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Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy

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Abstract

BACKGROUND—Intermittent androgen deprivation for prostate-specific antigen (PSA) elevation after radiotherapy may improve quality of life and delay hormone resistance. We assessed overall survival with intermittent versus continuous androgen deprivation in a noninferiority randomized trial.

METHODS—We enrolled patients with a PSA level greater than 3 ng per milliliter more than 1 year after primary or salvage radiotherapy for localized prostate cancer. Intermittent treatment was provided in 8-month cycles, with nontreatment periods determined according to the PSA level. The primary end point was overall survival. Secondary end points included quality of life, time to castration-resistant disease, and duration of nontreatment intervals.

RESULTS—Of 1386 enrolled patients, 690 were randomly assigned to intermittent therapy and 696 to continuous therapy. Median follow-up was 6.9 years. There were no significant between-group differences in adverse events. In the intermittent-therapy group, full testosterone recovery occurred in 35% of patients, and testosterone recovery to the trial-entry threshold occurred in 79%. Intermittent therapy provided potential benefits with respect to physical function, fatigue, urinary problems, hot flashes, libido, and erectile function. There were 268 deaths in the intermittent-therapy group and 256 in the continuous-therapy group. Median overall survival was 8.8 years in the intermittent-therapy group versus 9.1 years in the continuous-therapy group (hazard ratio for death, 1.02; 95% confidence interval, 0.86 to 1.21). The estimated 7-year

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cumulative rates of disease-related death were 18% and 15% in the two groups, respectively (P = 0.24).

CONCLUSIONS—Intermittent androgen deprivation was noninferior to continuous therapy with respect to overall survival. Some quality-of-life factors improved with intermittent therapy. (Funded by the Canadian Cancer Society Research Institute and others; ClinicalTrials.gov number, NCT00003653.)

Ever since Huggins and Hodges's work of 1941[1] showing the androgen dependence of prostate cancer, androgen deprivation has been the mainstay treatment for metastatic disease. With the development of reversible forms of medical castration, indications for androgen deprivation have been expanded to include nonmetastatic disease.[2-4] The introduction of prostate-specific antigen (PSA) testing into clinical practice in the early 1990s provided an objective evaluation of the efficacy of definitive treatment; biochemical failure became an accepted end point. The ability to diagnose early treatment failure created a clinical dilemma. The justification for lifelong androgen deprivation is more apparent in the case of obvious clinical disease than it is in the case of a slowly rising PSA level without symptoms.

The concept of intermittent androgen-deprivation therapy was first reported in reference to the intermittent administration of diethylstilbestrol, before the advent of PSA testing.[5] Subsequent laboratory work showed the ability of hormone-dependent cells to undergo repeated cycles of apoptosis secondary to cyclic hormonal withdrawal. Bruchovsky et al.[6] used the androgen-dependent Shionogi carcinoma as a model to suggest that castration followed by reexposure to androgens before tumor progression preserved androgen dependence in surviving stem cells, leaving them amenable to further androgen withdrawal. Successive castration and reexposure to androgens in mouse models produced multiple apoptotic regressions and a prolongation in the time to development of androgen independence that increased by a factor of 3.[7,8] Cycles of androgen deprivation followed by reexposure to testosterone form the basis of intermittent androgen-deprivation therapy.

With emerging data from phase 2 trials providing proof of principle in humans,[5,9-16] the NCIC Clinical Trials Group undertook a phase 3 trial with a primary end point of overall survival to investigate intermittent versus continuous androgen deprivation in men with a rising PSA level after definitive radiotherapy and no evidence of metastatic disease.

METHODS

STUDY OVERSIGHT

The study was designed by four of the authors representing the NCIC Clinical Trials Group, was opened in Canada in 1999, and was subsequently endorsed by the Southwest Oncology Group, the Radiation Therapy Oncology Group, the Cancer Trials Support Unit, and, within the United Kingdom, the Institute of Cancer Research Clinical Trials and Statistics Unit. Three authors affiliated with the NCIC Clinical Trials Group were responsible for the conduct and oversight of data collection. The first and last authors and the Trial Committee oversaw the trial process and data analysis. All authors had full access to the data. The study drugs were obtained according to the usual practice at each participating institution.

