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Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer

Christopher U. Jones, M.D., Daniel Hunt, Ph.D., David G. McGowan, M.B., Ch.B., Mahul B. Amin, M.D., Michael P. Chetner, M.D., Deborah W. Bruner, R.N., Ph.D., Mark H. Leibenhaut, M.D., Siraj M. Husain, M.D., Marvin Rotman, M.D., Luis Souhami, M.D., Howard M. Sandler, M.D., and William U. Shipley, M.D.

ABSTRACT

BACKGROUND

It is not known whether short-term androgen-deprivation therapy (ADT) before and during radiotherapy improves cancer control and overall survival among patients with early, localized prostate adenocarcinoma.

METHODS

From 1994 through 2001, we randomly assigned 1979 eligible patients with stage T1b, T1c, T2a, or T2b prostate adenocarcinoma and a prostate-specific antigen (PSA) level of 20 ng per milliliter or less to radiotherapy alone (992 patients) or radiotherapy with 4 months of total androgen suppression starting 2 months before radiotherapy (radiotherapy plus short-term ADT, 987 patients). The primary end point was overall survival. Secondary end points included disease-specific mortality, distant metastases, biochemical failure (an increasing level of PSA), and the rate of positive findings on repeat prostate biopsy at 2 years.

RESULTS

The median follow-up period was 9.1 years. The 10-year rate of overall survival was 62% among patients receiving radiotherapy plus short-term ADT (the combined-therapy group), as compared with 57% among patients receiving radiotherapy alone (hazard ratio for death with radiotherapy alone, 1.17; P=0.03). The addition of short-term ADT was associated with a decrease in the 10-year disease-specific mortality from 8% to 4% (hazard ratio for radiotherapy alone, 1.87; P=0.001). Biochemical failure, distant metastases, and the rate of positive findings on repeat prostate biopsy at 2 years were significantly improved with radiotherapy plus short-term ADT. Acute and late radiation-induced toxic effects were similar in the two groups. The incidence of grade 3 or higher hormone-related toxic effects was less than 5%. Reanalysis according to risk showed reductions in overall and disease-specific mortality primarily among intermediate-risk patients, with no significant reductions among low-risk patients.

CONCLUSIONS

Among patients with stage T1b, T1c, T2a, or T2b prostate adenocarcinoma and a PSA level of 20 ng per milliliter or less, the use of short-term ADT for 4 months before and during radiotherapy was associated with significantly decreased disease-specific mortality and increased overall survival. According to post hoc risk analysis, the benefit was mainly seen in intermediate-risk, but not low-risk, men. (Funded by the National Cancer Institute; RTOG 94-08 ClinicalTrials.gov number, NCT00002597.)

From Radiological Associates of Sacramento, Sacramento, CA (C.U.J., M.H.L.); the Radiation Therapy Oncology Group Statistical Center (D.H.) and the School of Nursing, University of Pennsylvania, (D.W.B.) — both in Philadelphia; the Department of Radiation Oncology, Cross Cancer Institute, Edmonton (D.G.M.); the Division of Urology, Department of Surgery, University of Alberta, Edmonton (M.P.C.); and the Department of Radiation Oncology, Tom Baker Cancer Centre, Calgary (S.M.H.) — all in Alberta, Canada; the Department of Pathology and Laboratory Medicine (M.B.A.) and the Department of Radiation Oncology, Samuel Oschin Comprehensive Cancer Institute, Cedars–Sinai Medical Center, Los Angeles (H.M.S.); the Department of Radiation Oncology, State University of New York Health Science Center at Brooklyn, Brooklyn (M.R.); the Department of Radiation Oncology, McGill University, Montreal (L.S.); and the Department of Radiation Oncology, Massachusetts General Hospital, Boston (W.U.S.). Address reprint requests to Dr. Jones at Radiological Associates of Sacramento, 1500 Expo Pkwy., Sacramento, CA 95816, or at jonesc@radiological.com.

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In the 1980s, advances in both surgery and radiotherapy for clinically localized prostate cancer led to their acceptance as successful treatments, with considerable reductions in harmful side effects as compared with earlier treatments.[1] In the 1990s, reversible androgen suppression with the use of luteinizing hormone–releasing hormone analogues and oral antiandrogen agents was shown to induce apoptotic regression in androgen-responsive cancers,[2] potentially improving the prospects of local control and the duration of survival free of metastatic disease. Among patients with locally advanced disease, phase 3 clinical trials[3,4] showed that when added to radiotherapy, long-term treatment with these agents (≥2 years) improved overall survival but also increased toxic effects, including erectile dysfunction and myocardial infarction.[5] Short-term androgen-deprivation therapy (ADT) could potentially mitigate these toxic effects. A Radiation Therapy Oncology Group (RTOG) phase 3 clinical trial, reported in 1994, showed that short-term ADT administered for 4 months before and during radiation therapy significantly improved local control and disease-free survival among patients with bulky stage T2c to T4 tumors.[6,7] Other trials have also shown benefits from this approach.[8,9]

The introduction of prostate-specific antigen (PSA) testing has resulted in increased diagnoses of early-stage disease.[1,10] Less is known about the role of short-term ADT in men receiving radiotherapy for these cancers. Accordingly, in 1994, the RTOG opened a large, randomized trial, RTOG 94-08, to evaluate whether adding short-term ADT to radiotherapy would improve survival among patients with nonbulky localized prostate adenocarcinomas and an initial PSA level of 20 ng per milliliter or less.

