ORIGINAL ARTICLE

Duration of Androgen Suppression in the Treatment of Prostate Cancer

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ABSTRACT

BACKGROUND

The combination of radiotherapy plus long-term medical suppression of androgens (≥2 years) improves overall survival in patients with locally advanced prostate cancer. We compared the use of radiotherapy plus short-term androgen suppression with the use of radiotherapy plus long-term androgen suppression in the treatment of locally advanced prostate cancer.

METHODS

We randomly assigned patients with locally advanced prostate cancer who had received external-beam radiotherapy plus 6 months of androgen suppression to two groups, one to receive no further treatment (short-term suppression) and the other to receive 2.5 years of further treatment with a luteinizing hormone–releasing hormone agonist (long-term suppression). An outcome of noninferiority of short-term androgen suppression as compared with long-term suppression required a hazard ratio of more than 1.35 for overall survival, with a one-sided alpha level of 0.05. An interim analysis showed futility, and the results are presented with an adjusted one-sided alpha level of 0.0429.

RESULTS

A total of 1113 men were registered, of whom 970 were randomly assigned, 483 to short-term suppression and 487 to long-term suppression. After a median follow-up of 6.4 years, 132 patients in the short-term group and 98 in the long-term group had died; the number of deaths due to prostate cancer was 47 in the short-term group and 29 in the long-term group. The 5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively; the observed hazard ratio was 1.42 (upper 95.71% confidence limit, 1.79; P=0.65 for noninferiority). Adverse events in both groups included fatigue, diminished sexual function, and hot flushes.

CONCLUSIONS

The combination of radiotherapy plus 6 months of androgen suppression provides inferior survival as compared with radiotherapy plus 3 years of androgen suppression in the treatment of locally advanced prostate cancer. (ClinicalTrials.gov number, NCT00003026.)

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Overall survival among patients with locally advanced prostate cancer has improved with the use of external-beam radiotherapy combined with long-term androgen suppression (≥2 years) as compared with the use of external-beam radiotherapy and deferral of hormonal treatment until relapse.[1-5] However, long-term androgen suppression can reduce the quality of life and increase the risk of fatal myocardial infarction,[6] fractures,[7] and the metabolic syndrome.[8] These risks might be lowered by replacing long-term androgen suppression with short-term suppression (6 months), which has been found to reduce mortality from localized prostate cancer.[9] The European Organization for Research and Treatment of Cancer (EORTC) conducted a trial (EORTC protocol 22961) to determine whether short-term androgen suppression would both preserve quality of life and achieve the overall survival rate obtained with long-term androgen suppression.

METHODS

INCLUSION CRITERIA

Criteria for participation in the trial included histologically confirmed prostate adenocarcinoma T1c to T2a–b, pathological nodal stage N1 or N2, and no clinical evidence of metastatic spread (M0) or with clinical tumor stages T2c to T4, clinical nodal stages N0 to N2, and no clinical evidence of metastatic spread (as defined in the International Union against Cancer [UICC] 1992 staging criteria),[10] a baseline level of prostate-specific antigen (PSA) of up to 40 times the upper limit of the normal range, and a World Health Organization (WHO) performance status of 0 to 2. Additional criteria were a hemoglobin level of 10 g per deciliter or more, a white-cell count of 2×10^9 per liter or more, and a platelet count of 100×10^9 per liter or more, as well as no prior treatment for prostate cancer (except hormone therapy for ≤3 weeks) and no previous cancer (except treated basal-cell skin cancer). The pathological specimens were not centrally reviewed. All patients gave written informed consent according to the Good Clinical Practice guidelines of the International Conference on Harmonisation and national regulations. The protocol was reviewed and approved by the ethics committee at each participating institution.

TRIAL DESIGN

On November 3, 1997, the protocol was amended to implement the central registration of all patients at the EORTC headquarters before they started external-beam radiotherapy combined with androgen suppression. After 6 months of androgen suppression, all patients whose disease had not progressed were randomly assigned to receive no further endocrine-suppression treatment (short-term group) or to receive continued endocrine suppression for another 2.5 years (long-term group). The randomization was performed centrally at the EORTC headquarters with the use of the minimization method[11] and with stratification according to the institution, clinical tumor stage (≤T2b or ≥T2c), nodal stage (N0, pN1, or pN2), baseline PSA (≤5 times, >5 to 10 times, or >10 times the upper limit of the normal range), and Gleason score (2 to 7 or 8 to 10).

The sponsor of the trial was the EORTC. Ipsen PHARMA provided an educational grant and supplied the luteinizing hormone–releasing hormone (LHRH) analogue triptorelin (Decapeptyl) used for the study but had no role in its design or conduct, the analysis or interpretation of the data, or the preparation of the manuscript. The trial design, data collection, and statistical analysis and interpretation were performed independently of all funding sources at the EORTC headquarters in Brussels.

