Addition of short-term androgen deprivation therapy to dose-escalated radiation therapy improves failure-free survival for select men with intermediate-risk prostate cancer

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Background: Dose-escalated (DE) radiation therapy (RT) and androgen deprivation therapy (ADT) improve prostate cancer outcomes over standard-dose RT. The benefit of adding ADT to DE-RT for men with intermediate-risk prostate cancer (IR-PrCa) is uncertain.

Patients and methods: We identified 636 men treated for IR-PrCa with DE-RT (>75Gy). The adult comorbidity evaluation-27 index classified comorbidity. Kaplan–Meier and log-rank tests compared failure-free survival (FFS) with and without ADT.

Results: Forty-five percent received DE-RT and 55% DE-RT with ADT (median 6 months). On Cox proportional hazard regression that adjusted for comorbidity and tumor characteristics, ADT improved FFS (adjusted hazard
Multiple treatment options are available for men with intermediate-risk localized prostate cancer including radical prostatectomy, brachytherapy, and external beam radiation therapy (EBRT). For those men who select EBRT, the optimal strategy for the administration of EBRT remains controversial. Specifically, the benefit of adding short-term androgen deprivation therapy (ADT) to dose-escalated (DE) EBRT is uncertain.

Several randomized clinical trials that included men with intermediate-risk prostate cancer (IR-PrCa), most notably those from MD Anderson Cancer Center [1, 2], The Netherlands [3], and the Massachusetts General Hospital and Loma Linda cancer centers [4], have demonstrated an improvement in disease control with the use of DE EBRT compared with standard-dose EBRT. Other randomized clinical trials have demonstrated a benefit from the administration of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone. The Radiation Therapy Oncology Group (RTOG) 94-08 [5], Trans-Tasman Radiation Oncology Group (TROG) 96-01 [6, 7], and Dana Farber Cancer Institute (DFCI) [8] trials reported an improvement in both disease control and survival with the addition of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone. The Radiation Therapy Oncology Group (RTOG) 94-08 [5], Trans-Tasman Radiation Oncology Group (TROG) 96-01 [6, 7], and Dana Farber Cancer Institute (DFCI) [8] trials reported an improvement in both disease control and survival with the addition of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone. The Radiation Therapy Oncology Group (RTOG) 94-08 [5], Trans-Tasman Radiation Oncology Group (TROG) 96-01 [6, 7], and Dana Farber Cancer Institute (DFCI) [8] trials reported an improvement in both disease control and survival with the addition of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone. The Radiation Therapy Oncology Group (RTOG) 94-08 [5], Trans-Tasman Radiation Oncology Group (TROG) 96-01 [6, 7], and Dana Farber Cancer Institute (DFCI) [8] trials reported an improvement in both disease control and survival with the addition of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone. The Radiation Therapy Oncology Group (RTOG) 94-08 [5], Trans-Tasman Radiation Oncology Group (TROG) 96-01 [6, 7], and Dana Farber Cancer Institute (DFCI) [8] trials reported an improvement in both disease control and survival with the addition of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone. The Radiation Therapy Oncology Group (RTOG) 94-08 [5], Trans-Tasman Radiation Oncology Group (TROG) 96-01 [6, 7], and Dana Farber Cancer Institute (DFCI) [8] trials reported an improvement in both disease control and survival with the addition of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone. The Radiation Therapy Oncology Group (RTOG) 94-08 [5], Trans-Tasman Radiation Oncology Group (TROG) 96-01 [6, 7], and Dana Farber Cancer Institute (DFCI) [8] trials reported an improvement in both disease control and survival with the addition of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone. The Radiation Therapy Oncology Group (RTOG) 94-08 [5], Trans-Tasman Radiation Oncology Group (TROG) 96-01 [6, 7], and Dana Farber Cancer Institute (DFCI) [8] trials reported an improvement in both disease control and survival with the addition of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone.

