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Addition of Androgen-Deprivation Therapy or Brachytherapy Boost to External Beam Radiotherapy for Localized Prostate Cancer: A Network Meta-Analysis of Randomized Trials

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abstract

PURPOSE In men with localized prostate cancer, the addition of androgen-deprivation therapy (ADT) or a brachytherapy boost (BT) to external beam radiotherapy (EBRT) have been shown to improve various oncologic end points. Practice patterns indicate that those who receive BT are significantly less likely to receive ADT, and thus we sought to perform a network meta-analysis to compare the predicted outcomes of a randomized trial of EBRT plus ADT versus EBRT plus BT.

MATERIALS AND METHODS A systematic review identified published randomized trials comparing EBRT with or without ADT, or EBRT (with or without ADT) with or without BT, that reported on overall survival (OS). Standard fixed-effects meta-analyses were performed for each comparison, and a meta-regression was conducted to adjust for use and duration of ADT. Network meta-analyses were performed to compare EBRT plus ADT versus EBRT plus BT. Bayesian analyses were also performed, and a rank was assigned to each treatment after Markov Chain Monte Carlo analyses to create a surface under the cumulative ranking curve.

RESULTS Six trials compared EBRT with or without ADT ($n = 4,663$), and 3 compared EBRT with or without BT ($n = 718$). The addition of ADT to EBRT improved OS (hazard ratio [HR], 0.71 [95% CI, 0.62 to 0.81]), whereas the addition of BT did not significantly improve OS (HR, 1.03 [95% CI, 0.78 to 1.36]). In a network meta-analysis, EBRT plus ADT had improved OS compared with EBRT plus BT (HR, 0.68 [95% CI, 0.52 to 0.89]). Bayesian modeling demonstrated an 88% probability that EBRT plus ADT resulted in superior OS compared with EBRT plus BT.

CONCLUSION Our findings suggest that current practice patterns of omitting ADT with EBRT plus BT may result in inferior OS compared with EBRT plus ADT in men with intermediate- and high-risk prostate cancer. ADT for these men should remain a critical component of treatment regardless of radiotherapy delivery method until randomized evidence demonstrates otherwise.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

For men with unfavorable intermediate- and high-risk prostate cancer, external beam radiotherapy (EBRT) alone has been shown to be inferior to combination treatment approaches for various end points. Two methods of treatment intensification for men treated with EBRT have been assessed in multiple independent randomized clinical trials: the addition of androgen-deprivation therapy (ADT) or the addition of a brachytherapy boost.¹⁻¹¹ The addition of ADT to EBRT has been shown in multiple randomized trials to reduce local treatment failure, improve biochemical control, reduce the incidence of metastases, and

improve overall survival (OS) in men with intermediate- and high-risk prostate cancer.^{1-3,5,7,9} The addition of a brachytherapy boost to EBRT serves as a form of local treatment intensification and has been shown to reduce local recurrence and improve biochemical control in multiple randomized trials, but not to significantly reduce the development of metastatic disease or improve survival.^{4,6,8,10}

It has been hypothesized that with radiotherapeutic dose escalation, the benefit of ADT would be abrogated. However, in EORTC 22991, ADT showed a similar benefit among all patients, independent of the radiation dose delivered (interaction P value = .82).¹ Whether

CONTEXT

Key Objectives

To compare the predicted outcomes of external beam radiotherapy plus androgen deprivation therapy to external beam radiotherapy plus a brachytherapy boost in men with intermediate and high-risk prostate cancer.

Knowledge Generated

We demonstrate with high probability that external beam radiation therapy plus androgen deprivation therapy results in improved survival compared to external beam radiation therapy plus a brachytherapy boost in men with intermediate and high-risk prostate cancer.

Relevance

Androgen deprivation therapy should not be omitted on the basis of available evidence in men with intermediate- or high-risk prostate cancer receiving external beam radiation therapy plus a brachytherapy boost.

