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Effect of Chemotherapy With Docetaxel With Androgen Suppression and Radiotherapy for Localized High-Risk Prostate Cancer: The Randomized Phase III NRG Oncology RTOG 0521 Trial

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abstract

PURPOSE Radiotherapy (RT) plus long-term androgen suppression (AS) are a standard treatment option for patients with high-risk localized prostate cancer. We hypothesized that docetaxel chemotherapy (CT) could improve overall survival (OS) and clinical outcomes among patients with high-risk prostate cancer.

PATIENTS AND METHODS The multicenter randomized NRG Oncology RTOG 0521 study enrolled patients with high-risk nonmetastatic disease between 2005 and 2009. Patients were randomly assigned to receive standard long-term AS plus RT with or without adjuvant CT.

RESULTS A total of 612 patients were enrolled; 563 were evaluable. Median prostate-specific antigen was 15.1 ng/mL; 53% had a Gleason score 9 to 10 cancer; 27% had cT3 to cT4 disease. Median follow-up was 5.7 years. Treatment was well tolerated in both arms. Four-year OS rate was 89% (95% CI, 84% to 92%) for AS + RT and 93% (95% CI, 90% to 96%) for AS + RT + CT (hazard ratio [HR], 0.69; 90% CI, 0.49 to 0.97; one-sided P = .034). There were 59 deaths in the AS + RT arm and 43 in the AS + RT + CT arm, with fewer deaths resulting from prostate cancer in the AS + RT + CT arm versus AS + RT (23 *v* 16 deaths, respectively). Six-year rate of distant metastasis was 14% for AS + RT and 9.1% for AS + RT + CT, (HR, 0.60; 95% CI, 0.37 to 0.99; two-sided P = .044). Six-year disease-free survival rate was 55% for AS + RT and 65% for AS + RT + CT (HR, 0.76; 95% CI, 0.58 to 0.99; two-sided P = .043).

CONCLUSION For patients with high-risk nonmetastatic prostate cancer, CT with docetaxel improved OS from 89% to 93% at 4 years, with improved disease-free survival and reduction in the rate of distant metastasis. The trial suggests that docetaxel CT may be an option to be discussed with selected men with high-risk prostate cancer.

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ASSOCIATED CONTENT

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Data Supplements

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

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INTRODUCTION

Prostate cancer is a common malignancy characterized by significant clinical heterogeneity and remains the second most common cause of death resulting from cancer among US men.[1] Advances in risk stratification have allowed identification of patients who are at increased risk of death resulting from prostate cancer. These patients are candidates for intensification of treatments aimed at improving survival. One standard treatment for clinically localized high-risk prostate cancer is radiotherapy (RT) and long-term (24 to 36 months) androgen-suppression (AS) therapy.[2-4]

Docetaxel-based chemotherapy (CT) has improved overall survival (OS) among men with castration-resistant cancer[5,6] and recently among men with castration-sensitive prostate cancer.[7,8] Clinical experience in other common malignancies suggests that CT may be more effective if used earlier in the course of disease. When used in the adjuvant setting, the tumor burden may be lower, and there is reduced potential for malignant cells to develop resistance to therapeutic agents. CT may also be able to target hormonally resistant cells, theoretically complementing the ability of AS to target hormonally sensitive cells. The phase III NRG Oncology RTOG (Radiation Therapy Oncology Group) 0521 trial hypothesized that cytotoxic CT with docetaxel, in addition to standard treatment with long-term AS plus RT, would result in improved disease control and survival compared with standard treatment of patients with high-risk disease, without demonstrated evidence of metastasis.

PATIENTS AND METHODS

Patients

Patients were enrolled by RTOG and other cooperative groups through the National Cancer Institute Cancer Trials Support Unit from 154 institutions. Patients within a high-risk subset of the conventional National Comprehensive Cancer Network high-risk population were eligible if they had either a Gleason score of 9 to 10, independent of prostate-specific antigen (PSA) or T stage; Gleason score of 7 to 8 and PSA of 20 ng/mL or greater, with any T stage; or Gleason score of 8 and PSA less than 20 ng/mL with T stage greater than or equal to T2. Maximum allowed PSA was 150 ng/mL. Other criteria included no evidence of nodal or distant metastasis (DM) by axial imaging or bone scan, Zubrod performance status of 0 to 1, and adequate hematologic and other organ laboratory indices. Prior AS was allowed if begun no later than 50 days before registration. Medical oncology consultation was required. Institutional review board approval was required. All patients were required to provide informed consent.

Treatment Plan

Patients were stratified on the basis of the risk criteria that led to eligibility and then randomly assigned at a one-to-one ratio to arm 1 (AS for 8 weeks followed by external-beam RT to 72.0 to 75.6 Gy with concurrent AS followed by adjuvant AS for a total of 24 months) or arm 2 (AS for 8 weeks followed by RT with concurrent AS followed by adjuvant AS for 24 months plus six cycles of docetaxel and prednisone administered concurrently with AS beginning 28 days after completion of RT).

Treatment groups were assigned based on the permuted-block randomization scheme described by Zelen.[9] Pelvic nodal RT was delivered as follows: 46.8 Gy in 26 fractions of 1.8 Gy to the prostate and regional lymphatics followed by cone-down RT consisting of 25.2 to 28.8 Gy in 1.8-Gy fractions. Either three-dimensional conformal RT or intensity-modulated RT was allowed. Centralized credentialing of treatment sites was required. Image-guided RT was not required. AS consisted of luteinizing hormone–releasing hormone (LHRH) agonist plus oral antiandrogen through the end of RT. A total of 24 months of LHRH was required. CT was started 26 to 33 days after RT and consisted of six cycles of docetaxel 75 mg/m^2 intravenously over 1 hour every 21 days and prednisone 10 mg orally daily until 21 days after the last cycle of CT. CT was discontinued if toxicities did not resolve by day 21 of a cycle or if there was a delay in chemotherapy greater than 16 weeks.

