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This supplementary material has been provided by the authors to give readers additional information about their work.
eFigure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flowchart

Records identified through database searching (n = 1043)

Records after duplicates removed (n = 148)

Records screened (n = 148)

Records excluded (n = 123)

Full-text articles assessed for eligibility (n = 25)

Full-text articles excluded (n = 19)

Randomized trials with available individual patient data (n = 6)

Data sharing applications submitted to RTOG and EORTC

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**eFigure 2: Network Plot of Randomized Trials with Available Direct Comparisons**

Lines represent the presence of direct comparison trial(s). The width of the line is proportional to the number of trials with direct comparisons.
eFIGURE 3. Forest Plots Derived from Network Meta-Analysis of Androgen Deprivation Therapy Effect on Survival Outcomes, Stratified by Gleason Grade Group 4 vs. 5. Note that the reference value (HR 1.00) for each forest plot is radiation therapy (RT) alone. The hazard ratios (HRs) and 95% confidence intervals (95% CI) are presented in ascending order, with their associated P-score (a frequentist analogue to the surface under the cumulative ranking curve). GG, Gleason grade group.
**eFigure 4. Forest Plots of the Effect of Gleason Grade Group 4 vs. 5 on Survival Outcomes, Stratified by Androgen Deprivation Therapy (ADT) Duration**

An overall hazard ratio (HR) and 95% confidence interval (95% CI) bestowed by having Gleason score 9-10 vs. Gleason score 8 disease is presented in boldface at the bottom right. HRs and 95% CI for each ADT duration stratum are presented, along with corresponding treatment effect (TE; log[HR]) and the standard error of the TE (seTE).

### Distant Metastasis

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG 5 vs. GG 4, Lifelong ADT</td>
<td>-0.28</td>
<td>0.14</td>
<td>0.75 [0.56; 1.01]</td>
<td>0.75</td>
<td>[0.56; 1.01]</td>
<td>11.5%</td>
</tr>
<tr>
<td>GG 5 vs. GG 4, Long-term ADT</td>
<td>0.17</td>
<td>0.08</td>
<td>1.18 [0.85; 1.63]</td>
<td>1.18</td>
<td>[0.85; 1.63]</td>
<td>12.2%</td>
</tr>
<tr>
<td>GG 5 vs. GG 4, RT Alone</td>
<td>-0.28</td>
<td>0.14</td>
<td>0.75 [0.56; 1.01]</td>
<td>0.75</td>
<td>[0.56; 1.01]</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

### Cancer-Specific Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG 5 vs. GG 4, Lifelong ADT</td>
<td>-0.32</td>
<td>0.19</td>
<td>0.72 [0.56; 0.93]</td>
<td>0.72</td>
<td>[0.56; 0.93]</td>
<td>10.3%</td>
</tr>
<tr>
<td>GG 5 vs. GG 4, Long-term ADT</td>
<td>0.28</td>
<td>0.14</td>
<td>1.33 [1.05; 1.68]</td>
<td>1.33</td>
<td>[1.05; 1.68]</td>
<td>12.2%</td>
</tr>
<tr>
<td>GG 5 vs. GG 4, RT Alone</td>
<td>-0.30</td>
<td>0.18</td>
<td>0.74 [0.58; 0.96]</td>
<td>0.74</td>
<td>[0.58; 0.96]</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