TREATMENT

Three-dimensional conformal radiotherapy was performed, with a three-field or four-field isocentric beam setup based on a computed tomographic (CT) definition of two planned target volumes. Photons of 10 MV or higher were recommended. The first planned target volume involved the whole pelvis, including the prostate, seminal vesicles, external and internal iliac lymph nodes, and lower part of the common iliac lymph nodes. Small pelvic irradiation fields, covering only the prostate and seminal vesicles, were allowed only when lymph nodes were not invaded. The second planned target volume encompassed the prostate and seminal vesicles. The dose was specified at the intersection of the beam axes according to the guidelines of the International Commission on Radiation Units.[12] Treatment was provided once a day, 5 days a week, for 7 weeks, at a dose of 50 Gy for the first planned target volume and an ad-

ditional dose of 20 Gy for the second planned target volume. Methods used for quality assurance (a dummy run and individual case review) have been reported elsewhere.[13]

The first 6 months of androgen suppression consisted of complete androgen blockade with an LHRH analogue, initiated on the first day of irradiation, and an antiandrogen agent (750 mg of flutamide per day or 50 mg of bicalutamide per day), initiated 1 week before the start of treatment with the LHRH analogue. The patients assigned to long-term suppression continued to be treated with the same LHRH analogue but without the antiandrogen for another 2.5 years. From March 1, 1998, through July 15, 1999, the LHRH analogue triptorelin was used exclusively and administered intramuscularly once a month; thereafter, when a new formulation became available, triptorelin was administered every 3 months.

STAGING AND FOLLOW-UP PROCEDURES

The initial staging included complete blood counts and PSA measurements, bone scanning, radiography of the chest, and CT or magnetic resonance imaging (MRI) of the abdomen and pelvis. Pelvic lymphadenectomy was allowed but was not mandatory. Clinical assessments, laboratory testing for toxicity, and PSA measurements were repeated every 6 months for 5 years and yearly thereafter. Imaging was repeated in cases in which clinical or biochemical progression was suspected. Acute toxicity was scored in accordance with the Expanded Common Toxicity Criteria of the National Cancer Institute of Canada Clinical Trials Group,[14] and late toxicity in accordance with the Late Radiation Morbidity Scoring Scheme of the EORTC–Radiation Therapy Oncology Group.[15] Quality of life was assessed with the use of the EORTC core quality-of-life questionnaire (QLQ-C30, version 2.0),[16] supplemented by an early version of the EORTC quality-of-life questionnaire for prostate cancer (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Assessments were made before initial treatment, at randomization, and 1, 1.5, 2.5, and 3.5 years after the start of irradiation.

END POINTS AND SAMPLE SIZE

Overall survival, the primary end point, was defined as the time from randomization to death from any cause. For overall survival, a hazard ratio of 1.35 or less was used to establish the noninferiority of short-term suppression to long-term suppression. The plan was to base this test on a total of 275 deaths for 80% power at the one-sided 5% significance level[17] and to execute the test 5 years after the last patient entered the study.

Secondary end points were survival free of clinical progression, survival free of regional and distant metastases, and survival free of biochemical progression. Clinical progression-free survival was defined as the time from randomization to clinical disease progression or death from any cause. Clinical progression was defined as palpable enlargement of an existing abnormality or regrowth of a previously regressed prostate gland by 25% or more, assessed on the basis of the product of its two largest diameters, or urethral obstruction. Regional and distant metastases were documented by imaging studies. Confirmation of local or regional progression by biopsy was not considered in the analysis of these end points. Biochemical progression was defined as a PSA level of more than 1.5 ng per milliliter and an increase in the PSA level on two successive occasions at least 3 months apart.[3]

STATISTICAL ANALYSIS

Overall survival was assessed with the use of the modified log-rank test for noninferiority.[18] Hazard ratios and confidence intervals were estimated with the use of the Cox model,[19] and the proportional-hazards assumption was tested at the 0.05 significance level with the use of the Kolmogorov-type supremum test.[20] Event rates were calculated with the use of Kaplan–Meier or cumulative-incidence estimates.[21] All analyses were conducted in accordance with the intention-to-treat principle, with data for all patients who underwent randomization included, but to protect against bias toward noninferiority, the analyses were repeated for the per-protocol population (all patients who underwent randomization and followed the assigned treatment regimen). Overall survival was also analyzed in the subgroup of patients in the per-protocol population who had cT2c–T3 pN0 disease. Quality-of-life end points were assessed as the change in scores between registration and randomization, and the data on the two randomized groups were compared with the use of linear mixed-effects regression models. For the quality-of-life end points, a P value of less than 0.01 was consid-

ered to indicate statistical significance, to account for multiple comparisons, and a between-group difference in mean scores of 10 points or more was considered to be clinically relevant.[22]

By March 2006 — 4 years after enrollment was completed — specified events had accumulated more slowly than anticipated, and the benefit of adding short-term androgen suppression to irradiation for localized disease had been confirmed.[23] For these reasons, the independent data monitoring committee authorized an interim analysis. Early stopping boundaries of the gamma family[24] (γ=−2 for noninferiority and γ=−4 for futility) were defined before data analysis. As of August 16, 2006 (at a median follow-up of 5.2 years), 173 deaths had been reported; the stopping boundaries were a hazard ratio of less than 0.981 for noninferiority and of more than 1.313 for futility. The actual point estimate of the hazard ratio was 1.43, and for this reason, the independent data monitoring committee recommended immediate release of the interim results[25] and publication of the final results of testing for noninferiority with the adjusted one-sided alpha level of 0.0429. Here we present updated results (with a final cutoff date of September 4, 2007, for data collection) with a median follow-up from the time of enrollment of 6.4 years and a total of 230 deaths. Two-sided confidence intervals adjusted for the interim analysis (i.e., 95.71% confidence intervals) are given for descriptive purposes only, since tests for differences in this setting are not supported by statistical theory and were not preplanned.

RESULTS

Between April 1997 and November 2001, a total of 1113 men entered the trial; 970 underwent randomization between October 1997 and May 2002 (483 to treatment with short-term androgen suppression and 487 to treatment with long-term suppression); 143 did not undergo randomization (Fig. 1). Among the patients undergoing randomization, 14 in the short-term group and 16 in the long-term group were deemed ineligible. The median follow-up period from registration was 6.4 years. The baseline characteristics of the patients were balanced between the two groups (Table 1).

