Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer

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IMPORTANCE In 5 published randomized clinical trials, dose-escalated external-beam radiation therapy (EBRT) for prostate cancer resulted in improved biochemical and local control. However, scarce evidence addresses whether dose escalation improves overall survival.

OBJECTIVE To examine the association between dose-escalated EBRT and overall survival among men with nonmetastatic prostate cancer.

DESIGN, SETTING, AND PARTICIPANTS We conducted a retrospective, nonrandomized comparative effectiveness study of dose-escalated vs standard-dose EBRT for prostate cancer diagnosed from 2004 to 2006 using the National Cancer Database (NCDB), which includes data from patients treated at Commission on Cancer-accredited community, academic, and comprehensive cancer facilities. Three cohorts were evaluated: men with low-risk (n = 12 229), intermediate-risk (n = 16 714), or high-risk (n = 13 538) prostate cancer.

EXPOSURES We categorized patients in each risk cohort into 2 treatment groups: standard-dose (from 68.4 Gy to <75.6 Gy) or dose-escalated (≥75.6 Gy to 90 Gy) EBRT (1 Gy = 100 rad).

MAIN OUTCOMES AND MEASURES We compared overall survival between treatment groups in each analytic cohort using Cox proportional hazard models with an inverse probability weighted propensity score (IPW-PS) approach. In secondary analyses, we evaluated dose response for survival.

RESULTS Dose-escalated EBRT was associated with improved survival in the intermediate-risk (IPW-PS adjusted hazard ratio [HR], 0.84; 95% CI, 0.80-0.88; P < .001) and high-risk groups (HR, 0.82; 95% CI, 0.78-0.85; P < .001) but not the low-risk group (HR, 0.98; 95% CI, 0.92-1.05; P = .54). For every incremental increase of about 2 Gy in dose, there was a 7.8% (95% CI, 5.4%-10.2%; P < .001) and 6.3% (95% CI, 3.3%-9.1%; P < .001) reduction in the hazard of death for intermediate- and high-risk patients, respectively.

CONCLUSIONS AND RELEVANCE Dose-escalated EBRT is associated with improved overall survival in men with intermediate- and high-risk prostate cancer but not low-risk prostate cancer. These results add to the evidence questioning aggressive local treatment strategies in men with low-risk prostate cancer but supporting such treatment in men with greater disease severity.
ive randomized clinical trials in men with nonmetastatic prostate cancer showed that treatment with dose-escalated external-beam radiation therapy (EBRT) resulted in lower rates of biochemical failure and local progression but did not affect overall survival.\textsuperscript{1-5} None of these studies were powered sufficiently to evaluate differences in overall survival.

Aggressive treatment approaches that do not affect overall survival are controversial in low-risk prostate cancer, where cancer-specific mortality is low and competing risks are high.\textsuperscript{6-10} Intermediate- and high-risk prostate cancers may be associated with significantly higher morbidity and mortality, and thus patients with this more severe disease may benefit from dose-escalated EBRT. The phase III Radiation Therapy Oncology Group (RTOG) 0126,\textsuperscript{11} a randomized trial testing whether dose-escalated EBRT improved survival in intermediate-risk prostate cancer, released early results suggesting no overall survival benefit with dose-escalated EBRT in the setting of a highly controlled efficacy trial.

The National Cancer Data Base (NCDB) tracks oncology outcomes on 71\% of newly diagnosed cancer cases nationwide from a broad set of hospitals and includes information on radiation dose.\textsuperscript{12,13} Therefore, using the NCDB, we conducted an observational study to examine the association of dose-escalated EBRT with overall survival among men with prostate cancer stratified by risk group in the setting of "real world" clinical care.

Methods

Data Collection and Cohort Definition

The NCDB collects information on patient demographics, tumor characteristics, first course of treatment, radiation therapy details (treatment site, modality, and dose), facility characteristics, and all-cause mortality from over 1500 institutions accredited by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Patients in the present study were classified into these subcategories, as defined by the NCDB.