Methods

Patients

Patients with histologically confirmed prostate adenocarcinoma, stage T1b, T1c, T2a, or T2b (according to the 1992 classification of the American Joint Committee on Cancer[11]), and a PSA level of 20 ng per milliliter or less were eligible for this international phase 3 study. Pretreatment evaluation included a digital rectal examination and bone scan. The regional lymph nodes were evaluated surgically by means of lymph-node sampling or clinically by means of lymphangiography or pelvic computed tomography. The Gleason score (the sum of the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 indicating the most aggressive pattern) was determined, and tumors were also classified as well differentiated, moderately differentiated, or poorly differentiated. Eligibility criteria included a Karnofsky performance score of 70 or more (on a scale of 0 to 100, with higher scores indicating better performance status), an alanine aminotransferase level that was no more than twice the upper limit of the normal range, no evidence of regional lymph-node involvement or distant metastatic disease, and no previous chemotherapy, radiotherapy, hormonal therapy, cryosurgery, or definitive surgery for prostate cancer. Patients with previous basal-cell or squamous-cell skin carcinomas who had been disease-free for 2 years or more before study entry, and patients with invasive cancers who had been disease-free for 5 years or more, were eligible if their participation was approved by the study cochairs. The institutional review boards of the participating institutions approved the study protocol, and all patients provided written informed consent. The protocol is available with the full text of this article at NEJM.org. The National Cancer Institute sponsored the study. The drugs were purchased from vendors. No commercial support was provided for this study.

Study Design

After stratification according to PSA level (<4 vs. 4 to 20 ng per milliliter), tumor grade (well differentiated, moderately differentiated, or poorly differentiated), and surgical versus clinical documentation of negative regional nodal status, patients were randomly assigned to receive either radiotherapy plus short-term ADT or radiotherapy alone, according to the permuted-block randomization method described by Zelen.[12] The RTOG carried out this trial and was responsible for data collection, statistical analysis, study design, and preparation of the manuscript.

Treatment

All patients began treatment within 21 days after randomization. Radiotherapy, administered in daily 1.8-Gy fractions prescribed to the isocenter of the treatment volume, consisted of 46.8 Gy delivered to the pelvis (prostate and regional lymph nodes), followed by 19.8 Gy to the prostate, for a

total dose of 66.6 Gy. Treatment of the regional lymph nodes was omitted in patients with negative lymph-node dissections or with a PSA level of less than 10 ng per milliliter and a Gleason score of less than 6. The study cochairs reviewed the simulation and portal films for each treatment field.

Patients assigned to short-term ADT received flutamide at a dose of 250 mg orally three times a day and either monthly subcutaneous goserelin at a dose of 3.6 mg or intramuscular leuprolide at a dose of 7.5 mg for 4 months. Radiotherapy commenced after 2 months of androgen deprivation. Flutamide was discontinued if the level of alanine aminotransferase increased to more than twice the upper limit of the normal range.

ASSESSMENTS

At the beginning and end of radiotherapy, assessments included a history taking and physical examination, performance status, complete blood count, and levels of alkaline phosphatase, alanine aminotransferase, PSA, and serum testosterone. Follow-up visits occurred at intervals of 3 months during the first year, 4 months during the second year, 6 months in years 3 through 5, and then annually. PSA values were obtained at each visit, along with the serum testosterone level and complete blood count during the first 2 years and the alkaline phosphatase level yearly. Repeat prostate biopsy 2 years after treatment was planned for patients without medical contraindications or evidence of local or distant disease and for patients who had not undergone orchiectomy or received hormonal treatment. Acute and late toxic effects were assessed with the use of the RTOG toxicity scales.[13] At each visit during the first 2 years, the first 793 patients enrolled in the study completed the Sexual Adjustment Questionnaire.[14] Erectile dysfunction was assessed with the question, "When sexually excited, are you able to get an erection?" The five levels of response were: always or almost always, sometimes, almost never or never, did not try, and no answer.

END POINTS

All end points were measured from the date of randomization. Overall survival, the primary end point, was calculated at the date of death from any cause. Secondary end points included disease-specific mortality, distant metastases, biochemical failure (an increasing level of PSA), and the rate of positive findings on repeat prostate biopsy at 2 years. Disease-specific mortality included all deaths from prostate cancer or treatment complications, as well as deaths from unknown causes in patients with either active cancer or a previously documented relapse. The study cochairs reviewed the reported causes of death, and complicated cases were reviewed by committee. The scoring of distant metastasis required documentation of metastatic disease. The Phoenix Consensus Conference definition[15] (an increase in the PSA level of >2 ng per milliliter above the nadir) was used to define biochemical failure.

STATISTICAL ANALYSIS

On the basis of previous studies, we expected patients treated with radiotherapy alone to have an 8-year overall survival rate of 60%.[16,17] Adding short-term ADT was projected to increase this rate to at least 67%.[7,18,19] Accordingly, the trial was designed to provide 90% power to detect a 7-percentage-point absolute difference in the 8-year survival rate, with the use of a one-sided log-rank test at the 0.025 significance level,[20] requiring 1980 patients and 716 deaths for definitive analysis. We conducted three planned interim analyses with a significance level of $P<0.001$ as the criterion for early stopping, which was not met in any of these analyses.

