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Brachytherapy Boost Utilization and Survival in Unfavorable-risk Prostate Cancer

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Abstract

Background: There are limited comparative survival data for prostate cancer (PCa) patients managed with a low-dose rate brachytherapy (LDR-B) boost and dose-escalated external-beam radiotherapy (DE-EBRT) alone.
Objective: To compare overall survival (OS) for men with unfavorable PCa between LDR-B and DE-EBRT groups.
Design, setting, and participants: Using the National Cancer Data Base, we identified men with unfavorable PCa treated between 2004 and 2012 with androgen suppression (AS) and either EBRT followed by LDR-B or DE-EBRT (75.6–86.4 Gy).
Outcome measurements and statistical analysis: Treatment selection was evaluated using logistic regression and annual percentage proportions. OS was analyzed using the Kaplan-Meier method, log-rank test, Cox proportional hazards, and propensity score matching.
Results and limitation: We identified 25 038 men between 2004 and 2012, during which LDR-B boost utilization decreased from 29% to 14%. LDR-B was associated with better OS on univariate (7-yr OS: 82% vs 73%; $p < 0.001$) and multivariate analyses (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.64–0.77). Propensity score matching verified an OS benefit associated with LDR-B boost (HR 0.74, 95% CI 0.66–0.89). The OS benefit of LDR-B boost persisted when limited to men aged <60 yr with no comorbidities. On subset analysis, there was no interaction between treatment and age, risk group, or radiation dose. Limitations include the retrospective design, nonrandomized selection bias, and the absence of treatment toxicity, hormone duration, and cancer-specific outcomes.
Conclusions: Between 2004 and 2012, LDR-B boost utilization declined and was associated with better OS compared to DE-EBRT alone. LDR-B boost is probably the ideal treatment option for men with unfavorable PCa, pending long-term results of randomized trials.
Patient summary: We compared radiotherapy utilization and survival for prostate cancer (PCa) patients using a national database. We found that low-dose rate brachytherapy (LDR-B) boost, a method being used less frequently, was associated with better overall survival when compared to dose-escalated external-beam radiotherapy alone for men with unfavorable PCa. Randomized trials are needed to confirm that LDR-B boost is the ideal treatment.

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1. Introduction

Prostate cancer (PCa) remained the second leading cause of cancer death among men in 2015 [1]. This is largely attributable to patients with unfavorable PCa (ie, intermediate- and high-risk disease), which is associated with 10-yr survival as low as 25% without treatment [2]. Multiple prospective trials of men with unfavorable PCa have shown that the combination of radiation therapy and androgen suppression (AS) improves overall survival (OS) when compared to either treatment alone [3–12]. However, these studies did not use dose-escalated external-beam radiation therapy (DE-EBRT), which has been shown to improve biochemical control, local progression, and distant metastases in contemporary randomized controlled trials [13–18]. Brachytherapy is a treatment modality that has been used to escalate radiation doses beyond those that can be delivered routinely with EBRT. Until recently, there were only limited data comparing DE-EBRT and brachytherapy among men with unfavorable PCa [19,20].

The ASCENDE-RT trial is a randomized phase 3 study comparing AS and whole-pelvis EBRT with either an EBRT boost or a low-dose rate brachytherapy (LDR-B) boost for men with intermediate- and high-risk PCa. Preliminary results suggest improved biochemical control for those receiving LDR-B boost. There was no difference in 7-yr OS, but there was a trend favoring LDR-B boost (85.7% vs 81.5%) [21]. At median follow-up of 6.5 yr, the study had not reached median survival, and if a difference exists, the results may not be available for many years. Therefore, we analyzed the National Cancer Data Base (NCDB) to compare survival outcomes between those treated with AS and EBRT followed by either EBRT alone or LDR-B boost in a large national cohort.