Study End Points

The primary end point was OS. Secondary end points included freedom from biochemical (PSA-based) failure (BF) using the Phoenix definition,[10] freedom from DM, disease-free survival (DFS; consisting of the first occurrence of BF, local or distant failure, or death resulting from any cause), and adverse events (AEs). Disease-specific survival (DSS) based on centrally reviewed cause of death was also reported. Outcome times were calculated from the date of random assignment to the date of failure or the date of last follow-up (including consent withdrawal). AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Testosterone was reported until normalization or initiation of salvage AS. Bone scans were used to assess for DM and were requested as clinically indicated and every 6 months after BF until DM was observed. Prostate biopsy was requested for BF or detectable clinical local relapse.

Statistical Considerations

The study was designed to detect an improvement in the 4-year OS rate from 86% (AS + RT) to 93% (AS + RT + CT) or, equivalently, a 51% relative reduction in hazard (hazard ratio [HR], 0.49), assuming an exponential survival distribution for each arm. Under a one-sided significance level of .05 and 90% power, at least 78 deaths were required to detect the hypothesized improvement in OS using the log-rank test. The failure rates in the control arm were based on the clinical experience from RTOG 9202 with a similar cohort. Because it was anticipated that AS + RT + CT would be more toxic and should only be considered if it could meaningfully prolong OS, the study was designed using a one-sided test. The choices of type I error and power were made at the time of study design to realistically compromise the rigor of evidence generation and feasibility (eg, sample size) such that the study could be completed and read out within a reasonable time frame. In consideration of a projected ineligibility/dropout rate of 10%, the final targeted accrual was 600 patients. Four interim analyses with early stopping criteria, overseen by an independent data monitoring committee, with O'Brien-Fleming–type Lan-DeMets alpha spending function[11,12] for efficacy and Gamma spending function[13] for futility, were planned after 31, 43, 59, and 67 deaths were observed. To maintain the overall type I error of 0.05 (one sided), after accounting for the planned interim analyses based on group sequential theory methods, the primary objective of detecting a clinically meaningful improvement in OS would be achieved if the one-sided *P* value from a log-rank test in a modified intent-to-treat (ITT) population were $< .04$. The modified ITT population, defined as all eligible patients analyzed per randomized treatment assignment, was prospectively specified in protocol and used in the primary analysis. As a sensitivity analysis, patients who received full protocol treatment (per-protocol analysis) were also reported. Cox proportional hazards model and the Wald method were used to estimate the HR of OS and the associated 90% CIs per study design. Rates of OS, DFS, and DSS were estimated by Kaplan-Meier method, and the associated 95% CIs were calculated using the Greenwood formula. The statistical inferences of DFS and DSS were based on

log-rank tests and Cox models. The actual rates of BF and DM were estimated using the cumulative incidence method,[14] accounting for deaths without the respective event as competing risks; statistical inferences were provided based on the cause-specific competing risk analysis method[15] using log-rank tests and Cox models. Scaled Schoenfeld residuals and interaction with log-transformed failure times were used to assess the proportional hazards assumptions when necessary. For all comparisons, stratified analyses based on the risk group strata at randomization were used. All statistical tests were two sided, and statistical significance was defined as $P < .05$, with the exception of OS, where a one-sided test was used per study design. The analyses are based on data received at the NRG Oncology RTOG Statistical and Data Management Center through April 12, 2015. All analyses were conducted using SAS software (version 9.4). The study was registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT00288080).

RESULTS

Patients

Between December 2005 and August 2009, 612 patients were enrolled in this study and randomly assigned to therapy with AS + RT versus AS + RT + CT; 563 patients were deemed eligible and available for the primary end point analysis. Ineligible patients were evenly distributed between the two arms. Most common ineligibility reasons were: AS beginning more than 50 days before registration (n = 10), withdrawing consent immediately after enrollment (n = 4), failure to assess baseline laboratories (ALT, n = 4; complete blood count, n = 4; and histologic diagnosis performed outside the required timeframe, n = 4). Treatment groups were well balanced (Table 1). Accrual of 13 patients per month exceeded the expected accrual of 11 patients per month. Figure 1 shows the CONSORT diagram. Per protocol, all eligible patients were analyzed per randomized treatment assignment.

Compliance

Protocol treatment reviews were performed to assess compliance with protocol specifications. All patients had RT reviews, and 97% in each arm were either protocol compliant or had acceptable variations. CT reviews of 249 patients (88.3%) were performed, and of these, 214 (85.9%) were protocol compliant. Eighty-two percent (175 of 214 protocol-compliant patients) received CT without modification or delay. All patients received LHRH agonist hormonal therapy, and 98% received an oral antiandrogen in combination with LHRH agonist treatment.

Outcomes

Four planned interim analyses for efficacy and futility were conducted. None led to premature termination. At the time of this analysis, median follow-up was 5.7 years for the 563 eligible patients and 6.1 years for the 461 surviving patients. The modified ITT population was used for all analyses; no adjustment for treatment compliance was made. All results reported were based on stratified analyses based on risk group stratification at randomization. Unstratified analyses were also conducted (Appendix Tables A1 and A2, online only; Appendix Figs A1A to A1D, online only), and results were similar to those of the stratified analyses.

