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Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

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Key Points

Question

Is there a difference in prostate cancer–specific mortality and distant metastasis associated with extremely dose-escalated radiotherapy, external beam radiotherapy, or radical prostatectomy in patients with Gleason score 9-10 prostate cancer?

Findings

In this retrospective cohort study that included 1809 men with biopsy Gleason score 9-10 prostate cancer, external beam radiotherapy with a brachytherapy boost and androgen deprivation therapy was associated with significantly better prostate cancer–specific survival and longer time to distant metastasis compared with external beam radiotherapy and androgen deprivation therapy (hazard ratios, 0.41 and 0.30, respectively) or with radical prostatectomy (hazard ratios, 0.38 and 0.27, respectively).

Meaning

Extremely dose-escalated radiotherapy combined with androgen deprivation therapy was associated with better clinical outcomes.

Abstract

Importance

The optimal treatment for Gleason score 9-10 prostate cancer is unknown.

Objective

To compare clinical outcomes of patients with Gleason score 9-10 prostate cancer after definitive treatment.

Design, Setting, and Participants

Retrospective cohort study in 12 tertiary centers (11 in the United States, 1 in Norway), with 1809 patients treated between 2000 and 2013.

Exposures

Radical prostatectomy (RP), external beam radiotherapy (EBRT) with androgen deprivation therapy, or EBRT plus brachytherapy boost (EBRT+BT) with androgen deprivation therapy.

Main Outcomes and Measures

The primary outcome was prostate cancer–specific mortality; distant metastasis-free survival and overall survival were secondary outcomes.

Results

Of 1809 men, 639 underwent RP, 734 EBRT, and 436 EBRT+BT. Median ages were 61, 67.7, and 67.5 years; median follow-up was 4.2, 5.1, and 6.3 years, respectively. By 10 years, 91 RP, 186 EBRT, and 90 EBRT+BT patients had died. Adjusted 5-year prostate cancer–specific mortality rates were RP, 12% (95% CI, 8%-17%); EBRT, 13% (95% CI, 8%-19%); and EBRT+BT, 3% (95% CI, 1%-5%). EBRT+BT was associated with significantly lower prostate cancer–specific mortality than either RP or EBRT (cause-specific HRs of 0.38 [95% CI, 0.21-0.68] and 0.41 [95% CI, 0.24-0.71]). Adjusted 5-year incidence rates of distant metastasis were RP, 24% (95% CI, 19%-30%); EBRT, 24% (95% CI, 20%-28%); and EBRT+BT, 8% (95% CI, 5%-11%). EBRT+BT was associated with a significantly lower rate of distant metastasis (propensity-score-adjusted cause-specific HRs of 0.27 [95% CI, 0.17-0.43] for RP and 0.30 [95% CI, 0.19-0.47] for EBRT). Adjusted 7.5-year all-cause mortality rates were RP, 17% (95% CI, 11%-23%); EBRT, 18% (95% CI, 14%-24%); and EBRT+BT, 10% (95% CI, 7%-13%). Within the first 7.5 years of follow-up, EBRT+BT was associated with significantly lower all-cause mortality (cause-specific HRs of 0.66 [95% CI, 0.46-0.96] for RP and 0.61 [95% CI, 0.45-0.84] for EBRT). After the first 7.5 years, the corresponding HRs were 1.16 (95% CI, 0.70-1.92) and 0.87 (95% CI, 0.57-1.32). No significant differences in prostate cancer–specific mortality, distant metastasis, or all-cause mortality (≤7.5 and >7.5 years) were found between men treated with EBRT or RP (cause-specific HRs of 0.92 [95% CI, 0.67-1.26], 0.90 [95% CI, 0.70-1.14], 1.07 [95% CI, 0.80-1.44], and 1.34 [95% CI, 0.85-2.11]).

Conclusions and Relevance

Among patients with Gleason score 9-10 prostate cancer, treatment with EBRT+BT with androgen deprivation therapy was associated with significantly better prostate cancer–specific mortality and longer time to distant metastasis compared with EBRT with androgen deprivation therapy or with RP.

This cohort study compares mortality and disease progression in patients with Gleason score 9-10 (aggressive) prostate cancer treated with external beam radiotherapy plus androgen deprivation therapy, radiotherapy plus brachytherapy boost, or radical prostatectomy.

Introduction

Definitive radiotherapy with androgen deprivation therapy and radical prostatectomy are standard treatment options for patients with high-risk prostate cancer, characterized by initial prostate-specific antigen levels greater than 20 ng/mL, biopsy Gleason score 8-10 disease, or lesions with clinical T stage greater than or equal to 3. Radiotherapy options include external beam radiotherapy (EBRT) alone and EBRT with a brachytherapy boost (EBRT+BT), with the latter constituting extreme dose escalation. Although randomized trials suggest a biochemical control benefit to EBRT+BT over EBRT, no differences in clinical outcomes have been established. Whether radical prostatectomy and radiotherapy (either EBRT or EBRT+BT) offer equivalent outcomes for high-risk prostate cancer remains controversial, with no clear evidence from randomized trials. Previous comparative retrospective series included patients treated during multiple decades to obtain enough person-years of follow-up to identify sufficient clinical events for valid statistical comparison. Thus, these studies have generally included patients treated with lower doses of radiotherapy or insufficient androgen deprivation therapy. As a result, the relevance of such studies to the contemporary setting is unclear.