ADT provides the same benefits in the setting of extreme dose escalation with the addition of a brachytherapy boost has never been tested.¹² Despite the lack of evidence supporting the omission of ADT in men with intermediate- and high-risk prostate cancer receiving EBRT plus a brachytherapy boost, practice patterns demonstrate that receipt of brachytherapy is independently associated with omission of ADT. In both intermediate- and high-risk prostate cancer, there is a 30% to 40% decreased rate of ADT use in these men.^{13,14}

The decreased use of ADT in men treated with EBRT plus a brachytherapy boost suggests that physicians may feel that only one form of treatment intensification is needed in addition to EBRT in men with intermediate- and high-risk prostate cancer. The addition of ADT or a brachytherapy boost to EBRT has never been directly compared in a clinical trial, and which form of treatment intensification is superior remains unclear. We therefore sought to perform a network meta-analysis to compare the predicted outcome of EBRT plus ADT versus EBRT plus a brachytherapy boost to help guide treatment decision making in men with intermediate- and high-risk prostate cancer.

MATERIALS AND METHODS

Search Strategy and Study Selection

A systematic review was performed of published randomized trials comparing EBRT with or without ADT, as well as trials assessing EBRT (with or without ADT) with or without a brachytherapy boost. This was in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.¹⁵ To be included, trials were required to have reported on biochemical recurrence-free survival (bRFS) and OS and to have been published in English between January 1980 and June 2018. Metastasis-free survival data were not collected because they were not reported consistently among the brachytherapy boost trials. The search was performed using the EMBASE and MEDLINE electronic databases. A PRISMA flow diagram can be found in [Figure 1](#), and a basic

diagram of the network meta-analysis performed can be found in the Data Supplement (online only).

Data Extraction and End Points

Data were extracted from the 9 identified randomized trials by W.C.J and D.E.S. Trial level data extracted included the years the trial accrued, median follow-up, patient age, National Comprehensive Cancer Network risk group, clinical T stage, pretreatment prostate-specific antigen, Gleason score, duration of ADT if administered, and hazard ratios (HRs) with corresponding 95% CIs for bRFS and OS.

Statistical Methods

Weighted descriptive statistics were calculated using study sample size as the weight. HRs for the randomized brachytherapy boost trial reported by Hoskin et al⁶ were estimated from Kaplan-Meier curves using methods from Tierney et al.¹⁶ The standard error of the log HRs was estimated from the log-rank *P* value provided and the estimated HRs. Data were extracted from the Kaplan Meier curve using WebPlotDigitizer¹⁷ using the “X Step w/ Interpolation” setting, and points were extracted along regular intervals for each curve. With the extracted data, median follow-up, recruitment time, and number of patients in each arm, the HR was estimated.¹⁶ Spearman correlation was calculated for ADT duration and log(HRs), thus examining the correlation between the value ranks so that trends could be nonlinear. HRs for the meta-analysis where only indirect comparisons were available were calculated using the consistency equation $\hat{\theta}_{BC} = \hat{\theta}_{AC} - \hat{\theta}_{AB}$ (where θ is a log HR estimate).¹⁸ To perform a network meta-analysis, the consistency equation is assumed to be true. Frequentist analysis using the meta package in R version 3.4.2 was performed. A generic inverse variance meta-analysis with fixed effects was used to estimate the HR for EBRT plus ADT versus EBRT alone and the HR for EBRT plus a brachytherapy boost versus EBRT alone. We also conducted a meta-regression using an exponential model of ADT effect to adjust for ADT use

