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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 (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 (SEER) 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—Brachytherapy 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

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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 radiotherapy (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 III 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 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. 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 cancer-specific survival 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 for EBRT + BT vs. EBRT not observed yet in ASCENDE-RT.

MATERIALS AND METHODS

Database and patient selection

We utilized the SEER database to identify men diagnosed with prostate adenocarcinoma between January 1, 2004 and December 31, 2011. The start date was chosen due to the availability of quantitative 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 due to 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 was coded as "negative/normal; within normal limits"; and all cases for which the PSA interpretation was 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 pre-treatment PSA not exceeding 40 ng/ml, and not receiving prior 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, 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, other), SEER region, tumor stage (AJCC 6th Ed.), type of radiation therapy (EBRT alone vs. EBRT + BT), pre-treatment 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 over age 25 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/countyattrs/hsa.html>). Quartiles reflect the rank of the patient's county relative to all counties nationwide.

Statistical analyses

Baseline characteristics were compared using the chi-square test or Wilcoxon rank-sum test. Event-free survival was compared using the log-rank test. Cumulative incidence of prostate cancer-specific mortality 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 prostate cancer-specific mortality, nearest-neighbor 1:1 propensity score matching 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 and R version 3.1.2 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 through 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 slightly lower PSA and more Gleason 7 histology, but no significant differences in tumor stage (Table 1). The proportion of intermediate- and high-risk disease was, respectively, 67.1% and 32.9% for the EBRT group and 69.0% and 31.0% for the EBRT + BT group. Subgroup analyses were performed for high- and intermediate-risk cases, with baseline characteristics for these subgroups listed in Supplemental Tables S1 and S2.

Univariable analysis

On univariable analysis, overall survival of the EBRT and EBRT + BT groups was, respectively, 86.1% vs. 91.3% at 5 years, and 72.7% vs. 80.8% at 8 years (log-rank $p < 0.0001$). However, the cumulative incidence of other-cause mortality was much greater than the cumulative incidence of prostate cancer-specific mortality (PCSM) in both treatment groups (Figure 1). Accordingly, most of the difference in overall survival was due to increased incidence of other-cause mortality in the EBRT group, which was also true of the high- and intermediate-risk subgroups when separately analyzed (Supplemental Figures S1–2). For this reason, and because prostate cancer is often an indolent disease with prolonged course, further analyses were focused on PCSM in the presence of other-cause mortality as a competing risk [17, 18].

In the total cohort, the cumulative incidence of PCSM in the EBRT and EBRT + BT groups was 2.2% vs. 1.6% at 5 years, and 4.5% vs. 3.1% at 8 years (Figure 1). The reduced PCSM in the EBRT + BT group was statistically significant ($p = 0.0004$, Gray's test). Qualitatively similar findings extended to the risk category subgroups. In the high-risk subgroup, PCSM in the EBRT and EBRT + BT groups was 4.3% vs. 3.4% at 5 years, and 7.9% vs. 6.1% at 8 years (Supplemental Figure S1; $p = 0.02$). In the intermediate-risk subgroup, PCSM in the EBRT and EBRT + BT groups was 1.1% vs. 0.9% at 5 years, and 2.9% vs. 1.8% at 8 years (Supplemental Figure S2; $p = 0.04$).

Multivariable analysis

To adjust for differences in baseline characteristics between the EBRT and EBRT + BT groups, propensity score matching (PSM) was used in the total cohort and in the risk category subgroups. After PSM, patient and tumor characteristics were well-balanced (Table 1 and Supplemental Tables S1–2). Afterward, the regression model of Fine and Gray was fitted to adjust for covariates and evaluate predictors of PCSM in the presence of other-cause mortality as a competing risk [17, 20].

In the multivariable model, the adjusted hazard ratio (AHR) of PCSM for EBRT + BT was 0.69 (95% confidence interval [CI], 0.55 – 0.87; $p = 0.002$) compared with EBRT alone (Table 2). EBRT + BT was also associated with significantly reduced PCSM in the high-risk subgroup (AHR 0.70; 95% CI, 0.52 – 0.94; $p = 0.02$), but not in the intermediate-risk subgroup (AHR 0.77; 95% CI, 0.53 – 1.12; $p = 0.18$). Other significant covariates included PSA, Gleason score, tumor stage, and race (Table 2 and Supplemental Tables S3–4). Adjusted cumulative incidence of PCSM (Figure 2) for the EBRT and EBRT + BT groups was, respectively, 1.4% vs. 1.0% at 5 years and 2.7% vs. 1.8% at 8 years in the total cohort;

4.2% vs. 2.9% at 5 years and 7.6% vs. 5.4% at 8 years in the high-risk subgroup; and 0.7% vs. 0.5% at 5 years and 1.3% vs. 1.0% at 8 years in the intermediate-risk subgroup.