We identified 360 142 patients with prostate cancer reported to the NCDB between 2004 and 2006 using International Classification of Diseases for Oncology, 3rd Edition, codes. We excluded patients with prior cancer, noninvasive disease, metastatic disease, or unconfirmed or nonadenocarcinoma disease. The patients with confirmed nonmetastatic prostate cancer were grouped into low-risk (n = 74 392, including very low-risk disease), intermediate-risk (n = 82 381), and high-risk (n = 56 769, including very high-risk disease) cohorts, as defined by National Comprehensive Cancer Network risk category using Gleason score, prostate-specific antigen level (PSA), and T stage (see eFigure 1 in the Supplement). Patients with at least 1 high-risk feature were categorized as high-risk, regardless of other missing data. Otherwise, patients with missing data were excluded (risk unclassifiable).

We included patients who received EBRT with or without androgen-deprivation therapy (ADT). Patients receiving multiple definitive treatments (eg, irradiation and surgery) were assigned to the first definitive treatment. Patients were excluded if they received unspecified or nonconventional EBRT modalities (eg, cobalt-60 or cesium-137, 2- to 5-MV photons or electrons, radiosurgery).

The NCDB registrars collect EBRT dose from radiation treatment summary records.\textsuperscript{13,14} Dose of EBRT was calculated as the sum of 2 NCDB dose variables: regional dose and boost dose. We excluded patients whose definitive EBRT dose was less than 68.4 Gy or greater than 90 Gy (1 Gy = 100 rad). The lower dose limit represents the lower limit used in the standard-dose arm of most randomized dose-escalation studies.

The final cohorts included 12 229, 16 714, and 13 538 patients in the low-, intermediate-, and high-risk groups, respectively. Survival data were not available for 1 patient in each of the low- and high-risk cohorts. Each risk group cohort was divided into 2 treatment groups: EBRT dose less than 75.6 Gy vs 75.6 Gy or greater. This study was approved by the University of Pennsylvania institutional review board, waiving patient written informed consent, and the data set was deidentified in accordance with the Health Insurance Portability and Accountability Act.

Primary Analyses

The primary aim of the present study was to determine the relation of EBRT dose to overall survival. We defined EBRT dose as a binary variable, with 75.6 Gy as a cutoff point to reflect most closely the division between high- and low-dose arms of the randomized clinical trials of EBRT dose in prostate cancer.\textsuperscript{1,4,11} In addition, National Comprehensive Cancer Network guidelines\textsuperscript{15} have recommended an EBRT dose of 75.6 Gy or higher in the definitive treatment of prostate cancer.

In secondary analyses, we examined whether a dose-response relationship existed in which higher radiation doses were associated with greater improvements in overall survival (or the inverse). Such a dose-response gradient is essential to the Bradford Hill criteria for causal inference in nonrandomized studies.\textsuperscript{16} To conduct these analyses, we defined dose categories to reflect the distribution of doses in the NCDB data. Dose prescriptions in the NCDB data were clustered in increments of approximately 1.8 to 2.0 Gy, corresponding to the dose of a conventional EBRT fraction. We classified each dose category using the upper dose limit (70.2, 72.0, 74.0, 76.0, 79.2, 81.0, and >81.0 Gy),
The primary outcome was time to death from any cause (all-cause mortality). The observation time for reported follow-up was the time from diagnosis until the NCDB date of death or end date of follow-up (December 31, 2012).

Other Variables
Clinical variables varied for each risk group, but included Gleason score, PSA, and clinical T-stage. Given the increased use of dose-escalated EBRT over time, we limited the period of the study to 3 years (2004-2006), and year of diagnosis was included as a clinical variable for all risk groups. Treatment variables included radiation treatment modality (intensity-modulated radiation therapy [IMRT] or non-IMRT) and ADT. Facility-level variables included facility EBRT volume and practice setting. Facility volume was defined as the number of patients treated with definitive EBRT for nonmetastatic prostate cancer annually. Facilities in the top volume quartile were categorized as high-volume facilities, and the remainder as low-volume facilities. For practice setting, the NCDB categorizes facilities into academic, comprehensive, community, or other. Other variables included in analyses are listed in Table 1, Table 2, and Table 3 and in eTable 1 in the Supplement. Race was included as a variable because it has been implicated in prostate cancer mortality.

Statistical Analysis
To adjust for measured confounding, we used traditional multivariable regression and propensity score approaches. To assess the possible effect of unmeasured confounding, we conducted sensitivity analyses for hypothetical unmeasured confounders.