The primary end point, overall survival, was estimated by means of the Kaplan–Meier approach,[21] and in the multivariate analyses, hazard ratios with 95% confidence intervals were estimated with the use of the Cox regression model.[22] The end points of disease-specific mortality, distant metastases, and biochemical failure were estimated by means of the cumulative incidence function[23] to account for competing risks. The Fine–Gray model was used to estimate hazard ratios for competing risks.[24] The chi-square test was used to test differences in patients' responses to the Sexual Adjustment Questionnaire.

Three subgroup analyses of treatment efficacy were conducted. One was planned: a comparison of treatments within racial groups (white and black). Two were unplanned; one compared treatments within three risk categories defined according to baseline characteristics, and the other evaluated treatments within two age groups (≤70 years and >70 years). The likelihood-ratio test was used to assess whether there was a statistically significant difference in the magnitude of treatment benefit (i.e., interaction effect) according to patient subgroups.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between October 1994 and April 2001, a total of 2028 patients from 212 centers in the United States and Canada were randomly assigned to radiotherapy plus short-term ADT (the combined-therapy group) or radiotherapy alone (Fig. 1). Forty-nine patients were ineligible, withdrew consent, or were lacking pretreatment data, leaving 1979 eligible patients who were available for evaluation (992 in the radiotherapy-alone group and 987 in the combined-therapy group). The treatment groups were balanced, with no significant differences in demographic or tumor-related characteristics (Table 1).

COMPLIANCE

Compliance with the radiotherapy protocol was assessed in a random sample of 61% of the patients in the combined-therapy group and 64% in the radiotherapy-alone group. Compliance was balanced between the two treatment groups; 65% of the patients were treated per protocol, 19% were treated with acceptable variations, and 5% were treated with unacceptable variations. Data were incomplete in 1% of the patients because of death or progressive disease or because the patient declined radiotherapy, and 9% were not available for evaluation. Compliance with hormonal therapy was reviewed in all randomly assigned patients; the therapy was delivered per protocol in 78% of the patients, with acceptable variation in 17% and unacceptable deviation in 4%. Data were incomplete or were not available for evaluation in 1% of these patients.

OUTCOMES

The median follow-up for surviving patients was 9.1 years (range, 0.01 to 13.5) in the group of patients who received radiotherapy plus short-term ADT and 9.2 years (range, 0.2 to 14.1) in the group of patients who received radiotherapy alone.

The 10-year rate of overall survival (Table 2 and Fig. 2A) was 57% in the radiotherapy-alone group and 62% in the combined-therapy group (hazard ratio for death with radiotherapy alone, 1.17; 95% confidence interval [CI], 1.01 to 1.35; P=0.03). The 10-year disease-specific mortality (Table 2 and Fig. 3A) was 8% in the radiotherapy-alone group and 4% in the combined-therapy group (hazard ratio, 1.87; 95% CI, 1.27 to 2.74; P=0.001). The 10-year rate of biochemical failure was 41% in the radiotherapy-alone group and 26% in the combined-therapy group (hazard ratio, 1.74; 95% CI, 1.48 to 2.04; P<0.001) (Table 2). The 10-year cumulative incidence of distant metastases was 8% in the radiotherapy-alone group and 6% in the combined-therapy group (hazard ratio, 1.45; 95% CI, 1.03 to 2.06; P=0.04) (Table 2). The 10-year cumulative incidence of death from causes other than prostate cancer was 37% in the radiotherapy-alone group and 34% in the combined-therapy group (P=0.56).

The multivariate analysis showed that a Gleason score of 7 or higher was a negative prognostic factor for overall survival, disease-specific mortality, distant metastases, and biochemical failure. Other identified negative prognostic factors were older age and nonwhite race or ethnic group for overall survival, clinical T2 lesions for disease-specific mortality, and a PSA level of 4 ng per milliliter or higher for biochemical failure.

A total of 439 patients (44%) in the combined-therapy group and 404 (41%) in the radiotherapy-alone group underwent a repeat prostate biopsy at 2 years (Table 2). The initial Gleason scores, PSA values, and rates of biochemical failure at 2 years were similar between the patients who underwent biopsy and those who did not undergo biopsy. Persistent cancer was detected in 20% of the biopsy specimens in the combined-therapy group as compared with 39% in the radiotherapy-alone group (P<0.001).

PATIENT-REPORTED ERECTILE DYSFUNCTION

At the pretreatment, 1-year, and 2-year evaluations, the Sexual Adjustment Questionnaire completion rates were 88%, 70%, and 27%, respectively. Before treatment, 48% of the respondents in the combined-therapy group and 54% of those in the radiotherapy-alone group reported that they were "always or almost always able to have an erection" (P=0.15); the respective rates at 1 year were 21% and 31% (P=0.004) (Table 3). Scores at 1 year, as compared with the pretreatment scores, were improved in 9% of the patients, the same in 33%, and worse in 58%, with no significant differences between the groups.