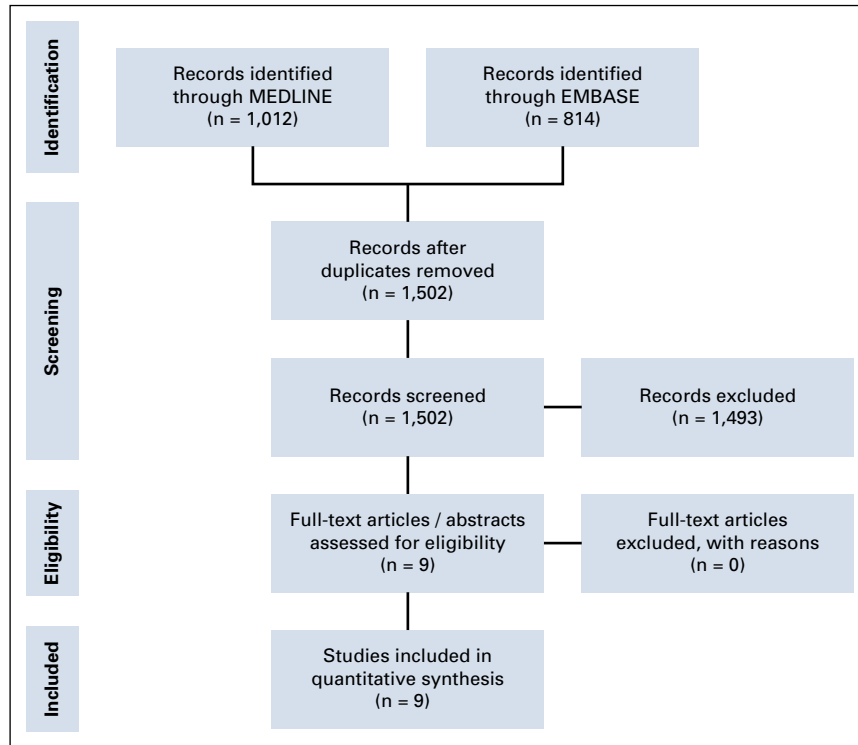


FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

and duration. We used the consistency equation to compare EBRT plus ADT with EBRT plus a brachytherapy boost. Cochran's Q test was used to examine heterogeneity.

Bayesian analyses were performed using rjags for network meta-analysis with fixed effects and a continuous outcome (log[HR] as the outcome).^{18,19} Regression using an exponential model of ADT effect to adjust for ADT duration was performed. We ran a Markov Chain Monte Carlo with 20,000 burn-in iterations and 20,000 iterations for each analysis. Autocorrelation was checked graphically. The consistency equation was used to estimate the HR for EBRT plus ADT versus EBRT plus a brachytherapy boost. The median was used as the sample estimate, and the 2.5th percentile and 97.5th percentile were used for the credible interval. The probability of the estimated HR being less than 1 is the percentage of the 20,000 iterations that were below 1.

For each iteration, the ranking of EBRT alone, EBRT plus ADT, and EBRT plus a brachytherapy boost was determined using the HRs from that iteration. Surface under the cumulative ranking curve (SUCRA) was calculated from these rankings²⁰ by summing the cumulative probabilities of all the ranks divided by the number of ranks minus 1. This statistic has no known distribution and is a means of summarizing treatment rankings. If a treatment always ranks 1, with a value of 1 denoting the most preferred treatment, then the SUCRA = 1. If a treatment always ranks last, then the SUCRA = 0, with a value of 0 denoting the least preferred treatment.

We estimated the sample sizes necessary to demonstrate statistical differences in OS between treatment modalities using a sample size equation for one arm:

$$\frac{(z_{\alpha} + z_{\beta})^2}{(\pi\delta^2)/(2)}$$

where z_{α} and z_{β} are the standard normal cumulative functions for α and β or the type I error and power specified, π is the event rate, and δ is the log HR.

Cumulative incidence curves were estimated by extracting the percentage of survival values for each year from the EBRT plus ADT Kaplan-Meier curve from EORTC 22991¹ using WebPlotDigitizer. Cumulative incidence was calculated as 1% survival. A locally weighted scatter-plot smoother curve was fit over the cumulative incidence points using the stat package included in the base packages in R version 3.4.2.

RESULTS

Trial and Patient Characteristics

Six trials were identified that compared EBRT with or without ADT in 4,663 men, and three trials were identified that compared EBRT with or without a brachytherapy boost in 718 men. The Data Supplement lists the included trials, with summary statistics for the included trials and descriptive statistics by treatment in Table 1. The majority of all men included had intermediate- or high-risk prostate cancer (84%). In two of the trials assessing the addition of a brachytherapy boost to EBRT,