DISCUSSION

Using the large cohort available in the SEER database, we detected a moderate reduction in PCSM associated with delivery of EBRT + BT compared to EBRT alone. This finding persisted in multivariable analysis after propensity score matching to adjust for baseline differences between the two treatment groups. Overall, patients with intermediate- or high-risk disease may see PCSM reduced by approximately 30% with BT boost. Our results support a role for combined modality RT in the management of localized, unfavorable-risk prostate cancer, especially in younger, high-risk patients, who are the ones most likely to die of their disease relative to non-prostate cancer-related causes.

We observed much higher other-cause mortality than PCSM, which was expected since most prostate cancer patients are elderly, comorbidities are common, and the natural course of disease is often prolonged and indolent. The high incidence of other-cause mortality compared to PCSM indicated a competing-risks analysis was most appropriate. Additionally, we found othercause mortality to be significantly lower in the EBRT + BT group compared to the EBRT group, suggesting that in general, healthier patients were selected for BT boost. This selection bias may reflect the requirement to tolerate spinal or general anesthesia to undergo BT; also, clinicians may treat the cancers of healthier patients more aggressively due to perceived longer life expectancy. Due to this selection bias, we focused our analysis on PCSM rather than all-cause mortality or overall survival.

Thus far, no randomized controlled trials (RCTs) comparing EBRT + BT with EBRT have found a difference in PCSM or related outcomes. Most often, the surrogate endpoint of biochemical relapse-free survival is used, which is based on PSA failure after RT. This outcome, but not clinical failure or cancer-specific survival, was improved by medium or HDR BT boost in two RCTs and several matched-pair retrospective studies [11–15]. Similar findings were reported by the investigators of ASCENDE-RT [10], which is the only RCT to examine LDR BT boost. However, all of these studies have been limited by sample size, relatively short follow-up, or both. We modeled our study cohort in SEER after the intermediate- and high-risk population of ASCENDE-RT and found a significant reduction in PCSM. Although the absolute survival differences we observed were small, they appeared to grow over time, suggesting that reduced PCSM might also be seen in ASCENDE-RT with longer follow-up, especially among younger and healthier patients.

Indeed, in contrast to our SEER cohort, the two treatment arms of ASCENDE-RT have shown equivalent other-cause mortality, indicating effective randomization; and the overall survival difference, while not statistically significant, has been driven entirely by increased PCSM in the EBRT-only arm (11 deaths vs. 7 in the EBRT + LDR arm by intention-to-treat analysis, and 11 vs. 6 according to treatment received) [22]. Of note, although we utilized selection criteria to model our SEER cohort after ASCENDE-RT, the proportion of high-risk patients within ASCENDE-RT was over twice as high as in our study (70% vs. 32%). Accordingly, the prevalence of adverse prognostic features was much higher in ASCENDE-

RT than in this study, such as tumor stage T3a (30% vs. less than 2%) and Gleason score 8–10 (40% vs. 25%). Therefore, our study population had overall lower risk of occult metastatic disease at diagnosis and correspondingly lower PCSM than the cohort of ASCENDE-RT (approximately 4% at 8 years vs. 7% at 9 years).

In subgroup analyses, we found reduced PCSM in the total cohort and in the high-risk subgroup, but not in the intermediate-risk subgroup. In contrast, the interim report from ASCENDE-RT found a much larger relative improvement in biochemical progression-free survival in its subgroup analysis of intermediate-risk patients (relative risk [RR] of PSA failure at 9-years, 0.20; log-rank $p < 0.001$) than in high-risk patients (RR 0.53; $p = 0.05$). One explanation to reconcile these data is that BT boost in high-risk patients, who are more likely to have micrometastatic disease, confers less relative benefit to local and biochemical control, but more of that benefit is translated into a survival advantage than in intermediate-risk patients, since the latter are much less likely to die of their disease even after PSA failure. Data from retrospective studies support this interpretation. A matched-pair analysis of 3DCRT + HDR BT vs. 3DCRT found a strong trend toward reduced efficacy of BT boost for biochemical outcomes in high-risk patients [13]. On the other hand, a multicenter retrospective study found that higher overall doses, which were achieved almost exclusively through EBRT + BT, resulted in improved overall survival, but only in the subgroup of Gleason score 8–10 [6].