TOXIC EFFECTS

In the group treated with short-term ADT, the proportions of patients who had acute hepatic toxic effects (occurring up to 90 days after the start of radiotherapy) of grade 1, 2, 3, and 4 were 20%, 5%, 3%, and less than 1%, respectively; late hepatic toxic effects were seen in 4%, 1%, less than 1%, and

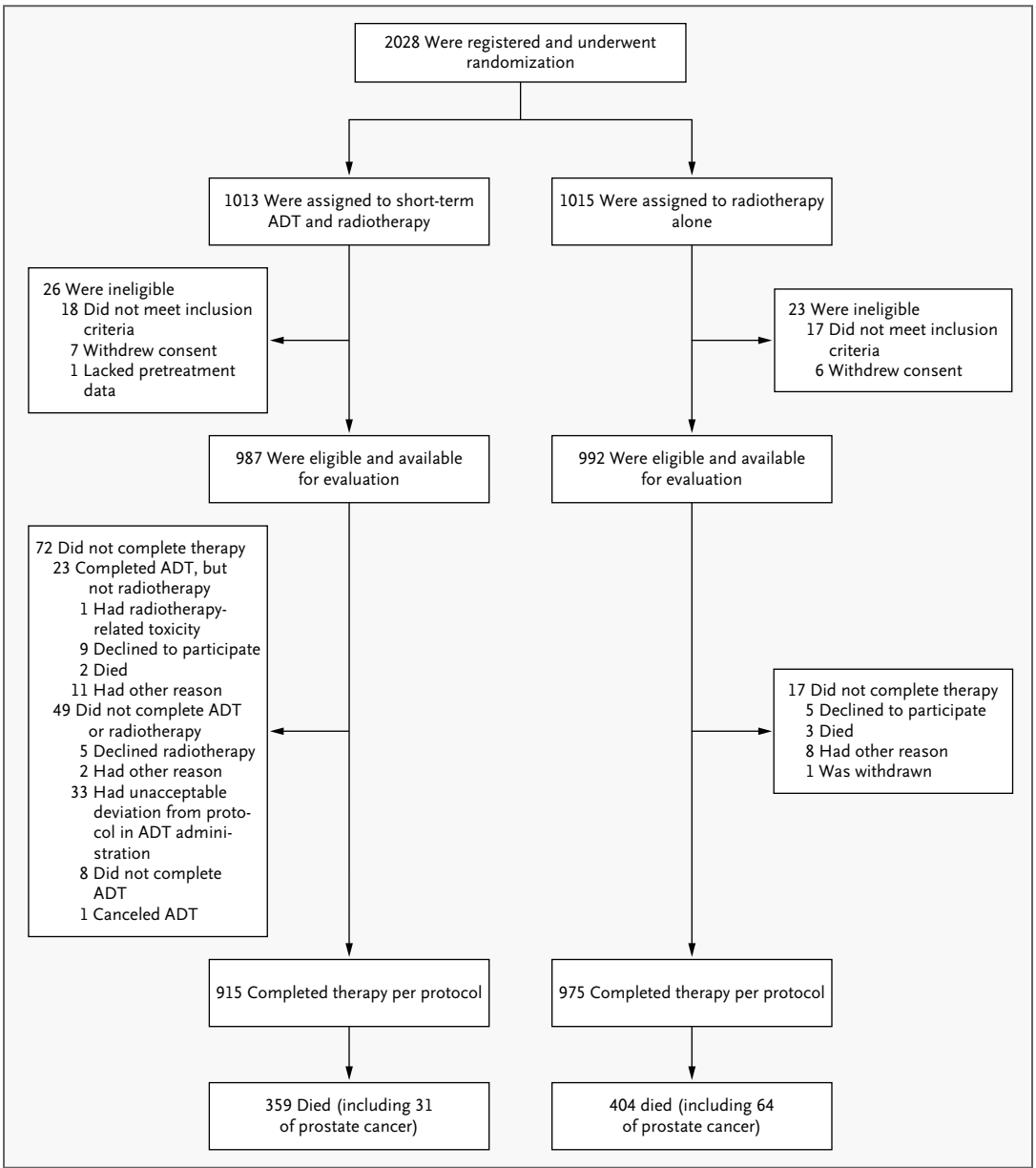

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.
ADT denotes androgen-deprivation therapy.

0 of these patients, respectively, as compared with 1%, 0, 0, and 0 in the radiotherapy-alone group. In both groups, the incidences of grade 3 or higher acute and late gastrointestinal toxic effects were 1% and 3%, respectively, with grade 5 toxic effects in three patients; two patients receiving radiotherapy alone died of obstruction of the colon, and one patient treated with radiotherapy plus short-term ADT died of colorectal bleeding. Acute grade 3 or higher genitourinary toxic effects were seen in 2% of patients in both groups, with late toxic effects in 8% of patients in the combined-therapy group and 6% of those in the radiotherapy-alone group.

