original reports

Radiation and Androgen Deprivation Therapy With or Without Docetaxel in the Management of Nonmetastatic Unfavorable-Risk Prostate Cancer: A Prospective Randomized Trial

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abstract

PURPOSE Although docetaxel is not recommended when managing men with unfavorable-risk prostate cancer (PC) given negative or inconclusive results from previous randomized trials, unstudied benefits may exist.

METHODS Between September 21, 2005, and January 13, 2015, we randomly assigned 350 men 1:1 with T1c-4N0M0 unfavorable-risk PC to receive radiation therapy (RT) and androgen deprivation therapy (ADT) plus docetaxel (60 mg/m^2 once every 3 weeks for three cycles before RT and 20 mg/m^2 once weekly during RT) versus ADT + RT. We evaluated the treatment effect of adding docetaxel to ADT + RT on the primary end point of overall survival (OS) and the incidence of RT-induced cancers and explored whether the impact of the treatment effect on OS differed within prostate-specific antigen (PSA) subgroups (< 4, > 20 *v* 4-20 ng/mL) using the interaction test for heterogeneity adjusted for age and PC prognostic factors.

RESULTS After a median follow-up of 10.2 years, 89 men died (25.43%); of these, 42 from PC (47.19%). Although OS was not significantly increased in the docetaxel arm (the restricted mean survival time over 10 years was 9.11 *v* 8.82 years; $P = .22$), significantly fewer RT-induced cancers were observed (10-year estimates: 0.61% *v* 4.90%; age-adjusted hazard ratio of 0.13; 95% CI, 0.02 to 0.97; $P = .046$). The treatment effect of adding docetaxel to ADT + RT on OS significantly differed in men with a PSA < 4 ng/mL versus 4-20 ng/mL (adjusted hazard ratio: 0.27 and 1.51, respectively) because of less PC-specific mortality on the docetaxel arm (0.00% *v* 28.57%) among men with PSA < 4 ng/mL.

CONCLUSION Adding docetaxel to ADT + RT did not prolong OS in men with unfavorable-risk PC, but decreased RT-induced cancer incidence, and may prolong OS in the subgroup of men with a PSA < 4 ng/mL by reducing PC-specific mortality.

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INTRODUCTION

Docetaxel was first approved by the US Food and Drug Administration (FDA) for use in prostate cancer (PC) in men with metastatic (M1) castration-resistant PC after an overall survival (OS) benefit was observed in two randomized controlled trials (RCTs).[1,2] Later, prolonged OS was observed in men with newly diagnosed M1 castration-sensitive PC when docetaxel was added to androgen deprivation therapy (ADT) in two RCTs.[3,4] Subsequently, for men with unfavorable-risk nonmetastatic (M0) PC, the addition of docetaxel to radical prostatectomy (RP)[5,10] or radiation therapy (RT) and ADT[6-9] was studied in seven RCTs; six have been reported to date[5-10] with negative or inconclusive results. Specifically, an OS benefit with a nonsignificant reduction in PC-specific mortality (PCSM) was observed in only two[6,10] of the six studies where $> 80\%$ of the patients had high-grade PC.

A plausible hypothesis for the OS benefit and a nonsignificant reduction in PCSM is that docetaxel reduced PCSM in the small subset of men with low prostate-specific antigen (PSA)–producing, high-grade PC that may be resistant to conventional ADT[11-16] while also reducing non-PCSM by reducing death from RT-induced cancers. Given that docetaxel at low doses (ie, 20 mg/m^2) is a potent radiosensitizer,[17] it is plausible that docetaxel as used in the current RCT can sterilize cells that survive RT-induced damage, preventing them from developing into an RT-induced cancer. Therefore, although docetaxel is not

ASSOCIATED CONTENT

Appendix

Protocol

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

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CONTEXT

Key Objective

We investigated whether previous randomized controlled trials missed the benefit of adding intravenous docetaxel to radiation therapy (RT) and androgen deprivation therapy (ADT) in the management of nonmetastatic, unfavorable-risk prostate cancer (PC).

Knowledge Generated

Among men randomly assigned to receive ADT + RT + docetaxel versus ADT + RT, significantly less RT-induced cancers were observed. The treatment effect of adding docetaxel to ADT + RT on overall survival in men with a prostate-specific antigen (PSA) < 4 ng/mL was driven by the absence of PC death, providing evidence to support a distinct biology in low PSA-producing, unfavorable-risk PC that is docetaxel-sensitive.

Relevance

Future study is needed to assess whether oral docetaxel, given its favorable toxicity profile, can reduce RT-induced cancer incidence, like intravenous docetaxel, across a wide variety of cancers. The absence of PC death that we observed among men with a PSA < 4 ng/mL randomly assigned to receive docetaxel could be explored further in a meta-analysis of previous randomized controlled trials.

recommended when managing men with unfavorable-risk PC given inconclusive results from previous randomized trials,[5-10] unstudied benefits may exist.

To test this hypothesis in the current RCT (ClinicalTrials.gov Identifier: NCT00116142), we evaluate the treatment effect of adding docetaxel to ADT + RT in men with newly diagnosed M0 unfavorable-risk PC on the primary end point of OS and the incidence of second cancers (RT-induced, all others) and explore this effect in men with a PSA < 4 ng/mL.

METHODS

Study Design and Oversight

This was an investigator-initiated multicenter phase III RCT conducted in both academic and community-based health centers in the United States, Australia, and New Zealand (Protocol, online only). The institutional review board at each participating institution approved the trial that was conducted in compliance with the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice.[18] Written informed consent was obtained, and an independent data safety and monitoring board reviewed unblinded safety data throughout the trial. The results of the interim analyses are shown in Appendix 1 (online only).

