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Significant association of brachytherapy boost with reduced prostate cancer–specific mortality in contemporary patients with localized, unfavorable-risk prostate cancer

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ABSTRACT

PURPOSE: A randomized trial recently found that adding brachytherapy (BT) boost to external beam radiation therapy (EBRT) improves biochemical recurrence-free survival but not prostate cancer–specific mortality (PCSM). We investigated the relationship between BT boost and PCSM in a modern cohort from a large population-based database.

METHODS AND MATERIALS: We conducted an analysis of patients in Surveillance, Epidemiology, and End Results diagnosed with intermediate- or high-risk prostate cancer in 2004–2011, treated with EBRT only or EBRT + BT. The cumulative incidence of PCSM was evaluated in the presence of other-cause mortality as a competing risk. Propensity score matching and multivariable Fine and Gray proportional hazard models were used to evaluate the association of combined modality RT on PCSM.

RESULTS: A total of 52,535 patients were identified, of which 19.6% were treated with EBRT + BT. One-third of cases were high-risk. On multivariable analysis, the adjusted hazard ratio (AHR) of PCSM for EBRT + BT vs. EBRT alone was 0.69 (95% confidence interval [CI], 0.55–0.87, $p = 0.002$), and the adjusted incidence of PCSM was 1.8% vs. 2.7% at 8 years, respectively. In subgroup analyses, the AHR for PCSM was also significantly reduced with EBRT + BT for high-risk disease (AHR 0.70; 95% CI, 0.52–0.94, $p = 0.02$; adjusted incidence of PCSM at 8 years, 5.4% vs. 7.6%), but not for intermediate-risk disease.

CONCLUSIONS: BT boost was associated with a moderate reduction to PCSM in men with localized unfavorable-risk prostate cancer. Those most likely to benefit are younger patients with high-risk disease.

Keywords: Prostate cancer; Brachytherapy; Radiation therapy

Introduction

In patients receiving radiation therapy for localized prostate cancer, a large body of evidence shows that dose escalation leads to improved outcomes, particularly for those with unfavorable disease (1–6). While external beam radiation therapy (EBRT) is the least invasive definitive therapy, dose escalation by EBRT alone is limited by toxicities to surrounding tissues (1, 3, 7). An alternate strategy is to combine EBRT with brachytherapy (BT), which allows for dose escalation and treatment advantages that cannot be achieved by either modality alone. BT provides for a highly conformal, larger dose that is able to account for organ movement; EBRT, compared to BT, provides greater radiation coverage to periprostatic tissues, which are routes for local microscopic spread (8). For these reasons, combined modality RT with EBRT and BT is increasingly common for patients with adverse prognostic features (9).

Recently, the Phase 3 androgen suppression combined with elective nodal and dose escalated radiation therapy (ASCENDE-RT) trial reported a significant improvement in biochemical progression-free survival after pelvic EBRT with

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low dose rate (LDR) boost compared to pelvic EBRT with conformal EBRT boost in men with intermediate- and high-risk disease treated by 12 months of androgen deprivation therapy (ADT) (10). However, there was no difference in prostate cancer-specific survival (CSS). Similarly, two randomized trials and several retrospective studies of EBRT boosted with medium or high dose rate (HDR) BT demonstrated improved freedom from biochemical failure, but no differences in clinical failure or CSS compared to EBRT alone (11–15).

To further investigate the efficacy of EBRT + BT in men with localized prostate cancer, we undertook a retrospective population-based analysis using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. In light of the recent data from the ongoing ASCENDE-RT trial, we focused on patients in SEER who were most similar to the patient population comprising ASCENDE-RT. We hypothesized that the much larger number of cases available in SEER could reveal differences in prostate cancer–specific mortality (PCSM) for EBRT + BT vs. EBRT not observed yet in ASCENDE-RT.