TABLE 1. Descriptive Statistics by Treatment Arm

Statistic	EBRT With or Without ADT	EBRT With or Without BT
No. of studies	6	3
Total No. of patients	4,663	718
Follow-up, months, median (range)	114 (86.4, 158)	110.3 (78, 168)
Age, years, median (range)	70.1 (67, 73)	67.8 (65, 70)
NCCN risk groups, % (range)		
Low	15 (0, 36)	1 (0, 7)
Intermediate	42 (9, 74.2)	34 (21, 44)
High	41 (11, 91)	63 (53, 70.2)
Clinical T stage, % (range)		
T1-2	78 (9, 100)	70 (60, 77)
T3	22 (0, 91)	30 (28.5, 40)
Gleason score, % (range)		
6	50 (26, 63)	19 (5, 37)
7	34 (26, 59)	47 (32, 55)
8-10	14 (9, 28)	29 (13, 41.4)
Pretreatment PSA, ng/mL (range)	14.6 (7.9, 33.8)	16.0 (13.2, 20.2)

Abbreviations: ADT, androgen-deprivation therapy; BT, brachytherapy boost; EBRT, external beam radiotherapy; NCCN, national comprehensive cancer network; PSA, prostate-specific antigen.

patients in both arms received ADT, either systematically in ASCENDE-RT or nonsystematically in the trial reported by Hoskin et al.^{6,8}

Network Meta-Analysis

In the meta-analysis of EBRT plus ADT versus EBRT alone, the Cochran's Q test for heterogeneity was significant without adjustment for ADT duration. After adjusting for ADT duration, this was no longer significant. In an analysis of trials comparing EBRT plus a brachytherapy boost versus EBRT alone, the test for heterogeneity was not significant, and as such, no adjustment for ADT use or duration was made (Cochran's Q = 2.61; $P = .3$). Compared with EBRT alone, the addition of ADT to EBRT improved OS (HR, 0.70; 95% CI, 0.62 to 0.81). Although this HR estimate is independent of baseline risk group, as a sensitivity analysis we repeated the analysis in the subset of randomized trials treating mostly men with high-risk prostate cancer (RTOG 8610, EORTC 22863, and TROG 9601) as well as in the remaining trials that were mostly men with intermediate-risk prostate cancer. This resulted in similar estimates of the HR for EBRT alone versus EBRT plus ADT (high-risk: HR, 0.66; 95% CI, 0.38 to 1.15; intermediate-risk: HR, 0.73; 95% CI, 0.51 to 1.04, with a P value of .74 for comparison of HRs). Conversely, compared with EBRT (with or without ADT), the addition of a brachytherapy boost to EBRT did not significantly improve OS (HR, 0.94; 95% CI, 0.70 to 1.27).

In a network meta-analysis using fixed-effects modeling, EBRT plus ADT was associated with improved OS compared with EBRT plus a brachytherapy boost (HR, 0.68; 95% CI, 0.52 to 0.89; Fig 2). Network meta-analysis findings were similar when only the brachytherapy boost trial reported by Sathya et al,¹⁰ the only brachytherapy boost trial to exclude the use of ADT, was included. A cumulative incidence curve of overall mortality using our calculated HR (0.68) comparing EBRT plus ADT to EBRT plus a brachytherapy boost assuming proportional hazards can be found in the Data Supplement, with the EBRT plus ADT curve estimated from EORTC 22991.¹ The estimated 10-year cumulative incidence of overall mortality was 28% for EBRT plus ADT versus 41% for EBRT plus a brachytherapy boost.

Given the estimated magnitude of the OS benefit of EBRT plus ADT compared with EBRT plus a brachytherapy boost, we estimated the number of men that would be required to be randomly assigned between these two treatments to have 80% power to detect an OS benefit of this magnitude in an attempt to inform future clinical trial design. Assuming an α of 0.05, an estimated 832 men would need to be randomly assigned to have 80% power to demonstrate a statistically significant difference in OS between these two treatment modalities, assuming a 20% event rate.

Bayesian Modeling

We next sought to compare EBRT plus ADT with EBRT plus a brachytherapy boost using Bayesian modeling. With this approach, there was an 88% probability that EBRT plus ADT would result in superior OS compared with EBRT plus a brachytherapy boost. Plots of the distributions of HRs from the Bayesian analysis can be found in the Data Supplement.

Last, we ranked the probability that each treatment option (EBRT alone, EBRT plus brachytherapy boost, and EBRT plus ADT) resulted in superior OS using the SUCRA. The SUCRA for EBRT alone, EBRT plus a brachytherapy boost, and EBRT plus ADT were 27%, 30%, and 90%, respectively, for OS. Overall, with this approach, there was an 87% probability that EBRT plus ADT ranked first in terms of superior OS outcomes among the three treatment methods (Fig 3). All bRFS analyses can be found in the Data Supplement.