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**eTable 1. Summary of Trials Included in Network Meta-Analysis**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>Inclusion*</th>
<th>Staging Workup</th>
<th>Primary Endpoint</th>
<th>ADT Regimen</th>
<th>RT Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 8531</td>
<td>RT vs RT+ Lifelong ADT</td>
<td>cT1-T2N+ or cT3-4 &lt;25 cm</td>
<td>Bone scan, chest X-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling</td>
<td>Survival and disease progression</td>
<td>q1month LHRH agonist</td>
<td>65-70 Gy to prostate 44-46 Gy to pelvis</td>
</tr>
<tr>
<td>RTOG 8610</td>
<td>RT vs RT+ STADT</td>
<td>cT2-T4 ≥25 cm</td>
<td>Bone scan, chest X-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling</td>
<td>Locoregional control</td>
<td>q1month LHRH agonist + 4 months AA</td>
<td>65-70 Gy to prostate 44-46 Gy to pelvis</td>
</tr>
<tr>
<td>RTOG 9202</td>
<td>RT+STADT vs RT+LTADT</td>
<td>cT2-4N0-X, PSA&lt;150</td>
<td>Bone scan, chest X-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling</td>
<td>Disease free survival</td>
<td>Q1month LHRH agonist + 4 months AA</td>
<td>65-70 Gy to prostate 44-46 Gy to pelvis</td>
</tr>
<tr>
<td>EORTC 22863</td>
<td>RT vs RT + LTADT</td>
<td>cT1-2N0 WHO grade 3 cT3-4N0</td>
<td>Bone scan, chest X-ray, liver ultrasound or CT; allowed lymph node assessment by CT, bipedal lymphangiography, lymphadenectomy</td>
<td>Disease free survival</td>
<td>q1month LHRH agonist + 1 month AA</td>
<td>70 Gy to prostate 50 Gy to pelvis</td>
</tr>
<tr>
<td>EORTC 22961</td>
<td>RT+STADT vs RT+LTADT</td>
<td>cT1c-2bN+ cT3-4N0 PSA&lt;40xULN</td>
<td>Bone scan, chest X-ray, CT or MRI of abdomen and pelvis; lymphadenectomy allowed</td>
<td>Overall survival</td>
<td>q1-3 month LHRH agonist + 6 mos AA</td>
<td>70 Gy to prostate 50 Gy to pelvis</td>
</tr>
<tr>
<td>EORTC 22991</td>
<td>RT vs RT+ STADT</td>
<td>cT1b-c, with PSAa 10 ng/mL or Gleason ≥ 7 cT2a with PSA&lt;50</td>
<td>Bone scan for PSAa&gt;10 ng/mL, chest x-ray, CT or MRI of abdomen and pelvis</td>
<td>Biochemical disease free survival</td>
<td>q3month LHRH agonist + 1 month AA</td>
<td>70-78 Gy to prostate 46 Gy to pelvis</td>
</tr>
</tbody>
</table>

AA, anti-androgen; ADT, androgen deprivation therapy; CT, computed tomography; LHRH, luteinizing hormone releasing hormone; LTADT, long term ADT; MRI, magnetic resonance imaging; RT, radiation therapy; STADT, short-term ADT

*Patients with cN+ or pN+ disease were included on several protocols, but were not included in our analysis.

**RTOG 8531 also included patients with high-risk features after radical prostatectomy, who were not included in our analysis.
## eTable 2. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GG 4</th>
<th>GG 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean, median</strong></td>
<td><strong>(range, min-maximum)</strong></td>
<td><strong>(years)</strong></td>
<td><strong>(years)</strong></td>
</tr>
<tr>
<td></td>
<td>69.8, 70</td>
<td>69.5, 70</td>
<td>70.2, 71</td>
</tr>
<tr>
<td></td>
<td>(43-88)</td>
<td>(49-88)</td>
<td>(43-88)</td>
</tr>
<tr>
<td><strong>Initial PSA, mean, median</strong></td>
<td><strong>(range, min-maximum)</strong></td>
<td><strong>(ng/dL)</strong></td>
<td><strong>(ng/dL)</strong></td>
</tr>
<tr>
<td></td>
<td>30.3, 18.8</td>
<td>28.76, 18.62</td>
<td>32.5, 18.9</td>
</tr>
<tr>
<td></td>
<td>(0.12-200)</td>
<td>(1.2-172.7)</td>
<td>(0.12-200)</td>
</tr>
<tr>
<td><strong>Clinical Tumor Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48 (5%)</td>
<td>35 (6%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>2</td>
<td>270 (27%)</td>
<td>175 (29%)</td>
<td>95 (24%)</td>
</tr>
<tr>
<td>3</td>
<td>636 (64%)</td>
<td>368 (62%)</td>
<td>268 (67%)</td>
</tr>
<tr>
<td>4</td>
<td>38 (4%)</td>
<td>15 (3%)</td>
<td>23 (6%)</td>
</tr>
</tbody>
</table>