Kaplan-Meier OS estimates are shown in Figure 2A; there were 102 events at the time of this analysis. Four- and 6-year OS rates were 88.7% (95% CI, 84.3% to 91.9%) and 80.6% (95% CI, 75.2% to 85.0%0 for the AS + RT arm and 93.3% (95% CI, 89.6% to 95.7%) and 86.0% (95% CI, 80.8% to 89.9%) for the AS + RT + CT arm, respectively. Median survival time was not reached in either arm. One-sided log-rank test P value was .034, lower than the predefined criterion but maintaining the overall one-sided .05 significance level. The HR was 0.69 (90% CI, 0.49 to 0.97). Centrally assessed causes of death using a multiphysician panel of two reviewers plus a third for adjudication are summarized in Table 2. Six-year centrally reviewed DSS rate was 92.0% (95% CI, 87.7% to 94.9%) for the AS + RT arm and 93.4% (95% CI, 89.1% to 96.0%) for the AS + RT + CT arm ($P = .18$).

Six-year DFS rate was 54.9% (95% CI, 48.2% to 61.0%) for the AS + RT arm and 65.4% (95% CI, 58.9% to 71.2%) for the AS + RT + CT arm (two-sided log-rank $P = .043$; Fig 2B). Median DFS time was 6.9 years (95% CI, 5.8 years to not reached) for the AS + RT arm and 8.5 years (95% CI, 6.8 to 12.7 years) for the AS + RT + CT arm. The HR was 0.76 (95% CI, 0.58 to 0.99).

There were 41 and 26 DM events in the AS + RT and AS + RT + CT arms, respectively. The cumulative probabilities of DM at 6 years were 14.0% (95% CI, 10.1% to 18.6%) and 9.1% (95% CI, 6.0% to 13.0%) in the two arms, and the HR of treatment was 0.60 (95% CI, 0.37 to 0.99; $P = .044$; Fig 2C) The PSA failure-free rates were similar in the two arms at 5 years: 75.1% (95% CI, 69.1% to 80.0%) and 78.5% (95% CI, 72.9% to 83.1%) in the AS + RT and AS + RT + CT arms, respectively ($P = .19$; Table 3; Fig 2D).

A sensitivity analysis was performed based on patients who received full protocol treatment (per protocol) rather than ITT (Table 4). This revealed that 4- and 6-year OS rates were 88.6% (95% CI, 84.2% to 91.9%) and 80.5% (95% CI, 75.0% to 84.9%) for the AS + RT arm and 94.1% (95% CI, 90.0% to 96.5%) and 87.6% (95% CI, 81.9% to 91.6%) for the AS + RT + CT arm, respectively. Median survival time was not reached for either arm. One-sided log-rank test P value was .009, with an HR of 0.59 (90% CI, 0.41 to 0.86). Six-year DFS rate was 54.5% (95% CI, 47.8% to 60.7%) for the AS + RT arm and 67.5% (95% CI, 60.3% to 73.7%) for the AS + RT + CT arm (two-sided log-rank $P = .013$). Median DFS time was 6.9 years (95% CI, 5.8 years to not reached) for the AS + RT arm and 8.5 years (95% CI, 6.8 to

TABLE 1. RTOG 0521: Pretreatment Characteristics

Characteristic	No. (%)		
	AS + RT (n = 281)	AS + RT + CT (n = 282)	Total (N = 563)
Age, years			
Median	66	66	66
Range	47-83	46-83	46-83
Q1-Q3	60-72	60-71	60-72
< 65	115 (40.9)	126 (44.7)	241 (42.8)
≥ 65	166 (59.1)	156 (55.3)	322 (57.2)
Race			
American Indian/Alaska Native	0 (0.0)	1 (0.4)	1 (0.2)
Asian	3 (1.1)	4 (1.4)	7 (1.2)
Black or African American	29 (10.3)	27 (9.6)	56 (9.9)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.4)	1 (0.2)
White	249 (88.6)	244 (86.5)	493 (87.6)
More than one race	0 (0.0)	2 (0.7)	2 (0.4)
Unknown or not reported	0 (0.0)	3 (1.1)	3 (0.5)
Ethnicity			
Hispanic or Latino	8 (2.8)	9 (3.2)	17 (3.0)
Not Hispanic or Latino	262 (93.2)	257 (91.1)	519 (92.2)
Unknown	11 (3.9)	16 (5.7)	27 (4.8)
Race/ethnicity grouping			
Non-Hispanic white	241 (85.8)	238 (84.4)	479 (85.1)
Hispanic or nonwhite	40 (14.2)	44 (15.6)	84 (14.9)
Zubrod performance status			
0	262 (93.2)	253 (89.7)	515 (91.5)
1	19 (6.8)	29 (10.3)	48 (8.5)
Prostate risk group			
Gleason ≥ 9, PSA ≤ 150, any T stage	149 (53.0)	148 (52.5)	297 (52.8)
Gleason 8, PSA < 20, ≥ T2	59 (21.0)	58 (20.6)	117 (20.8)
Gleason 8, PSA ≥ 20-150, any T stage	29 (10.3)	30 (10.6)	59 (10.5)
Gleason 7, PSA ≥ 20-150, any T stage	44 (15.7)	46 (16.3)	90 (16.0)
PSA, ng/mL			
Median	14.09	16.385	15
Range	1.2-145	0.7-135.4	0.7-145
Q1-Q3	7-32.46	7.6-33.8	7.2-33.7
Gleason score			
7	44 (15.7)	46 (16.3)	90 (16.0)
8	88 (31.3)	88 (31.2)	176 (31.3)
9	134 (47.7)	131 (46.5)	265 (47.1)
10	15 (5.3)	17 (6.0)	32 (5.7)
T stage			
T1	48 (17.1)	57 (20.2)	105 (18.7)
T2	161 (57.3)	144 (51.1)	305 (54.2)