Patients

Eligible patients included those with histologically proven adenocarcinoma of the prostate scored using the Gleason scoring system by an expert genitourinary pathologist (A.A.R.). They were required to have one or more of the following: Clinical Tumor (T) category T2c-T4 as per the 2002 American Joint Commission on Cancer staging or Clinical T1b-T2b and PSA level > 10 ng/mL or a biopsy Gleason score of 4 + 3 or higher or tertiary grade 5 PC or biopsy Gleason score 3 + 4 PC and at least 50% of the biopsy cores positive or a PSA velocity > 2 ng/mL/year or biopsy or radiographic evidence of seminal vesicle invasion. There must also be no prior pelvic RT or RP; however, ADT within 4 weeks before random assignment was permitted.

A radionuclide bone scan and computed tomography or magnetic resonance imaging assessment of the pelvic lymph nodes were performed to rule out the presence of bone and/or pelvic lymph node metastasis, respectively. Up to 1.5 cm (long axis) pelvic lymph nodes were permitted. Additional eligibility requirements can be found in Appendix 1.

Random Assignment and Interventions

As shown in the CONSORT diagram in Figure 1, patients were randomly assigned 1:1 to 6 months of ADT + RT versus 6 months of ADT + RT + 10 cycles of docetaxel (three cycles at 60 mg/m^2 once every 3 weeks before RT and then once weekly for seven cycles during RT at 20 mg/m^2). The daily RT dose was 1.8 Gy for 39 treatments to the prostate and seminal vesicles totaling 73.7 Gy (70.2 Gy normalized to 95%) delivered using 3-dimensional conformal RT technique or intensity-modulated RT. Pelvic lymph nodes could be treated at the discretion of the treating physician. ADT consisted of a luteinizing hormone releasing hormone agonist and antiandrogen that started 2 months before RT, continued during RT, and concluded 2 months after RT completion in both treatment arms. Before random assignment, patients were stratified by centrally reviewing a biopsy Gleason score ≤ 7 versus > 7 and a PSA level ≤ 20 versus > 20 ng/mL. Treatments were assigned using permuted blocks created by the biostatistician (W.X.) within strata with dynamic balancing within institutions, and patients were enrolled by the study team (M.L. and E.M.).

Assessments

Patient demographics, medical history including comorbidities scored using the Adult Comorbidity Evaluation-27

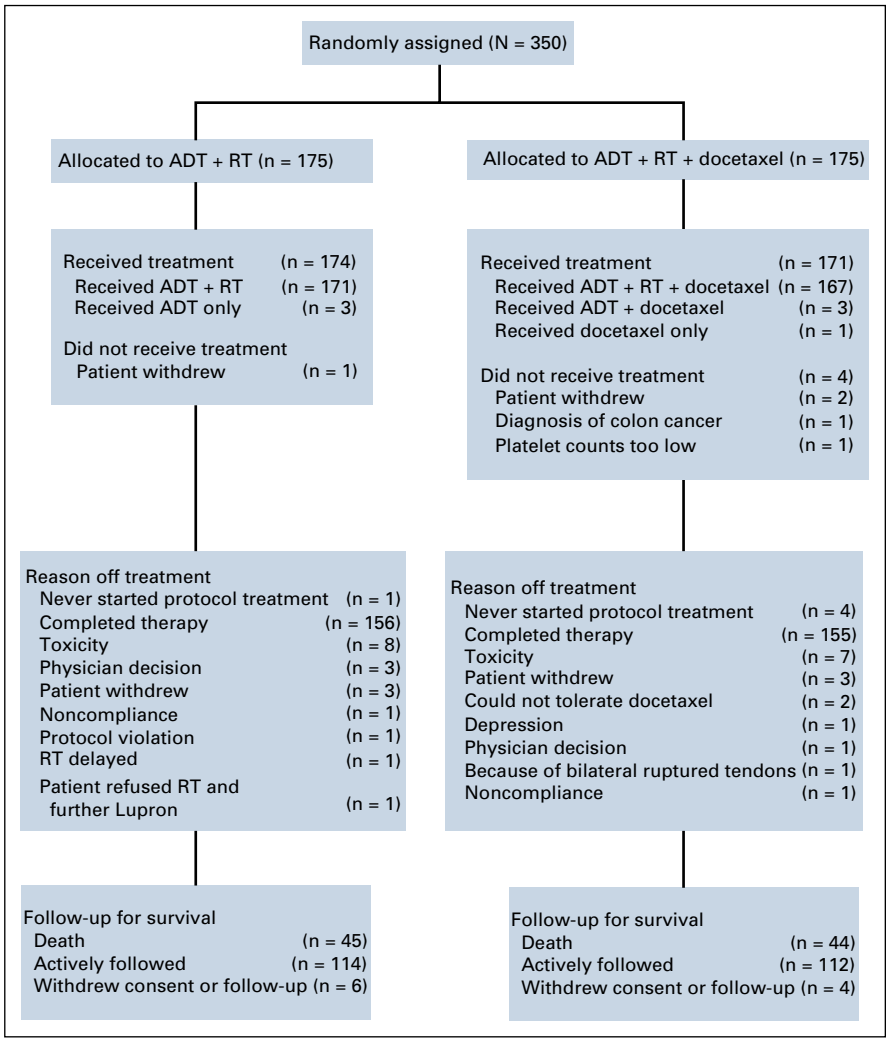

FIG 1. CONSORT diagram: random assignment, treatment, and follow-up. ADT, androgen deprivation therapy; RT, radiation therapy.

metric,[19] PC indices, and clinical T-category as per the digital rectal examination were assessed and recorded within 30 days before random assignment. Following the end of RT, patients were seen for follow-up every 6 months for 5 years and annually thereafter. At each follow-up, serum PSA and testosterone levels were obtained. If a patient experienced PSA failure defined as PSA nadir + 2 ng/mL, restaging with a bone scan and pelvic magnetic resonance imaging or computed tomography was performed. Collection of data at each follow-up visit on second cancer incidence including date of diagnosis, location, and histology was performed in addition to PSA failure, metastatic disease, and survival status permitting the assessment of second cancer incidence, PSA failure, metastatic, and OS status. Adverse event occurrence, severity, and whether they were treatment-related were recorded as per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. We also considered second cancers as part of the safety assessment and recorded their occurrence and whether they were treatment-related separate from the adverse events that are included in National Cancer Institute Common Terminology Criteria.