Patients with Gleason score 9-10 prostate cancer have particularly aggressive disease. Because of this aggressive nature, a comparative outcomes analysis of EBRT, EBRT+BT, and radical prostatectomy could examine clinical outcomes of patients treated in a contemporary period while maintaining the statistical power to detect differences between modalities.

Given that Gleason score 9-10 prostate cancer comprises only 7% to 10% of incident prostate cancer cases, a multi-institutional collaborative effort is necessary to evaluate treatment outcomes. A study of 487 patients reported that treatment with EBRT+BT was significantly associated with improved distant metastasis outcomes. However, this study included only 87 patients who received EBRT+BT. To examine whether those findings could be replicated or an association with improved prostate cancer–specific mortality could be identified, a large consortium of 1809 patients treated across 12 tertiary centers was established.

Methods

Participants

Institutional databases from 12 tertiary referral centers were queried for patients with biopsy Gleason score 9-10 prostate cancer treated between 2000 and 2013. Inclusion criteria included documentation of clinically localized disease and treatment with definitive intent. Patients receiving a diagnosis before adoption of the 2005 International Society of Urologic Pathology consensus conference guidelines were included if they had primary Gleason pattern 4 or 5 disease and tertiary pattern 5. Overall, 1809 patients with Gleason score 9-10 prostate cancer were identified, including 487 patients from the aforementioned earlier study. Deidentified data were shared in concordance with the Health Insurance Portability and Accountability Act, with each institution's institutional review board approving contribution of data to the coordinating data center (University of California, Los Angeles). Requirement for informed consent was waived by each institutional review board, given the retrospective nature of the study.

Exposure

Patients were grouped into 3 cohorts based on the definitive local treatment received: EBRT, EBRT+BT, or radical prostatectomy. Generally, androgen deprivation therapy is recommended with both EBRT and EBRT+BT, but can be relatively contraindicated for medical reasons or simply refused by patients. Therefore, lack of androgen deprivation therapy was not considered an exclusion criterion.

Outcomes

Because of the uncertain clinical implications of a biochemical recurrence and the different definitions of this outcome between patients undergoing radical prostatectomy and EBRT or EBRT+BT, focus was placed on prostate cancer–specific mortality, distant metastasis, and overall survival as end points of interest, with prostate cancer–specific mortality as the primary end point. Imaging evidence leading to a clinical diagnosis of metastatic disease (typically performed at a biochemical recurrence) was sufficient for classification as such for the purposes

of our analyses (ie, pathologic confirmation was not required). Prostate cancer–specific mortality was defined according to either clinical documentation or inclusion of prostate cancer as a primary cause of death on a death certificate.

Statistical Analyses

Differences in age and androgen deprivation therapy duration were evaluated with a 2-tailed *t* test, whereas initial prostate-specific antigen level distributions were compared with a Wilcoxon rank sum test. Categorical variables were compared with a 2-tailed χ^2 test (or Fisher exact test). Cox proportional hazards and Fine-Gray competing risks regression models with propensity scores included as covariates to control for confounding were used to evaluate distant metastasis, prostate cancer–specific mortality, and overall survival outcomes between treatment groups. Effect estimates are reported as cause-specific hazard ratios for Cox models or subdistribution hazard ratios for Fine-Gray models, with 95% CIs. To account for the multisite design, Cox models included site as a random effect, and Fine-Gray models used a robust standard error estimator with site as the cluster term. Adequacy of the proportional hazards assumption was evaluated by examining plots and tests of scaled Schoenfeld residuals.

Propensity scores were estimated with multinomial logistic regression, with treatment (radical prostatectomy, EBRT, and EBRT+BT) as the outcome and age, ln(initial prostate-specific antigen level), clinical T stage, and Gleason score as pretreatment, prognostic covariates. Missing covariate values were estimated with multiple imputation. Multiple imputation was carried out with the fully conditional specification model, in which an imputation model is specified for each incomplete variable. Age, tumor stage, ln(initial prostate-specific antigen level), Gleason score, site, and treatment were included in the imputation models. Inverse probability of treatment weights were calculated with the estimated propensity scores. To assess balance, standardized mean differences in covariate values were compared across treatment groups in an inverse probability of treatment weights sample. Propensity scores were fit iteratively by adding or deleting nonlinear terms and 2-way interactions and checking balance statistics until optimal balance was achieved. A standardized mean difference less than 0.1 has been suggested as a cutoff for adequate balance; if this was not achieved for a particular covariate, that covariate was included in the Cox and Fine-Gray models in addition to the propensity scores. Unadjusted 5- and 10-year cumulative estimates were obtained with Kaplan-Meier methods; covariate-adjusted survival curves and cumulative incidence estimates were generated with Kaplan-Meier methods with inverse probability of treatment weights. CIs for inverse probability of treatment weights–adjusted cumulative incidence estimates were obtained by bootstrapping. Patients were censored if they were lost to follow-up, if they had not experienced the event of interest at data collection, or if they experienced an event such that they were no longer at risk for the event of interest (eg, a prostate cancer–specific mortality event was a censoring event for distant metastasis).