While randomized trials have demonstrated an improvement in disease control with the use of DE EBRT compared with standard-dose EBRT and a survival advantage with the use of short-term ADT in conjunction with standard-dose EBRT compared with standard-dose EBRT alone, the incremental benefit of adding short-term ADT to DE EBRT is uncertain. Although the addition of short-term ADT may improve prostate cancer outcomes, it can cause also significant side-effects including fatigue, hot flashes, loss of libido, endocrine abnormalities, decreased bone density, and possibly cardiovascular complications. The ongoing RTOG 08-15 randomized trial will provide level 1 evidence on the effect of adding short-term ADT to DE radiation therapy (RT), but the results will not be available for several years. Therefore to determine the incremental benefit of adding short-term ADT to DE EBRT, we analyzed men with IR-PrCa treated at MD Anderson with DE EBRT (>75 Gy) with or without short-term ADT. Additionally, we identified a subgroup of men most likely to benefit from the addition of ADT based on patient and disease characteristics.
univariate and multivariate analysis

Descriptive statistics were generated for the study cohort. Analyses were conducted in SAS 9.2 or STATA 11 unless otherwise specified [11, 12]. Chi-square and Kruskal–Wallis tests compared men who did and did not receive ADT. The impact of patient, tumor, and treatment characteristics on FFS was examined using univariate and multivariate Cox proportional hazard regression models. The independent association of ADT on FFS was first evaluated in a multivariate model that assessed all explanatory variables (T stage, Gleason score, percent positive cores, PSA, comorbidity, and ADT administration) and selected covariates for inclusion by backward elimination. Subsequently, a multivariate model was constructed that included all explanatory variables without elimination. Since conclusions were the same, results of the model including all variables are reported. Hazard ratios (HRs) and adjusted HR (AHR) are presented with 95% confidence intervals (CIs). P value <0.05 was considered statistically significant.

defining an unfavorable subgroup

Recursive partitioning analysis was applied using the rpart routine in the R programming language to separate patients into similar groups with respect to risk of PSA failure [13, 14]. Gleason Score, PSA, at least 50% core involvement, T stage, overall comorbidities, and cardiovascular comorbidities were entered as potential explanatory variables. For this time to event analysis, the rpart routine grouped patients with similar values for the martingale residual from a null Cox model.

Kaplan–Meier survival estimates

Kaplan–Meier survival estimates were constructed to determine 5-year FFS for the entire cohort and for subgroups of patients. Patients were stratified by ADT administration and log-rank tests assessed the impact of ADT on FFS.

results

study cohort

Patient and disease characteristics for all patients and stratified by administration of ADT are shown in Table 1. Fifty-five percent of the men received ADT in addition to EBRT and 45% received EBRT alone. Median age at diagnosis was 70 years (interquartile range (IQR) 65–74). When ADT was administered, median length of administration was 6 months (IQR 5.7–8.3). Thirty-eight percent of men treated with ADT received a LH-RH (luteinizing hormone-releasing hormone) agonist alone, while 62 percent received an anti-androgen in addition to an LH-RH agonist. There was a slight predominance of more aggressive disease in the ADT group manifested by a greater percentage of men with higher T stage, Gleason score, and percent positive biopsy cores (all P < 0.001). Patient age (P = 0.444), severity of comorbidites (P = 0.132), and PSA level (P = 0.189) were similar between the groups. With a median follow-up of 4.3 years (IQR 2.8–5.7), 14 men in the ADT group and 28 men in the no ADT group failed treatment. Mean time to biochemical failure was 3.1 years.

impact of patient, tumor and treatment factors on FFS

On univariate analysis (Table 2), men with at least 50% positive cores were more likely to fail than men with <50% positive cores (HR 2.36, 95% CI 1.28–4.36; P = 0.006). Similarly, men with Gleason 4 + 3 = 7 disease were more likely to fail on univariate analysis versus Gleason 6 disease (HR 4.82, 95% CI 1.11–20.9; P = 0.036).

