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Adding Short-Term Androgen Deprivation Therapy to Radiation Therapy in Men With Localized Prostate Cancer: Long-Term Update of the NRG/RTOG 9408 Randomized Clinical Trial

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All data used in the publication will be de-identified and available for data sharing via NCI's NCTN/NCORP Data Archive at least 6 months from the publication date. Data dictionaries are provided with the data. Information about the archive and how to access the data can be found here: https://nctn-data-archive.nci.nih.gov/.

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Abstract

Purpose: For men with localized prostate cancer, NRG Oncology/Radiation Therapy Oncology Group (RTOG) 9408 demonstrated that adding short-term androgen deprivation therapy (ADT) to radiation therapy (RT) improved the primary endpoint of overall survival (OS) and improved disease-specific mortality (DSM), biochemical failure (BF), local progression, and freedom from distant metastases (DM). This study was performed to determine whether the short-term ADT continued to improve OS, DSM, BF, and freedom from DM with longer follow-up.

Methods and Materials: From 1994 to 2001, NRG/RTOG 9408 randomized 2028 men from 212 North American institutions with T1b-T2b, N0 prostate adenocarcinoma and prostate-specific antigen (PSA) ≤20ng/mL to RT alone or RT plus short-term ADT. Patients were stratified by PSA, tumor grade, and surgical versus clinical nodal staging. ADT was flutamide with either goserelin or leuprolide for 4 months. Prostate RT (66.6 Gy) was started after 2 months. OS was calculated at the date of death from any cause or at last follow-up. Secondary endpoints were DSM, BF, local progression, and DM. Acute and late toxic effects were assessed using RTOG toxicity scales.

Results: Median follow-up in surviving patients was 14.8 years (range, 0.16–21.98). The 10-year and 18-year OS was 56% and 23%, respectively, with RT alone versus 63% and 23% with combined therapy (HR 0.94; 95% confidence interval [CI], 0.85–1.05; $P = .94$). The hazards were not proportional ($P = .003$). Estimated restricted mean survival time at 18 years was 11.8 years (95% CI, 11.4–12.1) with combined therapy versus 11.3 years with RT alone (95% CI, 10.9–11.6; $P = .05$). The 10-year and 18-year DSM was 7% and 14%, respectively, with RT alone versus 3% and 8% with combined therapy (HR 0.56; 95% CI, 0.41–0.75; $P < .01$). DM and BF favored combined therapy at 18 years. Rates of late grade ≥3 hepatic, gastrointestinal, and genitourinary toxicity were ≤1%, 3%, and 8%, respectively, with combined therapy versus ≤1%, 2%, and 5% with RT alone.

Conclusions: Further follow-up demonstrates that OS converges at approximately 15 years, by which point the administration of 4 months of ADT had conferred an estimated additional 6 months of life.

Phase 3 clinical trials[1,2] have demonstrated that adding 2 or more years of reversible androgen suppression agents to radiation therapy (RT) improves survival in men with locally advanced prostate cancer. Long-term treatment with these agents, however, added toxic effects, including erectile dysfunction and myocardial infarction.[3] The question was then asked whether decreasing the duration of androgen suppression could mitigate these associated toxicities while still improving treatment efficacy. Subsequently, phase 3 clinical trials were completed that reported on the benefits of this approach.[4,5]

The introduction of prostate-specific antigen (PSA) testing resulted in increased diagnoses of early-stage disease.[6,7] Less was known about the role of short-term androgen deprivation therapy (ADT) in men receiving RT for these less aggressive tumors. Accordingly, in 1994, the Radiation Therapy Oncology Group (RTOG), now NRG Oncology, opened a large, randomized trial, NRG/RTOG 9408, to evaluate whether adding short-term ADT to RT would improve survival among patients with nonbulky localized prostate adenocarcinomas and an initial PSA of ≤20 ng/mL.

In 2011, the initial report of this trial[8] demonstrated that adding short-term ADT improved overall survival (OS) at 10 years from 57% to 62% (hazard ratio [HR] 1.17; 95% confidence interval [CI], 1.01–1.35; $P = .03$). Disease-specific mortality (DSM), biochemical failure (BF), freedom from distant metastases (DM), and 2-year positive rebiopsy rates were all also improved. Short-term ADT appeared to benefit both white and African American men as well as age groups of >70 and <70 years. Post hoc analysis by risk subgroup demonstrated that these survival benefits were seen in men with intermediate-risk cancer but not low-risk cancer. The incidence of acute and late radiation induced toxic effects, as well as cardiovascular mortality,[9] was similar in the 2 treatment groups.