Methods and materials

Database and patient selection

We used the SEER database to identify men diagnosed with prostate adenocarcinoma between January 1, 2004 and December 31, 2011. The start date was chosen because of the availability of quantitative prostate-specific antigen (PSA) data and detailed Gleason scores beginning in 2004. In a minority of cases, PSA scores were recently found to be reported incorrectly in SEER because of a misplacement of a decimal point, which was estimated to affect the risk classification of localized prostate cancer for 3–4% of patients (16). To minimize the effects of incorrect PSA scores, we excluded cases for which the PSA level was ≤4.0 ng/mL and the PSA interpretation was coded as "positive/elevated"; cases for which the PSA level was >4.0 ng/mL and the PSA interpretation were coded as "negative/normal; within normal limits"; and all cases for which the PSA interpretation were coded as "borderline" or "unknown."

To match the ASCENDE-RT enrollment criteria as closely as possible, we selected cases of intermediate- or high-risk T1c-T3a, N0, M0 disease, with pretreatment PSA not >40 ng/mL, and not receiving prior transurethral resection of the prostate (TURP) or any cancer-directed surgery. All cases were treated by EBRT alone or EBRT + BT. Prostate cancer was the only malignancy, or else was the first cancer diagnosed. Data regarding ADT use are not available in SEER. As in ASCENDE-RT, subgroup analyses were performed according to risk category using the National Comprehensive Cancer Network classification scheme: for high-risk, at least one of T3a, Gleason 8–10, and PSA >20 ng/mL; for intermediate-risk, at least one of T2b-T2c, Gleason 7, and PSA 10–20 ng/mL while not meeting high-risk criteria.

Patient demographic and disease characteristics

Data collected through SEER included age at diagnosis, year of diagnosis, race (white, black, and other), SEER region, tumor stage (American Joint Committee on Cancer, Sixth Edition), type of radiation therapy (EBRT alone vs. EBRT + BT), pretreatment PSA level (ng/mL), Gleason score, reason no cancer-directed surgery was performed, vital status or cause of death, number of months from date of diagnosis to death or last follow-up, marital status, and county. Further information was obtained from Area Health Resources Files (http://ahrf.hrsa.gov) according to the patient's county: quartile of median personal income, education quartile based on fraction of persons aged >25 years without a high school diploma, and number of radiation oncologists per million people in the patient's health service area (HSA). The mapping of counties to HSAs was obtained from SEER (http://seer.cancer.gov/seerstat/variables/countyattribs/hsa.html). Quartiles reflect the rank of the patient's country relative to all counties nationwide.

Statistical analyses

Baseline characteristics were compared using the χ^2 test or Wilcoxon rank-sum test. Event-free survival was compared using the log-rank test. Cumulative incidence of PCSM was estimated in the presence of other-cause mortality as a competing risk and compared using Gray's test (17, 18). Cases were censored if the patient was alive at last follow-up. To adjust for covariates and estimate their effect on PCSM, nearest-neighbor 1:1 propensity score matching (PSM) with caliper width equal to 0.2 of the standard deviation of the logit (19) was performed, followed by multivariable regression analysis by the proportional hazards model of Fine and Gray in the presence of other-cause mortality as a competing risk (17, 20). Median follow-up was computed using the reverse Kaplan–Meier method (21), in which being alive at last follow-up was the event of interest and death from any cause was censored. MATLAB version 2015a (MathWorks, Inc.; Natick, MA, USA) and R version 3.1.2 (R Foundation for Statistical Computing; Vienna, Austria) were used for calculations.

Results

Patient demographics

We identified a total cohort of 52,535 patients diagnosed with localized, intermediate- or high-risk prostate adenocarcinoma from 2004 to 2011 matching our selection criteria. Of these, 42,225 (80.4%) were treated with EBRT alone, and 10,310 (19.6%) were treated with EBRT + BT. Median follow-up was 44.2 months (3.7 years). Patients in the EBRT + BT group were slightly younger and more likely to be black, married, and reside in a southern SEER region, among other differences (see Table 1 for baseline characteristics). Tumors treated by EBRT + BT had