A series of secondary analyses were completed with methodology similar to that of the primary analyses. The association between androgen deprivation therapy duration on time until distant metastasis and prostate cancer–specific mortality was investigated in the entire radiotherapy cohort, within the EBRT+BT group alone, and within the EBRT group alone, and was stratified by EBRT dose (≥78 Gy vs ≤77.9 Gy). Interaction parameters were estimated to determine whether the effect of androgen deprivation therapy duration varied significantly across subgroups. All analyses included propensity score for androgen deprivation therapy category,

calculated in a fashion similar to that used for the primary analyses. Propensity scores for treatment (EBRT+BT vs EBRT) and dose (≥78 Gy vs ≤77.9 Gy) were also included when interactions were estimated between androgen deprivation therapy duration and treatment or dose. Interaction parameters were created by multiplying relevant exposure variables and tested for statistical significance with the Wald test. In addition, outcomes were examined as a function of dose within the EBRT group and between low- and high-dose-rate brachytherapy. Analyses were completed with R version 3.3.2, with the *Modern Applied Statistics With S* survival, coxme, and crrSC packages, at a 2-tailed level of significance of .05.

Results

Patient and Treatment Characteristics

Patient and treatment characteristics are presented in Table 1 and Table 2. Six hundred thirty-nine patients underwent radical prostatectomy, 734 underwent EBRT, and 436 underwent EBRT+BT. Prostate cancer–specific mortality and distant metastasis data were available for 1790 (98.9%) patients and 1804 patients (99.7%), respectively. Thirty-four patients (2%) were missing 1 or more covariate values, and these values were multiply imputed for the purposes of analysis. The median follow-up periods by treatment cohort were radical prostatectomy, 4.2 years (interquartile range, 2.5-7.0 years); EBRT, 5.1 years (interquartile range, 2.9-7.7 years); and EBRT+BT, 6.3 years (interquartile range, 3.9-9.4 years) (EBRT+BT follow-up significantly longer than that for EBRT or radical prostatectomy, and EBRT follow-up significantly longer than that for radical prostatectomy; $P < .05$ for all comparisons). From 2000-2005, 24% of patients underwent radical prostatectomy, 44% EBRT, and 31% EBRT+BT; from 2006-2010, these percentages changed to 32%, 43%, and 25%, respectively, and from 2011-2013, the percentages were 53%, 32%, and 15%, respectively. Patients treated with radical prostatectomy were significantly younger than those treated with either EBRT or EBRT+BT, had significantly lower initial prostate-specific antigen levels, and were less likely to have Gleason score 10 disease ($P < .001$ for all comparisons). Radical prostatectomy patients also had a significantly higher proportion of cT1-T2 lesions than either EBRT or EBRT+BT patients ($P < .001$ for all comparisons). Additional information on treatment distribution by institution and year is shown in eTables 1 and 2 in the Supplement.

The majority of EBRT and EBRT+BT patients had androgen deprivation therapy as part of their initial treatment strategy (89.5% and 92.4%, respectively), but the duration of the therapy was significantly shorter among patients receiving EBRT+BT (median 12.0 months vs 21.9 months; $P < .001$). Median equivalent dose in 2-Gy fractions (defined assuming an α/β ratio of 1.5) was 74.3 Gy with EBRT and 91.5 Gy with EBRT+BT. Among the EBRT+BT patients, 269 (62%) received low-dose-rate brachytherapy and 167 (38%) received high-dose-rate brachytherapy. Overall, 19% of radical prostatectomy patients received some form of neoadjuvant systemic therapy (generally androgen deprivation therapy) as part of institutional protocols, 8.7% received adjuvant radiotherapy, and 11.3% received adjuvant systemic therapy (generally androgen deprivation therapy). Salvage radiotherapy was used in 34.1% of patients treated with radical prostatectomy. Local salvage procedures after EBRT and EBRT+BT were rarely performed (rates of 2.5% and 0.1%, respectively). Systemic salvage therapies (generally androgen deprivation therapy) were ultimately given to 24.1% of radical prostatectomy patients, 12.1% of EBRT patients, and 5.5% of EBRT+BT patients.

Cause-Specific Regression Models and Competing Risk Analyses

Inverse probability of treatment weights–adjusted survival curves of time until prostate cancer–specific mortality, distant metastasis, and all-cause mortality are shown in the Figure. Crude incidence rates and cumulative incidence rate estimates are shown in Table 3, and cause-specific Cox regression models are shown in Table 4. Adjusted 5-year prostate cancer–specific mortality incidence rates were radical prostatectomy, 12% (95% CI, 8%-17%); EBRT, 13% (95% CI, 8%-19%); and EBRT+BT, 3% (95% CI, 1%-5%). Cause-specific hazard ratios for time to prostate cancer–specific mortality for EBRT+BT vs radical prostatectomy and EBRT+BT vs EBRT were 0.38 (95% CI, 0.21-0.68) and 0.41 (95% CI, 0.24-0.71) ($P < .001$). Adjusted 5-year incidence rates of distant metastasis were radical prostatectomy, 24% (95% CI, 19%-30%); EBRT, 24% (95% CI, 20%-28%); and EBRT+BT, 8% (95% CI, 5%-11%). In propensity-score-adjusted models, EBRT+BT was associated with significantly longer time until distant metastasis than either EBRT or radical prostatectomy, with cause-specific hazard ratios of 0.27 (95% CI, 0.17-0.43) and 0.30 (95% CI, 0.19-0.47), respectively ($P < .001$). No significant differences in prostate cancer–specific mortality or distant metastasis were found between patients treated with EBRT or radical prostatectomy (cause-specific hazard ratios of 0.92 [95% CI, 0.67-1.26] and 0.90 [95% CI, 0.7-1.14], respectively; $P > .40$).