During the 8 weeks of short-term ADT before the start of radiotherapy (in the combined-therapy group), 55% of patients had hot flashes, 3% had rash, and the incidences of hepatic toxic effects, decreased hemoglobin levels, and elevated white-cell counts were 16%, 16%, and 4%, respectively (all grade 1). Grade 1 cardiac toxic effects were observed in 11 patients (1%) within 2 years after treatment.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Short-Term ADT plus Radiotherapy (N=987)	Radiotherapy Alone (N=992)
Age — yr		
Median	70	71
Range	47–91	47–88
Karnofsky performance score — no. (%)		
90–100	905 (92)	920 (93)
70–80	82 (8)	72 (7)
Intercurrent disease — no. (%)		
Present	742 (75)	712 (72)
Absent	245 (25)	275 (28)
Unknown	0	5 (<1)
Tumor stage — no. (%)		
T1	488 (49)	476 (48)
T2	499 (51)	516 (52)
Nodal stage — no. (%)		
NX	944 (96)	954 (96)
N0	43 (4)	38 (4)
Differentiation — no. (%)		
Well differentiated	135 (14)	150 (15)
Moderately differentiated	625 (63)	620 (62)
Poorly differentiated or undifferentiated	227 (23)	222 (22)
Gleason score — no. (%)†		
2–6	623 (63)	592 (60)
7	252 (26)	286 (29)
8–10	93 (9)	87 (9)
Unknown	19 (2)	27 (3)
PSA — no. (%)		
<4 ng/ml	109 (11)	100 (10)
4–20 ng/ml	878 (89)	892 (90)
Race or ethnic group — no. (%)		
White	745 (75)	756 (76)
Black	198 (20)	197 (20)
Hispanic	27 (3)	26 (3)
Other or unknown	17 (2)	13 (1)
Risk subgroup — no. (%)‡		
Low risk	351 (36)	334 (34)
Intermediate risk	524 (53)	544 (55)
High risk	112 (11)	114 (11)

* Percentages may not sum to 100 because of rounding. ADT denotes androgen-deprivation therapy, and PSA prostate-specific antigen.

† The Gleason score is the sum of the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 indicating the most aggressive pattern.

‡ Low-risk disease was defined as a Gleason score of 6 or less, a PSA level of 10 ng per milliliter or less, and a clinical stage of T2a or lower; intermediate-risk disease as a Gleason score of 7 or a Gleason score of 6 or less with a PSA level of more than 10 and up to 20 ng per milliliter or clinical stage T2b; and high-risk disease as a Gleason score of 8 to 10.

Table 2. Antitumor Efficacy.*

End Point	Short-Term ADT plus Radiotherapy (N=987)		Radiotherapy Alone (N=992)		Hazard Ratio (95% CI)	P Value
	no. of patients	*% reaching end point*	*no. of patients*	*% reaching end point*		
Overall survival at 10 yr†						
All patients	987	62	992	57	1.17 (1.01–1.35)	0.03
Low risk	351	67	334	64	1.07 (0.83–1.39)	
Intermediate risk	524	61	544	54	1.23 (1.02–1.49)	0.03
High risk	112	53	114	51	1.16 (0.78–1.71)	
White	745	62	756	57	1.19 (1.01–1.41)	0.04
Black	198	61	197	55	1.15 (0.84–1.58)	
Age ≤70 yr	503	70	471	64	1.23 (0.98–1.54)	
Age >70 yr	484	54	521	50	1.11 (0.92–1.33)	
Disease-specific mortality at 10 yr†						
All patients		4		8	1.87 (1.27–2.74)	0.001
Low risk		3		1	0.63 (0.21–1.92)	
Intermediate risk		3		10	2.49 (1.50–4.11)	0.004
High risk		12		14	1.53 (0.72–3.26)	
White		4		8	2.33 (1.46–3.72)	<0.001
Black		5		7	1.27 (0.59–2.73)	
Age ≤70 yr		4		5	1.43 (0.79–2.57)	
Age >70 yr		5		10	2.19 (1.31–3.64)	0.004
Biochemical failure at 10 yr†‡						
All patients		26		41	1.74 (1.48–2.04)	<0.001
Low risk		22		32	1.53 (1.13–2.06)	<0.001
Intermediate risk		28		45	1.79 (1.45–2.21)	<0.001
High risk		31		53	1.98 (1.30–3.03)	0.002
White		29		42	1.62 (1.35–1.93)	<0.001
Black		19		40	2.27 (1.53–3.38)	<0.001
Age ≤70 yr		27		42	1.71 (1.37–2.13)	<0.001
Age >70 yr		25		41	1.78 (1.41–2.23)	<0.001
Distant metastases at 10 yr						
All patients		6		8	1.45 (1.03–2.06)	0.04
Repeat biopsy at 2 yr						
Not performed	548		588			
Performed	439		404			
Positive result§						
All patients	89/439	20	157/404	39		<0.001
Low risk	19/163	12	52/148	35		
Intermediate risk	56/229	24	85/205	41		
High risk	14/47	30	20/51	39		

* The Gleason score is the sum of the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 indicating the most aggressive pattern. Low-risk disease was defined as a Gleason score of 6 or less, a prostate-specific antigen (PSA) level of 10 ng per milliliter or less, and a clinical stage of T2a or lower; intermediate-risk disease, a Gleason score of 7 or a Gleason score of 6 or less with a PSA level of more than 10 and up to 20 ng per milliliter or a clinical stage T2b; and high-risk disease, a Gleason score of 8 to 10. The end points of disease-specific mortality, distant metastases, and biochemical failure were estimated by means of the cumulative incidence function to account for competing risks. ADT denotes androgen-deprivation therapy.

† For the end points of overall survival, disease-specific mortality, and biochemical failure at 10 years, the data reported for both age groups and all three categories of risk are derived from an unplanned post hoc analysis, whereas the data on race were derived from a planned post hoc analysis.

‡ The Phoenix definition of biochemical failure was used (an increase in the PSA level of >2 ng per milliliter above the nadir).

§ For numbers of patients, the first number is the number with a positive result, and the second number is the total number of patients in whom a biopsy was performed at 2 years.