The first author wrote the first draft of the manuscript, and all authors reviewed it and agreed to submit the manuscript for publication. All authors vouch for the accuracy of the reported data and analyses and the adherence of the study to the protocol, which, along with the statistical analysis plan, is available with the full text of this article at NEJM.org.

ELIGIBILITY CRITERIA

Men with histologically confirmed prostatic adenocarcinoma were eligible for the study if they had completed definitive radiotherapy (primary or salvage) more than 12 months before enrollment and had a rising PSA level, which was higher than 3 ng per milliliter and higher than the nadir that occurred after radiotherapy, provided that systemic staging showed no distant metastases. Prior androgen-deprivation therapy for up to 12 months in association with definitive treatment was permitted if it had been completed at least 12 months before enrollment. Additional eligibility criteria were a serum testosterone level that was greater than 5 nmol per liter (144 ng per deciliter), a life expectancy of more than 5 years, and completion of questionnaires regarding quality of life. Written informed consent was obtained from all patients according to local institutional review board requirements.

Stratification was planned according to status with respect to prior radical prostatectomy, time since completion of radiotherapy (<3 years vs. ≥3 years), baseline PSA value (3 to 15 ng per milliliter vs. >15 ng per milliliter), and status with respect to prior use of neoadjuvant, concurrent, or adjuvant androgen-deprivation therapy.

TREATMENT SCHEMA

Patients were randomly assigned in a 1:1 ratio to the two treatment groups. Continuous androgen-deprivation therapy consisted of a luteinizing hormone–releasing hormone agonist (LHRHa), combined with a nonsteroidal antiandrogen, with the latter continued for a minimum of 4 weeks, or orchiectomy. Intermittent androgen-deprivation therapy consisted of 8-month treatment cycles, each beginning with the administration of LHRHa injections, combined with a nonsteroidal antiandrogen, with the latter continued for a minimum of 4 weeks. Any LHRHa preparation was acceptable in any of the 1-month or longer depot formulations to achieve a treatment duration of 8 months. At the completion of the 8-month cycle, a nontreatment interval commenced if there was no evidence of clinical disease progression and if the PSA level was less than 4 ng per milliliter and not more than 1 ng per milliliter above the previous recorded value as monitored in that treatment cycle (see Fig. S1 and S2 in the Supplementary Appendix, available at NEJM.org).

During the nontreatment interval, the PSA level was monitored every 2 months until it reached 10 ng per milliliter, provided there was no intervening evidence of disease progression. Patient-reported quality of life was assessed with the use of the European Organization for Research and Treatment of Cancer quality-of-life core questionnaire (QLQ-C30), administered at baseline, every 4 months for 2 years, then every 8 months until castration-resistant disease developed, and annually thereafter. Follow-up until death was required in both groups. Castration-resistant disease was defined as three increases in the PSA level at least 1 month apart or evidence of new clinical disease while the patient was receiving androgen-deprivation therapy and the testosterone was at castrate levels. After the development of castration-resistant disease, management was determined by the local investigator, with annual reporting of the patient's vital status and in the case of death, the cause. Patients who were considered to be off protocol for reasons other than having castration-resistant disease were also followed to record interventions, quality of life, and vital status.

END POINTS

The primary end point was overall survival. Secondary end points included time to castration-resistant disease and quality of life. Additional end points for patients in the intermittent-therapy group were the duration of off-treatment intervals, the time to testosterone recovery, and the time to potency recovery.