DISCUSSION

Herein, we demonstrate a high probability that in men with mostly intermediate- and high-risk prostate cancer treated with EBRT the addition of ADT results in superior OS compared with the addition of a brachytherapy boost. As such, if only these two options are considered, our findings suggest that the addition of ADT provides a greater oncologic benefit than a brachytherapy boost. This said, recent evidence from ASCENDE-RT⁸ suggests that, compared with EBRT with ADT, the addition of a brachytherapy boost further improves biochemical and local

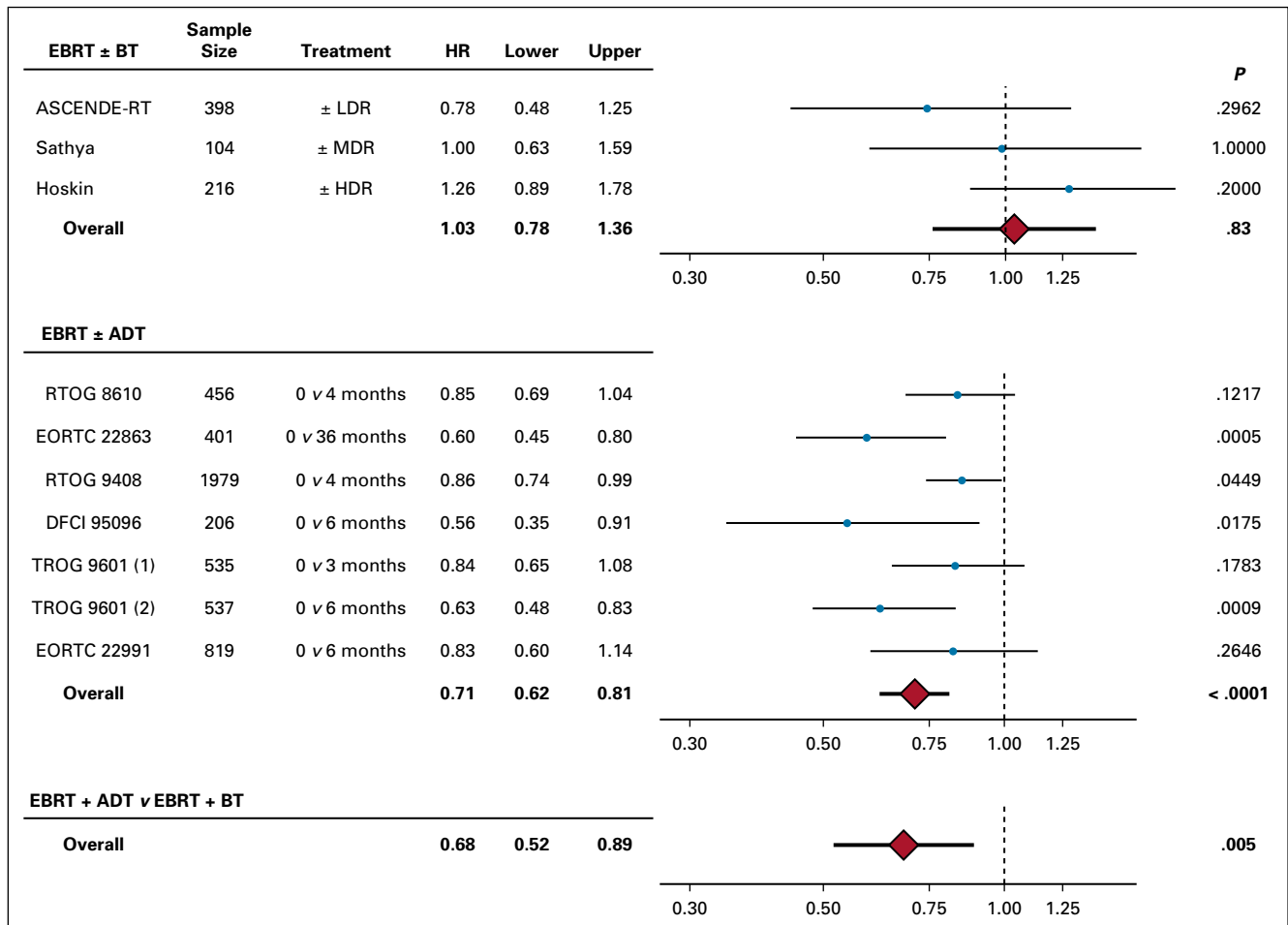


FIG 2. Network meta-analysis of overall survival.^{6,10} Meta-analysis from individual trials for overall survival for external beam radiotherapy (EBRT) with or without brachytherapy boost (BT) and EBRT with or without androgen-deprivation therapy (ADT), as well as results from fixed-effects network meta-analysis comparing EBRT plus ADT with EBRT plus BT. HDR, high-dose rate; HR, hazard ratio; LDR, low-dose rate; MDR, medium-dose rate.

control. Thus, if a brachytherapy boost is to be used for intermediate- or high-risk disease, our data suggest that the addition of ADT is required to prevent inferior survival compared with EBRT with ADT alone. On the basis of our findings, there is currently insufficient evidence to support the omission of ADT in men with intermediate- or high-risk prostate cancer treated with any form of definitive radiation therapy, including brachytherapy.

A recent review from the American Brachytherapy Society outlined the lack of clinical trials and the paucity of data assessing the benefit of ADT with brachytherapy.¹² Retrospective studies do not demonstrate a benefit from the addition of ADT to brachytherapy.