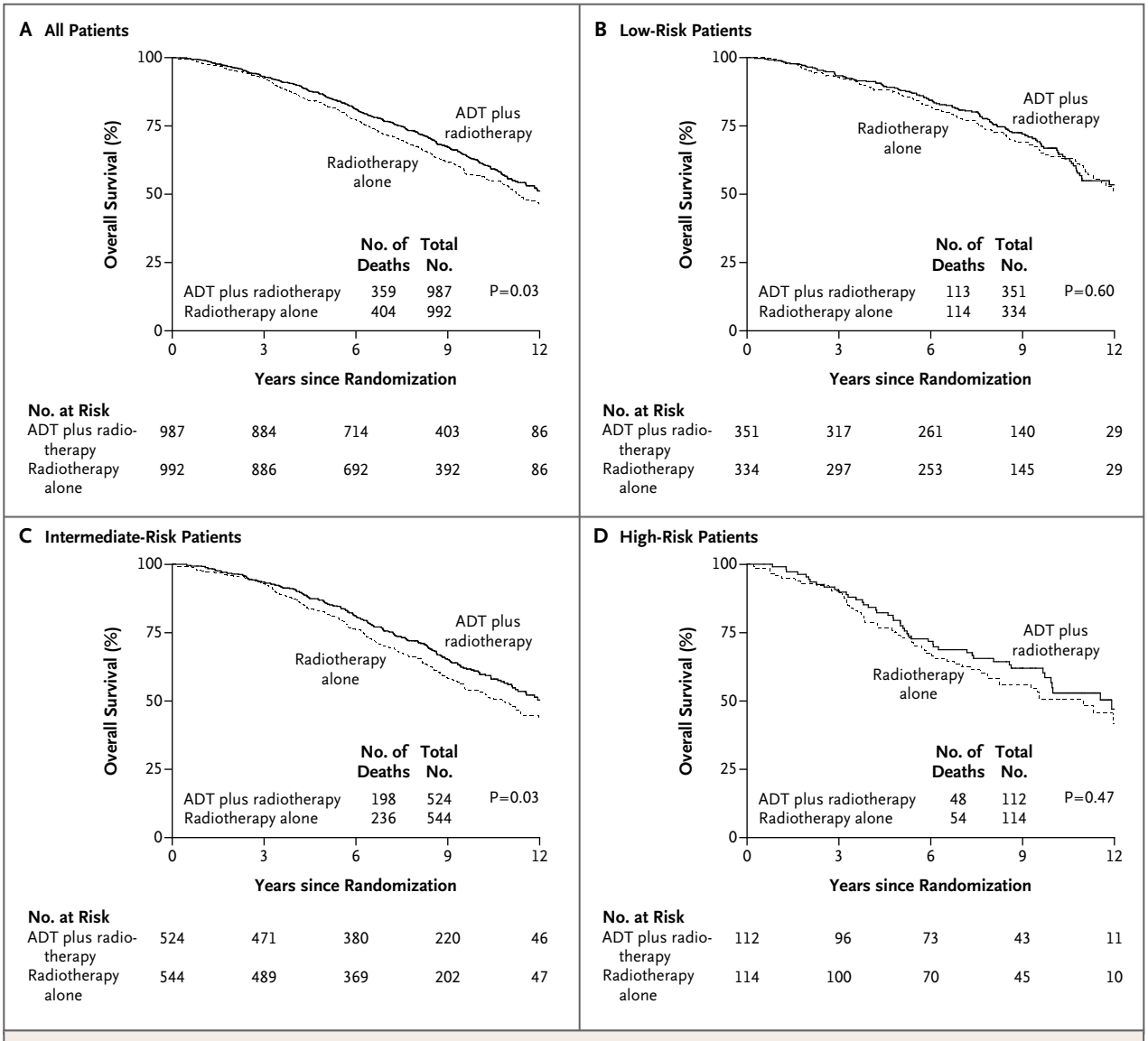

Figure 2. Kaplan–Meier Estimates of Overall Survival.

ADT denotes androgen-deprivation therapy. Panels B, C, and D show post hoc analyses.

SECONDARY ANALYSES

A subgroup analysis of treatment efficacy according to whether patients had low-, intermediate-, or high-risk disease, as defined in Table 1,[10] showed that the addition of short-term ADT to radiotherapy conferred the greatest clinical benefit in the intermediate-risk subgroup (Table 2 and Fig. 2C and 3C), with an increase in the 10-year rate of overall survival from 54 to 61% (hazard ratio for death with radiotherapy alone, 1.23; 95% CI, 1.02 to 1.49) and a reduction in the 10-year disease-specific mortality from 10 to 3% (hazard ratio, 2.49; 95% CI, 1.50 to 4.11). No significant benefit was shown in the low-risk subgroup (Table 2 and Fig. 2B and 3B), with an increase in the 10-year rate of overall survival from 64 to 67% (hazard ratio for death with radiotherapy alone, 1.07; 95% CI, 0.83 to 1.39) and an increase in the 10-year disease-specific mortality from 1 to 3% (hazard ratio, 0.63; 95% CI, 0.21 to 1.92). An interaction test revealed no significant interaction effect between treatment and risk category for overall survival (P=0.71) and only a weak suggestion of a differential benefit according to risk group for disease-specific mortality