Radiotherapy was performed in 1089 patients (97.8%); 1 patient declined radiotherapy, and data on radiotherapy were missing for 23 patients. Three-dimensional conformal radiotherapy was delivered to 1033 patients (94.9%). The median duration of this treatment was 51 days (range, 11 to 117; interquartile range, 50 to 53), and the median dose was 70 Gy (range, 12 to 74; interquartile range, 70 to 70), which was delivered in 35 fractions (range, 6 to 40; interquartile range, 35 to 35). The dose and duration of conformal radiotherapy were similar in the two groups. Radiotherapy was stopped prematurely in 13 patients because of toxicity (5 patients), diagnosis of another disease (5 patients, 1 of whom died), the patient's request (2 patients), and gastric hemorrhage (1 patient).

The initial 6-month complete androgen blockade was not initiated in 11 patients (4 declined treatment, 2 were ineligible, 2 had early disease progression, and 3 did not receive the treatment for other reasons), and documentation of initial treatment was missing for 22 patients. The initial hormonal treatment was started in 1080 patients, with 2 patients receiving only the antiandrogens and 2 receiving only the LHRH analogue. Triptorelin was administered to 672 patients (62.2%), and goserelin to 325 (30.1%); the other men received other types of LHRH or switched to triptorelin during treatment (10 patients). Androgen blockade was stopped before 6 months in 49 patients because of toxicity (20 patients), the patient's decision to decline treatment (13), death (6), or other reasons (10). Major deviations from the protocol for the 6-month androgen blockade were documented in 199 patients (18.4%); discontinuation of the antiandrogen after 1 month, an extra injection of LHRH analogue, or a delay in randomization by more than 1 month accounted for most of these deviations. The side effects of the 6-month androgen blockade were hot flushes more than three times daily in 311 patients (28.8%), gynecomastia in 77 patients (7.1%), diarrhea of grade 3 or higher (according to the National Cancer Institute of Canada Common Toxicity Criteria) in 23 patients (2.1%), and incontinence in 110 patients (10.2%). Adverse effects on sexual function were not systematically documented.

Of the 970 patients who underwent randomization, 3 of the 483 who were assigned to short-term suppression received long-term suppression. Of the 487 patients assigned to long-term suppression, 349 (71.7%) completed the 3-year course, 22 (4.5%) had less than 3 years of follow-up but were receiving treatment at their last visit, and 106 (21.8%) stopped treatment early (including 12 who received only short-term suppression); information after