In our propensity score approach, we estimated propensity scores separately within the 3 analytic cohorts using multivariable logistic regression models with receipt of dose-escalated EBRT as the outcome of interest, adjusting for all variables and interactions between radiation modality (ie, IMRT vs non-IMRT) and year of diagnosis, income, insurance status, facility volume, and facility type (Figure 1). We a priori included radiation modality as a primary variable in interaction terms because IMRT has facilitated the use of dose-escalated radiation.

We used Cochran-Mantel-Haenszel tests to determine whether covariates were balanced within propensity score quintiles. There were no significant imbalances in covariates between treatment groups in the low-risk and high-risk cohorts. For the intermediate-risk cohort, facility type was still imbalanced between treatment groups after propensity score adjustment.

We constructed multivariable Cox proportional hazard models to compare all-cause mortality between standard and dose-escalated groups. We present unadjusted Cox proportional hazards models and Cox models adjusted by traditional multivariable regression and propensity score methods. In our traditional regression approach, we compare all-cause mortality between treatment groups, adjusting for differences in patient, clinical, demographic, treatment, and demographic characteristics. In our propensity score approach, we used inverse probability-weighted (IPW) estimation additionally adjusting for facility type, since this variable was not balanced in the intermediate-risk cohort. In all models, we used generalized estimating equations to account for clustering of outcomes within facility assuming...
an independent correlation structure. Empirical robust sandwich variance estimates were used to construct 95% confidence intervals of hazard ratios (HRs).

To assess the proportional hazards assumption, we evaluated the Schoenfeld residuals test and complementary log-log plots and found that the proportional hazards assumption was not violated.22 The proportion missing among variables with any missing data was minor (<5%), except for missing Gleason-score (7.2%) and T-stage (7.4%) information in the high-risk cohort. These patients were not excluded from analysis because their missing Gleason-score and T-stage variables did not affect their risk classification. Missing values were entered into models as a separate category.23

To display adjusted differences in survival between treatment groups, we present adjusted plots of survival using the Breslow estimator for the cumulative hazard, setting the propensity score to 0.5.24

### Analysis of Dose-Response

To evaluate for a dose-response relationship between radiation dose and overall survival, we used the IPW propensity score (IPW-PS) Cox proportional hazards model as our primary working model, replacing the binary dose variable with the 7 dose categories (70.2, 72.0, 74.0, 76.0, 79.2, 81.0, and >81.0 Gy). Propensity scores were reestimated for each dose category.25 We included dose category as an ordinal variable to establish the presence or absence of a statistically significant dose gradient effect on survival. In separate models, we also included dose as a categorical variable to determine the relative effect on survival compared with the reference category (70.2 Gy).

### Sensitivity Analysis for Unmeasured Confounding

To address the potential effect of unmeasured confounding, we conducted sensitivity analyses to assess how strong and imbalanced a hypothetical unmeasured confounding vari-
able would need to be to change the significance of the estimated propensity score-adjusted HRs.26,27 As an example, we hypothesized a distribution for the presence of frailty, a variable not available in the NCDB. The presence of frailty could bias a patient’s treatment assignment toward standard-dose EBRT and might also be independently associated with worse survival. We assumed that frailty among the elderly was associated with a hazard of death ranging from 1.1 to 2.5 and a prevalence between 20% and 60%.28,29 We assumed a higher prevalence of frailty in the standard-dose group. We assessed whether various combinations of HR strength and prevalence imbalance associated with the unmeasured variable influenced the estimated propensity score-adjusted HRs and attenuated their statistical significance (ie, under which scenarios would the upper bound of the 95% CI cross 1.0).

We also attempted to conduct instrumental variable analyses.30 However, the candidate instruments we developed from the NCDB data set—including a local area treatment rate instrument and a distance instrument—were only weakly correlated with treatment assignment. Thus, we did not pursue instrumental variable analyses further.31

Statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc). Statistical significance was set at .05; all tests were 2-tailed.