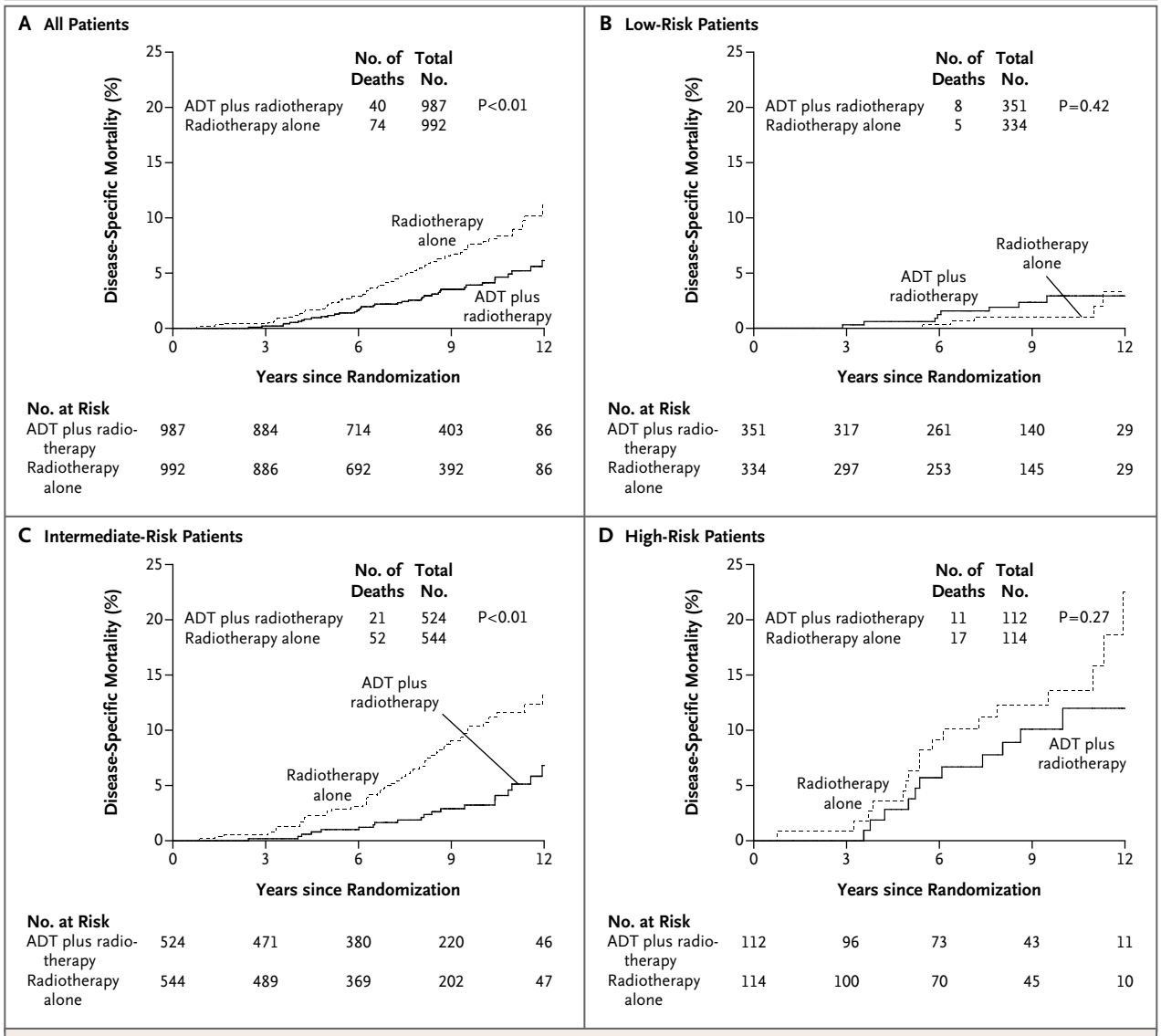

Figure 3. Cumulative-Incidence Estimate of Disease-Specific Mortality.

ADT denotes androgen-deprivation therapy. Panels B, C, and D show post hoc analyses.

(P=0.08). In all three risk subgroups, short-term ADT was associated with a significant reduction in biochemical failure (Table 2). The incidence of positive findings on repeat prostate biopsy in the low-risk, intermediate-risk, and high-risk subgroups was fairly uniform in the radiotherapy-alone group, at 35%, 41%, and 39%, respectively, as compared with 12%, 24%, and 30% in the combined-therapy group (Table 2).

Analyses of treatment efficacy separately in white and black patients and in patients who were 70 years of age or younger and those who were older than 70 years were also performed. The addition of short-term ADT was associated with a benefit in all these subgroups, with the 10-year rate of overall survival increasing from 57 to 62% among white patients (hazard ratio for death with radiotherapy alone, 1.19), 55 to 61% among black patients (hazard ratio, 1.15), 64 to 70% among patients who were 70 years of age or younger (hazard ratio, 1.23), and 50 to 54% among those older than 70 years of age (hazard ratio, 1.11), with no statistical evidence of a differential benefit between whites and blacks (interaction test,

Table 3. Effect of Short-Term ADT on Erectile Function, According to Responses to the Sexual Adjustment Questionnaire at Baseline and at 1 Year.*