Clinical Outcome Measures

The primary end point was OS defined from the date of random assignment to death from any cause with surviving patients censored at date of last follow-up. The cause of death was centrally reviewed by the principal investigator (A.V.D.) who was blinded to the randomized treatment arm. Second cancer incidence was defined from the date of random assignment to diagnosis of a new malignancy. An RT-induced cancer was defined as occurring within or juxtaposed to the radiation planning target volume.[20] Given the clinical significance of an RT-induced cancer, we evaluate the composite end point of OS or the occurrence of an RT-induced cancer in surviving patients. Secondary end points including PCSM, metastasis-free survival (MFS), and

PSA recurrence-free survival (PSA RFS) are described in Appendix 1.

Statistical Methods

Statistical design. The study was designed to detect a hazard ratio of 0.48, corresponding to an improved 5-year OS from 84% (ADT + RT) to 92% (ADT + RT + docetaxel) under the exponential distribution. Initially, a one-sided significance level of 0.05 and 80% power, which required at least 53 deaths and a target accrual of 350 patients for the final analysis using a log-rank test, were used. However, a protocol amendment was made in February 2018, which increased the event number to 86 deaths for the same hypothesized improvement in OS under the one-sided alpha of .025 and 90% power given that the statistical concerns raised over a similar previous randomized trial[6] that used a one-sided alpha of .05 and 90% power when first reported at the 2015 ASCO meeting (Chicago, IL). The target accrual needed to make this assessment remained unchanged at 350 patients.

Statistical Analysis

Prespecified end points. Intent-to-treat population was used for the primary and secondary efficacy analysis. Distribution of OS, MFS, and PSA RFS was estimated using the Kaplan-Meier methodology.[21] Cox proportional hazards models[22] estimated the treatment effect of adding docetaxel to ADT + RT (hazard ratios [HRs] and 95% CI) for OS, MFS, and PSA RFS, and the stratified log-rank test[20] was reported as the primary comparison. The proportional hazards assumption was visually checked and tested; restricted mean survival time (RMST) was provided if nonproportionality was evident. The RMST measures the average survival from time-zero to a specified time-point and may be estimated as the area under the survival curve up to that point. Cumulative incidence estimates of PCSM, RT-induced, and all other second cancers were calculated and compared between randomized treatment arms. Subdistribution of hazard ratios[23] and stratified Gray's test[24] were provided. All prespecified efficacy comparisons were based on stratified analyses at random assignment (Gleason score: ≤ 7 *v* > 7 and PSA: ≤ 20 *v* > 20 ng/mL).

Exploratory Analysis

To assess whether the treatment effect of adding docetaxel to ADT + RT on OS or the occurrence of an RT-induced cancer differed within PSA subgroups (< 4, > 20 *v* 4-20 ng/mL), the interaction test for heterogeneity of treatment effect across PSA subgroups was carried out. Adjustment was made for age and established PC prognostic factors (Gleason score, T-category, and percent positive biopsies) at random assignment, and unadjusted and adjusted HRs (aHRs) and 95% CI were reported. The reference group of PSA 4-20 ng/mL was selected for the interaction test given previous data[12] reporting a $>$ 2-fold increased risk of PCSM among men treated with ADT + RT for high-grade PC and a PSA < 4 or > 20 ng/mL compared with 4-10 ng/mL, whereas the PCSM risk was only slightly elevated among men with a PSA of 10.1-20 ng/mL versus 4-10 ng/mL.

All statistical tests were two-sided, and statistical significance was defined as a *P* value $\leq .05$, except for OS where the stratified two-sided log-rank test < 0.048 was required for statistical significance given the previous two interim analyses (Appendix 1). All analyses were performed using SAS Software version 9.4 (SAS Institute Inc, Carey, NJ).

RESULTS

Patients

Patients were enrolled between September 21, 2005, and January 13, 2015, from 18 centers (Appendix Table A1, online only), and data were entered until June 29, 2020, at which time the trial was stopped given that the number of prespecified deaths needed for final analysis was observed to have occurred. The intention-to-treat population included 350 men, 175 in both randomized treatment arms. As shown in Table 1, the patient clinical and demographic characteristics were similar between the two treatment arms. The median follow-up was 10.2 years (interquartile range: 8.00-11.40 years).

Clinical Outcome Measures

Prespecified end points. The primary end point of OS was analyzed after 89 deaths were observed (44 in the ADT + RT + docetaxel arm and 45 in the ADT + RT arm), 42 (47.19%) of which were from PC (22 in the ADT + RT + docetaxel arm and 20 in the ADT + RT arm). Similar to a previous RCT,[6] the OS curves initially diverged favoring the docetaxel arm, but then merged with further follow-up resulting in an HR (95% CI) comparing ADT + RT + docetaxel with ADT + RT of 0.99 (0.65 to 1.51) and $P = .98$ with 10-year estimates (95% CI) of survival of 72% (63 to 79) and 74% (66 to 80), respectively, as shown in Figure 2A. Given the evidence of nonproportionality, we evaluated RMST. The observed difference in RMST over 10 years was 0.29 (95% CI, –0.19 to 0.76) year ($P = .22$): 9.11 years in the ADT + RT + docetaxel arm and 8.82 years in the ADT + RT arm. There was no evidence of institutional heterogeneity between US and non-US sites in the treatment effect of adding docetaxel to ADT + RT on OS ($P_{\text{interaction}} = .86$).