(continued on following page)

TABLE 1. RTOG 0521: Pretreatment Characteristics (continued)

Characteristic	No. (%)		
	AS + RT (n = 281)	AS + RT + CT (n = 282)	Total (N = 563)
T3	67 (23.8)	76 (27.0)	143 (25.4)
T4	5 (1.8)	5 (1.8)	10 (1.8)
N stage pathologic			
pN0	100 (35.6)	85 (30.2)	185 (32.9)
pNX (no regional node sampling)	181 (64.4)	196 (69.8)	377 (67.1)
N stage clinical			
N0	279 (99.3)	279 (98.9)	558 (99.1)
NX	2 (0.7)	3 (1.1)	5 (0.9)
M stage			
M0	281 (100.0)	282 (100.0)	563 (100.0)

Abbreviations: AS, androgen suppression; CT, chemotherapy; PSA, prostate-specific antigen; Q, quartile; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

12.7 years) for the AS + RT + CT arm. The HR was 0.69 (95% CI, 0.52 to 0.93). The cumulative probabilities of DM at 6 years were 14.1% (95% CI, 10.2% to 18.7%) and 9.3% (95% CI, 5.9% to 13.6%) in the two arms, and the HR of treatment was 0.58 (95% CI, 0.34 to 0.98; $P = 0.04$). PSA failure-free rates were not significantly different in the two arms at 5 years: 74.9% (95% CI, 69.0% to 79.8%) and 79.5% (95% CI, 73.4% to 84.4%) in AS + RT and AS + RT + CT arms, respectively ($P = .12$).

Tolerability

There were no unexpected toxicity signals during the conduct of this trial. Regarding the worst AEs experienced that were definitely, probably, or possibly related to treatment, 53.4%, 20.6%, and 1.4% of patients experienced grade 2, 3, and 4 AEs as the worst AEs in the AS + RT arm, respectively, and 28.7%, 37.9%, 25.9%, and 0.7% of patients experienced grade 2, 3, 4, and 5 AEs as the worst AEs in the AS + RT + CT arm, respectively. The difference between the two arms was primarily related to greater hematologic toxicity in the AS + RT + CT arm, as expected. Rates of GI and genitourinary AEs were not significantly different between the two arms. The rates of worst hematologic AEs definitely, probably, or possibly related to treatment were as follows: in the AS + RT arm, 8.5%, 3.2%, and 1.8% of patients experienced grade 1, 2, and 3 hematologic AEs, respectively, and no patients experienced grade 4 or 5 hematologic AEs; in the AS + RT + CT arm, 13.1%, 12.1%, 22.0%, 22.3%, and 0% of patients experienced grade 1, 2, 3, 4, and 5 hematologic AEs, respectively. The difference between the rates of grade 3 or greater hematologic toxicities was significant ($P < .001$). The two grade 5 AEs were reported to be possibly or probably related to acute respiratory distress syndrome and multiorgan failure, respectively.

DISCUSSION

This phase III clinical trial was designed to test the hypothesis that docetaxel CT, known to improve OS for men with metastatic castration-sensitive prostate cancer, could improve OS among men with high-risk localized prostate cancer when used in an adjuvant fashion after standard RT and AS. An improvement in OS was observed with adjuvant CT in this setting. The CT was generally well tolerated. In addition, the cumulative incidence of DM was reduced, and there were improvements in DFS, although not DSS, using blinded central review of cause of death. The NRG Oncology RTOG 0521 study followed a previous adjuvant CT study, RTOG 9902, which was terminated early because of thromboembolic toxicity associated with estramustine.[16,17] Lack of unanticipated toxicity and better-tolerated CT led to timely completion of this protocol.

RT doses were standard at the time of study accrual.[18] Although the radiation doses in NRG Oncology RTOG 0521 (72 to 75.6 Gy) were modestly lower than contemporary RT doses (eg, 79.2 Gy), the hypothesized benefit of docetaxel was to be primarily in the reduction of DM. The study findings showed that the 6-year rate of DM was significantly lower at 9.1% in the AS + RT + CT arm versus 14.0% in the AS + RT arm ($P = .044$).

Since NRG Oncology RTOG 0521 was designed, there have been other studies examining the role of docetaxel CT earlier in the clinical course of prostate cancer. GETUG-12 (Groupe d'Étude des Tumeurs Urogénitales)[19] randomly assigned 413 patients with high-risk clinically localized disease treated with local therapy to AS (36 months) plus four cycles of adjuvant CT with docetaxel and estramustine or AS alone. Although the addition of CT increased relapse-free survival, a recent update of GETUG-12 demonstrated no statistically significant improvement in a prespecified