Table 1. Patient and tumor characteristics for all patients and stratified by administration of ADT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>No ADT</th>
<th>Received ADT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>636</td>
<td>288 (45%)</td>
<td>348 (55%)</td>
<td>0.444</td>
</tr>
<tr>
<td>Age [years, median (IQR)]</td>
<td>69.8 (64.7–74.1)</td>
<td>69.5 (65.1–73.7)</td>
<td>70.3 (64.3–74.6)</td>
<td>0.132</td>
</tr>
<tr>
<td>Overall comorbidity [% (%)]</td>
<td>458 (72.0%)</td>
<td>216 (75.0%)</td>
<td>242 (69.5%)</td>
<td>0.149</td>
</tr>
<tr>
<td>None or mild</td>
<td>178 (28.0%)</td>
<td>72 (25.0%)</td>
<td>106 (30.5%)</td>
<td>0.149</td>
</tr>
<tr>
<td>Cardiovascular comorbidity [% (%)]</td>
<td>521 (81.9%)</td>
<td>243 (84.4%)</td>
<td>278 (79.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None or mild</td>
<td>115 (18.1%)</td>
<td>45 (15.6%)</td>
<td>70 (20.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor stage [% (%)]</td>
<td>344 (54.1%)</td>
<td>177 (61.5%)</td>
<td>167 (48.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1</td>
<td>292 (45.9%)</td>
<td>111 (38.5%)</td>
<td>181 (52.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gleason score [% (%)]</td>
<td>85 (10.9%)</td>
<td>48 (16.7%)</td>
<td>21 (6.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>376 (59.1%)</td>
<td>189 (65.6%)</td>
<td>187 (53.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 + 4 = 7</td>
<td>191 (30.0%)</td>
<td>51 (17.7%)</td>
<td>140 (40.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent positive cores [% (%)]</td>
<td>206 (63.8%)</td>
<td>214 (74.3%)</td>
<td>192 (55.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>230 (36.2%)</td>
<td>74 (25.7%)</td>
<td>156 (44.8%)</td>
<td>0.189</td>
</tr>
<tr>
<td>PSA ng/ml [% (%)]</td>
<td>&lt;10</td>
<td>488 (76.7%)</td>
<td>228 (79.2%)</td>
<td>260 (74.7%)</td>
</tr>
<tr>
<td>10–20</td>
<td>148 (23.3%)</td>
<td>60 (20.8%)</td>
<td>88 (25.3%)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*Comparison of men who received ADT to men who did not receive ADT using chi-square (categorical variables) and Kruskal–Wallis tests (continuous variables). P-values presented in bold are statistically significant.

ADT, androgen deprivation therapy; IQR, inter quartile range; PSA, prostate-specific antigen.
On multivariate analysis (Table 2) that adjusted for differences in comorbidities, T stage, Gleason score, and percent positive cores, men who received ADT in addition to DE EBRT had improved FFS compared with men who did not receive ADT (AHR 0.36, 95% CI 0.18–0.72; P = 0.004). After adjustment for other factors, men with at least 50% positive cores had inferior FFS compared with men with <50% positive cores (AHR 2.43, 95% CI 1.28–4.63; P = 0.007). Additionally, men with Gleason 4 + 3 = 7 disease had worse FFS than men with Gleason 6 disease (AHR 6.70, 95% CI 1.45–30.97; P = 0.015).

Men with Gleason 4 + 3 = 7 disease or at least 50% positive cores were more likely to fail. Therefore, men with Gleason 4 + 3 = 7 disease or at least 50% positive cores were classified as having unfavorable disease. The remaining men were classified as having favorable disease. Kaplan–Meier curves for men not receiving ADT were constructed; 5-year FFS rates were 96.3% (95% CI 91.4% to 98.5%) for men with favorable disease and 81.6% (95% CI 72.3% to 88.1%) for men with unfavorable disease (P < 0.001), confirming our definitions (Figure 1).

incremental benefit of adding ADT to DE EBRT for subgroups of patients

An analysis of the 334 patients with unfavorable disease showed the addition of short-term ADT to DE EBRT improved disease control compared with DE EBRT alone (Figure 2A). The addition of ADT improved 5-year FFS from 81.6% (95% CI 72.3% to 88.1%) to 92.9% (95% CI 85.8% to 96.5%) (P = 0.009). This benefit was not seen among the 302 men with favorable disease. Five-year FFS was 96.3% (95% CI 91.4% to 98.5%) without ADT and 97.4% (95% CI 92.3% to 99.2%) with ADT (Figure 2B, P = 0.874).