STATISTICAL ANALYSIS

We calculated the sample size using a one-sided test of equivalence[17] and an assumed median survival of 7 years in the continuous-therapy group, with equivalence declared (95% certainty) if the between-group difference in overall survival at 7 years was less than 8 percentage points (i.e., the upper boundary of the 90% confidence interval [CI] was <0.08), which was equivalent to an upper boundary of the hazard ratio for death of less than 1.25. To reject the null hypothesis with 80% power at the 5% level, we needed to enroll 1340 patients in order to obtain the necessary number of events of 800. An interim analysis for noninferiority[18,19] was planned after 400 events, with a decision to stop the study early in favor of intermittent androgen deprivation if there was 99.5% certainty that the true difference in overall survival was less than 8 percentage points (hazard ratio, <1.25; 99% CI, <1.00 to <1.25).

The trial began in January 1999 and was closed to accrual in November 2005, with a total of 1386 patients enrolled. Of the patients enrolled, 1367 were eligible; the other 19 patients were initially considered eligible, were found to be ineligible on subsequent review, and were included in the analysis. The preplanned interim analysis was undertaken in April 2010, when 446 events had been documented. On the basis of this analysis, the data and safety monitoring committee determined that the preplanned threshold for stopping the study early had been met and recommended reporting the results. All reported P values are based on two-sided comparisons unless otherwise specified. Statistical analyses were performed with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of the 1386 patients who underwent randomization, 690 were randomly assigned to intermittent therapy and 696 to continuous therapy. Analyses of pretreatment characteristics and efficacy were performed with data from the intention-to-treat population (all 1386 patients who underwent randomization) and with data from the per-protocol population (the 1364 patients who underwent randomization and received at least one dose of the assigned treatment), with no notable differences between the two sets of results. The safety analysis was based on data from the astreated population (the 1381 patients who began treatment per protocol). The Supplementary Appendix provides details regarding patient accrual according to cooperative group (Table S1 in the Supplementary Appendix) and reasons for ineligibility (Table S2 in the Supplementary Appendix).

The median follow-up was 6.9 years (range, 2.8 to 11.2). Patients in the intermittent-therapy group completed one to nine 8-month treatment cycles. A total of 49 patients were lost to follow-up at a median of 4.0 years (range, 1 day to 9.6 years), with an equal distribution between the treatment groups. Baseline characteristics were balanced between the two groups (Table 1).

OVERALL SURVIVAL

Overall survival was calculated from the date of randomization to the date of death, with data censored at the last known date that the patient was alive. At a median follow-up of 6.9 years, a total of 524 patients had died (268 in the intermittent-therapy group and 256 in the continuous-therapy group). Figure 1 shows the Kaplan–Meier curve for overall survival according to treatment group. The causes of death, which were reported by the investigators and were not audited, are summarized in Table 2. The median overall survival was 8.8 years in the intermittent-therapy group and 9.1 years in the continuous-therapy group. The hazard ratio for death with intermittent therapy versus continuous therapy was 1.02 (95% CI, 0.86

to 1.21). The P value for noninferiority (hazard ratio, <1.25) was 0.009, supporting the hypothesis that intermittent therapy was not inferior to continuous therapy.

A multivariable Cox proportional-hazards model was used to adjust for potential prognostic factors, including age (<75 years vs. ≥75 years), Eastern Cooperative Oncology Group performance status (0 vs. 1, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction, and 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature), time since completion of radiotherapy (1 to 3 years vs. >3 years), baseline PSA level (3 to 15 ng per milliliter vs. >15 ng per milliliter), and neoadjuvant androgen-deprivation therapy (no vs. yes; maximum length of therapy allowed, 12 months), yielding an adjusted hazard ratio with intermittent therapy versus continuous therapy of 1.03 (95% CI, 0.86 to 1.22). A Cox regression model that included study treatment and Gleason score (≤6, 7, or 8 to 10, on a scale of 1 to 10, with higher scores indicating a worse prognosis) showed that there was no differential treatment effect among the three Gleason-score groups (Fig. S3 in the Supplementary Appendix).