Response	Short-Term ADT plus Radiotherapy	Radiotherapy Alone	P Value†
	number/total number (percent)		
At baseline			
Always or almost always	169/349 (48)	186/344 (54)	0.15
Sometimes	87/349 (25)	87/344 (25)	0.93
Almost never or never	54/349 (15)	44/344 (13)	0.33
Did not try	30/349 (9)	22/344 (6)	0.32
Not applicable or not answered	11/349 (3)	7/344 (2)	0.48
At 1 yr			
Always or almost always	59/284 (21)	85/274 (31)	0.004
Sometimes	66/284 (23)	62/274 (23)	0.95
Almost never or never	94/284 (33)	69/274 (25)	0.054
Did not try	58/284 (20)	55/274 (20)	1.00
Not applicable or not answered	13/284 (5)	4/274 (1)	0.04

* Responses were to the question, "When sexually excited, are you able to get an erection?" Percentages may not sum to 100 because of rounding. ADT denotes androgen-deprivation therapy.
† The chi-square test was used for the comparison of each response with the other categories.

P=0.79) or between age subgroups (P=0.47) (Table 2). Among black patients, the addition of short-term ADT to radiotherapy was associated with a decrease in the 10-year disease-specific mortality from 7 to 5% (hazard ratio with radiotherapy alone, 1.27) and a decrease in the 10-year rate of biochemical failure from 40 to 19% (hazard ratio, 2.27).

DISCUSSION

This phase 3 clinical trial evaluated whether the addition of short-term ADT to radiotherapy improved outcomes in patients who had early, localized prostate cancer and a PSA level of 20 ng per milliliter or less — the subgroup of patients with prostate cancer who were known to have the most favorable prognosis at the time the study was initiated. Because of the indolent nature of the disease, a median follow-up period of more than 9 years for surviving patients and vigilant PSA monitoring were required[1,19,24] to obtain meaningful results in a patient cohort in which most deaths were due to other causes (Fig. 1).

The study showed that the addition of short-term ADT to radiotherapy conferred a modest but significant increase in the 10-year rate of overall survival, from 57 to 62%. This increase was accompanied by a significant reduction in 10-year disease-specific mortality from 8% to 4% as well as reductions in the secondary end points of biochemical failure, distant metastases, and the rate of positive findings on repeat prostate biopsy at 2 years. The Gleason score was the only independent prognostic predictor for all end points measured. The lack of surgical staging for regional lymph nodes did not predict poor outcomes, validating the current practice of clinical staging in patients receiving radiotherapy.[10]

The efficacy gains were achieved with minimal temporary acute hepatic toxic effects and some decreased erectile function at 1 year, but with no increased risk of death from intercurrent disease, serious cardiovascular toxic effects, or acute or long-term gastrointestinal or genitourinary complications of radiotherapy. The rate of erectile dysfunction observed in this study is similar to that reported in previous studies that involved the use of similar doses of radiotherapy.[25,26]

Reanalysis of the data according to risk subgroups showed that the gains in overall survival and reductions in disease-specific mortality were mainly limited to men in the intermediate-risk subgroup, with a number needed to treat[27] of 14 based on the difference in overall survival seen at 10 years. Although the addition of short-term ADT

to radiotherapy also appeared to be beneficial in the high-risk patients, the persistent significant increase in 10-year disease-specific mortality provides support for observations from other clinical trials showing that more than 4 months of ADT is required for maximum benefit.[28,29]

Among men with low-risk disease, the addition of short-term ADT did not significantly increase the 10-year rate of overall survival or decrease the 10-year rate of disease-specific mortality but did significantly lower the incidence of biochemical failure and positive findings on repeat prostate biopsy at 2 years. It is conceivable that in patients with indolent disease, longer follow-up is required to show a benefit with respect to the disease-specific mortality and overall survival rates. However, short-term ADT is not without quality-of-life consequences, including hot flashes and higher rates of erectile dysfunction than with radiotherapy alone. Furthermore, erectile dysfunction may be less responsive to interventions after combined therapy than after radiotherapy alone.[30] In prospective studies, short-term ADT caused measurable muscle loss, fat accumulation, decreased insulin sensitivity, and increased cholesterol and triglyceride levels.[31] In the current study, the 10-year disease-specific mortality in the radiotherapy-alone group was 1%, a finding that does not provide support for the addition of short-term ADT in patients with low-risk prostate cancer.

A total of 395 black men participated in this study, allowing evaluation according to racial subgroups. Similar benefits from short-term ADT were seen in the white and black populations with respect to the 10-year rate of overall survival, 10-year disease-specific mortality, and biochemical failure. Overall survival among black men was worse than that among white men, but disease-specific mortality was similar.

The results of our trial show that the addition of short-term ADT provides a survival benefit for men with intermediate-risk prostate cancer who receive conventional doses of radiotherapy. In addition, our findings suggest a biologic interaction between short-term ADT and radiotherapy, in contrast to several randomized trials of surgery combined with short-term ADT, which did not show a benefit with respect to outcome.[32-34]

The adoption of current radiotherapy techniques such as intensity-modulated radiation therapy, intensity-guided radiation therapy, and low-dose-rate and high-dose-rate brachytherapy now permits the safe delivery of higher doses of radiation than was possible when this study was conducted.[35] These techniques have also been associated with improved efficacy,[36-39] bringing into question the value of adding short-term ADT in men with intermediate-risk cancers treated with current irradiation methods. The RTOG has opened a successor study, RTOG 08-15 (NCT00936390), to address this question.

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