-biased estimate of the total causal effect. If it is the case that cesarean delivery is an intermediate variable, the decision not to adjust is correct. But there is some evidence that may compromise the validity of this claim.

Previous reports have suggested that cesarean delivery may be requested in the absence of any medical indication when psychosocial adversity and maternal depression are present.\(^3\) Fear of child birth, previous negative or traumatic birth experiences, as well as the attitudes of midwives and obstetricians toward depressed patients have been found to be associated with cesarean delivery.\(^4,5\) Therefore, cesarean delivery may not only be an intermediate variable on the...