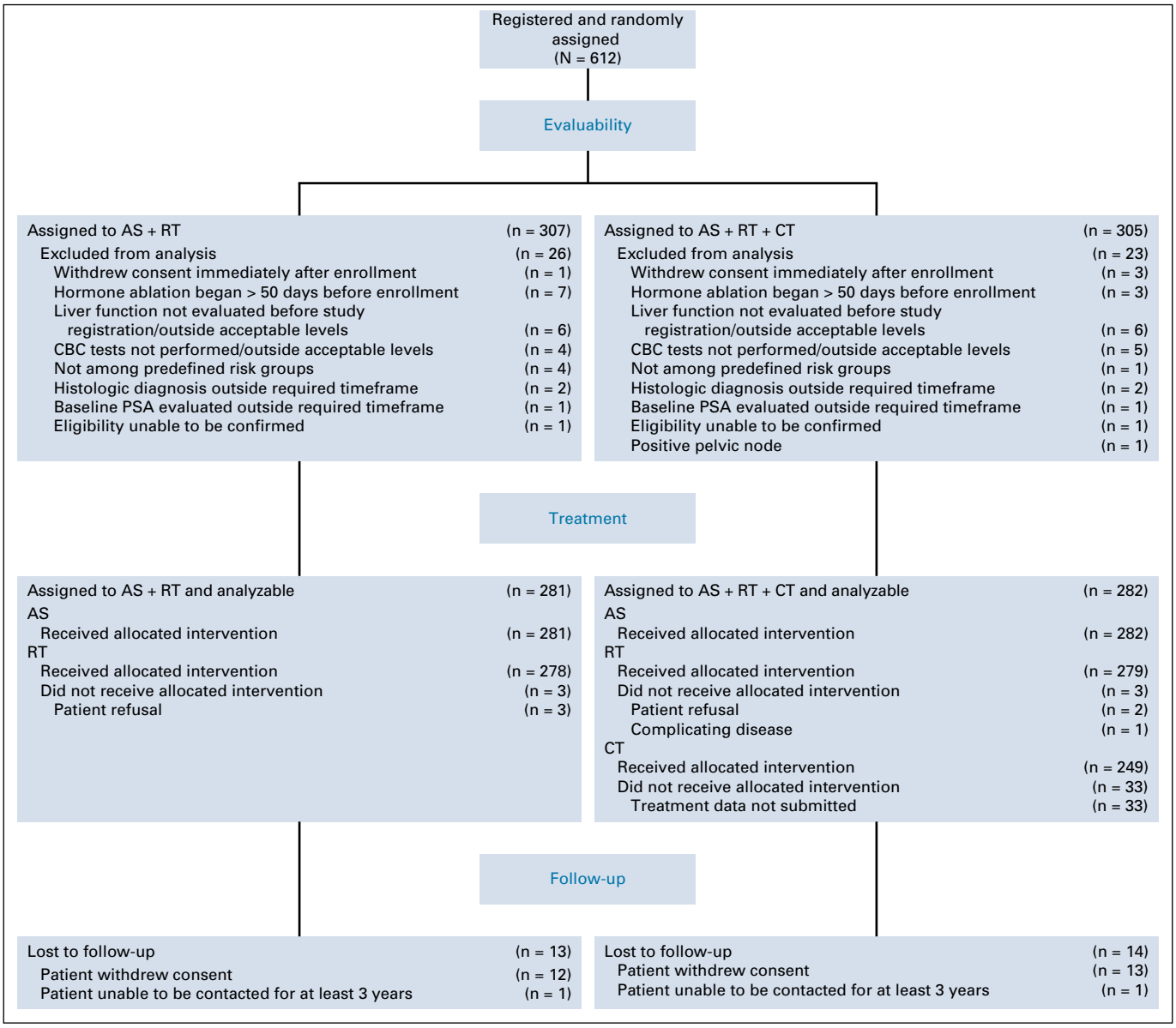

FIG 1. CONSORT flow diagram. AS, androgen suppression; CBC, complete blood count; CT, chemotherapy; PSA, prostate-specific antigen; RT, radiotherapy.

end point of metastasis-free survival.[20] In addition, the Scandinavian trial SPCG-13 (Scandinavian Prostate Cancer Group) demonstrated no benefit in biochemical DFS in a cohort of 378 men with intermediate- or high-risk disease randomly assigned to AS (12 months) plus adjuvant CT with six cycles of docetaxel CT versus AS alone.[21] Similarly, the SPCG-12 study showed no benefit in biochemical DFS for 459 high-risk patients randomly assigned to radical prostatectomy plus adjuvant CT with six cycles of docetaxel chemotherapy versus radical prostatectomy alone.[22] The discordance in results between RTOG 0521, which showed benefits in OS, DM, and DFS, and GETUG-12, SPCG-13, and SPCG-12 may stem from differences in patient populations among the studies. The RTOG 0521 cohort included patients with more aggressive disease; 84% of patients in RTOG 0521 had a Gleason score 8 to 10 disease, whereas a majority of patients in GETUG-12, SPCG-13, and SPCG-12 had a Gleason score less than or equal to 7 disease. These differences underscore the need to select high-risk patients with the most aggressive disease when considering treatment with adjuvant docetaxel.

Docetaxel-based CT has been used in castration-sensitive metastatic prostate cancer. In the CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) study,[7] 790 patients were randomly assigned to AS or AS + CT with six cycles of docetaxel. Median OS was improved with