Among men randomly assigned to receive docetaxel, significantly less RT-induced cancers and related deaths (1 *v* 8 [4 were fatal]; age-adjusted HR, 0.13 [95% CI, 0.02 to 0.97]; $P = .046$) were observed as shown in Figure 2B. Ten-year cumulative incidence estimates (95% CI) were 0.61% (0.06 to 3.09) versus 4.90% (2.13 to 9.40), respectively, and the observed difference of 4.29% was significant with a 95% CI that excluded 0.00 (0.51 to 8.07). Figure 2C illustrates no significant difference in the cumulative incidence of all other second cancers (HR, 0.89 [95% CI, 0.50 to 1.60]; $P = .70$), with 21 in the ADT + RT + docetaxel arm and 24 in the ADT + RT arm.

TABLE 1. Demographic and Clinical Characteristics of 350 Study Patients Further Stratified by Randomized Treatment Arm

Demographic or Clinical Characteristic	Men Randomly Assigned to ADT + RT (n = 175)		Men Randomly Assigned to ADT + RT + Docetaxel (n = 175)		All Men (N = 350)	
	No.	%	No.	%	No.	%
Race						
Asian	3	1.71	1	0.57	4	1.11
Black or African American	4	2.29	5	2.86	9	2.57
Others	29	16.57	37	21.14	66	18.86
White	139	79.43	132	75.43	271	77.43
Ethnicity						
Ethnicity not known	14	8.00	23	13.14	37	10.57
Hispanic or Latino	8	4.67	13	7.43	21	6.00
Non-Hispanic	153	87.43	139	79.43	292	83.43
2002 AJCC clinical T category at diagnosis per digital rectal examination						
T1c	37	21.14	56	32.00	93	26.57
T2a	29	16.57	17	9.71	46	13.14
T2b	25	14.29	18	10.29	43	12.29
T2c	35	20.00	34	19.43	69	19.71
T3a	28	16.00	38	21.71	66	18.86
T3b	19	10.86	12	6.86	31	8.86
T4	2	1.14	0	0.00	2	0.57
Endorectal coil magnetic resonance imaging evidence of seminal vesicle invasion						
Unknown	92	52.57	92	52.57	184	52.57
No	69	39.43	62	35.43	131	37.43
Yes	14	8.00	21	12.00	35	10.00
Biopsy Gleason score						
3 + 3	4	2.29	5	2.86	9	2.57
3 + 4	33	18.86	39	22.29	72	20.57
3 + 5	1	0.57	3	1.71	4	1.14
4 + 3	53	30.29	49	28.00	102	29.14
4 + 4	19	10.85	16	9.14	35	10.00
4 + 5	45	25.71	42	24.00	87	24.86
5 + 3	2	1.14	1	0.57	3	0.86
5 + 4	12	6.86	14	8.00	26	7.43

(continued on following page)

TABLE 1. Demographic and Clinical Characteristics of 350 Study Patients Further Stratified by Randomized Treatment Arm (continued)

Demographic or Clinical Characteristic	Men Randomly Assigned to ADT + RT (n = 175)		Men Randomly Assigned to ADT + RT + Docetaxel (n = 175)		All Men (N = 350)	
	No.	%	No.	%	No.	%
5 + 5	6	3.43	6	3.43	12	3.43
Testosterone at ADT initiation < lower limit of normal						
No	127	72.57	128	73.14	255	72.86
Yes	37	21.14	35	20.00	72	20.57
Unknown	11	6.29	12	6.86	23	6.57
ECOG performance status						
0	162	92.57	168	96.00	330	94.28
1	13	7.43	7	4.00	20	5.71
Adult Comorbidity Score-27[19]						
None	44	25.14	48	27.43	92	26.29
Minimal	89	50.86	74	42.29	163	46.57
Moderate	29	16.57	36	20.57	65	18.57
Severe	3	1.71	2	1.14	5	1.43
Unknown	10	5.71	15	8.57	25	7.14
PSA level in ng/mL at random assignment						
≤ 20	130	74.29	126	72.00	256	73.14
> 20	45	25.71	49	28.00	94	26.86
	Median	Range	Median	Range	Median	Range
Age at random assignment, years	66	49-85	66	43-86	66	43-86
Percent positive biopsies (n = 348)[a]	58	8-100	62.50	8-100	62	8-100

Abbreviations: ADT, androgen deprivation therapy; AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; RT, radiation therapy; T, tumor.

[a]Two men were missing percent positive biopsy data.