Table 3. Baseline Characteristics of the High-Risk EBRT Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)</th>
<th>P Value</th>
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<th>After PS Adjustment</th>
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<tr>
<td></td>
<td>EBRT Dose &lt;75.6 Gy (n = 4662)</td>
<td>EBRT Dose ≥75.6 Gy (n = 8876)</td>
<td>Total Patients, No.</td>
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</tr>
<tr>
<td>Clinical</td>
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<td></td>
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</tr>
<tr>
<td>Year of diagnosis</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>2004</td>
<td>1914 (41.1)</td>
<td>2455 (27.6)</td>
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<td>.001  .52</td>
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<td>2005</td>
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<td>2840 (32.0)</td>
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<td></td>
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<td>&lt;10</td>
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<td>1491 (16.8)</td>
<td>2271</td>
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<td>20-98</td>
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<td>246 (2.8)</td>
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<td>T2B-T2C</td>
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<td>≥T3</td>
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<td>&lt;7</td>
<td>662 (14.2)</td>
<td>1118 (12.6)</td>
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<tr>
<td>3 + 4</td>
<td>566 (12.1)</td>
<td>1193 (13.4)</td>
<td>1759</td>
<td>.02  .90</td>
</tr>
<tr>
<td>4 + 3</td>
<td>400 (8.6)</td>
<td>716 (8.1)</td>
<td>1116</td>
<td>.02  .90</td>
</tr>
<tr>
<td>&gt;7</td>
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<td>Non-IMRT</td>
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<td>5663</td>
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<td>ADT status</td>
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<td></td>
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<tr>
<td>None (EBRT alone)</td>
<td>1087 (23.32)</td>
<td>2086 (23.5)</td>
<td>3173</td>
<td>.81  .98</td>
</tr>
<tr>
<td>EBR + ADT</td>
<td>3575 (76.7)</td>
<td>6790 (76.5)</td>
<td>10 365</td>
<td>.81  .98</td>
</tr>
<tr>
<td>Facility</td>
<td></td>
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<td></td>
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<td>EBRT volume</td>
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<td></td>
</tr>
<tr>
<td>Low</td>
<td>2120 (45.5)</td>
<td>3645 (41.1)</td>
<td>5765</td>
<td>&lt;.001 .49</td>
</tr>
<tr>
<td>High</td>
<td>2542 (54.5)</td>
<td>5231 (59.0)</td>
<td>7773</td>
<td>&lt;.001 .49</td>
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<td>Comprehensive</td>
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<td>5236 (59.0)</td>
<td>7940</td>
<td>&lt;.001 .25</td>
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<tr>
<td>Community</td>
<td>783 (16.8)</td>
<td>903 (10.2)</td>
<td>1686</td>
<td>&lt;.001 .25</td>
</tr>
</tbody>
</table>

Abbreviations: ADT, androgen deprivation therapy; EBRT, external-beam radiation therapy; IMRT, intensity-modulated radiation therapy; PS, propensity score; PSA, prostate-specific antigen level.
Results

Characteristics of the Study Cohort

Most patients in the low-, intermediate-, and high-risk cohorts received dose-escalated EBRT (61.6%, 65.6%, and 65.6%, respectively; Tables 1, 2, and 3). Compared with patients who received standard-dose EBRT, patients who received dose-escalated EBRT were more likely to be diagnosed in 2006 and treated with IMRT, at a high-volume facility, and at an academic facility. Other statistically significant differences between treatment groups by risk category were not clinically meaningful.

Association of Dose-Escalated EBRT With Overall Survival

The median follow-up for surviving patients was 85 to 86 months for all risk cohorts. Table 4 lists the unadjusted, traditional multivariable-adjusted, and propensity score-adjusted hazards of death for dose-escalated EBRT.

In the low-risk cohort, dose-escalated EBRT was associated with a decreased hazard of death in the unadjusted model (HR, 0.89; 95% CI, 0.81-0.98; P = .02). However, in adjusted models, this association was not significant (IPW-PS adjusted HR, 0.98; 95% CI, 0.92-1.05, P = .54).

In both the intermediate- and high-risk cohorts, dose-escalated EBRT was associated with a statistically significant decreased hazard of death in all models (eg, IPW-PS adjusted HR, 0.84; 95% CI, 0.80-0.88; P < .001 for intermediate-risk and IPW-PS adjusted HR, 0.82; 95% CI, 0.78-0.85; P < .001 for high-risk disease).