On competing risk analysis, the 5-year incidence rates of prostate cancer–specific mortality after each treatment modality were radical prostatectomy, 10% (95% CI, 7%-12%); EBRT, 11% (95% CI, 8%-14%); and EBRT+BT, 3% (95% CI, 1%-4%) (eTable 3 in the Supplement). A cumulative incidence plot is shown in the eFigure in the Supplement. Unadjusted and propensity-score-adjusted competing risks regression models are shown in Table 5. In propensity-score-adjusted models, EBRT+BT was associated with a significantly reduced risk of prostate cancer–specific mortality compared with either radical prostatectomy or EBRT, with subdistribution hazard ratios of 0.38 (95% CI, 0.19-0.73) and 0.36 (95% CI, 0.18-0.70), respectively ($P < .001$). There was no difference between EBRT and radical prostatectomy (subdistribution hazard ratio, 1.05 [95% CI, 0.88-1.24]; $P > .60$).

When overall survival outcomes were compared between cohorts, the Cox proportional hazard assumption was found to be violated (ie, the cause-specific hazard ratio varied with time). Adjusted 5-year all-cause mortality incidence rates were radical prostatectomy, 17% (95% CI, 11%-23%); EBRT, 18% (95% CI, 14%-24%); and EBRT+BT, 10% (95% CI, 7%-13%). At 10 years, these rates were radical prostatectomy, 32% (95% CI, 25%-40%); EBRT, 39% (95% CI, 31%-44%); and EBRT+BT, 31% (95% CI, 25%-38%). Within the first 7.5 years of follow-up, EBRT+BT was associated with significantly longer overall survival compared with radical prostatectomy and EBRT, with cause-specific hazard ratios of 0.66 (95% CI, 0.46-0.96) and 0.61 (95% CI, 0.45-0.84), respectively ($P < .05$ for both). After the first 7.5 years, the corresponding cause-specific hazard ratios were 1.16 (95% CI, 0.70-1.92; $P = .56$) and 0.87 (95% CI, 0.57-1.32; $P = .52$). There was no difference between EBRT and radical prostatectomy in either interval (hazard ratios 1.07 [95% CI, 0.80-1.44; $P = .64$] and 1.34 [95% CI, 0.85-2.11; $P = .21$]).

Association of Androgen Deprivation Therapy With Outcomes

To determine the association of androgen deprivation therapy duration on prostate cancer–specific mortality and distant metastasis incidence in the EBRT and EBRT+BT cohorts, we stratified androgen deprivation therapy duration into 4 subgroups (eTable 4 in the Supplement).

Balance between androgen deprivation therapy subgroups was poor in the absence of propensity score adjustment. The association of androgen deprivation therapy duration on prostate cancer–specific mortality and distant metastasis did not significantly differ between the EBRT and EBRT+BT cohorts (*P* for interaction, .27 for prostate cancer–specific mortality and .77 for distant metastasis), and androgen deprivation therapy duration was not significantly associated with prostate cancer–specific mortality or distant metastasis in either group, or within EBRT dose strata (*P* for interaction, .21 for prostate cancer–specific mortality and .22 for distant metastasis across EBRT dose strata; eTable 5 in the Supplement).

Association of Radiotherapy Dose With Outcomes

Because these results suggested an association of extreme dose escalation with improved outcomes, we sought to determine whether a similar dose-response association could be identified within the EBRT cohort by defining 3 dose strata (eTable 6 in the Supplement). Patients receiving less than 70 Gy had a significantly higher rate of prostate cancer–specific mortality than those receiving greater than or equal to 78 Gy (cause-specific hazard ratio, 2.70 [95% CI, 1.01-7.24]; $P < .05$). However, there was no significant association between distant metastasis and dose (cause-specific hazard ratio, 1.55 [95% CI, 0.64-3.38] for <70 Gy vs ≥78 Gy; $P = .34$ for all).

Additional subset analyses (eTables 7-8 in the Supplement) revealed that the EBRT patient subset receiving greater than or equal to 78 Gy and greater than or equal to 24 months of androgen deprivation therapy (composing 11.4% of the EBRT cohort) was associated with superior prostate cancer–specific mortality and distant metastasis outcomes compared with radical prostatectomy (cause-specific hazard ratios of 0.45 [95% CI, 0.24-0.83] and 0.31 [95% CI, 0.12-0.86], respectively; $P < .05$). EBRT+BT was still associated with lower rates of distant metastasis outcomes than this “optimal” regimen (cause-specific hazard ratio, 0.53 [95% CI, 0.28-1.00]; $P = .05$), but prostate cancer–specific mortality outcomes were not significantly different (cause-specific hazard ratio, 1.24 [95% CI, 0.45-3.40]; $P > .75$). Comparison of outcomes between patients treated with low- and high-dose-rate brachytherapy revealed no differences in outcomes (eTable 9 in the Supplement).