In this report, we present the long-term update of NRG/RTOG 9408 with 6 additional years of follow-up.

Methods and Materials

Trial design and participants

Men with histologically confirmed prostate adenocarcinoma, stage T1b-T2b (1992 classification of American Joint Committee on Cancer),[10] and a PSA level of ≤20 ng/mL were eligible. Pretreatment evaluation included a digital rectal examination and bone scan. The regional lymph nodes were evaluated clinically with lymphangiography or pelvic computed tomography or surgically. The Gleason score was determined, and tumors were also classified as well differentiated, moderately differentiated, or poorly differentiated. Eligibility criteria included a Karnofsky performance score of ≥70, an alanine aminotransferase within twice the upper normal limit, no evidence of regional lymph-node or distant metastases, and no previous chemotherapy, RT, hormonal therapy, cryosurgery, or definitive surgery for prostate cancer. Patients free of invasive cancers for ≥5 years or basal cell or squamous cell skin carcinomas for ≥2 years were eligible if approved by the study cochairs. The institutional review boards of the participating institutions approved the study protocol, and all patients provided written informed consent.

Treatment

Patients were stratified according to PSA level (<4 vs 4–20 ng/mL), tumor grade (well differentiated, moderately differentiated, or poorly differentiated), and surgical versus clinical evaluation of regional nodes and then randomized to receive RT alone or RT plus short-term ADT, according to the permuted-block randomization method described by Zelen.[11] Treatment commenced within 21 days of randomization. RT, administered in daily 1.8 Gy fractions prescribed to the isocenter, consisted of 46.8 Gy to the pelvis (prostate

and regional lymph nodes), followed by 19.8 Gy to the prostate (66.6 Gy total). The nodes were not treated if surgically negative or if PSA <10 ng/mL and Gleason score <6. The study cochairs reviewed the simulation and portal films. ADT consisted of oral flutamide (250 mg 3 times a day) and either monthly subcutaneous goserelin (3.6 mg) or intramuscular leuprolide (7.5 mg) for 4 months. RT commenced after 2 months of androgen deprivation. Flutamide was discontinued if the alanine aminotransferase more than doubled the upper normal limit.

Patient assessment and endpoints

At the beginning and end of RT, assessments included history and physical examination, performance status, complete blood count, and alkaline phosphatase, alanine aminotransferase, PSA, and serum testosterone levels. Follow-up visits occurred every 3 months during year 1, 4 months during year 2, 6 months during years 3 through 5, and then annually. PSA values were obtained at each visit, along with serum testosterone and complete blood counts during the first 2 years and alkaline phosphatase yearly. Acute and late toxic effects were assessed with the use of RTOG toxicity scales.[12]

All endpoints were measured from the date of randomization. OS was calculated at the date of death from any cause or last known follow-up. Secondary endpoints included DSM, DM, and BF (using the Phoenix Consensus Conference definition).[13] DSM included all deaths from prostate cancer or treatment complications. Other mortality attributions included deaths from second primary cancers, deaths from other causes, and deaths from unknown causes. The study cochairs reviewed the reported causes of death, and complicated cases were reviewed by committee. The scoring of DM required documentation of metastatic disease.

Statistical analysis

The primary endpoint, OS, was estimated by means of the Kaplan−Meier approach,[14] with HR and 95% CI estimated with the Cox regression model.[15] The proportional hazards assumption was tested using the Kolmogorov-type supremum test.[16] Owing to the longer follow-up and nonproportional hazards between treatment arms, post hoc comparisons for OS and BF were performed by comparing restricted mean survival times with 18 years as the point of restriction; this comparison can be more powerful than the log-rank test in the presence of nonproportional hazards. The point of restriction should be one further out in follow-up while a reasonable number of patients are still at risk, making the restricted mean the average survival from time 0 to 18 years.[17] The covariate-adjusted restricted mean survival time was also determined. The Wilcoxon test is also reported because it places more emphasis on the earlier events when the hazards were proportional.