Figure 2 displays adjusted survival curves by risk group for patients with equal likelihood to receive standard or dose-escalated EBRT. In the low-risk cohort, adjusted 7-year overall survival was 86% (95% CI, 86%-87%) in both dose groups. In the intermediate-risk cohort, adjusted 7-year overall survival rates were 82% and 78% (95% CIs, 81%-82% and 77%-79%) in the dose-escalated and standard-dose groups, respectively. In the high-risk cohort, adjusted 7-year overall survival rates were 74% and 69% (95% CIs, 73%-74% and 68%-70%) in the dose-escalated and standard-dose groups, respectively.

Analyses of Dose-Response

Figure 2A illustrates the overall distribution of dose clustered in approximately 2-Gy increments. For the low-risk cohort (Figure 2B), incremental increases in dose were not associated with a difference in survival (IPW-PS HR, 0.98; 95% CI, 0.94-1.02; P = .27). For the intermediate-risk cohort, every approximately 2-Gy dose increase was associated with a 7.8% reduction in the hazard of death (IPW-PS HR, 0.92; 95% CI, 0.90-0.95; P < .001). Compared with the reference category (70.2 Gy), there was a statistically significant improvement in survival in the 76-, 79.2-, 81-, and greater than 81-Gy categories (Figure 1C).

For the high-risk cohort, every approximately 2-Gy increase was associated with a 6.3% reduction in the hazard of death (HR, 0.94; 95% CI, 0.91-0.97; P < .001). Dose categories 81 Gy and greater than 81 Gy were each associated with a statistically significant improvement in survival compared with 70.2 Gy (Figure 1D).

Sensitivity Analysis

For both intermediate- and high-risk cohorts, the sensitivity analysis showed that, for example, an extreme unmeasured confounding variable (HR, ≥2.0) would alter our observation

Figure 2. Dose-Escalated Irradiation and Nonmetastatic Prostate Cancer Survival

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regarding the association between dose-escalated EBRT and survival if its prevalence in the standard-dose treatment group were 2-fold higher than in the dose-escalated groups (see eTable 2 in the Supplement).

Discussion

Our study demonstrates that dose-escalated EBRT treatment (≥75.6 Gy) is associated with improved overall survival in men with intermediate- and high-risk prostate cancer, but not men with low-risk disease. Our findings have 4 main implications.

First, our findings are concordant with the growing literature that most men with low-risk prostate cancer have excellent survival without radical treatment. Even with standard-dose EBRT, we found that men with low-risk prostate cancer had an 86% adjusted survival rate at 7 years. This survival is similar to recent results from a prospective active surveillance study that included men with low-risk and favorable intermediate-risk prostate cancer.32

While radical treatment may not affect overall survival in low-risk prostate cancer, it does affect meaningful intermediate outcomes. For example, in PROG 95-09,3 a randomized trial of 79.2- vs 70.2-Gy EBRT in predominantly low-risk patients,
men derived a biochemical benefit from dose-escalation treatment. However, these intermediate outcomes must be weighed against the risks of dose-escalated EBRT, which can cause increased gastrointestinal and genitourinary toxic effects.

Second, the association of dose-escalated EBRT with improved survival for patients with intermediate- and high-risk prostate cancer is consistent with 2 efficacy dose-escalation trials and extends the evidence to routine real-world clinical practice. In the MD Anderson Cancer Center study, those with PSA higher than 10 ng/mL experienced the greatest benefit in biochemical and clinical control with dose-escalation therapy. Similarly, in the Dutch dose-escalation study, only intermediate- and high-risk subgroups had improved clinical or biochemical control with dose escalation. These studies complement our findings and suggest that improved cancer control with dose-escalation EBRT in intermediate- and high-risk patients leads to improvements in overall survival.

Third, our findings hint at a possible incremental dose-response. In our secondary analysis, we observed a 7.8% and 6.3% reduction in the hazard of death for every approximately 2-Gy incremental dose increase in intermediate- and high-risk patients, respectively. However, relative to 70.2 Gy, only categories 76.0 Gy and above in intermediate- and 81.0 Gy and above in high-risk cases were significant dose levels. These may represent threshold doses that need to be achieved to derive the mortality benefit observed, and beyond this threshold, our data do not exclude the possibility that even higher doses of EBRT, as delivered by approaches such as combined EBRT and brachytherapy, would be associated with better outcomes. However, incremental benefits of dose-escalation EBRT must still be validated and weighed against increased risks in the risk of toxic effects (eg, rectal and bladder effects).