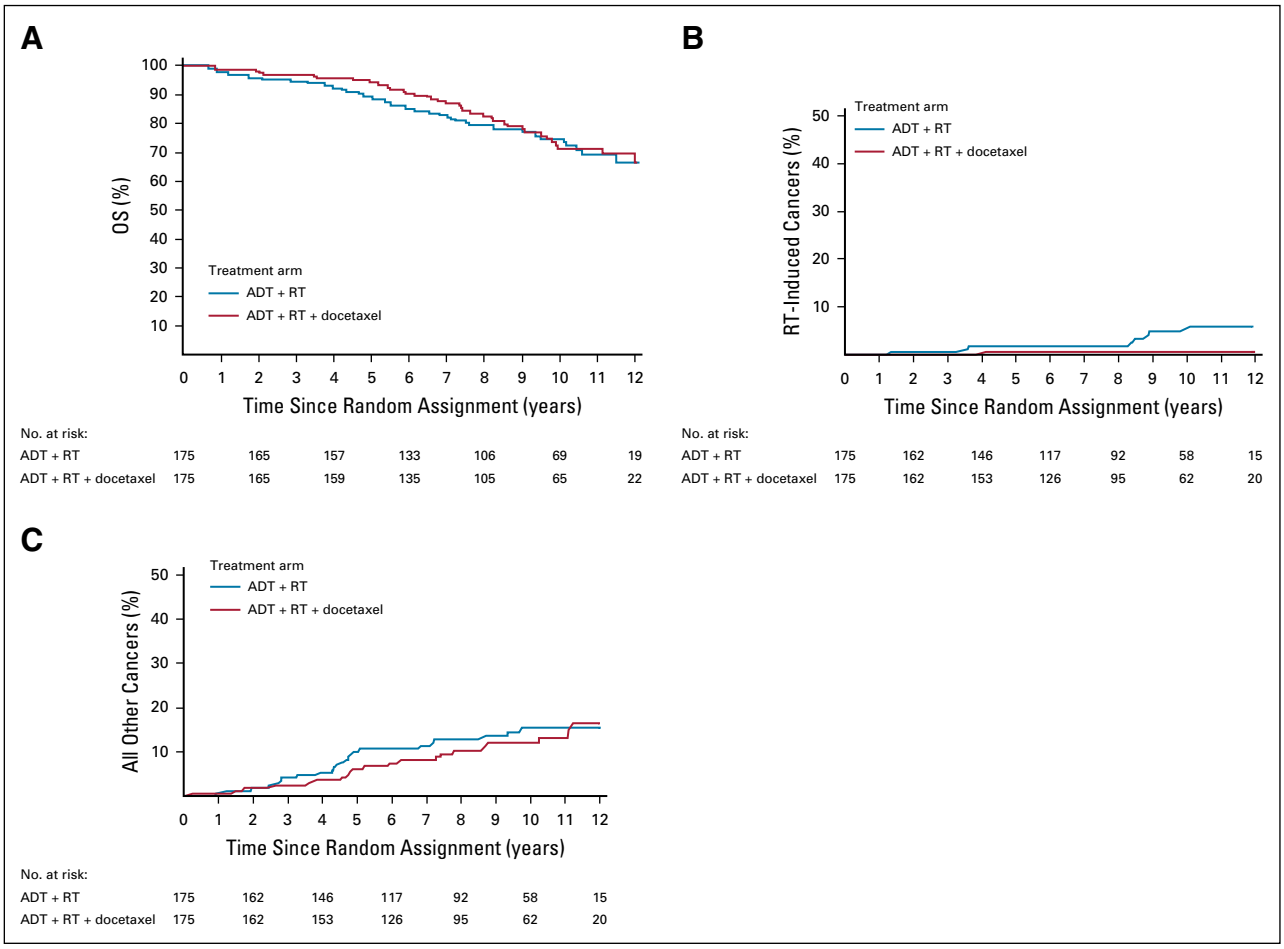

FIG 2. (A) Kaplan-Meier estimates of OS, (B) cumulative incidence estimates of RT-induced second cancers,[a] and (C) all other second cancers.[a]
[a]Without age adjustment and includes four bladder, three rectal, one colon (had pelvic lymph node radiation), and one prostate second cancer.
ADT, androgen deprivation therapy; OS, overall survival; RT, radiation therapy.

The secondary end point results are shown in Appendix 1 along with forest plots for the prespecified subgroup analyses for OS (Appendix Fig A1A, online only) and PCSM (Appendix Fig A1B).

Exploratory Analysis

As shown in Table 2, for men with a PSA < 4 ng/mL versus 4-20 ng/mL, the treatment effect of adding docetaxel to ADT + RT on OS differed (HR, 0.33, 1.40; $P_{interaction}$ = .09 and aHR, 0.27, 1.51; $P_{interaction}$ < .05, respectively) because of a lower PCSM in the docetaxel arm (0 of 13 [0.00%] *v* 4 of 14 [28.57%]) among men with PSA < 4 ng/mL (Table 3).

Among men with a PSA > 20 ng/mL versus 4-20 ng/mL, the treatment effect of adding docetaxel to ADT + RT on OS also differed (HR, 0.62, 1.40; $P_{interaction}$ = .08 and aHR, 0.60, 1.51; $P_{interaction}$ < .05 respectively). However, this difference could not be explained by a decrease in PCSM (Table 3) given that this rate was higher in the docetaxel arm ([10 of 49] 20.41% *v* [8 of 45] 17.78%). Analogous heterogenous treatment effects across PSA subgroups were also noted for the composite end point of OS or the occurrence of an RT-induced cancer (Table 2).

Safety

Both acute and late adverse events were analyzed in the 345 men who underwent protocol treatment (171 in the ADT + RT + docetaxel arm and 174 in the ADT + RT arm). Discontinuation of treatment because of toxicity occurred in 7 (4.09%) men in the ADT + RT + docetaxel arm and 8 (4.60%) men in the ADT + RT arm. Adverse acute events were reported by 26.90% of men randomly assigned to ADT + RT + docetaxel versus 10.34% in the ADT + RT arm. Most were grade 2 or 3 (18.13% in the ADT + RT + docetaxel arm and 8.05% in the ADT + RT arm). These respective estimates for grade 4 adverse events were 8.77% and 1.72%. There was 1 (0.57%) grade 5 adverse event (sudden death) in the ADT + RT arm that was not believed to be treatment-related.