DISEASE-SPECIFIC SURVIVAL

In view of the high proportion of deaths that were unrelated to prostate cancer (59%), disease-specific survival was added as an unplanned retrospective analysis to determine whether a significant difference in treatment effect was obscured by the data on deaths from causes other than prostate cancer. Disease-specific survival was calculated from the date of randomization to the date of death from prostate cancer or a complication of cancer treatment. A total of 214 patients died from prostate cancer or related causes: 120 in the intermittent-therapy group and 94 in the continuous-therapy group (hazard ratio with intermittent therapy, 1.18; 95% CI, 0.90 to 1.55; P = 0.24 by the log-rank test). After adjustment for stratification and confounding factors, the estimated disease-specific hazard ratio was 1.23 (95% CI, 0.94 to 1.60; P = 0.13) (Table 3). The 7-year cumulative disease-related death rates were estimated at 18% and 15% for the intermittent-therapy and continuous-therapy groups, respectively (Fig. S4 in the Supplementary Appendix).

TIME TO CASTRATION-RESISTANT DISEASE

Castration-resistant disease developed in a total of 445 patients (202 patients in the intermittent-therapy group and 243 in the continuous-therapy group). On the basis of a Cox regression analysis with adjustment for the stratification factors, the estimated hazard ratio for castration-resistant disease with intermittent therapy, as compared with continuous therapy, was 0.80 (95% CI, 0.67 to 0.98; P = 0.02). With adjustment for potential prognostic factors, the estimated hazard ratio was 0.81 (95% CI, 0.68 to 0.98; P = 0.03).

For patients in the intermittent-therapy group, there was an inherent delay in the identification of castration-resistant disease, because treatment had to be restarted in these patients and they had to have a “castrate-range” testosterone level and an additional three increases in the PSA level before being classified as having castration-resistant disease. This difference between the groups biased the result against continuous androgen-deprivation therapy regarding time to castration resistance by an unknown magnitude but probably accounted for the 4-month gain in survival after the diagnosis of castration-resistant disease in that group (Fig. S5 in the Supplementary Appendix).

DRUG EXPOSURE

The duration of androgen deprivation was calculated as the sum of the periods of treatment with LHRHa on the basis of the depot formulation. Patients in the continuous-therapy group received treatment with LHRHa for a median of 43.9 months (interquartile range, 19.5 to

74.5). Patients in the intermittent-therapy group received treatment for a median of 15.4 months (interquartile range, 8.5 to 23.9) and had a cumulative nontreatment period of 37.6 months (interquartile range, 20.0 to 59.6). Patients who withdrew from the perprotocol treatment were followed until death.

TREATMENT-PHASE DYNAMICS

The duration of the nontreatment intervals and the number of patients in the intermittent-therapy group who completed each interval are shown in Figure 2. The maximum number of nontreatment intervals was nine, with 95% of patients entering the first nontreatment period, 58% the second, and 32% the third. Attrition was due to an off-treatment interval of 2 or fewer months or the development of castration-resistant disease. The median duration of nontreatment periods decreased progressively; the first nontreatment period lasted for a median of 20.1 months, the second for 13.2 months, and the third for 9.1 months, with periods 4 through 7 lasting for approximately 4 to 5 months each.

QUALITY OF LIFE

Quality of life was assessed at fixed time points, regardless of the phase of treatment. Baseline quality-of-life scores were similar in the two groups for most items, with no clinically meaningful differences.[20] Responses were assessed with the use of an area-under-the-curve analysis; individual scores at each assessment between baseline and 5 years were multiplied by the duration of the interval and then summed and compared between groups with the use of the Wilcoxon rank-sum test. For functional domains (physical, role, and global health), the intermittent-therapy group had scores that were slightly better than those in the continuous-therapy group, but the differences were not significant. For items pertaining to symptoms, intermittent therapy was associated with significantly better scores for hot flashes ($P<0.001$), desire for sexual activity ($P<0.001$), and urinary symptoms ($P = 0.006$), with a trend toward improvement in the level of fatigue ($P = 0.07$).