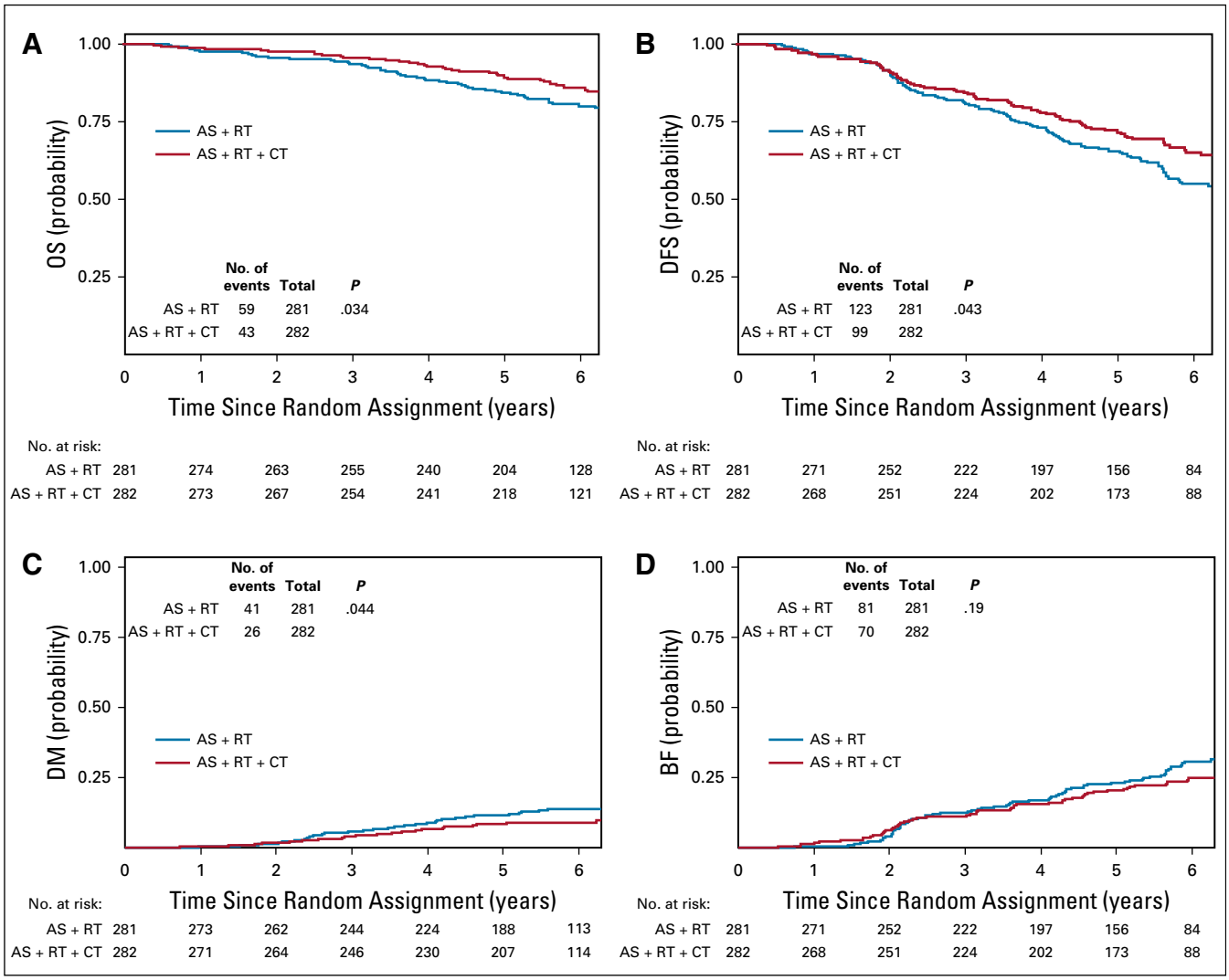

FIG 2. RTOG (Radiation Therapy Oncology Group) 0521 Kaplan-Meier curves for (A) overall survival (OS), (B) disease-free survival (DFS), (C) distant metastasis (DM), and (D) biochemical failure (BF). *P* values are from stratified log-rank tests. AS, androgen suppression; CT, chemotherapy; RT, radiotherapy.

CT from 44 to 58 months. The survival benefit seemed to be restricted to those with higher-volume metastatic disease. In addition, the GETUG-15 study, with a smaller sample size than CHAARTED, did not show an OS benefit,[23] although an update[24] showed a trend toward OS benefit among the subset with high-volume disease as defined in CHAARTED. In the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial, which included patients with metastatic and nonmetastatic disease, docetaxel improved survival for men with castration-sensitive prostate cancer, with the primary benefit seen in patients with metastatic disease.[8] Taken together, these studies suggest that there is a positive effect of docetaxel CT in subsets of men with castration-sensitive prostate cancer but reinforce the need for improved patient selection to better define these subsets. Studies in both nonmetastatic and metastatic castration-sensitive disease suggest a greater benefit of docetaxel in the subsets of patients with more aggressive disease features. In this

TABLE 2. RTOG 0521: Centrally Reviewed Cause of Death

	No. (%)	
Cause of Death	**AS + RT (n = 59)**	**AS + RT + CT (n = 43)**
Cancer under study	23 (39)	16 (37)
Protocol treatment	0 (0)	2 (5)
Other cause	24 (41)	16 (37)
Second primary	12 (20)	5 (12)
Unknown	0 (0)	4 (9)

Abbreviations: AS, androgen suppression; CT, chemotherapy; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

TABLE 3. RTOG 0521: Summary of Efficacy Results, ITT Analysis

End Point (years)	% (95% CI) AS + RT (n = 281)	% (95% CI) AS + RT + CT (n = 282)	HR (95% CI)	*P**
OS			0.69 (0.49 to 0.97)†	.034
4	88.7 (84.3 to 91.9)	93.3 (89.6 to 95.7)		
6	80.6 (75.2 to 85.0)	86.0 (80.8 to 89.9)		
Median	Not reached	Not reached		
DFS			0.76 (0.58 to 0.99)	.043
6	54.9 (48.2 to 61.0)	65.4 (58.9 to 71.2)		
Median	6.9	8.5		
DSS			0.65 (0.34 to 1.24)	.18
6	92.0 (87.7 to 94.9)	93.4 (89.1 to 96.0)		
Median	Not reached	Not reached		
DM			0.60 (0.37 to 0.99)	.044
6	14.0 (10.1 to 18.6)	9.1 (6.0 to 13.0)		
Freedom from PSA failure			0.81 (0.59 to 1.12)	.19
5	75.1 (69.2 to 80.0)	78.5 (72.9 to 83.1)		

Abbreviations: AS, androgen suppression; CT, chemotherapy; DFS, disease-free survival; DM, distant metastasis; DSS, disease-specific survival; HR, hazard ratio; ITT, intent to treat; OS, overall survival; PSA, prostate-specific antigen; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

*From stratified log-rank tests. One-sided *P* values for OS per study design; two-sided *P* values for the rest.