Our results are consistent with findings previously reported in the literature. In a case series of 181 high-risk patients treated with 45 Gy EBRT plus median 100 Gy of LDR BT and 9 months of ADT, the 8-year cancer-specific survival (CSS) was 87% [23]. In two other case series, both of LDR BT for high-risk disease in which over 90% of cases received supplemental EBRT and two-thirds received ADT, CSS was 94% at 10 and 12 years [24, 25]. A retrospective analysis of 958 high-risk patients comparing 78 Gy of dose-escalated EBRT (3DCRT or IMRT) vs. 45 Gy EBRT plus 100 Gy of LDR BT found that BT boost was associated with a reduction in 8-year PCSM from 13% to 7%, with HR for PCSM of 0.41 ($p = 0.004$), despite more extensive ADT use in EBRT-only patients [26]. Finally, a retrospective analysis of high-risk (Gleason 8–10) cancers diagnosed 1988–2002 in SEER found EBRT + BT to be associated with 10-year PCSM of 13.4% vs. 21.1% for EBRT alone, with a HR of 0.77 ($p < 0.01$) [27]. Unlike the previous SEER study, our analysis encompassed both intermediate- and high-risk patients and employed a competing-risks approach. Additionally, we examined a more recent cohort, with quantitative PSA reporting and detailed Gleason scores (both available since 2004) and use of more contemporary protocols regarding ADT and dose-escalated EBRT/IMRT.

Given the higher radiation doses delivered with combination EBRT + BT, any increase in efficacy must be balanced against the potential to incur greater toxicities. In the two RCTs comparing EBRT + medium or HDR BT vs. EBRT alone, no statistically significant increase in late grade 3 or higher GI or GU toxicities was observed [11, 12], although there was a four-fold higher relative risk of urethral strictures in the BT-boosted arm of the Hoskins' trial (8% vs. 2% at 7 years, $p = 0.10$). On the other hand, ASCENDE-RT found that EBRT + LDR BT resulted in significantly more late grade 3 GU toxicity compared with dose-escalated EBRT (19% vs. 5%; $p < 0.001$), and half of such events in the BT-boosted arm

were urethral strictures. A similar finding was reported in a retrospective analysis of 3DCRT + HDR BT, in which 6.6% of patients had late grade 3 urethral strictures requiring dilation or urethrotomy [15], and in a matched-pair analysis that found the 5-year cumulative incidence of such events to be 11.8% for 3DCRT + HDR BT vs. only 0.3% for 3DCRT alone ($p < 0.0001$) [13]. Interestingly, other retrospective series and uncontrolled prospective studies have found the incidence of late grade 3 GI/GU toxicities for EBRT + BT to be comparable to that historically observed with either modality alone, including dose-escalated EBRT [28–31], whereas others have noted increased GI and/or GU toxicity with BT boost [32].

Our study has multiple strengths, including large sample size, multivariable analysis using a competing-risks approach, propensity matching, and a modern cohort. This work also has a number of limitations. The study is retrospective and non-randomized, leaving open the possibility of confounding by unmeasured variables, and thus should be viewed as hypothesis-generating. SEER does not provide information on RT dose or fractionation schedule, and the cases we analyzed comprise a mixture of LDR and HDR BT. Additionally, no data are available for medical comorbidities, percent positive cores, presence of perineural invasion, or PSA values over time, all of which often influence clinical decision making. Also, SEER has recently reported problems in some of its PSA data, although we believe our approach eliminates many or most of the erroneous PSAs and that the overall trends in this paper are highly unlikely to be driven by any residual errors in PSA coding. Finally, SEER lacks data on ADT administration, although the vast majority of high-risk patients are likely to receive ADT in the modern era, and encouragingly, that subgroup appeared to benefit most robustly from BT boost in our analysis. Moreover, it is possible that ADT may not further improve outcomes in the setting of EBRT + LDR BT [33] or high total prostatic dose [34], although other studies have found the opposite [6, 11]. The ongoing RTOG 0815 trial will evaluate the impact of 6 months of ADT in patients receiving EBRT + BT.