Adverse late events were reported by 81.87% of men in the ADT + RT + docetaxel arm and 73.56% in the ADT + RT arm. Most were grade 1 or 2 (67.25% in the ADT

TABLE 2. Treatment Effect of Adding Docetaxel to ADT + RT on OS and on the Composite End Point of OS or the Occurrence of an RT-Induced Cancer Within PSA-Defined Subgroups

	OS (89 events)				OS or RT-Induced Cancer (93 events)		
PSA Subgroup	No. of Men	No. of Events	HR/aHR[a] (95% CI) ADT + RT + Docetaxel *v* ADT + RT	*P* Interaction[b]	No. of Events	HR/aHR[a] (95% CI) ADT + RT + Docetaxel *v* ADT + RT	*P* Interaction[b]
PSA < 4 ng/mL	27	8	0.33 (0.07 to 1.61)	.09	9	0.27 (0.06 to 1.28)	.06
			0.27 (0.05 to 1.34)	.05*		0.22 (0.05 to 1.08)	.03
PSA 4-20 ng/mL	229	50	1.40 (0.80 to 2.45)	Reference	53	1.33 (0.77 to 2.28)	Reference
			1.51 (0.86 to 2.67)			1.41 (0.82 to 2.43)	
PSA > 20 ng/mL	94	31	0.62 (0.30 to 1.26)	.08	31	0.61 (0.30 to 1.25)	.09
			0.60 (0.29 to 1.23)	.05**		0.61 (0.30 to 1.23)	.07

Abbreviations: ADT, androgen deprivation therapy; aHR, adjusted hazard ratio (348 patients; two men were missing percent positive biopsies); AJCC, American Joint Committee on Cancer; HR, hazard ratio (350 patients); OS, overall survival; PSA, prostate-specific antigen; RT, radiation therapy.

*$P = .047$.

**$P = .048$.

[a]Adjustment for age and percent biopsies as continuous covariates and Gleason score (8-10 *v* 7 or less) and 2002 AJCC tumor category (T3,4 *v* T1,2) as categorical covariates.

[b]Interaction test assessed whether the treatment effect of adding docetaxel to ADT + RT on OS and also on OS or RT-induced cancer differed between men with a PSA < 4 ng/mL or > 20 ng/mL versus a PSA of 4-20 ng/mL.

+ RT + docetaxel arm and 63.22% in the ADT + RT arm). These respective estimates for grade 3 or 4 adverse events were 14.62% and 10.34%.

DISCUSSION

Like previous RCTs,[5-9] men with unfavorable-risk M0 PC randomly assigned to receive ADT + RT + docetaxel compared with ADT + RT did not experience prolonged OS; however, neoadjuvant or concurrent docetaxel use in the current study resulted in a significant reduction in the incidence of RT-induced cancers. The ability to significantly reduce RT-induced cancer incidence is clinically relevant given that these cancers are typically radiation- and chemotherapy-resistant[25] and, as a result, often fatal as observed in this study. Moreover, the recent report of an oral formulation of docetaxel,[26] which has a much more favorable toxicity profile than intravenous (IV) docetaxel, provides the opportunity to study oral docetaxel use to reduce the risk of RT-induced cancer with minimal patient impact and across a wide variety of cancers where RT and docetaxel use is part of the management approach. In addition, we observed that the treatment effect of adding docetaxel to ADT + RT on OS differed in men with a PSA < 4 ng/mL versus 4-20 ng/mL because of the absence of PCSM in the docetaxel arm among men with PSA < 4 ng/mL, providing evidence to support the presence of a distinct biology in low PSA-producing, unfavorable-risk PC that is docetaxel-sensitive. Therefore, although docetaxel is not recommended when managing men with unfavorable-risk PC given the inconclusive results from previous randomized trials,[5-10] a subgroup may benefit.

TABLE 3. Distribution of the Causes of Death by Randomized Treatment Arm for All Men and Men With PSA Levels < 4 ng/mL, 4-20 ng/mL, and > 20 ng/mL at Registration

PSA Subgroup	< 4 ng/mL		4-20 ng/mL		> 20 ng/mL		All	
Randomized Treatment Arm	ADT + RT	ADT + RT + Docetaxel	ADT + RT	ADT + RT + Docetaxel	ADT + RT	ADT + RT + Docetaxel	ADT + RT	ADT + RT+ Docetaxel
Total No. of patients	14	13	116	113	45	49	175	175
Total No. of deaths	6	2	22	28	17	14	45	44
Cause of death, No. (%)								
Prostate cancer	4 (28.57)	0 (0.00)	8 (6.90)	12 (10.62)	8 (17.78)	10 (20.41)	20 (11.43)	22 (12.57)
RT-induced second cancer	0 (0.00)	0 (0.00)	2 (1.72)	0 (0.00)	2 (4.44)	0 (0.00)	4 (2.29)	0 (0.00)
All other second cancers	0 (0.00)	0 (0.00)	4 (3.45)	4 (3.54)	2 (4.44)	2 (4.08)	6 (3.42)	6 (3.42)
Cardiovascular	1 (7.14)	1 (7.69)	4 (3.45)	4 (3.54)	3 (6.66)	1 (2.04)	8 (4.56)	6 (3.42)
Others	1 (7.14)	1 (7.69)	4 (3.45)	8 (7.08)	2 (4.44)	1 (2.04)	7 (4.00)	10 (5.71)

Abbreviations: ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RT, radiation therapy.