Fourth, dose escalation was associated with extended survival even in the presence of ADT. In the intermediate- and high-risk cohorts, 49% and 77% of patients, respectively, received ADT. Only 2 of 6 large randomized dose-escalation studies included men who received ADT—the Dutch study, in which only 22% received ADT, and the MRC RT01, in which almost all received ADT but the dose-escalated arm received only 74 Gy, below current standards for dose-escalation treatment. Our results support the controversy hypothesis that dose escalation even in intermediate- and high-risk patients receiving ADT is associated with a survival benefit.

Some may question the internal validity of our findings for patients with intermediate-risk disease given the preliminary results of RTOG 0126, a randomized trial specifically designed to test the overall survival benefit of dose-escalated EBRT in intermediate-risk prostate cancer. These results, released in abstract form, showed that dose escalation lowered biochemical failure and distant metastasis rates. However, in contrast to our study, there was no improvement in overall survival.

This discordance could be explained by several possible mechanisms. First, residual unmeasured confounding might have led our study to falsely associate dose escalation with survival. However, our findings are consistent with the Bradford Hill model for causal inference in observational data because they (1) are biologically plausible based on randomized trials that have shown that local cancer control with radiation therapy reduces cancer-specific and overall mortality; (2) are consistent across 2 analytic techniques to adjust for known confounding in nonrandomized comparative effectiveness research; (3) are robust to all but extreme unmeasured confounding; and (4) show a dose-response relationship between increasing radiation dose and mortality.

Second, it is possible that RTOG 0126 was underpowered to detect the more modest survival advantage revealed in our study and excluded patients with higher disease severity who may be more likely to benefit from dose-escalated EBRT. The RTOG 0126 study was designed to detect a hazard of death of 0.77 for dose-escalated EBRT, included 1499 analyzable patients, and excluded intermediate-risk patients with a Gleason score of 7 and PSA between 15 and 20 ng/mL. Our observational cohort included 16 706 intermediate-risk patients, 5.1% of whom had a Gleason score of 7 and PSA between 15 and 20 ng/mL, and still the hazard of death was 0.84.

Third, it is also plausible that our observational study captures more modest but still significant association of dose and survival in routine clinical practice that was not seen in the highly selected clinical trial population of RTOG 0126. Furthermore, the concordance between survival estimates from the standard-dose arm in our study and the survival rates observed in control arms of the randomized evidence support the external validity of our data set.

Our study has limitations. First, we cannot establish a causal relationship between dose-escalated EBRT and overall survival based on our observational cohort. Second, even after traditional regression and propensity score methods, we cannot rule out residual bias from unknown variables. Third, while our study lacks intermediate outcomes like biochemical, local, or distant disease control or cancer-specific survival, we might support the association of dose escalation with overall survival, extensive randomized evidence published previously and summarized herein has already shown important effects of dose escalation on prostate cancer control outcomes.

Fourth, NCDB does not record data on ADT duration or treatment toxic effects. Our propensity score approach balanced ADT use, and possibly ADT duration, between treatment groups—if ADT duration is strongly associated with ADT use.

Fifth, NCDB EBRT dose records are subject to heterogeneity. Radiation oncologists prescribe the dose either to an axis point near the target center (isocenter) or to the target periphery, and the dose can vary up to 10% between these points. While the NCDB advises recording the isocenter dose, in some cases these data are not readily available. However, dose heterogeneity is unlikely to be differential between dose-escalated and standard-dose groups after balancing for the use of IMRT in the propensity score model, suggesting that its potential to bias our results is minimal.

Finally, NCDB collects data only from Commission on Cancer-approved facilities; thus, our results are generalizable to patients treated at facilities that tend to be larger and urban.
Conclusions

In summary, we found that dose-escalated EBRT was associated with improved survival for men with intermediate- and high-risk, but not low-risk, prostate cancer. Our results add to the body of evidence questioning aggressive local treatment strategies in men with low-risk prostate cancer but supporting such treatment in men with greater disease severity.

REFERENCES