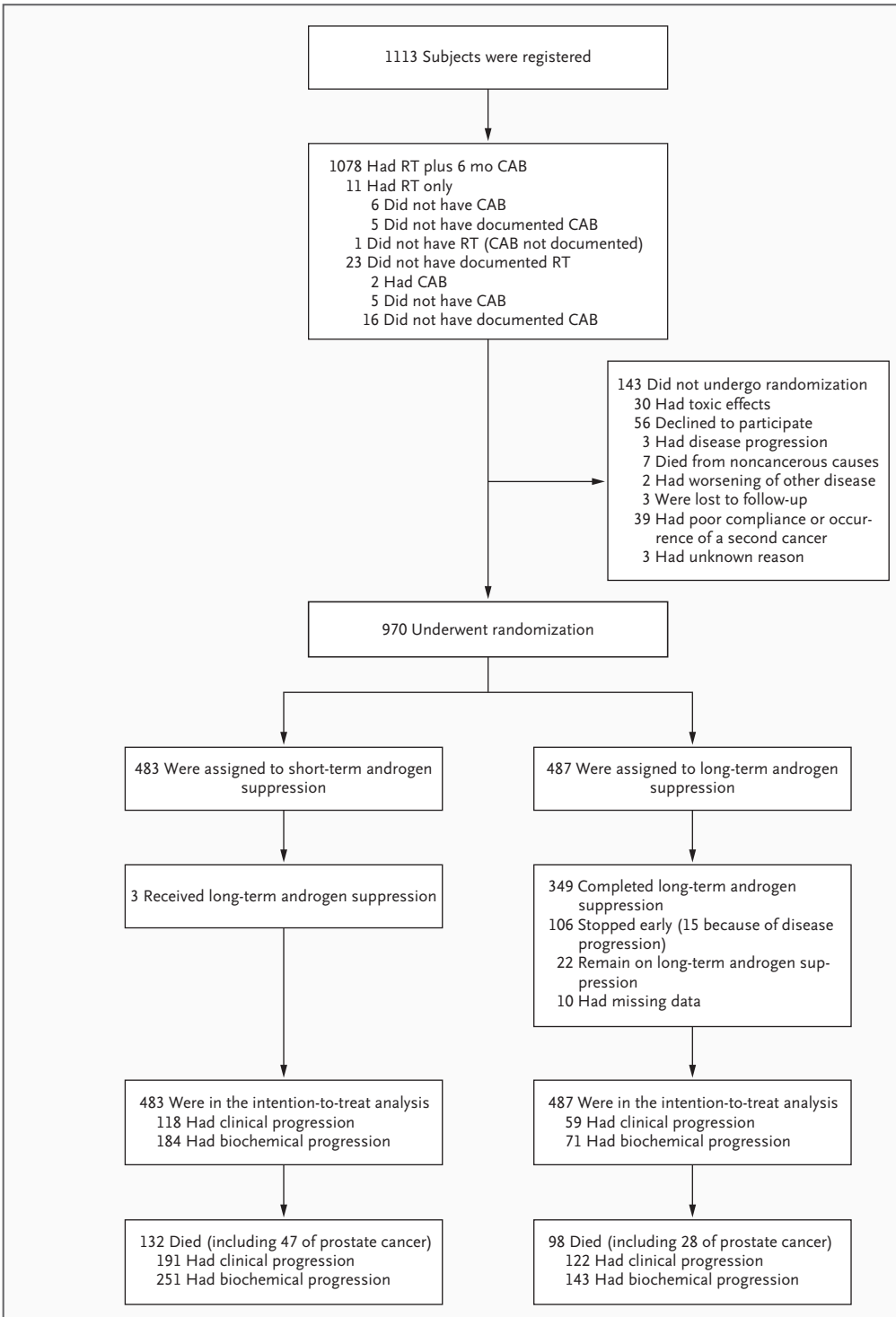

Figure 1. Enrollment and Follow-up of Study Patients.

CAB denotes complete androgen blockade, and RT radiotherapy.

Table 1. Characteristics of the Patients at Study Entry.*

Characteristic	Patients Who Did Not Undergo Randomization (N=143)	Patients Who Underwent Randomization		All Patients (N=1113)
		Short-Term Androgen Suppression (N=483)	Long-Term Androgen Suppression (N=487)	
Age — yr				
Median	69	70	69	69
Range	47–83	44–85	44–84	44–85
Interquartile range	65–74	65–74	64–73	64–73
WHO performance status — no. (%)				
0	116 (88.1)	405 (83.9)	412 (84.6)	933 (83.8)
1	23 (16.1)	71 (14.7)	61 (12.5)	155 (13.9)
2	1 (0.7)	6 (1.2)	10 (2.1)	17 (1.5)
Unknown	3 (2.1)	1 (0.2)	4 (0.8)	8 (0.7)
Chronic diseases — no. (%)				
None	88 (61.5)	301 (62.3)	296 (60.8)	685 (61.5)
Cardiovascular only	26 (18.2)	112 (23.2)	120 (24.6)	258 (23.2)
Other or multiple	25 (17.5)	69 (14.3)	71 (14.6)	165 (14.8)
Unknown	4 (2.8)	1 (0.2)	0	5 (0.4)
Clinical tumor stage (UICC 1992 staging criteria) — no. (%)				
T1c to T2a–b (N+ or pN+)	4 (2.8)	14 (2.9)	16 (3.3)	34 (3.1)
T2c	27 (18.9)	86 (17.8)	97 (19.9)	210 (18.9)
T3	104 (72.7)	365 (75.6)	346 (71.0)	815 (73.2)
T4	5 (3.5)	17 (3.5)	26 (5.3)	48 (4.3)
Tx	3 (2.1)	1 (0.2)	2 (0.4)	6 (0.5)
Clinical or pathological nodal stage (UICC 1992 staging criteria) — no. (%)				
N0	133 (93.0)	440 (91.1)	445 (91.4)	1018 (91.5)
cN1 or pN1	7 (4.9)	35 (7.2)	28 (5.7)	70 (6.3)
cN2 or pN2	0	7 (1.4)	12 (2.5)	19 (1.7)
cNx or pNx	3 (2.1)	1 (0.2)	2 (0.4)	6 (0.5)
Combination of tumor and nodal stages — no. (%)				
T1c to T2a–b pN+	4 (2.8)	14 (2.9)	16 (3.3)	34 (3.1)
T2c to T4 N0	133 (93.0)	440 (91.1)	445 (91.4)	1018 (91.5)
T2c to T4 pN+	3 (2.1)	28 (5.8)	24 (4.9)	55 (4.9)
Tx or Nx	3 (2.1)	1 (0.2)	2 (0.4)	3 (0.3)
Gleason total score — no. (%)				
2 to 5	42 (29.4)	102 (21.1)	102 (20.9)	246 (22.1)
6	36 (25.2)	126 (26.1)	118 (24.2)	280 (25.2)
7	36 (25.2)	148 (30.6)	146 (30.0)	330 (29.6)
8 to 10	20 (14.0)	90 (18.6)	95 (19.5)	205 (18.4)
Unknown	9 (6.3)	17 (3.5)	26 (5.3)	53 (4.8)
PSA — ng/ml†				
Median	15.6	18.8	18.8	18.4
Range	0.8–127.2	1.6–156.0	1.2–159.2	0.8–159.2
Interquartile range	8.0–26.8	11.2–34.0	10.8–35.2	10.8–33.2

* PSA denotes prostate-specific antigen, UICC the International Union against Cancer, and WHO the World Health Organization.
† The values for median PSA were standardized to an upper limit of the normal range of 4 ng per milliliter.

randomization was missing for 10 patients. For the 106 patients who stopped long-term suppression before month 36, the reasons were disease progression or death (29 patients, or 6.0%), toxicity (23 patients, or 4.7%), the patient's decision to stop the treatment (40 patients, or 8.2%), or other or unspecified reasons (14 patients, or 2.9%). At least one extra injection was administered to 46 patients, including 13 who continued treatment beyond 4 years. The median duration of long-term suppression therapy was 36 months (range, 5 to 88; interquartile range, 33 to 38). Adverse reactions to the additional 2.5 years of LHRH treatment in the long-term suppression group were hot flushes 3 times daily or less in 156 patients (32.0%) and more than 3 times daily in 191 (39.2%) and gynecomastia in 88 patients (18.1%). Twenty-seven patients (2.8%) reported late grade 3 side effects from irradiation. (For more information on the late effects of radiotherapy, see the Supplementary Appendix.)