TESTOSTERONE AND POTENCY RECOVERY

The time to testosterone recovery during the first nontreatment interval in the intermittent-therapy group was defined as the time until a return to the pretreatment level. Although only 35% of patients in this group had a return to pretreatment levels within 2 years after completing the first period of treatment, 79% had a level of at least 5 nmol per liter (144 ng per deciliter; the threshold for study entry). Data from patients who never had a recovery were censored on the date that treatment was restarted. A Cox regression model showed that patients who were older than 75 years of age were less likely than younger patients to have a return to the pretreatment level ($P = 0.001$). Only 29% of the men who were potent at baseline had a recovery of potency.

DISCUSSION

The toxic effects of androgen deprivation have been well described, with numerous potential adverse effects on quality of life, including sexual dysfunction, hot flashes, fatigue, anemia, decreased bone density and muscle mass, an altered blood lipid profile, depression, cognitive dysfunction, and worsening of the metabolic syndrome, with effects on glucose metabolism and cardiovascular morbidity.[21-27] All adverse events associated with per-protocol treatment are shown in Table S3 in the Supplementary Appendix. The early diagnosis of failure of definitive treatment, as determined according to the PSA level, subjects otherwise asymptomatic men to many years of androgen deprivation, adversely affecting their quality of life.

Compelling laboratory evidence from animal models has suggested that reexposure to androgens after a period of androgen ablation helps preserve hormonal responsiveness, and a number of phase 2 and 3 clinical studies with different inclusion criteria and treatment schedules have shown that the cyclic approach to androgen deprivation is feasible and is associated with a reduction in toxic effects (Tables S4 and S5 in the Supplementary Appendix). However, assessment of the effect on overall survival requires a randomized trial with sufficient power and duration of follow-up.

For these reasons, the NCIC Clinical Trials Group undertook this phase 3 study in 1999, enrolling 1386 patients over a period of 6 years in an international cooperative effort. On the basis of the planned interim analysis, which showed that the prespecified noninferiority threshold for intermittent therapy had been met, the data and safety monitoring committee recommended early reporting of results. The longer-than-expected median survival of 9 years for all patients with biochemical evidence of disease progression supports the need for a reduction in the toxicity of treatment. However, the finding that overall survival was not reduced by using the study-defined intermittent androgen-deprivation approach should not be extrapolated to other treatment schedules. In addition, this trial did not address the question of when, or at what PSA level, treatment should be initiated; the PSA level of 3 ng per milliliter used as an eligibility criterion for this study was chosen to facilitate accrual.

Although intermittent androgen-deprivation therapy appears to provide an overall quality-of-life benefit, as compared with continuous androgen-deprivation therapy, the difference is not as profound as one might expect. Part of the explanation for this lies in the timing of the qualityof-life assessments, which were performed at regular intervals in both treatment groups without regard to the treatment phase (on or off treatment). For the first 8 months, the two study groups received identical treatment. Within a few months after the start of the first off-treatment period (median duration, 20 months), we observed a benefit in the intermittent-therapy group. Later in the off-treatment period, the effect diminished because of dilution by patients entering the next treatment cycle. The longer the time from randomization, the more likely that patients in the intermittent-therapy group were distributed between treatment and nontreatment phases. Quality-of-life benefits for an individual patient may depend on the treatment cycle, status with respect to testosterone recovery, and age.

The role of predictive factors such as age, Gleason score, and PSA kinetics in the selection of patients for intermittent therapy remains to be defined. The time that it took for the PSA level to double before study entry was not available, but stratification was planned on the basis of the interval since the completion of radiotherapy (1 to 3 years vs. >3 years) as a surrogate for the doubling time. Men who had been treated with radiotherapy more than 3 years before being enrolled in the study had better disease-specific survival (Table 3), with no significant difference according to the treatment they received ($P = 0.65$). Furthermore, there was no significant difference in treatment effect according to the Gleason score, but this was an unplanned subgroup analysis and the trial was not powered to detect a difference of this magnitude. Whether the Gleason score should be used in the selection of patients for intermittent androgen-deprivation therapy remains a matter of clinical judgment (Fig. S3 in the Supplementary Appendix).