†90% CI for HR of OS.

study, PSA failure rates were not significantly different between the arms. It is possible that docetaxel, when used in combination with long-term AS + RT, may be focused on the androgen-insensitive clones that produce less PSA. This underlines the need for future investigation of the molecular profiles of patient samples from clinical trials to identify the biologic drivers of tumors in patients who benefit from docetaxel-based CT.

TABLE 4. RTOG 0521: Summary of Efficacy Results, Per-Protocol Analysis

End Point (years)	% (95% CI) AS + RT (n = 278)	% (95% CI) AS + RT + CT (n = 225)	HR (95% CI)	*P**
OS			0.59 (0.41 to 0.86)†	.009
4	88.6 (84.2 to 91.9)	94.1 (90.0 to 96.5)		
6	80.5 (75.0 to 84.9)	87.6 (81.9 to 91.6)		
Median	Not reached	Not reached		
DFS			0.69 (0.52 to 0.93)	.013
6	54.5 (47.8 to 60.7)	67.5 (60.3 to 73.7)		
Median	6.9 years	8.5 years		
DSS			0.58 (0.28 to 1.18)	.13
6	92.0 (87.6 to 94.8)	94.0 (89.3 to 96.7)		
Median	Not reached	Not reached		
DM			0.58 (0.34 to 0.98)	.04
6	14.1 (10.2 to 18.7)	9.3 (5.9 to 13.6)		
Freedom from PSA failure			0.76 (0.54 to 1.08)	.12
5	74.9 (69.0 to 79.8)	79.5 (73.4 to 84.4)		

Abbreviations: AS, androgen suppression; CT, chemotherapy; DFS, disease-free survival; DM, distant metastasis; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

*From stratified log-rank tests. One-sided *P* values for OS; two-sided *P* values for the rest.

†90% CI for HR of OS.

NRG Oncology RTOG 0521 was designed to detect an improvement in OS at 4 years. This early time point was derived from previous trials performed by RTOG in consideration of the practical issues related to trial accrual and the long natural history. Accordingly, a one-sided hypothesis was proposed, and the trial was designed with a one-sided *P* value along with a strong power of 90% to detect a positive effect with relative certainty. Although the magnitude of reduction in hazard (HR, 0.69) was not as large as the prestated HR goal of 0.49, in part because of higher-than-expected survival in the control group, the study was positive as hypothesized, and the clinically significant reduction in deaths is summarized in Table 2. There was not only improvement in OS but also improvement in DFS and reduction in 6-year rate of DM (Table 3). Sensitivity analysis of the patients treated per protocol (Table 4) confirmed the benefit noted in OS (HR, 0.59). Improvement in DFS and reduction in 6-year rate of DM were also confirmed with this analysis. Longer follow-up may better define the results, although competing risks are always a concern. Improved methods of risk stratification, including the emerging use of molecular profiling, may help to better identify patients who will benefit from intensification of treatment with CT in the future.

Although there are multiple management options, on the basis of the results of this trial, adjuvant CT with docetaxel can be reasonably discussed with selected men with high-risk localized prostate cancer who are fit for CT.

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

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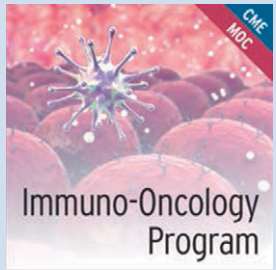

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Effect of Chemotherapy With Docetaxel With Androgen Suppression and Radiotherapy for Localized High-Risk Prostate Cancer: The Randomized Phase III NRG Oncology RTOG 0521 Trial

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APPENDIX

TABLE A1. RTOG 0521: Summary of Efficacy Results, ITT Analysis (unstratified)

	% (95% CI)			
End Point (years)	**AS + RT (n = 281)**	**AS + RT + CT (n = 282)**	**HR (95% CI)**	***P****
OS			0.70 (0.51 to 0.98)†	.039
4	88.7 (84.3 to 91.9)	93.3 (89.6 to 95.7)		
6	80.6 (75.2 to 85.0)	86.0 (80.8 to 89.9)		
Median	Not reached	Not reached		
DFS			0.77 (0.59 to 1.00)	.049
6	54.9 (48.2 to 61.0)	65.4 (58.9 to 71.2)		
Median	6.9 years	8.5 years		
DSS			0.67 (0.38 to 1.00)	.21
6	92.0 (87.7 to 94.9)	93.4 (89.1 to 96.0)		
Median	Not reached	Not reached		
DM			0.61 (0.38 to 1.00)	.049
6	14.0 (10.1 to 18.6)	9.1 (6.0 to 13.0)		
Freedom from PSA failure			0.82 (0.59 to 1.13)	.22
5	75.1 (69.2 to 80.0)	78.5 (72.9 to 83.1)		

Abbreviations: AS, androgen suppression; CT, chemotherapy; DFS, disease-free survival; DM, distant metastasis; DSS, disease-specific survival; HR, hazard ratio; ITT, intent to treat; OS, overall survival; PSA, prostate-specific antigen; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

*From stratified log-rank tests. One-sided *P* values for OS; two-sided *P* values for the rest.

†90% CI for HR of OS.