The endpoints of DSM, DM, and BF were estimated by means of the cumulative incidence function.[18] The Fine-Gray model was used to estimate subdistribution HR.[19] Methodology for life years lost, the counterpart to RMST when competing risks are present, was used to determine years lost due to specific events, such as biochemical failure, for endpoints with competing risks in which the proportional hazards assumption was violated.[20]

Three sets of subgroup analyses, not specified in the protocol, were conducted: (1) risk group (low vs intermediate vs high), (2) age (≤70 vs >70 years), (3) race (white vs

nonwhite). Low-risk was defined as Gleason score 2 to 6, PSA ≤10 ng/mL, and clinical stage of ≤T2a. Intermediate risk was defined as either clinical stage T2b, Gleason score of 7, or Gleason score 2 to 6 with a PSA >10 and ≤20 ng/mL. High-risk was defined as Gleason score 8 to 10. Tests of the interaction between the subgroup and treatment arm were conducted. Survival estimates were calculated within each subset.

The R package “lillies” was used for analysis of life years lost, and SAS software v.94 was used for all other analyses.[21]

Results

Study population

From October 31, 1994, to April 30, 2001, 2028 patients from 212 centers in North America were randomly assigned to RT alone or RT plus short-term ADT. Thirty-nine patients were ineligible, and 15 withdrew consent, leaving 1974 eligible patients available for evaluation (990 in the RT-alone group and 984 in the combined-therapy group) (Fig. 1). The treatment groups were balanced, with no significant differences in demographic or tumor-related characteristics (Table 1). There were 23 patients who were missing institutional Gleason score, so central Gleason score was used. For the risk subgroup classification, the 24 patients without institutional or central Gleason score were categorized as high risk.

The median follow-up for all patients was 10.4 years (range, 0.11–21.98), and the median follow-up for surviving patients was 14.8 years (range, 0.16–21.98). Not unexpectedly, more patients were lost to follow-up with the longer duration of the study. By 10 and 20 years, 12.7% and 19% of patients, respectively, on the combined-therapy arm and 10.6% and 17.8% on the RT-alone arm were lost to follow-up. The percentage of deaths attributed to “unknown cause” averaged 7% for the first 5 years, 17% for years 6 through 10, 22% for years 11 through 15, and 31% for years 16 through 20.

Treatment efficacy

The 10-year and 18-year OS rates (Table 2, Fig. 2) were 56% and 23%, respectively, in the RT-alone group and 63% and 23% in the combined-therapy group (HR 0.94; 95% CI, 0.85–1.05; $P = .94$). The log-rank P value was .28, and the Wilcoxon test P value was .036. The hazards were not proportional ($P = .003$). The estimated restricted mean survival time at 18 years of follow-up was 11.76 years (95% CI, 11.41–12.10) in the hormones plus RT arm and 11.26 years in the RT-alone arm (95% CI, 10.90–11.62), a difference of 0.50 years (or 6 months) with P value of .052. Alternatively, the average difference in survival rates over the 18-year period was 0.50/18 (0.028 or 2.8%). The covariate-adjusted restricted mean survival time was 11.69 years (95% CI, 11.36–12.00) for combined therapy and 11.35 years (95% CI, 11.00–11.70) for the RT-alone arm ($P = .060$).

The 10-year and 18-year DSM (Table 2, Fig. 3) was 7% and 14%, respectively, in the RT-alone group and 3% and 8% in the combined-therapy group (HR 0.56; 95% CI, 0.41–0.75; $P < .001$). The 10-year and 18-year cumulative incidence of DM was 8% and 13%, respectively, in the RT-alone group and 5% and 9% in the combined-therapy group (HR 0.67; 95% CI, 0.49–0.92; $P = .012$) (Table 2 and Fig. 3).

The 10-year and 18-year rates of BF were 47% and 53%, respectively, in the RT-alone group and 34% and 40% in the combined-therapy group (HR 0.70; 95% CI, 0.61–0.80; P <.001) (Table 2 and Fig. 3). The hazards were not proportional (P = .021). Using 18 years as the point of restriction, patients on the RT-alone arm lost 6.78 years (95% CI, 6.33–7.27) without a biochemical failure and patients on the combined-therapy arm lost 5.12 years (95% CI, 4.66–5.57). Salvage hormonal therapy was administered to 34.8% of patients in the combined-modality arm versus 44.0% in the RT-alone arm (P <.001). The combined-modality arm had a significantly longer time to salvage hormone use at 10 years (HR 1.89; 95% CI, 1.55–2.31; P < .001).