2. Patients and methods

2.1. Data source

We performed an analysis of the NCDB, a clinical oncology database containing hospital registry data from >1500 Commission on Cancer (CoC)–accredited centers [22]. Detailed information on OS, first treatment, clinical characteristics, demographics, radiation type, site, dose, and with AS are included in the database. The CoC of the American College of Surgeons has not validated the database and is not responsible for the conclusions of this study.

2.2. Cohort identification

Men diagnosed between 2004 and 2012 with intermediate- or high-risk PCa, defined according to National Comprehensive Cancer Network Guidelines [23], and treated with definitive radiotherapy were identified in the database. Inclusion and exclusion criteria for our study population are summarized in Supplementary Figure 1 and are based on the ASCENDE-RT trial [21]. Administration of neoadjuvant AS was limited to those who started AS within 8 mo before EBRT followed by LDR-B or DE-EBRT. Patients in the DE-EBRT arm were limited to those who received a dose between 75.6 and 86.4 Gy. Patients who did not receive radiation to the prostate and/or pelvis were excluded.

2.3. Patient covariates and outcomes

Treatment modality following AS and EBRT (DE-EBRT vs LDR-B boost) was the primary independent variable. Covariates identified in the database were age, race (black, non-Hispanic white, other), insurance (Medicare, uninsured, private, Medicaid or government/unknown), geography (Northeast, South, Midwest, West), facility (academic or non-academic), Charlson comorbidity score (CCS) (0, 1, or ≥2), risk group (intermediate or high), Gleason score (GS; 6, 7, or 8–10), prostate specific antigen (PSA; <10, ≥10 to <20, or ≥20 to <40 ng/ml), and clinical T stage (T1c–T2a, T2b–T2c, or ≥T3a). OS was the primary outcome of interest.

2.4. Statistical methods

Descriptive statistics for patient characteristics were compared between the DE-EBRT and LDR-B arms using χ^2 and t tests for categorical and continuous variables, respectively. To identify covariates associated with LDR-B treatment selection, logistic regression was used. Treatment groups were compared by evaluating the proportion of patients treated each year with LDR-B boost compared to DE-EBRT. Univariate analyses (UVA) were carried out using Cox proportional hazards regression, the log-rank test, and Kaplan-Meier survival analysis. OS time was calculated from the time of diagnosis to date of death. Multivariate analyses (MVA) and subset survival analyses were carried out using Cox proportional hazards to control for covariates found to be significant ($p < 0.05$) on UVA, including treatment type, age, race, insurance type, geographic region, facility type, CCS, GS, PSA, and clinical stage. To further adjust for unbalanced variables, propensity score matching was carried out using covariates associated with treatment selection on logistic regression. Covariates were matched between treatment groups using one-to-one nearest-neighbor matching without replacement. A matched sensitivity analysis was conducted by varying GS from 7 to 8–10 in 5% increments for those receiving DE-EBRT to investigate the degree of underadjustment that would result in a null result. Subset survival analyses were performed using log-rank testing, Kaplan-Meier survival analysis, and testing of interactions on Cox proportional hazards regression. The first subset analysis was limited to men aged <60 yr with no comorbidities to exclude patients more likely to have non-PCa causes of death. This age was chosen as it reflects a large proportion of patients with no comorbidities [24]. Interactions between treatment (DE-EBRT vs LDR-B boost) and age, treatment and risk group (high and intermediate risk), treatment and dose, and risk group and dose were tested. Statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, TX, USA) and statistical tests were two-tailed with $\alpha = 0.05$.

3. Results

3.1. Patient characteristics

For median follow-up of 63 mo (interquartile range 37–88 mo) we identified 25 038 patients treated with AS and definitive radiation, of whom 20 522 (82%) were treated with DE-EBRT and 4516 (18%) with EBRT followed by LDR-B boost. A comparison of patient characteristics is shown in Table 1.

3.2. Treatment selection and care patterns

The relative odds of receiving LDR-B compared to DE-EBRT are reported in Supplementary Table 1. Between 2004 and 2012, the proportion of patients receiving LDR-B boost decreased from 29% to 14%, while patients receiving

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