In summary, our population-based analysis of a large modern cohort using the SEER database identified significantly reduced PCSM in patients with localized unfavorable-risk prostate cancer treated with EBRT + BT compared with EBRT alone. The patients who appear most likely to benefit from BT boost are young, high-risk patients, who have lower competing risks for mortality and more aggressive disease, and thus are more likely to die of prostate cancer. These results, taken together with prior findings in the literature, suggest that boosting EBRT with BT may confer a true cancer-specific survival advantage, and can be considered as a viable treatment option in suitable patients. At the same time, although the data are mixed, the potential for increased efficacy may come at the cost of greater toxicities, in particular urethral strictures. It will be worthwhile to follow the results of ASCENDE-RT and other RCTs to see if a discernible benefit to cancer-specific or overall survival outcomes emerges over time, especially in high-risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Al-Mamgani A, van Putten WL, Heemsbergen WD, van Leenders GJ, Slot A, Dielwart MF, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *International journal of radiation oncology, biology, physics*. 2008; 72:980–988.
2. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *The Lancet Oncology*. 2007; 8:475–487. [PubMed: 17482880]
3. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *International journal of radiation oncology, biology, physics*. 2008; 70:67–74.
4. Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, Adams JA, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *Jama*. 2005; 294:1233–1239. [PubMed: 16160131]
5. Martinez AA, Gonzalez J, Ye H, Ghilezan M, Shetty S, Kernen K, et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. *International journal of radiation oncology, biology, physics*. 2011; 79:363–370.
6. Stone NN, Potters L, Davis BJ, Ciezki JP, Zelefsky MJ, Roach M, et al. Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with Gleason score 7–10 prostate cancer treated with permanent prostate brachytherapy. *International journal of radiation oncology, biology, physics*. 2009; 73:341–346.
7. Beckendorf V, Guerif S, Le Prise E, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *International journal of radiation oncology, biology, physics*. 2011; 80:1056–1063.
8. Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2007; 84:114–120. [PubMed: 17531335]
9. Terakedis BE, Rossi PJ, Liauw SL, Johnstone PA, Jani AB. A surveillance, epidemiology, and end results registry analysis of prostate cancer modality time trends by age. *American journal of clinical oncology*. 2010; 33:619–623. [PubMed: 20051808]
10. Morris WJ, Tyldesley S, Pai HH, Halperin R, McKenzie MR, Duncan G, et al. ASCENDERT*: A multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRTB) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015
11. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2012; 103:217–222. [PubMed: 22341794]
12. Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005; 23:1192–1199. [PubMed: 15718316]
13. Khor R, Duchesne G, Tai KH, Foroudi F, Chander S, Van Dyk S, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external beam radiation therapy alone for prostate cancer. *International journal of radiation oncology, biology, physics*. 2013; 85:679–685.
14. Kestin LL, Martinez AA, Stromberg JS, Edmundson GK, Gustafson GS, Brabbins DS, et al. Matched-pair analysis of conformal high-dose-rate brachytherapy boost versus external-beam