This trial raises provocative questions. The non-significant increase in deaths from other causes among patients in the continuous-therapy group cannot be attributed to any specific type of toxic effect. Although the cost savings from the reduction in drug use in the intermittent-therapy group (approximately one third of that in the continuous-therapy group) may be partially offset by the closer follow-up required, this follow-up may have undefined health benefits.

An intermittent approach to androgen deprivation for men with a rising PSA level after definitive radiotherapy does not result in inferior survival, as compared with continuous androgen deprivation. Although testosterone recovery was not universal, benefits in some aspects of quality of life were observed. These results cannot be extrapolated to other intermittent-treatment schedules or disease characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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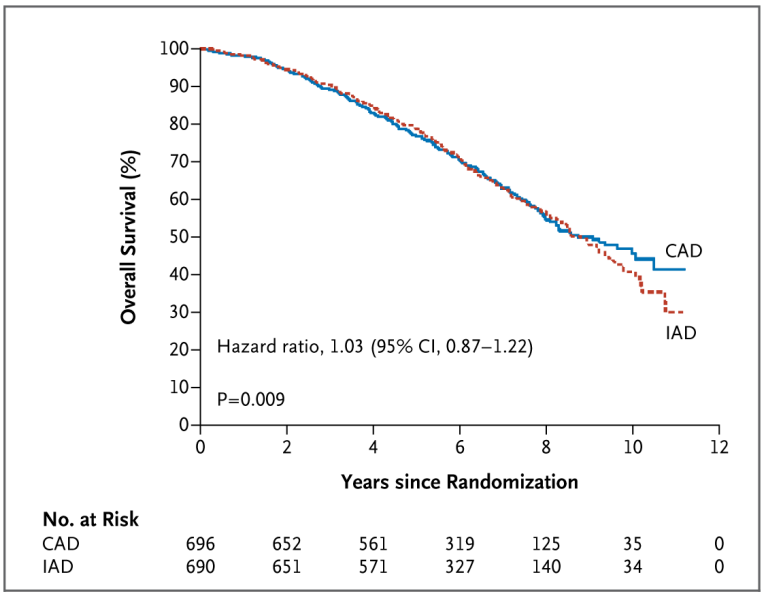

Figure 1. Overall Survival in the Intention-to-Treat Population

The per-protocol analysis yielded very similar results to the analysis presented here, with an estimated hazard ratio for death with intermittent androgen-deprivation therapy (IAD), as compared with continuous androgen-deprivation therapy (CAD), of 1.03 (95% CI, 0.86 to 1.23). The P value for noninferiority (hazard ratio, <1.25) was 0.01.

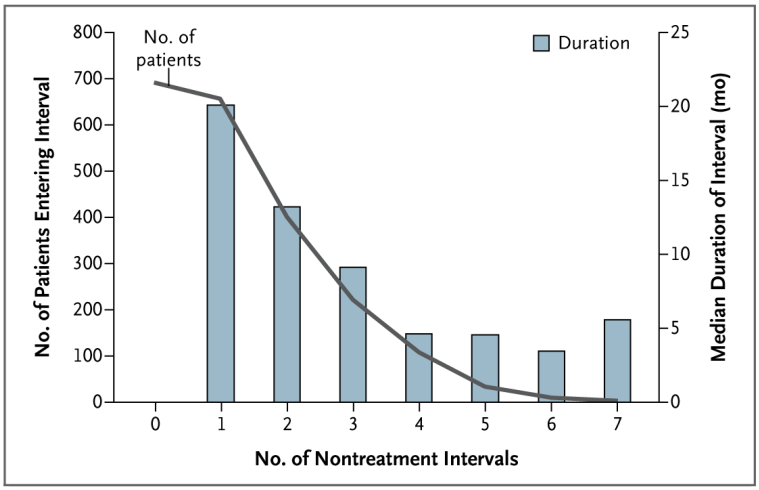

Figure 2. Numbers of Patients Completing Treatment Cycles and the Median Duration of Off-Treatment Periods in the Intermittent-Therapy Group

The maximum number of nontreatment intervals observed was nine, with 95% of patients entering the first nontreatment period, 58% the second, and 32% the third.