Discussion

In this study of patients with Gleason score 9-10 prostate cancer, EBRT+BT was associated with lower rates of prostate cancer–specific mortality and distant metastasis outcomes compared with either radical prostatectomy or EBRT, whereas EBRT and radical prostatectomy were associated with similar prostate cancer–specific mortality and distant metastasis outcomes compared with each other. Although the majority of patients treated with EBRT and EBRT+BT received androgen deprivation therapy as a component of their initial therapy, the median duration was 22 months with EBRT vs only 12 months with EBRT+BT. Local treatments were rarely performed after either EBRT or EBRT+BT, whereas 43% of radical prostatectomy patients received some form of postoperative radiotherapy. Overall, these data suggest that treatment with EBRT+BT is significantly associated with better outcomes in this high-risk group of patients.

Three randomized trials demonstrated a biochemical recurrence-free survival benefit to EBRT+BT over EBRT but failed to show significant improvements in distant metastasis or prostate cancer–specific mortality outcomes. The Gleason score 9-10 prostate cancer patient population in the current study is at significantly higher risk for distant metastasis and prostate cancer–specific mortality outcomes—on competing risk analysis, prostate cancer–specific mortality was more frequent than other-cause mortality—likely explaining the identification of a significant association of EBRT+BT with improved outcomes. Few studies have compared outcomes after EBRT+BT and radical prostatectomy, with an underpowered randomized trial of patients receiving either radical prostatectomy or EBRT+BT reporting similar prostate cancer–specific mortality outcomes. Retrospective studies comparing outcomes after EBRT and radical prostatectomy have shown conflicting results. Generally, these studies included patients treated with lower doses of radiotherapy or insufficient androgen deprivation therapy. In contrast, the median equivalent dose in 2-Gy fractions in the current study was 74 Gy, and the median duration of androgen deprivation therapy was 22 months. Even before propensity score adjustment, the EBRT cohort had distant metastasis and prostate cancer–specific mortality outcomes similar to those of the radical prostatectomy cohort.

The robust association of EBRT+BT with better outcomes compared with both EBRT and radical prostatectomy is, to our knowledge, a novel finding. EBRT+BT potentially offers improved local control over EBRT, which may prevent a “second wave” of metastases. EBRT+BT is unlikely to offer improved local control over radical prostatectomy, yet it was still associated with improved distant metastasis and prostate cancer–specific mortality. Outcomes in the radical prostatectomy cohort may have been improved had a rigorous postoperative radiotherapy protocol been in place. Nonetheless, postoperative radiotherapy is widely underused in the general population, and the postoperative radiotherapy frequency of 43% among the radical prostatectomy patients in this study was relatively high. The proportional hazard for time to all-cause mortality varied over time, with EBRT+BT associated with significantly improved overall survival before 7.5 years of follow-up, but with all cohorts having similar overall survival outcomes afterward. It is possible that this is reflective of a prostate cancer–specific mortality benefit to EBRT+BT emerging early, only to eventually dissipate as other-cause mortality increases over time.

These findings must be considered in context of the findings of an earlier study of 487 patients, all of whom were included in the present analysis. In that series, EBRT+BT was associated with significantly improved distant metastasis–free survival, but not prostate cancer–specific mortality. The current study has greater statistical power to identify prostate cancer–specific mortality differences and its results are more generalizable. The increased sample size allowed the use of propensity score adjustment and inverse probability of treatment weights to attempt to minimize significant baseline differences in clinical and demographic variables between patient cohorts. Although the incidence rates of distant metastasis at 5 and 10 years were numerically lower for all 3 cohorts in the earlier publication, the patterns observed were consistent with the present results. The prostate cancer–specific mortality rates were numerically similar between the 2 studies, yet the hazard ratios for the comparison of prostate cancer–specific mortality between EBRT+BT vs EBRT and EBRT+BT vs radical prostatectomy were statistically significantly lower in the present study. This is likely reflective of a more comprehensive ability to control for confounding with the use of propensity score adjustment.