- radiation therapy alone for locally advanced prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2000; 18:2869–2880. [PubMed: 10920135]
15. Zwahlen DR, Andrianopoulos N, Matheson B, Duchesne GM, Millar JL. High-dose-rate brachytherapy in combination with conformal external beam radiotherapy in the treatment of prostate cancer. *Brachytherapy*. 2010; 9:27–35. [PubMed: 19846348]
 16. Penson DF. The Power and the Peril of Large Administrative Databases. *The Journal of urology*. 2015
 17. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2007; 13:559–565. [PubMed: 17255278]
 18. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone marrow transplantation*. 2007; 40:381–387. [PubMed: 17563735]
 19. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharmaceutical statistics*. 2011; 10:150–161. [PubMed: 20925139]
 20. Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. *Bone marrow transplantation*. 2010; 45:1388–1395. [PubMed: 20062101]
 21. Shuster JJ. Median follow-up in clinical trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1991; 9:191–192. [PubMed: 1985169]
 22. Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai HH, McKenzie MR, et al. LDR brachytherapy is superior to 78 Gy of EBRT for unfavourable risk prostate cancer: the results of a randomized trial. 3rd ESTRO Forum. 2015
 23. Stock RG, Cesaretti JA, Hall SJ, Stone NN. Outcomes for patients with high-grade prostate cancer treated with a combination of brachytherapy, external beam radiotherapy and hormonal therapy. *BJU international*. 2009; 104:1631–1636. [PubMed: 19493260]
 24. Fang LC, Merrick GS, Butler WM, Galbreath RW, Murray BC, Reed JL, et al. High-risk prostate cancer with Gleason score 8–10 and PSA level ≤ 15 ng/mL treated with permanent interstitial brachytherapy. *International journal of radiation oncology, biology, physics*. 2011; 81:992–996.
 25. Merrick GS, Butler WM, Galbreath RW, Lief J, Bittner N, Wallner KE, et al. Prostate cancer death is unlikely in high-risk patients following quality permanent interstitial brachytherapy. *BJU international*. 2011; 107:226–232. [PubMed: 20707801]
 26. Shilkrut M, Merrick GS, McLaughlin PW, Stenmark MH, Abu-Isa E, Vance SM, et al. The addition of low-dose-rate brachytherapy and androgen-deprivation therapy decreases biochemical failure and prostate cancer death compared with dose-escalated external-beam radiation therapy for high-risk prostate cancer. *Cancer*. 2013; 119:681–690. [PubMed: 22893254]
 27. Shen X, Keith SW, Mishra MV, Dicker AP, Showalter TN. The impact of brachytherapy on prostate cancer-specific mortality for definitive radiation therapy of high-grade prostate cancer: a population-based analysis. *International journal of radiation oncology, biology, physics*. 2012; 83:1154–1159.
 28. Koontz BF, Chino J, Lee WR, Hahn CA, Buckley N, Huang S, et al. Morbidity and prostate-specific antigen control of external beam radiation therapy plus low-dose-rate brachytherapy boost for low, intermediate, and high-risk prostate cancer. *Brachytherapy*. 2009; 8:191–196. [PubMed: 19433320]
 29. Hurwitz MD, Halabi S, Archer L, McGinnis LS, Kuettel MR, DiBiase SJ, et al. Combination external beam radiation and brachytherapy boost with androgen deprivation for treatment of intermediate-risk prostate cancer: long-term results of CALGB 99809. *Cancer*. 2011; 117:5579–5588. [PubMed: 22535500]
 30. Martinez-Monge R, Moreno M, Ciervide R, Cambeiro M, Perez-Gracia JL, Gil-Bazo I, et al. External-beam radiation therapy and high-dose rate brachytherapy combined with long-term androgen deprivation therapy in high and very high prostate cancer: preliminary data on clinical outcome. *International journal of radiation oncology, biology, physics*. 2012; 82:e469–e476.
 31. Hsu IC, Bae K, Shinohara K, Pouliot J, Purdy J, Ibbott G, et al. Phase II trial of combined high-dose-rate brachytherapy and external beam radiotherapy for adenocarcinoma of the prostate:

preliminary results of RTOG 0321. International journal of radiation oncology, biology, physics. 2010; 78:751–758.

32. Lee WR, Bae K, Lawton C, Gillin M, Morton G, Firat S, et al. Late toxicity and biochemical recurrence after external-beam radiotherapy combined with permanent-source prostate brachytherapy: analysis of Radiation Therapy Oncology Group study 0019. Cancer. 2007; 109:1506–1512. [PubMed: 17340591]
33. Strom TJ, Hutchinson SZ, Shrinath K, Cruz AA, Figura NB, Nethers K, et al. External beam radiation therapy and a low-dose-rate brachytherapy boost without or with androgen deprivation therapy for prostate cancer. International braz j urol : official journal of the Brazilian Society of Urology. 2014; 40:474–483.
34. Martinez A, Galalae R, Gonzalez J, Mitchell C, Gustafson G, Kovacs G. No apparent benefit at 5 years from a course of neoadjuvant/concurrent androgen deprivation for patients with prostate cancer treated with a high total radiation dose. The Journal of urology. 2003; 170:2296–2301. [PubMed: 14634400]

List of abbreviations used

BT	brachytherapy
EBRT	external beam radiation therapy
PCSM	prostate cancer-specific mortality
SEER	Surveillance, Epidemiology, and End Results
AHR	adjusted hazard ratio
PSM	propensity score matching
ADT	androgen deprivation therapy
HDR	high dose rate
LDR	low dose rate
AJCC	American Joint Committee on Cancer
RCT	randomized controlled trial
Gy	Gray
ng	nanogram
ml	milliliter

Figure 1. Cumulative incidences of prostate cancer-specific mortality and other-cause mortality according to type of RT received in the total cohort. PC, prostate cancer.

Figure 2. Adjusted cumulative incidence of prostate cancer-specific mortality according to type of RT received. A) Adjusted PCSM in the total cohort. B) Adjusted PCSM in the high-risk subgroup. C) Adjusted PCSM in the intermediate-risk subgroup.