Toxicity

In the RT-plus-ADT group, the proportions of patients who had grade 1, 2, 3, 4, and 5 late hepatic toxic effects were 3%, <1%, <1%, 0%, and 0%, respectively, compared with <1%, 0%, 0%, 0%, and 0% in the RT-alone group. The incidences of grade ≥3 late gastrointestinal toxic effects were 3% in the combined-therapy group and 2% in the RT-alone group (P = .028), with grade 5 toxic effects in 3 patients; 2 patients receiving RT alone died of obstruction of the colon, and 1 patient treated with RT plus ADT died of colorectal bleeding. Late grade ≥3 genitourinary toxic effects were seen in 8.6% of patients in the combined-therapy group and 9.3% of the RT-alone group (P = .56). One patient in the combined-therapy group died of bladder-related complications. The 18-year cumulative incidence of death from causes other than prostate cancer was 63% in the RT-alone group and 70% in the combined-therapy group (HR 1.09; 95% CI, 0.97–1.22; P = .146). A similar proportion of patients in the combined-therapy and RT-alone groups reported second primaries (17.9% vs 17.0%, respectively; P = .59).

Subgroup analyses

Subgroup analyses of OS by risk groups (low vs intermediate vs high), age (≤70 vs >70 years), and race (white and black) demonstrated that, in all subgroups, OS favored the RT-plus-ADT arm at 10 years, but then the 2 arms converged and OS was similar at 18 years (Table 2). There were no significant differences in the tests of interaction between each subgroup and treatment arm (results not shown). Estimated RMST at 18 years showed a trend in favor of the combined-modality arm for all the subgroups (Table 2).

For men ≥70 years old, 10-year and 18-year DSM was 8% and 15%, respectively, in the RT-alone group and 3% and 8% in the combined-therapy group (HR 0.52; 95% CI, 0.34–0.78; P <.01). For men younger than 70, it was 6% and 12% in the RT-alone group and 3% and 7% in the combined-therapy group (HR 0.62; 95% CI, 0.39–0.97; P = .05) (Table 2).

For white patients, 10-year and 18-year DSM was 7% and 15%, respectively, in the RT-alone group and 3% and 8% in the combined-therapy group (HR 0.52; 95% CI, 0.37–0.73; P <.01). For black patients, it was 7% and 10% in the RT-alone group and 4% and 7% in the combined-therapy group (HR 0.67; 95% CI, 0.32–1.41; P > .05) (Table 2).

For the intermediate-risk subgroup, 10-year and 18-year DSM was 9% and 16%, respectively, in the RT-alone group and 3% and 9% in the combined-therapy group (HR 0.53; 95% CI, 0.36–0.77; P < .01.) For the low-risk subgroup, 10-year and 18-year DSM

was 1% and 6%, respectively, in the RT-alone group and 1% and 5% in the combined-therapy group (HR 0.63; 95% CI, 0.31–1.29; $P > .05$) (Table 2). There were no significant tests of interaction between each subgroup and treatment arm for DSM (results not shown).

Discussion

This phase 3 clinical trial previously reported that the addition of short-term ADT to moderate doses of RT conferred a modest but significant increase in 10-year OS for patients with early, localized prostate cancer and a PSA level of ≤20 ng/mL. This was accompanied by a significant reduction in 10-year DSM and reductions in the secondary endpoints of BF, DM, and local progression. These efficacy gains were achieved with no increased risk of death from intercurrent disease, serious cardiovascular toxic effects, or either acute or long-term gastrointestinal or genitourinary complications of RT. Because of the indolent nature of the disease, additional follow-up with vigilant PSA monitoring was obtained to acquire meaningful results in a patient cohort in which most deaths are due to other causes (Fig. 1).

The long-term update continues to show that the addition of short-term ADT improves OS during the first 10 years of follow-up. However, after 10 years, a higher mortality rate in the combined-modality arm caused the OS curves to converge at about 15 years (Fig. 2). Due to this pattern of OS, the mean expected survival, at 18 years of follow-up, was 11 years and 3 months in the RT-alone arm compared with 11 years and 9 months with the addition of hormones. This pattern of OS was seen in all risk, age, and white-versus-nonwhite subgroups (Table 2).