We stratified patients based on severity of comorbidities into those with no or minimal comorbidity (ACE-27 score 0 or 1) and those with moderate to severe comorbidity (ACE-27 score 2 or 3). Among the 235 men with unfavorable disease and no or minimal comorbidity, the addition of ADT to DE EBRT significantly improved 5-year FFS from 84.3% (95% CI 73.9% to 90.8%) to 95.5% (95% CI 87.9% to 98.4%) (Figure 3A, P = 0.006). Among the 99 men with unfavorable disease and moderate to severe comorbidity, the addition of ADT to DE EBRT numerically improved 5-year FFS from 74.1% (95% CI 50.9% to 87.6%) to 87.9% (95% CI 70.7% to 95.4%) but


defining an unfavorable subgroup of patients

Recursive partitioning analysis of men who did not receive ADT identified the subgroup of men with unfavorable disease.
analysis had limited numbers, the survival curves converged, and the difference was not statistically significant (Figure 3B, \(P = 0.380\)). Among the 223 men with favorable disease and no or minimal comorbidities, the addition of ADT to DE EBRT did not significantly improve 5-year FFS. Five-year FFS was 95.3% (95% CI 89.0% to 98.0%) without ADT and 98.8% (95% CI 91.9% to 99.8%) with ADT (\(P = 0.263\)). Similarly, among the 79 men with favorable disease and moderate to severe comorbidity, the addition of ADT to DE EBRT did not improve 5-year FFS. Five-year FFS was 100% (95% CI undefined) without ADT and 93.9% (95% CI 77.7% to 98.4%) with ADT (\(P = 0.115\)).

discussion

Our results demonstrate the addition of short-term ADT to DE EBRT improves FFS for men with unfavorable IR-PrCa (Gleason 4 + 3 = 7 disease or involvement of at least half of the biopsy cores). This benefit was specifically seen among men with unfavorable disease and no or minimal comorbidities. It is not clear if this benefit extends to men with unfavorable disease and moderate to severe comorbidities due to the limited number of men with these characteristics in our study.

Our results suggest men with favorable intermediate-risk disease may not benefit from the addition of short-term ADT to DE EBRT.

Radiation dose escalation and short-term ADT have both been shown independently to improve prostate cancer outcomes over standard-dose EBRT alone. Three randomized trials that included men with IR-PrCa demonstrated a benefit from radiation dose escalation over standard-dose radiation. A trial of 301 patients at MD Anderson concluded that 78 Gy EBRT decreases biochemical failure compared with 70 Gy EBRT [1, 2]. A trial of 393 men conducted at Massachusetts General Hospital and Loma Linda showed a biochemical disease-free survival benefit from dose escalation to 79 Gy compared with 70 Gy [4]. Additionally, a Dutch trial of 664 men reported improved freedom from failure with 78 Gy compared with 68 Gy [3]. Similarly, three randomized trials that included men with IR-PrCa have demonstrated a benefit from the addition of short-term ADT to standard-dose EBRT. DFCI reported improvement in overall survival and disease-specific survival benefit with the addition of 6 months of ADT to 70 Gy EBRT [8]. RTOG 94-08 demonstrated overall survival and disease-specific survival benefits with the addition of 4 months of ADT to 67 Gy EBRT [5]. Furthermore, the TROG showed...
improvement in disease-free survival and prostate cancer-specific survival with the addition of 6 months of ADT to 66 Gy EBRT [6]. However, there is limited data on the benefit of combining ADT with DE EBRT. While the MRC RT01 randomized trial showed improvement in progression-free survival when DE EBRT (74 Gy) was combined with ADT compared with lower dose EBRT (64 Gy) combined with ADT, the study does not provide insight as to whether there is an incremental benefit from adding ADT to DE EBRT. In contrast to our finding that the addition of ADT to DE EBRT improved FFS for men with IR-PrCa, a reanalysis of 292 men enrolled in the RTOG 94-06 trial, initially designed to assess maximum-tolerated radiation dose, did not show a benefit from the addition of ADT to DE EBRT [15]. Additionally, in a retrospective analysis by Zelefsky et al. [16], ADT did not improve biochemical control for men with IR-PrCa in a multivariate analysis that included the effects of dose escalation. In both the reanalysis of RTOG 94-06 and the Zelefsky retrospective analysis, the authors may not have seen a benefit from the addition of ADT because they did not adjust for potential imbalances in adverse features between the two groups due to differences in the proportion of men with Gleason 4 + 3 = 7 disease and proportion of men with at least 50% positive cores.

The population of men with IR-PrCa is a heterogeneous group. Through characterization of favorable and unfavorable subsets of disease and assessment of differences in comorbid conditions, we identified a group of men most likely to benefit from the addition of ADT to DE EBRT. The two criteria identified for inclusion in our unfavorable subgroup, Gleason 4 + 3 = 7 disease or at least 50% positive biopsy cores, have been linked with inferior prostate cancer outcomes in other studies. Gleason score breakdown of 4 + 3 = 7 has been correlated with increased prostate cancer death compared with a breakdown of 3 + 4 = 7 in several studies [9, 17]. Likewise, retrospective analyses have shown that a greater percentage of positive cores is an independent predictor of biochemical failure in men with intermediate-risk disease [18–20].