¹² However, many retrospective or observational studies also show no benefit of adding ADT to EBRT, in stark contrast to multiple randomized controlled trials. Despite the lack of quality data to omit ADT with brachytherapy, one of the strongest factors that predicts the omission of ADT in intermediate- and high-risk prostate cancer is the concurrent use of brachytherapy.¹⁴ Many have advocated that the use of brachytherapy can spare patients from ADT or shorten ADT duration,

despite the lack of evidence for this approach. Our data question the validity of this practice and suggest that the use of EBRT plus ADT provides a high probability of superior OS in comparison with EBRT plus a brachytherapy boost without ADT.

To the best of our knowledge, only two small randomized trials have assessed the role of ADT in men treated with brachytherapy, one assessing 3 months of neoadjuvant ADT before low-dose rate monotherapy, and the second assessing combination EBRT plus a high-dose rate brachytherapy boost with or without ADT, with the duration of ADT not reported.^{21,22} Both trials have only been published in abstract form, and neither was powered to assess the impact of ADT on metastasis-free survival or OS.^{21,22} As such, these trials will not elucidate the role of ADT for men receiving either brachytherapy as monotherapy or as a boost. In addition, although the yet to be reported RTOG 0815, a randomized trial of dose-escalated radiation therapy with or without short-term ADT, allowed for men to receive a brachytherapy boost as a component of their treatment, this trial was not powered to assess the effect of

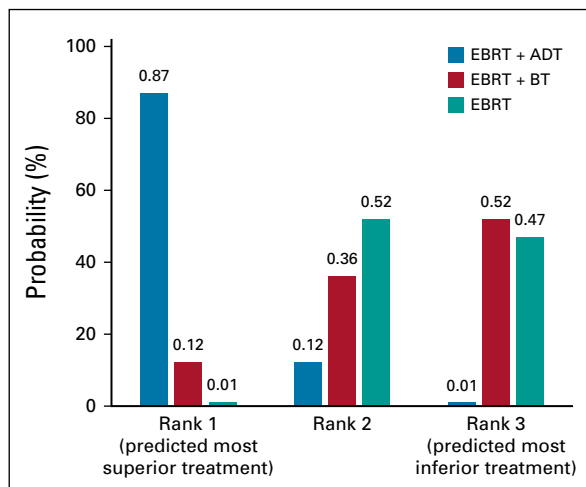


FIG 3. Predicted treatment rankings for overall survival. ADT, androgen deprivation therapy; BT, brachytherapy boost; EBRT, external beam radiotherapy.

ADT solely in men receiving a brachytherapy boost. Thus, there is a great need for trials to be performed to understand the role of brachytherapy with the use of ADT in contemporary practice and with the potential integration of newer systemic treatment options.