Table 1

Baseline characteristics of the total cohort and after propensity score matching (PSM).

Variable		Baseline			After PSM		
		EBRT (N = 42225)	EBRT+BT (N = 10310)	P-value	EBRT (N = 10034)	EBRT+BT (N = 10034)	P-value
Race	White	74.8%	73.5%	< 0.0001	73.6%	73.6%	0.66
	Black	16.8%	19.9%		20.0%	19.7%	
	Other	8.4%	6.6%		6.4%	6.7%	
SEER region	Non-South	79.8%	57.8%	< 0.0001	58.6%	59.1%	0.43
	South	20.2%	42.2%		41.4%	40.9%	
T stage	T1c	59.0%	58.8%	0.33	58.3%	58.7%	0.79
	T2	39.5%	39.4%		40.0%	39.5%	
	T3a	1.5%	1.7%		1.7%	1.7%	
PSA, ng/ml (median)		8.6	7.4	< 0.0001	7.7	7.4	0.01
Gleason class	≤ 6	15.3%	11.3%	< 0.0001	11.3%	11.4%	0.99
	7	59.5%	64.2%		63.9%	63.9%	
	8–10	25.2%	24.5%		24.8%	24.7%	
Reason no surgery	Not recommended	88.4%	92.3%	< 0.0001	92.4%	92.2%	0.51
	Other reason	11.6%	7.7%		7.6%	7.8%	
Marital status	Married	67.2%	73.6%	< 0.0001	72.5%	73.2%	0.24
	All other statuses	32.8%	26.4%		27.5%	26.8%	
Age, years (median)		70	67	< 0.0001	67	67	0.50
Income quartile	First	69.7%	62.1%	< 0.0001	61.4%	61.9%	0.78
	Second	14.3%	16.4%		16.4%	16.2%	
	Third	9.6%	12.1%		12.4%	12.4%	
	Fourth	6.4%	9.5%		9.8%	9.4%	
Education quartile	First	19.5%	13.0%	< 0.0001	13.7%	13.3%	0.12
	Second	18.4%	18.6%		19.9%	18.8%	
	Third	38.6%	35.9%		34.9%	36.1%	
	Fourth	23.4%	32.5%		31.5%	31.8%	

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Variable	Baseline			After PSM		
	EBRT (N = 42225)	EBRT+BT (N = 10310)	P-value	EBRT (N = 10034)	EBRT+BT (N = 10034)	P-value
RadOncs per million (median)	13.4	14.4	< 0.0001	13.4	14.4	0.07
Year of diagnosis (median)	2007	2006	< 0.0001	2006	2006	0.64
Risk group	Intermediate	69.0%	0.0002	69.4%	68.8%	0.29
	High	32.9%		30.6%	31.2%	

Table 2

Multivariable model of predictors of prostate cancer-specific mortality in the total cohort. AHR, adjusted hazard ratio.

Variable		Fine/Gray regression model		
		AHR, PCSM	95% CI	P-value
RT	EBRT only	1		
	EBRT + BT	0.69	0.55 – 0.87	0.002
Race	White	1		
	Black	0.81	0.59 – 1.12	0.20
	Other	0.60	0.34 – 1.06	0.08
SEER region	Non-South	1		
	South	1.17	0.88 – 1.56	0.28
T stage	T1c	1		
	T2	1.51	1.19 – 1.91	0.0006
	T3a	2.42	1.37 – 4.28	0.002
PSA, ng/ml		1.03	1.02 – 1.05	< 0.0001
Gleason class	≤ 6	1		
	7	1.40	0.88 – 2.24	0.16
	8–10	5.71	3.64 – 8.97	< 0.0001
Reason no surgery	Not recommended	1		
	Other reason	0.86	0.55 – 1.34	0.50
Marital status	Married	1		
	All other statuses	1.16	0.90 – 1.50	0.26
Age, years		0.99	0.98 – 1.01	0.36
Income quartile	First	1		
	Second	0.79	0.55 – 1.12	0.18
	Third	0.86	0.57 – 1.31	0.48
	Fourth	0.94	0.59 – 1.49	0.79
Education quartile	First	1		
	Second	1.04	0.71 – 1.53	0.83
	Third	0.94	0.63 – 1.39	0.75
	Fourth	0.76	0.51 – 1.14	0.18
RadOncs per million		0.99	0.98 – 1.01	0.45
Year of diagnosis (year - 2004)		0.89	0.82 – 0.96	0.005