Our results demonstrate the addition of short-term ADT to DE EBRT improves FFS for men with unfavorable IR-PrCa. The improvement is clinically significant, with a 10% absolute improvement in 5-year FFS. It is equally important to identify subgroups of men for whom ADT does not provide a benefit. ADT is not a benign treatment and can cause fatigue, decreased libido, and hot flashes in addition to less common side-effects such as weight gain, decreased muscle mass, increased lipid levels, and decreased bone density. Additionally, ADT may exacerbate comorbid conditions like diabetes and cardiovascular disease [21]. These side-effects can negatively impact a patient’s quality of life. Therefore, it is important to omit ADT when it does not improve cancer outcomes. Our results suggest men with favorable IR-PrCa may not benefit from ADT and therefore can be spared the unnecessary side-effects of ADT.

When comorbid conditions were taken into account, the benefit of adding ADT to DE EBRT was specifically seen among men with unfavorable disease and no or minimal comorbidities. Consistent with our finding, reanalysis of the DFCI randomized trial showed the addition of ADT to standard-dose EBRT improved overall survival among the intermediate-risk patients with low comorbidity scores [22, 23]. In the DFCI analysis, the improvement was not seen in men with high comorbidity scores. In our study, it is not clear whether men with unfavorable disease and moderate to severe comorbidities benefit from the addition of ADT due to the limited number of men with these characteristics in our study. It is postulated patients with severe comorbidities may not benefit from the addition ADT because of competing risks of death from non-prostate cancer causes and because they may be more likely to experience the detrimental endocrine and cardiovascular effects of ADT.

A few points deserve further consideration. This study was a retrospective analysis; therefore, the results can suggest an association but cannot definitely determine causation. The length of follow-up was limited; however, the length was similar to follow-up reported in initial publications from several trials establishing the superiority of DE EBRT and the benefit of ADT to standard-dose EBRT [2–4, 6, 8]. While median duration of ADT was 6 months, the study was not designed to evaluate the optimal duration of ADT administration. Additionally, the number of death events was limited; therefore, we could assess the impact of ADT on FFS but could not assess the impact of adding ADT on overall survival or prostate cancer mortality. Longer follow-up of this cohort will be necessary to determine the impact of ADT on survival.

The ongoing RTOG 08-15 prospective randomized trial of DE radiotherapy with or without short-term ADT for patients with IR-PrCa will provide definitive level 1 evidence regarding the magnitude of the benefit of adding short-term ADT to DE EBRT. The study stratifies patients by severity of comorbidity conditions (based on ACE-27) and by severity of disease. Therefore, RTOG 08-15 will also help determine which subsets of patients benefit most from the addition of ADT to DE radiotherapy. The trial is still enrolling patients and results are not expected for several years.

While we await the results of RTOG 08-15, data from retrospective studies can help guide clinical decisions and counsel patients, acknowledging the limitations of these studies. Our study concluded the addition of short-term ADT to DE EBRT improves FFS for men with unfavorable IR-PrCa (Gleason 4 + 3 = 7 disease or at least 50% involved cores). Therefore, short-term ADT should be discussed with men with unfavorable intermediate-risk disease who will be receiving DE EBRT. This benefit was specifically seen among men with unfavorable disease and no or minimal comorbidities. It is not clear if this benefit extends to men with unfavorable disease and moderate to severe comorbidities due to a limited number of men in our study with these characteristics. Our results also suggest men with favorable intermediate-risk disease may not benefit from the addition of short-term ADT to DE EBRT. Longer follow-up and results from RTOG 08-15 are needed to confirm our findings.

disclosure

The authors declare no conflicts of interest.

references

Circulating tumor cells (CTCs) provide prognostic information in patients with metastatic tumors. Recent studies have shown that CTCs are released in circulation in an early phase of cancer disease so that their presence is under investigation in the adjuvant setting. Few studies investigated the prognostic significance of CTCs enumeration in patients with metastatic and advanced bladder cancer. The current study has analyzed the presence of CTC in patients.

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