Completion rates for the quality-of-life questionnaire were similar in the two groups, ranging from 89% at randomization to 63% 3.5 years after the start of treatment (see the Supplementary Appendix). Scores on the quality-of-life questionnaire are shown in Figure 2. After radiotherapy and 6 months of androgen blockade, fatigue, hot flushes, and sexual problems increased significantly — both statistically ($P<0.001$) and clinically[22] (Table 2). After randomization, there were statistically significant differences between the groups in terms of insomnia ($P=0.006$), hot flushes ($P<0.001$), and sexual interest and activity ($P<0.001$); the differences were clinically relevant only for hot flushes, sexual interest, and sexual activity (Table 2). Overall quality of life did not differ significantly between the two groups ($P=0.37$).

As of September 4, 2007, a total of 132 patients receiving short-term suppression and 98 receiving long-term suppression had died; prostate cancer was the cause of death in 47 and 28 patients, respectively, and cardiac events in 31 and 25, respectively. One patient in the long-term group died of radiation-induced grade 4 proctitis 3 years after irradiation. The 5-year overall mortality was 15.2% for the long-term group (95% confidence interval [CI], 12.1 to 18.9) and 19.0% for the short-term group (95% CI, 15.5 to 23.0), corresponding to an observed hazard ratio of 1.42 (upper one-sided 95.71% confidence limit, 1.79; $P=0.65$ for noninferiority). The two-sided 95.71% CI of 1.09 to 1.85 is a post hoc indication that short-term suppression was inferior, for overall survival, to long-term suppression (Fig. 3A). The results were similar when adjusted for the stratification factors in the per-protocol population and in the subgroup of patients in the per-protocol population who had T2c–T3 pN0 disease.

For prostate-specific mortality, the 5-year cumulative rate was 4.7% (95% CI, 2.7 to 6.7) in the short-term group and 3.2% (95% CI, 1.6 to 4.8) in the long-term group, and the prostate-cancer–specific survival curves were significantly different (hazard ratio, 1.71 [95% CI, 1.14 to 2.57]; $P=0.002$ by the log-rank test) (Fig. 3A). The 5-year cumulative mortality for causes unrelated to prostate cancer was 9.0% (95% CI, 6.3 to 11.7) in the short-term group and 7.4% (95% CI, 5.0 to 9.9) in the long-term group (hazard ratio, 1.30; 95% CI, 0.98 to 1.72). There was no significant difference in the cumulative incidence of fatal cardiac events at 5 years: 4.0% in the short-term group and 3.0% in the long-term group (Fig. 3B). There was no evidence against the proportional-hazards assumption for any end point. Results for the end points of survival free of clinical progression and survival free of distant metastases are provided in the Supplementary Appendix.

DISCUSSION

A previous trial of the treatment of locally advanced prostate cancer (EORTC protocol 22863)[1,2] showed that radiotherapy plus 3 years of androgen suppression as compared with radiotherapy alone provided a benefit with respect to overall survival. We conducted the current trial to determine whether overall survival after radiotherapy plus 6 months of androgen suppression is inferior to radiotherapy plus 3 years of androgen suppression. We found that at 5 years, overall mortality was higher with short-term androgen suppression than with long-term suppression, as was prostate-cancer–specific mortality (increased by 3.8% and 1.5%, respectively). However, since most patients in this study had a tumor in stage T2c or higher according to the UICC 1992 staging criteria (i.e., a large tumor involving both lobes of the prostate or beyond), our results may not apply to patients with small tumors and high Gleason scores.