Several points require further discussion. First, docetaxel has been FDA-approved for treatment[27] of locally advanced non–small-cell lung, gastric, head and neck, and breast cancer and in the postoperative setting for node-positive breast cancer and metastatic PC. Yet, the observation of reduced RT-induced cancer incidence with docetaxel use has not been previously reported. This can be explained by the short life expectancy of patients because of the advanced stage of some of these cancers relative to the time to onset of an RT-induced cancer and/or the lack of RT use in the studies[27] that led to FDA approval of docetaxel. Also, an RP control arm was not available to adjust for the incidence of expected cancers[28] that can arise in the bladder and/or rectum that are juxtaposed to the radiation planning target volume.[20] This means that the point estimates of RT-induced cancers we report could include those expected cancers and, therefore, may overestimate the true incidence of RT-induced cancers. However, given the random assignment, the occurrence of expected cancers between randomized treatment arms should be balanced and cancel out when evaluating differences over time. Therefore, the age-adjusted HR of RT-induced cancer we report reflects a significant decrease in the true incidence of RT-induced cancer among men randomly assigned to the neoadjuvant and concurrent docetaxel arm. Of importance, previous RT-based RCTs[6-10] used adjuvant and not neoadjuvant and concurrent docetaxel. Therefore, comparing the age-adjusted HR of RT-induced cancer observed in the current RCT with the values calculated using data from previous RCTs[6-10] would inform whether the use of adjuvant versus neoadjuvant and concurrent docetaxel affects RT-induced cancer incidence in a similar manner.

Second, the ADT duration in this study was six and not 24-36 months as it was in previous RCTs.[5-10] However, the observation that adding docetaxel to ADT + RT may prolong OS in men with a PSA $<$ 4 ng/mL should not be affected by this difference in ADT duration. Specifically, high-grade PCs that are low or non-PSA producing often have a short-lived PSA response to ADT suggesting ADT resistance,[11-16] making any duration of ADT unlikely to affect the risk of death. Nevertheless, whether docetaxel can prolong OS in men with a PSA $<$ 4 ng/mL is hypothesis-generating given that our prerandomization stratification for PSA level was defined at 20 ng/mL and not 4 ng/mL and that the 95% CI for the OS HR comparing ADT + RT + docetaxel with ADT + RT in men with a PSA $<$ 4 ng/mL included 1.00. However, this hypothesis is strengthened by adjustment for age, known PC prognostic factors, and the absence of PCSM among men who had a PSA $<$ 4 ng/mL and were randomly assigned to receive docetaxel, which could be explored further using individual patient data from previous RCTs[5-10] in a meta-analysis.

In conclusion, adding docetaxel to ADT + RT did not prolong OS in men with unfavorable-risk PC, but decreased RT-induced cancer incidence, and may prolong OS in the subgroup of men with a PSA $<$ 4 ng/mL by reducing PCSM.

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DISCLAIMER

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Radiation and Androgen Deprivation Therapy With or Without Docetaxel in the Management of Nonmetastatic Unfavorable-Risk Prostate Cancer: A Prospective Randomized Trial

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APPENDIX 1

Additional Eligibility Requirements

Eligible patients needed to be at least 30 years old and have an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate hematologic (WBC $>$ 3,000/mm^3, platelet count $>$ 105/mm^3, and hemoglobin $>$ 8.0 g/dL) and organ function (creatinine $<$ 2.0 mg/dL; total bilirubin $<$ upper limit of normal [except for Gilbert's syndrome]; AST, ALT, and alkaline phosphatase meeting combined constraints [described in the Protocol]; and peripheral neuropathy $<$ grade 1).

Interim Analyses

Two interim analyses of overall survival (OS) were performed according to the initial design and overseen by an independent Data Safety Monitoring Board. Early stopping criteria are based on O'Brien and Fleming's[29] use function for efficacy and the repeated confidence interval methodology for the futility monitoring, as described in the Protocol. The first interim analysis was conducted for the June 2012 Data Safety Monitoring Board meeting when 18 deaths (18 of 53, 34% information time under the original design) were observed. The second interim analysis was conducted for the 2015 November meeting when 34 deaths (34 of 53, 64% information time under the original design) were observed. Both efficacy and futility analysis were conducted at the two planned interim analyses, and neither led to premature termination per prespecified criteria from the Protocol.

A Protocol amendment was made in February 2018, which increased the event number to 86 deaths for the same hypothesized improvement in OS under the one-sided α = .025 and 90% power. The decision to amend the analysis plan was made without knowledge by the study team of the blinded interim analyses. To maintain the overall type I error of 0.05 (two-sided), after accounting for the interim analyses on the basis of group sequential theory, a two-sided *P* value from the stratified log-rank test $<$ .048 would indicate that the primary end point OS was significantly improved in the experimental arm.

Secondary End Points

Secondary end points included prostate cancer–specific mortality (PCSM), metastasis-free survival (MFS), and prostate-specific antigen recurrence-free survival (PSA RFS) and were compared between randomized treatment arms. PCSM was defined similarly to OS, but non-PC death was counted as competing risk under a competing risk model. MFS was measured from the date of random assignment to the date of the first evidence of recorded distant metastases or death from any cause or was censored at the date of last disease assessment if free from distant disease. PSA RFS was defined as the time from the date of random assignment to the earliest date of PSA failure (nadir + 2 ng/mL), initiation of salvage therapy or death from any causes, or censored at the date of last disease assessment for those alive and without PSA failure.

To assess the consistency of the treatment effect on OS and PCSM, we conducted prespecified subgroup analysis by (1) biopsy Gleason score ($\leq$ 7 *v* $>$ 7), (2) baseline serum testosterone levels (low *v* normal), and (3) comorbidity subgroups (no or minimal *v* moderate or severe) defined using the Adult Comorbidity Evaluation-27 metric.[19] Hazard ratios (HRs) reported for subgroup analyses were unadjusted. The results are shown in Appendix Figures A1A and A1B.