In contrast, the benefits of short-term ADT persisted at 18 years for the secondary endpoints of DSM, BF, and DM, including all age and white-versus-nonwhite subgroups with regard to DSM and BF (Table 2 and Fig. 3). We are not reporting long-term local progression data because it is suspected that rectal examinations were only uncommonly performed at long-term follow-up visits. Also, the protocol mandated prostate biopsies at 2 years, which should be expected to be a superior measure of local treatment effect. For the different risk subgroups (Table 2), post hoc analysis revealed that short-term ADT improved 18-year DSM for men in the intermediate-risk subgroup. For the low-risk subgroup, 18-year DSM continued to be low and similar in both arms, further justifying the practice of omitting short-term ADT in these patients. In the high-risk subgroup, the high rate of DSM at 18 years in both arms continues to provide support for observations from other clinical trials showing that more than 4 months of ADT is required for maximum benefit.[22,23]

Clinical trials evaluating therapeutic questions are difficult in this patient population due to the indolent nature of the disease and resultant length of time required to obtain meaningful OS and DSM data. BF has been proposed as an earlier, more expeditious surrogate endpoint,[24] although recent meta-analyses indicate that it is not a good surrogate for the OS endpoint.[25,26] The long-term results of NRG/RTOG 9408 presented here indicate that increased BF appears associated with later increased DSM, both when comparing the RT-alone arm to the combined-modality arm as well as comparing intermediate-risk patients

to low-risk patients (Table 2). However, there were no signals in the BF data that predicted the convergence of OS at 15 years.

Only a minority of patients who had BF at 8 to 10 years actually developed DM or died of prostate cancer at 18 years. In the RT-alone arm, for low-risk and intermediate-risk patients, 10-year BF rates were 36% and 50%, respectively, whereas 18-year DSM rates were 6% and 16%. Similarly, in the combined-modality arm, the 10-year BF rates were 28% and 38%, respectively, whereas 18-year DSM rates were 5% and 9%. The incidence of DM at 18 years for all patients was also low at 13% in the RT-alone arm and 9% in the combined-modality arm (Table 2, Fig. 3). One possible explanation for this discrepancy might be that, after BF, incidences of DM or deaths from prostate cancer might be delayed longer than 10 years, either due to salvage hormonal therapy or slow progression of disease. Our data suggest that the number of DM and DSM events shows no evidence of plateauing at 18 years (Fig. 3). On the other hand, a second potential explanation could be that the moderate doses of radiation employed in this study might, in some patients, allow substantial recovery of PSA production in normal prostate tissue, which would imply that some biochemical failures may not necessarily signal the presence of residual carcinoma. Long-term results from more recent trials using higher doses of RT to the prostate could be helpful in answering this question.

Increased late mortality in the combined-modality arm caused the OS curves to converge at about 15 years. This late excess mortality could be explained if short-term ADT merely delayed prostate cancer recurrences instead of increasing the rate of cure. However, our data indicate that the DSM benefit of hormones is maintained in the long term (Fig. 3). Alternatively, the addition of ADT could promote late deaths from other causes. However, we observed no statistically significant difference in non−prostate cancer mortality between the 2 arms.

This discrepancy might be explained by the high incidence of “unknown cause” as a death attribution in the later years of follow-up, potentially masking late mortality from either prostate cancer or other causes. It seems unlikely that 4 months of ADT would significantly increase the incidence of non−prostate cancer deaths at such a remote time point. An analysis of cardiovascular toxicity in NRG/RTOG 9408 patients[9] has previously been reported and revealed no increased risk of these types of deaths with the addition of short-term ADT. Our current analysis also shows that the incidence of grade 3 or greater long-term gastrointestinal, genitourinary, or hematologic toxicity was low and similar in both arms, making it doubtful that we are underestimating ADT-related deaths from these causes as well. On the other hand, it is conceivable that some of the men who were lost to long-term follow-up and were scored as dying from of unknown causes may have instead actually have died of unrecognized late recurring prostate cancer.