GG, Gleason grade group

*Initial PSA not available for RTOG 8531 and EORTC 22961, and only available for some patients on RTOG 8610, EORTC 22863, and EORTC 22991
<table>
<thead>
<tr>
<th>Study</th>
<th>DMFS</th>
<th>CSS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG 4</td>
<td>GG 5</td>
<td>GG 4</td>
</tr>
<tr>
<td>RTOG 8531: Lifelong ADT vs RT alone</td>
<td>0.80 (0.52-1.22)</td>
<td><strong>0.36 (0.23-0.56)</strong></td>
<td>0.70 (0.36-1.34)</td>
</tr>
<tr>
<td>RTOG 8610: STADT vs RT alone</td>
<td>0.63 (0.37-1.08)</td>
<td>1.17 (0.69-1.99)</td>
<td>0.68 (0.32-1.44)</td>
</tr>
<tr>
<td>RTOG 9202: LTADT vs STADT</td>
<td><strong>0.69 (0.5-0.95)</strong></td>
<td>0.72 (0.51-1.03)</td>
<td><strong>0.45 (0.26-0.79)</strong></td>
</tr>
<tr>
<td>EORTC 22863: LTADT vs RT alone</td>
<td>0.30 (0.12-0.81)</td>
<td><strong>0.09 (0.02-0.49)</strong></td>
<td><strong>0.19 (0.04-0.97)</strong></td>
</tr>
<tr>
<td>EORTC 22961: LTADT vs STADT</td>
<td>0.88 (0.49-1.57)</td>
<td>0.57 (0.24-1.39)</td>
<td>1.89 (0.51-6.97)</td>
</tr>
<tr>
<td>EORTC 22991: STADT vs RT alone</td>
<td>0.42 (0.15-1.13)</td>
<td>0.99 (0.20-4.88)</td>
<td>0.53 (0.07-3.78)</td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; CSS, cancer-specific survival; DMFS, distant metastasis-free survival; GG, Gleason grade group; LTADT, long term ADT; OS, overall survival; RT, radiation therapy; STADT, short-term ADT

Hazard ratios are shown above, with 95% confidence intervals in parentheses.

*The DMFS and CSS estimates from EORTC 22863 are unstable.
**eTable 4. Network Meta-Analysis of Androgen Deprivation Therapy on Survival Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>DMFS</th>
<th>CSS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG 4</td>
<td>GG 5</td>
<td>GG 4</td>
</tr>
<tr>
<td>RT Alone As Reference (n=140 GG 4, 91 GG 5)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STADT</td>
<td>0.82 (0.39, 1.70)</td>
<td>0.96 (0.59, 1.56)</td>
<td>0.60 (0.31, 1.14)</td>
</tr>
<tr>
<td>LTADT</td>
<td>0.84 (0.36, 1.98)</td>
<td>0.63 (0.35, 1.10)</td>
<td><strong>0.32 (0.15, 0.69)</strong></td>
</tr>
<tr>
<td>Lifelong ADT***</td>
<td>0.80 (0.29, 2.20)</td>
<td><strong>0.35 (0.23, 0.56)</strong></td>
<td>0.70 (0.35, 1.35)</td>
</tr>
<tr>
<td>STADT as Reference (n=214 GG 4, 151 GG 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTADT</td>
<td>1.04 (0.54, 2.00)</td>
<td><strong>0.65 (0.47, 0.90)</strong></td>
<td><strong>0.54 (0.33, 0.87)</strong></td>
</tr>
<tr>
<td>Lifelong ADT</td>
<td>0.98 (0.28, 3.42)</td>
<td><strong>0.37 (0.19, 0.72)</strong></td>
<td>1.17 (0.46, 2.96)</td>
</tr>
<tr>
<td>LTADT as Reference (n=59 GG 4, 49 GG 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifelong ADT</td>
<td>0.94 (0.25, 3.35)</td>
<td>0.57 (0.27, 1.17)</td>
<td>2.18 (0.70, 6.00)</td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; CSS, cancer-specific survival; DMFS, distant metastasis-free survival; GG, Gleason grade group; LTADT, long term ADT; OS, overall survival; RT, radiation therapy; STADT, short-term ADT

Hazard ratios are shown above, with 95% confidence intervals in parentheses.

*Due to instability in estimates (due to the small sample size and event size), GG 6 patients enrolled on EORTC 22863 were excluded from analysis for CSS, hence the slightly different numbers than in Table 1** Indicates p<0.05