TABLE A2. RTOG 0521: Summary of Efficacy Results, Per-Protocol Analysis (unstratified)

	% (95% CI)			
End Point (years)	**AS + RT (n = 278)**	**AS + RT + CT (n = 225)**	**HR (95% CI)**	***P****
OS			0.60 (0.42 to 0.87)†	.011
4	88.6 (84.2 to 91.9)	94.1 (90.0 to 96.5)		
6	80.5 (75.0 to 84.9)	87.6 (81.9 to 91.6)		
Median	Not reached	Not reached		
DFS			0.70 (0.52 to 0.93)	.014
6	54.5 (47.8 to 60.7)	67.5 (60.3 to 73.7)		
Median	6.9 years	8.5 years		
DSS			0.60 (0.30 to 1.20)	.15
6	92.0 (87.6 to 94.8)	94.0 (89.3 to 96.7)		
Median	Not reached	Not reached		
DM			0.57 (0.33 to 0.97)	.04
6	14.1 (10.2 to 18.7)	9.3 (5.9 to 13.6)		
Freedom from PSA failure			0.76 (0.54 to 1.08)	.13
5	74.9 (69.0 to 79.8)	79.5 (73.4 to 84.4)		

Abbreviations: AS, androgen suppression; CT, chemotherapy; DFS, disease-free survival; DM, distant metastasis; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

*From stratified log-rank tests. One-sided *P* values for OS; two-sided *P* values for the rest.

†90% CI for HR of OS.

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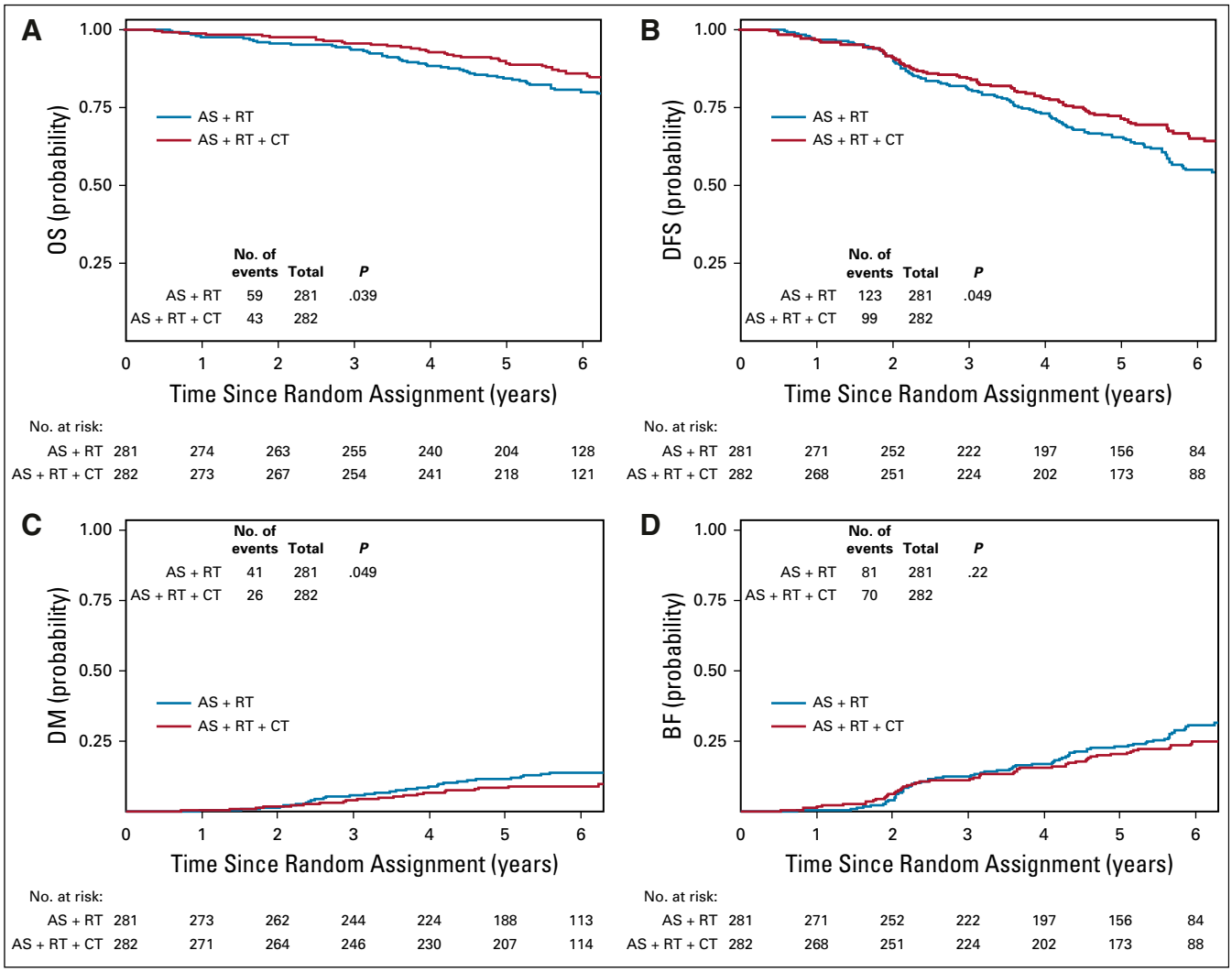

FIG A1. RTOG (Radiation Therapy Oncology Group) 0521 Kaplan-Meier curves for (A) overall survival (OS), (B) disease-free survival (DFS), (C) distant metastasis (DM), and (D) biochemical failure (BF). *P* values are from unstratified log-rank tests. AS, androgen suppression; CT, chemotherapy; RT, radiotherapy.