Limitations

The main limitation of this study is that it was conducted before the adoption of RT techniques such as intensity modulated radiation therapy, image guided radiation therapy, and low-dose-rate and high-dose-rate brachytherapy. These techniques now permit the safe delivery of higher doses of radiation with improved efficacy,[27–32] bringing into question the

value of adding short-term ADT in men with intermediate-risk cancers treated with modern irradiation methods. Fourteen years after the opening of NRG/RTOG 9408, a successor study, NRG/RTOG 0815 (NCT00936390), was initiated to address this question. This study has completed accrual, and we await the results with interest.

Another limitation is that accurate death attribution was challenging in this elderly group of men with a median follow-up reaching nearly 15 years. Some patients had data unavailable for many years before their recorded death. It is not surprising that numerous patients in their late 80s or 90s, residing in nursing homes or assisted-living facilities, would have difficulty completing the study mandated follow-up visits or PSA draws. This is reflected in the increasing incidence of “Unknown Cause” as a death attribution with longer follow-up times.

Conclusions

NRG/RTOG 9408 showed that the addition of short-term ADT provided a survival benefit for men with intermediate-risk prostate cancer who received moderate doses of RT. Although the analysis of the long-term update demonstrates that OS in the 2 arms converges at approximately 15 years, by that point, the administration of 4 months of ADT conferred, on average, an estimated additional 6 months of life.

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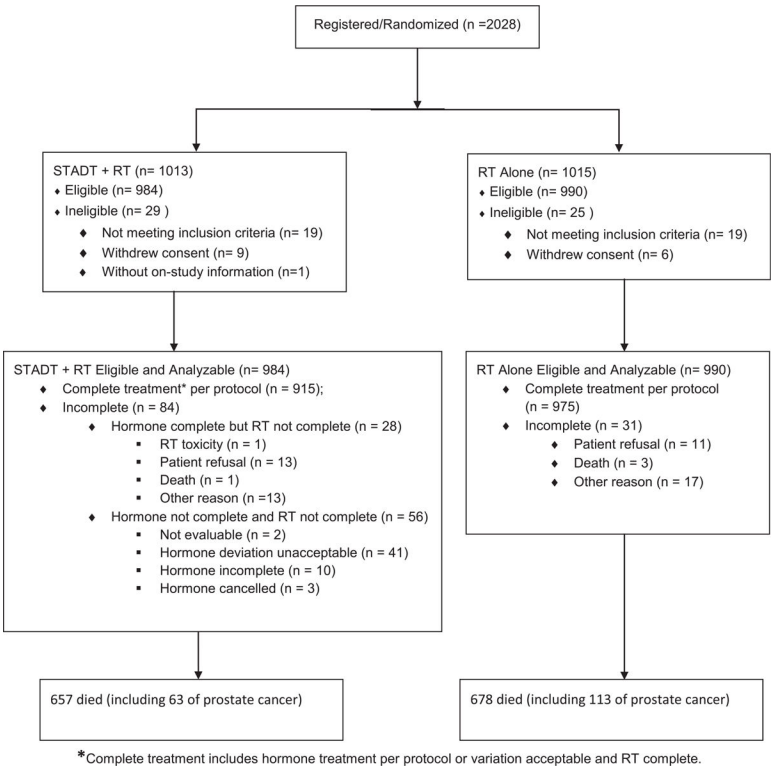

Fig 1.
CONSORT flow diagram.

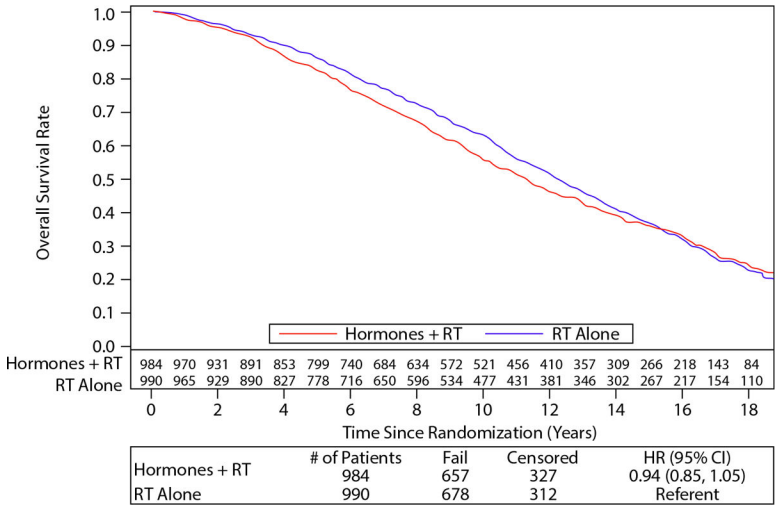

Fig 2.
Overall survival.