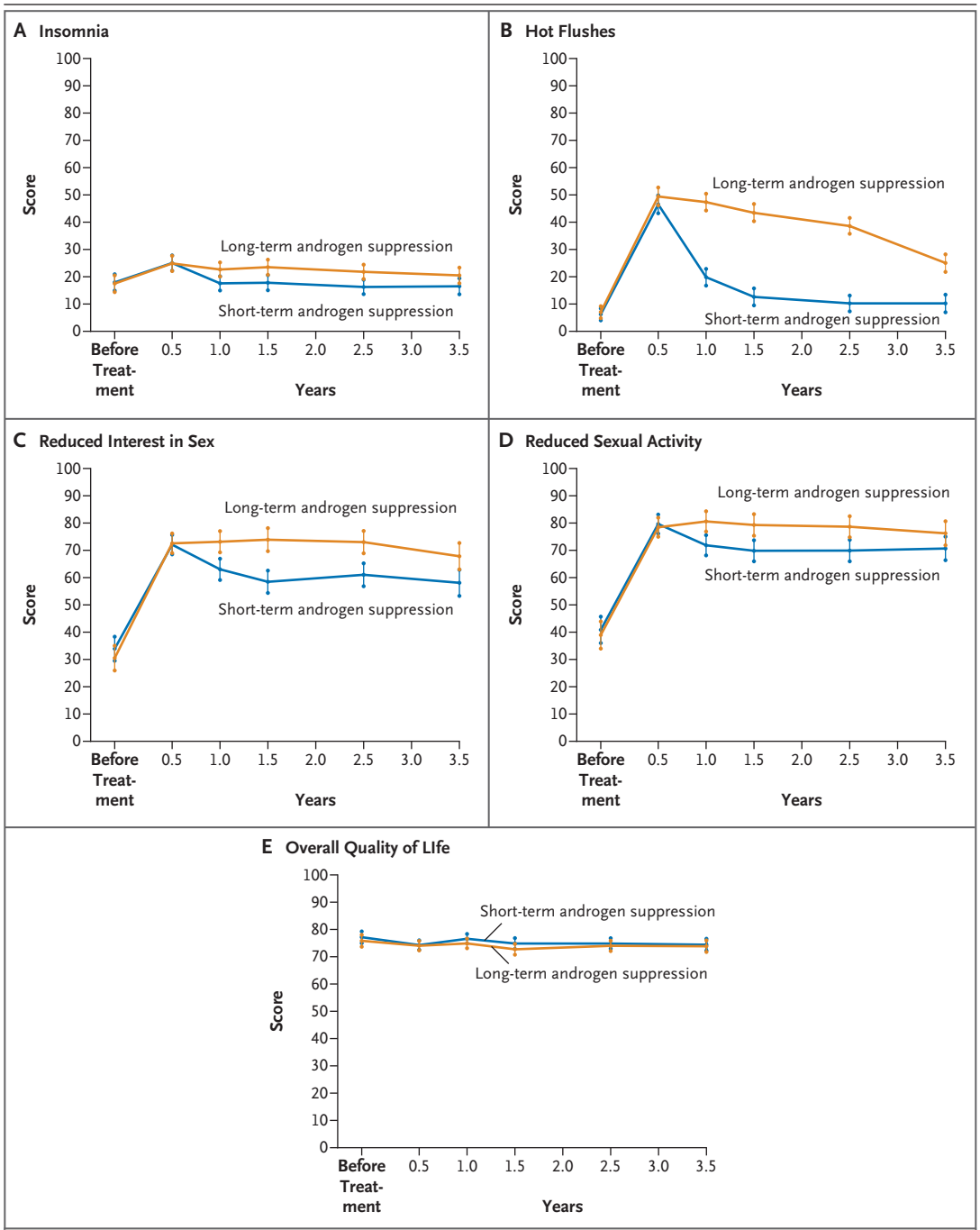

Figure 2. Mean Scores on Quality-of-Life Assessment Scales.

The mean scores for the 970 patients who underwent randomization are shown for insomnia (0 indicates no symptoms and 100 most severe symptoms) (Panel A), hot flushes (0 indicates no symptoms and 100 most severe symptoms) (Panel B), reduced interest in sex (0 indicates no reduction and 100 greatest reduction) (Panel C), reduced sexual activity (0 indicates the least reduction and 100 the greatest reduction) (Panel D), and overall quality of life and health status (0 indicates the worst rating and 100 the best rating) (Panel E). I bars indicate 95% confidence intervals.

Table 2. Quality of Life for Patients before and after Initial Treatment with Radiation and 6 Months of Complete Androgen Blockade, and Long-Term Results for Patients Who Underwent Randomization.*

Variable	Mean Score before RT+CAB	Mean Score after RT+CAB	Mean Change in Score†	P Value‡	Mean Score at 1.5 Yr for STAS (1 yr after end of STAS)	Mean Score at 1.5 Yr for LTAS (at 1.5 yr of LTAS)	Overall P Value for LTAS vs. STAS‡
EORTC QLQ-C30 function scales§							
Global health status and quality of life	76.36±1.03	73.22±1.04	−3.14±1.08	0.004	74.9±1.00	72.7±1.00	0.37
Physical functioning	89.20±0.95	81.58±1.15	−7.62±1.10	<0.001	80.7±1.22	77.7±1.22	0.10
Cognitive functioning	87.10±1.01	84.49±1.13	−2.61±1.03	0.01	84.2±1.02	84.6±1.02	0.51
Emotional functioning	79.62±1.16	80.05±1.18	0.44±1.14	0.70	84.7±1.01	83.6±1.02	0.37
Role functioning	88.81±1.06	80.64±1.38	−8.17±1.43	<0.001	81.8±1.3	79.4±1.30	0.39
Social functioning	92.65±0.87	83.92±1.26	−8.73±1.19	<0.001	87.9±1.09	87.6±1.10	0.95
EORTC QLQ-C30 symptom scales¶							
Appetite loss	4.82±0.75	5.11±0.86	0.29±1.00	0.77	4.2±0.7	3.8±0.70	0.80
Constipation	5.67±0.82	8.11±0.92	2.44±1.01	0.02	7.2±0.95	7.9±0.95	0.51
Diarrhea	3.59±0.61	12.11±1.09	8.53±1.22	<0.001	10.4±0.98	8.2±0.99	0.13
Dyspnea	12.27±1.15	21.74±1.49	9.47±1.23	<0.001	17.7±1.38	20.5±1.39	0.17
Fatigue	15.61±1.01	27.52±1.37	11.91±1.32	<0.001	21.9±1.19	25.5±1.19	0.02
Nausea or vomiting	1.25±0.29	2.36±0.45	1.11±0.49	0.02	1.7±0.38	2.3±0.39	0.72
Pain	9.67±0.96	12.55±1.18	2.87±1.30	0.03	11.2±1.08	11.4±1.08	0.49
Insomnia	18.60±1.47	26.45±1.68	7.85±1.60	<0.001	18.0±1.4	23.6±1.40	0.006
Ad hoc questions‖							
Hot flushes	6.42±0.95	50.83±1.89	44.41±1.99	<0.001	12.6±1.59	43.5±1.60	<0.001
Enlarged nipples or breasts	0.24±0.17	5.40±0.90	5.16±0.92	<0.001	5.7±0.96	6.4±0.97	0.009
Swelling of legs	4.83±0.90	9.88±1.23	5.05±1.18	<0.001	8.5±1.14	12.5±1.15	0.02
Problems passing urine	24.81±1.61	20.38±1.48	−4.43±1.74	0.01	12.6±1.3	15.2±1.31	0.05
Reduced interest in sex	32.24±2.09	72.75±2.05	40.51±2.75	<0.001	58.5±2.08	73.9±2.15	<0.001
Reduced sexual activity	38.51±2.18	77.02±2.06	38.51±2.90	<0.001	69.8±1.98	79.2±2.03	<0.001