Limitations

This study has several limitations. First, and most significantly, the data were gathered retrospectively, and even after adjustment for propensity score there likely remained significant biases in regard to treatment selection and follow-up that could not be accounted for, including comorbidity status. Patients with less comorbidity have been shown to have improved prostate cancer–specific mortality outcomes after aggressive treatment. It is likely that patients undergoing radical prostatectomy had the least comorbidity, whereas those undergoing EBRT had the most. Although adjusting for comorbidity is thus unlikely to have altered the result for the EBRT+BT vs radical prostatectomy comparison, the EBRT+BT vs EBRT comparison results could have changed. Prospective validation of these findings would strengthen their interpretation. However, Gleason score 9-10 disease is relatively rare, which may make such a study infeasible. Second, toxicity outcomes, and particularly patient-reported outcomes, were not available for analysis. Patient-reported outcomes after radical prostatectomy and EBRT are known to have differential toxicity profiles. To our knowledge, toxicity outcomes after EBRT+BT and radical prostatectomy have never been directly compared, but patient-reported outcomes analyses from the Androgen Suppression Combined With Elective Nodal and Dose Escalated Radiation Therapy trial indicated worsened overall urinary function and physical function with EBRT+BT than with EBRT. Third, only 41% of patients treated with EBRT received both radiotherapy doses greater than or equal to 70 Gy and at greater than or equal to 24 months of androgen deprivation therapy, although this would be considered a minimal standard of care today. Considering that these patients were treated at major academic institutions, this likely reflects a generalizable issue with tolerance of this regimen, particularly long-term androgen deprivation therapy. Fourth, the median follow-up was relatively short, ranging from 4.2 to 6.3 years. However, the cohort with the best results had the longest follow-up period, and the incidence rates were high even in an early period by virtue of the high-risk population studied. Including patients with median follow-up of 10 to 15 years would result in the inclusion of many patients treated with anachronistic treatment paradigms (low doses of radiotherapy or insufficient androgen deprivation therapy). Fifth, not all centers that contributed data provided data for all 3 treatments (ie, certain centers provided only EBRT+BT, certain centers provided only EBRT and radical prostatectomy, and certain centers provided only EBRT and EBRT+BT). This is largely because EBRT+BT is offered only at selected tertiary centers, or because prostate cancer–specific mortality (primary outcome) data are not universally available. EBRT+BT was significantly associated with better outcomes in this study; however, unaccounted-for variables related to the center where patients received treatment may have confounded our results. A randomized clinical trial would mitigate this problem but is likely impractical, given the relative rarity of Gleason score 9-10 disease.

Conclusions

Among patients with Gleason score 9-10 prostate cancer, treatment with EBRT+BT with androgen deprivation therapy was associated with significantly better prostate cancer–specific mortality and longer time to distant metastasis compared with EBRT with androgen deprivation therapy or with radical prostatectomy.

Notes

Supplement.

eFigure 1. Adjusted cumulative incidence of prostate-cancer specific and other-cause mortality, by treatment group

eTable 1. Patient Contribution and Median Follow-up by Treatment Cohort, Stratified by Institution

eTable 2. Treatment Cohort Stratified by Year of Treatment

eTable 3. Crude Event Rates and Cumulative Incidence Estimate for Competing Risk Analysis

eTable 4. Distribution of EBRT and EBRT + BT Patients by ADT Duration

eTable 5. Cause-specific Cox regression models (propensity score-adjusted) of the effect of androgen deprivation therapy duration on time until prostate cancer-specific mortality and distant metastasis

eTable 6. Cause-specific Cox regression models (propensity score-adjusted) of the effect of external beam radiotherapy dose on time to prostate cancer-specific mortality and distant metastasis

eTable 7. Cause-specific Cox regression models of time until prostate cancer-specific mortality and distant metastasis among optimally treated patients (propensity score-adjusted); minimum external bream radiotherapy dose of 78 Gy

eTable 8. Cause-specific Cox regression models of time until prostate cancer-specific mortality and distant metastasis among optimally treated patients (propensity score-adjusted); minimum external bream radiotherapy dose of 70 Gy

eTable 9. Cause-specific regression of the effect of LDR vs. HDR brachytherapy on clinical outcomes (propensity-score adjusted)

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Figures and Tables

Table 1.

Clinical Characteristics of Patients With 9-10 Gleason Score

	Unadjusted, No. (%)			*P* Value[a]			Propensity Sco
	Prostatectomy (n=639)	EBRT (n=734)	EBRT+BT (n=436)	EBRT vs Prostatectomy	EBRT+BT vs Prostatectomy	EBRT+BT vs EBRT	EBRT vs Prostatectomy
					Clinical Characteristics		
Age, mean (median) [range], y	61.0 (61.2) [39-77.1]	67.7 (68) [39.7-98]	67.5 (68.0) [48-83]	< .001	<.001	>.52	63.78 (6.90)
Initial PSA level, mean (median) [range], ng/mL	11.26 (6.9) [0.4-378.6]	21.5 (9.93) [0.4-525.5]	14.8 (9.6) [0.1-273.5]	<.001	<.001	<.001	2.26 (0.80)
Biopsy Gleason score							
9	613 (95.9)	686 (93.5)	398 (91.3)	<.001	<.001	>.15	7.7
10	26 (4.1)	48 (6.5)	38 (8.7)				
Clinical tumor stage							
1c	327 (51.2)	212 (28.9)	148 (33.9)				39.3
2a	138 (21.8)	137 (18.7)	63 (14.4)				19.1
2b	72 (11.3)	111 (15.1)	88 (20.2)				14.3
2c	20 (3.1)	52 (7.1)	44 (10.1)	<.001	<.001	<.001	5.6
3a	36 (5.6)	103	63 (14.4)				11.2

Abbreviations: EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost; PSA, prostate-specific antigen.

[a] *P* values calculated before propensity score adjustment.

[b] Standardized mean differences were calculated among the 3 groups via a method proposed by Flury and Riedwyl.

[c] Propensity score includes age, ln(initial prostate-specific antigen level), clinical tumor stage, and Gleason score.

Table 2.