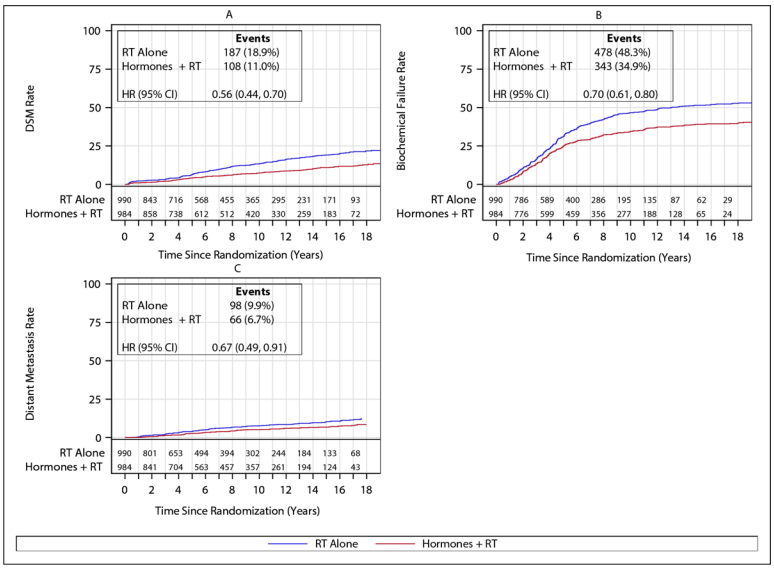

Fig 3.
3-box panel.

Table 1

Characteristics of the patients

	Hormones plus RT (n = 984)	RT alone (n = 990)
Age		
≤70 y	502 (51.0%)	470 (47.5%)
>70 y	482 (49.0%)	520 (52.5%)
Race		
White	743 (75.5%)	754 (76.2%)
Black, not of Hispanic origin	197 (20.0%)	197 (19.9%)
Hispanic	27 (2.7%)	26 (2.6%)
Other or Unknown	17 (1.7%)	13 (1.3%)
KPS		
70–80	82 (8.3%)	72 (7.3%)
90–100	901 (91.7%)	918 (92.7%)
T stage		
T1	486 (49.4%)	476 (48.1%)
T2	497 (50.6%)	514 (51.9%)
Nodal status *		
N0	43 (4.4%)	37 (3.7%)
NX	940 (95.6%)	953 (96.3%)
PSA		
<4	109 (11.1%)	100 (10.1%)
4–20	874 (88.9%)	89 (89.9%)
Differentiation *		
Well differentiated	135 (13.7%)	150 (15.2%)
Moderately differentiated	622 (63.2%)	618 (62.4%)
Poor/undifferentiated	227 (23.1%)	222 (22.4%)
Gleason score †		
2–6	624 (63.4%)	595 (60.1%)
7	255 (25.9%)	274 (27.7%)
8–10	94 (9.6%)	91 (9.2%)
Unknown	11 (1.1%)	13 (1.3%)
Risk subgroup		
Low	360 (36.6%)	343 (34.6%)
Intermediate	530 (53.9%)	556 (56.2%)
High	94 (9.6%)	91 (9.2%)

* Stratification factors.

† Institutional Gleason score was used. Because 47 patients were missing an institutional Gleason score, a central Gleason score was used for the 23 patients who had it available. For risk group classification, the remaining 24 were categorized as high risk. One patient, who in the previous analysis was missing Gleason score, was found to be ineligible.Low risk includes Gleason 6 or less, PSA 10 or less, and Clinical Stage T2a or less; intermediate risk includes Gleason 7 or Gleason 6 or less with PSA 10–20 or clinical stage T2b; high risk includes Gleason 8–10.Abbreviations: KPS = Karnofsky Performance Scale; PSA = prostate-specific antigen; RT = radiation therapy.