* Plus–minus values are means ±SD. CAB denotes complete androgen blockade, EORTC European Organization for Research and Treatment of Cancer, LTAS long-term androgen suppression, RT radiotherapy, and STAS short-term androgen suppression.
† A change of 10 points or more is considered to be clinically relevant.
‡ P values are based on linear mixed-effects models and Student's t-test. Because of multiple comparisons, a P value of less than 0.01 was considered to indicate statistical significance.
§ For the EORTC Quality-of-Life Questionnaire C30 (QLQ-C30) function scales, 0 indicates the lowest function and 100 the best.
¶ For the EORTC Quality-of-Life Questionnaire C30 (QLQ-C30) symptom scales, 0 indicates the fewest symptoms and 100 the most.
‖ For the ad hoc questions, 0 indicates the fewest symptoms and 100 the most.

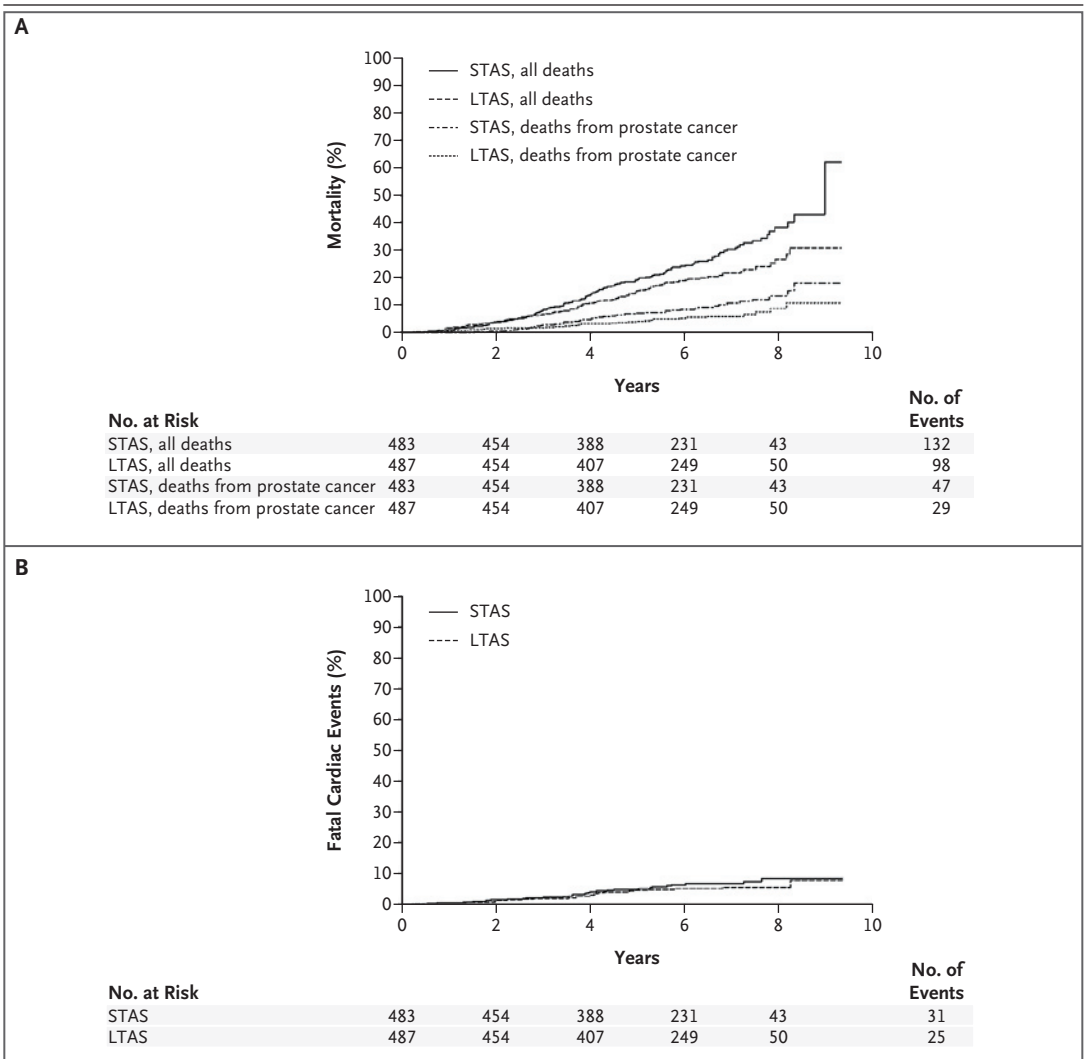

Figure 3. Cumulative Mortality.

Panel A shows overall mortality and prostate-cancer–specific mortality, and Panel B shows cardiac-event–specific mortality. LTAS denotes long-term androgen suppression, and STAS short-term androgen suppression.