Pathologic and Treatment Details of Patients With 9-10 Gleason Score

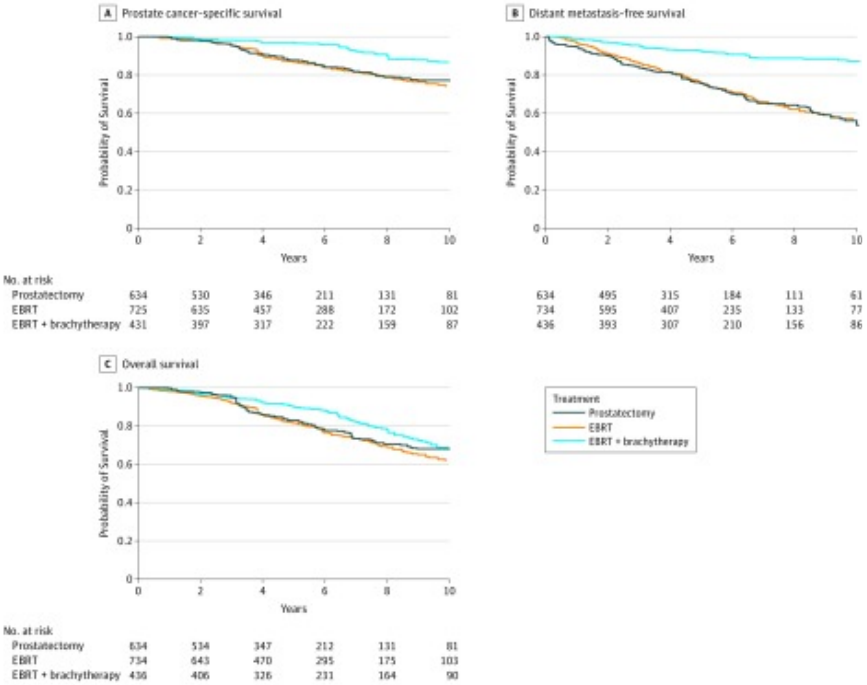
	Unadjusted, No. (%)		
	Prostatectomy (n=639)	**EBRT (n=734)**	**EBRT+BT (n=436)**
Pathologic Characteristics			
Pathologic stage			
2a	24 (3.8)		
2b	117 (18.3)		
2c	22 (3.4)		
3a	188 (29.4)		
3b	263 (41.2)		
4	25 (3.9)		
Pathologic Gleason score			
7	92 (14.4)		
8	24 (3.8)		
9	290 (45.4)		
10	129 (20.2)		
Treatment effect[a]	104 (16.3)		
Adverse pathologic features			
Positive margins	250 (39.1)		
Positive lymph nodes at surgery	108 (16.9)		
Treatment Characteristics			
Radiotherapy patients			
Equivalent dose in 2-Gy fractions, median (range), Gy		74.3 (65-81.4)	91.5 (75.8-131.4)
Initial androgen deprivation therapy		657 (89.5)	403 (92.4)
Duration of androgen deprivation therapy, median (range), mo		21.9 (1-160)	12.0 (1-100)
Pelvic nodal irradiation		299 (40.7)	320 (73.4)
Brachytherapy type			
Low-dose rate			262 (62.0)
High-dose rate			174 (38.0)
Prostatectomy patients			

Abbreviations: EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost.

[a]Treatment effect refers to the scenario in which a pathologic Gleason score cannot be given due to histologic alteration by neoadjuvant therapy"

[b]Local salvage procedures refer to salvage radiotherapy directed at the prostatic fossa (with or without pelvic nodal radiation) or local ablative procedures such as cryoablation, high-intensity focused ultrasound, or salvage brachytherapy. All *P* values, calculated before propensity score adjustment, were significant at <.001 except EBRT+BT vs EBRT for local salvage.

Figure.



Adjusted Survival Curves for Prostate Cancer–Specific Survival, Distant Metastasis–Free Survival, and Overall Survival by Treatment Group, Weighted by the Inverse Probability of Treatment

EBRT indicates external beam radiotherapy; and EBRT+BT, external beam radiotherapy with a brachytherapy boost. Median follow-up for each treatment cohort was as follows: EBRT, 5.1 years (interquartile range, 2.9-7.7 years); EBRT+BT, 6.3 years (interquartile range, 3.9-9.4 years); and surgery, 4.2 years (interquartile range, 2.5-7.0 years). Adjusted curves were generated with Kaplan-Meier methods with inverse probability of treatment weights, calculated with propensity scores that were determined by using multinomial logistic regression with treatment cohort as the outcome and age, ln(initial prostate-specific antigen level), clinical T stage, and Gleason score as pretreatment, prognostic covariates. Numbers at baseline differ for A from both B and C because not all patients had known cause-of-death information to compute prostate cancer–specific survival.

Table 3.

Crude Event Rates and Cumulative and Adjusted Cumulative Incidence Estimate Rates