Table 2

Antitumor efficacy by time

	Short-term ADT plus radiation therapy (n = 984)				Radiation therapy alone (n = 990)				Hazard ratio (95% CI)	*P* value
Endpoint		10 y	18y	RMST (95% CI)		10 y	18 y	RMST (95% CI)		
Overall survival	No. of patients	Survival rate			No. of patients	Survival rate				
All patients	984	63%	23%	11.8 y (11.4–12.1)	990	56%	23%	11.3 y (10.9–11.6)	0.94 (0.85–1.05)	.05
Low risk	360	69%	26%	12.4 y (11.8–12.9)	343	62%	31%	12.0 y (11.4–12.7)	1.01 (0.83–1.22)	.47
Intermediate risk	530	60%	21%	11.5 y (11.0–12.0)	556	53%	20%	10.9 y (10.5–11.4)	0.92 (0.79–1.05)	.10
High risk	94	55%	19%	10.9 y (9.7–12.0)	91	52%	16%	10.3 y (9.1–11.4)	0.89 (0.63–1.23)	.47
Age ≤70 y	502	71%	35%	13.0 y (12.5–13.5)	470	64%	34%	12.4 y (11.8–12.9)	0.93 (0.79–1.10)	.10
Age >70 y	482	55%	11%	10.5 y (10.0–11.0)	520	49%	14%	10.3 y (9.8–10.7)	0.99 (0.86–1.14)	.46
White	743	64%	23%	11.8 y (11.4–12.2)	754	57%	24%	11.4 y (10.9–11.8)	0.95 (0.93–1.18)	.10
Black	241	60%	22%	11.6 y (10.8–12.4)	236	53%	20%	10.7 y (9.9–11.6)	0.88 (0.68–1.14)	.16
Disease-specific mortality		Failure rate				Failure rate				
All patients		3%	8%			7%	14%		0.56 (0.41–0.75)	<.01
Low risk		1%	5%			1%	6%		0.63 (0.30–1.29)	
Intermediate risk		3%	9%			9%	16%		0.53 (0.36–0.77)	<.01
High risk		13%	17%			15%	25%		0.59 (0.30–1.13)	
Age ≤70 y		3%	7%			6%	12%		0.62 (0.39–0.97)	.05
Age >70 y		3%	8%			8%	15%		0.52 (0.34–0.78)	<.01
White		3%	8%			7%	15%		0.52 (0.37–0.73)	<.01
Black		4%	7%			7%	10%		0.67 (0.32–1.41)	-
Biochemical failure		Failure rate		LYL (95% CI)		Failure rate		LYL (95% CI)		
All patients		34%	40%	5.12 y (4.66–5.57)		47%	53%	6.78 y (6.33–7.27)	0.70 (0.61–0.80)	<.01
Low risk		28%	33%	4.22 y (3.54–4.89)		36%	42%	5.26 y (4.53–5.96)	0.78 (0.60–1.00)	.05
Intermediate risk		38%	43%	5.59 y (4.98–6.22)		50%	57%	7.37 y (6.78–7.99)	0.69 (0.58–0.83)	<.01
High risk		38%	45%	5.86 y (4.48–7.39)		62%	65%	8.87 y (7.38–10.36)	0.56 (0.37–0.84)	<.01
Age ≤70 y		37%	43%	5.56 y (4.93–6.18)		47%	54%	6.95 y (6.34–7.62)	0.75 (0.62–0.91)	<.01
Age > 70 y		32%	36%	4.69 y (4.10–5.31)		46%	51%	6.62 y (5.95–7.20)	0.64 (0.53–0.79)	<.01
White		36%	42%	5.37 y (4.86–5.91)		47%	54%	6.88 y (6.38–7.37)	0.69 (0.59–0.81)	<.01
Black		29%	32%	4.53 y (3.52–5.65)		44%	46%	6.36 y (5.30–7.43)	0.59 (0.42–0.83)	.02

	Short-term ADT plus radiation therapy (n = 984)		Radiation therapy alone (n = 990)		Hazard ratio (95% CI)	*P* value
Distant metastases	Failure rate		Failure rate			
All patients	5%	9%	8%	13%	0.67 (0.49–0.92)	.01

P value from RMST between arm χ^2 test where RMST is provided.

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; LYL = life years lost; RMST = restricted mean survival time.