Several phase 3 trials have examined the effect of androgen suppression combined with radiotherapy on overall survival among patients with prostate cancer.[4,5,26] In a study conducted by the Radiation Therapy Oncology Group (protocol 92-02), long-term androgen suppression improved 10-year overall survival among patients with a Gleason score of 8 to 10 (P=0.006) and improved 10-year prostate-cancer–specific survival in the whole study population (P=0.004).[4] In our study, the Gleason score did not influence the difference in outcome between the two groups. Recently, Widmark et al. showed that the radiotherapy component of the combined treatment is necessary: cancer-specific and overall mortality rates at 10 years were significantly lower with the combined treatment than with androgen suppression alone.[27]

With a median follow-up of 6.4 years, we found no serious long-term genitourinary or gastrointestinal toxicity from radiotherapy and no increase in the risk of fatal cardiovascular events. In an updated analysis of protocol 22863,[28] the EORTC group reported a 10-year risk of death from cardiac events of 6% in the group receiving radiotherapy and long-term androgen suppression as

compared with 4.2% in the group receiving radiotherapy alone.

In that study, radiotherapy plus 6 months of complete androgen suppression caused fatigue, severe hot flushes, and deterioration of sexual function. These symptoms persisted for the duration of androgen suppression and tended to diminish or resolve after the treatment was stopped. The additional 2.5 years of androgen suppression had no further clinically relevant effect on other quality-of-life measures. These results reflect the known effects of androgen suppression on health-related quality of life and sexual function.[28-31]

In our study, the difference in the effect of short-term and long-term androgen suppression on 5-year mortality was modest, but we believe that the advantage of long-term suppression is likely to be maintained at 10 years, whereas the benefit of short-term suppression may be dissipated by then.[28] We recommend radiotherapy plus long-term androgen suppression for men with locally advanced prostate cancer (classified as stage T2c or above, with a WHO performance status of 0 to 2) who have no contraindicating coexisting conditions.

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APPENDIX

The following physicians and institutions from the EORTC Radiation Oncology and Genito-Urinary Tract Cancer Groups participated in this study: *the Netherlands* — Academisch Medisch Centrum, Amsterdam (T.M. de Reijke, G. van Tienhoven), University Medical Center Groningen, Groningen (A.C.M. van den Bergh), Jeroen Bosch Medisch Centrum, s'Hertogenbosch (J. Oddens [formerly A.P.M. van der Meijden]), Bernard Verbeeten Instituut, Tilburg (P.M.P. Poortmans), Sint-Elisabeth Ziekenhuis, Tilburg (P. Kil), Onze Lieve Vrouw Gasthuis Amsterdam, Amsterdam (G. van Andel), Arnhem's RadioTherapeutisch Instituut, Arnhem (E.M. van der Steen-Banasik), Academisch Ziekenhuis Maastricht, Maastricht (C. van de Beek), University Medical Center Leiden, Leiden (now at Arnhem's RadioTherapeutisch Instituut) (E. Schimmel); *France* — Centre Hospitalier Régional de Grenoble, Grenoble (M. Bolla, J.L. Descotes), Centre Hospitalier Régional de Besançon, Besançon (J.-F. Bosset), Régional de Lutte Contre le Cancer Val d'Aurelle, Montpellier (M.H. Hay), Centre Claudius Regaud, Toulouse (J.-M. Bachaud), Centre George François Leclerc, Dijon (P. Maingon), Centre Antoine Lacassagne, Nice (A. Courdi), Hopital Bretonneau, Tours (I. Barillot), Centre Leon Bérard, Lyon (C. Carrie), Centre Hospitalier de Chambéry, Chambéry (F. Rothe-Thomas); *Israel* — Rambam Medical Center, Haïfa (E. Gez); *Turkey* — Marmara University Hospital, Istanbul (A. Akdas), Celal Bayar University Hospital, Manisa (M. Lekili); *Belgium* — Universitair Zienkenhuis der Vrije Universiteit Brussel, Brussels (G. Soete), Universitair Ziekenhuis Gasthuisberg, Leuven (H. van Poppel), Virga Jesse Hospital, Hasselt (K. Vekemans), Hôpital Universitaire Jules Bordet-Erasme, Brussels (P. Van Houtte), Universiteit Gent, Ghent (A. Verbaeys), Universitair Ziekenhuis Antwerpen, Antwerp (L. Hoekx); *Russia* — Medical Radiation Research Center Obninsk, Obninsk (O. Kariakine); *Malta* — Saint Luke's Hospital, Guardamagna (C.L. Cutajar); *Switzerland* — Centre Hospitalier Universitaire Vaudois, Lausanne (R. Mirimanoff); *Italy* — Università degli Studi di Brescia, Brescia (S.M. Magrini), Ospedale Umberto I Mestre, Mestre (M. Busetto), Ospedale del Circolo I Fundazione Macchi, Varese (A. Bono); *Spain* — CSU de Bellvitge–Hospital Duran i Reynals, Barcelona (now at Hospital Germans Trias I Pujol, Barcelona) (S. Villa), Instituto Valenciano di Oncologia, Valencia (L. Arribas [formerly J. Lopez Lopez Torrecilla]), Hospital Vall D'Hebron, Barcelona (X. Maldonado); *United Kingdom* — University of Wales, College of Medicine, Cardiff (H. Kynaston), Velindre Hospital, Cardiff (J. Barber), City Hospital, Stoke on Trent (M. Saxby); *Bosnia and Herzegovina* — University Clinical Center Sarajevo, Sarajevo (N. Obralic).

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