Table 1

Baseline Characteristics of the Patients.*

Characteristic	Intermittent Therapy (N = 690)	Continuous Therapy (N = 696)	Total (N = 1386)
Prior radical prostatectomy — no. (%)			
Yes	79 (11.4)	79 (11.4)	158 (11.4)
No	611 (88.6)	616 (88.5)	1227 (88.5)
Missing data	0	1 (0.1)	1 (0.1)
Time since radiotherapy — no. (%)			
1 to 3 yr	146 (21.2)	150 (21.6)	296 (21.4)
>3 yr	542 (78.6)	543 (78.0)	1085 (78.3)
Missing data	2 (0.3)	3 (0.4)	5 (0.4)
Baseline PSA level — no. (%)			
3–15 ng/ml	531 (77.0)	535 (76.9)	1066 (76.9)
>15 ng/ml	159 (23.0)	160 (23.0)	319 (23.0)
Missing data	0	1 (0.1)	1 (0.1)
Prior hormone therapy — no. (%)			
No	419 (60.7)	424 (60.9)	843 (60.8)
Yes	271 (39.3)	271 (38.9)	542 (39.1)
Missing data	0	1 (0.1)	1 (0.1)
Age — yr			
Median	74.2	74.4	74.2
Range	29.4–89.7	45.3–88.9	29.4–89.7
ECOG performance status — no. (%)†			
0	548 (79.4)	568 (81.6)	1116 (80.5)
1	142 (20.6)	127 (18.2)	269 (19.4)
Missing data	0	1 (0.1)	1 (0.1)
Malignant prostate — no. (%)‡			
No	517 (74.9)	503 (72.3)	1020 (73.6)
Yes	135 (19.6)	150 (21.6)	285 (20.6)
Missing data or unknown	38 (5.5)	43 (6.2)	81 (5.8)

[*] There were no significant between-group differences in the distribution of these characteristics. PSA denotes prostatespecific antigen.

[†] On the Eastern Cooperative Oncology Group (ECOG) scale, a performance status of 0 indicates that the patient is fully active and able to carry on all predisease activities without restriction, and a status of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature.

[‡] A malignant prostate was defined on the basis of an abnormal finding on digital rectal examination that was suspicious for recurrence of cancer.

Table 2

Investigator-Reported Causes of Death (Intention-to-Treat Population).

Cause	Deaths in Intermittent-Therapy Group (N = 268)	Deaths in Continuous-Therapy Group (N = 256)	Total Deaths (N = 524)
		number (percent)	
Disease-specific			
Prostate cancer	110 (41.0)	87 (34.0)	197 (37.6)
Prostate cancer and off-protocol treatment	10 (3.7)	5 (2.0)	15 (2.9)
Complication of per-protocol treatment	0	2 (0.8)	2 (0.4)
Unrelated to prostate cancer			
Complication of off-protocol treatment*	2 (0.7)	5 (2.0)	7 (1.3)
Other primary cancer	59 (22.0)	54 (21.1)	113 (21.6)
Other cause	75 (28.0)	92 (35.9)	167 (31.9)
Unknown	12 (4.5)	11 (4.3)	23 (4.4)

* Treatment was initiated off protocol after the development of castration-resistant disease.

Table 3

Hazard Ratio for Death from Prostate Cancer or Treatment Complication in the Intention-to-Treat Population.*

Variable	Hazard Ratio (95% CI)	P Value
Group		
Continuous therapy	1.00	
Intermittent therapy	1.23 (0.94–1.66)	0.13
Age		
<75 yr	1.00	
≥75 yr	1.58 (1.20–2.08)	0.001
Time since radiotherapy		
1–3 yr	1.00	
<3 yr	0.41 (0.31–0.55)	7lt;0.001
Baseline PSA level		
3–15 ng/ml	1.00	
<15 ng/ml	1.98 (1.50–2.61)	<0.001
Prior hormone therapy		
No	1.00	
Yes	1.66 (1.25–2.19)	<0.001

*The analysis was performed with the use of a Cox model.