Treatment Cohort	Evaluable Patients at Time 0	Interval, y	No. of Events	No. of Patients Censored[a]	No. at Risk (End of Interval)	Cumulative Incidence at End of Interval, % (95% CI)	Adjusted Cumulative Incidence at End of Interval, % (95% CI)[b]
Prostate Cancer-Specific Mortality							
Radical prostatectomy	634	0-5	41	314	279	9 (7-12)	12 (8-17)
		>5-10	27	171	81	24 (18-29)	23 (18-30)
EBRT	725	0-5	65	281	379	12 (9-14)	13 (8-19)
		>5-10	39	238	102	27 (21-32)	26 (20-32)
EBRT+BT	431	0-5	11	149	271	3 (1-5)	3 (1-5)
		>5-10	21	163	87	14 (9-19)	13 (8-19)
Distant Metastasis							
Radical prostatectomy	634	0-5	102	285	247	21 (17-25)	24 (19-30)
		>5-10	44	142	61	43 (36-49)	46 (38-54)
EBRT	734	0-5	153	262	319	26 (22-29)	24 (20-28)
		>5-10	54	188	77	45 (40-51)	44 (38-50)
EBRT+BT	436	0-5	30	147	259	8 (5-11)	8 (5-11)
		>5-10	10	163	86	13 (9-17)	13 (9-17)
All-Cause Mortality (Presented in 5-y Intervals)							
Radical prostatectomy	634	0-5	52	302	280	12 (9-15)	17 (11-23)
		>5-10	39	160	81	30 (24-36)	32 (25-40)
EBRT	734	0-5	113	231	390	19 (16-22)	18 (14-24)
		>5-10	73	214	103	42 (36-47)	39 (31-44)
EBRT+BT	436	0-5	40	117	279	10 (7-14)	10 (7-13)
		>5-10	50	139	90	33 (26-39)	31 (25-38)
All-Cause Mortality (Presented in 7.5-y Intervals)							
Radical prostatectomy	634	0-7.5	79	409	146	23 (18-28)	27 (21-34)
		>7.5-15	26	106	14	52 (40-62)	53 (42-66)
EBRT	734	0-7.5	162	369	203	32 (27-36)	29 (23-35)
		>7.5-15	55	132	16	70 (61-78)	68 (59-78)
EBRT+BT	436	0-7.5	69	193	174	22 (17-26)	20 (15-25)

Abbreviations: EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost.

[a]Patients were censored if they were lost to follow-up, if they had not experienced the event of interest at data collection, or if they experienced an event such that they were no longer at risk for the event of interest (eg, prostate cancer–specific mortality was a censoring event for distant metastasis).

[b]Adjusted cumulative incidence estimates were generated with Kaplan-Meier methods with inverse probability of treatment weights, calculated by using propensity scores that were determined with multinomial logistic regression with treatment cohort as the outcome and age, ln(initial prostate-specific antigen level), clinical T stage, and Gleason score as pretreatment, prognostic covariates.

Table 4.

Cause-Specific Cox Regression Models of Time Until Prostate Cancer–Specific Mortality, Distant Metastasis, or All-Cause Mortality

Model and Parameter	Cause-Specific Hazard Ratio (95% CI)	*P* Value
Prostate Cancer–Specific Mortality		
Unadjusted		
EBRT vs radical prostatectomy	1.08 (0.81-1.44)	.60
EBRT+BT vs radical prostatectomy	0.42 (0.24-0.74)	.003
EBRT+BT vs EBRT	0.39 (0.23-0.67)	<.001
Propensity score adjusted[a]		
EBRT vs RP	0.92 (0.67-1.26)	.60
EBRT+BT vs radical prostatectomy	0.38 (0.21-0.68)	.001
EBRT+BT vs EBRT	0.41 (0.24-0.71)	.002
Distant Metastasis		
Unadjusted		
EBRT vs radical prostatectomy	0.99 (0.80-1.23)	.94
EBRT+BT vs radical prostatectomy	0.29 (0.18-0.47)	<.001
EBRT+BT vs EBRT	0.29 (0.18-0.46)	<.001
Propensity score adjusted[a]		
EBRT vs radical prostatectomy	0.90 (0.70-1.14)	.38
EBRT+BT vs radical prostatectomy	0.27 (0.17-0.43)	<.001
EBRT+BT vs EBRT	0.30 (0.19-0.47)	<.001
Overall Survival		
≤7.5 y (propensity score adjusted)		
EBRT vs radical prostatectomy	1.07 (0.80-1.44)	.64
EBRT+BT vs radical prostatectomy	0.66 (0.46-0.96)	.03
EBRT+BT vs EBRT	0.61 (0.45-0.84)	.002
>7.5 y (propensity score adjusted)		
EBRT vs radical prostatectomy	1.34 (0.85-2.11)	.21
EBRT+BT vs radical prostatectomy	1.16 (0.70-1.92)	.56
EBRT+BT vs EBRT	0.87 (0.57-1.32)	.52

Abbreviations: EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost.

[a]Propensity score includes age, ln(initial prostate-specific antigen level), clinical tumor stage, and Gleason score.

Table 5.

Competing Risks Regression Model of Prostate Cancer–Specific Mortality, Treating Other-Cause Mortality as a Competing Risk

Model and Parameter	Subdistribution Hazard Ratio (95% CI)	*P* Value
Unadjusted		
EBRT vs radical prostatectomy	1.13 (0.98-1.30)	.10
EBRT+BT vs radical prostatectomy	0.39 (0.20-0.76)	.005
EBRT+BT vs EBRT	0.34 (0.18-0.67)	.002
Propensity score adjusted[a]		
EBRT vs radical prostatectomy	1.05 (0.88-1.24)	.61
EBRT+BT vs radical prostatectomy	0.38 (0.19-0.73)	.004
EBRT+BT vs EBRT	0.36 (0.18-0.70)	.003

Abbreviations: EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost.

[a]Propensity score includes age, ln(initial prostate-specific antigen level), clinical tumor stage, and Gleason score.