Distant failure from pre-existing micrometastatic disease, which will not be eradicated through local treatment intensification, remains an important mode of failure for high-risk men. Thus, one plausible hypothesis for the etiology of our findings is that although the addition of a brachytherapy boost enhances local eradication of disease, ADT has a greater survival impact by sterilizing both local and distant sites. Multimodality approaches are likely necessary for optimal outcomes. This can be appreciated in ASCENDE-RT. Despite improved bRFS with the addition of a brachytherapy boost to EBRT plus ADT, rates of distant metastases were nearly identical, driven by similar rates in both arms of early metastases.⁸ Importantly, this trial did not use long-term adjuvant ADT, which may have prevented or delayed the time to develop these early metastatic events. Conversely, nearly all trials included in this analysis assessing the addition of ADT to EBRT demonstrated a reduction in the development of distant metastases. On the basis of the available evidence, there is clearly a need for ADT or other forms of systemic treatment intensification, even in the context of effective local therapies.

Our analyses have limitations. First, we are limited by the number and sample size of randomized trials assessing the addition of a brachytherapy boost to EBRT. Furthermore, we were unable to control for total dose delivered in our analysis. Two of the three brachytherapy trials used radiation treatment doses that are lower than those currently used in clinical practice. Nonetheless, these are the only randomized data that currently exist to support this

treatment method, and as such, they form the basis for the role of a brachytherapy boost in the treatment of men with intermediate- and high-risk prostate cancer. In addition, we were unable to meaningfully compare treatment-related toxicity between EBRT plus ADT and EBRT plus a brachytherapy boost, given the nonoverlapping toxicity profiles of these two forms of treatment intensification. Future trials comparing ADT and brachytherapy boost should include patient-reported quality of life as a secondary outcome. Another limitation is that we were unable to assess the impact of ADT or a brachytherapy boost on distant metastases, because the brachytherapy boost trial reported by Hoskin et al⁶ reported only bRFS and OS. Last, two of the three randomized trials of EBRT with or without a brachytherapy boost either selectively or uniformly included ADT. In the randomized trial from the United Kingdom reported by Hoskin et al,⁶ patients non-systematically received neoadjuvant ADT followed by an additional 6 to 36 months of ADT, with 76% of men receiving ADT. ADT was administered to men with more aggressive disease, likely accounting for the finding in the multivariable analysis that ADT use predicted for worse bRFS. Conversely, all men in the ASCENDE-RT trial were to receive ADT; however, the timing and duration of ADT were nonstandard. ADT was given neoadjuvantly for 8 months, and then all men received an additional 4 months of ADT with and after their radiation therapy. As such, we are unable to provide insight on the potential benefits or appropriate duration of ADT in men treated with EBRT plus a brachytherapy boost. It is unlikely that the use of ADT in two of the three trials assessing the use of a brachytherapy boost confounded our findings because there was no heterogeneity among the 3 trials, although the power to detect heterogeneity is likely low. Furthermore, the results from the trial reported by Sathya et al,¹⁰ the only brachytherapy boost trial to exclude ADT, were similar to the meta-analyzed results of the three brachytherapy boost trials, and the network-meta analysis findings were similar when excluding the two brachytherapy boost trials in which patients received ADT.

In our analysis of men with intermediate- or high-risk prostate cancer, the addition of ADT to EBRT seems to improve survival, whereas the addition of a brachytherapy boost did not, and this remained true on meta-analysis. Our findings demonstrate that there is a high probability that EBRT plus ADT provides superior OS compared with EBRT plus a brachytherapy boost in men with intermediate- and high-risk prostate cancer. Our study suggests that ADT should not be omitted on the basis of available evidence in men with intermediate- or high-risk prostate cancer receiving EBRT plus a brachytherapy boost. Randomized trials are needed if the omission of ADT is to be recommended with EBRT and a brachytherapy boost.

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EQUAL CONTRIBUTION

W.C.J. and H.E.H. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.03217>.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Addition of Androgen-Deprivation Therapy or Brachytherapy Boost to External Beam Radiotherapy for Localized Prostate Cancer: A Network Meta-Analysis of Randomized Trials**

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