There was no advantage to adding docetaxel to androgen deprivation therapy plus radiation therapy with respect to the end points of PCSM (subdistribution HR, 1.15 [95% CI, 0.63 to 2.09]; P = .65), MFS (HR, 1.07 [95% CI, 0.75 to 1.54]; P = 0.69), and PSA RFS (HR, 1.05 [95% CI, 0.79 to 1.40]; P = 0.72).

TABLE A1. Accrual by Site

Treatment Center	Patients (No.)
Beth Israel Deaconess Medical Center	10
BWH/DFCI	128
Boston VA Medical Center	6
Calvary Mater Newcastle Hospital	44
Cancer Center of North Carolina	1
Cape Cod Hospital	8
City of Hope Medical Center	1
Dunedin Hospital, New Zealand	7
Hartford Hospital	2
Massachusetts General Hospital	1
Memorial Hermann Southwest Hospital	5
Milford Regional Cancer Center (BWH/DFCI affiliate)	3
Norris Comprehensive Cancer Center—University of Southern California	25
Sir Charles Gairdner Hospital	55
South Shore Hospital (BWH/DFCI affiliate)	5
St Anne's Hospital	8
Urorad Healthcare	9
Wellington Hospital	32
	Total = 350

Abbreviations: BWH, Brigham and Women's Hospital; DFCI, Dana Farber Cancer Institute.

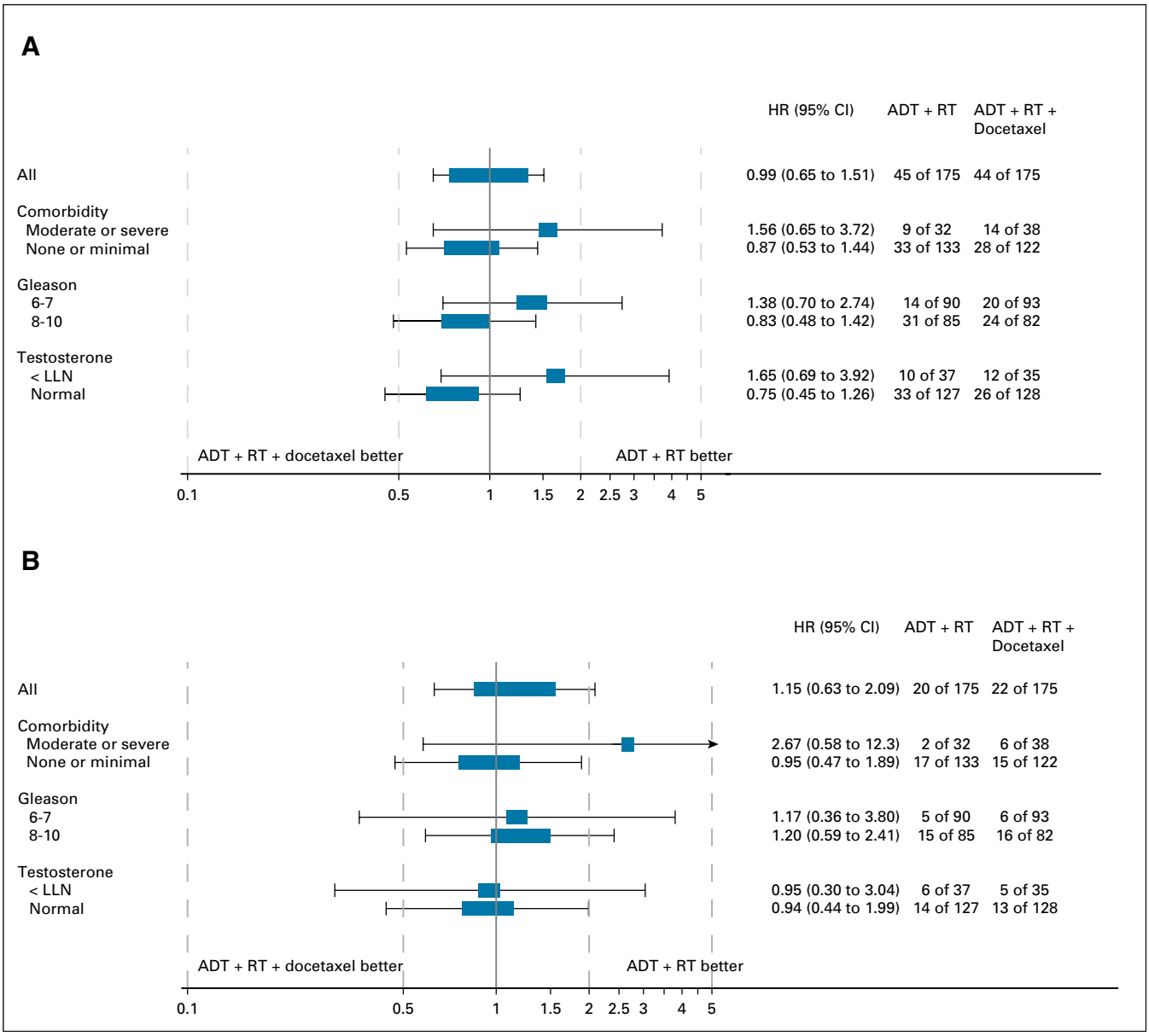

FIG A1. (A) HR and 95% CI. (B) Subdistribution HR and 95% CI. ADT, androgen deprivation therapy; HR, hazard ratio; LLN, lower limit of normal; RT, radiation therapy.